PREFACE

Part I

Participation by both σ and π carbon-carbon bonds has been well demonstrated in many solvolytic reactions. These phenomena in solvolytic reactions have been attributed to the intervention of non-classical carbonium ion intermediates. For the past ten years, investigators have failed to demonstrate the intervention of non-classical free radical intermediates in free-radical addition reactions. However, free-radical addition reactions could be complicated by steric and strain factors. The purpose of this part of the work was to synthesize exo and endo t-butyl norbornan-2-percarboxylate and exo and endo t-butyl norborn-5-ene-2-percarboxylate such that a comparative decomposition of the four peresters could be carried out to further investigate σ and π participation in free radical reactions.

Part II

In recent years, chemists have made many structure modifications and related analogs of biologically active compounds that are found in nature for the purpose of improving their usefulness as therapeutic agents. Recently, a new group of penicillin-like antibiotics known as the cephalosporins have been discovered. The purpose of this part of the work was to carry out exploratory synthesis of an isoquinoline derivative with structure related to cephalosporin C. Attempts were also made to prepare α-ketopropionate-β-lactam as an intermediate in the synthesis of other cephalosporin C related compounds.

The author gratefully thanks his research supervisors, professor R. R. Fraser and professor B. Belleau, for their unfailing guidance, invaluable advice and constant encouragement throughout the course of this research.

The technical assistance of the technical staff of the University of Ottawa is gratefully acknowledged as well as the helpful discussion and constructive criticism of fellow students.

Finally, acknowledgement is made to the National Research Council of Canada and Bristol Laboratories for their studentships.

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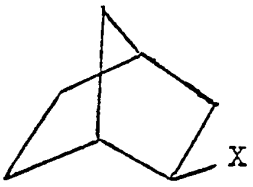
PART I

The Generation of
Norbornyl and Norbornenyl Free Radicals
by
Thermal Decomposition of Peresters

INTRODUCTION

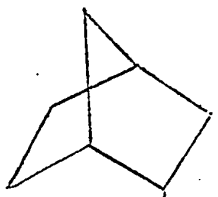
The ability of the C_1-C_6 single bond in norbornane or the C_5-C_6 double bond in norbornene to stabilize a carbonium ion developing at C_2 has been demonstrated by the solvolytic behavior of norbornane-2 and norbornene-2 derivatives. However, experimental evidence for these types of stabilization in the corresponding free radical systems have yet to be found.

S. Winstein and his co-workers[1,2] have found that sulfonate esters of exo-norbornan-2-ol (Ia, Ib and Ic) solvolized 350 times faster than sulfonate esters of the endo-norbornane-2-ol (IIa, IIb and IIc), and that sulfonate esters of exo-norborn-5-ene-2-ol (VIa, VIb, and VIc) solvolized 7000 times faster than their corresponding endo isomers (VIIa, VIIb and VIIc). J. D. Roberts[3,4,5], found a smaller exo-endo solvolysis rate factor in the 2-chloronorbornanes and 2-chlornorborn-5-enes than S. Winstein's sulfonate esters, but, there is a general agreement that there is an accelerated rate of solvolysis in the exo isomers. Solvolysis of the optically active exo-norbornyl brombobenzenesulfonate (Ia) in acetic acid and in aquous acetone was found to give racemic exo-norbornyl-2-acetate (IVa and Va) and exo-norbornane-2-ol (IVb and Vb) respectively. Solvolysis of the optically active endo-norbornyl bromobenzenesulfonate gives only racemic exo products also. S. Winstein and D. Trifan argued convincingly that a bridged-type of non-classical carbonium ion intermediate (III)similar to the one proposed to explain the rearrangement of camphene hydrochloride to isobornylchloride[6] was involved. The isomer with the leaving group exo to the ethano bridge has the favourable geometry for σ participation, that is, the participation by C_1- C_6 bonding electron



I

X = (a) $BrC_6H_4SO_2$
(b) $CH_3C_6H_4SO_2$
(c) $C_6H_5SO_2$



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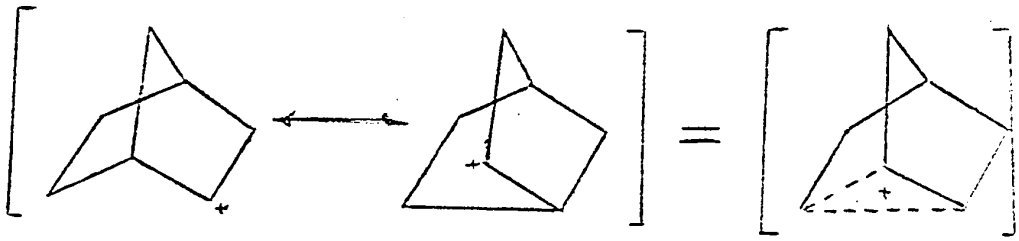

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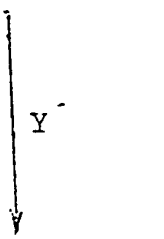
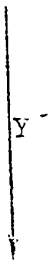
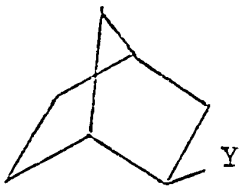
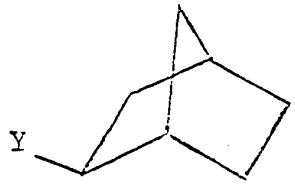




Y = (a) Ac
(b) OH



IV

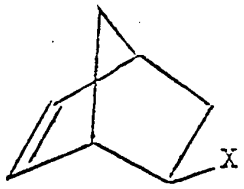


V

pair in the rate determining ionization process, which results in an enhanced ionization rate. The isomer with the leaving group endo to the ethano bridge does not have this favourable geometry for σparticipation; thus, upon ionization, it initially forms the classical carbonium ion which rearranges to the more stable bridged structure. Since both the exo and endo isomers ultimately produce the same intermediate (III) and since positions 1 and 2 of this intermediate are equivalent, an attack by an incoming group at position 2 would give the exo product (IV), while an attack by an incoming group at position 1 would give the exo product (V). This would explain the racemic exo products resulting from the solvolysis of both exo and endo norbornyl p-bromobenzenesulfonates.

The above interpretation of the high exo-endo rate ratio in norbornyl system as attributed to the intervention of non-classical carbonium ion has recently been challenged by H. C. Brown[7], who has found that the rate of ethanolysis of 2-phenyl-exo-norboryl chloride at 25° is 10,000,000 times greater than that of the 1-phenyl-exo-norbonyl derivative. He argued that, if non-classical carbonium ion was involved then, phenyl subsitutions at 1 and 2 position should resulted in similar rate of solvolysis, since position 1 and 2 in the non-classical carbonium ion intermediate are equivalent. However, the question of non-classical carbonium ion intervention, and the question of the structure of the carbonium ion intermediate involved, whether it is a single mesomeric species or a rapidly equilibrating pair of classical ions, have been subjected to much speculation and controversy[8].

In the norbornenyl system, solvolysis of the exo isomer

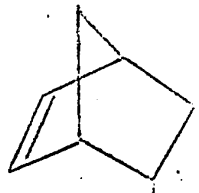


VI

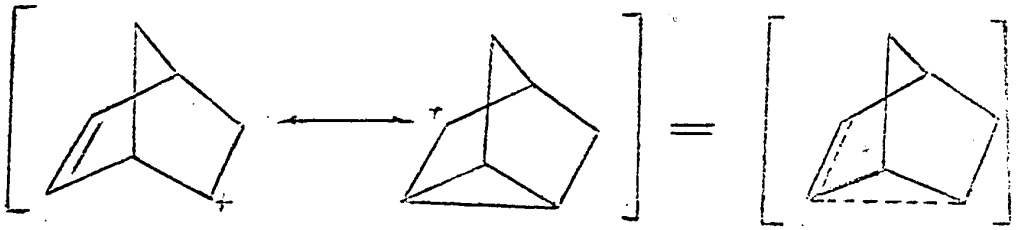
X = (a) $BrC_6H_4SO_2$

(b) $CH_3C_6H_4SO_2$

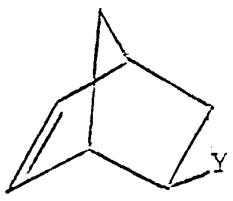
(c) $C_6H_5SO_2$



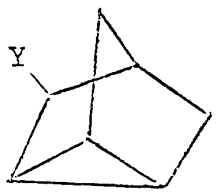
VII



VIII



IX



X

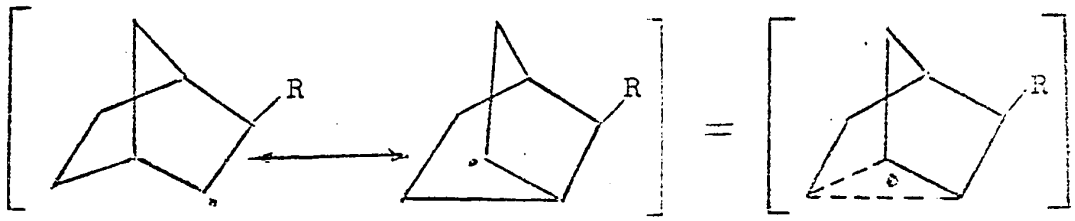
Y = (a) Ac

(b) OH

(VI), or the endo isomer (VII) gave a mixture consisting of the unsaturated product (IX) and the homoallylic rearranged tricyclic product (X). In this case too, the intervention of the non-classical carbonium ion intermediate (VIII) has been suggested[2,3,4]. The isomer with the leaving group exo has a favourable geometry for π participation, that is, the participation by the C_5-C_6 double bond in the rate determining ionization process, which results in an enhanced rate of ionization. The isomer with the leaving group endo does not have this favourable geometry for π participation, thus ionization must take place unassisted. This type of interaction was first noted for the cholesterol system[9], and later also noted for the anti-7-norbornenyl system[10] as well as the bicyclo [2.2.2] octene system[11].

