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**LA THÈSE A ÉTÉ  
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"Once a hundred men were shut into an enormous dark room, each one of them with an unlit lamp. One of them managed to light his lamp, and so they could see. As the rest lit their lamps, more and more of the objects around them came into view, until finally everything in the room stood out as good and beautiful. There were a hundred lamps, only one idea: Yet it took the light of all the lamps to reveal the details of everything in the room."

- Giovanni Guareschi

ACKNOWLEDGEMENT

The author wishes to express her sincere thanks to her research director, Professor Peter Morand for his capable supervision and constant encouragement during the course of this work.

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ABSTRACT

The reduction of unsymmetrically substituted cyclic anhydrides with metal hydrides often leads to the preferential formation of one of the two possible lactones. The electronic factors and steric restrictions influencing regioselectivity in several model cyclic anhydrides, dicarboxylic acids and an ester are discussed in the light of recent experimental findings and theories concerning nucleophilic addition to the carbonyl function. A mechanism for the reduction of unsymmetrical cyclic anhydrides with metal hydrides is proposed and the observed patterns of regioselectivity are rationalized in view of this mechanism.

Several model anhydrides were synthesized and the products of their reduction by  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  were separated and characterized.

A brief survey of a variety of reduction methods was conducted in order to develop selective synthetic routes to one or the other isomeric lactone possible.

GLOSSARY OF ABBREVIATIONS

The following abbreviations are used:

i.r.	infra red
$H^1$ n.m.r.	proton nuclear magnetic resonance
$C^{13}$ n.m.r.	Carbon-13 nuclear magnetic resonance
G.l.c.	Gas-liquid chromatography
m.p.	melting point

Solvents:

$CDCl_3$	deuterated chloroform	THF	THF	tetrahydrofuran
DMF	dimethylformamide			
AcOH	acetic acid			
EtOH	ethanol			
MeOH	methanol			

Reagents:

$LiAlH_4$	lithium aluminum hydride	LDA	lithium diisopropylamine
$NaAlH_4$	sodium aluminum hydride		
$NaBH_4$	sodium borohydride		
$(CH_3)_4NBH_4$	tetramethyl ammonium borohydride		
$(CH_3)_2S:BH_3$	dimethyl sulfide diborane complex		
HCl	hydrochloric acid		
$H_2SO_4$	sulfuric acid		
HBr	hydrobromic acid		
$MgSO_4$	magnesium sulfate		

Groups:

Et	ethyl
Me	methyl

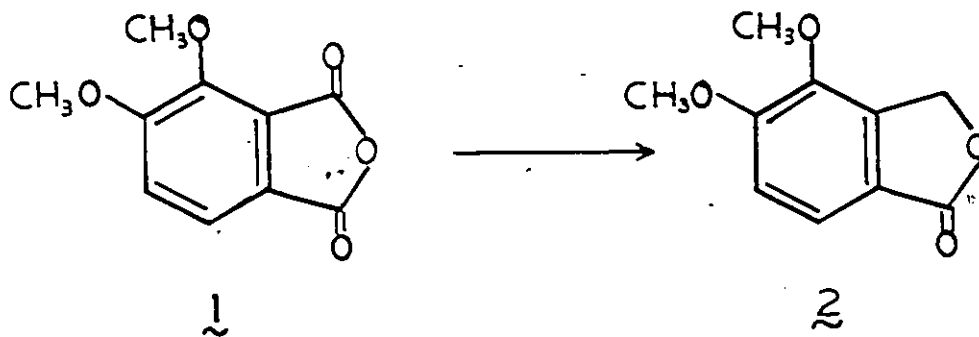
Pr	propyl
iPr	isopropyl
Bu	butyl
t-Bu	tertiary butyl
Ph-	phenyl

## CHAPTER 1

### INTRODUCTION

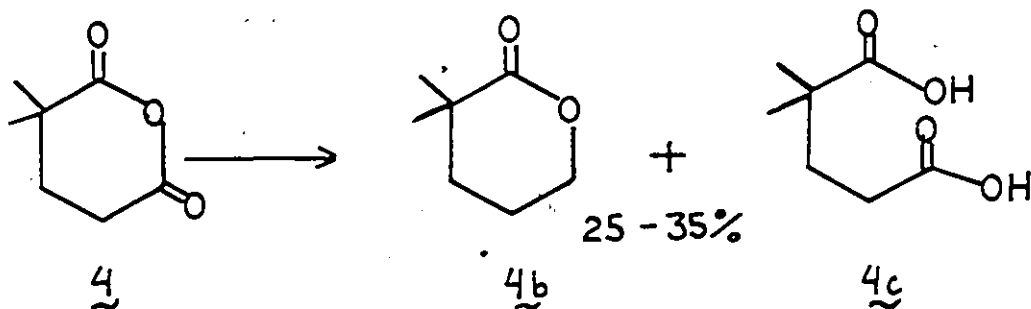
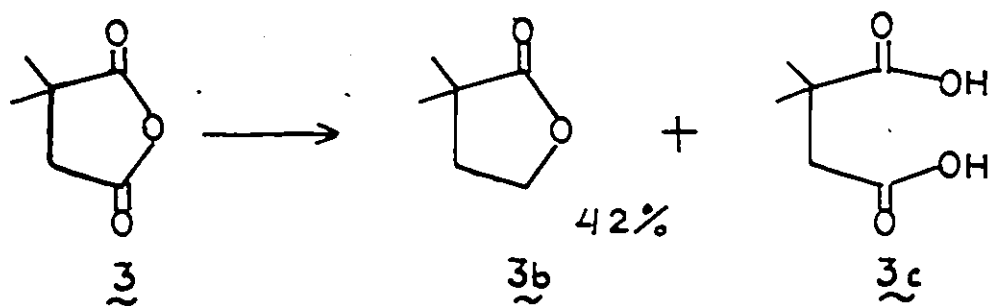
Among lactones widely distributed in nature, many are biologically active. Recently, their allergenic<sup>1</sup> and antitumor<sup>2</sup> activities provoked increased interest in exploring synthetic routes to  $\gamma$ - and  $\delta$ -lactones<sup>3</sup>. However, the importance of lactones as intermediates in organic synthesis or as precursors in biosynthesis was recognized long before the current interest in their biological activity produced an avalanche of publications. Reduction of a cyclic anhydride is a convenient route to the corresponding lactone, and it was often with the intention of making lactones that cyclic anhydrides have been reduced for almost a hundred years.

Several methods were used to accomplish this conversion. In 1887 Salomon<sup>4</sup> prepared 4-mecconine 2 by reduction of 3,4-dimethoxyphthalic anhydride 1, with zinc in acetic acid.

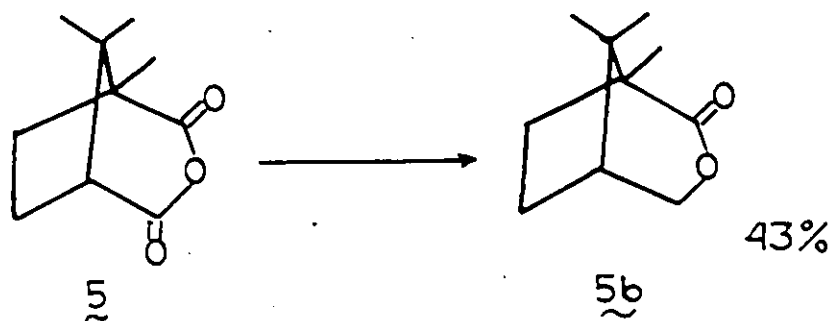


At the turn of the century, reductions with sodium and aluminum amalgam were commonly used although the procedure was tedious and yields depressingly low<sup>5</sup>. Sodium in ethanol reduction, developed by Bouveault and

Blanc<sup>6</sup>, was a great improvement over the older methods and became an important member of a new class of "dissolved metal" reductions. The Bouveault-Blanc procedure, originally intended for the reduction of ester functions had the additional advantage of sparing the carboxylic group. Blanc<sup>7</sup> tested the selectivity of the new method on unsymmetrically substituted anhydrides. Upon reduction of 2,2-dimethylsuccinic anhydride 3, 2,2-dimethyl- $\gamma$ -butyrolactone 3b was isolated as the only lactonic product in 42% yield. Blanc reported that the residue contained the unreacted acid 3c, which could be recovered by continuous extraction\*. Similar results<sup>7</sup> were obtained in the reduction of anhydrides 4 and 5.



\* In fact, the reduction yields a mixture of two lactones (see p.119,120 of this thesis).



Blanc was satisfied since these results confirmed his earlier observation that "... la réduction très aisée avec un acide à carboxyle lié à un atome de carbone primaire devient de plus en plus difficile au fur et à mesure que cet atome de carbone porte plus de substitutions, ..."\*

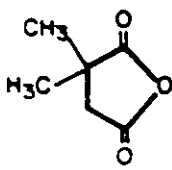
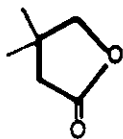
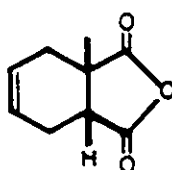
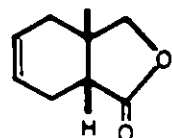
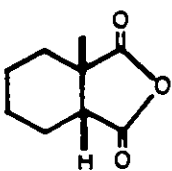
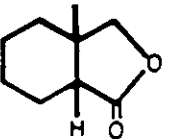
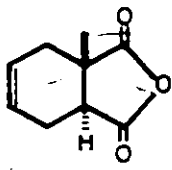
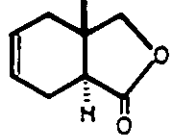
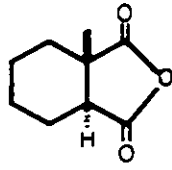
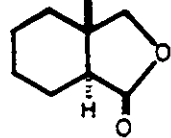
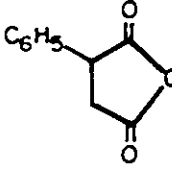
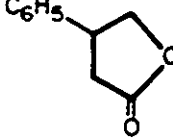
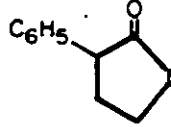
In time the Bouveault-Blanc method was replaced by catalytic hydrogenation<sup>8</sup> and metal hydride reduction<sup>9,10,11</sup> in the routine preparation of lactones from anhydrides. However, while catalytic hydrogenation of unsymmetrically substituted cyclic anhydrides produced lactones and hemiacetals resulting from the reduction of the less hindered carbonyl function<sup>12,13</sup>, metal hydrides (often, but not always<sup>9,14</sup>) reduced preferentially the more hindered carbonyl group<sup>10,15</sup> (see Table 1).

To account for the selective reduction of the more sterically encumbered carbonyl function, Bloomfield and Lee<sup>15</sup> proposed a mechanism involving initial attack of metal cation on the less hindered carbonyl function, followed by the transfer of a hydride ion to the more hindered carbonyl group. The intermediate aldehyde is then rapidly reduced to an

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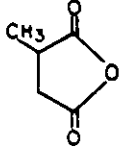
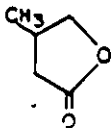
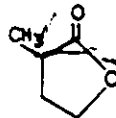
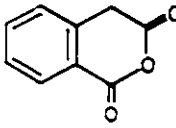
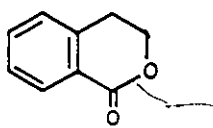
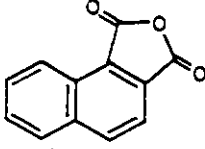
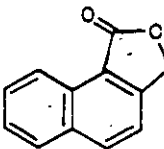
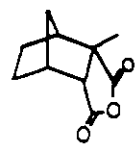
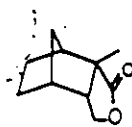
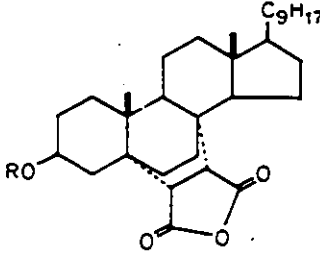
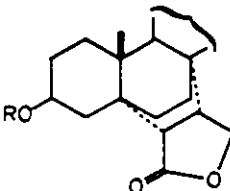
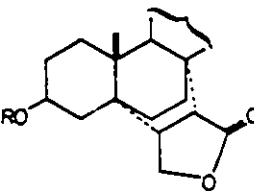
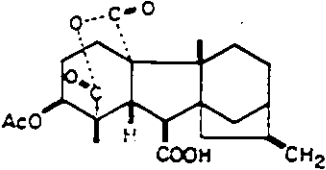
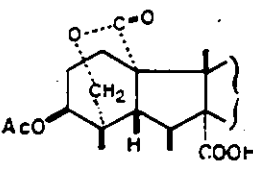
\* Author's translation: "the very easy reduction of a carboxylic function attached to a primary carbon atom becomes progressively more difficult as this carbon atom becomes more highly substituted."

Table 1. Metal hydride reductions of unsymmetrically substituted cyclic anhydrides reported prior to 1975.

Starting anhydride	№	Products		% yield of lactonic products	Ratio a : b	Reference №
		a	b			
	3		—	74 <sup>b, e</sup>	—	17
	11		—	70 <sup>a, d, e</sup> 65 <sup>b, d, e</sup>	—	10 17
	12		—	78-82 <sup>a, d, e</sup> 80 <sup>b, d, e</sup>	—	15 17
	13		—	75 <sup>a, d, e</sup>	—	15
	14		—	85 <sup>a, d, e</sup>	—	15
	9			72 <sup>a, c</sup> 67 <sup>b, c</sup>	1.5:1 1.5:1	15 17

a - LiAlH<sub>4</sub> reduction; b - NaBH<sub>4</sub> reduction; c - Gas-liquid chromatography analyzed;  
d - Column chromatography analyzed; e - Only one product detected.

Table 1. (Concluded)

Starting anhydride	N <sup>o</sup>	Products		% yield of lactonic products	Ratio a : b	Reference N <sup>o</sup>
		a	b			
	10			69 <sup>a,c</sup>	2.2:1	15
	15	—		55 <sup>b,c,e</sup>	—	17
	16	—		67 <sup>a,e</sup>	—	9
	17	—		83 <sup>b,e</sup>	—	14
	6			47 <sup>a,d</sup> 30 <sup>b,d</sup>	13:1 1:1	16 18
	7	—		50 <sup>a,e</sup>	—	19

a - LiAlH<sub>4</sub> reduction; b - NaBH<sub>4</sub> reduction; c - Gas-liquid chromatography analyzed; d - Column chromatography analyzed; e - Only one product detected.

alcohol and cyclization occurs upon acidification (Figure 1).

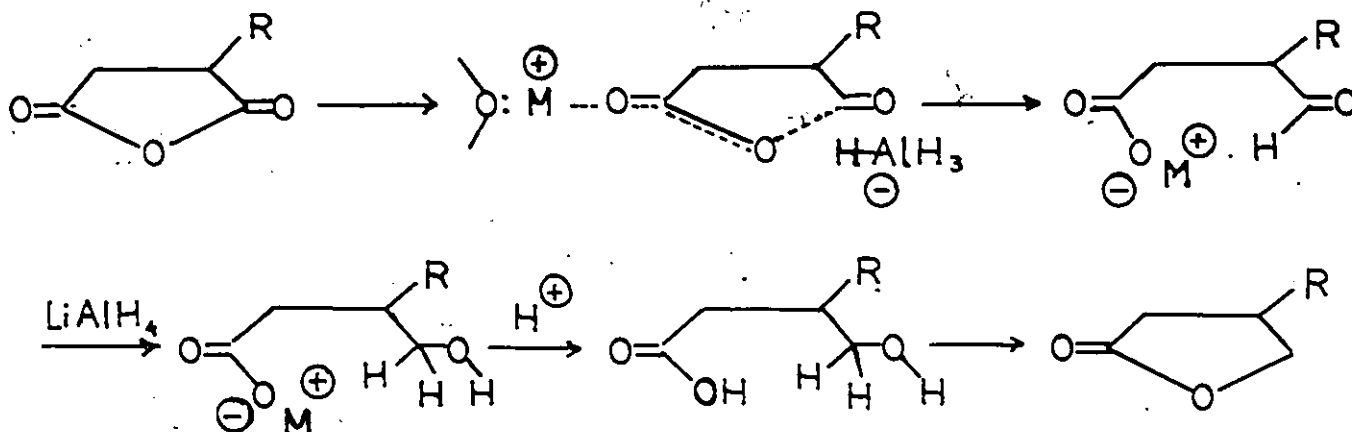


Figure 1. Mechanism for metal hydride reduction of cyclic anhydrides proposed by Bloomfield and Lee<sup>15</sup>.

House<sup>16</sup> commented briefly on "the curious feature" of these reductions and suggested a slightly modified version of Bloomfield and Lee's mechanism (Figure 2).

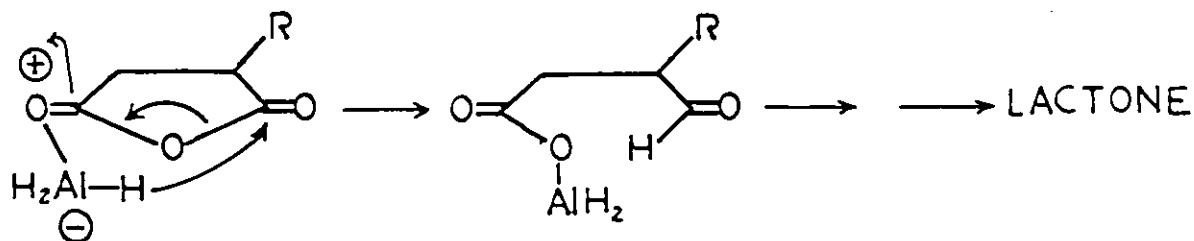
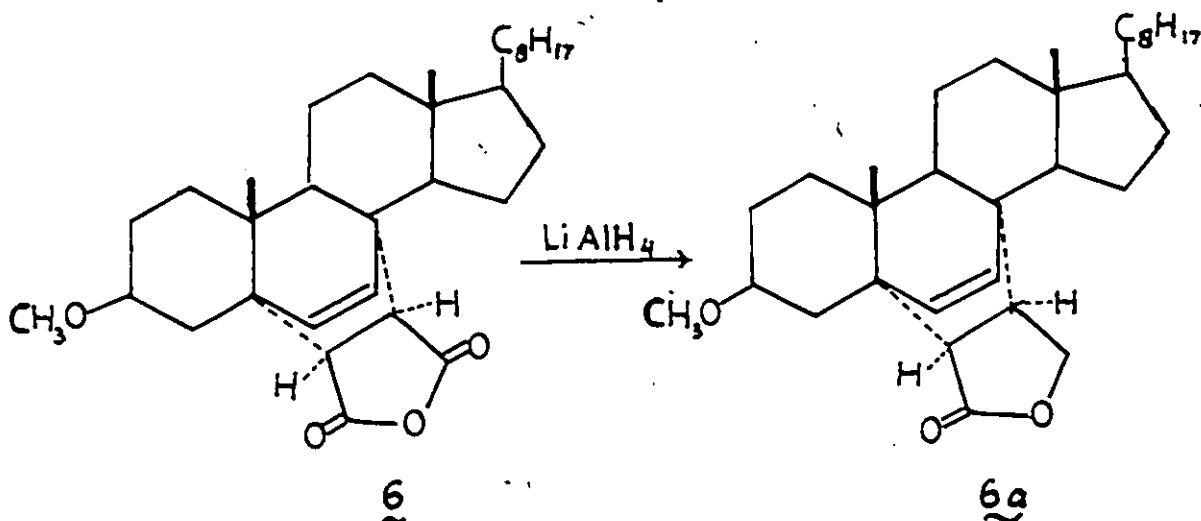


Figure 2. Mechanism for metal hydride reduction of cyclic anhydrides suggested by House<sup>16</sup>.

Bailey and Johnson's<sup>17</sup> study of  $\text{NaBH}_4$  reduction of five unsymmetrical cyclic anhydrides (Table 1) confirmed Bloomfield and Lee's observation that the more hindered carbonyl group was the preferred site of reduction. Similar regioselectivity was reported for  $\text{LiAlH}_4$  reduction of the steroidal cyclic anhydride 6.<sup>18</sup> In contrast, reduction of

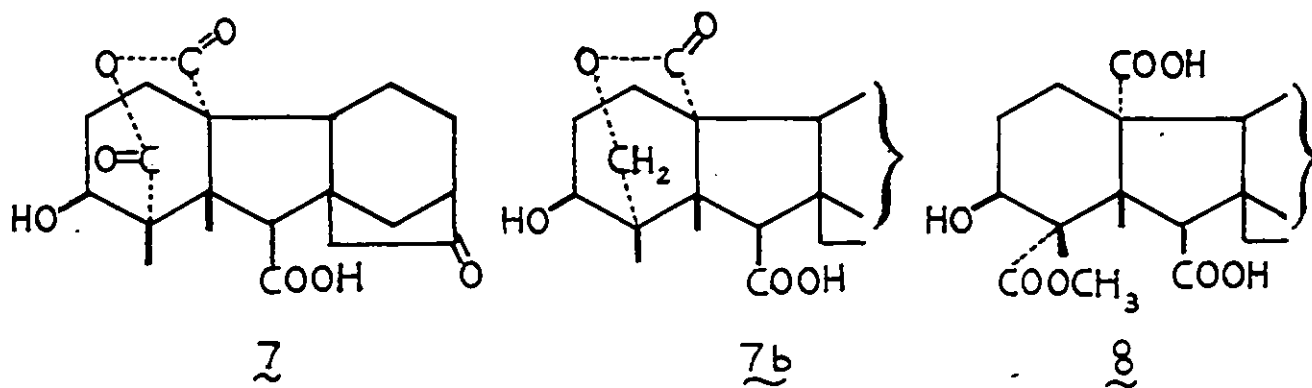
the six-membered ring anhydride 7 derived from gibberellin A<sub>13</sub> gave the  $\delta$ -lactone 7b, resulting from reduction of the less hindered carbonyl group.<sup>19</sup>

Reduction of the Inhoffen adduct 6 presents an interesting but ambiguous problem. Due to the very similar steric environment around the two carbonyl groups, the perception of which of the two carbonyl functions is more hindered remains disputable. Examination of the



Dreiding model of 7 shows that the carbonyl group undergoing reduction (resulting in formation of lactone 7b) is slightly more accessible.

This conclusion is confirmed chemically by the reaction of anhydride 7 with methanol which gives only one ester 8:



Although never challenged, both mechanisms discussed earlier<sup>15,16</sup> fail to explain known cases of preferential reduction of the less hindered carbonyl group in 15, 16, 17 and of diminished selectivity observed in the reduction of 9 and 10. In terms of Bloomfield and Lee's mechanism (Figure 1), the reduction of 2-phenylsuccinic anhydride 9 should lead to a higher ratio in favour of the lactone 9a (formed by reduction of the more hindered carbonyl group), than 2-methylsuccinic anhydride 10, since a phenyl group is more important sterically\* than a methyl group<sup>20</sup>. However, the experimental results show that 9 is reduced to a lesser extent at the more hindered carbonyl function<sup>15,17</sup>.

In view of the growing number of results which could not be interpreted by Bloomfield and Lee's mechanism, it became apparent that the reductions of unsymmetrically substituted cyclic anhydrides by metal hydrides as well as the factors influencing regioselectivity of these reactions had to be re-examined. Moreover, if the investigation was to lead to reliable and general conclusions, the information had to be obtained by analysis of model systems embodying as many different structures as possible. With this objective in mind we have studied a series of cyclic anhydrides representing diverse types of structures (see Table 2).<sup>\*\*</sup>

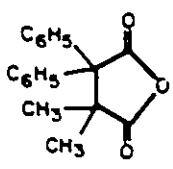
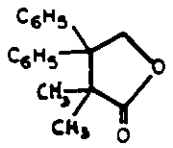
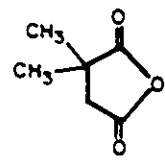
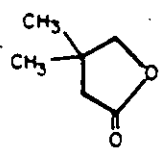
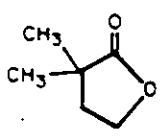
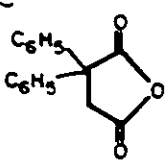
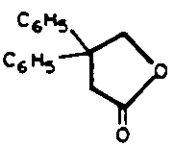
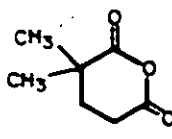
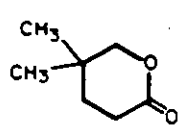
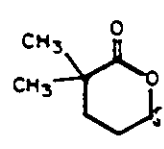
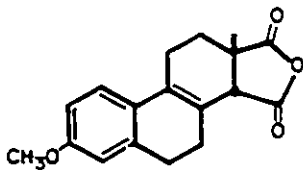
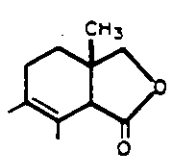
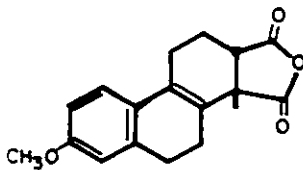
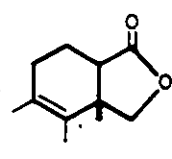
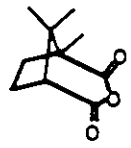
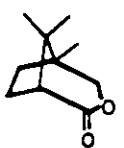
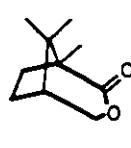
Our results, combined with those previously published, provided a fairly large base from which to study structure-regioselectivity relationships. It soon became apparent that the reaction centre is affected by the substituents in at least three different ways: through inductive,

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\* The phenyl group has a "large effective size". In some cases it behaves as if it were bigger than a t-butyl group.<sup>21</sup>

\*\* The majority of compounds were reduced by  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ . Experimental conditions (solvent, concentration and temperature) were consistent.

Table 2. Reductions of unsymmetrically substituted cyclic anhydrides by metal hydrides.

Starting anhydride	No	Products		% yield of lactonic products	Ratio a : b
		a	b		
	18		—	95 <sup>a, f</sup> 85 <sup>b, f</sup>	—
	3			75 <sup>a, c</sup>	19 : 1
	19		—	86 <sup>a, f</sup> 84 <sup>b, f</sup>	—
	4			72 <sup>a, c</sup>	9 : 1
	20		—	80-90 <sup>a, b, d</sup>	—
	21		—	80-90 <sup>a, b, d</sup>	—
	5			70-80 <sup>a, c</sup>	3 : 2

a - LiAlH<sub>4</sub> reduction; b - NaBH<sub>4</sub> reduction; c - Gas-liquid chromatography analyzed; d - Column chromatography analyzed; e - Only one product detected. f - 100 MH n.m.r. analyzed.

Table 2. (Concluded)

Starting material	No.	Products		% yield of lactonic products	Ratio
		a	b		
	22	trace		84 <sup>a, b, f</sup>	—
	23	—		86 <sup>a, b, f</sup>	—
	25			80 <sup>a, d, f</sup> 75 <sup>b, d, f</sup>	2 : 1 5 : 1
	26			40 <sup>a, d, f</sup> 56 <sup>b, d, f</sup>	1.5 : 1 1.2 : 1
	24			82-87 <sup>a, b, c</sup>	9 : 1
	28			78 <sup>a, b, d, f</sup>	2 : 1
	29			35 <sup>b, d, f</sup>	1.2 : 1
	27			98 <sup>a, b, d, f</sup>	1 : 1.5

a - LiAlH<sub>4</sub> reduction; b - NaBH<sub>4</sub> reduction; c - Gas-liquid chromatography analyzed;  
d - Column chromatography analyzed; e - Only one product detected.  
f - 100 MHz n.m.r. analyzed.

conjugative-resonance and steric effects. These three effects are rarely observed in isolation, as often two or all three are operative in a specific compound. Unraveling the overall effect to evaluate the individual contributions of various electronic and steric factors is a difficult, often impossible, task. Nevertheless, when enough results are available, the dominant effect can be tentatively identified.

To rationalize the observed patterns of regioselectivity in metal hydride reductions of unsymmetrical cyclic anhydrides, we propose an alternative mechanism based on the following assumptions:

(a) the mechanism of cyclic anhydride reduction bears a fundamental resemblance to the mechanism of hydride addition to the carbonyl group in ketones;

(b) the attack of the cation and hydride ion occurs on the same carbonyl function;

(c) the site of attack is controlled by electronic and/or steric factors. When the two carbonyl groups are electronically non-equivalent, electronic effects are generally dominant;

(d) the path of nucleophilic approach is determined by strict stereoelectronic restraints, thus the concept of "steric hindrance" must be re-evaluated with regard to these restraints.

The results described in this study provide initial evidence for the utility of such an approach in predicting the preferred site of reduction in unsymmetrical cyclic anhydrides. It is our hope that our results may also contribute to a better understanding of the factors influencing regio- and stereoselectivity in metal hydride reductions of the carbonyl group per se.

It only remains to point out that: "A mechanism is good only insofar as it explains the experimental data. The data are facts, the mechanism is a theory deduced from these facts."\* As new facts are discovered, the mechanism may be subject to change - this is the normal fate of every hypothesis, mechanism and theory.

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\* T.H. Lowry, K.S. Richardson, Mechanism and Theory in Organic Chemistry, p.174, Harper and Row, New York, 1976.

CHAPTER 2

THE MECHANISM OF METAL HYDRIDE REDUCTION OF  
UNSYMMETRICALLY SUBSTITUTED CYCLIC ANHYDRIDES

The first point of our hypothesis<sup>22</sup> outlined in the Introduction states that reduction of cyclic anhydrides resembles fundamentally the reduction of the carbonyl function in ketones. However, since the mechanism and the factors influencing stereochemistry of ketone reductions remain an area of considerable speculation and controversy, it is necessary to outline briefly our views and to survey some of the more recent developments which provided the guidelines for our mechanistic model.

1. Kinetics of metal-hydride reductions

Kinetic studies have shown that the reaction of a ketone with  $\text{LiAlH}_4$  or  $\text{NaAlH}_4$  in THF is of the second order; first order in both ketone and metal hydride. However, the rate of reduction with  $\text{NaAlH}_4$  is eleven times slower than the rate of reduction with  $\text{LiAlH}_4$ .<sup>23</sup> Reduction of ketones by metal borohydrides was similarly found to be first order in each reactant<sup>24,25</sup> and dependent on the nature of the metal cation present.<sup>26,27</sup> The transfer of hydride ion from the metal hydride to the carbonyl function was established to be the rate-determining step in reductions by aluminum hydrides<sup>23</sup> and borohydrides.<sup>28</sup>

## 2. Role of the alkaline cation

The importance of the cation in the reduction of ketones with borohydrides was first noted by Brown<sup>26</sup> and Lansbury<sup>27</sup>. These authors demonstrated that the addition of  $\text{Li}^+$  or  $\text{Mg}^{++}$  cations to the  $\text{NaBH}_4$  reduction of esters or ketones catalyzed the reaction. Ashby<sup>23</sup> suggested that the cation is implicated somehow in the transition state not only because the reaction rates of aluminum hydride reduction of ketones varied dramatically with different cations ( $\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$ ) but also because stereoselectivity of reaction appeared to be dependent on the nature of the cation\* present.<sup>29</sup>

Superior catalytic activity<sup>23</sup> and stereoselectivity<sup>29,30</sup> of  $\text{Li}^+$  with respect to  $\text{Na}^+$  has been attributed to solvation effects. Conductance experiments<sup>31</sup> indicate that  $\text{LiAlH}_4$  in THF exists predominantly as solvent-separated ion pairs (Figure 3a), whereas  $\text{NaAlH}_4$  appears to be a mixture of solvent-separated and contact ion pairs (Figure 3b). The solvent-separated ion pair is expected to be more reactive since the degree of ion pair separation is directly related to the ability of the cation to complex with the carbonyl oxygen atom.

The actual complexation of ketones with  $\text{Li}^+$  and  $\text{Na}^+$  ions in THF solutions of lithium and sodium salts has been demonstrated.<sup>23</sup> A

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\* In the case of cyclic anhydrides we have shown that the rate of reduction is also dependent on the nature of the cation. Reduction of 2,2-dimethylsuccinic anhydride **3** with  $\text{NaAlH}_4$  yielded, after 120 min, a mixture consisting of 3,3-dimethyl- $\gamma$ -butyrolactone **3a** (15%) and the unreacted 2,2-dimethylsuccinic acid. The reduction, carried out under identical conditions of solvent, temperature, concentration and time, but with added  $\text{LiCl}$  led to the formation of **3a** in 86% yield (see Experimental section, page 124).

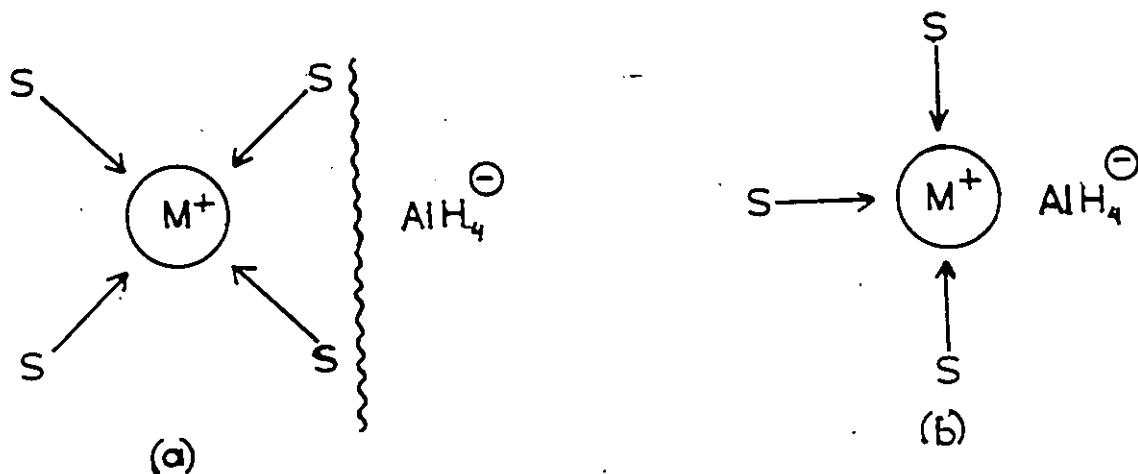


Figure 3. Solvent-separated (a) and contact (b) ion pairs.

study of the entropies of activation of these complexes has shown that  $\text{Li}^+$  is coordinated more strongly, in the transition state, to the carbonyl oxygen atom than  $\text{Na}^+$ . The stronger the association with a cation, the more polarized is the  $\text{C}=\text{O}$  bond and, consequently, the more facile the hydride transfer becomes.

Pierre and Handel<sup>32</sup> have shown that in the absence of the cation (removed from the reaction with the appropriate crown ether) a number of aliphatic ketones studied did not react with  $\text{LiAlH}_4$ . The unreacted ketones were recovered after quenching. Other functional groups such as aldehydes, amides, esters, nitriles, epoxides and oximes similarly were not reduced by  $\text{LiAlH}_4$  in the reaction medium from which the cation had been abstracted.<sup>33</sup> A parallel study conducted on the reduction of ketones by  $\text{NaBH}_4$  in the presence of crown ethers has shown that no reduction occurred before hydrolysis. However, addition of water or acid provoked immediate and rapid reaction. These results confirm what was generally believed, namely, that  $\text{NaBH}_4$  reduction may

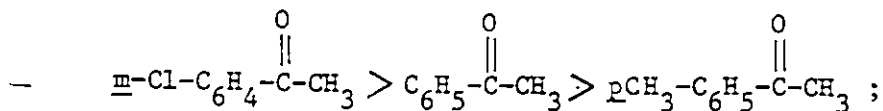
be catalyzed by protic solvents or by acid or water, during the isolation process.<sup>34</sup>

Pierre and Mandel's conclusion<sup>30,33</sup> that the electrophilic assistance of an alkaline cation is indispensable in metal hydride reductions is not general. Loupy, Seyden-Penne and Tchoubar<sup>35</sup> observed that aromatic aldehydes and ketones could be reduced by  $\text{LiAlH}_4$  in the presence of a crown ether (specific for  $\text{Li}^+$ ), albeit at a much slower rate. Electrophilic assistance by  $\text{Li}^+$  was shown to be due to the formation of an activated complex (more reactive than the ketone itself). Retardation of reduction in the presence of a crown ether could be caused by displacement of the equilibrium to the right (as in Figure 4). Assuming that "a" were still the reacting species we would have expected



Figure 4. Possible equilibrium between carbonyl group- $\text{Li}^+$  complex "a" and crown ether {2,1,1} specific for  $\text{Li}^+$ .

the fastest reaction with the compound having the most basic carbonyl group, since the latter would complex with a cation most readily. However, the rate of reduction decreased in order:



which is opposite to the order of decreasing basicity of the carbonyl oxygen atom. The authors consider this to be evidence that under their

reaction conditions and for the specific compounds studied, the carbonyl-Li<sup>+</sup> complex is not implicated and the hydride ion may add to an unactivated carbonyl function.

### 3. Molecular orbital representation of electrophilic and nucleophilic addition to the carbonyl group

Of the various ways in which these results can be assessed, perhaps the most enlightening is the molecular orbital treatment. In terms of molecular orbital (M.O.) theory for electrophilic and nucleophilic addition to the carbonyl function, the most favourable mechanism which is generally accepted<sup>36</sup> occurs in the following manner: the electrophile attacks the frontier highest occupied molecular orbital-HOMO, the so-called non-bonding orbital of the carbonyl oxygen atom. The complex has a plane of symmetry, i.e., the five atoms implicated remain in one plane, while the  $\pi$  bond of the carbonyl group is orthogonal to this plane (Figure 5). The association of a cation with the

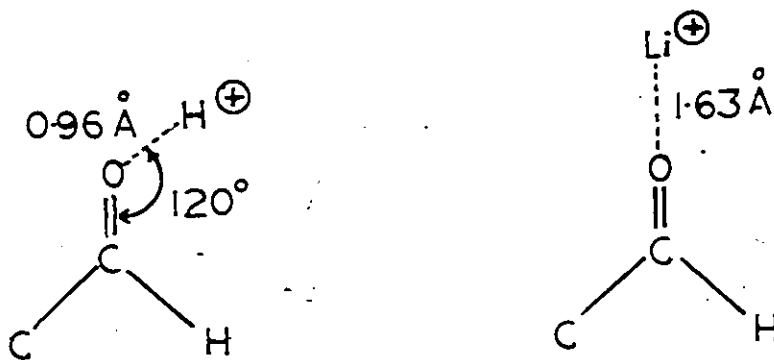


Figure 5. Geometries suggested for the activated complex. <sup>37</sup>

oxygen atom of the carbonyl function enhances the addition of a nucleo-

phile to the lowest unoccupied molecular orbital - LUMO  $\pi^*$  and, specifically, to the carbon atom of the carbonyl group.

According to the theory of perturbation,<sup>38</sup> the reaction rate increases as the energy levels of the HOMO of the nucleophile ( $\text{AlH}_4^-$ ) and the LUMO  $\pi^*_{\text{C=O}}$  of the electrophile become closer. Association of  $\text{Li}^+$  cation with the carbonyl function lowers the energy level of LUMO  $\pi^*_{\text{C=O}}$  bringing it energetically closer to the HOMO of the nucleophile. The energy level of the LUMO  $\pi^*_{\text{C=O}}$  is considerably lower in aromatic ketones and aldehydes than in aliphatic compounds, apparently low enough for the reaction to occur without the catalyzing effect of the cation.<sup>35</sup> Evidently, an electron-withdrawing group substituted on the aromatic ring further facilitates nucleophilic addition<sup>35</sup> (see also page 46).

#### 4. Restrictions encountered in nucleophilic addition to the carbonyl function

For a long time, the general belief was that for maximum overlap in the transition state the initial nucleophilic approach must be perpendicular to the molecular plane. However, the polarity of the molecule favours an angle greater than  $90^\circ$  between nucleophile and the oxygen atom.\* This conclusion was inferred by Bürgi, Dunitz, Lehn and Wipff<sup>39</sup> from the analysis of crystal structure data, and confirmed by theoretical calculations of the minimum energy path for addition of

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\* A perpendicular attack gives the best interatomic orbital overlap but not the best intermolecular overlap (except in the case when the two interacting atoms are both molecular centres of symmetry, which of course is not the situation in nucleophilic addition to a carbonyl group). The best intermolecular overlap between nucleophile and carbonyl group leads to an angle of attack always greater than  $90^\circ$  with a mean value of  $107^\circ$ .<sup>37</sup>

hydride ion to formaldehyde. At a distance of 1.12 Å the line of approach of a nucleophile is not perpendicular but forms an angle of about 110° with the C=O bond (Figure 6).

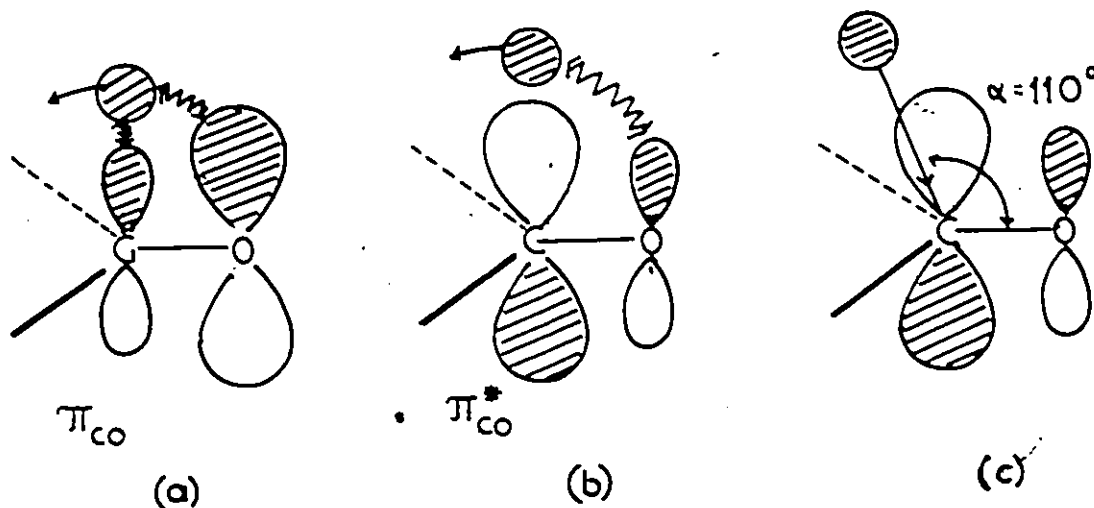


Figure 6. The attack of hydride ion on the plane of a trigonal carbon atom. (a) To minimize repulsion, the nucleophile seeks the smallest overlap away from the oxygen atom. (b) The negative out-of-phase overlap between nucleophile and the oxygen atom causes a lateral displacement away from the carbon-oxygen region. (c) The favoured path of nucleophilic attack thus results in an angle  $\alpha$  of  $\sim 110^\circ$ .<sup>37</sup>

Calculation of the transition state energies of an aldehyde complexed with  $\text{Li}^+$  or  $\text{H}^+$  (see Figure 5)<sup>37</sup> indicates that complexation by the cation increases the rate of reduction but does not modify the geometry of the favoured transition state for the approach of hydride ion described above.<sup>37</sup>

Baldwin<sup>40</sup> extended these results into a simple method for assessing the stereochemical restraints in hydride reductions of carbonyl functions other than ketones or aldehydes. Using Baldwin's approximation, the approach vector of  $\text{H}^-$  (representing the most favourable reaction coordinate) on an amide or ester (or anhydride) function is shifted

(angle  $\beta$ ) from the symmetric position, as in a ketone (Figure 7a), to a position in space away from the oxygen atom (Figure 7b) and at an angle ( $\alpha$ ) of approximately  $110^\circ$  (Figure 7c) to the molecular plane.

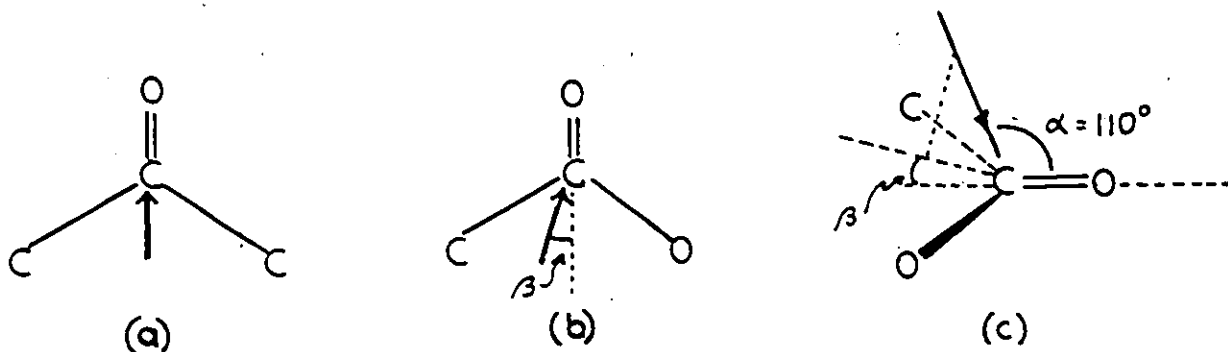


Figure 7. The projections of the approach vector of  $\text{H}^-$  on ketone and ester functions.

#### 5. Mechanism of metal hydride reduction of the carbonyl group

In terms of the above considerations the mechanism of metal hydride reduction can therefore be considered to involve the following steps:

- (1) association of the cation with the oxygen atom of the carbonyl group (a fast process in which the solvent-separated ion pair falls apart);
- (2) approach of the nucleophile  $\text{AlH}_4^-$  (rate determining step) from above or below the molecular plane to the carbon end of the carbonyl group\* at an angle of approximately  $110^\circ$ ;
- (3) passage through the transition state;
- (4) formation of product(s).

\* A variety of steric and/or electronic factors determine the direction of hydride approach. Obvious steric congestion,<sup>41</sup> and in the case of non-hindered carbonyl groups, torsional interactions<sup>42</sup> and unequal distortion of electron density about the carbonyl group<sup>43,44</sup> are examples of such effects.

We assume as a working hypothesis that the same principal steps apply to the reduction of anhydrides. However, in the case of unsymmetrically substituted cyclic anhydrides, there are two different carbonyl groups which may undergo reduction. Thus the element of regioselectivity is introduced. In the majority of anhydrides studied (Table 2, page 9) there is a definite preference for reduction to occur at the more electron-rich carbonyl function. The preferential association of an alkaline cation with the carbonyl group bearing the most basic, most isolated, non-bonding electrons on its oxygen atom is followed by the addition of the hydride ion to the carbon end of the activated carbonyl function (i.e., 1, 2 addition). The association of the cation with the more electron-rich carbonyl dipole fixes the site of nucleophilic addition. Since the geometry of the transition state for nucleophilic addition is not altered by complexation with a cation<sup>37</sup> and since hydride reduction is believed to proceed through a "reactant-like" transition state,<sup>45</sup> the geometry of the substrate must be examined now in terms of the most favourable path for nucleophilic approach to the activated carbonyl function (see Figure 8).

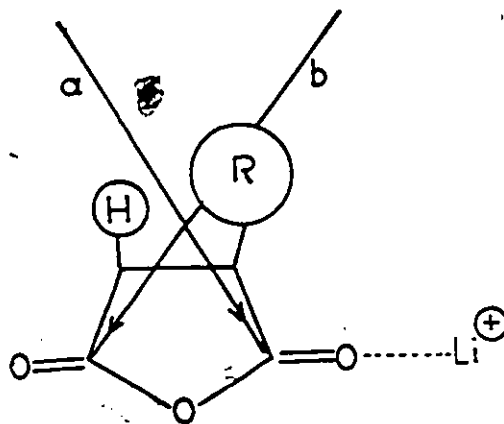


Figure 8. The geometry of nucleophilic attack on the plane of a five-membered cyclic anhydride, where 'a' is shown to be the most favourable path for nucleophilic approach.

Evidently the situations may arise where the activated carbonyl group is not sterically favoured for hydride addition and this may lead to a lesser degree of regioselectivity.

It is worthwhile, at this stage, to point out that reductions with simple metal hydrides (i.e.,  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ ) appear to be less sensitive to steric hindrance than they are to electronic effects. An interesting example of steric versus electronic control in the reduction of ketones, has been recently reported by Chèrest, Felkin and Tacheau.<sup>44</sup> A number of 3-alkyl bicyclo-[2,2,2]-octan-2-ones (example, Figure 9) having "Cram's model conformation" built-in, undergo reduction with  $\text{LiAlH}_4$  from the more hindered side leading to trans alcohols when R is a methyl, ethyl or isopropyl group. However, when R is a t-butyl group the cis alcohol is obtained as the major product.\* (Figure 9).

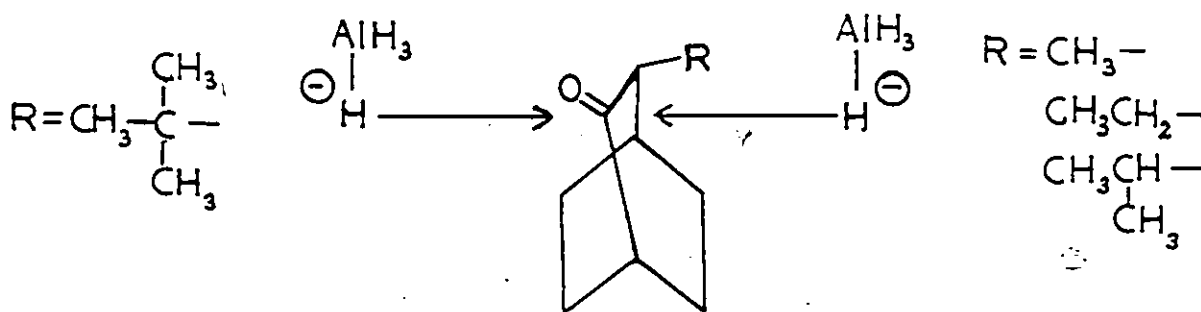


Figure 9. Example of a ketone having Cram's model conformation built-in. Stereochemistry of  $\text{LiAlH}_4$  reduction.

The authors attribute these results to the anisotropic inductive effects of the alkyl groups which lead to differences in electron density on the

\*The cis alcohol is the major product also when group R is phenyl.<sup>46</sup>

two faces of the plane containing the trigonal carbon atom. However, when the R group becomes large enough to block completely the path of nucleophilic attack, the reaction becomes subject to steric control. A similar set of reactions carried out with  $\text{LiAl}(\underline{t}\text{-OBu})_3\text{H}$  as reducing agent resulted in the formation of cis alcohols from the four ketones studied, (Figure 10).

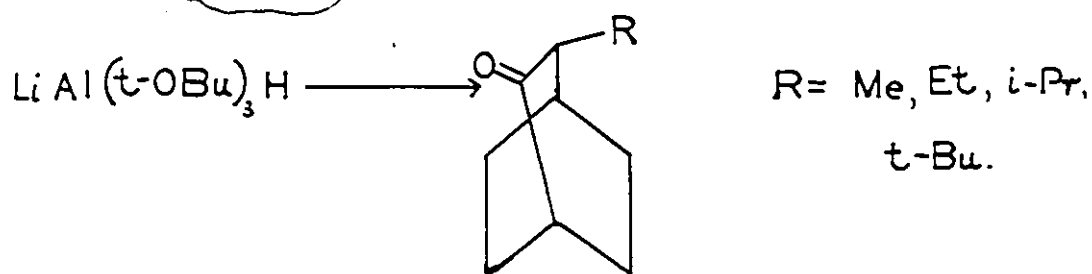


Figure 10.  $\text{LiAl}(\underline{t}\text{-OBu})_3\text{H}$  reduction. Hydride addition occurs selectively from the less hindered side.

The same situation may arise in the reduction of cyclic anhydrides. The increased size of the reagent, more sensitive to steric hindrance, may produce results entirely different from those obtained in reductions with  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ . The proposed electronic control of regioselectivity, therefore, applies to the reduction of moderately hindered cyclic anhydrides by simple metal hydrides ( $\text{LiAlH}_4$  and  $\text{NaBH}_4$  used in excess amount).

Consequently, in order to predict the site of reduction in unsymmetrical cyclic anhydrides, we must evaluate the relative basicity of the two carbonyl oxygen atoms.\* It is a reasonable assumption that

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\* Polar, inductive and resonance effects, which may activate or deactivate the carbonyl group toward complex formation will be discussed in the sections dealing with analyses of individual anhydride reductions.

$\text{Li}^+$  complexes preferentially with the carbonyl oxygen atom bearing the most basic non-bonding electrons. It is also reasonable to expect that, due to the planar geometry of the electrophilic attack, the steric influence of the substituents above and below the plane of a flat anhydride molecule would not affect significantly this step of the reaction (Figure 11). Examination of the favoured transition state geometry for the nucleophilic attack provides a clue to the circumstances in which a severe steric interaction might prevent the addition of hydride ion to the activated carbonyl function. (Experience shows that moderate steric hindrance does not deter nucleophilic attack).

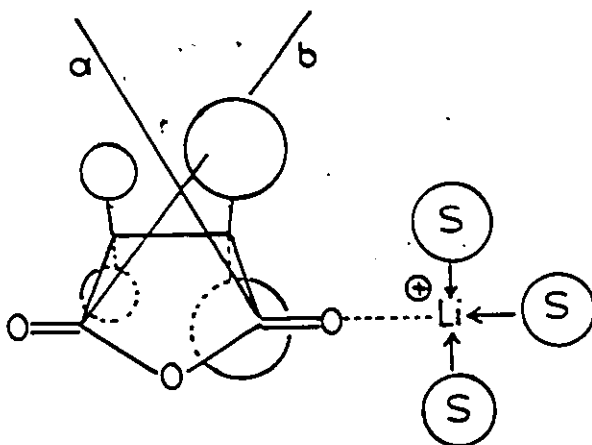


Figure 11. Geometry of electrophilic attack on a five-membered cyclic anhydride.

Finally, it is necessary to point out that, in the absence of electronic differences, steric interactions alone dictate the site for hydride addition.

We shall turn now to the presentation of specific examples illustrative of the application of our hypothesis in predicting the site of reduction. Evidently, each case has its own unique features and

must be examined carefully for all possible electronic and steric effects. In some instances the results of the reductions already performed may serve as a helpful guide. In some cases, alas, only hindsight, not foresight will provide the correct answer.

### CHAPTER 3

#### STERICALLY CONTROLLED REDUCTIONS

In the absence of electronic differences between the two carbonyl groups in an unsymmetrically substituted cyclic anhydride, regioselectivity of the reduction should be controlled by steric factors. Superficial examination of the geometrical data does not provide us with an immediate insight into the significance of steric interactions (or it may provide us with an incorrect one!). Various steric restrictions arise as a result of the transition state geometry and consequently steric hindrance must be assessed with regard to the geometry of the optimum transition state.

We assume that the two carbonyl groups in a cyclic anhydride fully substituted with alkyl and/or aryl groups are electronically very similar. It is true that for a long time alkyl groups bonded to a saturated carbon atom were considered electron donating<sup>47</sup> while the phenyl group was thought to be an electron-attractor.<sup>48</sup> However, recent experiments show that the polar (inductive and/or field effects) influence of a methyl group bonded to an  $sp^3$  carbon atom is not necessarily electron-donating. Alkyl groups, having greater polarizability than hydrogen atoms, appear to be either electron-withdrawing or electron-donating depending on the electronic demands of the neighbouring atoms.<sup>49a</sup> Thus, both methyl and phenyl groups may behave as electron donors or attractors, depending on circumstances. The effect of a neighbouring carbonyl function is evidently such that both methyl and phenyl

substituents behave as electron donors, i.e., reinforce the dipole character of a carbon oxygen double bond. The magnitude of this effect is not exactly the same but it is close enough to suppose that the two carbonyl groups in 18 are electronically quite similar. This implication is based on the fact that both 2,2-dimethylsuccinic anhydride 3 and 2,2-diphenylsuccinic anhydride 19 are reduced with very high regioselectivity at the carbonyl function next to the fully substituted carbon atom (see Table 2, page 9). Actually 19 is reduced regiospecifically, while  $\text{LiAlH}_4$  reduction of 3 yields a small amount (ca. 5%) of the isomeric lactone. This slight discrepancy in regioselectivity is attributed to the more pronounced steric effect of the phenyl substituent since, in terms of polar influences, the phenyl group appears to be a somewhat weaker electron-donor than the methyl group.\*

2,2-Dimethyl-3,3-diphenylsuccinic anhydride 18 is planar and rigid with the substituents looming above and below the molecular plane. In terms of the most favourable path of nucleophilic attack onto the plane of the trigonal carbon atom, the approach toward the carbonyl group  $\alpha$  to the phenyl substituents (Figure 12, path a) is sterically less restricted than the approach toward the other carbonyl function (Figure 12, path b), which is obstructed by the phenyl groups. As a result, reduction of anhydride 18 with  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  leads to the formation of a single product, 2,2-dimethyl-3,3-diphenyl- $\gamma$ -butyrolactone 18a, in yields ranging from 87-95%. This example provides the most dramatic proof for the correctness of the non-

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\* By analogy to the acidities<sup>49b</sup> of  $\text{HCOOH}$  ( $\text{p}K = 3.77$ ),  $\text{CH}_3\text{COOH}$  ( $\text{p}K = 4.80$ ) and  $\text{C}_6\text{H}_5\text{COOH}$  ( $\text{p}K = 4.20$ ) the polar effect of a phenyl group is electron donating compared to a hydrogen atom but slightly weaker than that of a methyl substituent.

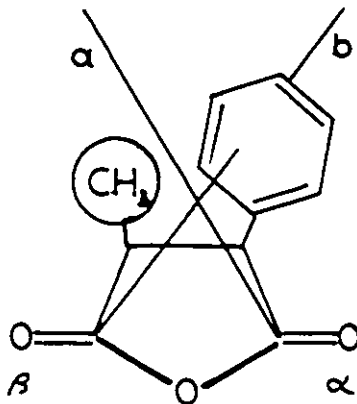


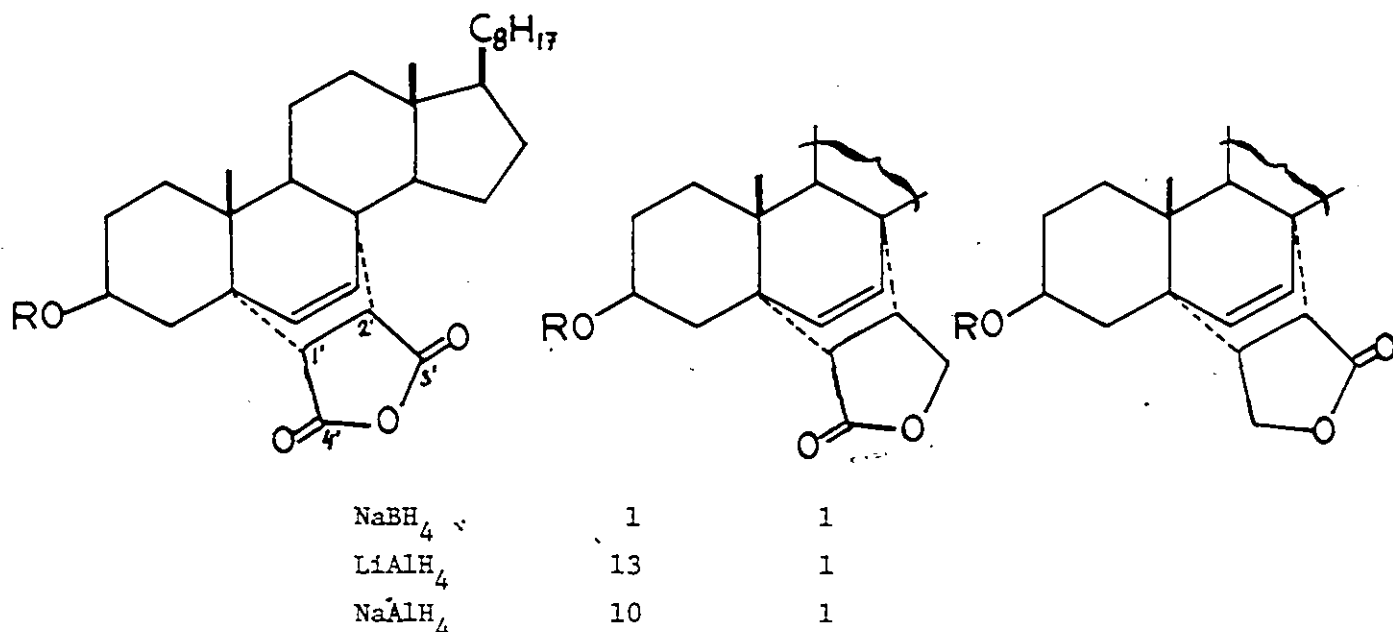
Figure 12. Upon cursory examination of anhydride 18 the  $\alpha$  carbonyl function (adjacent to the phenyl substituents) appears to be considerably more encumbered than the  $\beta$  carbonyl group (adjacent to the methyl substituents). However, in terms of the most favourable geometry for the transition state, the  $\alpha$  carbonyl function is actually more accessible to the nucleophile and, as a consequence, it is reduced regio-specifically.

perpendicular, restricted geometry of the transition state in the metal hydride reduction of the carbonyl function.

Steric restrictions encountered in reductions of natural products  $\underline{6}$  and  $\underline{7}$  (see Table 1, page 4), viewed in the light of a non-perpendicular approach, are far more difficult to assess. Both molecules  $\underline{6}$  and  $\underline{7}$  are complex. Inspection of the Dreiding model of  $\underline{7}$  suggests that the carbonyl group which undergoes the reduction is slightly more accessible to a non-perpendicular attack. The same conclusion may be drawn by examination of the model of the Inhoffen adduct  $\underline{6}$ . However, the steric environment about the two carbonyl functions in  $\underline{6}$  is very similar and the perception of the "more accessible" path of approach is disputable. Moreover, the high degree of regio-

selectivity observed in the reduction of 6 by  $\text{LiAlH}_4$  and  $\text{NaAlH}_4$  as compared to  $\text{NaBH}_4$  remains puzzling.\*

\*The authors<sup>18</sup> attribute regioselectivity to the superior solvation of  $\text{Li}^+$ . The solvated  $\text{Li}^+$  associates with the "slightly less" hindered C-4' carbonyl group (see Figure below). The addition of  $\text{H}^-$  is assumed to occur in a 1,4 fashion (Bloomfield and Lee's mechanism).<sup>15</sup> Reduction with  $\text{NaBH}_4$  shows no preference for either carbonyl group, yet the reaction with  $\text{NaAlH}_4$  is highly regioselective (10:1). Considering:



(a) steric similarity of the two carbonyl functions, (b) low yields of lactonic products isolated, (c) inconsistent pattern of regioselectivity of  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  compared to  $\text{NaAlH}_4$ , we would suggest that no viable conclusions can be drawn from these results.

CHAPTER 4

ELECTRONIC AND STERIC FACTORS INVOLVED IN REDUCTIONS OF  
2,2-DISUBSTITUTED ANHYDRIDES

1. Activating effects

It appears that in the event when electronic and steric effects both favour reduction of the same carbonyl function, high regioselectivity should be expected. These conditions are met in cyclic anhydrides having one carbonyl function  $\alpha$  to a tertiary carbon atom while the other one is next to a primary or a secondary carbon atom (see Table 2, page 9 anhydrides 3, 4, 19, 20, 21). Not surprisingly, greater reactivity toward the cation is exhibited by the carbonyl group adjacent to the fully substituted carbon atom. This is due to the positive inductive effects of alkyl (or aryl) groups which increase the electron density of the  $\alpha$ -carbonyl function (Figure 13) and, in particular, of the carbonyl oxygen atom (see Chapter 3, p.26).

The geometry of electrophilic attack implies that steric interactions between the cation and the substituents above and below the plane of a flat, five-membered cyclic anhydride should be minimal. In the absence of steric constraints, the cation attacks preferentially the more basic (more electron-rich) carbonyl dipole (Figure 13). Hydride transfer to the activated function follows and the preferred path (a, in Figure 13) for nucleophilic approach involves the same carbonyl group ( $\alpha$ , in Figure 13). Thus the high regioselectivity

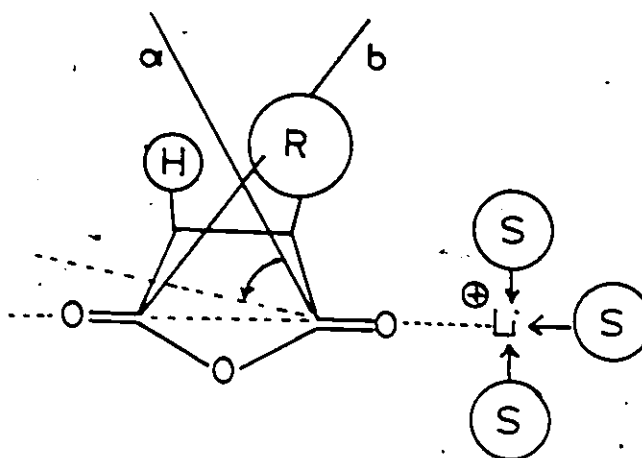


Figure 13. Geometry of electrophilic and nucleophilic attack on the carbonyl group of an unsymmetrically substituted cyclic anhydride.

observed in the reduction of 3, 19, 20, 21 (as well as of 11, 12, 13 and 14) is the result of combined electronic and steric factors acting in the same direction.

We have found that the six-membered cyclic anhydride 4 shows slightly diminished preference for the "more hindered" carbonyl group (9:1 compared to 19:1 for the five-membered homologue). This fact is attributed to the lack of pronounced steric promotion of either of the two carbonyl groups. In a flexible, six-membered cyclic anhydride (such as 4) both carbonyl functions are able to form the favoured transition state with comparable ease (Figure 14). The site of the reduction is therefore determined mainly by electronic factors.

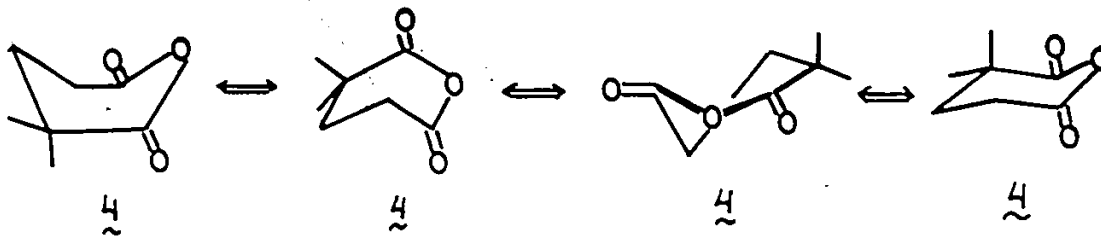


Figure 14. The steric restrictions encountered in flat, relatively rigid, five-membered rings are not operative in the more flexible six-membered cyclic anhydrides.

## 2. Deactivating effects

We have been discussing, so far, the activating electronic influences which increase electron availability on the carbonyl oxygen atom. It is possible to envisage the reverse, i.e., deactivating effects. Diminished preference for a carbonyl function may reflect deactivation toward complexation with a cation or retardation of the  $H^-$  addition. An electron-withdrawing substituent will displace electron density away from the carbonyl oxygen atom, thus deactivating it toward complexation with the cation. Electron delocalization through resonance, conjugation or hyperconjugation will inevitably result in retardation of reduction of the carbonyl group affected.

### i) Enolization

As already discussed in 2,2-disubstituted cyclic anhydrides the carbonyl function next to a tertiary carbon atom is more likely to form a complex with the cation than the carbonyl group adjacent to a primary (or a secondary) carbon atom. In addition, carbonyl function  $\beta$  (see

Figure 13) may potentially form an enolate ion. It is well known that formation of enolates greatly inhibits the reduction of carbonyl groups.<sup>50</sup> Since metal hydrides can function as strong bases, a ketone having an  $\alpha$ -hydrogen atom (particularly a relatively acidic  $\alpha$ -hydrogen atom) may be converted to its enolate which will be reduced at a much slower rate than a non-enolized carbonyl group. Small amounts of ketones, presumably formed by hydrolysis of intermediate enolates are usually recovered from metal hydride reductions.<sup>50</sup> This will obviously limit the yield of alcohol one can isolate from such reactions.

Evidence for formation of enolate ion during reaction with metal hydrides is provided by the reduction of a ketone with an enolizable, optically active centre  $\alpha$  to the carbonyl group. The product of this reduction (an alcohol) is formed without racemization, but the recovered unreacted ketone is racemized (Figure 15).

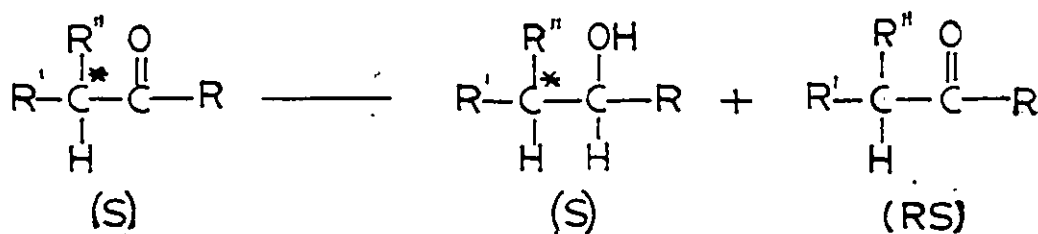


Figure 15. Reduction of an optically active ketone yields the corresponding optically active alcohol and unreacted but racemized ketone.

The resistance of an enolized carbonyl group to reduction with metal hydrides has been demonstrated recently by Barton et al.<sup>51a</sup> In the steroidal model, the selective formation of an enolate provided protection for the carbonyl group against reduction by  $\text{EtAlH}_4$ . This,

of course, could also happen in the reduction of anhydrides. The selective formation of an enolate could retard, or prevent entirely, the reduction of this group. The possibility of this effect being a major factor responsible for the high regioselectivity encountered in the reduction of unsymmetrical cyclic anhydrides (such as 3, 4, 11, 19, etc.) became even more appealing in view of the recent work demonstrating formation of the enolate ion of succinic anhydride.<sup>51b</sup>

We have carried out a series of experiments aimed at finding out if an enolate is actually generated during the reaction of our anhydrides with  $\text{LiAlH}_4$ . If an enolate ion were produced under the reduction conditions, we should be able to trap the hydrogen gas formed (see Figure 16).

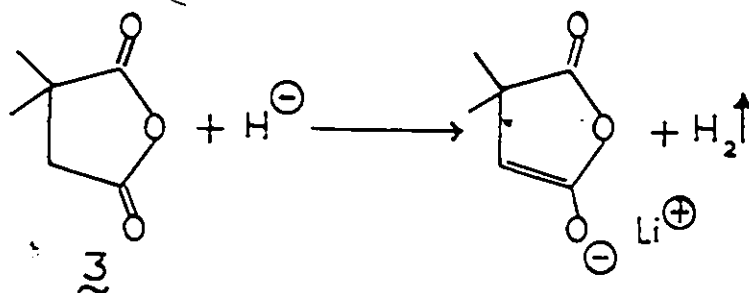


Figure 16. Possible formation of the enolate of 2,2-dimethylsuccinic anhydride.

However, under the reaction conditions employed, we were unable to detect significant  $\text{H}_2$  evolution in anhydrides (such as 3) which do not possess a particularly acidic  $\alpha$ -hydrogen atom\*. Volume changes which could be attributed to  $\text{H}_2$  formed as a result of enolization averaged 7 ml per 0.01 mole of anhydride, which correspond to approximately 3%

\* Evidence has been adduced for enolization in an anhydride containing a more acidic  $\alpha$ -hydrogen atom (for example, see pp.62, 99).

enolization. This low figure is too close to the estimated experimental error to be considered significant\*. The results, therefore are inconclusive, and although the possibility of some enolization actually occurring cannot be entirely dismissed, its effect on hydride addition (to either carbonyl function\*\*) does not appear to be a major deactivating factor

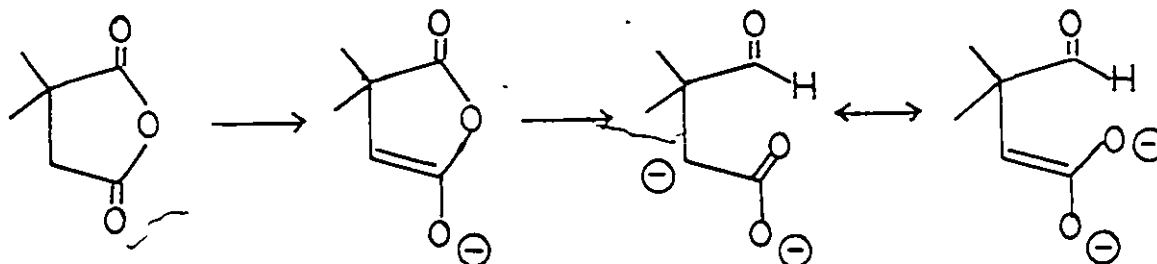
\* To check our trapping procedure we experimented with  $\text{LiAlH}_4$  reductions of three ketones. The results are shown in the table below. The initial surge of gas cannot account for the unreacted ketone found in the reaction mixture after quenching. Brown, Weissman and Yoon<sup>52</sup> reported corresponding quantities of  $\text{H}_2$  evolved in reductions of analogous ketones. Unfortunately no yields were reported. Since neither Brown nor we could detect any initial gas evolution in the reduction of benzophenone (Experimental section, see page 130) we feel that small as it is, the evolution of  $\text{H}_2$  observed for the other ketones (containing  $\alpha$ -hydrogen atom) must be real.

Reaction of  $\text{LiAlH}_4$  with Representative Ketones in THF

Ketone (a) (10 mmole)	Product (b)		Gas evolution ( $\text{H}_2$ )		
	Alcohol	Ketone	% yield	(Initial gas evolution (ml))	(Reported in ref.51 (mmoles))
Cyclohexanone	90	10	12.5	0.55	not reported
2-Heptanone	-	-	-	-	0.81
Acetophenone	74	26	10.0	0.45	0.37
Benzophenone	68	32	0	0	0

(a) 10 mmoles ketone to 10 mmoles of  $\text{LiAlH}_4$ ; (b) Glc analyzed.

\*\* Addition of hydride ion to the carbonyl function not affected by enolization (the one adjacent to the tertiary carbon atom) implies formation of an intermediate dianion (see figure below). Such dianions have been generated under strongly basic conditions (e.g., with lithium diisopropyl amine).<sup>53</sup> So far, we have no evidence for the existence of such an intermediate.



### ii) Hyperconjugation

The concept of hyperconjugation was introduced by Baker and Nathan<sup>54a</sup> in 1935 to explain effects which are associated with the presence of methyl or methylene groups close to  $\pi$  bonds in unsaturated systems.

The authors observed that the order of reactivity ( $\text{Me} > \text{Et} > \underline{i}\text{-pr} > \underline{t}\text{-Bu}$ ) for a series of p-alkyl substituted benzyl bromides was opposite to that expected on the basis of the inductive effect ( $\underline{t}\text{-Bu} > \underline{i}\text{-Pr} > \text{Et} > \text{Me}$ ).

This led them to postulate their theory of hyperconjugation, a concept which still remains controversial. However, for a large body of experimental data it provides the most consistent and satisfactory explanation.<sup>54b</sup>

In the language of perturbation theory<sup>54c</sup> two-electron interactions of the highest filled,  $\pi$ -symmetry orbital on a methyl group with the vacant p-orbital at  $\text{C}^+$  results not only in net energetic stabilization of the cation but also in significant charge reorganization. Specifically, electron density is displaced from the methyl C-H linkages (thus weakening these bonds) into the region connecting the two carbon atom centres, resulting in a shortening of the C-C bond. Such a delocalization of charge can be responsible for the retardation of nucleophilic addition to the carbonyl function possessing an  $\alpha$ -hydrogen atom.

### 3. Summary

The net electronic effect in 2,2-disubstituted cyclic anhydrides is the result of:

- (a) positive inductive effect of the substituents, promoting complexation of the  $\alpha$  carbonyl function with the cation,

(b) deactivation toward the nucleophilic addition (due to hyperconjugative electron delocalization) of the carbonyl group possessing an  $\alpha$  hydrogen atom.

In addition, five-membered cyclic anhydrides are subject to the steric constraints which favour reduction of the carbonyl group  $\alpha$  to the fully substituted carbon atom (Figure 17). These factors

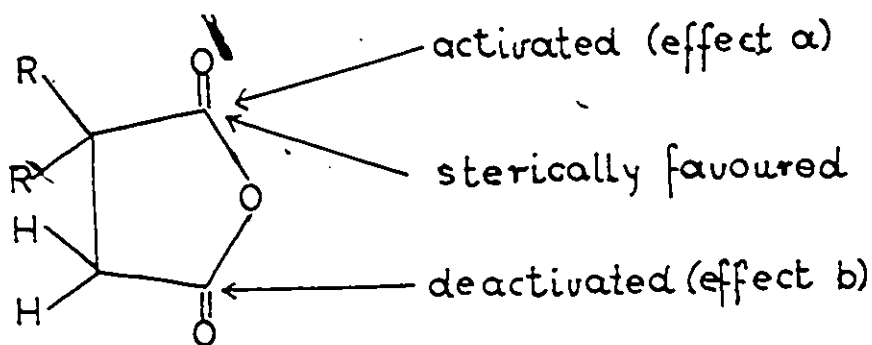


Figure 17. Factors influencing regioselectivity in 2,2-disubstituted succinic anhydrides.

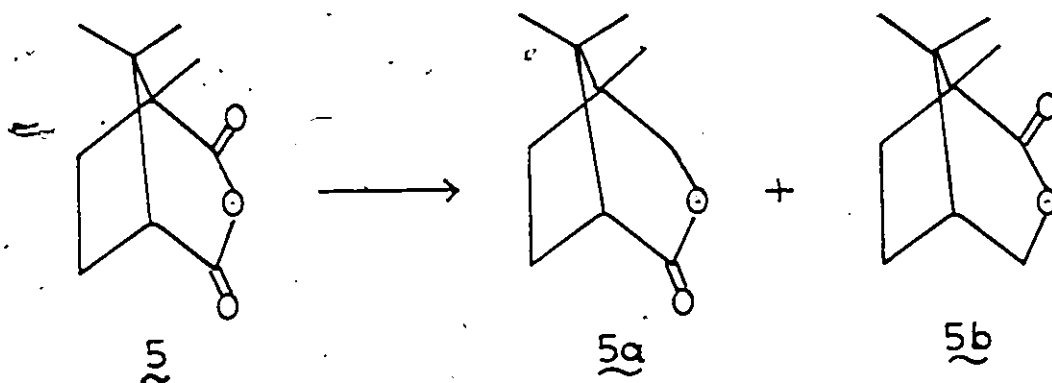
combined are responsible for the high regioselectivity observed in metal hydride reductions of 2,2-disubstituted succinic anhydrides.

CHAPTER 5

REDUCTION OF BRIDGED CYCLIC ANHYDRIDES

1. Camphoric Anhydride

The high regioselectivity observed in the reductions of some 2,2-disubstituted cyclic anhydrides is ascribed to the fact that both electronic and steric effects favour reaction at the same carbonyl function. Reduction of camphoric anhydride with  $\text{LiAlH}_4$  is less selective. The ratio of isomeric lactones obtained is 3:2 in favour of  $\beta$ -campholide 5a. The observed preference for the more hindered carbonyl function is attributed to the positive inductive effect of the angular methyl group.



Deactivation of the "less hindered" carbonyl function through hyperconjugative delocalization of electrons cannot occur due to the bridgehead position of the  $\alpha$ -hydrogen atom. Moreover, steric interactions do not favour one carbonyl group over the other. The exo side of the camphoric anhydride molecule is effectively and symmetrically blocked by methyl substituents at the bridge. By analogy to the stereoselectivity

exhibited in the reduction of camphor,<sup>41</sup> it appears that hydride attack should take place mainly on the *endo* side of the molecule. In terms of the constraints due to non-perpendicular approach, steric restrictions about the two carbonyl groups are almost identical (Figure 18).

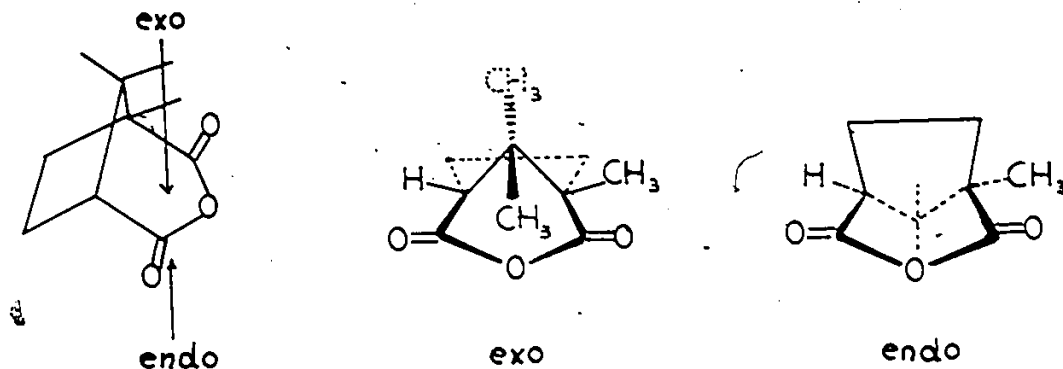
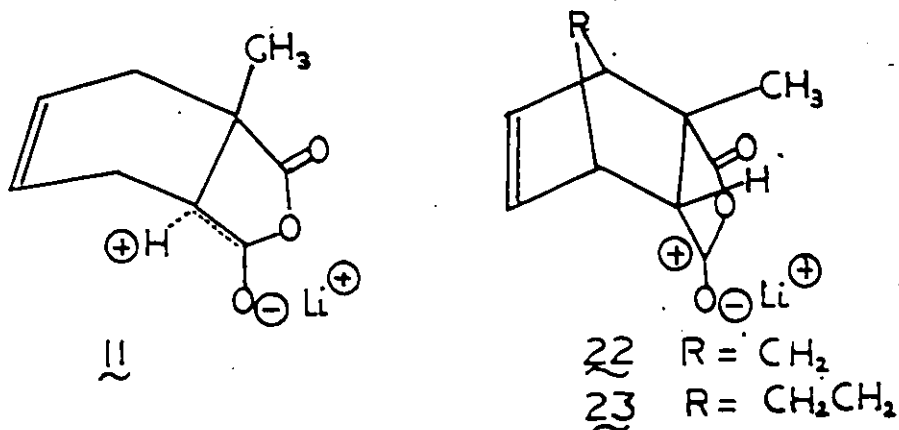


Figure 18. Nucleophilic attack *exo* and *endo* on the camphoric anhydride molecule.

## 2. Bridged, tricyclic anhydrides

The geometry of the ring system to which the anhydride is attached appears to influence greatly the site of metal hydride reduction. A case in point is the complete reversal in regioselectivity observed in the reduction of anhydrides 22 and 23 compared to 11. The former two compounds differ from 11 only by having a methylene or ethylene bridge respectively. Since delocalization of electrons through hyperconjugation is considered to retard hydride addition to the carbonyl group (see page 36), we were tempted to explain the above results by evoking hyperconjugation in 11 as opposed to the resistance to such electron delocalization in the rigid, bridged compound 22 (or 23). Thus, the electronic situation encountered in 22 or 23 parallels that of camphoric anhydride 5



(see page 38) and cannot explain the reversed regioselectivity observed. In addition steric interactions should favour reduction of the more hindered carbonyl group  $\alpha$ .

Examination of the Dreiding models of  $\underline{\underline{22}}$  and  $\underline{\underline{23}}$  reveals that nucleophilic attack is more likely to take place on the "convex" face of the molecule (Figure 19).

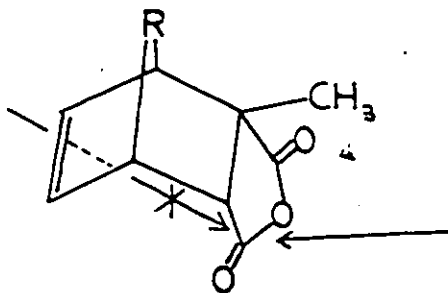


Figure 19. The "convex" face of anhydrides  $\underline{\underline{22}}$  and  $\underline{\underline{23}}$  is more open to nucleophilic attack than the "concave" side.

This assumption is supported by the stereoselectivity observed in the metal hydride reduction of the ketone's carbonyl group attached to the analogous ring system (see Figure 20).<sup>55</sup> In effect, steric interactions arising in the reduction of  $\underline{\underline{22}}$  and  $\underline{\underline{23}}$  should resemble the previously

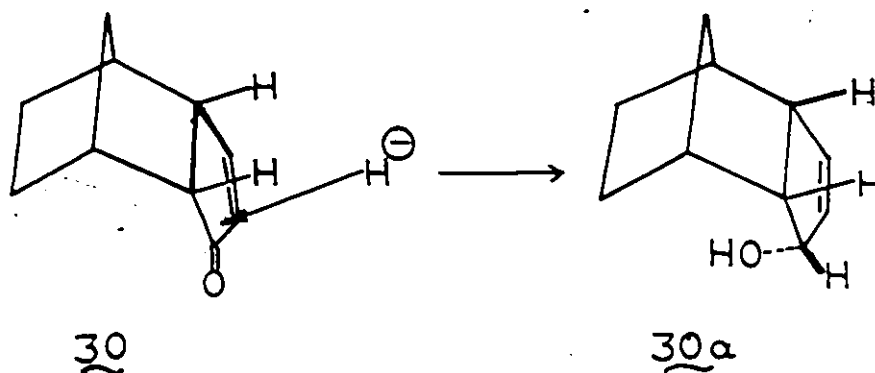
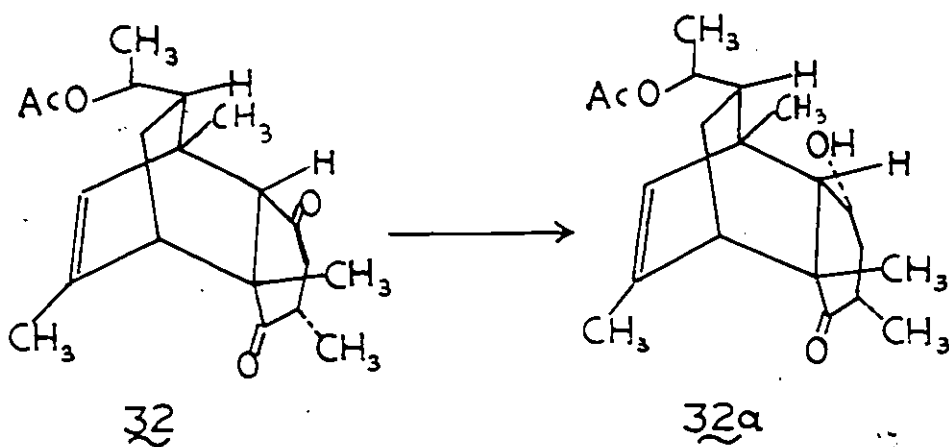
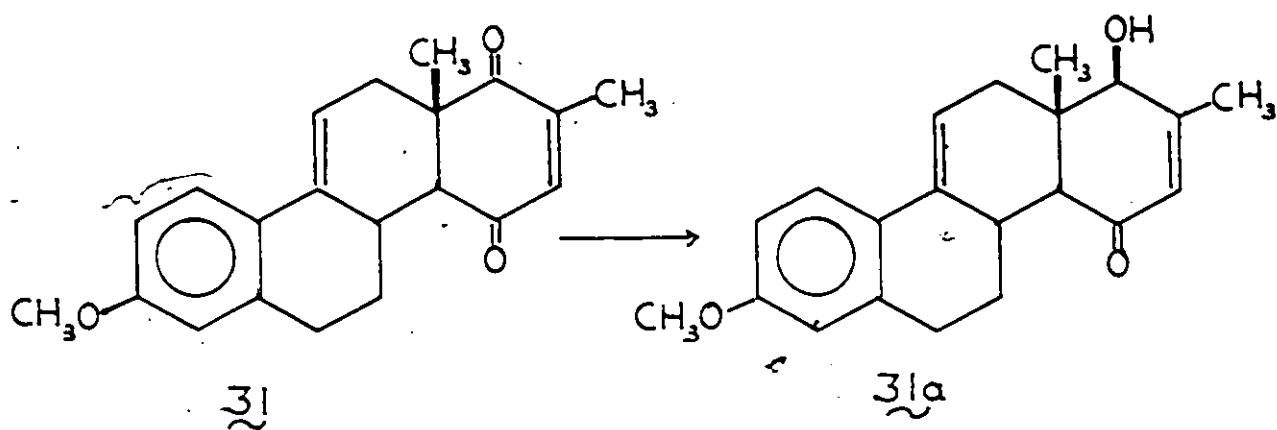


Figure 20. Stereochemistry of hydride addition observed in metal hydride reduction of ketone 30.

discussed steric interactions encountered in the reduction of anhydrides 3, 11 and 20 (see page 30). Thus the "more hindered"  $\alpha$ -carbonyl group should be reduced preferentially but this clearly is not the case.

At this stage we do not have an adequate explanation for the peculiar behaviour of compounds 22 and 23. However, there must be an overriding effect specifically activating the "less hindered"  $\beta$  carbonyl function. This effect appears to be related to a particular type of ring system to which the anhydride is attached. A significant analogy is observed in the metal hydride reduction of structurally related diketones. Reduction of the tetracyclic compound 31 with  $\text{LiAl}(\text{t-Bu})_3\text{H}$  yields selectively alcohol 31a resulting from reduction of the more hindered carbonyl group <sup>56</sup> (compare with the reduction of anhydride 20, Table 2, page 9). On the other hand the bridged diketone 32 upon reduction with  $\text{NaBH}_4$  gives only ketoalcohol 32a resulting from the reduction of the less hindered carbonyl group, <sup>57</sup> (compare with the reduction of 22 and 23).



### 3. Summary

The regioselectivity observed in the reductions of diketones 31 and 32 parallels the results obtained in the reductions of the analogous cyclic anhydrides. The reduction of compound 31 may be rationalized in terms of our mechanism, by evoking a different electronic character for the two carbonyl groups.\* The reversal of regioselectivity

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\* It is quite likely that the same mechanism could explain the results of the reductions of unsymmetrical succinimides.<sup>58</sup>

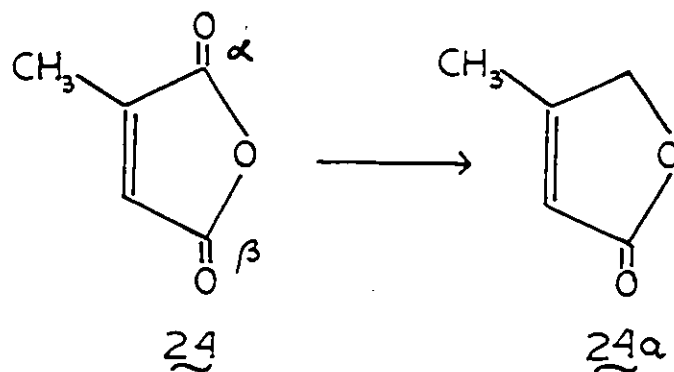
in 32 resembles the situation observed in the reduction of anhydrides 22 and 23. These results do not provide an explanation for the unusual behaviour of bridged tricyclic compounds, but they do point out two facts: (a) the addition of  $H^-$  does take place from the "convex" face of the molecule as suggested before; (b) the reversal of regioselectivity is associated somehow with the geometry of the bridged ring system.

CHAPTER 6

PLANAR CYCLIC ANHYDRIDES

Planar conjugated cyclic anhydrides and cyclic anhydrides attached to aromatic systems constitute a class of compounds in which the type of steric interactions discussed previously (i.e., restrictions of non-perpendicular approach) is not operative. This, of course, does not mean that all steric effects are absent. Actually such systems are affected by a multitude of effects, both electronic and steric, acting in unison or in opposition, often impossible to unravel. Since each of the model anhydrides studied presents its own particular set of parameters we shall discuss them individually.

1. Citraconic anhydride



Reduction of citraconic anhydride 24 with metal hydrides yields essentially one lactone 24a (only traces of the isomeric lactone can be detected by  $^1\text{Hn.m.r.}$  in the crude reduction product). Steric influence of the methyl group located in the molecular plane appears

minimal and should not affect electrophilic or nucleophilic addition. However, we must reckon with the electronic effects. Positive inductive effect of the methyl substituent activates the  $\alpha$ -carbonyl function\* toward electrophilic addition. At the same time the  $\beta$ -carbonyl group is deactivated toward nucleophilic addition due to the stabilizing effect of the methyl group on the structure 33 (relative to ion 34, see Figure 21). Consequently, since both electronic effects favour the

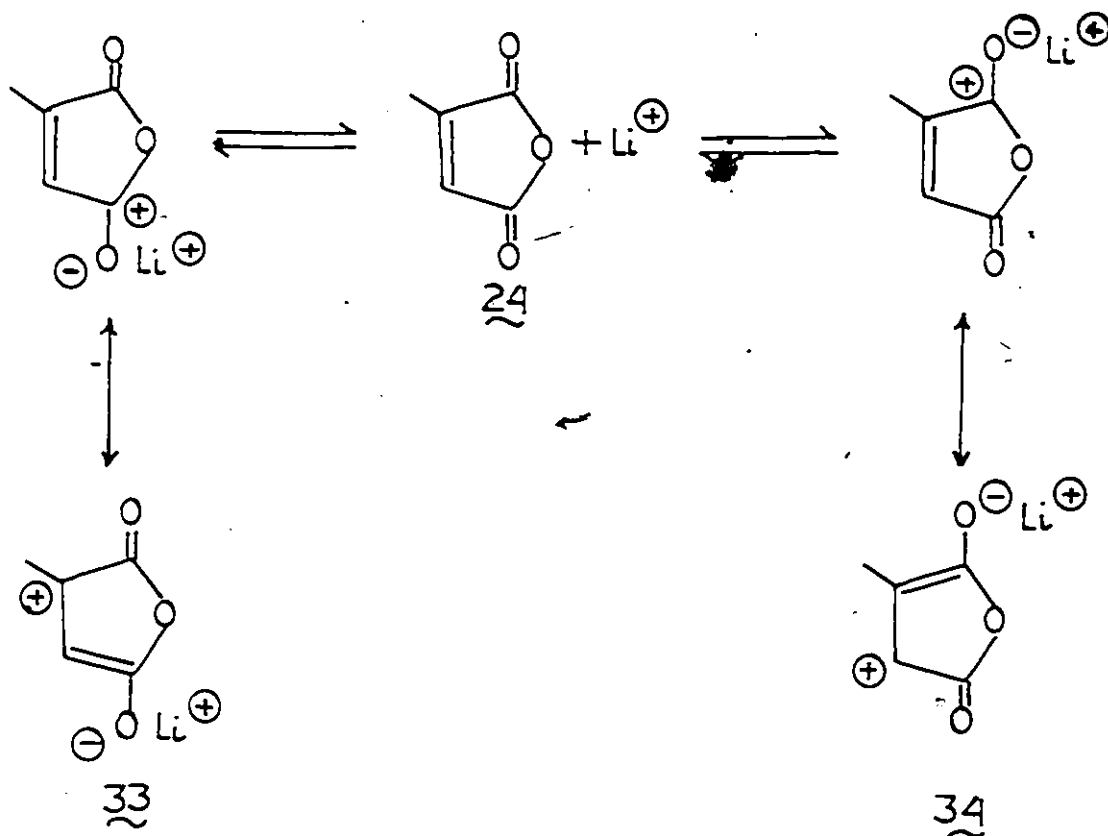


Figure 21. Of the two possible structures 33 and 34, 33 is of lower energy and therefore more stable.