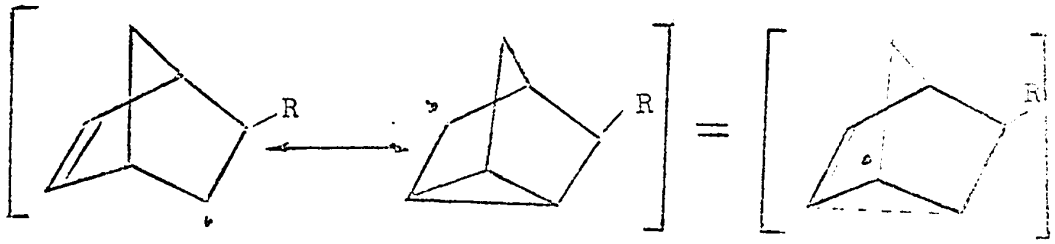
With σ and π participation well demonstrated in solvolytic reactions, it would be of interest to investigate whether similar types of σ and π participation can occur in analogous free radical reactions, and whether non-classical free radical intermediates (XI and XII) have to be considered.

In 1954, S. J. Cristol and G. D. Brindell[12] found that the addition of p-thiocresol to norbornene gave pure exo-norbornyl p-thioether without contamination with measurable amount of either the endo isomer, or the anticipated rearrangement produce, 7-p-thiocresoxy norbornane. If a symetric non-classical free radical intermeidate was involved, a Wagner-Meerwein type of rearrangement would occur and would give 7-p-thiocresoxy norbornane as one of the products. On this basis they concluded that non-classical free radical intermediate need not be considered. However, they found



XI

R = H



XII

norbornene to be 45 times as reactive towards the p-thiocresoxy radical as is cyclohexene, and they have no evidence to show whether this enhancement in reactivity is due to destabilization owing to the strained norbornene molecule or due to stabilization in the transition for the norbornene addition reaction.

J. A. Berson and W. M. Jones[13] later carried out the addition of p-thiocresol to exo-cis-3,6-endomethylene tetrahydrophthalic anhydride. Upon desulfurization of the addition product, they found only exo-cis-3,6-endomethylene hexahydrophthalic anhydride. Thus, the main product was the unarranged p-tolythioether. If Wagner-Meerwein type of rearrangement was involved, they should also find the endo-cis anhydride upon desulfurization. This finding confirms the fact that Wagner-Meerwein type of rearrangement is not a common phenomenon in radical additions. On the other hand, if the non-classical free radical was involved, rearrangement would necessarily appear only if position C_1 and C_2 are equivalent which is not true in this case.

E. C. Kooyman and G. C. Vegter[14] from competitive free radical initiated monohalogenations of norbornene and cyclohexene by various reagents viz. Cl_2, CCl_4, SO_2Cl_2, PCl_5, Br_2, $CBrCl_3$, and N-bromosuccinimide indicated that the methylene groups in cyclohexene and in the six-member ring of norbornane are about equally reactive towards various attacking radicals. They concluded that the 2-norbornyl radical is not appreciably stabilized by addition resonance as compared with the cyclohexyl radical.

In 1960, N. LeBel[15] carried out the gaseous hydrogen

bromide addition to 2-bromo-2-norbornene and found the main products to be trans-2,3 -dibromonorbornane and exo-cis-2,3 dibromonorbornene. The ratio of trans-2,3-dibromonorbornane to exo-cis-2,3-dibromonorbornane varies from 2.8 to 1.8 depending on the reaction condition. He believed that exo-cis-2,3-dibromonorbornane represents a trans free radical addition and its formation is due to fast hydrogen abstraction before conformational changes can take place. No endo-cis-2,3-dibromonorbornane was formed. He concluded that the preponderant formation of trans-2,3-dibromonorbornane by a cis addition process contributes to the evidence against a bridged non-classical free radical intermediate. In the following year, S. J. Cristol and J. A, Reeder[16] came to the same conclusion when they found that the free radical addition of p-toluenesulfonyl chloride to norbornene and to aldrin led to the formation of trans 1,2 addition products without skeletal rearrangement or cis-exo addition products being noted.

In 1958, S. J. Cristol, G. D. Brindell and J. A. Reeder[17] found that the addition of p-thiocresol to norbornadiene under free radical condition lead to a mixture of exo-5-norbornen-2-ylearyl thioether due to 1,2 addition and 3-nortricycloyl aryl thioethers due to 1,5 homo-conjugative addition. These products can be derived from the two isomeric free radicals or from a non-classical mesomeric homallylic radical for which the two isomeric free radical might be considered resonance structures. To determine which type of intermediate was actully involved, they devised an experiment based on the method of Seubold[18]. When the mechanistic scheme involving the

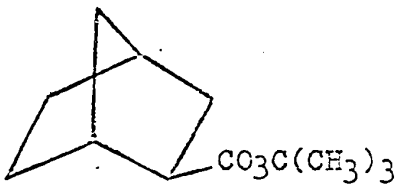
non-classical free radical as intermediate was considered, and the relationship between the two products was derived, it was found that the ratio of the unsaturated product and the tricyclo product should be constant and independent of the concentration. However, it was observed that the ratio depended upon the initial thiol concentration; thus, they decided against the non-classical free radical as the reaction intermediate. But, it was observed that p-thiocresoxy radical reacts more rapidly with norbornadiene than with norbornene and cyclohexene. This enhanced reactivity again might be due to either resonance stabilization or to ring strain as compared to cyclohexene.

Recently, E. S. Huyser and G. Echegaray[19], from competitive addition of trichloromethyl radical to 5-methylene-bicyclo(2.2.1) hept-2-ene, 2-methylenenorbornane and norbornene, found that 2-methylenenorbornane is 4.4 times more reactive towards the trichloromethyl free radical than norbornene, and that 5-methylenebicyclo (2.2.1) hept-2-ene is only 1.23 times more reactive than 2-methylenenorbornane. Thus, they concluded that the two double bonds in 5-methlenebicyclo (2.2.1) hept-2-ene react independently and ruled out the non-classical free radical as a reaction intermediate.

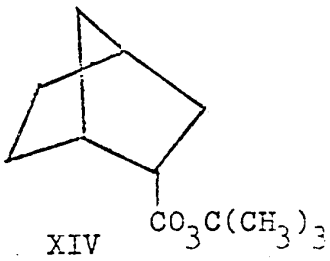
However, previous studies have suffered from several drawbacks which might obscure the observance of non-classical free radical intermediates. In the addition to a double bond the resultant radical might be stabilized by neighbouring group participation due to the formation of π complexes.[20] Further-more, the estimation of steric and strain factors are difficult. A more stringent examination of the stability of radicals for the presence of stabilization of a non-classical type would be to generate radicals strictly analogous

to the carbonium ions studied by Winstein and Roberts. It has already been shown by Bartlett and Hiatt[21] that the rate of decomposition of t-butyl peresters depends on the stability of the resultant radical intermediate. For this reason, a study of the comparative rates of decomposition of exo-and endo-norbornane-2-carboxylic acid (XIII and XIV), and exo- and endo-norborn-5-ene-2-carboxylic acid (XV and XVI) was carried out.

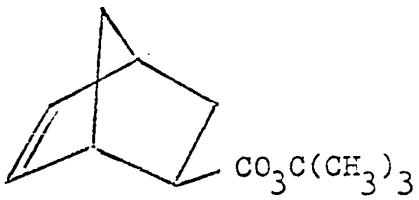
There seem to be two main modes of unimolecular thermal decomposition of t-butyl peresters in non-polar solvents; one involves the homolytic rupture of the oxygen-oxygen bond, and the other, a concerted decomposition which involves the simultaneous rupture of oxygen-oxygen bond and a carbon-carbon bond with the formation of carbon dioxide in the primary step. When a series of t-butyl peresters is considered, the perester will decompose by the non-concerted path if the group R in $RCO_3C(CH_3)_3$ is not a stable radical (methyl, phenyl, 2-phenyl ethyl or 3-phenylpropyl[22]). If the radical R is stable (benzyl, phenylmethyl and diphenylmethyl), the perester will decompose by the concerted path way. As the R group is resonance stabilized the rate of decomposition will be accelerated. Bartlett and Hiatt[20] have demonstrated by the series: t-butyl peracetate, t-butyl phenyl peracetate, and t-butyl diphenyl peracetate showed an acceleration of rate covering a ring of more than 10^4 as they gradually change from one path-way of decomposition to the other through the series. If there is σ and π participation, then it should be reflected in the differences in reactivity of the two pairs of bicyclic peresters. The pair of exo isomers (XIII and XVI) should decompose faster than the endo isomers (XIV and XVI), since only the exo isomers have the favourable geometry for σ or π participation, as demonstrated by solvolytic studies. If



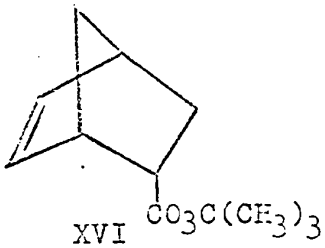
XIII



XIV



XV

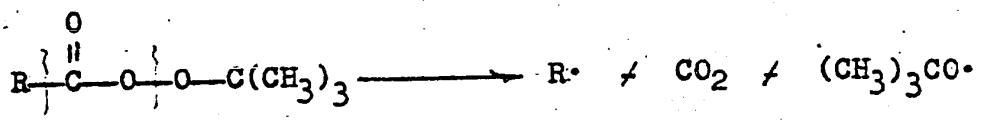


XVI

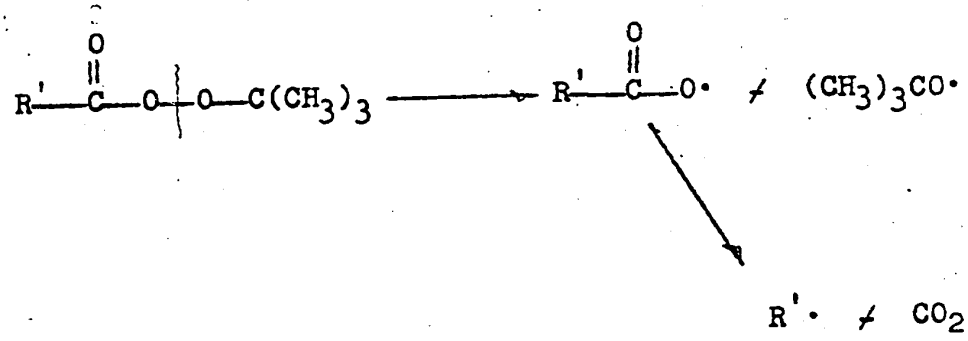
there is no σ or π participation, then the rate for the decomposition for the two pairs of isomer should not be too different.

Unimolecular Thermal Decomposition of t-Butyl Peresters

(a) Concerted Decomposition:



(b) Non-Concerted Decomposition:



R = benzyl, phenylmethyl or diphenylmethyl.

R' = methyl, phenyl or 2-phenylethyl.

EXPERIMENTAL

A mixture of exo- and endo- ethyl norborn-5-ene-2-carboxylate was obtained by a Diels Alder condensation of 1,3 cyclopentadiene with ethyl acrylate. The procedures were the same as those described by J. D. Roberts et al[23] for the synthesis of exo- and endo-methyl norborn-5-ene-2-carboxylate. The fraction that distilled at 90°-94°C (15mm) was collected. The yield was 80% of the theoretical.

A mixture of exo-and endo- norborn-5-ene-2-carboxylic acid was obtained in 90% yield from the hydrolysis of the equilibrated mixture of exo and endo ethyl norborn-5-ene-2-carboxylate. The procedures were the same as those described by J. D. Roberts et al[23] for the hydrolysis of exo- and endo- methyl norborn-5-ene-2-carboxylate except that sodium ethoxide and ethanol were used instead of sodium methoxide and methanol. The fraction distilled at 127°-132°C (6-7mm) was collected. (Literature b.p. 103°-104°C 2.2mm)[23]

exo-Norborn-5-ene-2-carboxylic acid was obtained by separating the exo- and endo-norborn-5-ene-2-carboxylic acid mixture by iodolactionization as described by C. D. Nooy and C. S. Ronsdestvedt[24]. The yield of the pure exo isomer was 13.0 g. m.p. 44°-45°C (Literature m.p. 44°-45°C)[24]

The yield of iodolactone of the endo isomer was 17 g. m.p. 57°-58°C. (Literature m.p. 58°-59°C)[24].

Endo- norborn-5-ene-2-carboxylic acid was obtained by reduction of the above iodolactone with zinc dust in glacial acetic acid using the procedure described by Alder and Gunzl[25] for endo-norborn-5-ene-2-methyl-2-carboxylic acid. The yield was 70% of the theoretical., m.p. 43°-44°C (Literature m.p. 43°-44°C)[26].

The proof of configuration of the COOH in the exo- and endo-norborn-5-ene-2-carboxylic acids obtained by this method is based on the method of separation and was confirmed by the examination of their N.M.R. Spectra.[27] The exo proton attached to the 2-carbon in the endo isomer will be deshielded by the double bond while the same proton in the exo isomer is shielded by the double bond. (N.M.R. Spectrum I and 2).

endo-Norbornane-2-carboxylic acid was obtained by hydrogenation of the sodium salt in water over palladium on charcoal at temperature and pressure as described by K. Alder and G. Stein.[26] The yield was 86% of the theoretical m.p. 64°-65°C. (Literature m.p. 62°-63°C [26] and 65°C [29]).

exo-Norbornane-2-carboxylic acid was obtained as above using the corresponding exo- norborn-5-ene-2-carboxylic acid in 86% yield m.p. 55°-56°C (Literature 56°-57°C [28], 58.0°-58.5°C [29]).

exo- Norborn-2-ene-5-carbonyl Chloride:- a mixture of 13.7 gm (0.1 mole) of the corresponding acid and 23.6 gm (0.2 mole) of thionyl chloride was left standing for 2 hours at room temperature, and then warmed in a steam bath for another hour. The excess thionyl chloride was removed under reduced pressure, and the product distilled at 67°-68° (12 mm). The yield was 68% of the theoretical.

endo-Norborn-2-ene-5-carbonyl Chloride:- The acid chloride was obtained as above from the corresponding acid with thionyl chloride in 60% yield. The acid chloride distilled at 70°-73° (12

exo-Norborn-2-carbonyl Chloride:- reaction of the corresponding acid with thionyl chloride gave acid chloride in 75% yield. The acid chloride was distilled at 87°-89° (15 mm).

endo-Norbornane-2-carbonyl Chloride:- reaction of the

corresponding acid with thionyl chloride gave the acid chloride in 70% yield which distilled at 89° - 91° (15mm).

exo-t-Butyl Norborn-5-enê-2-percarboxylate:- a mixture of 20ml. of 45° - 50° petroleum ether, 1 gm of pyridine (distilled from BaO) and 1.81 gm (0.012 mole) of the corresponding acid chloride was kept in a salted ice bath. To this mixture, t-butyl hydroperoxide (freshly distilled) was added slowly. The resulting mixture was kept in a refrigerator for 2 days, then, it was poured onto 10 gm of ice and the petroleum ether layer was separated and washed with 10% sulfuric acid, followed by water. The petroleum ether solution was dried over magnesium sulfate and concentrated in a rotary evaporator and then passed through a 10 cm florisil column. The resulting product was obtained in 70% yield as a colorless oil which solidified when kept in a refrigerator. m.p. about 10°C, IR spectrum 5.

Anal. Calcd. for $C_{12}H_{18}O_3$:		C, 68.53;	H, 8.63.
	Found :	C, 68.73;	H, 8.81

endo-t-Butyl norborn-5-ene-2-percarboxylate was obtained in the same way as above in 72% yield. It was a colorless oil, melting at about 13°C, IR spectrum 6.

Anal. Calcd. for $C_{12}H_{18}O_3$:		C, 68.53;	H, 8.63.
	Found :	C, 68.70;	H, 8.72.

exo-t-Butyl norbornyl-2-percarboxylate was obtained in 90% yield. This material crystallized as a white solid when cooled, and it melts at 26°C, IR spectrum 3.