\*The inductive effect on the  $\beta$ -carbonyl group is weaker since the intensity of this effect decreases sharply with distance (in contrast to resonance effects, which are transmitted with no significant decrease in intensity with distance).

same site, the reduction of citraconic anhydride proceeds with high regioselectivity.

## 2. Substituted phthalic anhydrides

Various influences on the reaction centre in substituted aromatic compounds can be summarized in a simple rule: resonance is the dominant effect of a substituent in the para position; inductive and, to some extent, resonance effects\* are exerted by a substituent in the meta position; steric effects are usually the major influence of a substituent in the ortho position, except when the substituent is of relatively small size (e.g. F) and induction and resonance become more prominent.<sup>60</sup>

We have discussed, in previous chapters, the importance of catalysis by alkaline cation in metal hydride reductions. If association with a cation catalyzes the reaction, an electron-donating substituent should promote complexation with a cation and therefore accelerate the reduction. Conversely, an electron-withdrawing group would decelerate the reaction. Unfortunately, the problem is more complex. The above argument is valid only when electron-donating and electron-attracting substituents activate or deactivate the carbonyl function through induction. When complexation with the cation is accompanied by electron

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\* Inductive and mesomeric effects do not always reinforce each other. An electron donor, through resonance, may be an electron-withdrawing group through induction (e.g., -OH, -SH, -NH<sub>2</sub>). In general, conjugation is more important for substituents involving first-row elements (-F, OH, NH<sub>2</sub>), while inductive effects become increasingly important for the second and third row elements (e.g., Cl<sup>-</sup>, Br<sup>-</sup>, -SH, etc.)<sup>61</sup>.

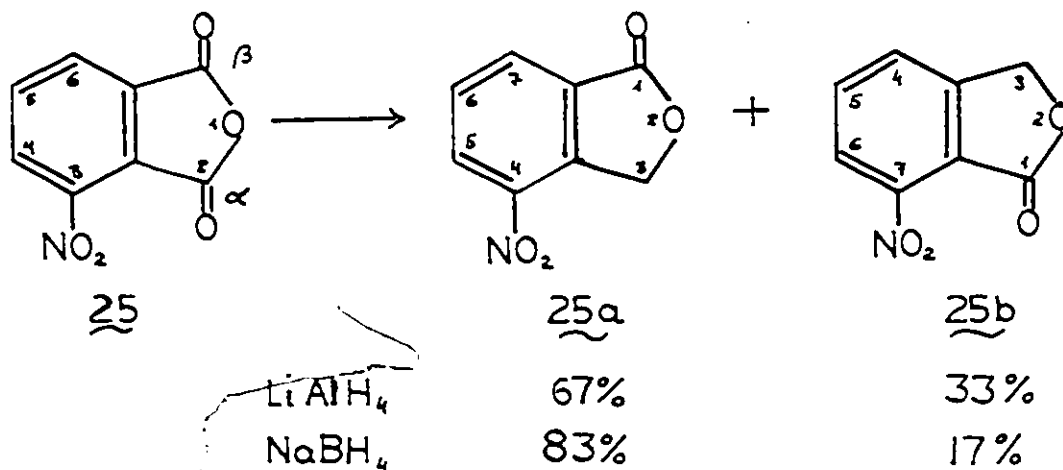
delocalization (as is often the case in aromatic and conjugated systems), the subsequent (rate-determining) hydride addition step is retarded.

Loupy, Seyden-Penn and Tchoubar<sup>35</sup> have shown that the "essential role" of the cation applies only to reductions of saturated aliphatic carbonyl compounds. The interactions between the HOMO of the nucleophile and the LUMO of the electrophile are strongest for orbitals that lie closest in terms of energy levels (see discussion in Chapter 2). Apparently the energy level of the LUMO $\pi^*$  of the aliphatic carbonyl group (not complexed with a cation) is too high for the nucleophile's HOMO and reaction does not take place. On the other hand, aromatic ketones and aldehydes can be reduced in the absence of a cation, although at a considerably slower rate.<sup>35</sup> Evidently, in aromatic carbonyl compounds, the electron-withdrawing aromatic ring sufficiently lowers the energy level of the LUMO $\pi^*_{C=O}$  for addition to occur.

As a result, metal hydride reduction of carbonyl groups conjugated with an aromatic system can proceed through a catalyzed or a non-catalyzed mechanism. Usually the catalyzed reaction is significantly faster but, in certain cases, the difference between catalyzed and non-catalyzed reduction rates may not be very large. For example, an electron-withdrawing substituent on an aromatic ring lowers the probability of the formation of a complex with the cation while, at the same time, it increases the rate of non-catalyzed reduction. It is entirely possible that in such a situation the two mechanisms may be operative.

i) Reduction of 3-nitrophthalic anhydride

Reduction of 3-nitrophthalic anhydride 25 occurs with a high degree of regioselectivity at the more hindered  $\alpha$ -carbonyl function. Preference for this group was also observed in the  $\text{NaBH}_4$  reduction of three other ortho-substituted phthalic anhydrides.<sup>62</sup> In order to account for such selectivity the authors invoke "steric inhibition of resonance",<sup>63</sup> a powerful effect known to cause acceleration of a variety of reactions.\* In terms of this effect the reduction of 3-nitrophthalic anhydride 25 may be envisaged in the following manner: due to the proximity of the ortho



carbonyl function, the nitro group is twisted from co-planarity with the aromatic ring and thus the resonance-effect is greatly diminished. The removal (by reduction) of the carbonyl function allows the nitro

---

\* A distortion of the resonating groups in ortho substituted aromatic compounds affects reaction rates and equilibria. For example, all ortho substituted benzoic acids show increased acidity, a trend that cannot be due to ordinary steric effects since the steric requirements of the  $\text{H}^+$  ion are negligible.<sup>61</sup>

substituent to assume a position in the plane of the molecule  
(Figure 22).\*

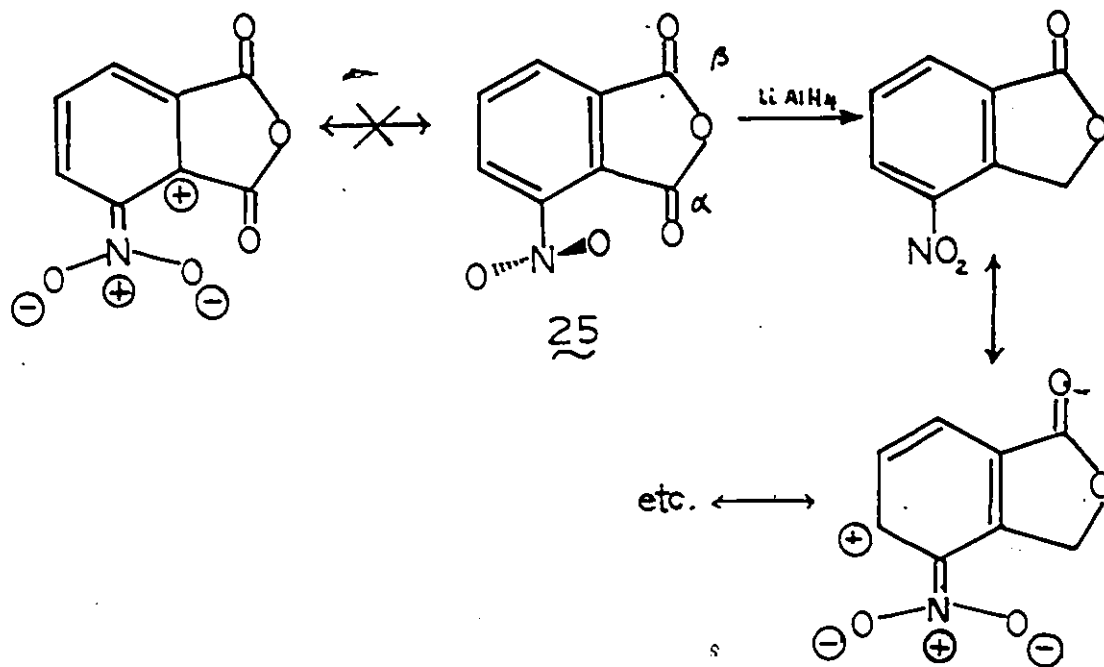


Figure 22. Steric inhibition of resonance existing in 25 is removed to a great extent when reduction occurs at the α-carbonyl function.

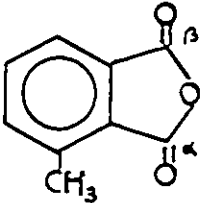
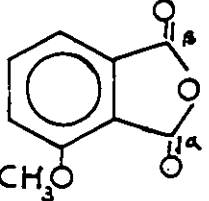
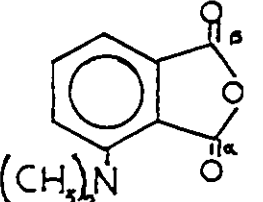
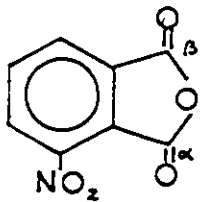
Let us for a moment forget the possible steric effects and attempt to determine the electronic influences on the two carbonyl functions. Since the nitro group in 25 can exhibit an inductive effect (while its resonance effect is minimal) the α-carbonyl group is more strongly deactivated toward association with the cation than the β-carbonyl group

\* This author is not entirely satisfied with the above explanation. An important reservation to this concept is that it implies a product-like transition state in which the observed ratio of isomeric lactones reflects the stability of the product. As was stated before, hydride reduction is a kinetically controlled reaction with early, reactant-like transition state. We feel that the nature of the transition state should be similar for fundamentally similar reaction.

(the inductive effect falls off rapidly with distance from the electron attractor). In the absence of steric acceleration, we should therefore expect preferential reduction of the  $\beta$ -carbonyl function. It is possible that in this particular case "steric hindrance of resonance" is the dominant factor controlling regioselectivity. However, the significantly higher yield of 7-nitrophthalide 25b observed in reduction with  $\text{LiAlH}_4$  as compared to  $\text{NaBH}_4$  (33% versus 17%) may be attributed to the superior catalytic activity of  $\text{Li}^+$  with respect to  $\text{Na}^+$  cation.

Similar arguments can be extended to the results of  $\text{NaBH}_4$  reduction of all four 3-substituted phthalic anhydrides, recently reported by McAlees, McCrindle and Sneddon,<sup>62</sup> (see Table 3 in which their results are

TABLE 3.  $\text{NaBH}_4$  reduction of 3-substituted phthalic anhydrides<sup>61</sup>

Anhydride	No.	Total yield of lactonic product %	Ratio of reduction products*		
			$\alpha$	$\beta$	$\sigma_m$
	35	77	57	: 43	-0.07
	36	52	87	: 13	+0.12
	37	45	80	: 20	-0.16
	25	81	100	—	+0.71

\*These ratios may not be accurate, see page 52 paragraph 2.

correlated with  $\sigma_m$  values).\*

The authors<sup>62</sup> assume that steric acceleration is the governing factor in the reduction of all four 3-substituted phthalic anhydrides. Yet, steric acceleration alone cannot adequately explain the product distribution observed.\*\* It is evident that electronic effects play an important, if not controlling, role in determining regioselectivity of this reaction. For example, in the reduction of 3-methylphthalic anhydride 35, the

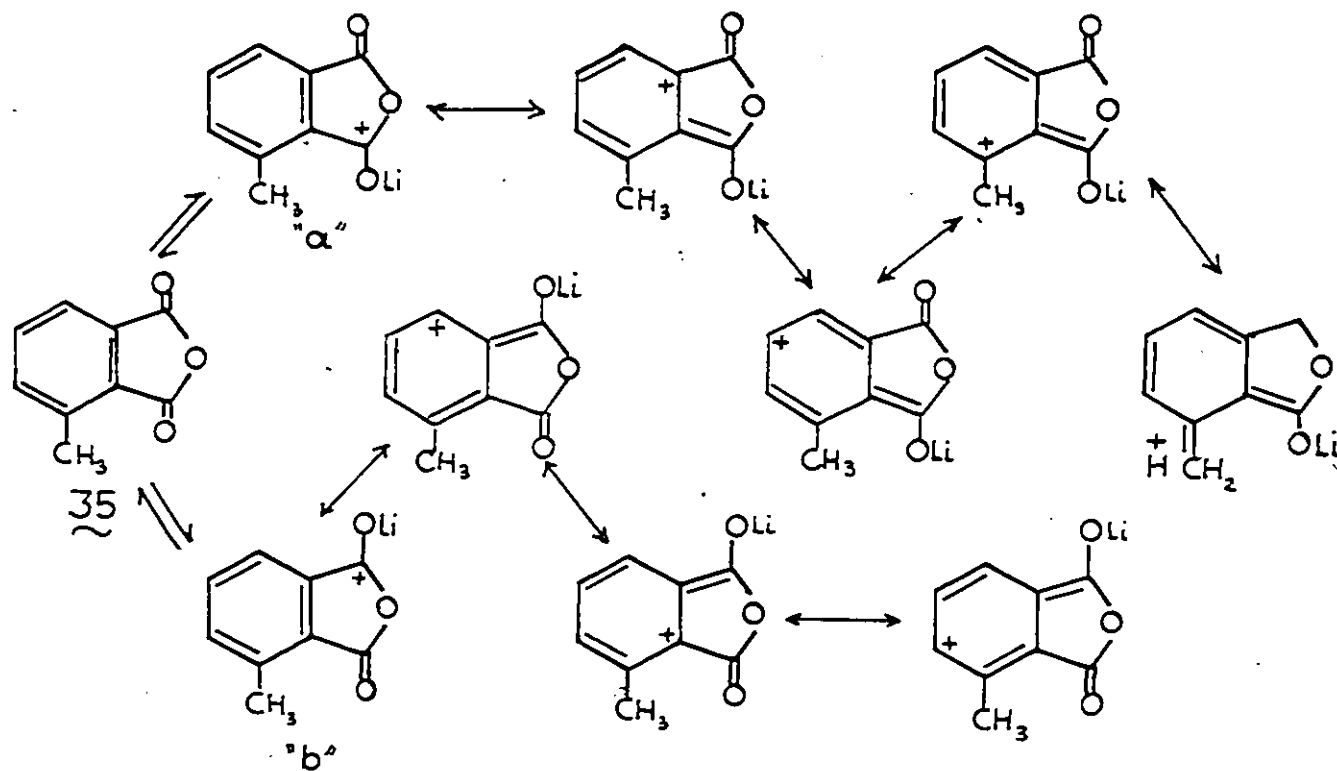


Figure 23. Resonance structures for the intermediates "a" and "b".

\* The  $\sigma_m$  value is characteristic of the substituent in the meta position and represents its ability to attract or repel electrons through combined resonance and inductive effects.<sup>61</sup>

\*\* Reduction of 35 yields two lactones in almost equal amounts. Since the methyl group does not participate in resonance steric acceleration can only be due to "steric hindrance of hyperconjugation." There is some evidence<sup>64</sup> that hyperconjugation is also subject to steric hindrance. However, since hyperconjugation effects are relatively small it is difficult to disentangle effects supposedly due to inhibition of hyperconjugation from other effects which may be present.

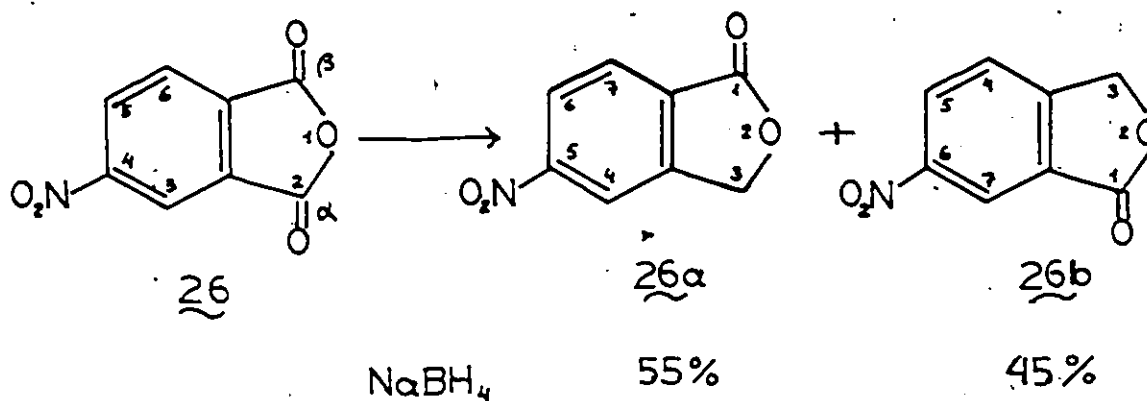
Inductive electron-donating effect of the methyl substituent activates both  $\alpha$ - and  $\beta$ -carbonyl groups toward complexation with a cation ( $\alpha$  more than  $\beta$ ). However, at the same time, hydride transfer to the  $\alpha$ -carbonyl function may be retarded due to superior stabilization of the intermediate "a" versus "b" (Figure 23), thus resulting in somewhat increased reduction of the  $\beta$ -carbonyl group. Similarly, electron donating effect of the substituents, rather than steric acceleration may be responsible for the preferential reduction of the  $\alpha$ -carbonyl function in 36 and 37.

The general trend observed in the reduction of 3-substituted phthalic anhydrides may be justified in terms of such considerations. However, too much importance should not be placed on the exact ratios of isomeric lactones, since these do not appear to be accurate. For example, reduction of 3-nitrophthalic anhydride 25 was reported<sup>62</sup> to yield only one lactonic product 25a but in our hands under identical experimental conditions, reduction of 25 never failed to produce small quantities (>10%) of the isomeric lactone 25b as well.

ii) 4-Nitrophthalic anhydrides

In 4-substituted phthalic anhydrides, the substituent lies far enough from the reaction centre that steric interactions between the substituent and the carbonyl groups (in the para and meta positions) are negligible. The influence of the substituent on the reaction centre may be considered to be due solely to inductive and resonance effects.

$\text{LiAlH}_4$  reduction of the anhydride 26 did not proceed cleanly and a mixture of several products was obtained. Although we managed to isolate both lactones from the mixture (26a:26b = 60:40), it was not possible to establish accurately the original ratio of the two lactones.



$\text{NaBH}_4$  reduction yielded 56% of lactonic product.  $^1\text{Hn.m.r.}$  analysis showed the ratio of  $\underline{26a}:\underline{26b}$  to be 55:45. Due to the electron-withdrawing effect of the nitro substituent both carbonyl groups in  $\underline{26}$  are deactivated toward association with the cation - the carbonyl group in the para position somewhat more than the carbonyl group in the meta position, according to the  $\sigma_p$  and  $\sigma_m$  values (Figure 24).<sup>61</sup>

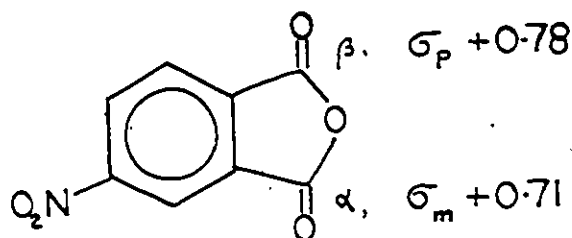


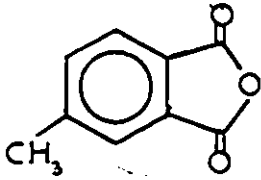
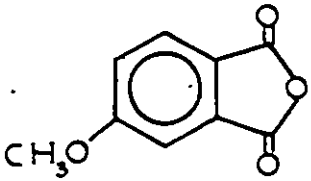
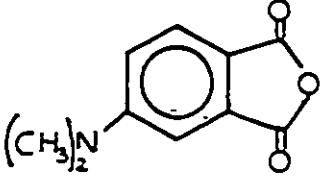
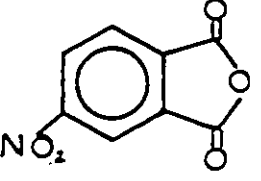
Figure 24. Hammett substituent constants ( $\sigma$ ) for the two carbonyl groups in 4-nitrophthalic anhydride.

Therefore, the catalyzed reaction has a better chance to occur at the  $\alpha$ -carbonyl group\*. The results obtained by McAlees, McCrindle and

\*We should keep in mind that non-catalyzed reduction is more likely to occur at the  $\beta$ -carbonyl function.

Sneddon<sup>62</sup> for three other 4-substituted phthalic anhydrides shed some light on the rôle played by inductive and mesomeric effects in regioselectivity (see Table 4).

TABLE 4. NaBH<sub>4</sub> reduction of 4-substituted phthalic anhydrides<sup>62</sup>

Anhydride	No	Total yield of lactonic prod. %	Reduction in <u>para</u> position (%)	Reduction in <u>meta</u> position (%)	$\sigma_p$	$\sigma_m$
	38	55	33	67	-0.17	-0.07
	39	67	30	70	-0.27	+0.12
	40	54	0	100	-0.66	-0.16
	26	65	50	50	+0.78	+0.71

In all four cases (26, 38, 39 and 40) there is less reduction at the para position. We attribute this to the fact that although the carbonyl group in the para position is activated toward complexation with the cation more than the carbonyl group in the meta position (see  $\sigma$  values for 38, 39 and 40), the accompanying electron delocalization (resonance in 39 and 40, hyperconjugation in 38) will retard hydride addition to the  $\beta$ -groups (Figure 25).

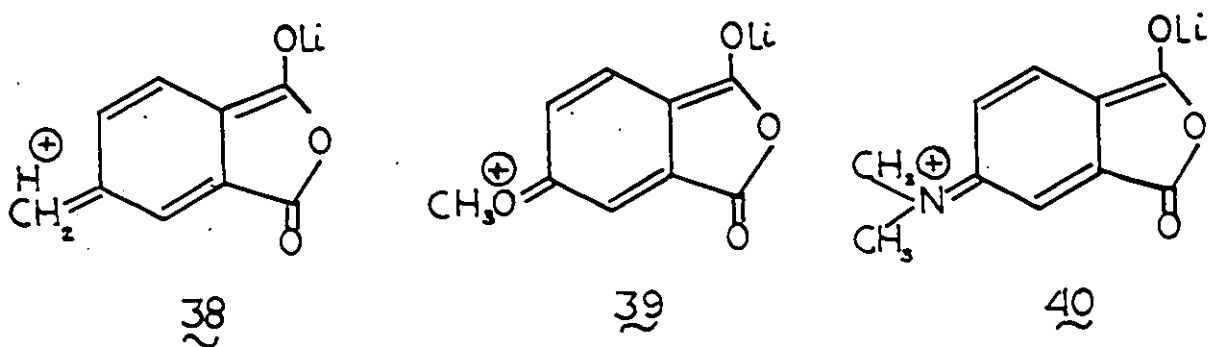


Figure 25. Resonance and hyperconjugative electron delocalization in 38, 39 and 40.

In 40 the  $\alpha$ -carbonyl function is also activated toward association with the cation ( $\sigma_m$ , -0.16). However, there is diminished possibility of resonance, and, as a result, reduction occurs regioselectively at this carbonyl group. Electronic effects in methyl substituted phthalic anhydride 38 resemble the situation encountered in 40, but deceleration of the nucleophilic addition to the  $\beta$ -carbonyl function is caused by the weaker hyperconjugative electron delocalization. In 4-methoxyphthalic anhydride 39, regioselectivity is diminished since the meta position is actually deactivated ( $\sigma_m$ , +0.12) toward the cation.

It is therefore possible to rationalize the results of these reductions and possibly to predict which carbonyl group might be a

favoured target but the degree of regioselectivity cannot, at this stage, be estimated.

iii) Summary

Almost all substituents (electron-attracting and electron-donating) in position 3 favour reduction of the  $\alpha$ -carbonyl group (Figure 25a). The degree of regioselectivity is dependent on the nature

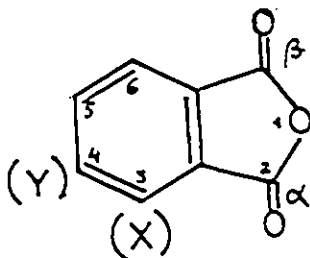


Figure 25a. 3- and 4-substituted phthalic anhydride.

of the substituent but interpretation of data is complicated. Clearly, when the substituent is ortho to the reaction centre, both induction and resonance effects operate strongly, but superimposed on these may be steric effect which in some instances may mask existing polar effects.

The steric influence of the substituent on the meta or para carbonyl functions is assumed to be negligible (this assumption is justified in view of the success of the Hammett equation which implies the same premise). The net effect of an electron-donating group in position 4 is relative deactivation of the para carbonyl group with respect to the meta carbonyl function. An electron-withdrawing substituent in the 4-position deters association of the carbonyl group with

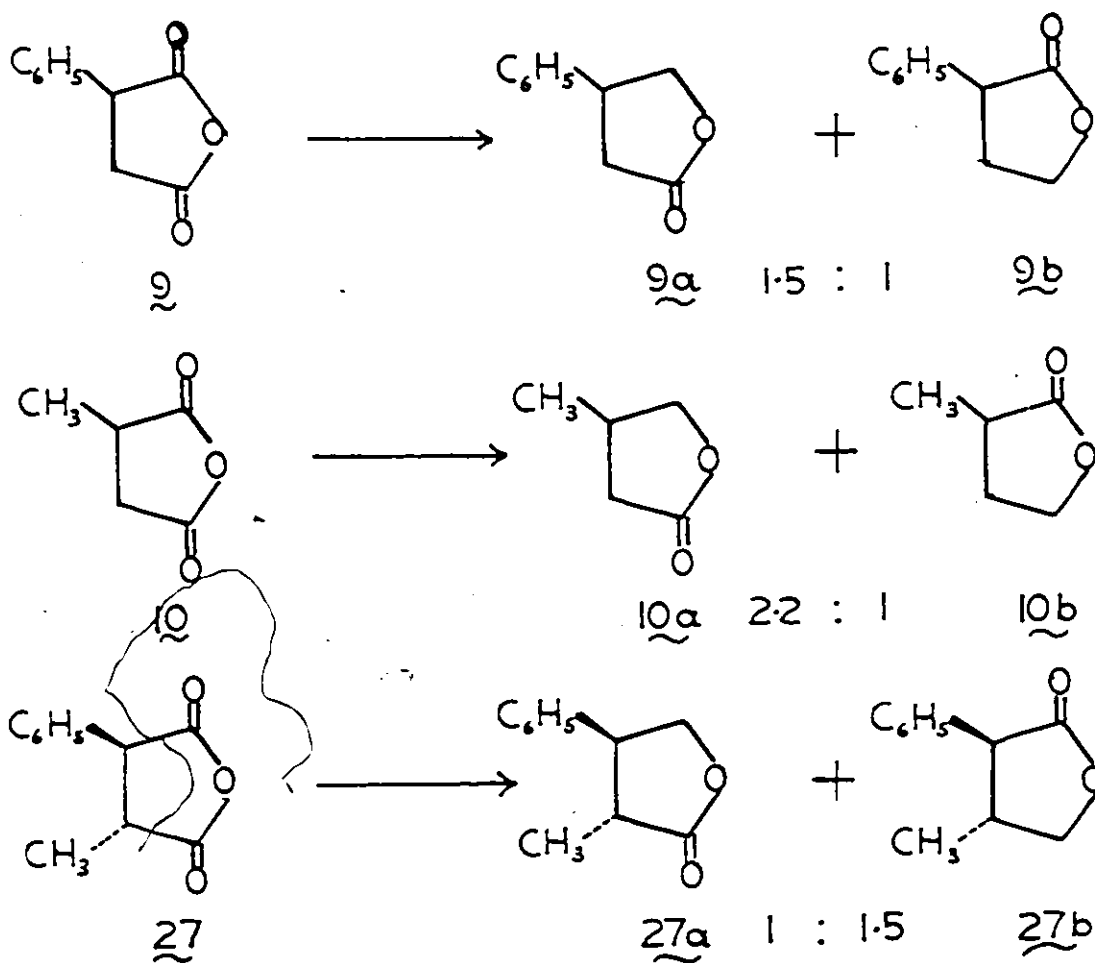
the cation and at the same time lowers the energy of the LUMO  $\pi_{C=O}^*$  even more than does the aromatic ring alone. As a result, the reduction may proceed to some extent by the non-catalyzed mechanism even in the presence of the cation.

An interesting auxiliary conclusion, derived from the above arguments, suggests that in substituted aromatic anhydrides the catalyzed and non-catalyzed reductions may, in some cases, yield different ratios of isomeric lactones.

CHAPTER 7

MONO AND 2,3-DISUBSTITUTED SUCCINIC ANHYDRIDES

When a variety of conflicting effects influence the reduction, mixtures of isomeric lactones are usually formed. The ratio of the two isomers may reflect the dominance of steric or electronic effects.



Reduction of 2-methylsuccinic anhydride<sup>15</sup> 10 yielded a mixture of lactones 10a and 10b in the ratio 2.2:1, whereas reduction of 2-phenylsuccinic anhydride 9 showed diminished preference for the more hindered carbonyl

group ( $\rho_a:\rho_b = 1.5:1$ ). From steric considerations alone the opposite trend would be expected (see Chapter 2, page 18). To explore further the effects of phenyl versus methyl substituent, reduction of trans-2-methyl-3-phenylsuccinic anhydride 27 was undertaken. Here, the sterically more important phenyl group is in direct competition with the less bulky methyl group. trans-2-Phenyl-3 methyl- $\gamma$ -butyrolactone 27b ( $\rho_a:\rho_b=1:1.5$ ) was found to be the major product, indicating preferential reduction at the carbonyl function next to the methyl substituent.

A crucial problem associated with stereoelectronic effects is the ordering of the substituents with respect to their polarity and "effective size".<sup>21</sup> The phenyl group is particularly troublesome in its steric behaviour, since it can act sometimes (but not always) as if it were bulkier than the t-butyl group. Nguyen and Eisenstein<sup>37</sup> suggest that when a phenyl group is attached to the carbon atom next to a carbonyl function (Figure 26) the  $\pi^*$  orbitals of the phenyl ring may interact through space with  $\pi^*_{C=O}$ . Extra stabilization is obtained for the

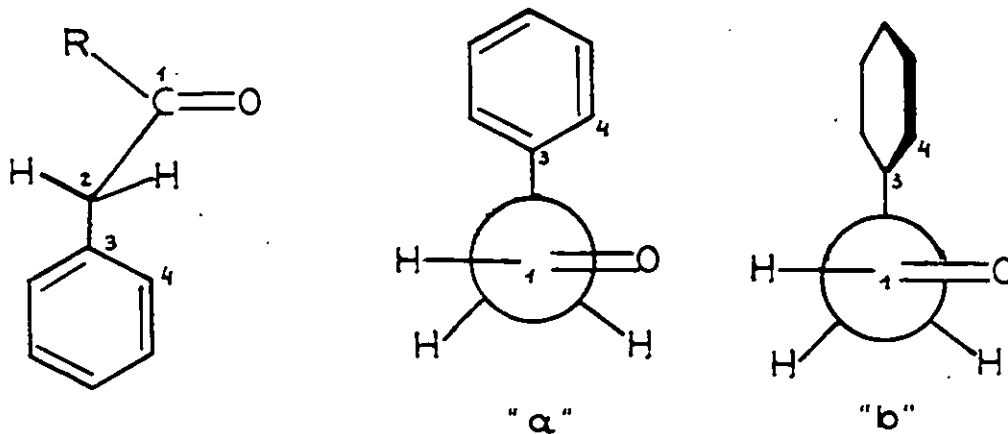


Figure 26. In the stabilized form "a" the dihedral angle  $C_1-C_2-C_3-C_4$  is  $90^\circ$ ; in the less favourable form "b" dihedral angle  $C_1-C_2-C_3-C_4$  is  $<90^\circ$ .

molecule when the dihedral angle  $C_1-C_2-C_3-C_4$  is  $90^\circ$  (see Figure 26). Examination of Dreiding models reveals that a phenyl substituent in the stabilized form "a" blocks the favoured path of nucleophilic approach to the carbonyl function far more effectively than when it is in the conformation "b" (Figure 27)

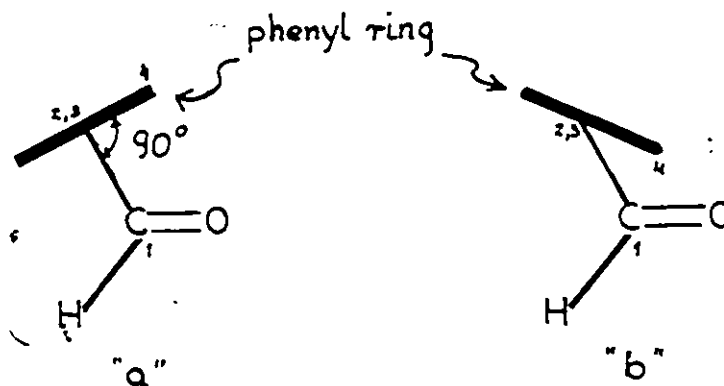
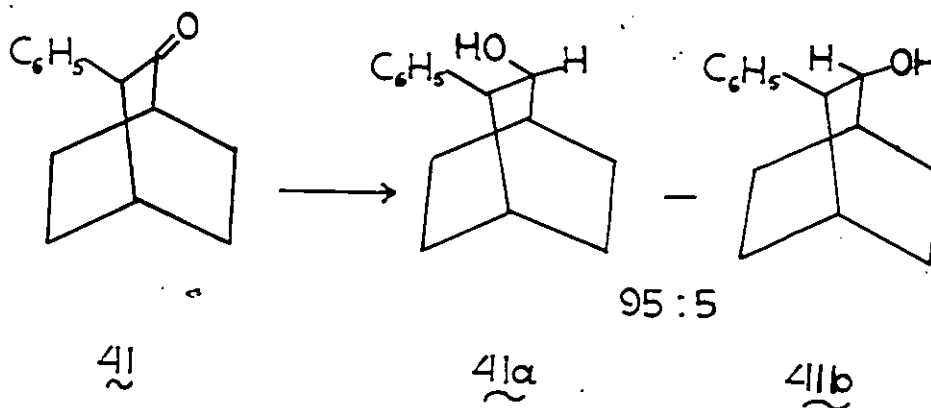


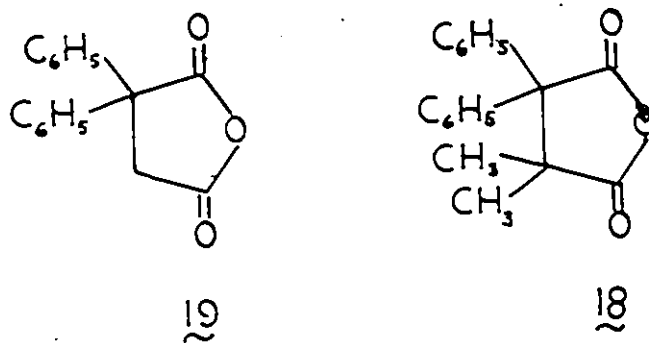
Figure 27. Projections of forms "a" and "b" on the plane of trigonal carbon atom.

$LiAlH_4$  reduction of 3-phenylbicyclo[2,2,2]octan-2-one 41 yields the cis alcohol 41a with a high degree of stereoselectivity (cis:trans = 95:5).<sup>46</sup> The same selectivity is observed when R is t-butyl; with R =  $CH_3$ ,  $C_2H_5$  or i- $C_3H_7$  trans alcohol is the major product<sup>44</sup> (see discussion in Chapter 2).



The high stereoselectivity observed in the reduction of 41 can be rationalized if the phenyl substituent does indeed assume the stabilized form "a" (Figure 27), which hinders efficiently nucleophilic addition to this face of the trigonal carbon atom.

In 2,2-diphenylsuccinic anhydrides (such as 18 and 19), the phenyl substituents are not able to assume the preferred conformation "a" (due to steric interaction with one another). However, in the mono-



substituted succinic anhydrides 9 and 27, the phenyl group can (and most likely does) take up the energetically more stable form "a". As a result, the steric restrictions due to phenyl substituents in 18 and 19 are not the same as in compounds 9 and 27 (Figure 28).

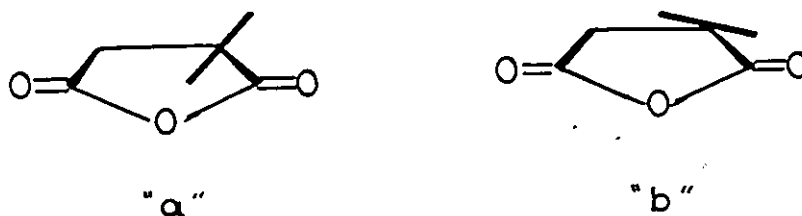


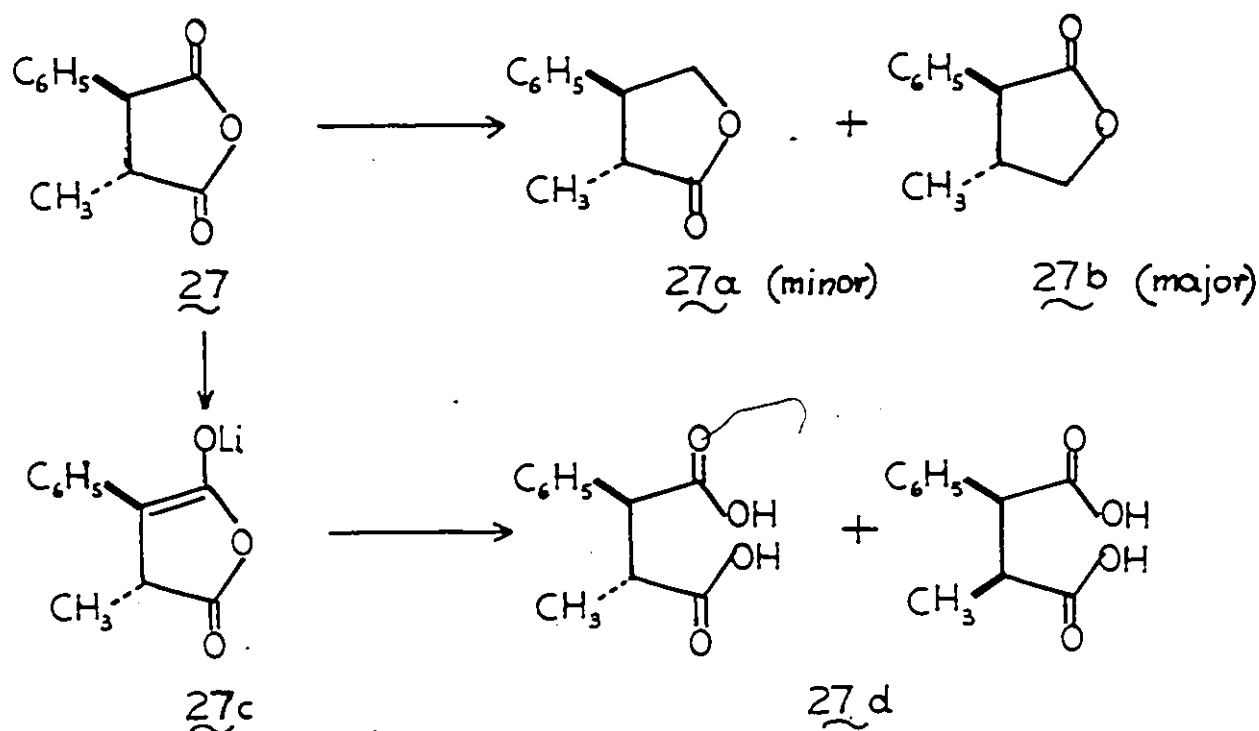
Figure 28. Projection on the plane of five-membered cyclic anhydride; phenyl group in form "a" (9 and 27) and in form "b" (18 and 19).

It is quite probable that in monosubstituted phenylsuccinic anhydride very little hydride addition takes place from the side bearing the phenyl substituent. If that is the case (and we tend to believe so) the regioselectivity observed in the reduction of 9 must be due entirely to electronic factors.

It appears that both phenyl and methyl substituents exert a positive inductive (and field?) effect on the adjacent carbonyl group (see discussion in Chapter 3). However, the activating effect of the phenyl group is counterbalanced by its ability to stabilize enolate ion.\*

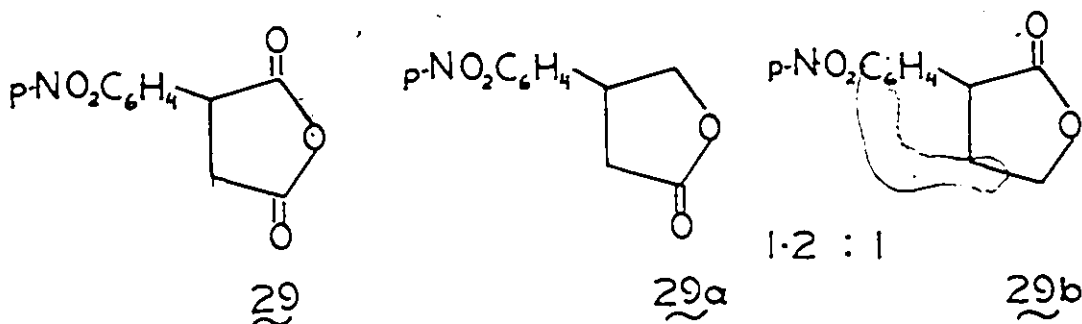
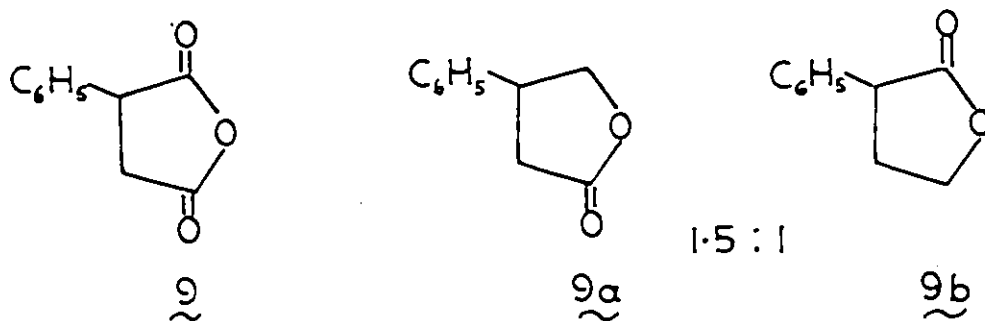
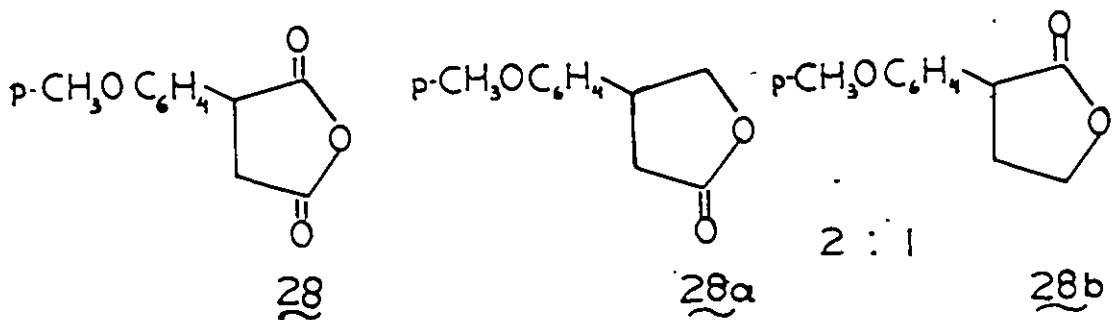
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\*<sup>1</sup>Hn.m.r. analysis of the crude product obtained by reduction of trans-2-methyl-3-phenylsuccinic anhydride 27 showed, in addition to lactonic product, some unreacted but isomerized diacid 27d. This suggests that an anhydride having an acidic hydrogen atom does convert to its enolate under the reaction conditions (enolization is not negligible in 27) and that the enolized anhydride 27c is not reduced readily at either the carbonyl function involved or the other one (see page 99).



As a result a lower proportion of 9a than 10a is produced in metal hydride reduction.

The study of substituted phenylsuccinic anhydrides 28 and 29 confirms the dominance of polar effects on regioselectivity in metal hydride reductions. The p-methoxyphenyl group is a better electron-donor than a simple phenyl group and consequently activates the adjacent carbonyl function more effectively while at the same time it has less of a stabilizing effect on the enolate ion. The net result is an increased proportion of



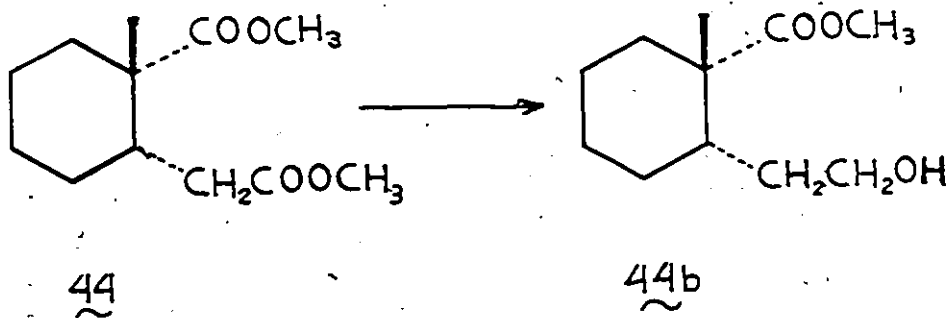
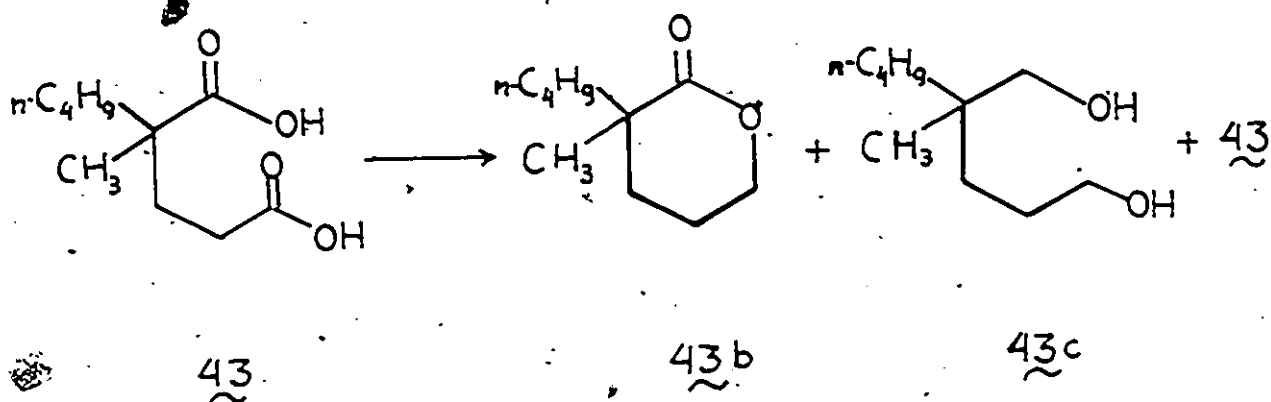
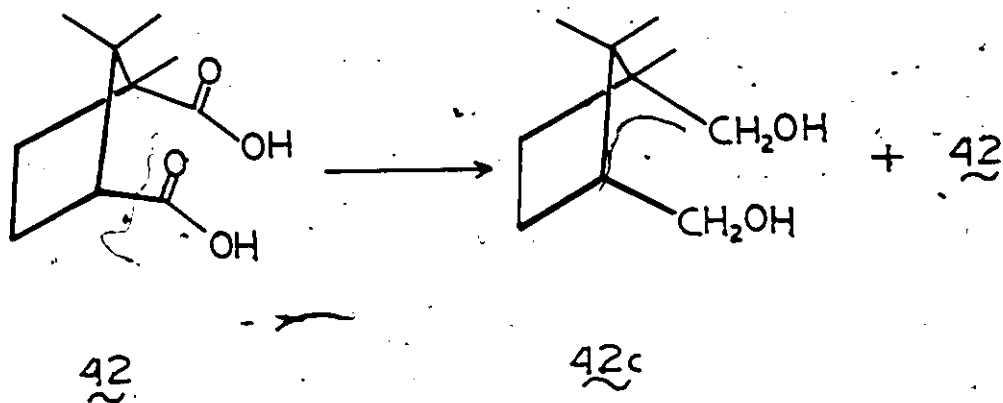
lactone 28a. The effect of the p-nitrophenyl substituent is in the opposite direction. The ~~electron~~-attracting property of the nitro group, coupled with greater stabilization of the enolate ion, results in diminished reduction at the carbonyl function adjacent to the substituent (the ratio of two lactones obtained is 29a:29b = 1.2:1).

CHAPTER 8

METAL HYDRIDE REDUCTIONS OF UNSYMMETRICALLY  
SUBSTITUTED DIESTERS AND DIACIDS

Preference for the more hindered carbonyl function is especially pronounced in the metal hydride reduction of cyclic anhydrides containing a tertiary and a primary carbonyl group. We have attributed this regioselectivity to a positive inductive effect of the substituents on the contiguous carbonyl function and to steric restraints controlling hydride transfer to the flat, five-membered cyclic anhydrides. Since both effects favour reduction of the more hindered function, it is not possible to assess polar versus steric content of the combined effect. However, if polar influence is a major factor, preferential reduction of the carbonyl group adjacent to a tertiary carbon atom should be observed in the reduction of diacids and diesters.

A search of the literature provided a few examples of such reductions but the results reported were not encouraging in view of the above stated considerations. In the study of the  $\text{LiAlH}_4$  reduction of camphoric acid 42 and 1-ethyl-1-butylglutaric acid 43, Noyce and Denney<sup>65</sup> found that the former gave only the corresponding diol 42c and recovered starting material, whereas the latter yielded a mixture of the original acid 43 (14%), diol 43c and a lactone (40%) identified as 1-ethyl-1-butyl- $\gamma$ -valerolactone 43b. Similarly, selective reduction of the primary carbomethoxy group (44b, 53% yield) of the dimethyl ester of cis-2-methyl-2-carboxycyclohexaneacetic acid 44 was reported by Bachman and Dreiding.<sup>66</sup>



Since we had observed the opposite trend in the reduction of cyclic anhydrides, we decided to examine the degree of regioselectivity in the reduction of carboxylic diacids and diesters corresponding to some of the anhydrides already investigated. The reduction of diacids 3c and 19c yielded, apart from recovered starting material, mixtures of lactones. In both cases the lactone obtained in major yield (see Table 5) corresponded to reduction of the carboxyl group adjacent to the tertiary carbon atom. Under comparable reaction conditions diacid 11c was not reduced. Reduction of the diisopropyl ester of 2,2-dimethylsuccinic acid 45 proved to be the most regioselective, yielding only one reduction product, 2,2-dimethyl- $\gamma$ -butyrolactone 3a. In terms of yields and regioselectivity observed, reduction of dicarboxylic acids does not have the same synthetic potential as the reduction of the corresponding cyclic anhydrides\* (see Table 5). However, the ratio of lactones obtained in the reduction of the two diacids 3c and 19c is of considerable interest in view of the mechanism of nucleophilic addition to the carbonyl function.

Recent theoretical and experimental<sup>39</sup> evidence (see Chapter 2, page 18) point to a non-perpendicular approach in nucleophilic additions to a carbonyl group. Baldwin's modification<sup>40</sup> implies that the path of an incoming nucleophile may be further restricted when neighbouring atoms such as N (amide function) or O (ester or carboxylic function) are present.

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\* When the carboxylic groups are separated by more than three carbon atoms, selective reduction through the intermediate cyclic anhydride is not useful. In cases where the groups are attached to carbon atoms of varying substitution it should be possible to regioselectively reduce the corresponding diester.

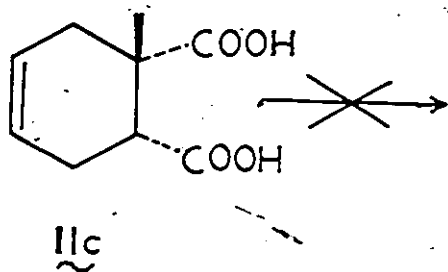
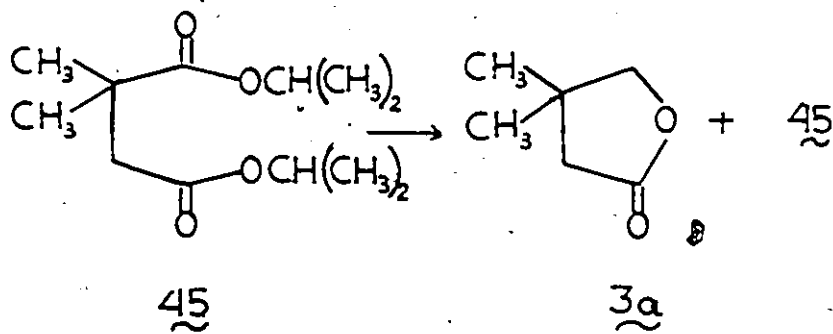
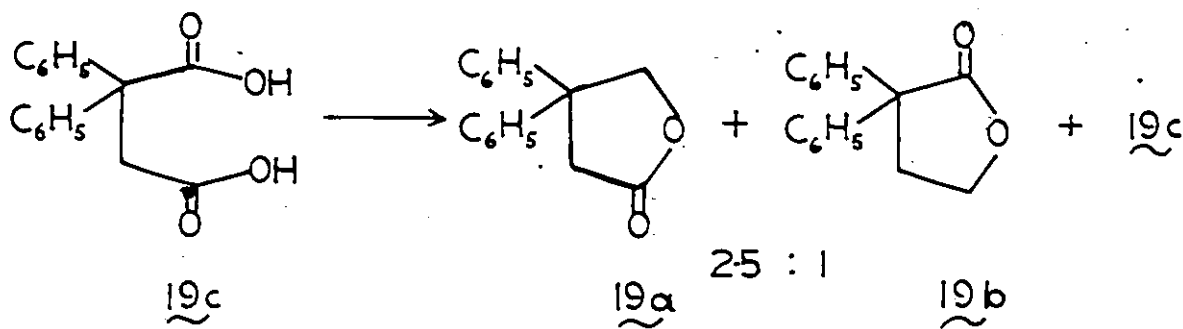
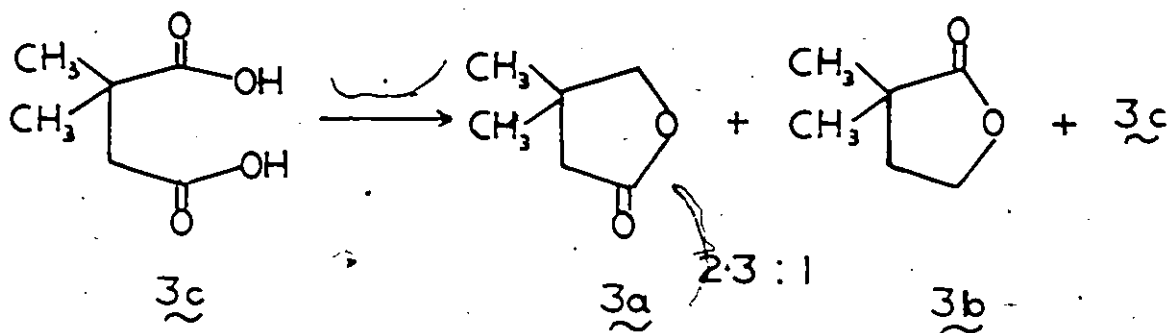
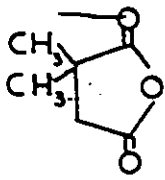
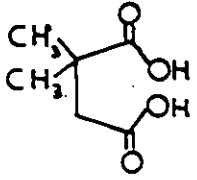
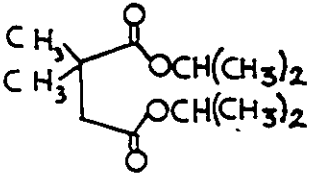
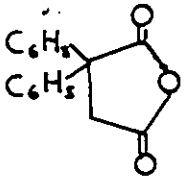
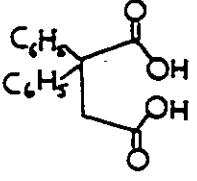
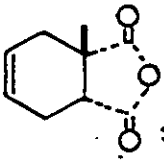
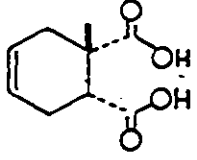


TABLE 5. Product distribution in  $\text{LiAlH}_4$  reductions

Compound	No.	Total yield	Recovered starting material %	Lactonic product %	Ratio of product a:b
	3	80	10	70	19 : 1
	3c	84	58	26	2.3 : 1
	45	67	45	22	a only
	19	89	0	89	a only
	19c	81	41	40	2.5 : 1
	11	75	0	75	a only
	11c	85	85	0	—

We have suggested<sup>22</sup> that these steric restrictions should be considered in explaining the preferential reduction of the more sterically hindered carbonyl group in unsymmetrical cyclic anhydrides. However, the results of metal hydride reductions of several cyclic anhydrides indicate that regioselectivity of these reactions is also controlled by electronic factors (see Chapter 4, page 30). In five-membered cyclic anhydrides such as 2,2-dimethylsuccinic anhydride 3 or 2,2-diphenylsuccinic anhydride 19 steric effects promote reduction of the more hindered carbonyl group. The situation is clearly not comparable in the diacids and diesters.

As can be expected diacids 3c and 19c are capable of forming strong intramolecular hydrogen bonds.. The hydrogen-bonded ring is large

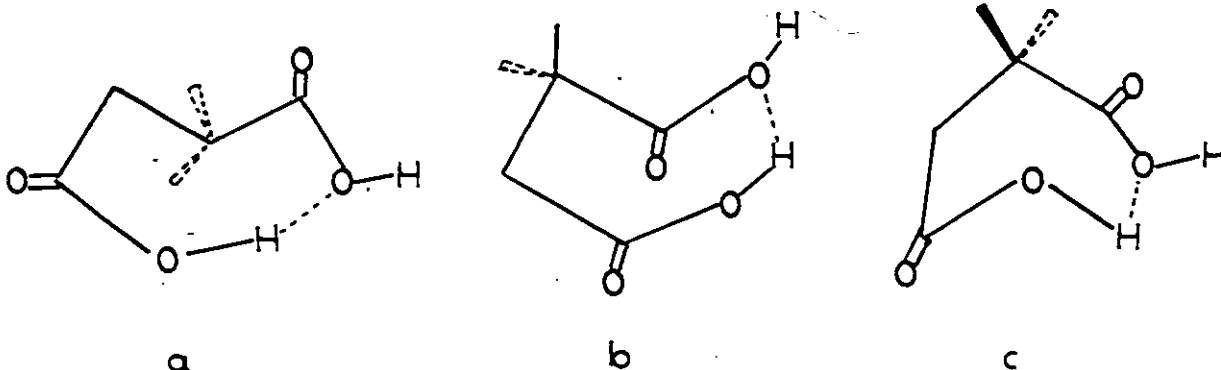
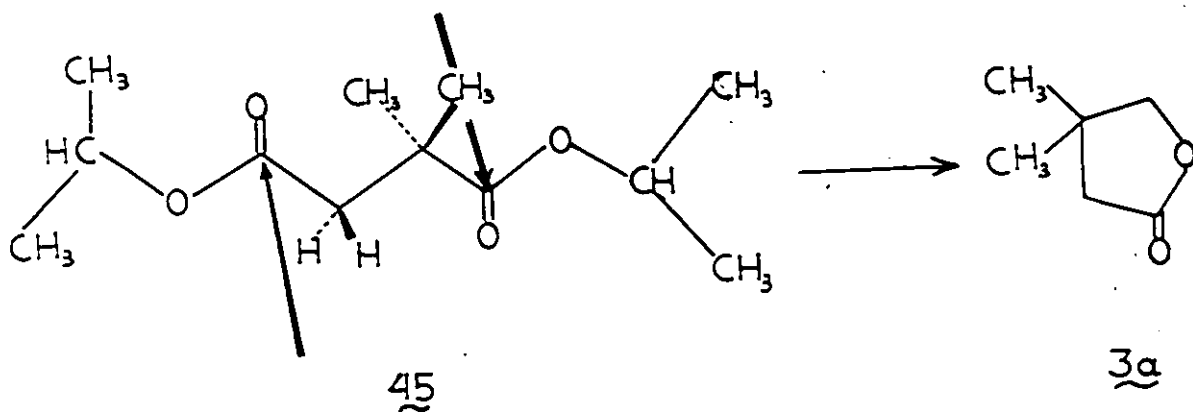


Figure 29. The ring resulting from hydrogen bonding may assume a variety of configurations. For example: in a and b, illustrated above, both carbonyl groups are relatively open to nucleophilic attack; in c the methyl substituent hinders quite effectively the favoured path of nucleophilic approach leading to either of the two carbonyl functions.

and flexible (Figure 29) and, consequently, the steric restrictions encountered by the nucleophile are different from those illustrated for the flat and rigid anhydrides (see Chapter 3, page 26).

Electronic factors, however, remain the same and are probably responsible for the preferential reduction of the carbonyl group adjacent to the tertiary carbon atom. The primary carboxyl group in diester 45 appears to be sterically more accessible to nucleophilic attack than the



tertiary group. Since the only reduction product observed is the lactone resulting from reduction of the more encumbered carboxyl function it appears that the site of reduction is fixed from the initial association of Li<sup>+</sup> cation with the more basic of the two oxygen atoms (of the carbonyl groups).

In conclusion, these results suggest that electronic effects play an important role in controlling regioselectivity in metal hydride reduction of diester 45 where electronic influences compete against steric hindrance. In this particular case the steric restrictions are not severe and therefore electronic effects dominate the regioselectivity of the reaction.

We do not wish to comment on the reductions reported<sup>65,66</sup> for the compounds 43 and 44 discussed in the introduction of this chapter, since we have not repeated these experiments.

CHAPTER 9

SYNTHESIS OF MODEL ANHYDRIDES AND ANALYSIS OF THE  
REDUCTION PRODUCTS

In the preceding chapters we have attempted to rationalize the regioselectivity observed in the reduction of a variety of cyclic anhydrides representing diverse structural types. Our mechanistic proposals are based on the degree of regioselectivity observed and for this reason it was important to analyze as accurately as possible the ratio of isomeric lactones formed.

G.l.c. analysis was found to be the most reliable method for ascertaining that only one lactone was formed or for determining the ratio of the isomers present in the reduction mixture. Unfortunately, in many cases we were unable to employ g.l.c. analysis due to the nature of lactones and the limitations of the instrument available.  $^1\text{H}$  n.m.r. analysis proved to be very helpful except in a few cases where complex overlap of chemical shifts occurred or where the crude reduction mixture contained considerable quantities of other products. Very often isolation and purification procedures altered the original ratio of the two lactones formed and it was therefore more desirable to analyze the crude reduction mixtures rather than the isolated lactonic products.

With this in mind we tried, whenever possible, to analyze the crude product by both g.l.c. and  $^1\text{H}$  n.m.r. In a few instances where  $^1\text{H}$  n.m.r. analysis was ambiguous, due to the complexity of the spectrum of the mixture, the composition of the reduction mixture was obtained

from the weights of compounds separated on thick layer chromatography plates. Often,  $^1\text{H}$  n.m.r. spectra of the lactones synthesized independently helped in the interpretation of the spectra of crude reduction products.

1. 2,2-Dimethyl-3,3-diphenylsuccinic anhydride 18

Our first attempt to prepare 2,2-dimethyl-3,3-diphenylsuccinic anhydride employed the synthetic route illustrated in Figure 30.

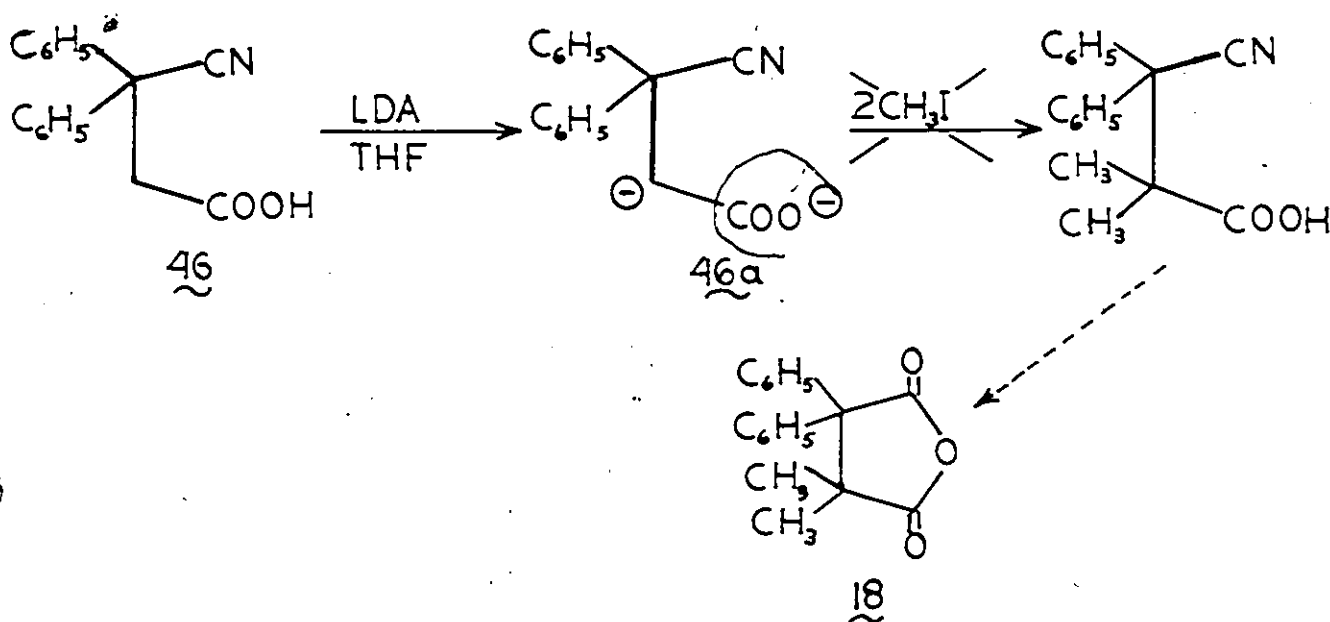
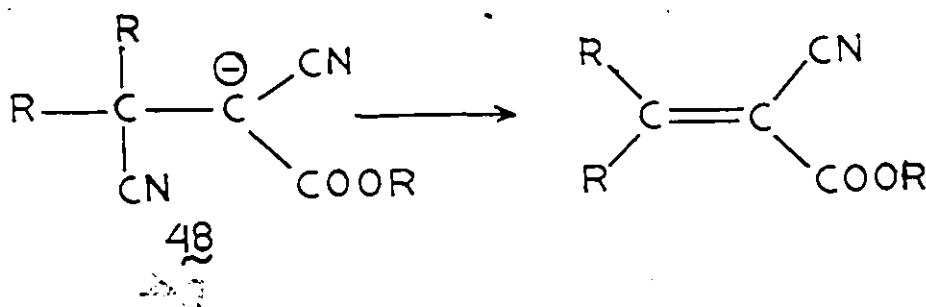
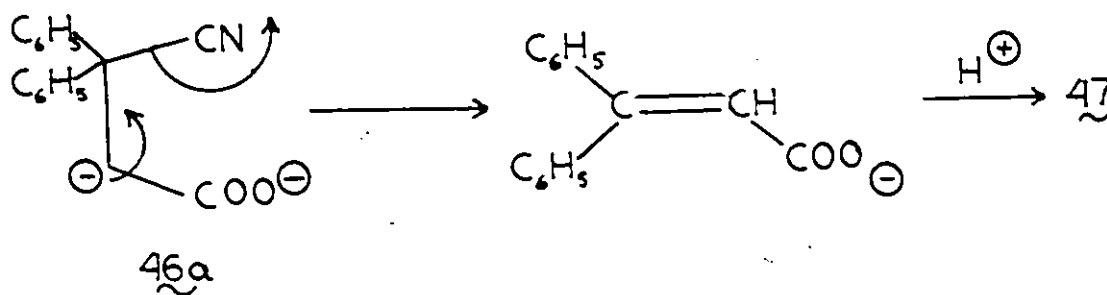


Figure 30. Proposed synthesis of 2,2-dimethyl-3,3-diphenylsuccinic anhydride.

The projected synthesis was not successful. However, we wish to mention it briefly because of a rather interesting elimination from the intermediate carbanion 46a which apparently was the reason for our failure. 3,3-Diphenyl-3-cyanopropionic acid 46 was treated with LDA in THF at  $-78^\circ\text{C}$ . Upon addition of methyl iodide followed by the usual work-up

procedure, the only product isolated was identified as 8-phenylcinnamic acid 47. A search of the literature revealed a precedent; in 1964 a group of French workers reported<sup>67</sup> a similar elimination from the related carbanion 48.



2,2-Dimethyl-3,3-diphenylsuccinic anhydride 18 was prepared by condensing diphenylacetonitrile 49 with ethyl 2-bromoisobutyrate 50. The intermediate 2,2-dimethyl-3,3-diphenyl-3-cyanpropionic acid 51, upon hydrolysis, carried out in refluxing concentrated HCl, gave directly the anhydride 18. The corresponding diacid could not be isolated.<sup>68</sup> Reduction of anhydride 18 with LiAlH<sub>4</sub> or with excess of NaBH<sub>4</sub> gave lactone 18a, m.p. 130-132°C. An excellent yield of hemiacetal 52 was the result of incomplete reduction with NaBH<sub>4</sub>. Compound 52 reacted with excess NaBH<sub>4</sub> (or with LiAlH<sub>4</sub>) to give lactone 18a. The



isomeric lactone 18b has been described in the literature<sup>69</sup> and the melting point is some 10° lower than that observed for 18a.

In order to establish more firmly the assigned structure, lactone 18a was reduced ( $\text{LiAlH}_4$ ) to the corresponding diol 53, which was in turn cyclized to 3,3-dimethyl-4,4-diphenyltetrahydrofuran 54. Comparison of the chemical shifts for the methylene groups ( $-\text{CH}_2-\text{O}$ ) in the three related lactones (3a, 18a and 19a) and the cyclic ether 54 confirmed the structure 18a assigned to the reduction product (Figure 31).

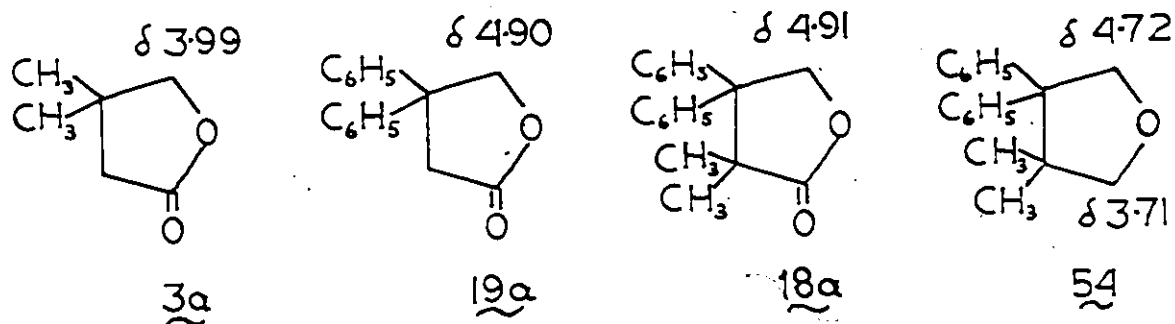
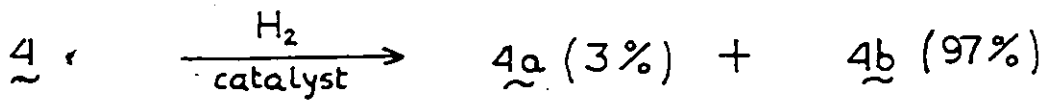
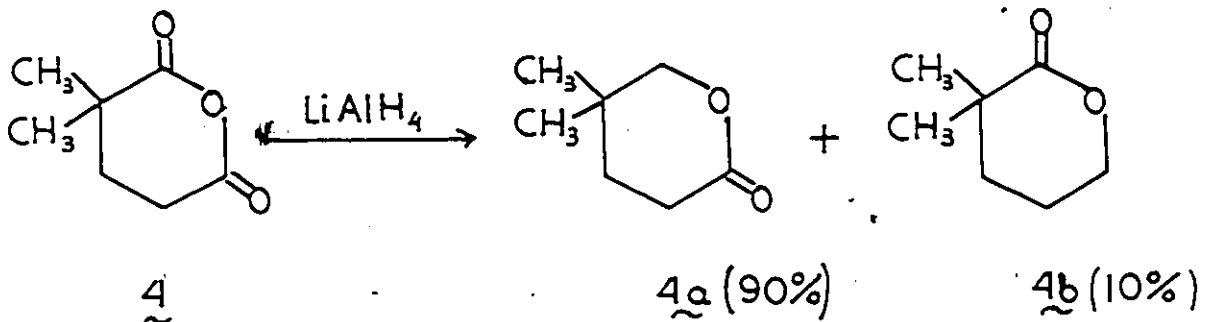
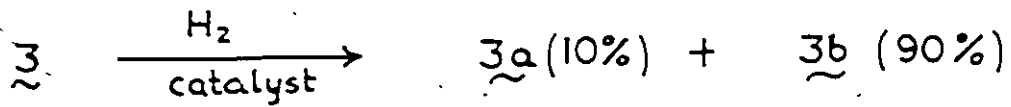
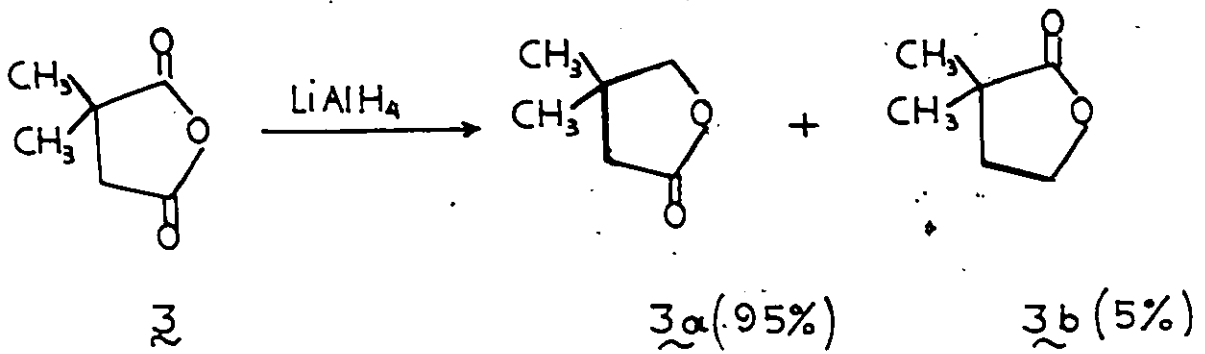
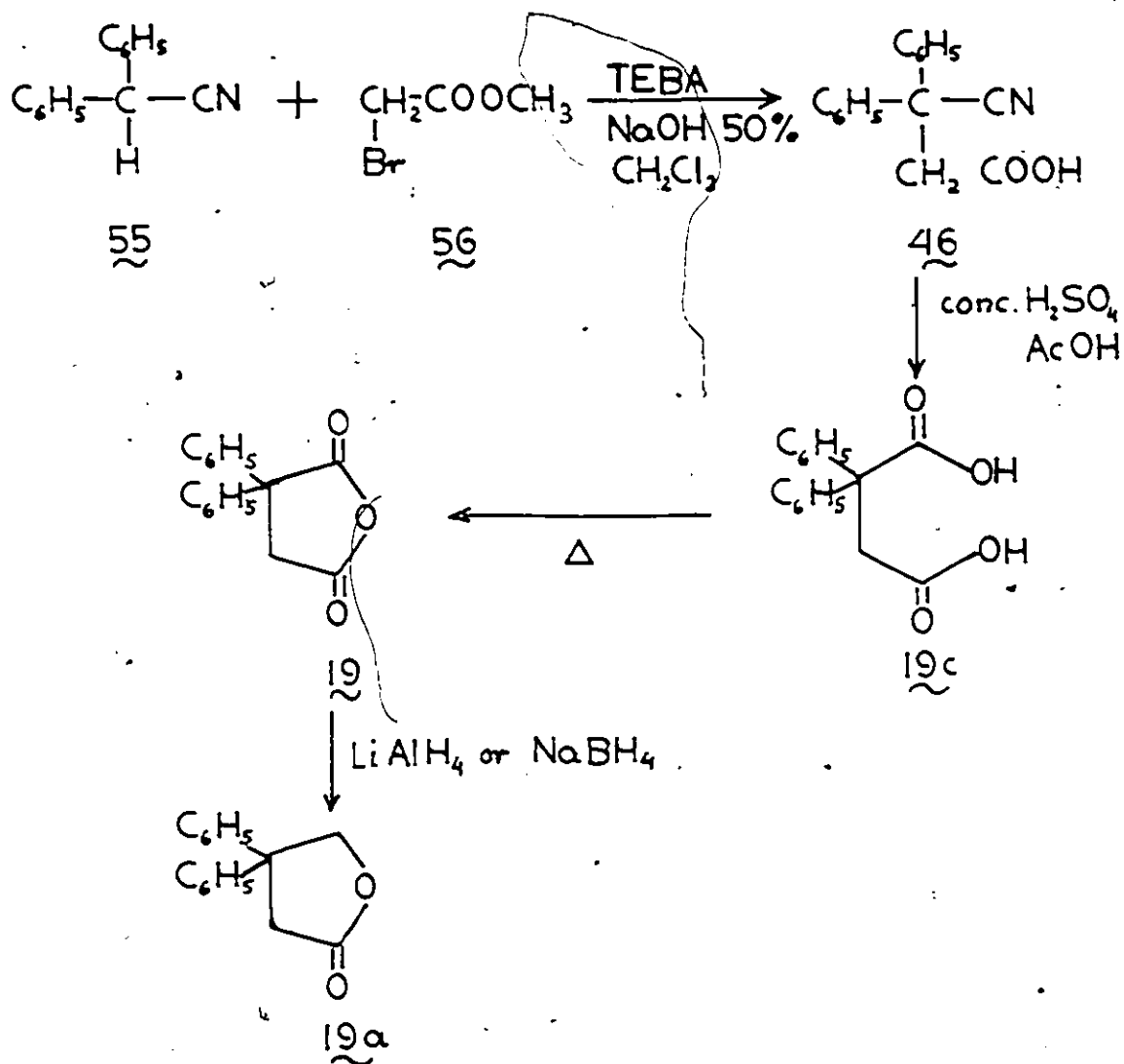


Figure 31. Chemical shifts for the methylene group ( $-\text{CH}_2-\text{O}$ ) in 3a, 18a, 19 and 54.

## 2. 2,2-Dimethylsuccinic and 2,2-dimethylglutaric anhydride

Product ratios obtained from  $\text{LiAlH}_4$  reduction of 2,2-dimethylsuccinic anhydride 3 and 2,2-dimethylglutaric anhydride 4 were determined by g.l.c. and  $^1\text{H}$  n.m.r. analyses. 3,3-Dimethyl- $\gamma$ -butyrolactone 3a and 4,4-dimethyl- $\delta$ -valerolactone 4a were compared with the isomeric lactones 3b and 4b obtained from the catalytic hydrogenation (with  $\text{RuCl}_2[(\text{C}_6\text{H}_5)_3\text{P}]_3$  as a catalyst) of anhydrides 3 and 4.





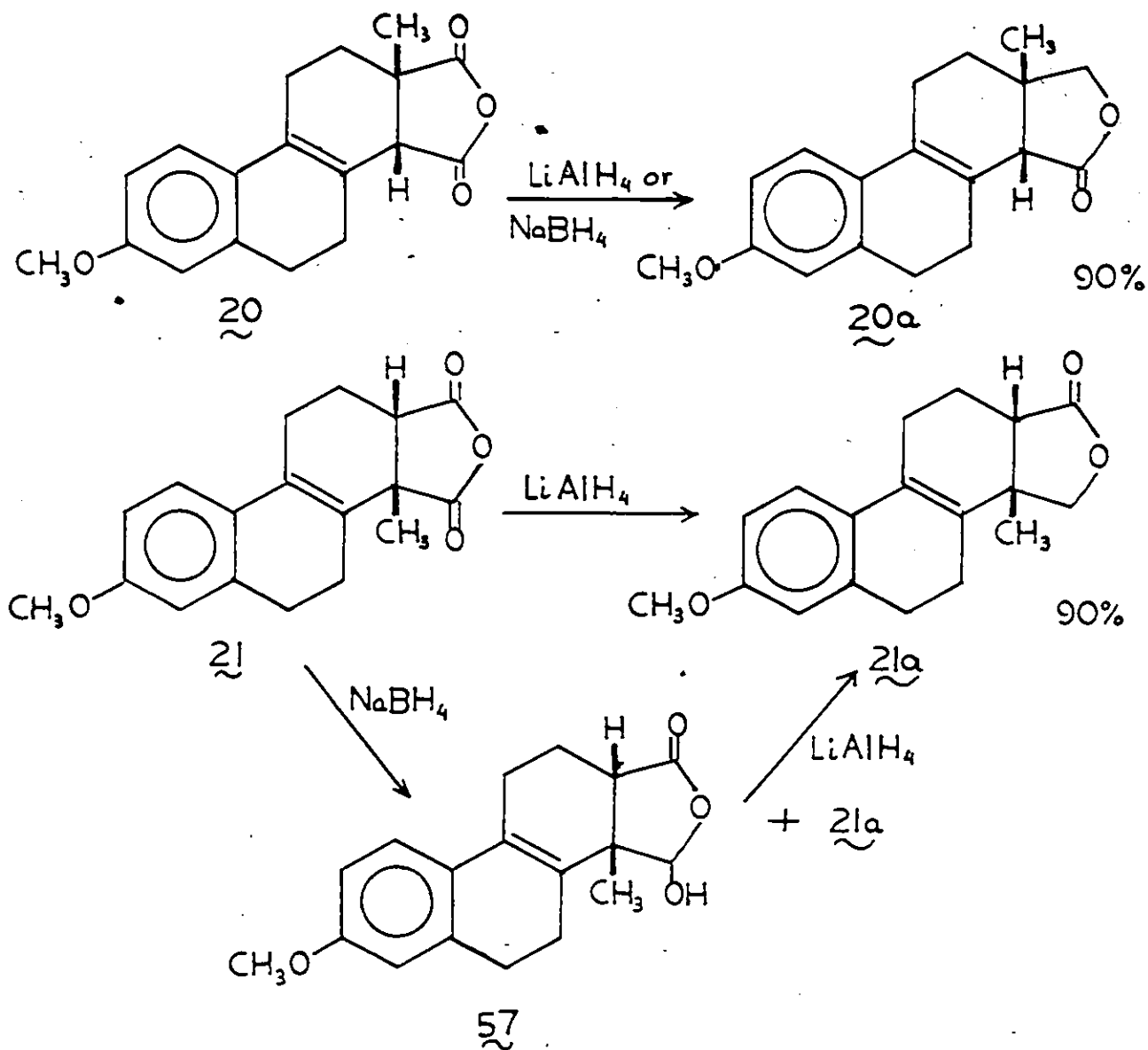
### 3. 2,2-Diphenylsuccinic anhydride 19

2,2-Diphenylsuccinic acid 19c was prepared according to the method of Małosza<sup>70</sup> by condensing, under phase transfer conditions, diphenyl acetonitrile 55 with methylbromoacetate 56. Triethylbenzyl ammonium chloride (TEBA chloride) was used as a catalyst. The product 46 was hydrolyzed to give the diacid 19c which, upon gentle heating

cyclized to 19. Reduction of anhydride 19 with  $\text{LiAlH}_4$  or with  $\text{NaBH}_4$  produced a high yield of 3,3-diphenyl- $\gamma$ -butyrolactone 19a.

4. Steroidal anhydrides 20 and 21\*

Reduction of the steroidal anhydride 20 with  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  produced only lactone 20a in 90% yield. The  $^1\text{H}$  n.m.r. spectrum of the



\*Prepared by P. Crosby in this laboratory.

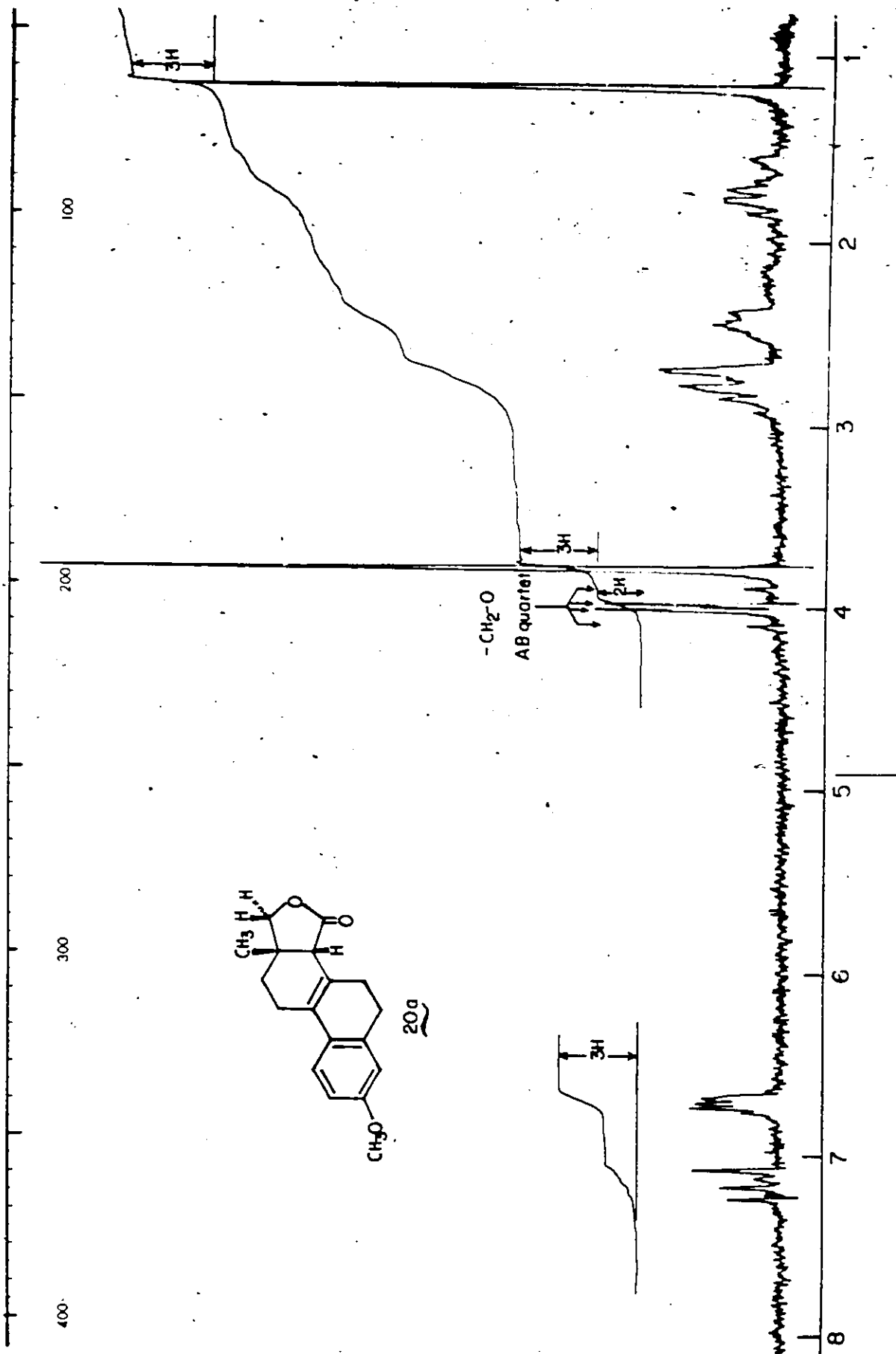


Figure 32. The n.m.r. spectrum of the reduced tetracyclic Diels-Alder adduct 20a.

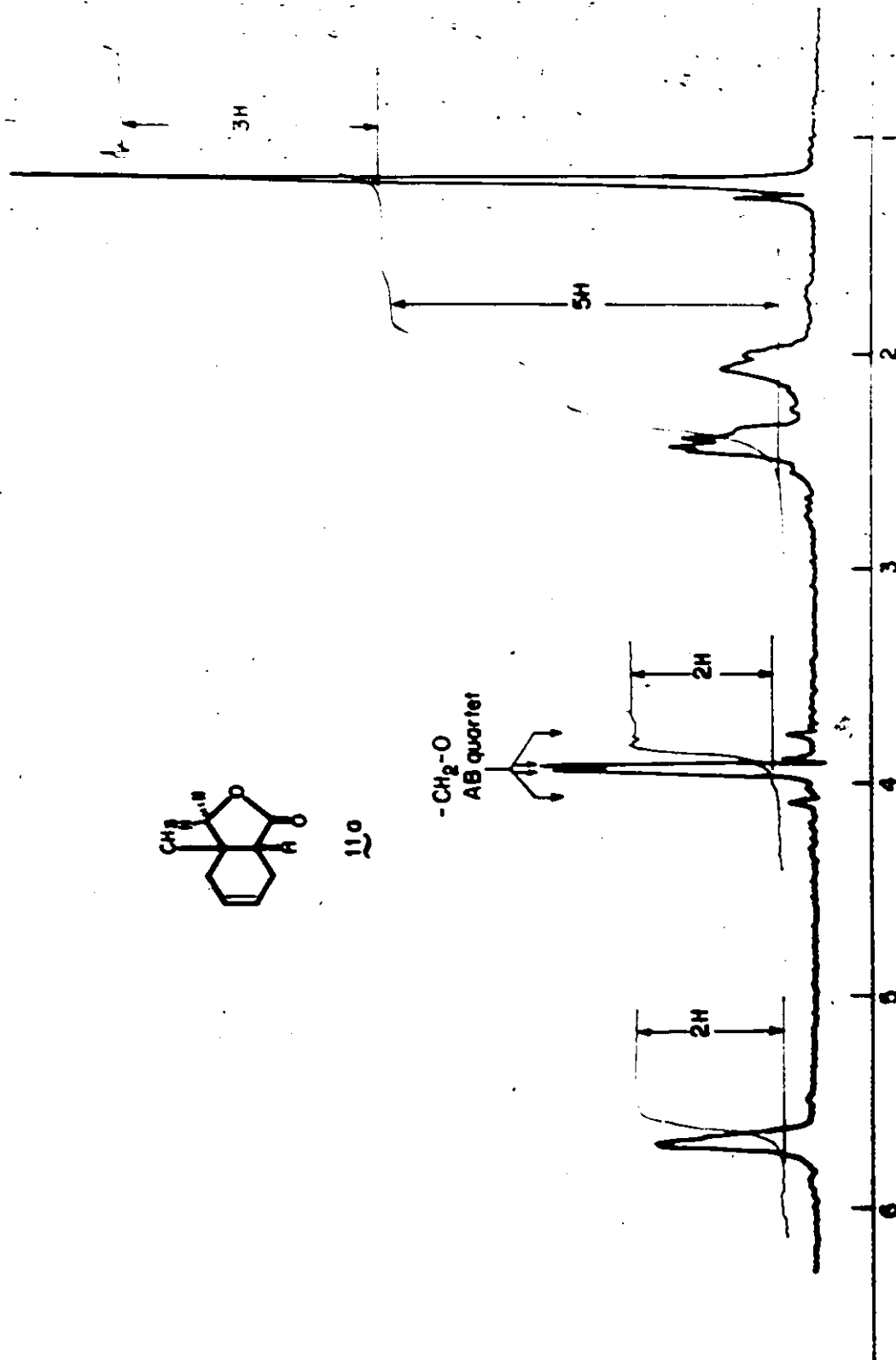


Figure 33. The n.m.r. spectrum of *cis*-1-methyl-1-hydroxymethyl-cyclohex-4-ene carboxylic acid- $\gamma$ -lactone 11a.

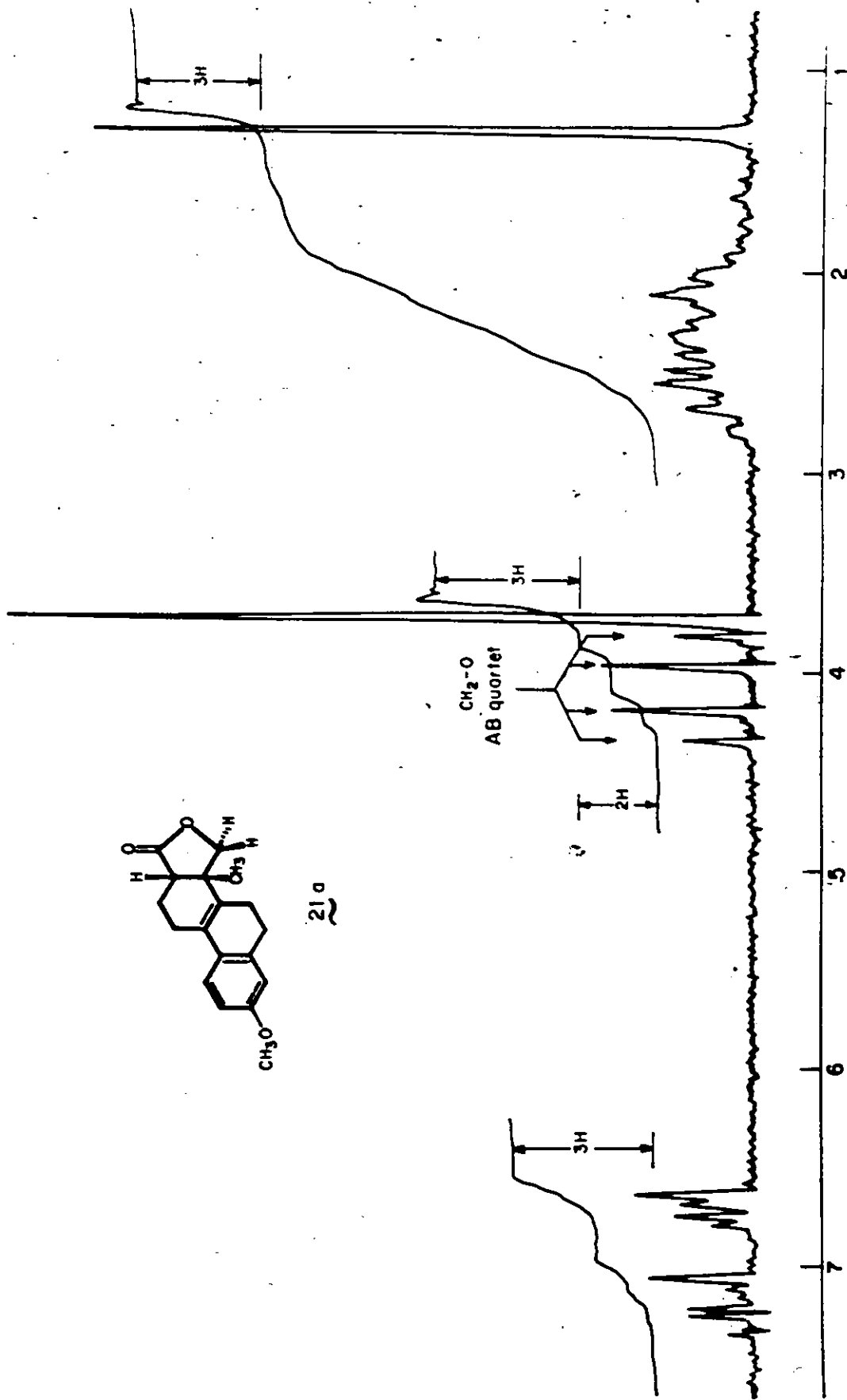
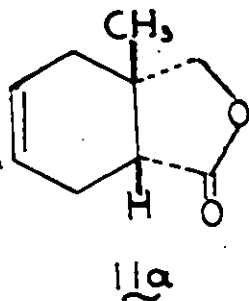


Figure 34. The n.m.r. spectrum of the reduced tetracyclic Diels-Alder adduct 21a.

compound 20a showed a characteristic AB quartet for the methylene group ( $-\overset{\text{O}}{\text{C}}-\text{CH}_2-\text{O}$ , Figure 32) resembling closely the AB quartet observed for the methylene group in compound 11a<sup>15</sup> (Figure 33).