Anal. Calcd. for $C_{12}H_{20}O_3$:		C, 67.89;	H, 9.50.
	Found :	C, 68.08;	H, 9.62.

endo-t-Butyl norbornyl-2-percarboxylate was obtained in 90% yield. It is a white solid at room temperature, m.p. 33 - 34°C,

IR spectrum 4.

Anal. Calcd. for $C_{12}H_{20}O_3$:		C, 67.89;	H, 9.50.
	Found :	C, 68.11;	H, 9.38.

Procedure for Kinetic Run;-

A weighed sample of the perester (1.5 m. mole) in a 5.00 ml. volumetric flask was made up to the volume with chlorobenzene. The volumetric flask was fitted with a water condenser and immersed in an oil-bath maintained at constant temperature of $98.0^{\circ}C \pm 0.05^{\circ}$. After 1 minute, 0.3 ml was withdrawn and placed into a previously cooled vial. This sample was considered to represent zero time. Similar aliquot were withdrawn every ½ hour and kept in the refrigerator until analyzed. Points were taken until over 75% of the original perester had decomposed.

Determination of Relative concentration of Peresters by Infrared:-

The analytical method was essentially the same as described by Bartlett and Hiatt.[21] The carbonyl peak of the perester in the 1780 cm^{-1} region was scanned and its disappearance was followed. The analysis was carried out on a Perkin-Elmer model G 13 using a 0.2 mm sodium chloride cell for the sample, and a variable reference cell for solvent compensation. Each sample was warmed to room temperature and the percentage transmission ($100\ I/I^{\circ}$) was measured.

Treatment of Data:-

From a series of chlorobenzene solutions of known perester concentration, it has been found that a plot of absorbance (A) due to the carbonyl of the perester Vs molar concentrations of the perester solution was linear (graph I). From first order rate equation:-

Ln C^{o}/C = kt since C is portional to A then ln A^{o}/A = kt

C^{o} = initial concentration

C = molar concentration at time t

K = first order rate constant

A^{o} = optical density of initial concentration

A = optical density of concentration at time t.

Thus, a plot of log A^{o}/A Vs time was found to be linear (graph II) and the first order rate constants were determined by calculating the slope of the least square line. For the exo and endo saturated perester XIII and XIV and the exo unsaturated perester XV, all points taken until 75% of the original perester which had decomposed were used. For the endo unsaturated perester XVI, only the transmissions taken up to 30% of the original perester had decomposed were used because the change in transmission at 1778 cm^{-1}, does not represent an accurate measure of the perester concentration due to a second absorption of some expected 6-hydroxynorbornane-2-carboxylic acid lactone. After 30% of the original perester had decomposed, a small shoulder appeared at 1790 cm^{-1} which obviously interfered with the perester carbonyl peak.

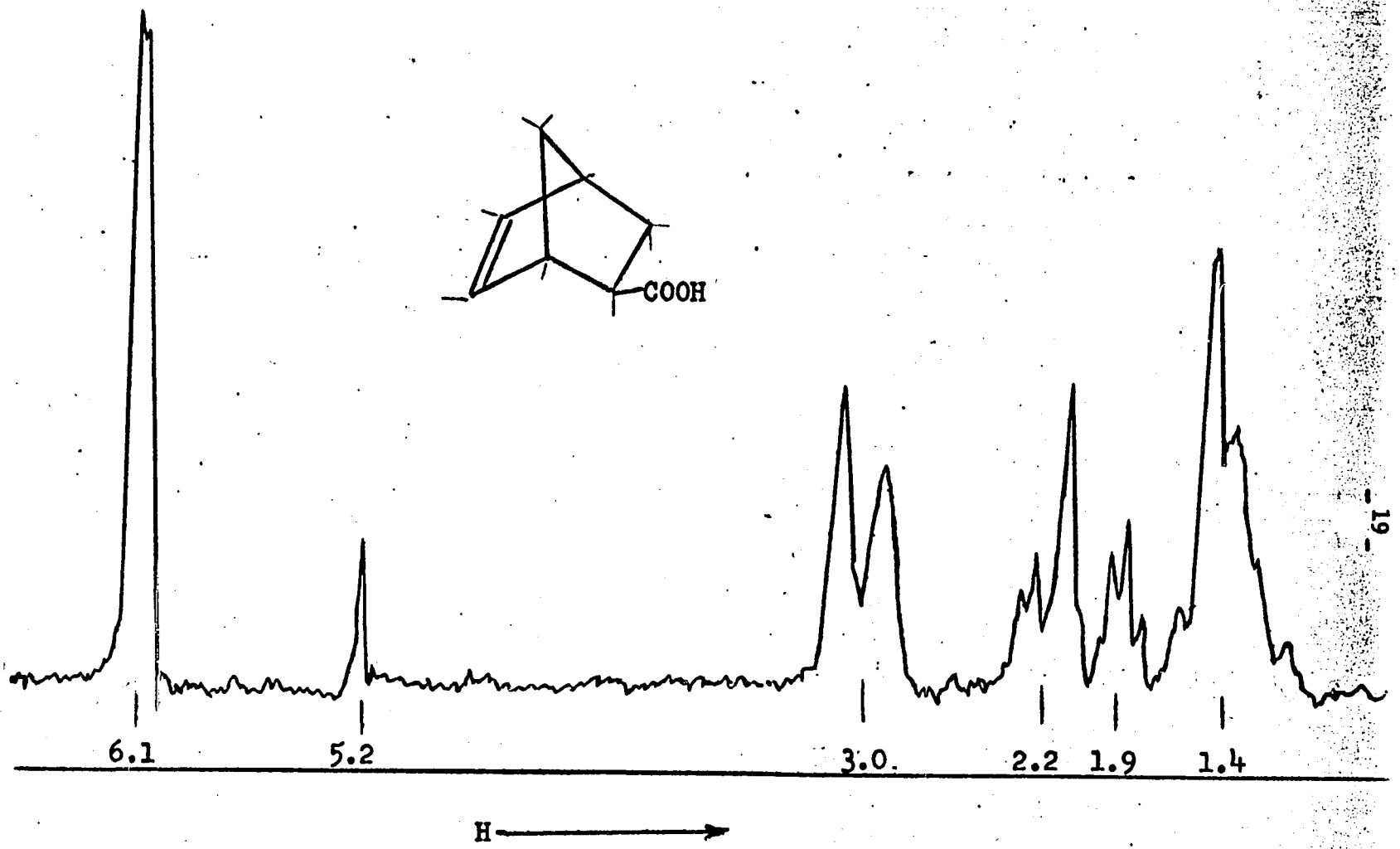


Fig.1. N.M.R. Spectrum of exo-norborn-5-ene-2-carboxylic acid measured in carbon tetrachloride.