Anhydride 21 was reduced with  $\text{LiAlH}_4$  to lactone 21a. Reaction of 21 with  $\text{NaBH}_4$  yielded a mixture of the lactone 21a and hemiacetal 57, which could be reduced readily with  $\text{LiAlH}_4$  (or excess  $\text{NaBH}_4$ ) to 21a. The n.m.r. spectrum of the product 21a showed an AB quartet due to the methylene protons ( $\text{CH}_2-\text{O}$ , Figure 34).

#### 5. Camphoric anhydride 5

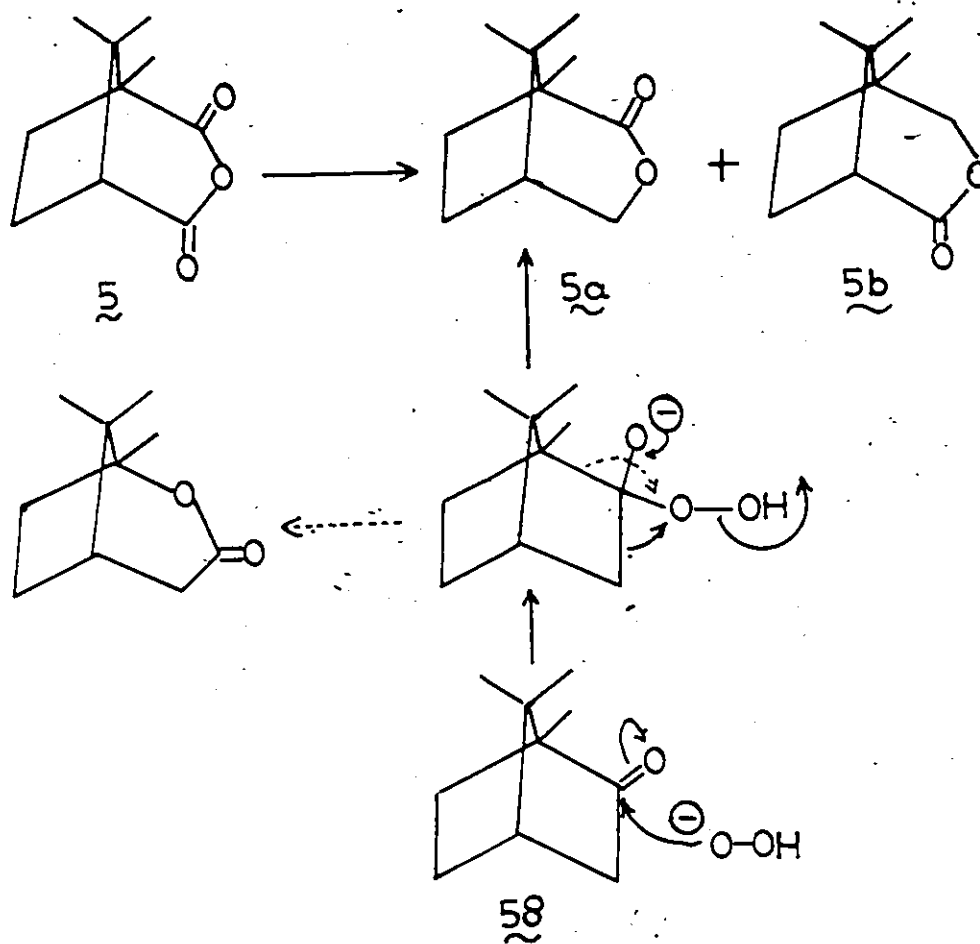
Camphoric anhydride 5 was reduced with  $\text{LiAlH}_4$ . G.l.c. analysis of the product showed the presence of two lactones and of unreacted anhydride 5. The isomeric campholides 5a and 5b were separated by column chromatography. To confirm the identity of 5a and 5b,  $\alpha$ -campholide 5a was independently synthesized by Baeyer-Villiger oxidation of camphor 58.

#### 6. Bridged, tricyclic anhydrides 22 and 23

Anhydrides 22 and 23 were prepared\* respectively by Diels-Alder addition of cyclopentadiene and 1,3-cyclohexadiene to citraconic anhydride. Reductions with  $\text{NaBH}_4$  and  $\text{LiAlH}_4$  produced lactones 22b and 23b in excellent

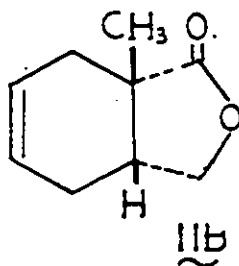
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\* Prepared by P. Crosby in this laboratory.

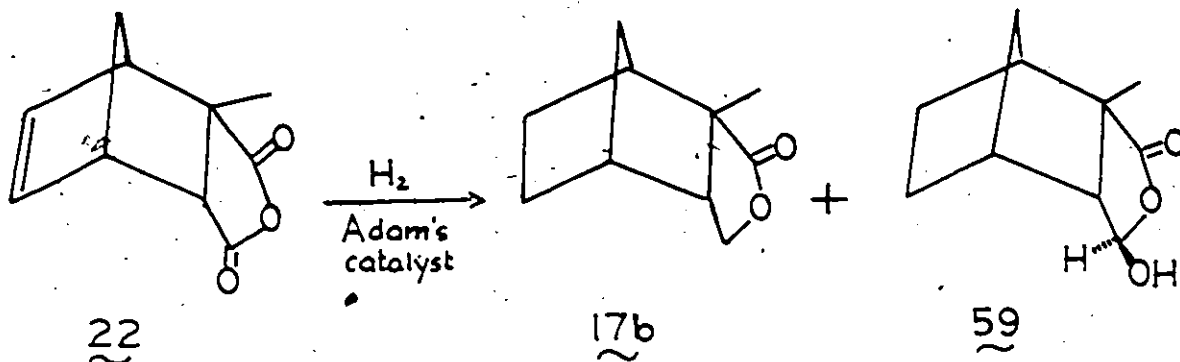


yields. Elemental analyses, i.r. and  $C^{13}$  n.m.r. spectra were consistent with the assigned structures. The  $^1H$  n.m.r. of both lactones showed a complex multiplet consisting of a characteristic four-peak (1H) and three-peak (1 H) pattern\* for the methylene protons (-CH-CH<sub>2</sub>-O-). The

\* Bloomfield and Lee<sup>15</sup> described such a pattern for the methylene protons in lactone 11b.



lactone 17b and hemiacetal 59, prepared by catalytic hydrogenation of anhydride 22, exhibited n.m.r. spectra closely resembling<sup>13</sup> the n.m.r. spectra obtained for the corresponding unsaturated compounds 22b and 60.



Nonetheless, since the results of reduction of 22 and 23 were contrary to our expectation, we attempted to provide further evidence for the assigned structures 22b and 23b. The alternating LiAlH<sub>4</sub> and LiAlD<sub>4</sub> reductions of the anhydride 22 (as shown in Figure 35) furnished isomeric diols 62 and 63. (The same reduction scheme was repeated for 23 and the results obtained paralleled those described for the anhydride 22). Since free rotation about the C-C bonds in diols 62 and 63 is prevented by hydrogen bonds, the protons of the methylene groups are non-equivalent. Thus, we observed, as expected, an AB quartet for the methylene protons (-C-CH<sub>2</sub>-O) in 62 and a complex multiplet for the methylene group (-CH-CH<sub>2</sub>-O) in compound 63. The characteristic patterns (AB and ABX) were clearly discernible in the n.m.r. spectra of the crude corresponding ethers prepared by warming the diols with HBr solution. The n.m.r. spectra of 22b, 23b, 61, 62 and 63 are reproduced in Figures 36, 37, 38, 39 and 40.

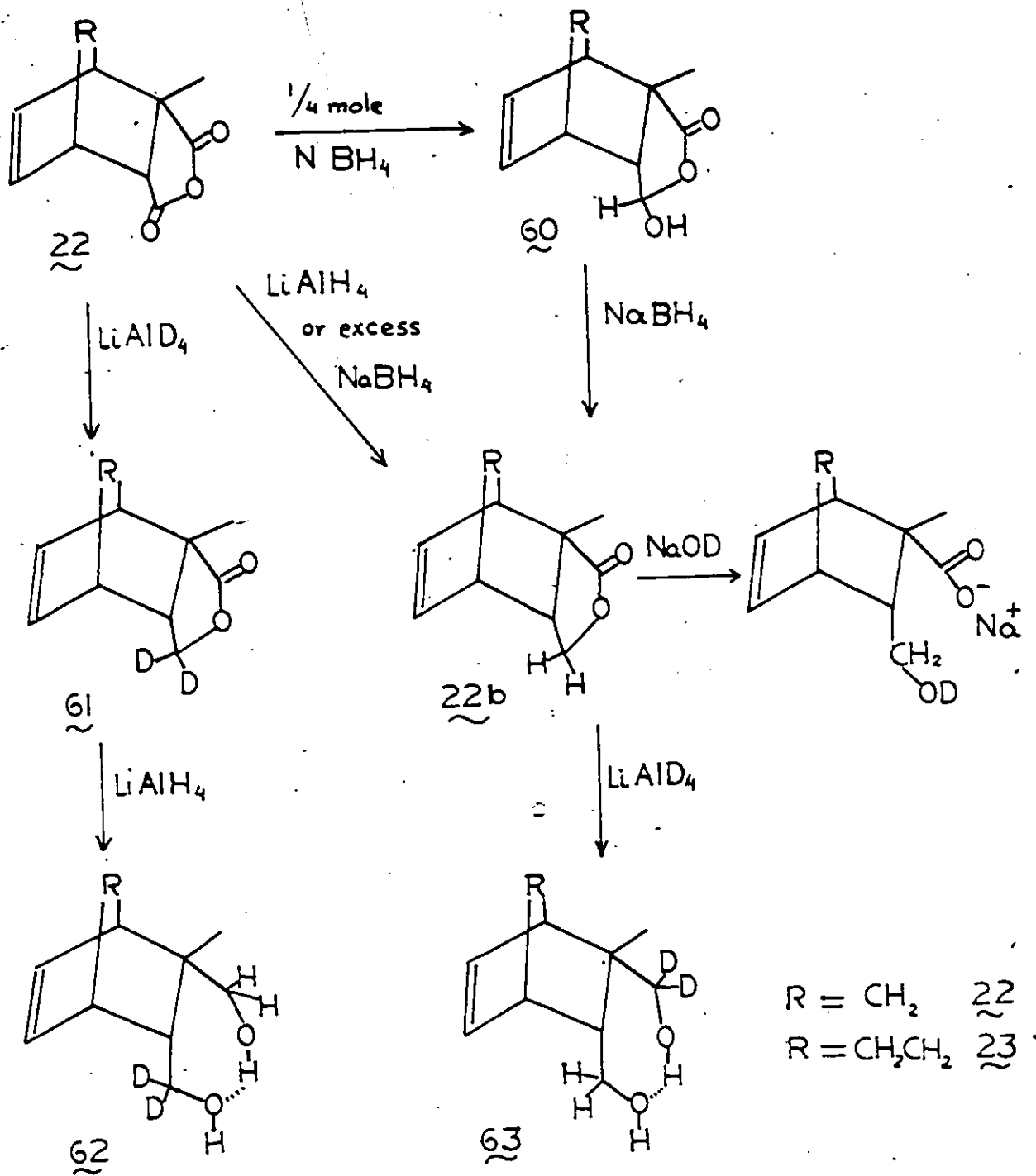


Figure 35. The synthesis of deuterated lactones and diols.

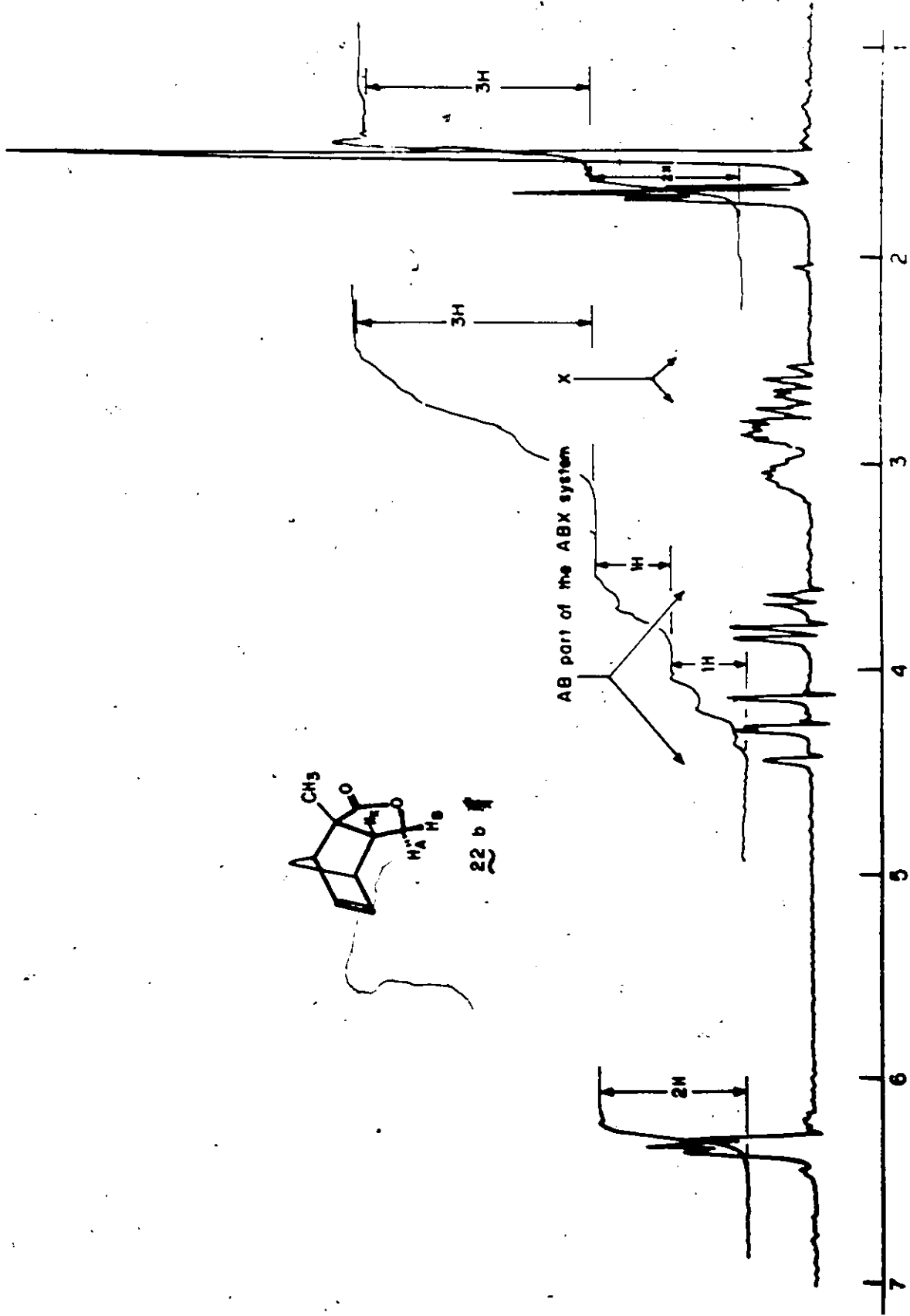


Figure 36. The n.m.r. spectrum of exo-2-methylnorborn-5-ene-endo (3-methyl-2-carbo-3a) lactone 22b.

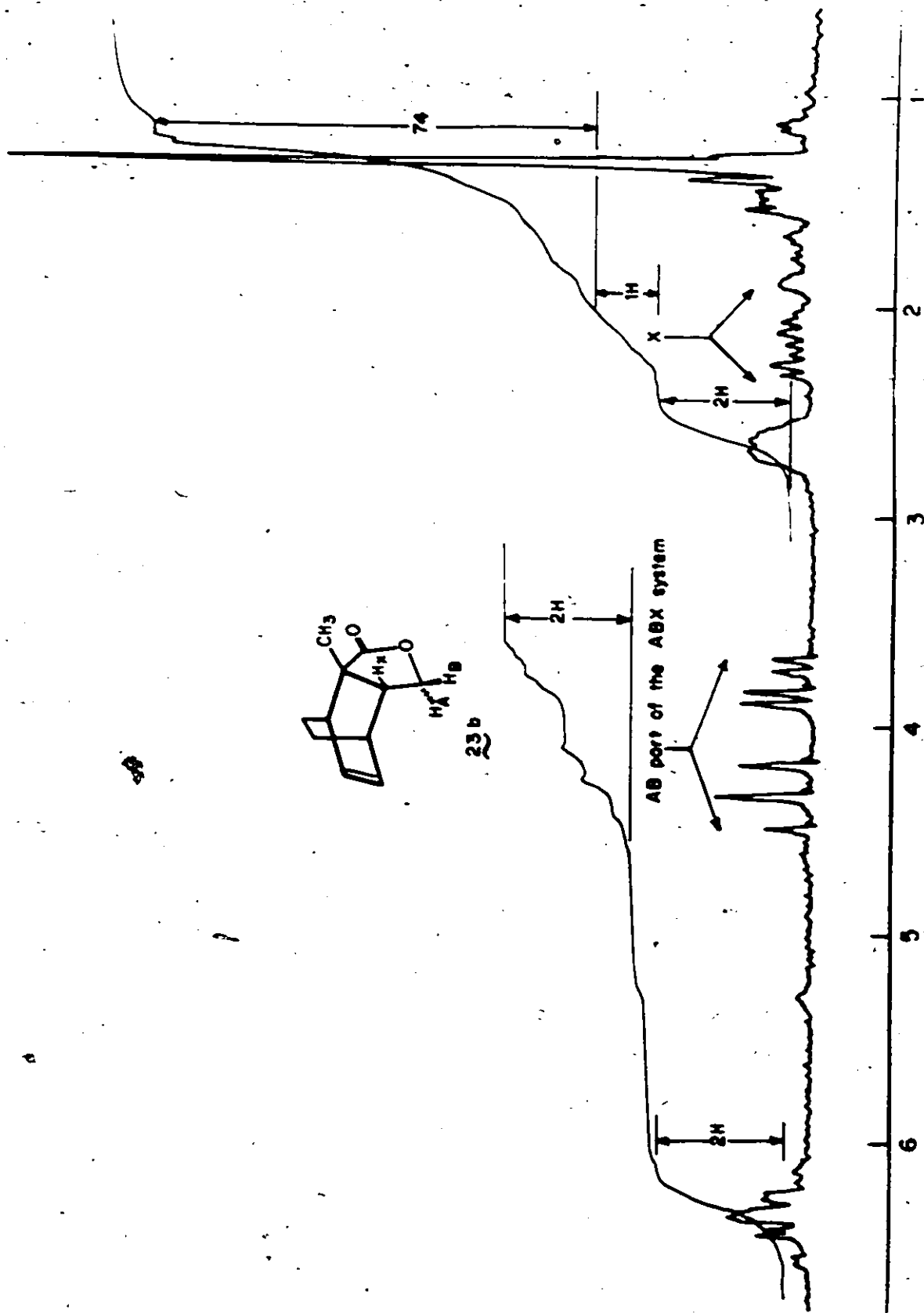


Figure 37. The n.m.r. spectrum of exo-2-methylbicyclo[2,2,2]oct-5-ene-endo (3-methyl-2-carbo-3a) lactone 23b.

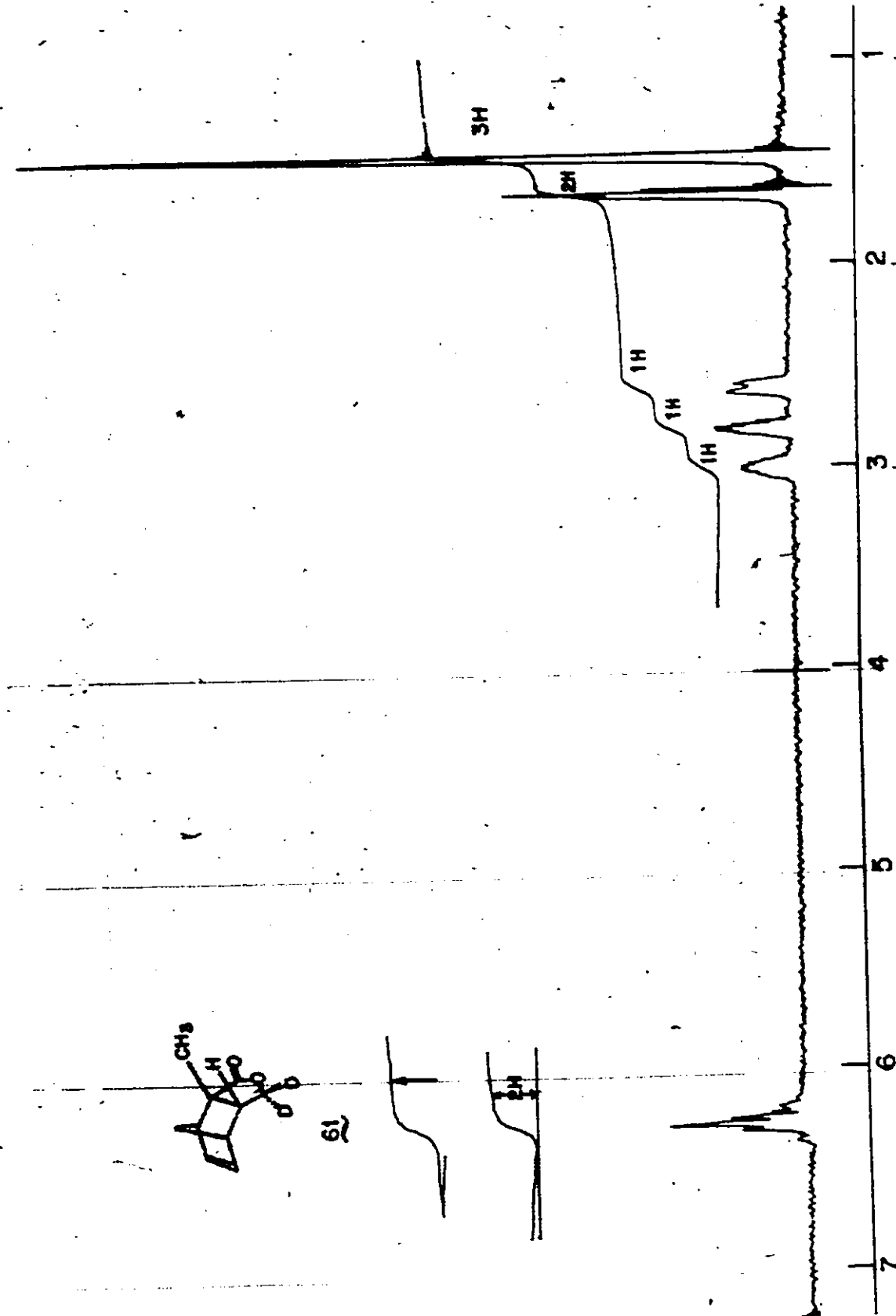


Figure 38. The n.m.r. spectrum of exo-2-methylnorborn-5-ene-endo-(5-dideutero-3-methyl-2-carbo)- $\gamma$ -lactone 61.

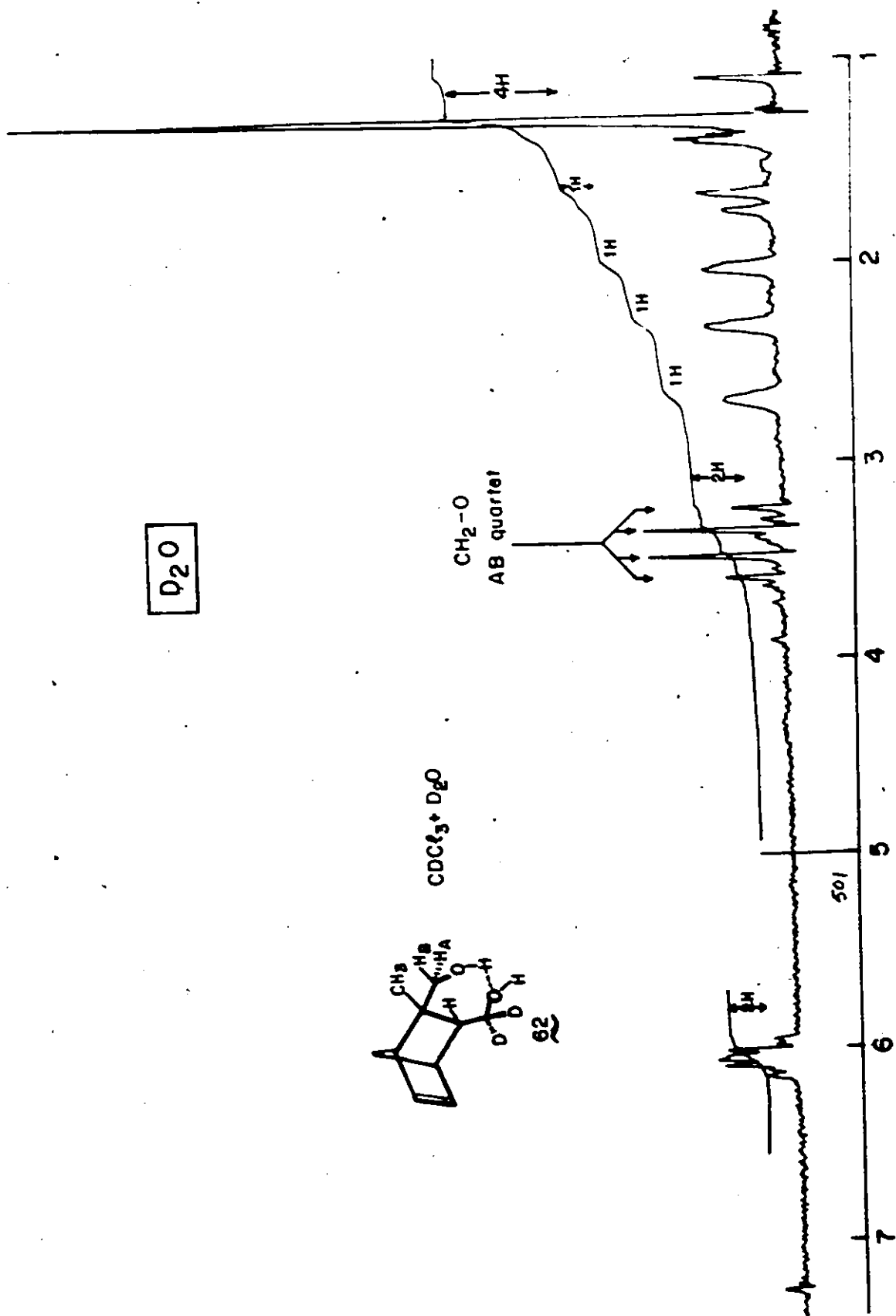


Figure 39. The n.m.r. spectrum of the product of LiAlH<sub>4</sub> reduction of the lactone 61.

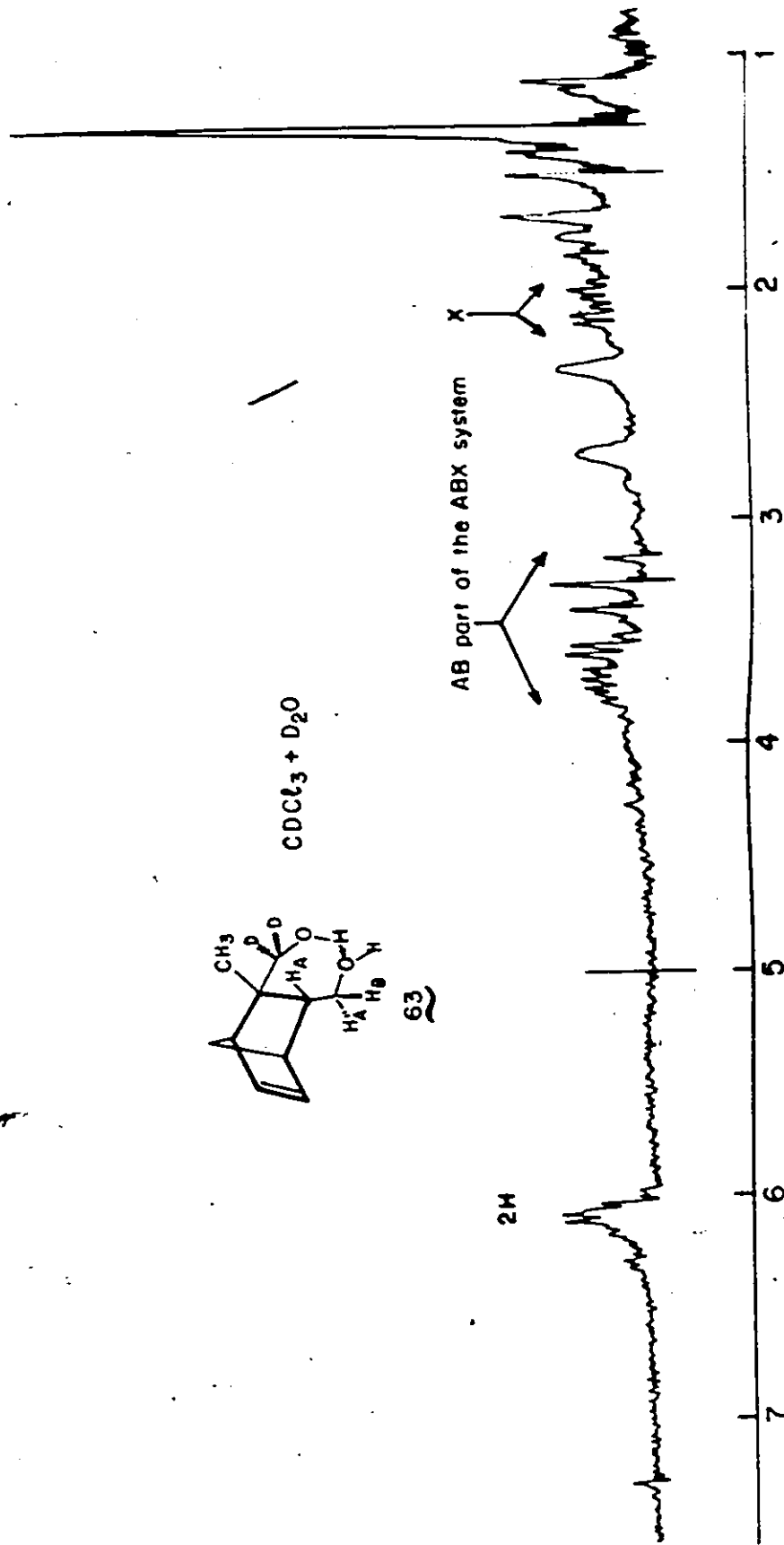
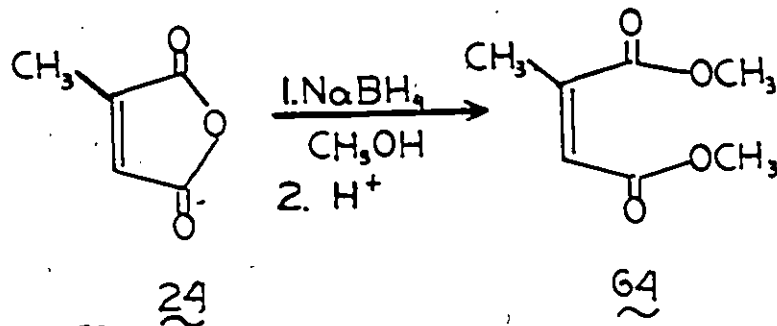


Figure 40. The n.m.r. spectrum of the product of  $LiAlH_4$  reduction of the lactone 22b.

7. Citraconic anhydride 24.

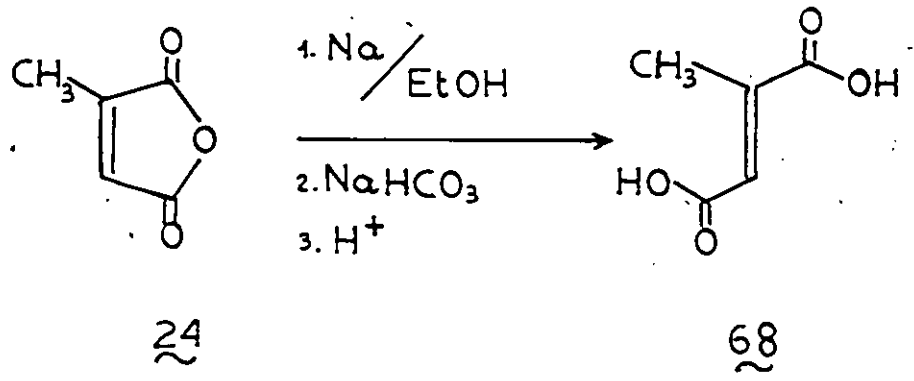
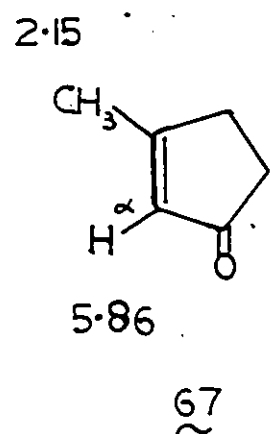
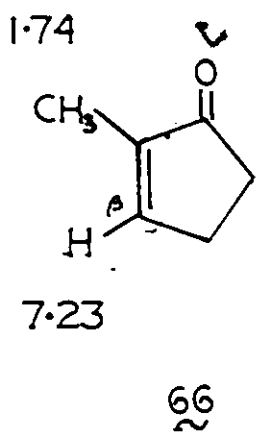
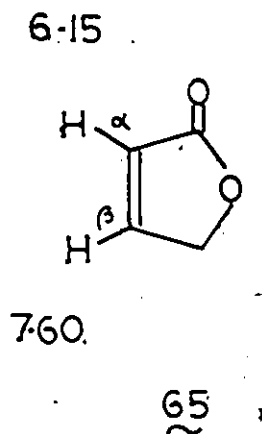
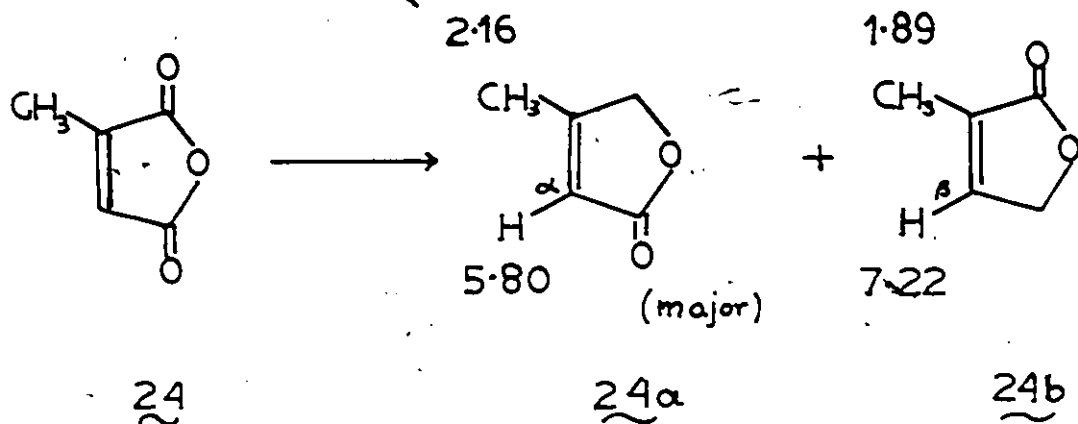
Reaction of citraconic anhydride 24 with  $\text{NaBH}_4$  in methanol gave the diester 64 as principal product and only traces of the lactone 24a and citraconic acid could be detected in the crude product.



Citraconic anhydride was reduced to lactone 24a with  $\text{LiAlH}_4$  in THF or  $\text{NaBH}_4$  in DMF. A small quantity of what we suspect to be isomeric lactone 24b could be inferred from examination of the  $^1\text{H}$  n.m.r. spectrum of the crude product (Figure 41).

The assignment of structure 24a to the lactone isolated was based on analogy to the related five-membered cyclic lactone and ketones (65, 66 and 67). The resonances corresponding to protons  $\alpha$  and  $\beta$  to the carbonyl group in lactone 65 show that proton  $\beta$  is shifted downfield.<sup>71</sup> A similar downfield shift of the proton  $\beta$  is observed in five-membered cyclic, conjugated ketone 66.<sup>72</sup> The chemical shifts for allylic methyl group protons are also informative (see 66 and 67).<sup>72</sup>

Reaction of citraconic anhydride with Na in absolute ethanol gave mesaconic acid 68 as the only product isolated. The spectral data and melting point of 68 were identical with those of commercially available mesaconic acid.



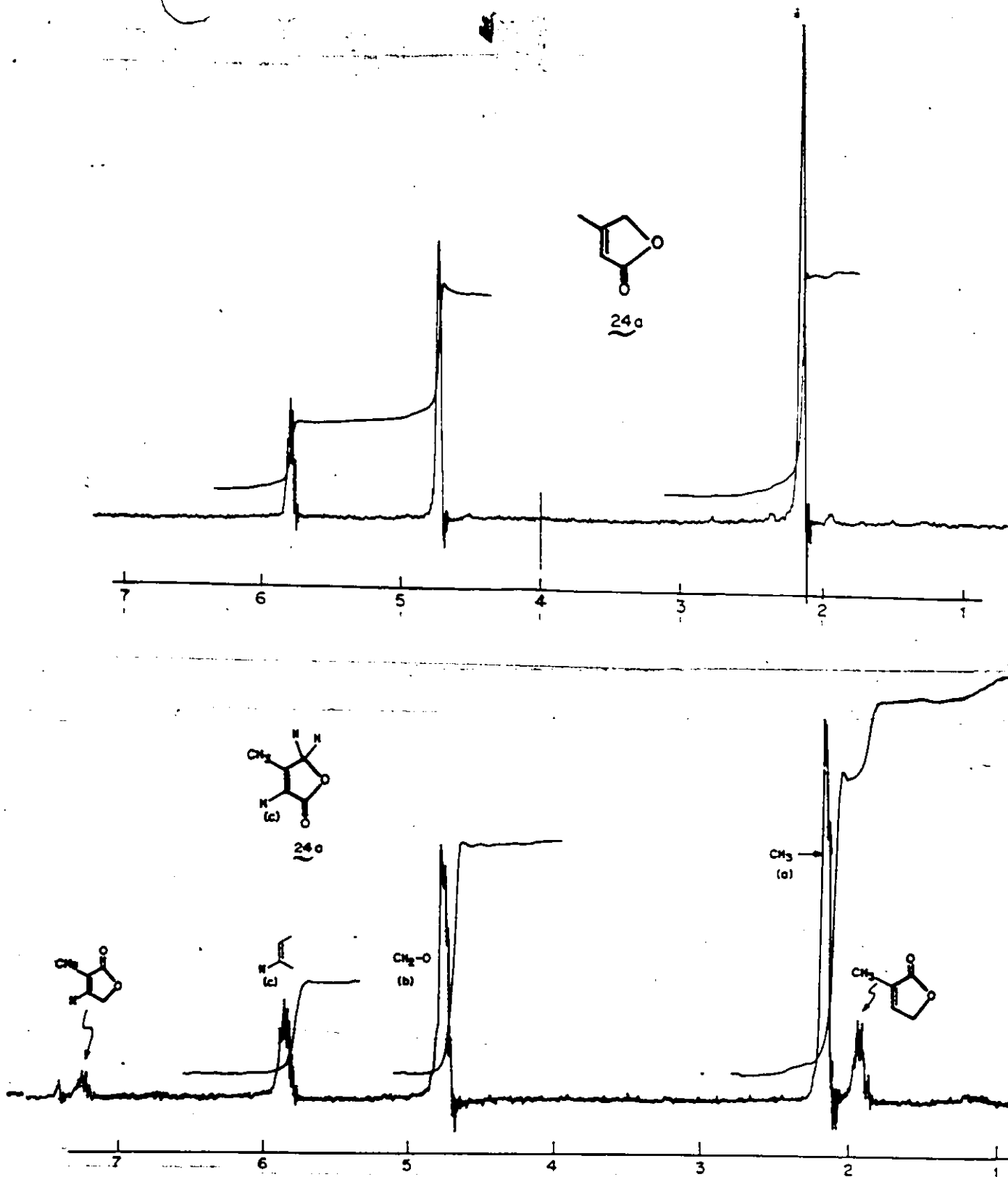
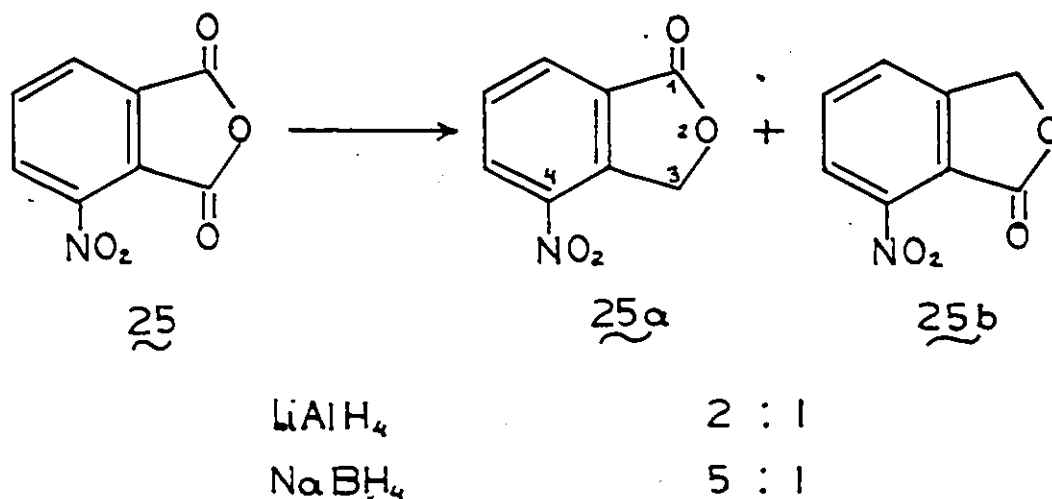


Figure 41. The n.m.r. spectrum of the product of the reduction of citraconic anhydride 24.

8. 3-Nitrophthalic anhydride 25

$\text{LiAlH}_4$  reduction of 3-nitrophthalic anhydride 25 yielded a mixture of two lactones. Proton n.m.r. analysis clearly indicated the presence of both isomers, and the ratio of 25a to 25b could be estimated reasonably accurately since the chemical shifts for the two methylene groups (in 25a and 25b) do not overlap (Figure 42). Since McAlees,



McCrindle and Sneddon<sup>62</sup> reported the formation of lactone 25a as the only lactonic product upon reduction with  $\text{NaBH}_4$ , we have reduced repeatedly 25 (under the conditions described by these authors) and we are satisfied that both lactones are in fact present. The isomeric products were separated by column chromatography and their structures confirmed by spectral data and melting points (see experimental section).

9. 4-Nitrophthalic anhydride 26

Reduction of 4-nitrophthalic anhydride 26 with  $\text{LiAlH}_4$  gave a mixture of several products. It was not possible to estimate the ratio

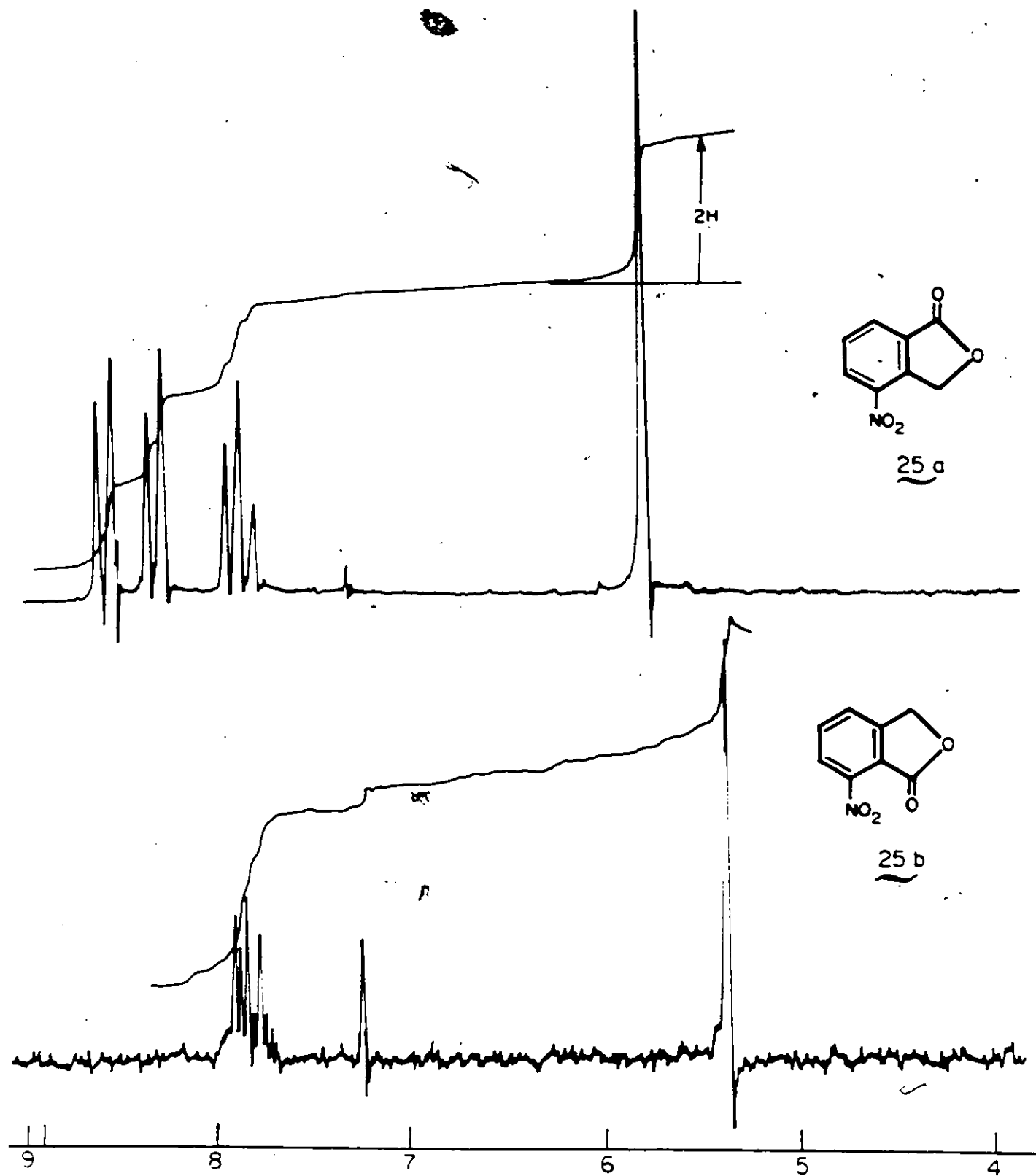


Figure 42. The n.m.r. spectra of 4-nitrophthalide 25a and 7-nitrophthalide 25b.