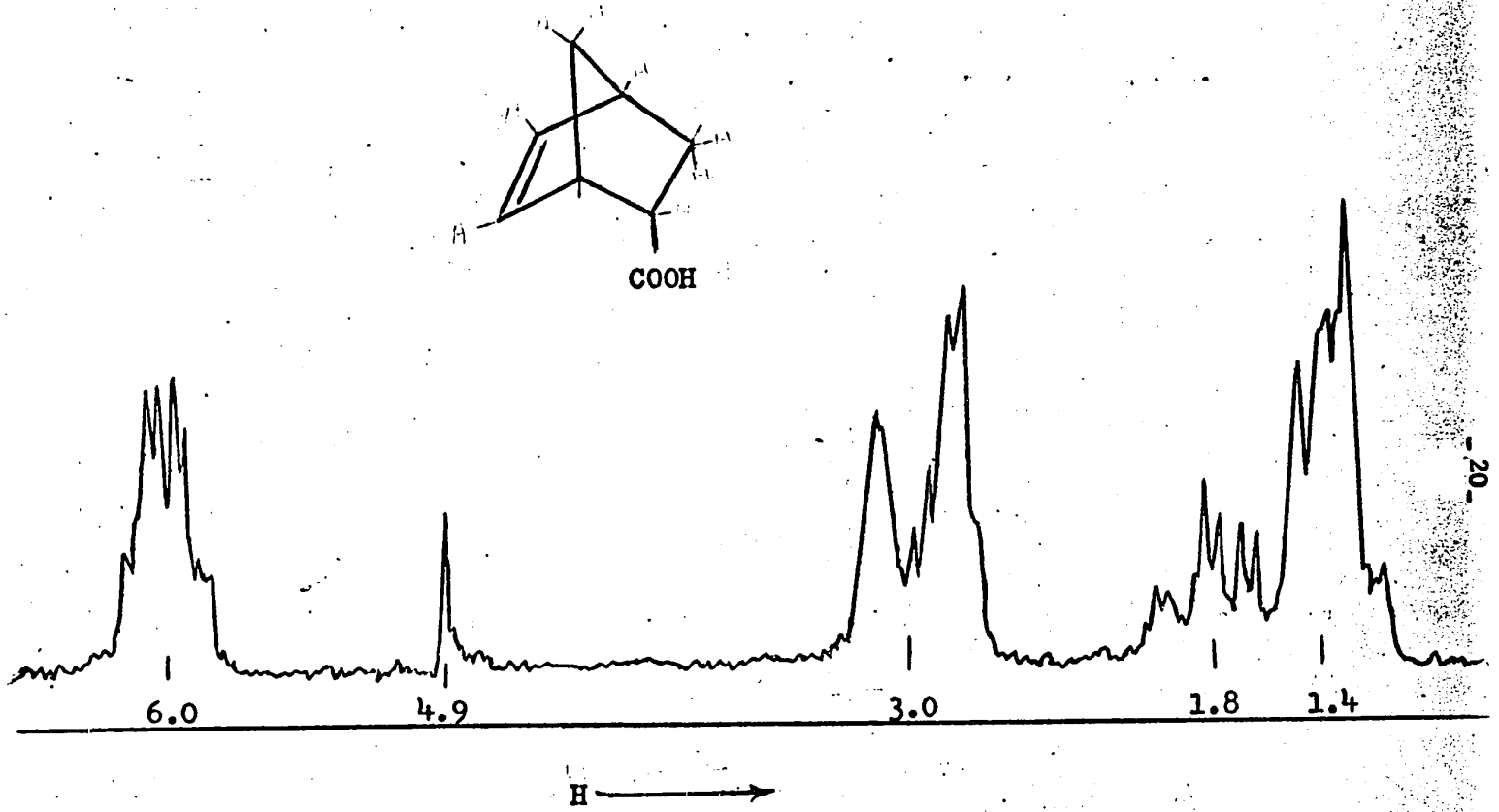


Fig.2. N.M.R. Spectrum of endo-norborn-5-ene-2-carboxylic acid measured in carbon tetrachloride.

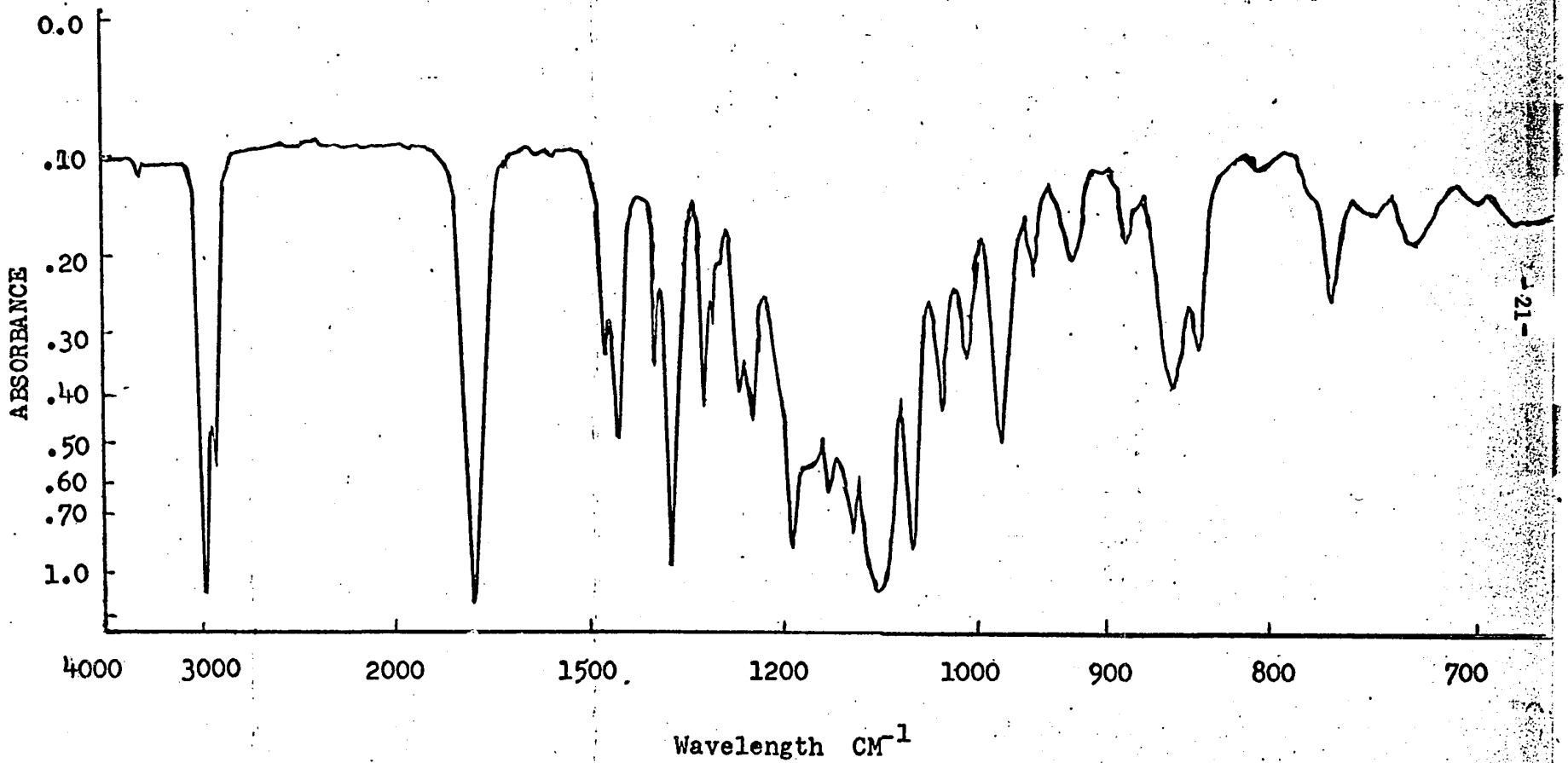


Fig.3. Infrared spectrum (liquid film) of exo-t-butyl norbornane-2-percarboxylate.