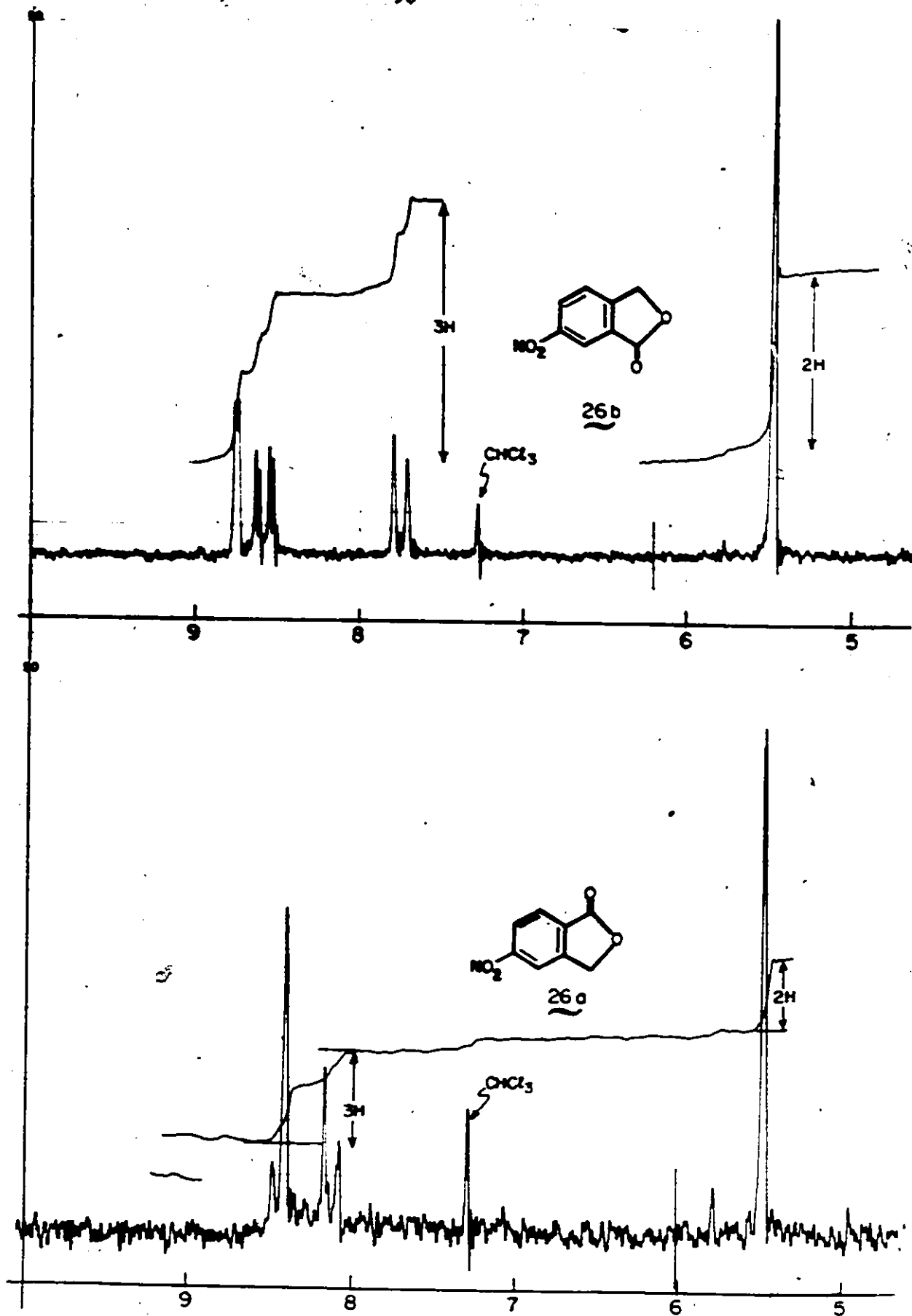
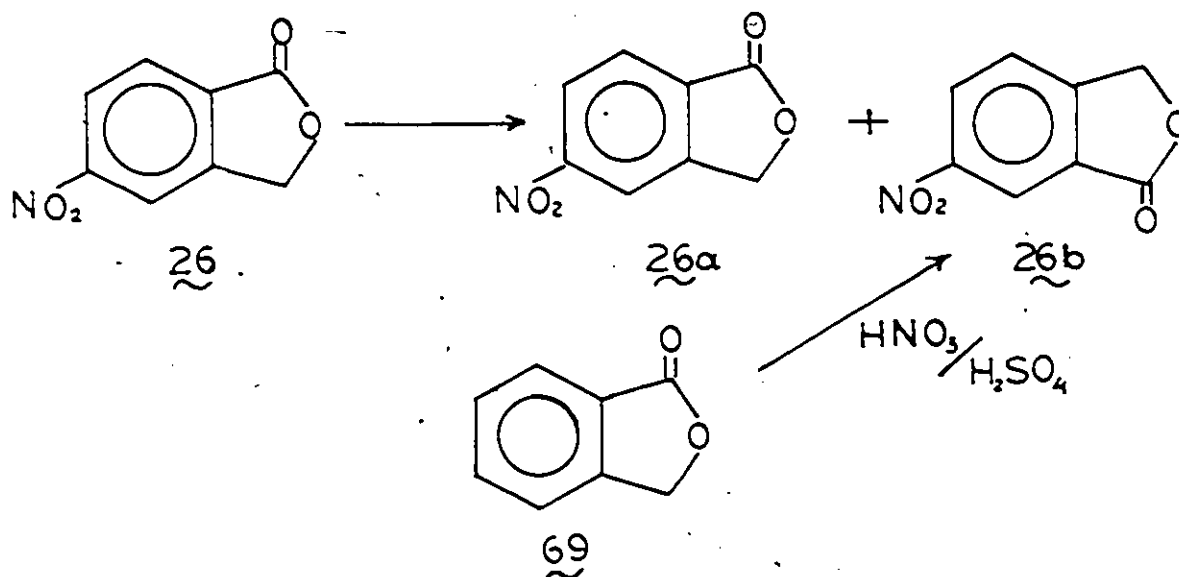


Figure 43. The n.m.r. spectra of 5-nitrophthalide 26a and 6-nitro-phthalide 26b.

of the two lactones from the n.m.r. spectrum of the crude reaction product. The weights of lactones obtained upon separation by column chromatography showed  $\underline{26a}:\underline{26b} = 60:40$ . Reduction of  $\underline{26}$  with  $\text{NaBH}_4$  gave a 56% yield of the lactonic product. The n.m.r. analysis of the crude product indicated the ratio  $\underline{26a}:\underline{26b}$  to be 55:45. The isomers were separated by column chromatography. Unequivocal proof of identity was obtained by comparison of lactone  $\underline{26b}$  with 6-nitrophthalide prepared by nitration of phthalide  $\underline{69}$  (Figure 43).



#### 10. trans-2-Methyl-3-phenylsuccinic acid

trans-2-Methyl-3-phenylsuccinic acid was prepared by condensing benzylcyanide  $\underline{70}$  with ethyl 2-bromopropionate  $\underline{71}$  under phase transfer conditions, followed by acid hydrolysis. Two isomers  $\underline{74}$  and  $\underline{75}$  were formed as witnessed by the n.m.r. spectrum of the isolated product, where two distinct doublets indicated the presence of two different methyl groups (Figure 44). The mixture of diastereoisomers was refluxed with acetyl chloride in an attempt to provoke cyclization to the

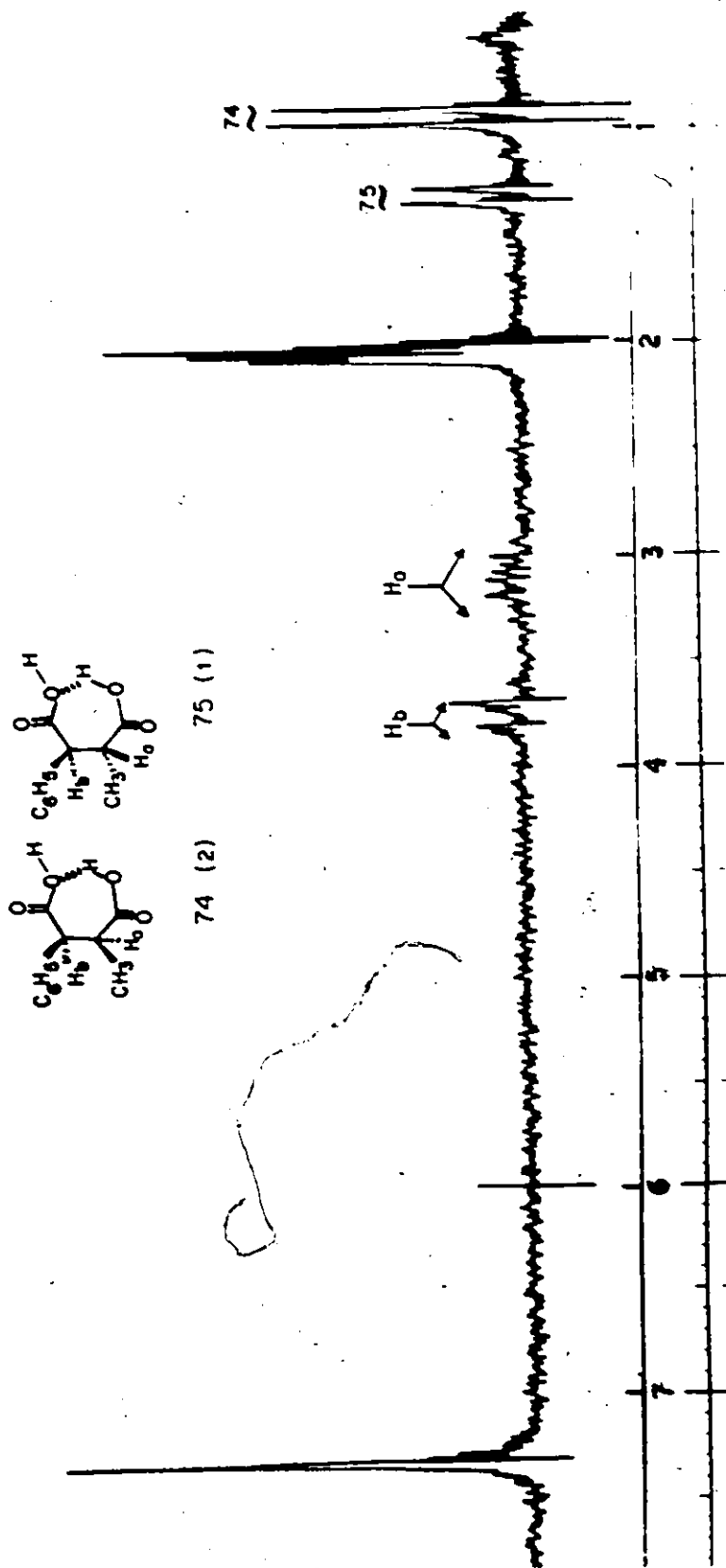
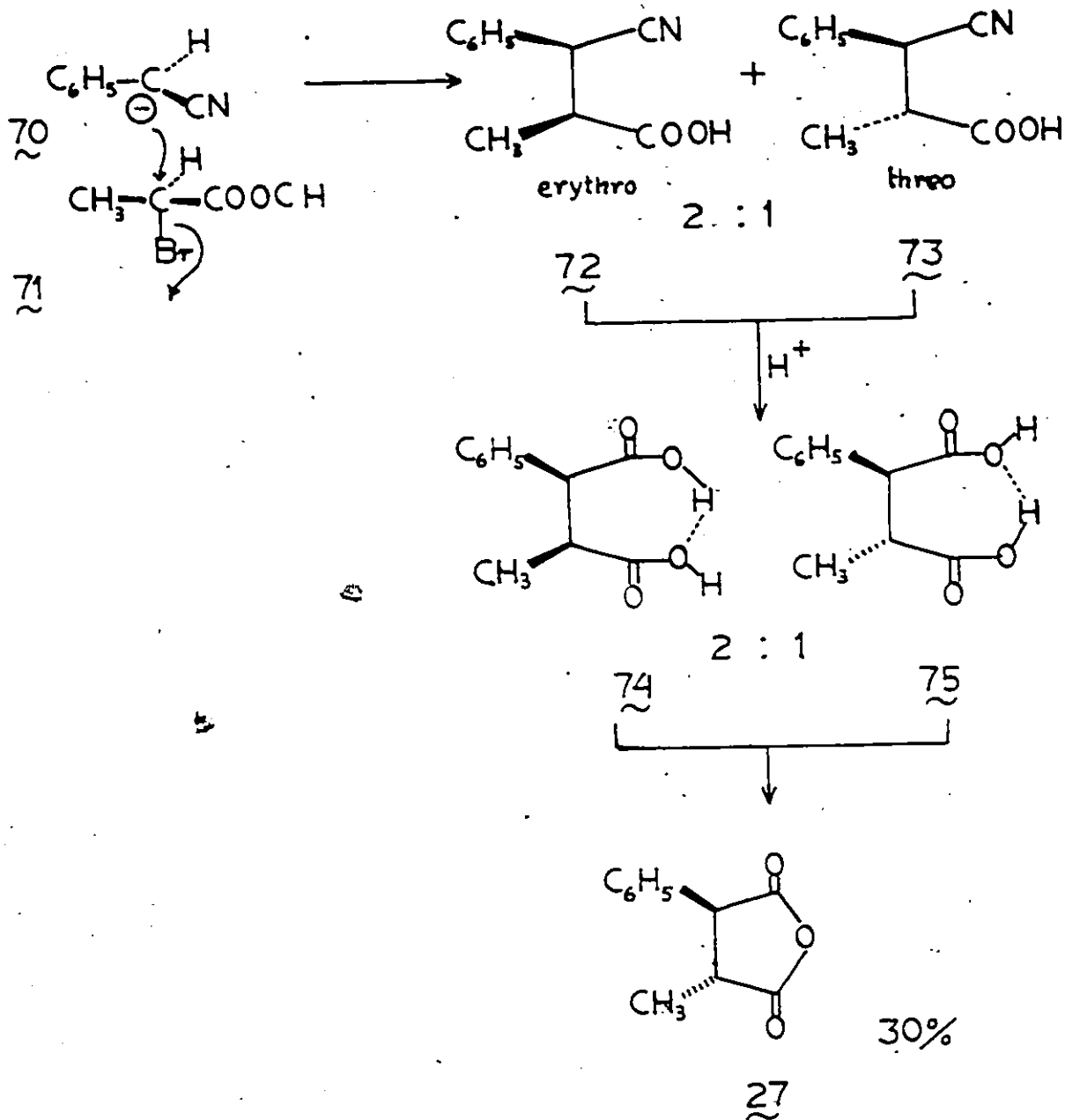
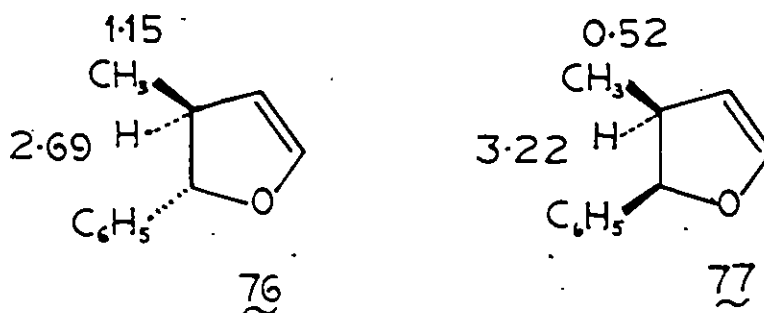


Figure 44. The n.m.r. spectrum of the mixture of cis and trans-2-methyl-3-phenylsuccinic acids 74 and 75.

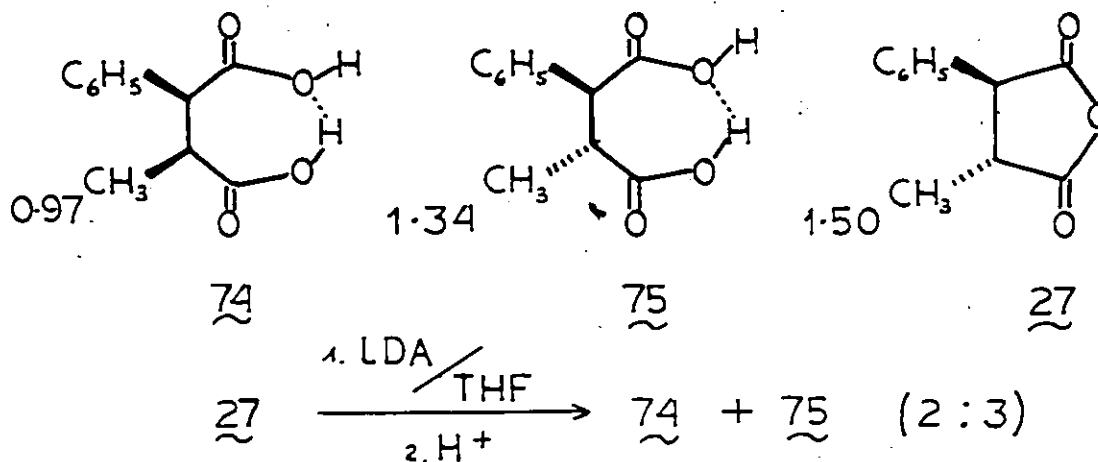


corresponding anhydride. The crystalline compound obtained (in 30% yield) was identified as the more stable trans-2-methyl-3-phenylsuccinic anhydride  $\tilde{27}$ . Mother liquor, which failed to crystallize, contained several products including acid  $\tilde{74}$  (characteristic doublet at  $\delta 0.97$  in the n.m.r. spectrum).

Although the assignment of cis-trans relationships in flexible ring systems is often uncertain, nevertheless regularities do exist. The phenyl substituent shields the cis-vicinal methyl group thus causing the resonances due to this group to appear upfield of the resonances due to the trans-vicinal methyl group. The chemical shifts for methyl protons in 76 and 77 illustrate this effect.<sup>74</sup>



The original mixture of 74 and 75 shows two methyl doublets at  $\delta$ 0.97 and  $\delta$ 1.34. The chemical shift for the methyl group in the anhydride 27 appears at  $\delta$ 1.50 (Figure 45). Anhydride 27, upon treatment with base,



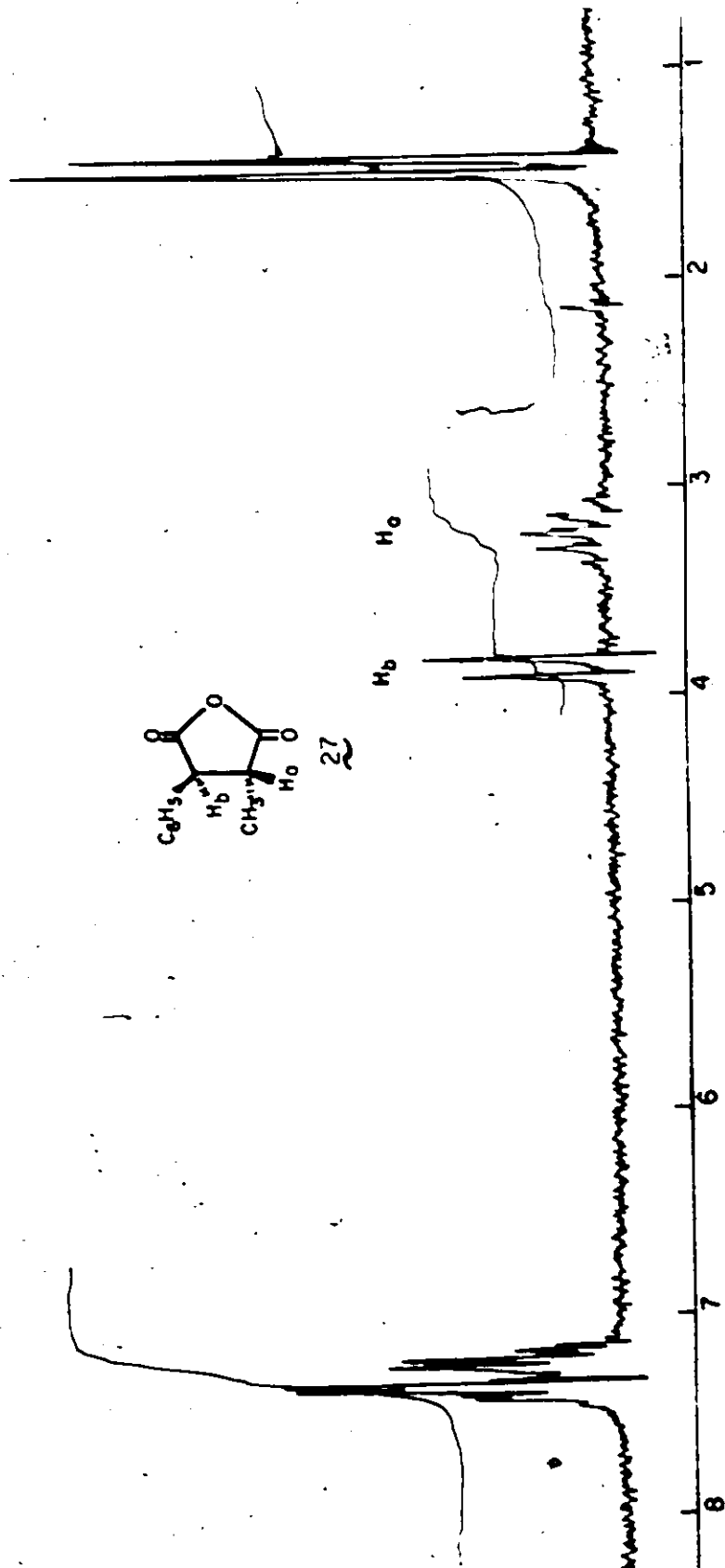


Figure 45. The n.m.r. spectrum of trans-2-methyl-3-phenylsuccinic anhydride 27.

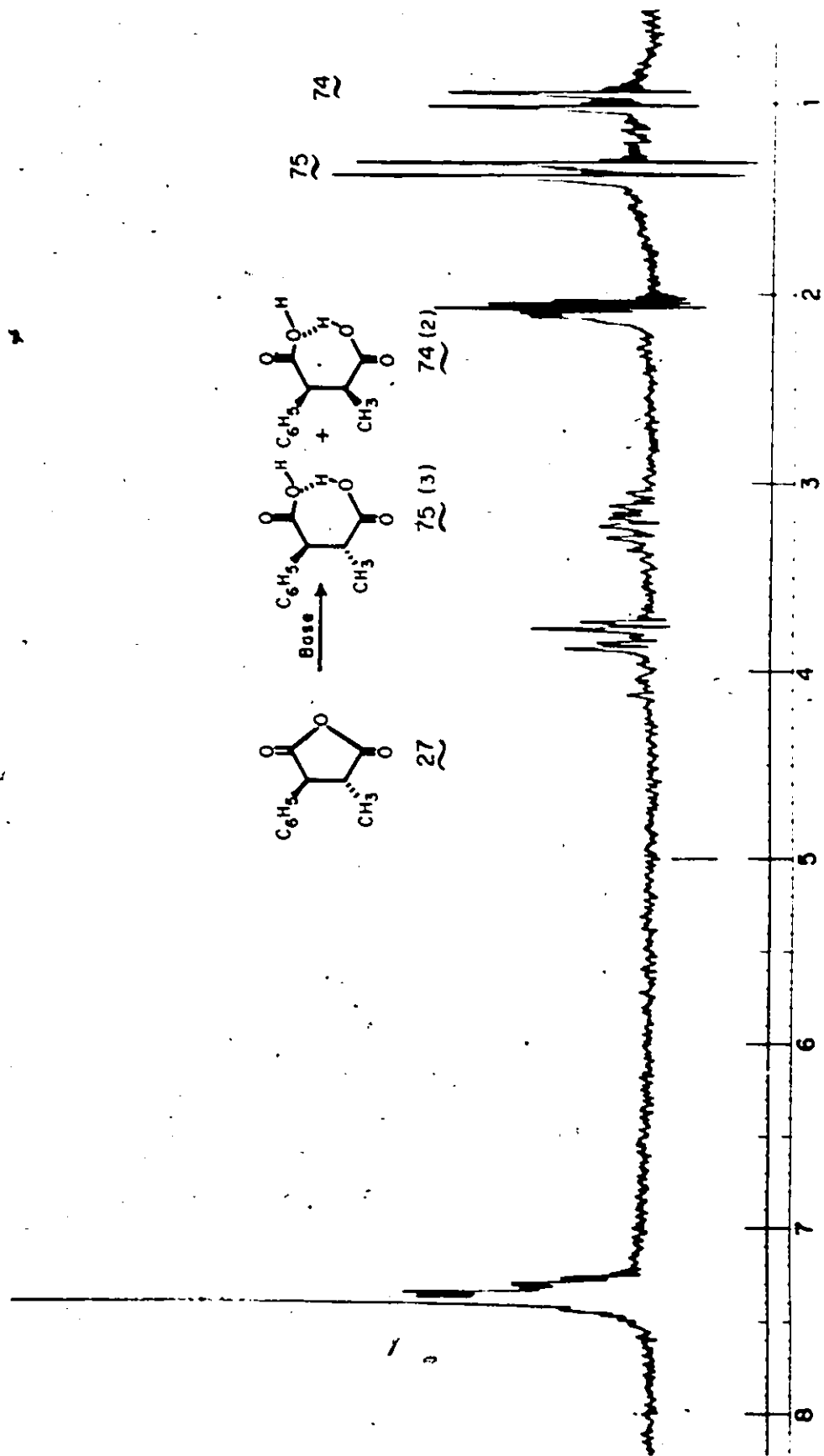


Figure 46. The n.m.r. spectrum of the mixture of *cis* and *trans*-2-methyl-3-phenylsuccinic acids obtained from the reaction of the anhydride **27** with LDA.

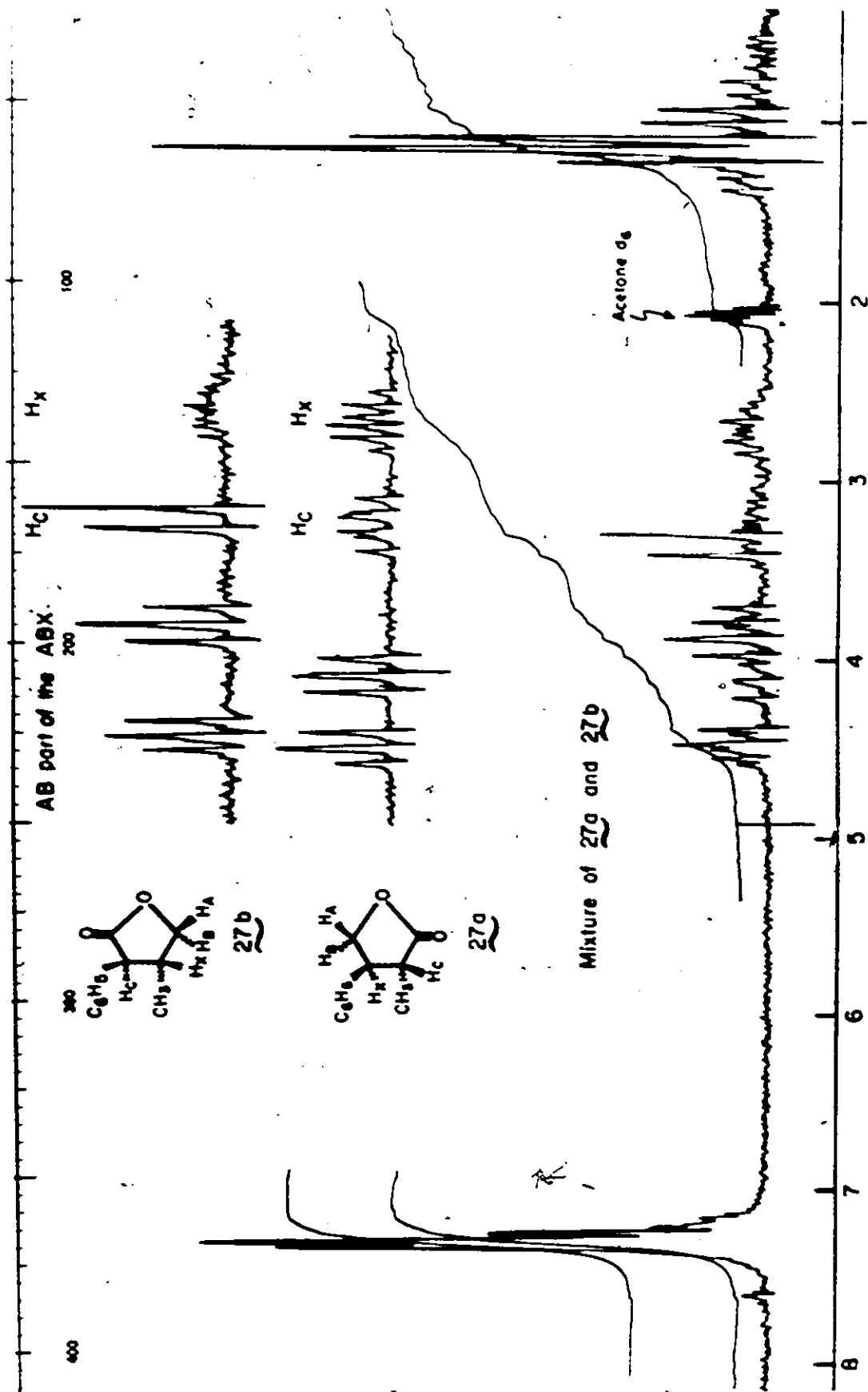
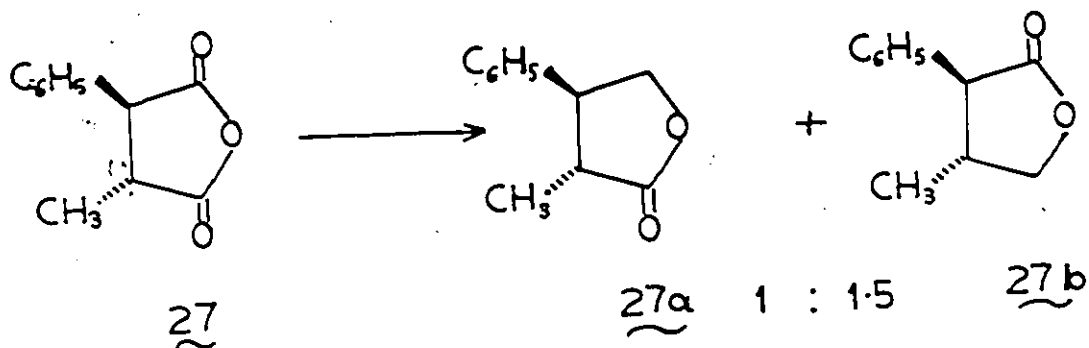


Figure 47. The n.m.r. spectra of 2-methyl-3-phenyl- $\gamma$ -butyrolactone 27a and 3-methyl-2-phenyl- $\gamma$ -butyrolactone 27b.

gave both acids 74 and 75 (Figure 46).

Reduction of 27 with  $\text{NaBH}_4$  gave two lactones 27a and 27b in the ratio 1:1.5 (Figure 47). The crude product contained also unreacted isomerized acids 74 and 75. Separation on thick layer chromatography

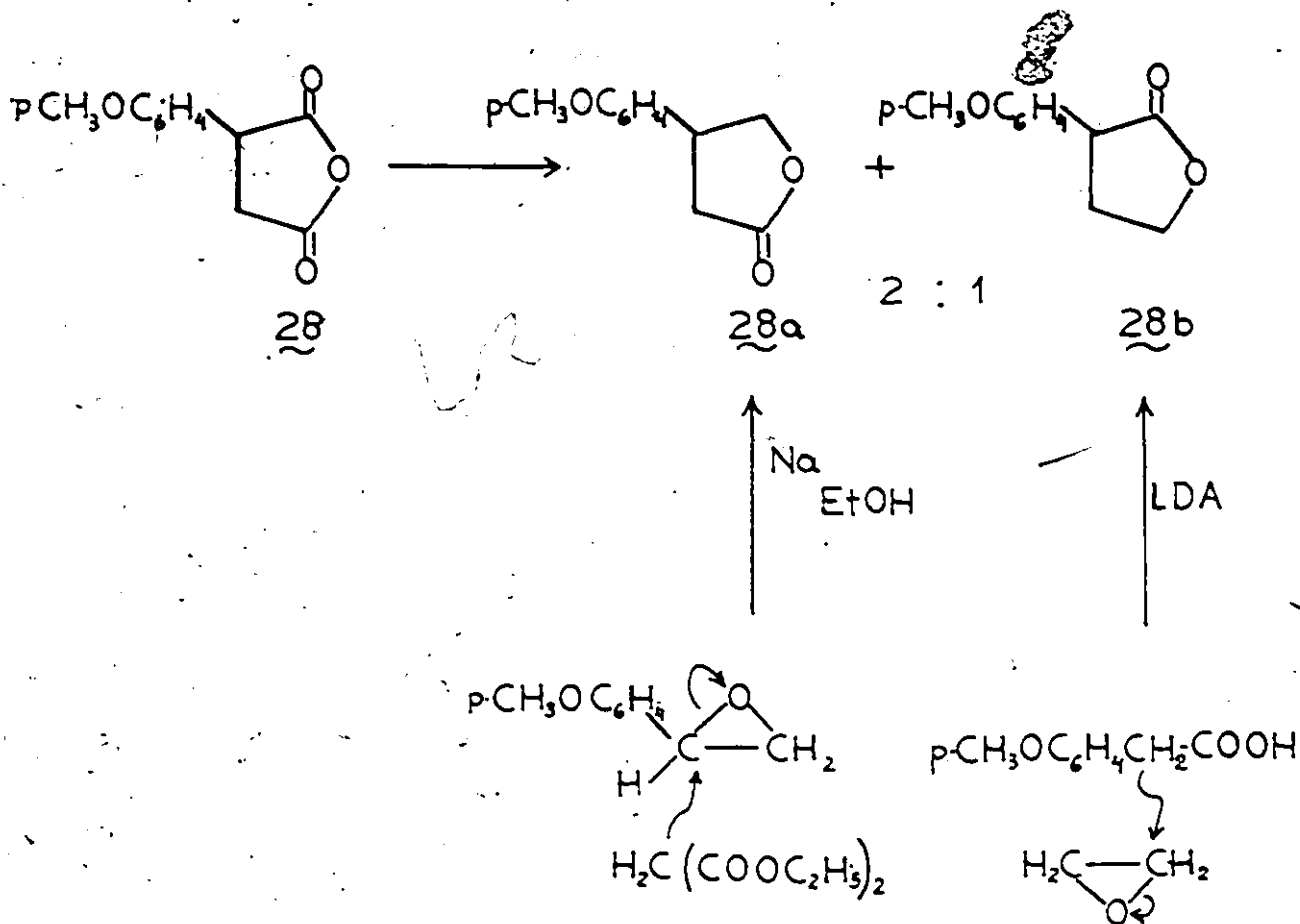


plates furnished both lactones (the isolated ratio of 27a:27b was 30:70). Reduction of 27 with  $\text{LiAlD}_4$  proceeded less cleanly. The major lactonic product 27b (deuterated) crystallized from ether solution and the mother liquor contained several products, among them the isomeric deuterated lactone 27a. It was not possible to establish the exact ratio of two lactones produced in the  $\text{LiAlH}_4$  reduction. However, an approximate ratio 27a to 27b is of the order of 1:2.3.

#### 11. p-Methoxyphenylsuccinic anhydride 28

p-Methoxyphenylsuccinic anhydride 28 was reduced with  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ . In both cases a mixture of two lactones was obtained in the ratio 2:1 in favour of 3-p-methoxyphenyl- $\gamma$ -butyrolactone 28a. The lactones were separated on thick layer chromatography plates and compared with the authentic samples prepared by alternate routes.\*

\* Independent syntheses of 28a and 28b were carried out by G. Beauchamp in this laboratory.



The analysis of the  $^1\text{H}$  n.m.r. spectrum of the crude product was facilitated by the fact that the methylene groups ( $-\text{CH}_2-\text{O}$ ) in the two isomers do not overlap (Figure 48).

12. p-Nitrophenylsuccinic anhydride 29

Reduction of p-nitrophenylsuccinic anhydride 29 with  $\text{LiAlH}_4$  produced a dark-coloured mixture containing several products. The presence of lactonic material was shown by a characteristic lactonic band

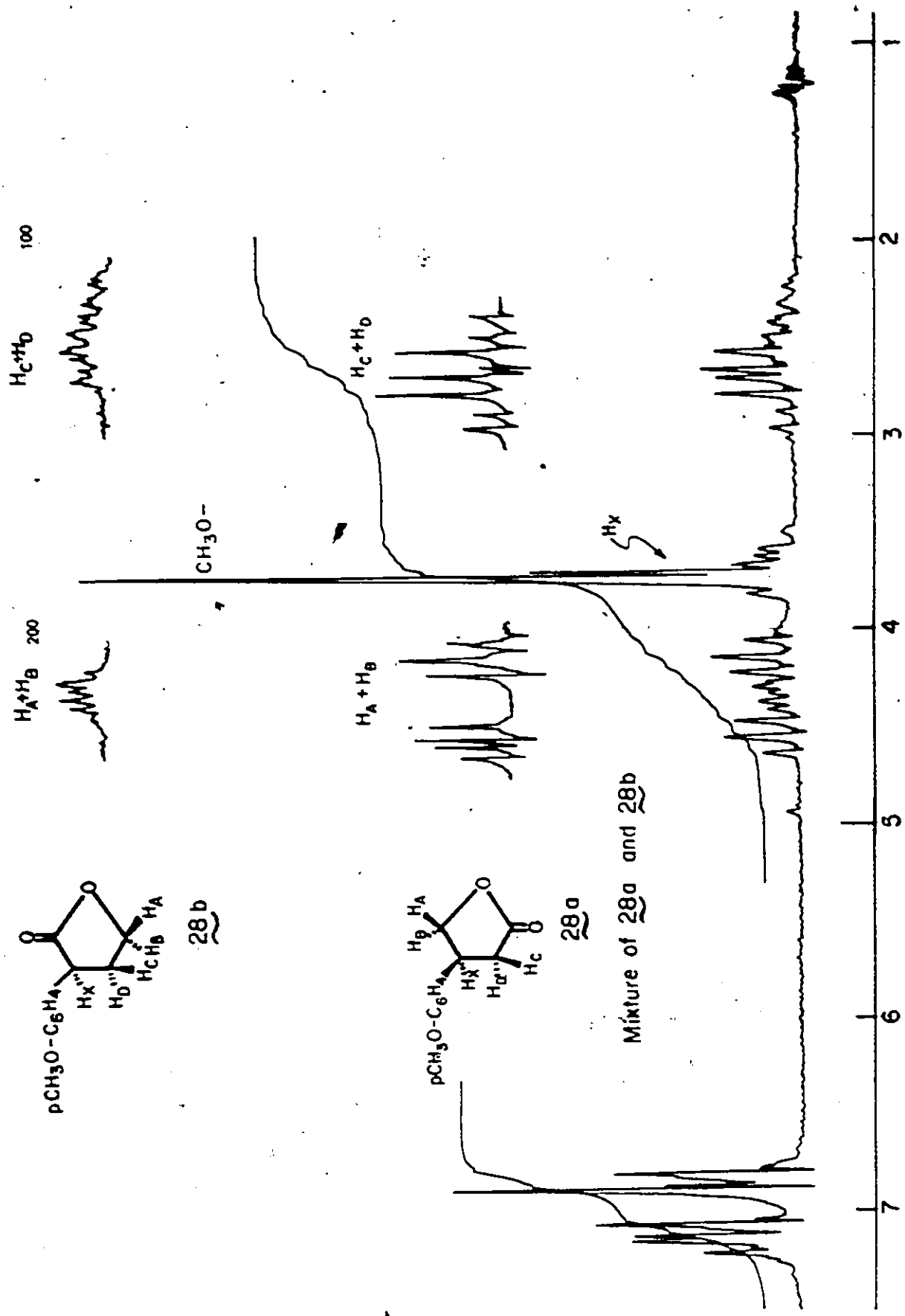
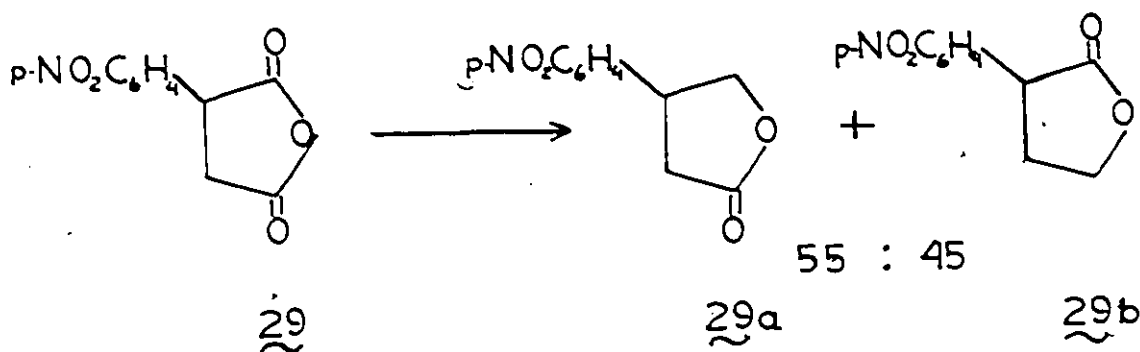


Figure 48. The n.m.r. spectra of 3-p-methoxyphenyl- $\gamma$ -butyrolactone 28a and 2-p-methoxyphenyl- $\gamma$ -butyrolactone 28b.

in the i.r. spectrum ( $1770\text{ cm}^{-4}$ ). It was not possible to estimate the ratio of the two lactones in the original mixture. The reduction of 29 with  $\text{NaBH}_4$  was somewhat cleaner. However, the product mixture contained, apart from the two lactones some p-nitrophenylsuccinic acid (Figure 49). The two lactones were separated on thick layer chromatography plates and compared with authentic samples prepared by alternate synthetic routes.\* The approximate ratio of 29a to 29b (55:45) was



estimated from the proton n.m.r. spectrum of the product mixture obtained by  $\text{NaBH}_4$  reduction. The weights of lactones 29a and 29b, separated by thick layer chromatography, were not indicative, since there was a fair amount of overlap between the two compounds on the plates.

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\* 29a and 29b were prepared by G. Beauchamp in this laboratory.

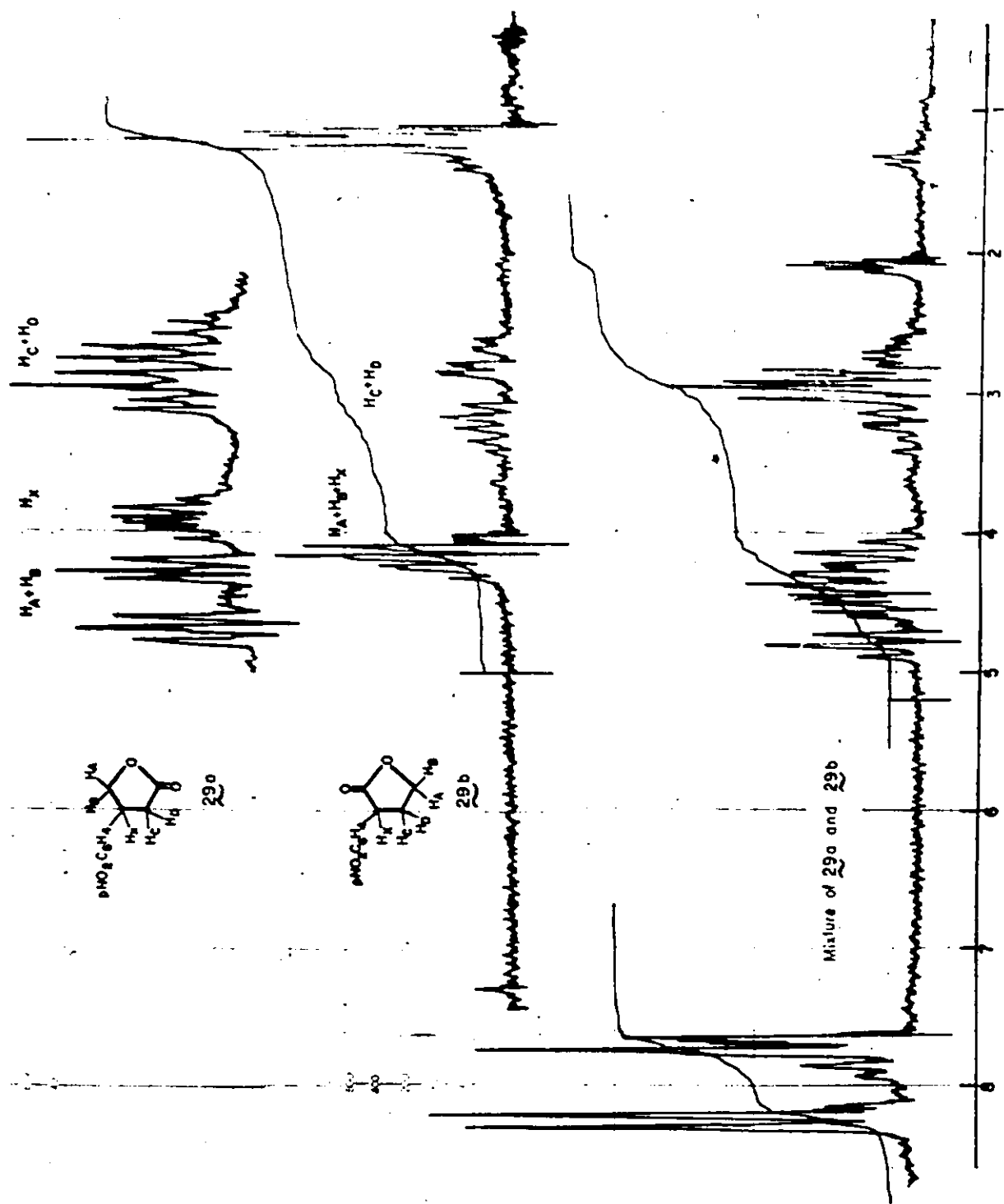


Figure 49. The n.m.r. spectra of 3-p-nitrophenyl- $\gamma$ -butyrolactone 29a and 2-p-nitrophenyl- $\gamma$ -butyrolactone 29b.