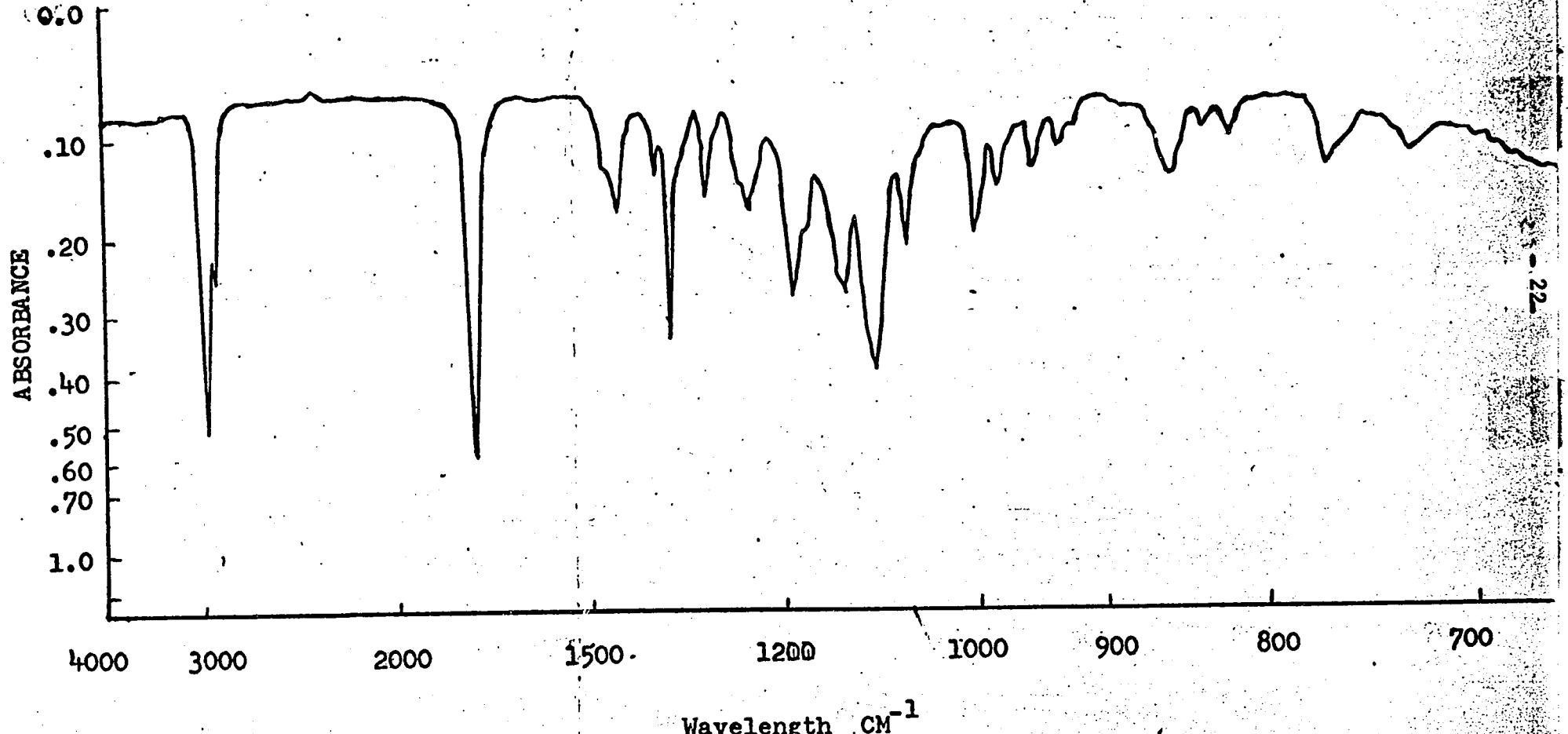


Fig.4. Infrared spectrum (liquid film) of <u>endo</u>-t-butyl norborn

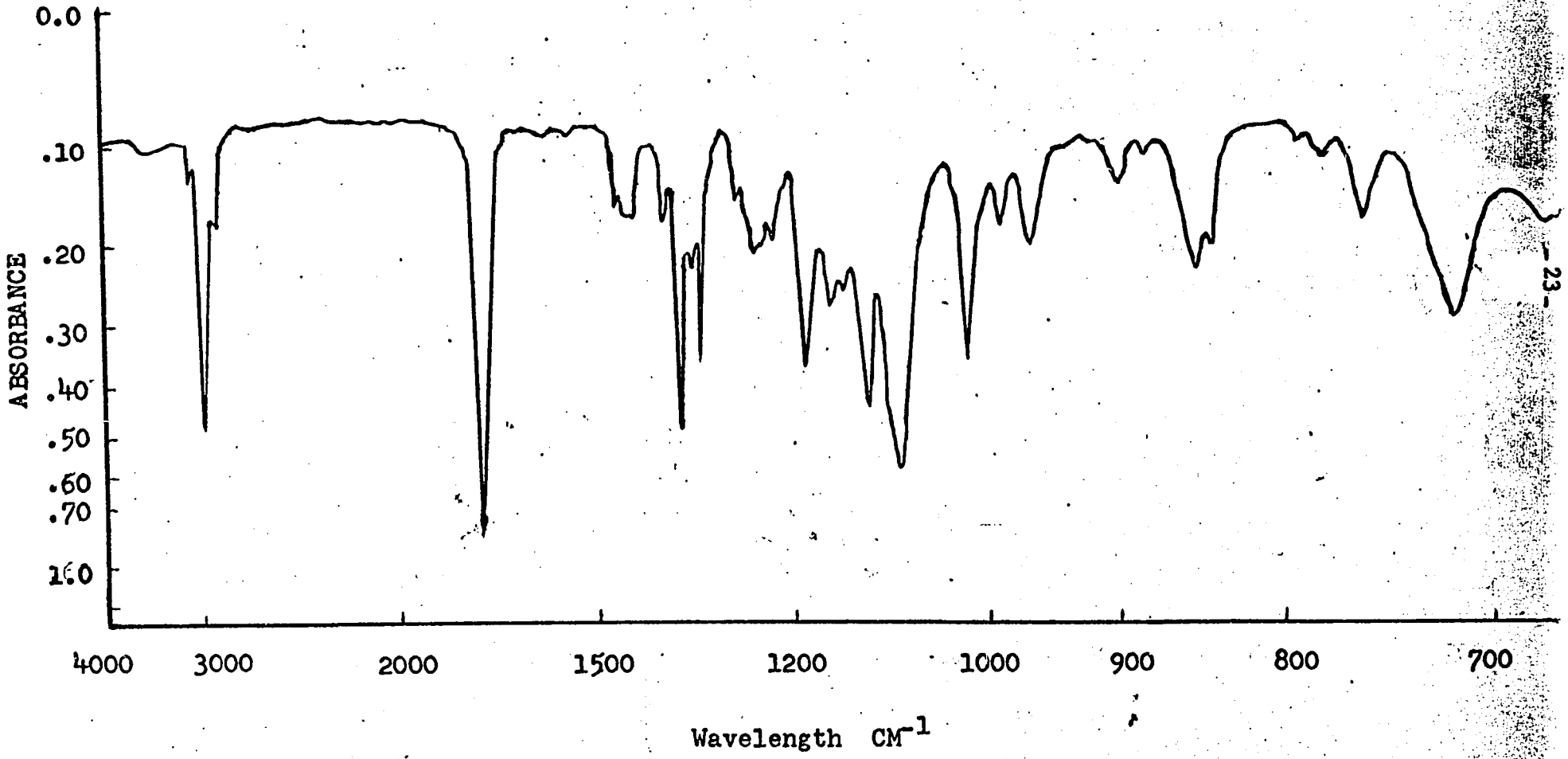


Fig.5. Infrared spectrum (liquid film) of exo-t-butyl norborn-5-ene-2-percarboxylate.

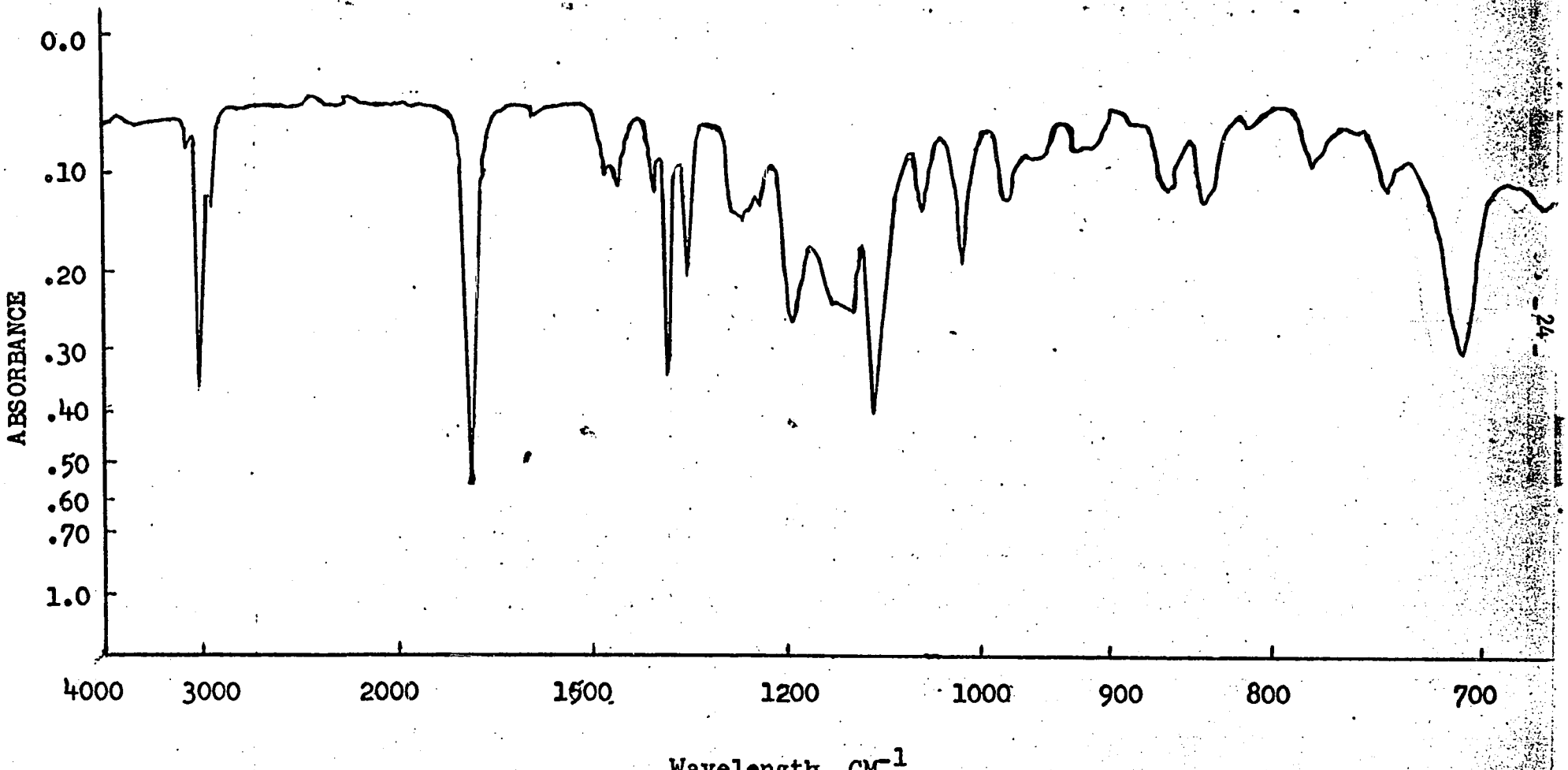
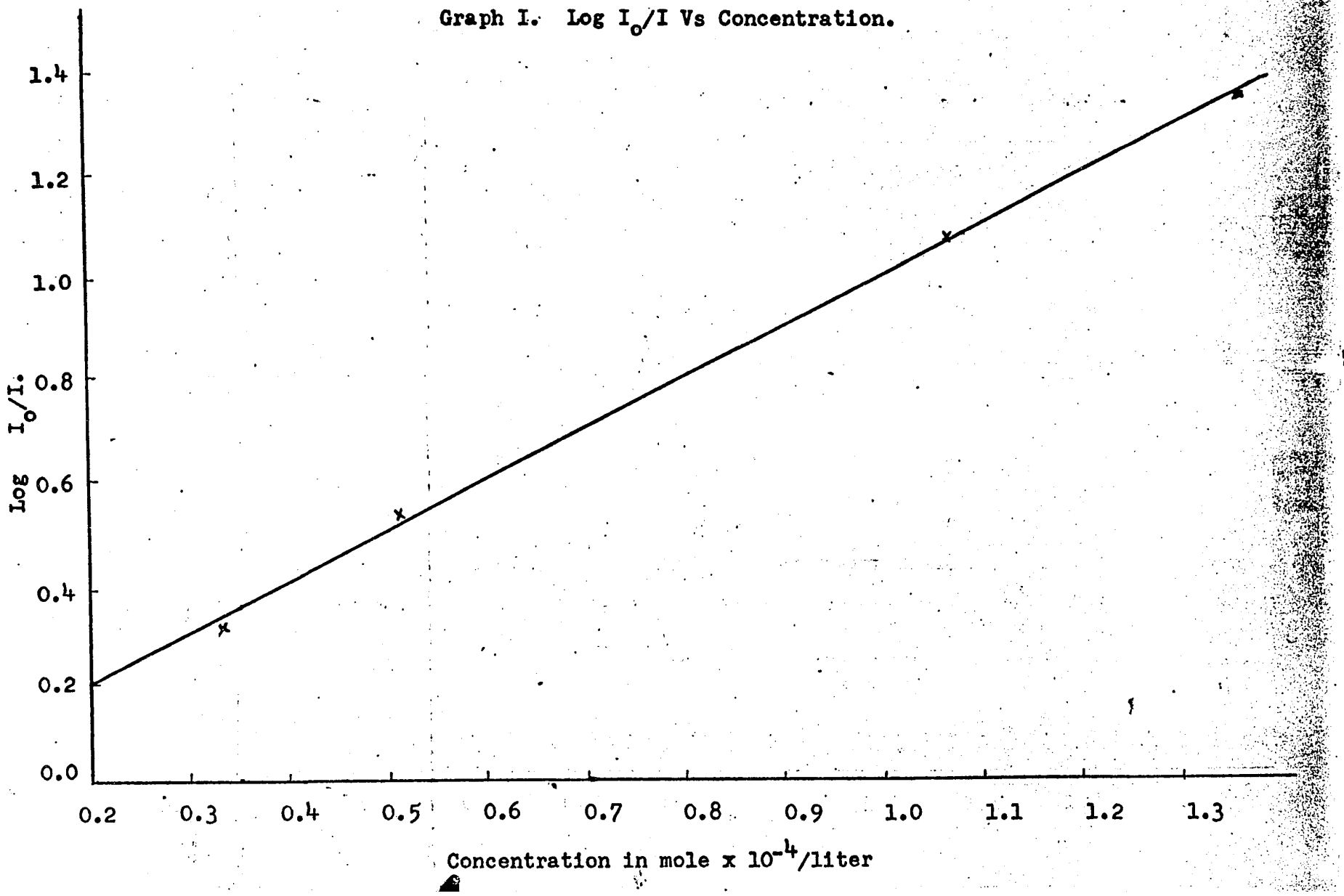
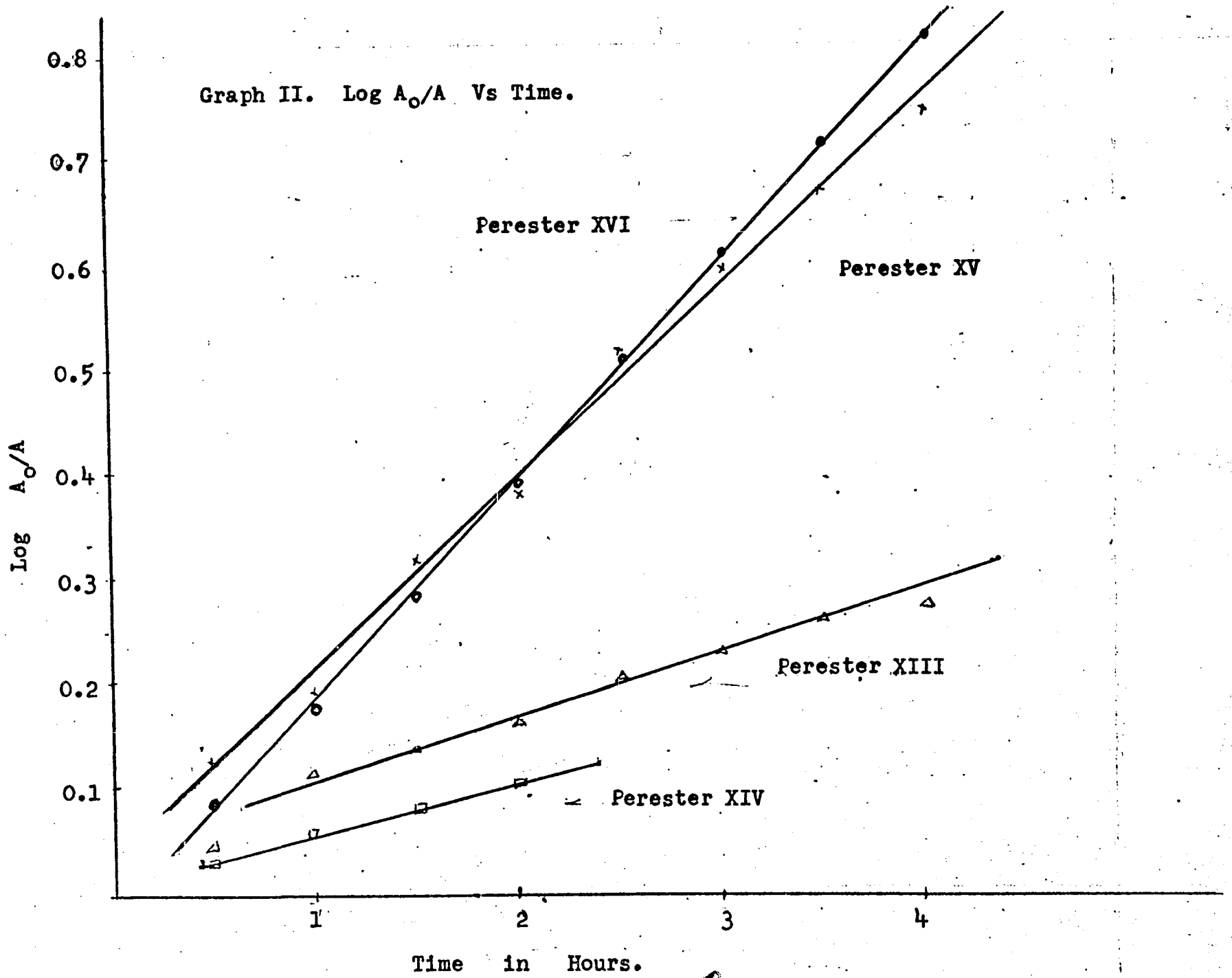


Fig.6. Infrared spectrum (liquid film) of <u>endo</u> t-butyl-norborn-5-ene-2-percarboxylate.


Graph I. Log I_o/I Vs Concentration.
Log I_o/I.
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
Concentration in mole x 10^{-4}/liter


Graph II. Log A_o/A Vs Time.
Perester XVI
Perester XV
Perester XIII
Perester XIV
Log A_o/A
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
1
2
3
4
Time in Hours.

RESULTS AND DISCUSSION

Endo-norborn-5-ene-2-carboxylic acid was first reported by K. Alder and G. Stein[26] in 1934. It was synthesized by a Diels Alder condensation of 1,3 cyclopentadiene with acrylic acid and the product was first believed to be pure endo-norborn-5-ene-2-carboxylic acid. In 1955, C. D. Nooy and C. S. Rondestredt[24] found that the product obtained by the method of K. Alder and G. Stein consists of 30% exo isomer and 70% endo isomer as indicated by the products obtained from iosolactonization of the mixture. The pure endo isomer has always been obtained previously through successful recrystallization of this mixture. The method is tedious and only gives a poor yield. The regeneration of the pure endo-norborn-5-ene-2-carboxylic acid from its iodolactone was shown to be an excellent method. This method has been used successfully by K. Alder and W. Gunzl[25] to obtain pure 2 and 3 alkyl or aryl substituted endo-norborn-5-ene-2-carboxylic acid.