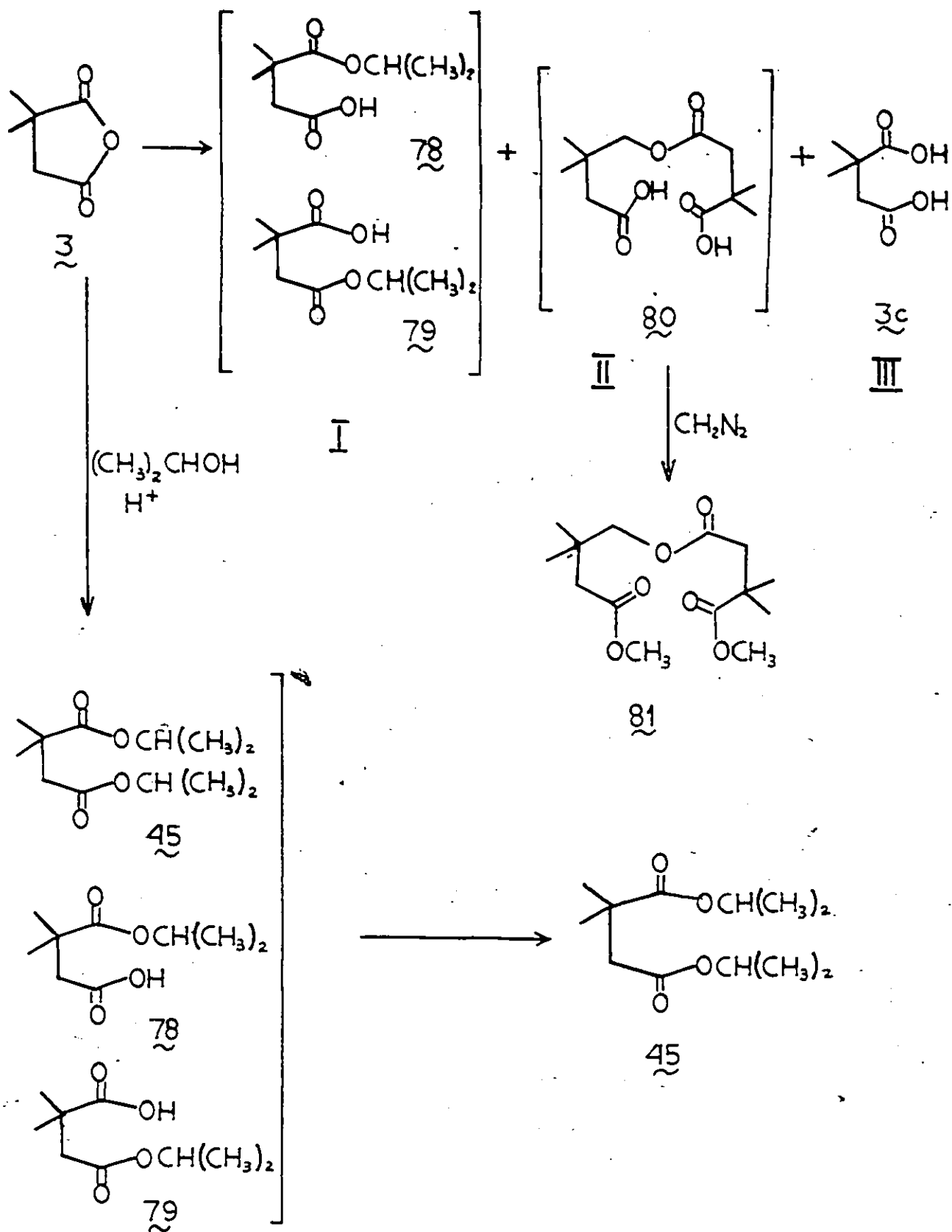
CHAPTER 10

REDUCTION WITH  $(\text{CH}_3)_4\text{N BH}_4$

2,2-Dimethylsuccinic anhydride 3, when treated with  $(\text{CH}_3)_4\text{NBH}_4$  in isopropyl alcohol yielded three major fractions (separated either by column chromatography or by bulb to bulb distillation under reduced pressure). G.l.c. analysis of the crude reduction mixture showed also the presence of small amounts of 3,3-dimethyl- $\gamma$ -butyrolactone 3a. The fraction eluted first appeared to be a mixture of two half esters 78 and 79. The direct esterification of 2,2-dimethylsuccinic anhydride 3 with isopropyl alcohol confirmed the identity of the mixture. After several crystallizations one of the two half esters was isolated and tentatively identified as 79 (Figure 50).

The second fraction contained a single product, having elemental analysis and spectral data consistent with the assigned structure 80 (Figure 51). Esterification, using diazomethane confirmed the presence of two carboxylic groups (80 + 81). The third fraction consisted of pure 2,2-dimethylsuccinic acid 3c. We have not proven which carboxylic function of the succinic acid 3c is esterified and the structures 79 and 80 are assigned arbitrarily.

Cason<sup>75</sup> reported selective preparation of  $\alpha$ -butyl- $\alpha$ -ethyl-glutarate 83 from anhydride 82, thus implying preferential esterification at the primary carbonyl group. Our own attempt to prepare selectively half ester 79 (or 78) according to the procedure described by Cason<sup>75</sup> failed (a mixture of two half esters and the diester was



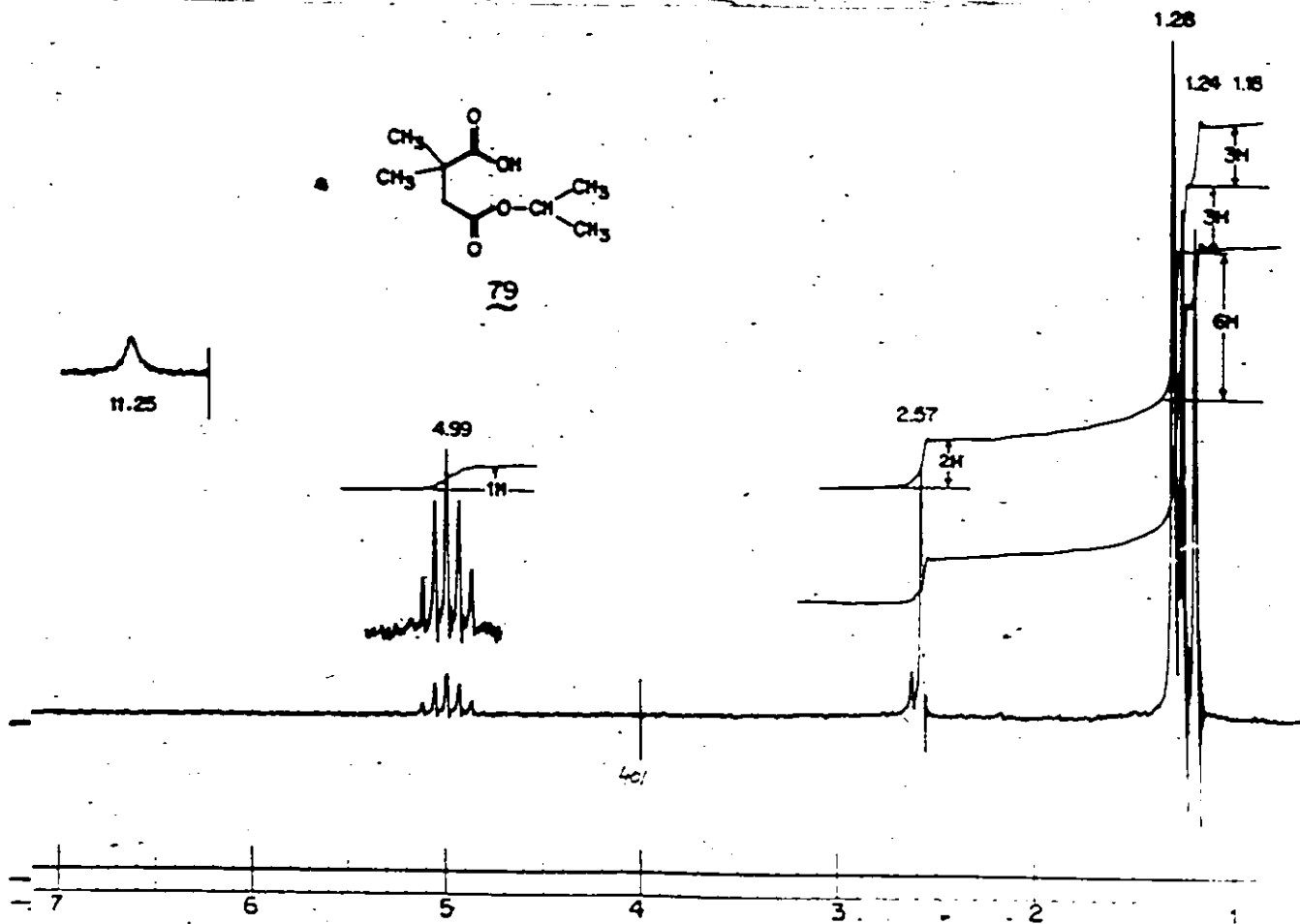
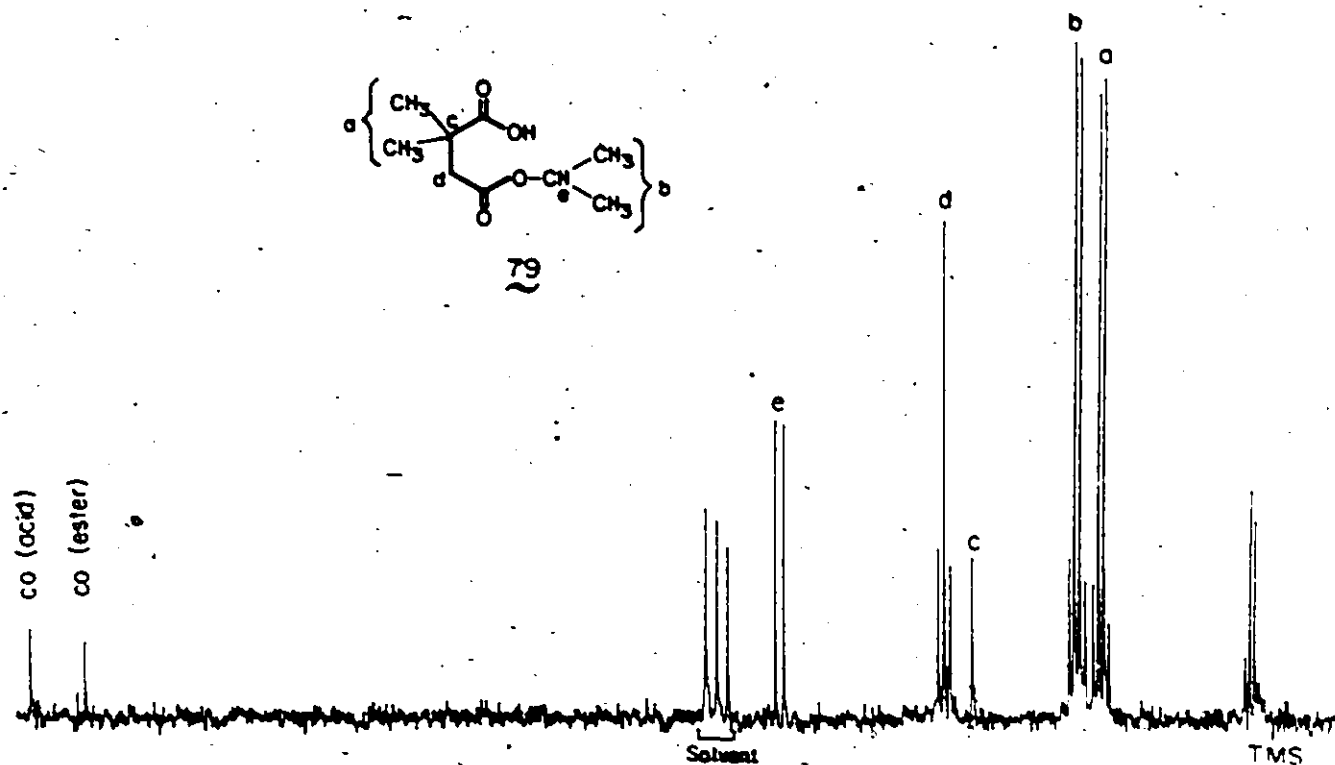
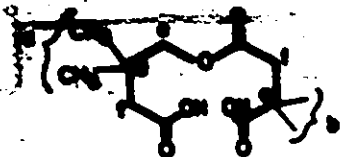


Figure 50. The n.m.r. spectrum of the half ester 79 of 2,2-dimethylsuccinic acid.



80

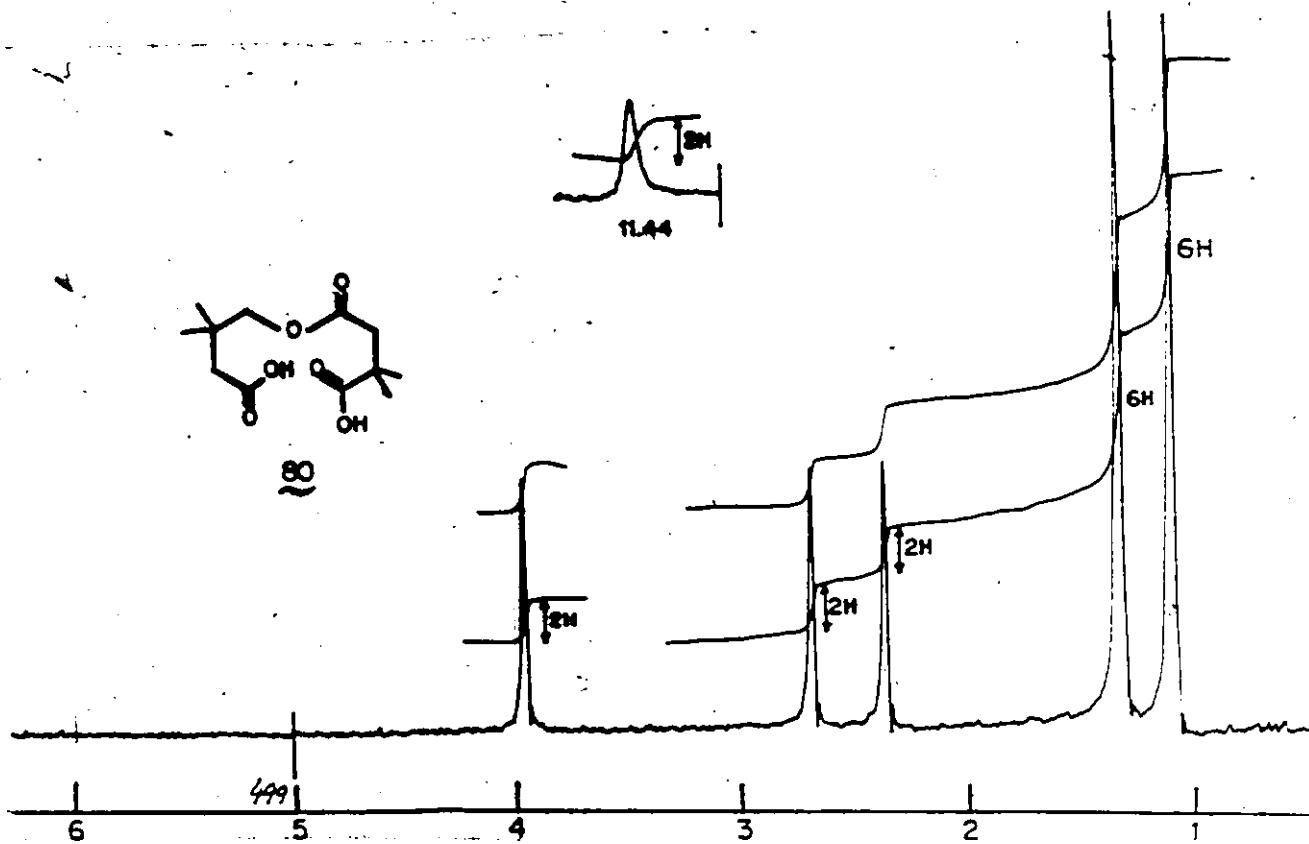
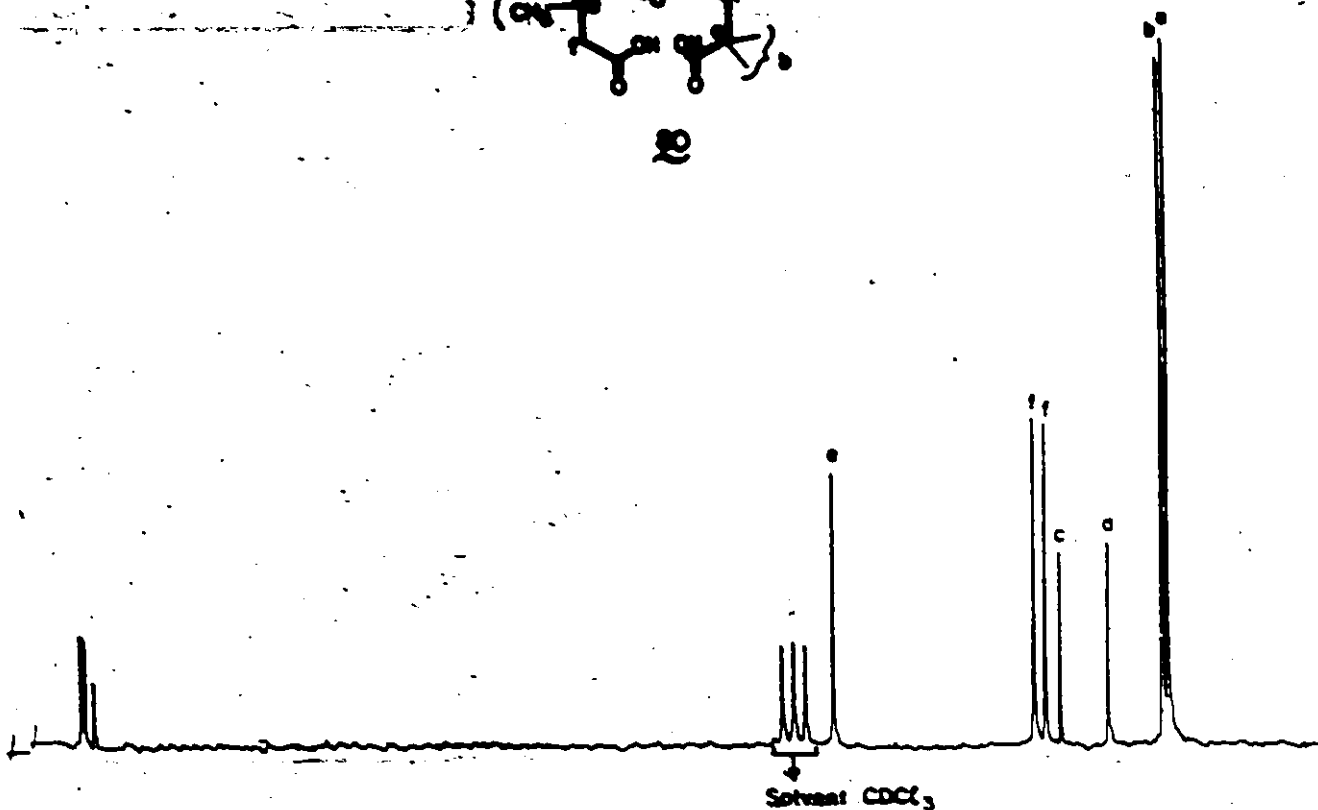
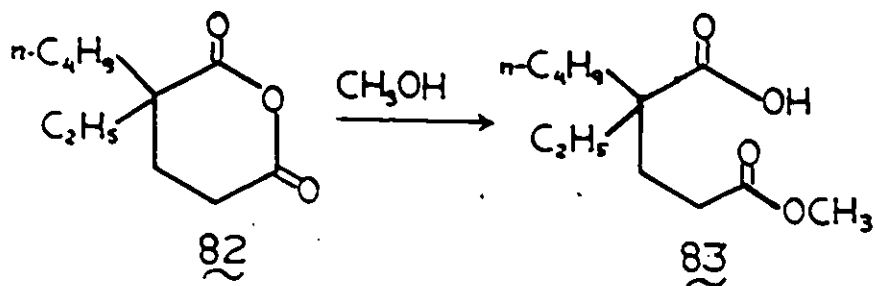
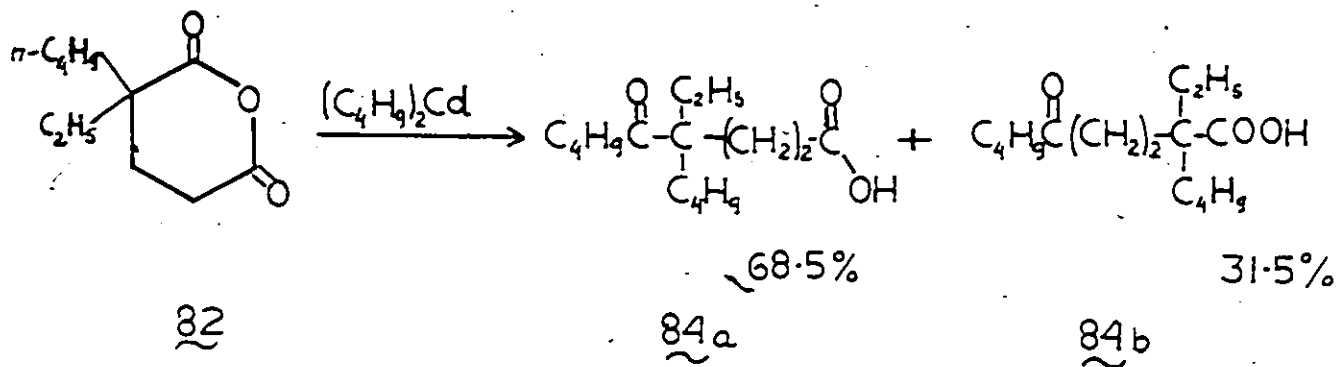


Figure 51. The n.m.r. spectrum of the half ester 80 of 2,2-dimethylsuccinic acid.



produced). This mixture was esterified further to yield the diester **45**, Figure 52).

It is possible that somewhat greater reactivity toward nucleophilic addition in the esterification reaction may be exhibited by the carbonyl group adjacent to a tertiary carbon atom. Such selectivity has been observed in metal hydride reduction of unsymmetrical cyclic anhydrides (see Chapter 4), diacids and diester (see Chapter 8) as well as in the reaction of the anhydride **82** with dibutylcadmium<sup>75</sup>. The keto acid obtained from the latter reaction consisted of 68.5% of the isomer resulting from addition of the butyl group to the hindered carbonyl group.



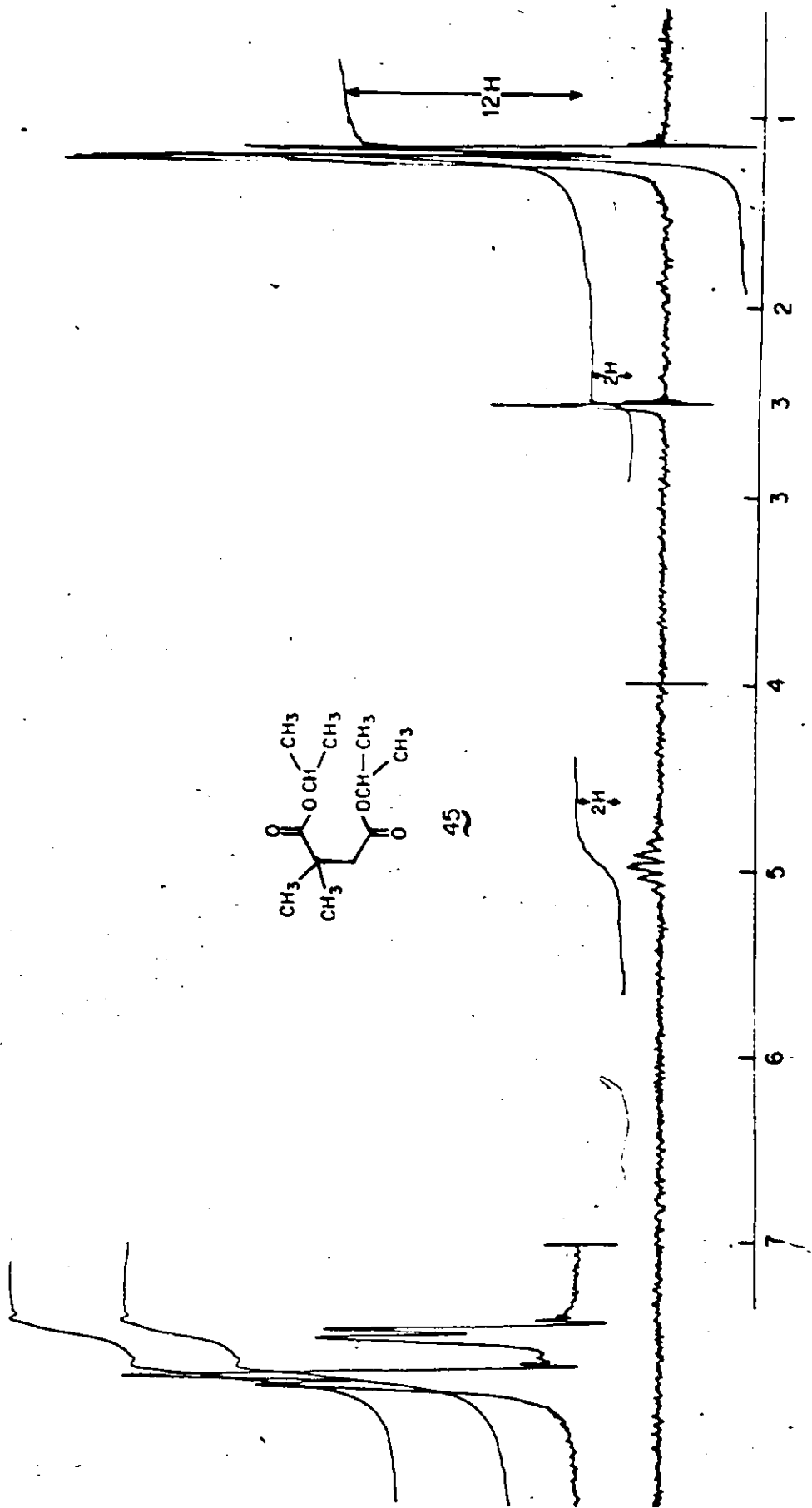
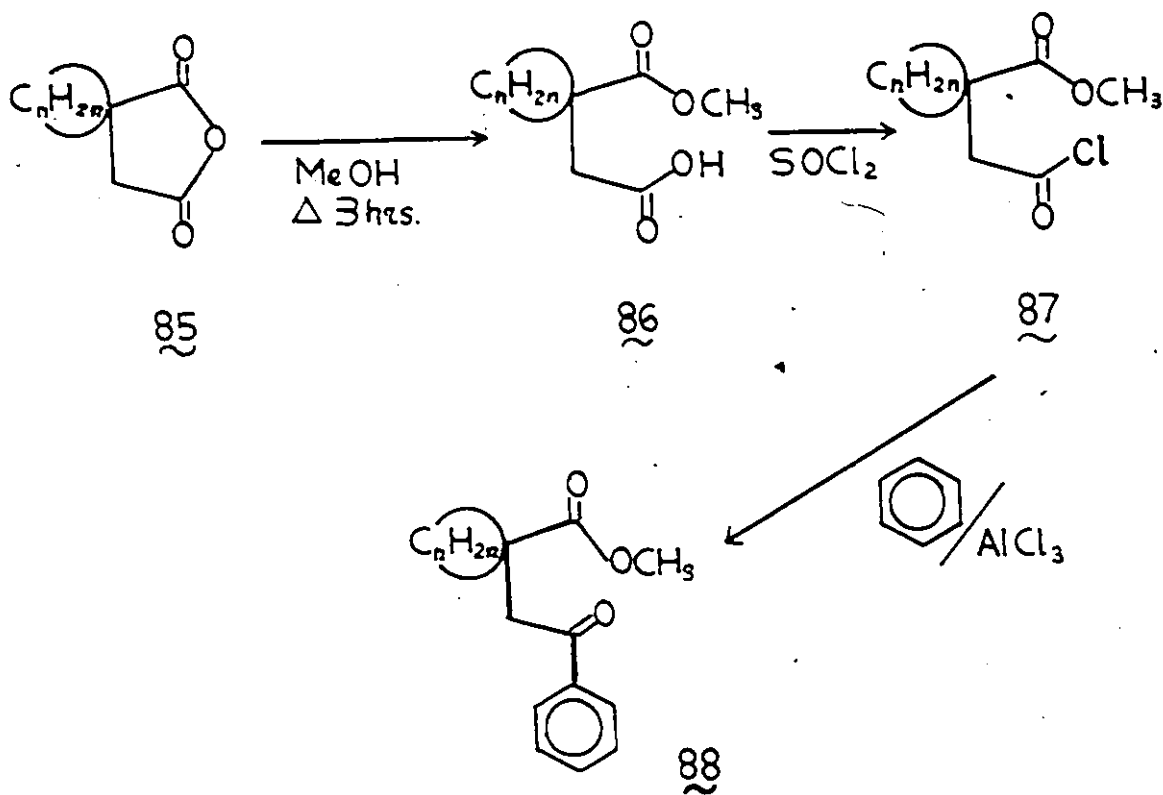


Figure 52. The n.m.r. spectrum of diisopropyl ester of 2,2-dimethylsuccinic acid.

Preferential esterification at the more hindered carbonyl group has been recently reported for the unsymmetrical cyclic anhydride 85.<sup>76</sup> However, the proof of structure for the half ester 86 is not entirely convincing, in view of the fact that the ester acid chloride such as 87 can rearrange to a mixture of the two possible ester acid chlorides.<sup>76</sup> Consequently, regioselectivity (or lack of it) in esterification reactions requires further investigation.



CHAPTER 11

EVALUATION OF REDUCTION METHODS

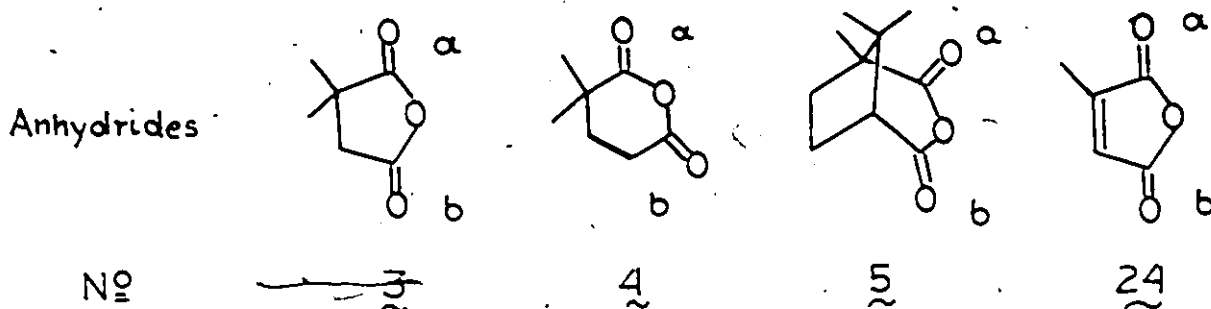
Using model cyclic anhydrides, we have surveyed a variety of reduction methods, in order to assess their potential usefulness and selectivity in the preparation of lactones from cyclic anhydrides. The results are shown in Table 6.

The regioselectivities of metal hydride reductions have been discussed at length. In 2,2-disubstituted succinic anhydrides, reduction occurs with high regioselectivity at the more hindered carbonyl function.  $\text{NaBH}_4/\text{THF}$  is the preferred method of reduction for these compounds since the procedure is simple and yields are high with minimum contamination by side products.  $\text{LiAlH}_4/\text{THF}$  reduction gives generally equally excellent yields, but, the procedure is more involved (requiring  $\text{N}_2$  atmosphere, low temperature, etc.) and appears to be less suitable for reducing cyclic anhydrides substituted with phenyl or nitrophenyl groups. Due to the superior electrophilicity of  $\text{Li}^+$ , there may occasionally be small differences in regioselectivity observed in  $\text{LiAlH}_4$  compared to  $\text{NaBH}_4$  reductions.

$\text{NaBH}_4$  in alcohol is not a suitable reduction method for cyclic anhydrides as esterification may occur preferentially (e.g., reduction of citraconic anhydride 24 with  $\text{NaBH}_4$  in methanol gave diester). Esterification also is the main reaction when  $(\text{CH}_3)_4\text{N}^+\text{BH}_4^-$  in isopropyl alcohol is used.

Catalytic hydrogenation with  $\text{RuCl}_2(\text{Ph}_3\text{P})_3$  as a catalyst yields

TABLE 6. Evaluation of reduction methods



Method	Yield %	Ratio <sup>2</sup> a:b	Yield <sup>1</sup>	Ratio <sup>2</sup> a:b	Yield <sup>1</sup>	Ratio <sup>2</sup> a:b	Yield <sup>1</sup>	Ratio <sup>2</sup> a:b
LiAlH <sub>4</sub> /THF	75	19:1	72	9:1	78	3:2	82	b trace
NaAlH <sub>4</sub> /THF	15	a only	-	-	-	-	-	-
NaAlH <sub>4</sub> /THF+Li <sup>+</sup>	80	a only	-	-	-	-	-	-
NaBH <sub>4</sub> /THF	90	a only	-	-	-	-	80	b trace
NaBH <sub>4</sub> /Alcohol	-	-	-	-	-	-	esterification	
(CH <sub>3</sub> ) <sub>2</sub> S:BH <sub>3</sub> /Alcohol	esterification + a trace							
Catalytic Hydrogenation	72	1:9	40	b	-	-	-	-
Na/EtOH	65	9:11	-	-	-	b	-	-
Na/EtOH+Li	60	6:11	-	-	-	-	-	-
Na/Ethylacetate/AcOH	many products some esterification							
Na <sub>2</sub> Fe(CO) <sub>4</sub>	Inconclusive							
(CH <sub>3</sub> ) <sub>2</sub> S:BH <sub>3</sub>	No reaction							

1 Yield = total yield of lactonic product %;

2 Ratio of lactone (a) reduced at the more hindered carbonyl group to lactone (b) reduced at the less hindered carbonyl function.

lactones resulting from the reduction of the less hindered carbonyl group. Similar results may be obtained with Adams (platinum oxide) catalyst although formation of lactone is usually accompanied by some of the corresponding hemiacetal.

Dimethyl sulfide-diborane complex  $\{(CH_3)_2S:BH_3\}$  which is a useful reagent for the reduction of cyclic imides, did not react with a model cyclic anhydride (2,2-dimethylsuccinic anhydride 3).

The reaction with Colman reagent ( $Na_2Fe(CO)_4$ ) was particularly tedious. Examination of the i.r. spectrum of the reaction mixture suggested that some hemiacetal was formed. This intermediate could only be the product of reduction at the more hindered carbonyl function, since the following reduction of the crude mixture with  $NaBH_4$  gave 3a as the only lactonic product. In view of the simplicity of metal hydride reduction and the complexity of reaction with Colman reagent, we did not pursue the investigation of this reagent any further.

Sodium in absolute ethanol showed little selectivity in the reduction of 2,2-dimethylsuccinic anhydride 3. However, the irradiation of the reaction mixture with a sun lamp somewhat increased preference for the less hindered carbonyl group (see Table 6). Reduction of severely hindered camphoric anhydride gave predominantly lactone 5b (reduced at the less hindered carbonyl function). The yields were generally mediocre and several by-products were formed.

Reaction of model anhydride 3 with sodium/ethylacetate/acetic acid yielded diester as a main product.

CHAPTER 12

EXPERIMENTAL

1. Apparatus and Materials

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Beckman IR-20 and Unicam SP1100 Infrared spectrometers with chloroform as the solvent. Proton nuclear magnetic resonance spectra were recorded on Varian T-60 or HA-100 instruments, with chloroform-d or acetone-d<sub>6</sub> as the solvents and tetramethylsilane as the internal standard. Carbon-13 nuclear magnetic resonance spectra were obtained on a Varian FT-80 NMR spectrometer with chloroform-d as the solvent and tetramethylsilane as the internal standard. Mass spectra were recorded on AEI MS902S instrument.

Gas-liquid chromatography analyses were carried out with an Autoprep Model A-700 gas chromatograph. (6 ft. 10% carbowax column was used). The lactone reduced at the less hindered carbonyl function had a shorter retention time in all cases. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., U.S.A. Silica gel "Baker Reagent" was used for column chromatography, unless otherwise stated. A 100 fold ratio of adsorbent to product was used and here again the lactone reduced at the less hindered carbonyl function was eluted first in all cases.

THF was dried overnight over sodium hydroxide pellets, then distilled under nitrogen from LiAlH<sub>4</sub> into an oven dried and nitrogen-flushed flask containing the pre-weighed LiAlH<sub>4</sub>. All reduction experiments involving LiAlH<sub>4</sub> were carried out under nitrogen atmosphere; hypodermic syringes were used to transfer solutions. LiAlH<sub>4</sub> and NaBH<sub>4</sub> were obtained from BDH Chemicals Ltd.,

NaAlH<sub>4</sub> from the Ventron Corporation.

2. General Procedures for Reduction with LiAlH<sub>4</sub> and NaBH<sub>4</sub>

LiAlH<sub>4</sub> reduction of cyclic anhydrides to lactones. LiAlH<sub>4</sub> (0.01 mole) was placed in an oven-dried, nitrogen-swept, three-neck flask into which 50 ml of THF were subsequently distilled. The flask was fitted with an inlet port for syringes, a magnetic stirrer, a thermometer and a gas inlet/outlet tube. LiAlH<sub>4</sub> in THF was stirred at room temperature for approximately 15 minutes, then the flask, swept with a slow stream of nitrogen, was cooled in a dry ice/acetone bath. An anhydride (0.01 mole) was injected slowly into the flask. The temperature of the reaction mixture was maintained below -50°C throughout the addition process. The stirred solution was slowly warmed to 0°C over a period of 90 minutes - 2 hrs, then cooled to -20°C and the reaction quenched with distilled water and 6 N HCl. The mixture was stirred overnight at room temperature. The acidity of the solution was checked before work-up. The layers were separated and the aqueous layer extracted several times with ether. The combined organic extracts were dried over anhydrous MgSO<sub>4</sub> and the solvents evaporated under reduced pressure.

NaBH<sub>4</sub> reduction of cyclic anhydrides to lactones. A solution of an anhydride (0.01 mole) in dry THF (20-50 ml) was added dropwise to a stirred, ice-cold suspension of NaBH<sub>4</sub> (0.01 mole) in THF (50 ml). The reaction mixture was warmed to room temperature and stirring was continued for an additional 2-3 hrs. During that period 3-4 drops of 6 N HCl were added to the reaction mixture. After quenching with 3 N HCl

the layers were separated and the acidic aqueous layer was extracted several times with ether. The combined organic layers were dried over anhydrous  $\text{MgSO}_4$  and the solvents removed on a rotatory evaporator.

$\text{LiAlH}_4$  reduction of lactones to diols. A solution of a lactone (0.01 mole) in dry THF was added dropwise over a period of 15 minutes to a stirred, ice-cold solution of  $\text{LiAlH}_4$  (0.01 mole) in dry THF (50 ml). The temperature of the reaction was raised slowly to  $25^\circ\text{C}$ , and stirring continued for an additional 2 hrs. The solution was cooled to  $-20^\circ\text{C}$  (dry ice acetone bath) and distilled water and 6 N HCl were added until the solution was slightly acidic. After stirring for a few hours the organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were processed in the usual manner.

Cyclization of diols to the corresponding ethers.

A diol (0.05 mole) was refluxed gently with HBr (10 ml) for 1 hour, after cooling the reaction mixture was diluted with water and extracted three times with ether. The combined organic layers were extracted two times with the sat.  $\text{NaHCO}_3$  solution and then with water, dried over anhydrous  $\text{MgSO}_4$ . The solvent was evaporated.

3. Reductions of 2,2-dimethylsuccinic anhydride  $\underline{3}$

a.  $\text{LiAlH}_4$  and  $\text{NaAlH}_4$  reductions

2,2-Dimethylsuccinic anhydride  $\underline{3}$ <sup>77</sup> was prepared from 2,2-dimethylsuccinic acid by dehydration with acetyl chloride<sup>78</sup> and was reduced with  $\text{LiAlH}_4$  according to the standard procedure. Yields of lactonic product ranged from 50-75% and 10-15% of diacid was recovered. G.l.c. analysis (6 ft, 10% carbowax,  $120^\circ\text{C}$ ) showed the ratio of two isomeric lactones to be 19:1. The major product,  $\beta, \beta$ -dimethyl- $\gamma$ -butyrolactone  $\underline{3a}$ ,<sup>17,79</sup> was purified by distillation under reduced pressure.  $\nu_{\text{max}}$ ,  $1775 \text{ cm}^{-1}$  (lactone  $\text{C}=\text{O}$ );  $\delta$  1.20 (s, 6H, 2 x  $\text{CH}_3$ ), 2.34 (s, 2H,  $\text{CH}_2-\text{C}=\text{O}$ ), 3.99 (s, 2H,  $\text{CH}_2-\text{O}$ ).

$\text{NaAlH}_4$  (0.27 g, 0.05 mole) was stirred in warm dry THF (100 ml) under nitrogen atmosphere for 1/2 hour. The solution was cooled in a dry ice/acetone bath. 2,2-Dimethylsuccinic anhydride 3 (6.4 g, 0.05 mole) in THF (100 ml) was added slowly over a period of 40 minutes. The reaction mixture was stirred and brought up slowly to 10°C over a period of 2 hours. After cooling to -15°C, the reaction was quenched with distilled water and HCl. Work-up in the usual manner yielded 4.96 g of the crude product. Proton n.m.r. analysis showed the presence of  $\beta,\beta$ -dimethyl- $\gamma$ -butyrolactone 3a (15%) and 2,2-dimethylsuccinic acid 3c (85%).

The reduction run under the identical conditions but in the presence of LiCl (0.25 g, added to the solution of  $\text{NaAlH}_4$  in THF) led to the formation of  $\beta,\beta$ -dimethyl- $\gamma$ -butyrolactone 3a in 80% yield. Traces of the isomeric lactone 3b could be detected by g.l.c.

b. Catalytic hydrogenation with  $\text{RuCl}_2(\text{Ph}_3\text{P})_3$  as catalyst

2,2-Dimethylsuccinic anhydride 3 was reduced according to the method of Lyons.<sup>80</sup> After usual work-up 90% of crude material was obtained. Upon chromatography on Florisil, 72% of lactonic product was obtained. G.l.c. and  $^1\text{H}$  n.m.r. analyses showed the ratio of the two isomeric lactones to be 9:1, the major product being  $\alpha,\alpha$ -dimethyl- $\gamma$ -butyrolactone 3b,  $\nu_{\text{max}}$  1770  $\text{cm}^{-1}$ ;  $\delta$  1.28 (s, 6H, 2 $\text{CH}_3$ ), 2.12 (t, 2H,  $\text{CH}_2\text{-C=O}$ ), 4.26 (t, 2H,  $\text{CH}_2\text{-O}$ ).

c. Tetramethylammonium borohydride [(CH<sub>3</sub>)<sub>4</sub>NBH<sub>4</sub>] reduction

(CH<sub>3</sub>)<sub>4</sub>NBH<sub>4</sub> (4.4 g, 0.05 mole) was added portionwise to a stirred solution of 2,2-dimethylsuccinic anhydride 3 (4.0 g, 0.03 mole) in isopropyl alcohol (45 ml). The stirred reaction mixture was maintained at 55°C for 3-1/2 hrs. After usual work-up, the crude product (3.9 g) was analyzed by g.l.c. and proton n.m.r. Apart from the two principal products A and B (present in the ratio 1:2) a small quantity of the diacid 3c and traces of β,β-dimethyl-γ-butyrolactone 3a could be detected. The mixture was separated by bulb to bulb distillation at reduced pressure (0.4 mm Hg). A small quantity of the diacid 3c (m.p. 139-140°, correct proton n.m.r.) was recovered as well as the two principal products: fraction A - white, semicrystalline solid and fraction B - white, crystalline compound.

Fraction A: Appeared to be a mixture of two half esters. Repeated crystallization of A from ethylacetate/petroleum ether (30-60°) gave large, white crystals of a half ester, isopropyl 2,2-dimethylsuccinate, tentatively identified as 79, m.p. 65-67°C; m/e 188 (M<sup>+</sup>);  $\nu_{\max}$  1705 cm<sup>-1</sup> (C=O acid), 1725 cm<sup>-1</sup> (C=O ester), 1200 cm<sup>-1</sup> (ester) also a characteristic broad acid peak 3500 cm<sup>-1</sup> to 2500 cm<sup>-1</sup>;  $\delta$  1.18 (s, 3H, CH<sub>3</sub>), 1.24 (s, 3H, CH<sub>3</sub>), 1.28 (s, 6H, 2xCH<sub>3</sub>), 2.56 (s, 2H, -CH<sub>2</sub>-C=O), 4.99 (quintuplet, 1H, >CH-O), 11.25 (broad s, 1H, -COOH); <sup>13</sup>C n.m.r.  $\delta$  21.72 (q, CH<sub>3</sub>), 25.21 (q, CH<sub>3</sub>), 40.60 (s, -C-), 44.58 (t, -CH<sub>2</sub>-C=O), 68.03 (d, >CH-O), 170.60 (s, -COOR), 178.76 (s, -COOH).

Esterification of 2,2-dimethylsuccinic anhydride with isopropyl alcohol carried out according to the method described by Cason,<sup>75</sup> yielded a mixture of two half esters (78,79) and diester 45 (78:79:45 = 1:2:6).

Fraction B; 80: The major product of the reduction, purified by distillation (0.4 mm Hg fraction 130-165°C) was crystallized from benzene to give white crystals, m.p. 80-81°C. Elemental analysis calculated for  $C_{12}H_{20}O_6$  (260): C:55.38, H:7.69, O:36.92; found: C:55.53, H:7.66, O:36.97; m/e 201 (260-59);  $\nu_{max}$  1705  $cm^{-1}$  with shoulder at 1725  $cm^{-1}$ ;  $\delta$  1.06 (s, 6H, 2xCH<sub>3</sub>), 1.32 (s, 6H, 2xCH<sub>3</sub>), 2.34 (s, 2H, CH<sub>2</sub>-C=O), 2.66 (s, 2H, CH<sub>2</sub>-C=O), 3.94 (s, 2H, CH<sub>2</sub>-O), 11.44 (broad singlet, 2H -COOH); <sup>13</sup>C n.m.r.  $\delta$  24.84 (q) 25.57 (q), 33.69 (s), 40.61 (s), 42.62 (t), 44.18 (t), 71.55 (t), 176.40 (s), 177.73 (s), 178.22 (s). This half ester of 2,2-dimethylsuccinic acid was tentatively identified as 80. Compound 80 was treated with diazomethane prepared from Diazald (Aldrich) and the product 81 was analyzed by proton n.m.r.  $\delta$  1.06 (s, 6H, 2xCH<sub>3</sub>), 1.32 (s, 6H, 2xCH<sub>3</sub>), 2.34 (s, 2H, CH<sub>2</sub>-C=O), 2.66 (s, 2H, CH<sub>2</sub>-C=O), 3.66 (s, 6H, CH<sub>3</sub>O-), 3.94 (s, 2H, -CH<sub>2</sub>-O).

d. Other reduction methods

Sodium in absolute ethanol. The reduction of 3 with Na/EtOH was executed according to the method of Blanc.<sup>7</sup> The material isolated consisted of 65% lactonic product and 20% diacid 3c. G.l.c. and <sup>1</sup>H n.m.r. analyses indicated the ratio of two lactones to be 11:9 in favour of  $\alpha,\alpha$ -dimethyl- $\gamma$ -butyrolactone 3b. The same reaction irradiated with a sun lamp gave the ratio of the two lactones 3a:3b = 6:11. The total yield of lactonic product was 60%.

Sodium in ethylacetate/glacial acetic acid. Anhydride 3 (0.05 moles) was added to a saturated aqueous solution of ethylacetate (150 ml). The

mixture was cooled to  $-5^{\circ}\text{C}$ . Sodium (12 g) was added in small pieces alternately with glacial AcOH (70 ml) in such a manner that the reaction medium was at all times neutral or faintly acid (pH 5-7). The reaction mixture was stirred for 2-1/2 hrs (ice was allowed to melt and temperature slowly raised to  $20^{\circ}\text{C}$ ). The reaction mixture was diluted with distilled water and extracted twice with ether. Organic layers were combined, dried over anhydrous  $\text{MgSO}_4$  and evaporated to give a yellow oil. The aqueous layer was acidified and extracted to give 2.08 g of 2,2-dimethylsuccinic acid 3c. The oily product was distilled at reduced pressure (0.5 mm Hg).  $\nu_{\text{max}}$   $1725\text{ cm}^{-1}$  (C=O ester),  $1700\text{ cm}^{-1}$  (C=O acid);  $\delta$  1.28 (m-singlet over triplet, 9H), 2.60, 2.63 (two singlets, 2H,  $\text{CH}_2\text{-C=O}$ ), 4.18 (two superimposed quartets, 2H,  $\text{CH}_3\text{-CH}_2\text{-O}$ ), 10.2 (s, 1H,  $\text{-COOH}$ ). This mixture when treated with diazomethane (Diazald) gave mixture of two isomeric methyl, ethyl esters of 2,2-dimethylsuccinic acid.  $\nu_{\text{max}}$   $1720\text{ cm}^{-1}$  (C=O ester),  $\delta$  1.26 (singlet over triplet 9H), 2.59 (s, 2H,  $\text{CH}_2\text{-C=O}$ ), 3.66 (s, 3H,  $\text{CH}_3\text{-O}$ ), 4.10 (two superimposed quartets, 2H).

Dimethylsulfide-diborane complex  $(\text{CH}_3)_2\text{S}:\text{BH}_3$  reduction. The reaction was carried out according to the procedure described by Süess.<sup>82</sup> Two attempts were made, one at a bath temperature of  $40^{\circ}\text{C}$  (18 hrs) and the other at  $68^{\circ}\text{C}$  (18 hrs). In both cases no reduction products could be detected by g.l.c. analysis.

Reduction with Colman reagents  $[\text{Na}_2\text{Fe}(\text{CO})_4]$ . 2,2-Dimethylsuccinic anhydride 3 (0.01 mole) in THF (10 ml) was added with stirring to  $\text{Na}_2\text{Fe}(\text{CO})_4$  (0.01 mole) in THF (50 ml) at room temperature under argon atmosphere. After 20 minutes, the reaction mixture was treated with glacial AcOH

(1.2 ml) and stirred for an additional 5 minutes. Then it was diluted with water and extracted with ether. The crude reduction product was highly coloured and gave poor i.r. spectrum. However, the bands characteristic for the anhydride seemed to have disappeared. The crude oil was treated with  $\text{NaBH}_4$  in THF. Apart from the diacid 3c, lactone 3a was the only other compound present (no trace of the isomeric lactone 3b could be detected by g.l.c.).

e) Hydrogen trapping experiments

Hydrogen evolution in  $\text{LiAlH}_4$  reduction of 2,2-dimethylsuccinic anhydride 3. The assembly shown in Figure 53 was used in  $\text{H}_2$  trapping experiments. All glass apparatus was dried in an oven and cooled in a stream of nitrogen.  $\text{LiAlH}_4$  (0.01 mole) was placed in the reaction vessel and THF (50 ml) distilled directly into the flask. The anhydride (0.01 mole) was melted and poured into the pail containing a magnet. The reaction apparatus was assembled, and the solution was stirred at room temperature under a slow stream of argon for 15 minutes. The gas burette was flushed with argon, then closed to the air. The reaction vessel was placed in a dry ice/acetone bath and allowed to equilibrate for 15 minutes and the argon flow was stopped. The three-way stopcock was opened to the gas burette and after a few minutes of equilibration the reading on the burette was taken. At this point, the pail containing the anhydride was dropped (with the help of a strong magnet) into the  $\text{LiAlH}_4/\text{THF}$  solution. The vigorously stirred reaction was allowed to warm to  $0^\circ$  over a period of 90 minutes. The final reading on the burette was taken. The average figure for three trials was 44 ml (47 ml, 42 ml, 44 ml). The blank run

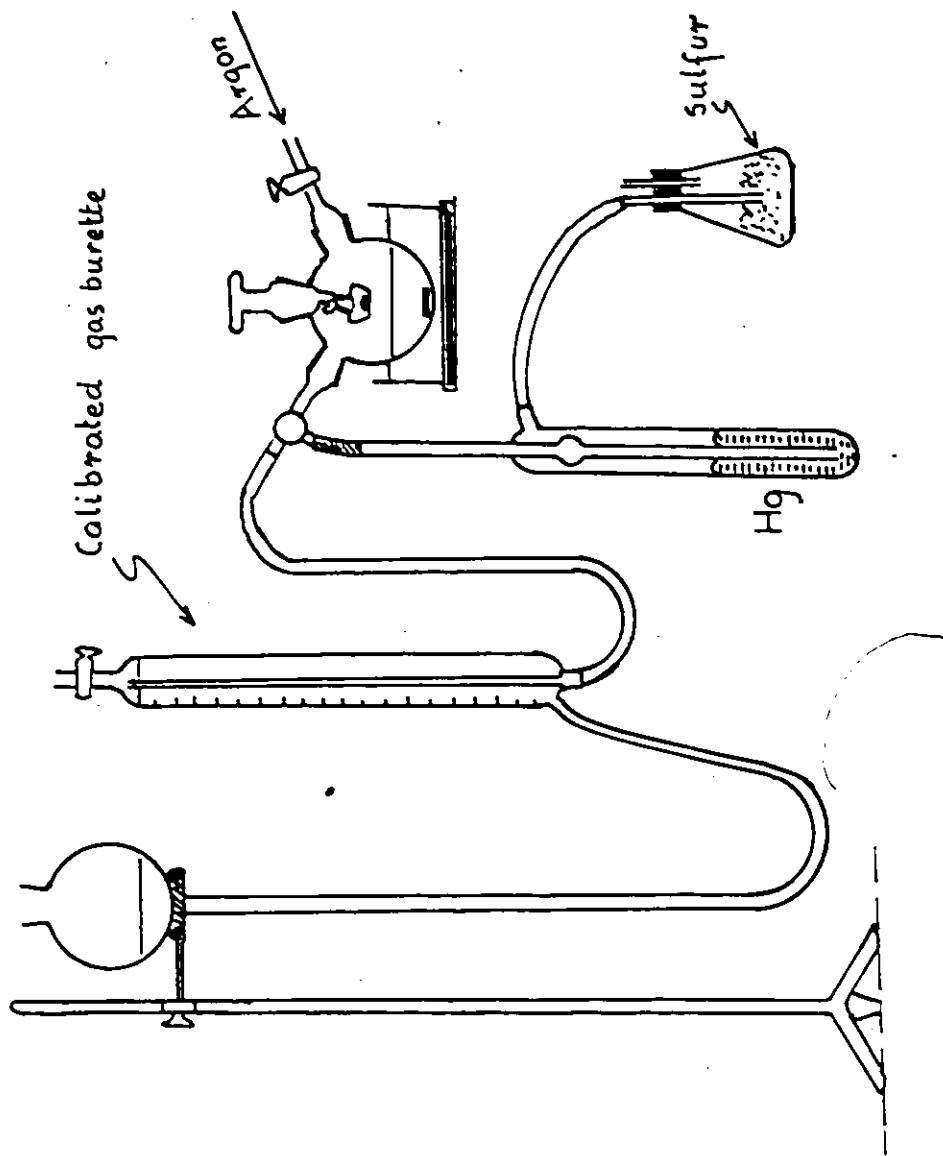


Figure 53. The apparatus used in  $H_2$  trapping experiments.

showed that volume expansion due to the warming of the reaction flask from dry ice/acetone bath temperature to 0°C was on average 37 ml (4 blank runs).

It may be deduced that the 7 ml increase in volume is due to H<sub>2</sub> evolution. However, this figure is small and lies within the range of experimental error. Consequently, these results are inconclusive. Furthermore, the reaction mixture quenched with D<sub>2</sub>O/DCl did not show deuterium incorporation into the product (proton n.m.r. analysis). This, however, is to be expected since 7 ml (gas evolution) per 0.01 mole of anhydride corresponds to only 3% enolization.

Hydrogen evolution in LiAlH<sub>4</sub> reduction of three model ketones. The apparatus was assembled as shown in Figure 53. The reduction of ketones was commenced at 0°C (ice/water bath) and terminated at room temperature (23°C). Otherwise, the general procedure described above was utilized. The products were analyzed by g.l.c.

Cyclohexanone (0.01 mole) was added to the solution of LiAlH<sub>4</sub> (0.01 mole) in THF (50 ml). There was a surge of gas (12.5 ml within 30 seconds). The total volume increase (noted after 1-1/2 hrs at 23°C) was 37 ml. The analysis of the product showed 90% cyclohexanol and 10% of cyclohexanone.

Acetophenone (0.01 mole) was added to the solution of LiAlH<sub>4</sub> (0.01 mole) in THF (50 ml). 10 ml of gas were collected within 30 seconds. At the end of the reaction (1-1/2 hrs, 23°C) an additional 27 ml volume increase was observed. The g.l.c. analysis of the product showed a mixture of alcohol (74%) and unreacted acetophenone (26%).

Benzophenone (0.01 mole). Under the reduction conditions described above no initial gas evolution was observed. Total reading on the burette at the end of reaction was 35 ml. The product consisted of alcohol (68%) and ketone (32%).

Blank runs. The blank runs (4) showed the volume expansion due to warming of the reaction flask from 0°C to room temperature to be on average 25 ml (24 ml, 25 ml, 25 ml, 27 ml).

4. Reductions of 2,2-dimethylglutaric anhydride 4

a. LiAlH<sub>4</sub> reduction

2,2-Dimethylglutaric anhydride 4 was reduced under standard conditions. The crude product was isolated in 89% yield. Lactonic product (72%) was obtained by column chromatography. G.l.c. analysis (6 ft, 10% carbowax, 135°C) of the crude product showed a ratio of 4a:4b to be 9:1. 4,4-Dimethyl-δ-valerolactone 4a<sup>84</sup>  $\nu_{\max} 1730 \text{ cm}^{-1}$ ;  $\delta$  1.06 (s, 6H, 2xCH<sub>3</sub>), 1.69 (t, 2H), 2.56 (t, 2H, CH<sub>2</sub>-C=O), 3.97 (s, 2H, CH<sub>2</sub>-O).

b. Catalytic hydrogenation [with RuCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>3</sub>]<sup>80</sup>

The crude reduction product (79%) was analyzed by g.l.c.. Essentially one lactonic product 2,2-dimethyl-δ-valerolactone (4b) was present,  $\delta$  4.22 (t, 2H, CH<sub>2</sub>O). Only traces of the isomeric lactone 4a could be detected by g.l.c.

5. Reduction of steroidal anhydrides 20 and 21

The anhydrides 20 and 21 were prepared by P. Crosby. The analyses, i.r. and proton n.m.r. spectra were consistent with the assigned structures.

Reduction of anhydride 20

The anhydride 20 was reduced with  $\text{LiAlH}_4$  in THF according to the general procedure. Crystalline lactonic product 20a was isolated in 90% yield. After recrystallization from chloroform/petroleum ether, (60-90°C), m.p. was 174-176°C,  $\nu_{\text{max}}$  1770  $\text{cm}^{-1}$  (C=O lactone);  $\delta$  1.18 (s, 3H,  $\text{CH}_3$ -), 3.80 (s, 3H,  $-\text{OCH}_3$ ), 4.00 (q, 2H,  $-\text{CH}_2-\text{O}$ ). This product was identical with the lactone obtained from the  $\text{NaBH}_4$  reduction according to the method of Belleau and Puranen.<sup>11</sup>

Reduction of anhydride 21

$\text{LiAlH}_4$  reduction of the anhydride 21 under the general conditions gave the lactone 21a (74% yield). Recrystallization from chloroform/petroleum ether (30-60°C) gave product melting at 159-160°C, identical with the sample obtained from  $\text{NaBH}_4$  reduction according to the method of Belleau and Puranen.<sup>11</sup>  $\nu_{\text{max}}$  1775  $\text{cm}^{-1}$  (C=O lactone);  $\delta$  1.35 (s, 3H,  $\text{CH}_3$ ), 3.72 (s, 3H,  $\text{CH}_3\text{O}$ -), 4.09 (q, 2H,  $-\text{CH}_2-\text{O}$ ).

6. Synthesis and reduction of 2,2-diphenylsuccinic anhydride 19

2,2-Diphenylsuccinic acid 19c was prepared according to the method of Makosza<sup>70</sup> by condensing, under phase transfer conditions, diphenyl-

acetonitrile with methyl bromoacetate. The product, 3,3-diphenyl-3-cyanopropionic acid 46 was obtained in 76% yield, m.p. 178-181°C, m/e 251 ( $M^+$ );  $\nu_{\max}$  2220  $\text{cm}^{-1}$  (C≡N);  $\delta$  3.5 (s, 2H), 7.3 (s, 10H).

Hydrolysis of the pure 46 by refluxing for 12 hrs in a mixture of conc.  $\text{H}_2\text{SO}_4$  and glacial AcOH (1:1) gave 2,2-diphenylsuccinic acid 19c (60% yield), m.p. 179-180°C, m/e 252 ( $M-\text{H}_2\text{O}$ );  $\nu_{\max}$  1710  $\text{cm}^{-1}$ ;  $\delta$  3.6 (s, 2H), 7.33 (s, 10H). The diacid 19c was heated gently to melting; needle-like crystals of 2,2-diphenylsuccinic anhydride 19 were formed upon cooling, m.p. 89-91°C (Lit<sup>89</sup> m.p. 90.5-92°C);  $\nu_{\max}$  1735  $\text{cm}^{-1}$  and 1800  $\text{cm}^{-1}$  (C=O anhydride);  $\delta$  3.66 (s, 2H), 7.36 (s, 10H).

2,2-Diphenylsuccinic anhydride 19 was reduced with  $\text{LiAlH}_4$  according to the general method. After the acidification step, the mixture was extracted with ether and the extract was processed in the usual manner to give a solid which was recrystallized from chloroform-petroleum ether, (yield 86%) m.p. 98-99°C. Purification by chromatography gave the sample of lactone 19a melting at 108-109° (Lit<sup>90</sup> m.p. 109-110°);  $\nu_{\max}$  1780  $\text{cm}^{-1}$  (C=O lactone),  $\delta$  3.28 (s, 2H), 4.90 (s, 2H), 7.36 (m, 10H). The reduction of 19 with  $\text{NaBH}_4/\text{THF}$  gave 84% yield of the identical product 3,3-diphenyl- $\gamma$ -butyrolactone 19a.

#### 7. Synthesis and reduction of 2,2-dimethyl-3,3-diphenylsuccinic anhydride 18

##### Attempted methylation of 3,3-diphenyl-3-cyanopropionic acid 46.

Freshly distilled diisopropyl amine (2.75 ml, 0.02 mole) dissolved in dry THF was cooled to -78°C. Butyl lithium (12.5 ml, 1.6 M solution in hexane) was added with argon-swept syringe. Compound 46 (1.35 gm, 0.005

mole) dissolved in dry THF was added slowly to the stirred solution of LDA in THF (nitrogen atmosphere,  $-78^{\circ}\text{C}$ ). The resulting bright red solution was slowly warmed to  $0^{\circ}\text{C}$  and methyl iodide (1.5 ml) was added (upon addition of methyl iodide red colour faded rapidly). The solution was diluted with distilled water, acidified with 6N HCl and extracted with chloroform. The extract was processed in the usual manner. The solid residue was crystallized from hot methanol-water to give white crystals (73% yield), m.p.  $157-159^{\circ}\text{C}$ . This product was identified as  $\beta$ -phenylcinnamic acid 47. (Lit.<sup>88</sup> m.p.  $159-160^{\circ}\text{C}$ ); m/e 224 ( $\text{M}^+$ );  $\nu_{\text{max}}$   $1690\text{ cm}^{-1}$ ;  $\delta$  6.34 (s, 1H), 7.33 (s, 10H).

2,2-Dimethyl-3,3-diphenylsuccinic anhydride 18 described by Salmon-Legagneur and Neveu<sup>68</sup> was prepared by an alternate condensation procedure. Diphenylacetonitrile (19.3 g, 0.1 mole) dissolved in dry DMF (dried overnight over  $\text{P}_2\text{O}_5$ , then distilled over molecular sieves) was mixed with NaH (4.7 g, 0.11 mole, 57% oil dispersion), and stirred under nitrogen atmosphere. Ethyl 2-bromoisobutyrate (19.5 g, 0.1 mole) was added slowly. The reaction mixture was refluxed for 2-1/2 hrs, then cooled and poured into ice/water slush. This was extracted with ether and the extract was decolourized with neutral charcoal, dried over anhydrous  $\text{MgSO}_4$  and evaporated under reduced pressure. The crude oil was refluxed with conc. HCl (6 hrs). After usual work-up, the solid anhydride 18 was crystallized from methanol (57% yield), m.p.  $88-90^{\circ}\text{C}$ ;  $\nu_{\text{max}}$   $1770\text{ cm}^{-1}$ ,  $1865\text{ cm}^{-1}$  (C=O anhydride);  $\delta$  1.32 (s, 3H,  $\text{CH}_3$ ), 7.44 (m, 5H,  $\text{C}_6\text{H}_5$ ).

Reduction of 2,2-dimethyl-3,3-diphenylsuccinic anhydride 18 with  $\text{LiAlH}_4$  gave a single lactonic product 2,2-dimethyl-3,3-diphenyl- $\gamma$ -butyrolactone 18a (95% yield), m.p.  $130-132^{\circ}\text{C}$  (the isomeric lactone 18b described

in literature<sup>69</sup> has m.p. 120°C). Elemental anal. calcd. for  $C_{18}H_{18}O_2$ :  
C: 81.17, H: 6.81, found: C: 81.45, H: 6.99,  $\nu_{\max}$  1770  $cm^{-1}$  (C=O lactone);  
 $\delta$ (Acetone- $d_6$ ), 1.25 (s, 3H,  $CH_3$ ), 4.91 (s, 1H,  $CH_2-O$ ), 7.24 (m, 5H,  $C_6H_5$ ).

$LiAlH_4$  reduction of the lactone 18a to the corresponding diol 53  
afforded 95% yield of the crude product. This product, without further  
purification, was refluxed with excess HBr for 1 hour. The solution was  
cooled, diluted with water and extracted with ether. The combined ether  
solution was extracted with saturated solution of sodium bicarbonate and  
then with water. The organic layer was dried over anhydrous  $MgSO_4$  and pro-  
cessed in the usual manner to give a solid which was recrystallized from  
methanol-water. 3,3-Dimethyl-4,4-diphenyltetrahydrofuran 54 crystallized  
as pale yellow needles (74% yield), m.p. 70-71°C; m/e 252 ( $M^+$ );  $\delta$  1.15  
(s, 3H,  $CH_3$ ), 3.71 (s, 1H), 4.72 (s, 1H), 7.24 (m, 5H,  $C_6H_5$ ).

Reduction of the anhydride 18 with  $NaBH_4$  (mole to mole ratio) carried  
out according to the general procedure gave the hemiacetal 52 (87% yield),  
m.p. 149-150°C, Anal. calcd for  $C_{18}H_{18}O_3$ : C: 76.56, H: 6.43, found:  
C: 76.36, H: 6.52,  $\nu_{\max}$  3755  $cm^{-1}$  (OH), 1765  $cm^{-1}$  (C=O),  $\delta$  ( $CDCl_3$ ) 1.1  
(s, 3H,  $CH_3$ ), 1.47 (s, 3H,  $CH_3$ ), 1.9 (d, 1H), 6.44 (d, 1H), 7.34 (m, 10H),  
(when proton n.m.r. was run with addition of  $D_2O$  (d, 1H) at  $\delta$  1.9 dis-  
appeared and (d, 1H) at  $\delta$  6.44 became singlet);  $C^{13}$  n.m.r.  $\delta$  21.29 (q),  
24.65 (q), 49.47 (s), 63.89 (s), 100.18 (d), 127.14 (m).

The hemiacetal 52 was reduced with  $LiAlH_4$  to give 18a. Reduc-  
tion of 18 with excess  $NaBH_4$  (2 moles  $NaBH_4$  to 1 mole 18) afforded the  
lactone 18a (85% yield).

## 8. Reductions of camphoric anhydride 5

### LiAlH<sub>4</sub> reduction

LiAlH<sub>4</sub> reduction under standard conditions gave 70-78% yield of a lactonic product. The unreacted anhydride (20-25%) was recovered. The composition of the mixture was determined by g.l.c. analysis. The ratio of β-campholide 5a to α-campholide 5b was shown to be 3:2. The two lactones were separated on alumina, Woelm basic (activity III), crystallized from low boiling petroleum ether and sublimed. β-Campholide 5a, m.p. 214-216°C (Lit<sup>85,86</sup>, m.p. 213-216°C);  $\nu_{\max}$  1735 cm<sup>-1</sup> (lactone C=O);  $\delta$  0.90 (d, 6H, 2xCH<sub>3</sub>), 1.08 (s, 3H, CH<sub>3</sub>), 4.05 (q, 2H, CH<sub>2</sub>-O). α-Campholide m.p. 210-211°C (Lit<sup>3</sup>, m.p. 210-211°C);  $\nu_{\max}$  1730 cm<sup>-1</sup> (lactone C=O);  $\delta$  0.95 (s, 3H, CH<sub>3</sub>), 1.10 (s, 3H, CH<sub>3</sub>), 1.20 (s, 3H, CH<sub>3</sub>), 4.35 (m, 2H, CH<sub>2</sub>-O). Unequivocal proof of structure for the two lactones was obtained by direct comparison of the lactone 5b with α-campholide prepared by Baeyer-Villiger oxidation of camphor<sup>87</sup>.

### Na/EtOH reduction of camphoric anhydride

Camphoric anhydride was reduced with Na/EtOH under the same conditions as described for the reduction of anhydride 3. The reaction was not clean and many products were formed. The major lactonic product was shown to be α-campholide 5b, identical with the product of Baeyer-Villiger oxidation of camphor. G.l.c. analysis showed only a trace of β-campholide 5a.

9. Reduction of bridged, tricyclic anhydrides

exo-2-Methylnorborn-5-ene-endo-2,3-dicarboxylic acid anhydride 22.

a product of Diels-Alder addition was prepared by P. Crosby, m.p. 139-141°C, Anal. calcd for  $C_{10}H_{10}O_3$ : C: 67.42, H: 5.62; found: C: 67.71, H: 5.76,  $\nu_{\max}$  1770  $cm^{-1}$  and 1850  $cm^{-1}$  (anhydride C=O);  $\delta$  1.6 (s, 3H,  $CH_3$ ), 1.86 (m, 2H), 3.08 (m, 1H), 3.15 (d, 1H), 3.46 (m, 1H), 6.38 (m, 2H).

The anhydride 22 was reduced with  $LiAlH_4$  according to the general procedure to give exo-2-methylnorborn-5-ene-endo-(3-methyl-2-carbo-3a) lactone 22b. Recrystallization from ethylacetate-petroleum ether (30-60°C) gave white crystals (84% yield), m.p. 137-139°C. Anal. calcd for  $C_{10}H_{12}O_2$ : C: 73.17, H: 7.31, found: C: 73.01, H: 7.54;  $\nu_{\max}$  1765  $cm^{-1}$  (lactone C=O),  $\delta$  1.52 (s, 3H,  $CH_3$ ); 4.02 (m, 2H,  $CH_2-O$ ), 6.33 (m, 2H);  $\delta$  (0.5N, NaOD), 3.6 (d, 2H,  $CH_2-O$ );  $C^{13}$  n.m.r.  $\delta$  22.44 (q), 46.71 (t), 47.59 (d), 49.61 (d), 51.91 (d), 53.57 (s), 68.83 (t), 134.24 (d), 137.97 (d), 180.87 (s). A trace of the isomeric lactone 22a could be detected by g.l.c.

The lactone 22b was reduced with  $LiAlD_4$  in THF under the usual conditions to the diol 63. Proton n.m.r. showed a complex multiplet centered at  $\delta$ 3.50. This diol 63 was cyclized to the corresponding ether,  $\delta$ 3.5 (m).

The anhydride 22 was reduced with  $LiAlD_4$  to give the lactone 61, m.p. 142-143°C,  $\delta$ 1.45 (s, 3H,  $CH_3$ ), 1.64 (2H,  $-CH_2$ ), 2.57 (1H), 2.78 (1H), 2.96 (1H), 6.22 (2H).

The lactone 61 was reduced with  $LiAlH_4$  in THF according to the general procedure to give the corresponding diol 62. Proton n.m.r.

showed a characteristic AB quartet centered at  $\delta$ 3.41 (2H,  $-\text{CH}_2-\text{O}$ ). The diol 62 was refluxed with HBr to furnish the corresponding ether, which was not purified further,  $\delta$ 3.42 (q, 2H).

exo-2-Methylbicyclo[2,2,2] oct-5-ene,2,3-endo-dicarboxylic acid anhydride 23, was prepared by P. Crosby, m.p. 182-184°C; Anal. calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_3$ : C: 68.73, H: 6.17, found C: 68.92, H: 6.29;  $\nu_{\text{max}}$  1775  $\text{cm}^{-1}$  and 1850  $\text{cm}^{-1}$  (anhydride C=O);  $\delta$  1.41 (s, 3H,  $\text{CH}_3$ ) superimposed on the multiplet integrating for 4H, 2.62 (d, 1H), 2.80 (m, 1H), 3.4 (m, 1H), 6.33 (m, 2H).

The anhydride 23 was reduced with  $\text{LiAlH}_4$  according to the general procedure to give the crystalline lactone 23b. The sublimed product melted at 184-185°C, (86% yield). Anal. calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2$ : C: 74.15, H: 7.86, found C: 74.75, H: 7.91;  $\nu_{\text{max}}$  1755  $\text{cm}^{-1}$  (lactone C=O);  $\delta$  1.37 (s, 3H,  $\text{CH}_3$ ), 4.05 (m, 2H,  $\text{CH}_2-\text{O}$ ), 6.30 (m, 2H).

Reduction of the anhydride 23 with  $\text{LiAlD}_4$  gave the crystalline deuterated lactone, m.p. 176-179°C,  $\delta$  1.33 (s over multiplet, 7H), 2.19 (1H), 2.66 (2H), 6.32 (2H). Reduction of the deuterated lactone with  $\text{LiAlH}_4$  gave the corresponding diol. Proton n.m.r. showed a characteristic AB quartet centered at  $\delta$ 3.44 (2H,  $\text{CH}_2-\text{O}$ ).

#### 10. Reduction of citraconic anhydride 24

##### $\text{LiAlH}_4$ reduction

Citraconic anhydride was reduced with  $\text{LiAlH}_4$  as described in the general procedure. Upon work-up a yellow oil was recovered (82-87% yield). Proton n.m.r. of the crude product showed 4-hydroxy-3-methyl-

cis-crotonic acid lactone 24a to be the major product. The mixture contained some unreacted anhydride and a small quantity of the isomeric lactone 24b (24a:24b = 9:1).

The lactone 24a was purified by distillation at reduced pressure, b.p. 84-89°C<sup>91</sup>;  $\nu_{\max}$  1780 cm<sup>-1</sup>,  $\delta$  2.16 (s, 3H, CH<sub>3</sub>), 4.74 (s, 2H, CH<sub>2</sub>O), 5.80 (m, 1H, H-C=C).

The isomeric lactone 24b<sup>92</sup> showed  $\delta$  1.92 (m, CH<sub>3</sub>), 7.22 (m, H-C=C-O).

The reduction of citraconic anhydride with NaBH<sub>4</sub> according to the method of Belleau and Puranen<sup>11</sup> gave lactone 24a as the principal product (ratio of 24a:24b in the crude product was 85:15).

#### NaBH<sub>4</sub>/MeOH reduction

Citraconic anhydride (11.2 g, 0.1 mole) was dissolved in spectral grade MeOH. The stirred solution was cooled in an ice-water bath. NaBH<sub>4</sub> (2.27 g, 0.05 mole) was added carefully, portion wise (vigorous reaction!).

After the addition of NaBH<sub>4</sub> was completed, the reaction mixture was allowed to warm to room temperature and stirring was continued for 1-1/2 hours. The usual work-up yielded 8.9 gm of yellow oil. The crude product consisted of citraconic acid dimethyl ester, citraconic acid and a small quantity of the lactone 24a. The distilled product was a mixture of diester and lactone 24a.  $\nu_{\max}$  1730 cm<sup>-1</sup> (C=O ester), 1780 cm<sup>-1</sup> (C=O lactone),  $\delta$  3.85 (doublet, 6H, -OCH<sub>3</sub>).

Sodium in EtOH reduction

Citraconic anhydride 24 (6.3 g, 0.056 mole) dissolved in absolute EtOH (100 ml) was added slowly to sodium (8.5 g) cut in small pieces. The solution was refluxed for 1-1/2 hrs. After cooling, the reaction mixture was diluted with water, acidified with 6N HCl and extracted with ether. The organic layer was extracted with NaHCO<sub>3</sub> solution, which was then acidified and extracted with ether. The ether extract was treated in the usual manner to give crystalline product. It was identified as mesaconic acid 68, m.p. 199-201°C;  $\delta$ (acetone-d<sub>6</sub>), 2.24 (m, 3H), 6.86 (m, 1H), 8.22 (broad band, 2H). No reduction product could be detected in the crude reaction mixture.

11. Reduction of 3- and 4-nitrophthalic anhydrides

Reduction of 3-nitrophthalic anhydride 25 with LiAlH<sub>4</sub> was carried out according to the general procedure. The product, a yellow crystalline substance was isolated in 80% yield. The proton n.m.r. analysis showed the presence of two lactones in the ratio 2:1, where 4-nitrophthalide 25a was the major product. Chromatography on silica gel yielded pure 25a, m.p. 135-136°C (Lit.<sup>93</sup>, m.p. 136°C);  $\nu_{\max}$  1780 cm<sup>-1</sup> (lactone C=O), 1550 cm<sup>-1</sup> and 1370 cm<sup>-1</sup> (NO<sub>2</sub>);  $\delta$  5.75 (s, 2H, CH<sub>2</sub>-O), 7.82 (1H), 8.38 (2H), and 7-nitrophthalide 25b, m.p. 163°C; m/e 179 (M<sup>+</sup>);  $\nu_{\max}$  1765 cm<sup>-1</sup> (lactone C=O), 1530 cm<sup>-1</sup> and 1350 cm<sup>-1</sup> (NO<sub>2</sub>);  $\delta$  5.40 (s, 2H), 7.95 (m, 3H).

Reduction of 3-nitrophthalic anhydride 25 with NaBH<sub>4</sub> in THF according to the procedure described by McAlees, McCrindle and Sneddon<sup>62</sup> gave a mixture of two lactones (total yield 75%), 4-nitrophthalide 25a

(83%) and 7-nitrophthalide 25b (17%). The two lactones were separated by column chromatography and compared with 25a and 25b obtained from the  $\text{LiAlH}_4$  reduction of 25.

4-Nitrophthalic anhydride 26 was produced by refluxing 4-nitrophthalic acid with acetyl chloride.<sup>78</sup> The product (45% yield) was recrystallized from AcOH (glacial), m.p.  $114^\circ\text{C}$ ,  $\nu_{\text{max}}$   $1790\text{ cm}^{-1}$  and  $1860\text{ cm}^{-1}$  (C=O anhydride),  $1550\text{ cm}^{-1}$  and  $1350\text{ cm}^{-1}$  ( $\text{NO}_2$ ).

Reduction of 4-nitrophthalic anhydride 26 with  $\text{NaBH}_4$  according to the procedure of McAlees, McCrindle and Sneddon<sup>62</sup> did not proceed cleanly. The lactonic product was isolated in 56% yield. Chromatography on silica gel afforded pure 5-nitrophthalide 26a, m.p.  $148\text{--}149^\circ\text{C}$  (Lit.<sup>94</sup>, m.p.  $151^\circ\text{C}$ );  $\nu_{\text{max}}$   $1760\text{ cm}^{-1}$  (lactone C=O),  $1525\text{ cm}^{-1}$  and  $1330\text{ cm}^{-1}$  ( $\text{NO}_2$ ),  $\delta$  5.45 (s, 2H,  $\text{CH}_2\text{O-}$ ), 8.27 (m, 3H) and 6-nitrophthalide 26b, m.p.  $140\text{--}141^\circ\text{C}$  (Lit.<sup>95</sup>, m.p.  $141^\circ$ ); m/e 179 ( $\text{M}^+$ );  $\nu_{\text{max}}$   $1780\text{ cm}^{-1}$  (C=O lactone),  $1530\text{ cm}^{-1}$  and  $1350\text{ cm}^{-1}$  ( $\text{NO}_2$ );  $\delta$  5.45 (s, 2H), 7.75 (d, 1H), 8.62 (m, 2H).

Proton n.m.r. analysis of the crude reduction product and the isolated weights of the two lactones showed that 5-nitrophthalide 26a was in slight excess (26a:26b = 55:45).

The proof of structure for the lactone 26b was obtained by comparing it with 6-nitrophthalide prepared by nitration ( $\text{HNO}_3/\text{H}_2\text{SO}_4$ ) of phthalide 69.

Reduction of 26 with  $\text{LiAlH}_4$  gave a poor yield (40%) of lactonic product. The ratio of 26a:26b was estimated to be 60:40.

12. Synthesis and reduction of *trans*-2-methyl-3-phenylsuccinic anhydride 27

Synthesis of the anhydride 27

Benzyl cyanide (11.7 g, 0.1 mole) was dissolved in warm methylene chloride (30 ml). Sodium hydroxide (50% solution in water, 20 ml) containing triethylbenzylammonium chloride (TEBA chloride 0.2 g) was added slowly and the mixture, stirred vigorously, was cooled in an ice-water bath. Ethyl-2-bromopropionate (18.1 g, 0.1 mole) was added dropwise over a period of 20 minutes (10 ml of methylene chloride were added at this point). The reaction mixture was stirred for 1 hour at room temperature, then warmed to 70°C for an additional 1/2 hour and the methylene chloride was evaporated. The resulting brown solid was filtered, then dissolved in water. The aqueous solution was acidified with 6N HCl and upon standing overnight a white-gray solid precipitated (12.82 g, 67% yield). A sample recrystallized from ethanol melted at 183-185°C;  $\nu_{\max}$  3090  $\text{cm}^{-1}$  (characteristic, broad acid peak), 1720  $\text{cm}^{-1}$  (C=O acid). The proton n.m.r. suggested a mixture of two isomers *erythro* 72 and *threo* 73 in the ratio 2:1;  $\delta$ {0.96 (d) and 1.32 (d)}, 3.12 (m), {3.76 (d) and 3.80 (d)}, 7.34 (s).

The mixture of 72 and 73 (9.02 g) was hydrolyzed by refluxing in HCl-glacial AcOH (1:1) for 12 hrs, then poured into ice-water. The precipitate was filtered, dried in air and crystallized from AcOH. 2-Methyl-3-phenylsuccinic acid (two isomers 74 and 75) was isolated in 77% yield, m.p. 175-182°C (lit. 169-172°C<sup>96</sup>, 138-181°C<sup>97</sup>). The mixture of 74 and 75 was refluxed with acetyl chloride.<sup>78</sup> Upon crystallization from AcOH creamy-white crystals were obtained (30% yield), m.p. 118-125°C,

$\nu_{\max}$  1860  $\text{cm}^{-1}$ , 1780  $\text{cm}^{-1}$  (anhydride C=O);  $\delta$  1.50 (d, 3H,  $\text{CH}_3$ ), 3.24 (m, 1H), 3.88 (d, 1H), 7.34 (m, 5H). This product was identified as trans-2-methyl-3-phenylsuccinic anhydride 27. (Proton n.m.r. of the mother liquor showed  $\delta$  0.97 (d) indicating presence of uncyclized acid 74).

Reduction of the anhydride 27 with  $\text{NaBH}_4$  according to the general procedure gave a mixture of lactones 27a and 27b, (total yield of crude lactonic product 98%). Product ratio was determined, by proton n.m.r. analysis, to be 60:40 in favour of the lactone 27b (reduced at the carbonyl group next to methyl substituent). The mixture was separated on a thick layer chromatography plates. The ratio of the isolated lactones 27b:27a was 70:30 (65% total isolated yield). The major product lactone 27b was crystallized from petroleum ether (60-80°C); m.p. 92-94°C (Lit<sup>98</sup> 93-94°C);  $\nu_{\max}$  1765  $\text{cm}^{-1}$  (C=O lactone);  $\delta$  1.23 (d, 3H,  $\text{CH}_3$ ), 2.66 (m, 1H), 3.28 (d, 1H), 4.18 {m, 2H-(3.86(t,1H), 4.49(t,1H))}, 7.34 (m, 5H). The isomeric lactone 27a did not crystallize,  $\nu_{\max}$  1770  $\text{cm}^{-1}$ ;  $\delta$  1.28 (d, 3H,  $\text{CH}_3$ ), 2.73 (m, 1H), 3.30 (m, 1H), 4.34 {m, 2H-(4.13(t, 1H), 4.54(t,1H))}.

Reduction of the anhydride 27 with  $\text{LiAlD}_4$  according to the general procedure gave a mixture of several products, which was difficult to analyze by proton n.m.r. The major product, deuterated lactone 27b, was isolated upon two crystallizations from dry ether, (40% yield) m.p., 91-93°C;  $\nu_{\max}$  1775  $\text{cm}^{-1}$  (lactone C=O);  $\delta$  1.12 (d, 3H,  $\text{CH}_3$ ), 2.52 (m, 1H), 3.26 (d, 1H), 7.28 (m, 5H). The significant quantity of the major lactone 27b remained in the mother liquor. Separation by thick layer chromatography afforded the isomeric lactone,  $\delta$  1.17 (d, 3H,  $\text{CH}_3$ ), 2.61 (m, 1H), 3.19 (d, 1H), 7.26 (m, 5H).

Proton n.m.r. of the crude reduction product and the quantities of the isomeric lactones isolated by the thick layer chromatography indicate that lactone 27b is the major product (approximately  $\underline{27b}:27a = 70:30$ ). However, it is not possible to indicate accurately the original ratio of the two lactones formed during the reduction.

### 13. Synthesis and reduction of p-methoxyphenylsuccinic anhydride 28

#### Synthesis of the anhydride 28

p-Methoxyphenylsuccinic acid was prepared according to the method of Askam and Linnell.<sup>97</sup> The diacid (0.5 mole) was refluxed with acetyl chloride (1.5 mole) for 2 hrs. Acetyl chloride and acetic acid were distilled under vacuum. The dark brown residue was dissolved in dry  $\text{CHCl}_3$ , a white precipitate formed rapidly, m.p. 83-84°C;  $\nu_{\text{max}}$  1870  $\text{cm}^{-1}$  and 1790  $\text{cm}^{-1}$  (anhydride, C=O);  $\delta$  3.24 (m, 2H,  $-\text{CH}_2$ ), 3.82 (s, 3H,  $\text{CH}_3\text{O}$ ), 4.28 (m, 1H), 7.04 (sym m 4H).

The anhydride 28 was reduced with  $\text{NaBH}_4$  according to the general procedure. Work-up afforded a mixture of two isomeric lactones (crude yield 97%). Proton n.m.r. analysis showed the ratio of 28a:28b to be 2:1. The lactones were separated by thick layer chromatography (78% yield of the isolated lactonic product). 3-p-Methoxyphenyl- $\gamma$ -butyrolactone 28a, m.p. 68-69°C,  $\nu_{\text{max}}$  1765  $\text{cm}^{-1}$  (lactone C=O);  $\delta$  2.72 (octet, H), 3.76 (s over multiplet, 4H), 4.4 (sym. m -{4.20 (t; 1H), 4.61(t, 1H)}), 7.0 (sym. m. 4H). 2-p-Methoxyphenyl- $\gamma$ -butyrolactone 28b, m.p. 60-63°C;  $\nu_{\text{max}}$  1760  $\text{cm}^{-1}$  (lactone C=O),  $\delta$  2.50 (m, 2H), 3.78 (s over multiplet, 4H), 4.4 (m, 2H), 7.0 (sym. m. 4H). Unequivocal proof of structure for the two lactones was obtained

by comparison of 28a and 28b with 3-p-methoxyphenyl- $\gamma$ -butyrolactone and 2-p-methoxyphenyl- $\gamma$ -butyrolactone prepared by alternate methods by G. Beauchamp in this laboratory.

Reduction of the anhydride 28 with  $\text{LiAlH}_4$  gave a mixture of two lactones (75% yield). The ratio of 28a:28b was found to be 2:1 (68:32).

14. Synthesis and reduction of p-nitrophenylsuccinic anhydride 29.

Synthesis of the anhydride 29. p-Nitrophenylsuccinic acid was prepared by the modified method of Lange and Korykowska.<sup>100</sup> Phenylsuccinic acid (24.3 g) dried overnight in the oven at 125°C was added portion-wise to an ice-cold mixture of fuming  $\text{HNO}_3$  (16.0 g), acetic anhydride (25.5 g), glacial AcOH (15.0 g) and a few drops of conc.  $\text{H}_2\text{SO}_4$ . The mixture was stirred overnight at room temperature then poured into ice-water. The precipitate was crystallized from boiling water (72% yield), m.p. 218-219°C. (lit.<sup>100</sup> 219-221°C);  $\delta$ (acetone  $d_6$ ) 3.01 (m, 2H), 4.28 (m, 1H), 7.96 (sym. m., 4H).

p-Nitrophenylsuccinic acid (3.0 g) was refluxed with acetyl chloride (7.5 g) for 1 hour. Unreacted acetyl chloride was removed by careful distillation under reduced pressure. In order to remove acetic acid, the crude anhydride (contaminated with AcOH) was placed in a beaker in a desiccator containing fresh NaOH pellets. The desiccator was evacuated (5 mm Hg, for 18 hours). The resulting dark brown oil was dissolved in reagent grade chloroform and decolourized with activated charcoal. Upon evaporation of the solvent a pale yellow oil was obtained (1.2 g)  $\nu_{\text{max}}$  1870  $\text{cm}^{-1}$ , 1790  $\text{cm}^{-1}$  (anhydride C=O).

Reduction of p-nitrophenylsuccinic anhydride 29 (0.6 g) with  $\text{NaBH}_4$  under the standard conditions yielded a yellow oil. Proton n.m.r. and i.r. spectra showed presence of the lactonic product and the diacid. Separation on thick layer chromatography plates gave 2-p-nitrophenyl- $\gamma$ -butyrolactone 29b (0.05g) and 3-p-nitrophenyl- $\gamma$ -butyrolactone 29a (0.065g), a mixture of both lactones (0.1 g) and the diacid (0.23 g). The total yield of lactonic product was estimated to be 35%. The ratio of 29a:29b was estimated to be 55:45 from the proton n.m.r. spectrum of the crude reaction product.

The lactone 29a was a yellow crystalline substance melting at 105-108°C;  $\nu_{\text{max}}$  1770  $\text{cm}^{-1}$  (lactone C=O);  $\delta(\text{CDCl}_3)$ , 2.8 (octet, 2H), 3.8 m, 1H), 4.4 (m, 2H); 7.78 (sym. multiplet, 4H). The isomeric lactone 29b failed to crystallize;  $\nu_{\text{max}}$  1765  $\text{cm}^{-1}$ ,  $\delta(\text{CDCl}_3)$ , 2.95 (m, 2H); 4.22 (m, 3H), 7.85 (m, 4H).

The proof of structure for the two lactones was obtained by comparison of 29a and 29b with 3- and 2-p-nitrophenyl- $\gamma$ -butyrolactone prepared by alternate synthetic routes by G. Beauchamp in this laboratory.

#### 15. Reduction of dicarboxylic acids

##### Reduction of 2,2-dimethylsuccinic acid 3c

A solution of 2,2-dimethylsuccinic acid, 3c (6.5 g; 0.045 mole) in anhydrous ether (200 ml) was added at -20° to a stirred solution of  $\text{LiAlH}_4$  (0.95 g, 0.025 mole) in anhydrous ether (50 ml over a period of 40 minutes). After allowing to warm to room temperature, the reaction mixture was cooled in an ice-bath and acidified with 6N HCl. Stirring was continued until the reaction mixture became clear (1.5 hrs.). The organic layer was separated and the aqueous layer extracted twice with ether. The combined

organic layers were dried with anhydrous  $\text{MgSO}_4$  and concentrated. The unreacted diacid (3.8 g) crystallized and was filtered. The remaining mixture was concentrated further to give an oily product (1.7 g). The g.l.c. and proton n.m.r. analyses showed a mixture of two lactones:  $\beta,\beta$ -dimethyl- $\gamma$ -butyrolactone 3a and  $\alpha,\alpha$ -dimethyl- $\gamma$ -butyrolactone 3b in a ratio of 2.3:1.

Reduction of 2,2-diphenylsuccinic acid 19c

(a) A solution of 2,2-diphenyl succinic acid 19c (2.7 g, 0.01 mole) in dry THF (50 ml) was added at  $-15^\circ\text{C}$  to a stirred solution of  $\text{LiAlH}_4$  (0.19 g, 0.005 mole) in THF (25 ml). The reaction mixture was warmed to room temperature over a period of 4 hrs. After cooling in an ice-bath the reaction mixture was acidified with 6N HCl. The organic layer was separated and the aqueous layer extracted twice with ether. The combined organic layers were dried over anhydrous  $\text{MgSO}_4$  and concentrated. The oil obtained (2.18 g, 81%) was analyzed by proton n.m.r. The mixture consisted of 50% lactonic product and 50% unreacted acid. The acid was removed by extraction with saturated  $\text{NaHCO}_3$  solution. The remaining lactones were found to be present in a ratio of 2.5:1 in favour of  $\beta,\beta$ -diphenyl- $\gamma$ -butyrolactone 19a.

(b) Overnight reduction at room temperature yielded crude corresponding diol. The product, analyzed by proton n.m.r., showed a mixture of 80% corresponding ether and 20% of lactonic material with  $\beta,\beta$ -diphenyl- $\gamma$ -butyrolactone 19a being more abundant (2:1).

Reduction of cis-1-methylcyclohex-4-ene-1,2-dicarboxylic acid 11c

The reduction of 11c according to methods A and B yielded only crude starting material on usual work-up.

16. Reduction of diisopropyl 2,2-dimethylsuccinate 45

Preparation of the diester 45

2,2-Dimethylsuccinic anhydride 3 (0.05 mole), isopropyl alcohol (45.0 g, 0.75 mole) and conc.  $H_2SO_4$  (3.8 ml) were refluxed for 180 hours. Isopropyl alcohol was removed by distillation and product was distilled at reduced pressure,  $\delta$ 1.19 (d, 6H), 1.24 (d, 12H), 2.53 (s, 2H,  $CH_2-C=O$ ), 4.98 (split quintuplet, 2H, CH-O).

Reduction of diisopropylester of 2,2-dimethylsuccinic acid 45

The diester 45 (1.4 g, 0.006 mole) dissolved in dry THF (20 ml) was cooled and added dropwise to a stirred solution of  $LiAlH_4$  (0.19 g, 0.005 mole) in THF (10 ml), cooled in a dry-ice-acetone bath. The reaction mixture was stirred for 4-1/2 hrs. at  $-15^\circ C$ , then quenched with distilled water and acidified with 6N HCl. The reaction mixture was worked up in the usual manner to give an oil (0.99 g). The reduction product was analyzed by g.l.c. and proton n.m.r. The mixture consisted of 2,2-dimethyl- $\gamma$ -butyrolactone 2a (22%) and unreacted diester 45 (45%).

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## CLAIMS TO ORIGINAL RESEARCH

1. Mechanism for the reduction of unsymmetrically substituted cyclic anhydrides with metal hydrides:
  - a) application of the results of crystallographic studies and of theoretical calculations to predict the path of the nucleophilic approach to the carbonyl group in cyclic anhydrides;
  - b) definition of a new set of steric restrictions for the transition state of the  $H^-$  addition to the carbonyl group in unsymmetrically substituted cyclic anhydrides;
  - c) proposition that preferential attack of the alkaline cation occurs on the carbonyl group most basic in nature;
  - d) proposition that such an attack is site-determining in moderately hindered anhydrides;
  - e) proposition that cation and hydride ion add to the same carbonyl group;
  - f) experimental evidence suggesting that the above stated factors are operative in the reductions of cyclic anhydrides with metal hydrides.
2. Experimental evidence supporting the proposition that electronic factors play an important role also in controlling regioselectivity in the reduction of unsymmetrically substituted diacids and diesters.
3. Several new reductions of unsymmetrical cyclic anhydrides. Analysis and structure determination of products.
4. Optimization of the method appropriate for the reduction of cyclic anhydrides.
5. Development of reduction method selective for the less hindered carbonyl function in 2,2-disubstituted cyclic anhydrides.

LIST OF PUBLICATIONS FROM THE THESIS

P. Morand and M. Kayser J.C.S. Chem. Commun., 314 (1976).

M. Kayser and P. Morand Can.J. Chem., 56 1524 (1978).

M. Kayser and P. Morand Tetrahedron Lett., 695 (1979).

M. Kayser and P. Morand accepted for publication, J. Org. Chem.