The first order rate constants for the thermal decomposition of the four peresters; (XIII - XVI) are shown in table I. At this stage, it was found that Michael M. Martin and Don C. De Jongh[30] were also studying the same systems by the same method; and, a month later, P. D. Bartlett and R. E. Pincock[31] published their studies on the norbornyl system. After we received an advanced copy of M. M. Martin and Don C. De Jongh's paper and found that our results were in agreement, the present work was then discontinued, since they had already determined the reaction products and activation parameters. Some of their results are listed in table I for comparison.

As shown in table I, in the norbornyl system, the exo isomer (XIII) decomposed 3.3. times faster than its endo isomer (XIV), and in

Table I

First order Rate Constants

Perester	Init.Conc.	Ref.	Solvent	T°C *	K 10^4 sec.$^{-1}$
XIII	0.0979 M.	**	chlorobenzene	98.00	1.38
	0.0480 M.	30	chlorobenzene	101.90	1.43
	0.0968 M.	30	cumene	101.90	1.36
	0.0518 M.	31	chlorobenzene	100.1	1.88
XIV	0.0928 M.	**	chlorobenzene	98.00	0.42
	0.0948 M.	30	chlorobenzene	101.90	1.96
	0.0980 M.	30	cumene	101.90	1.16
	0.0501 M.	31	chlorobenzene	100.1	0.461
XV	0.0955 M.	**	chlorobenzene	98.00	1.19
	0.1039 M.	30	chlorobenzene	101.90	1.53
	0.1007 M.	30	cumene	101.90	1.11
XVI	0.0961 M.	**	chlorobenzene	98.00	0.27
	0.1148 M.	30	cumene	94.50	0.311
	0.1148 M.	30	cumene	101.90	0.735

* Temperature within 0.05°

** Present work

the norbornenyl system, the exo isomer (XV) decomposed 4.4 times faster than its endo isomer (XVI). Since the rates of decomposition of the pair of exo peresters are hardly accelerated comparing to their corresponding endo isomers, the norbornyl and norbornenyl radical are not appreciable stabilized. Even if the difference in rate was all due to the participation, it would be insignificant when compared to the exo/endo ionization factor in solvolysis. Harold Hart and Frank J. Chloupek[32] arrived at the same conclusion from their studies of the diacyl peroxide of norbornyl and norbornenyl systems.

As to why there is σ and π participation in the cation case and not in the free radical case, a popular theoretical explanation is that: in the norbornyl system, the cation has a pair of electrons in a bonding orbital made up by an overlap of atomic orbitals from C_1, C_2 and C_6, while the corresponding free radical would have to use a second molecular orbital of higher energy to accommodate the odd electron; in the norbornenyl system, the added electron here may out weigh the stabilization resulting from delocalization in a non-classical structure. Thus, the free radical will have less resonance energy than the corresponding cation. For example, it has been shown that the resonance energy of the allyl radical is about 35% of that of the allyl cation.[33]

It must be concluded that the decomposition of t-butyl peresters, like diacyl peroxides, does not form non-classical free radicals. This might, in part, be due also to the fact that these free radicals are very reactive. As shown by E. J. Casanova Jr., P. A. Vatakencherry and Roland Winter.[34] the deamination of exo- and endo-

norbornylamine in acetic acid produces an unsymetric carbonium ion, whereas those produced from solvolytic reactions are symmetrical. Jerome A. Berson[35, 36] had found that the 2-bornyl radical does not undergo the Wagner-Meerwein rearrangement when generated by decarbonylation of 2-formylbornane at 128°; but, when the 2-bornyl radical is generated from decomposition of 2-azobornane, the products were bornane, 1-p-methene and 2,3,3-trimethyl norbornane. The latter compound arises by formal Wagner-Meerwein rearrangement.

PART II

Exploratory Synthesis of Derivatives Related to Cephalosporin C

INTRODUCTION

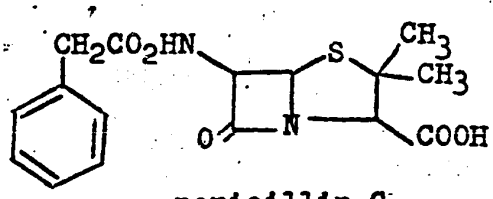
There are many biologically active sulfur containing compounds in which the soft electron cloud provided by the sulfur atom participates in binding at specific bioreceptors. It has been shown that the sulfur atom in some of these compounds can be replaced without the loss of activity by a carbon-carbon double bond or a benzene ring, which can also provide the required polarizable electrons.[37] The soft electron cloud provided by the sulfur atom of the five member ring of the penicillin antibiotics was shown to be essential for biological activity. This was demonstrated by the decrease in biological activity when the sulfur atom was oxidized to the sulfoxide or sulfone.[38] Numerous penicillins differing in the nature of the side chain attached to the 6-amino group are known. Recently, a new group of penicillin related antibiotics has been discovered in which the five-membered thiazolidine ring of penicillin is replaced by a six membered thiazine ring.[39] This new group of antibiotics known as the cephalosporin C are active against penicillin-resistant strains of micro-organisms and thus are potentially useful as therapeutic agents.[40] It is of special interest that enlargement of the penicillin thiazolidine ring to a thiazine should preserve antibiotics activity. It was the original intention of the present work to explore the possibility of synthesizing cephalosporin C related structures, and it is hoped that this very preliminary work can serve as a basis for further investigations along these lines.

Structure XVII, an isoquinoline derivative related to cephalosporin C in which the sulfur atom in the thiazine ring is being replaced by a benzene ring. A most expediant route to the desired

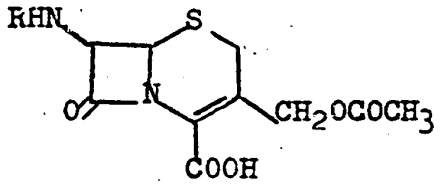
structure would consist of a condensation of o-phthalaldhyde with hippuric acid to give the bis-azlactone (XVIII) which includes all of the required functional groups for completion of the desired molecule. Hydrolysis of the two azlactone rings should proceed readily to give the diacid (XIX) which would be expected to ring close spontaneously to the isoquinoline (XX). Subsequent reduction of the double bond followed by hydrolysis should afford the diamino-diacid (XXI) which may be convertible through the application of well-known prodecures to the final β-lactam (XXII).

As part of another program, methods were explored for the synthesis of α-ketopropionic β-lactam (XXIII). Such a structure is not only of interest from the theoretical standpoint but can also be used as an intermediate for the synthesis of cephalosporin C related compounds (XXIV). The cephalosporin C type of ring system has been shown only recently to be accessible through a ring expansion reaction of the penicillin sulfoxide ester[41].

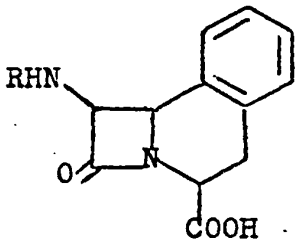
E. Testa and L. Fontanella[42] have synthesized a series of α-alkyl and α-aryl substituted β-lactams through the application of the Grignard reagent method to the appropriate esters of β-aminopropionic acids. The yield of β-lactam was found to depend largely on the size of the substituents. Also, the yield of β-lactam was always greater with disubstituted β-amino esters; when no substitue substituents are present, the yield of β-lactam is negligible. For our purposes, a special kind of α-substituents must be present which would allow for their easy removal at a later stage; moreover, the removal step would have to lead to an α-carbonyl function. It was decided initially that a ketal function, perferable cyclic, might be suitable for the preparation of the α-keto β-lactam derivative. The application



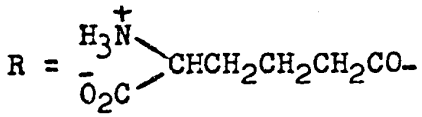
penicillin G

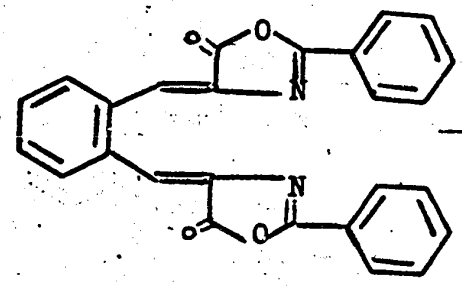


cephalosporin C

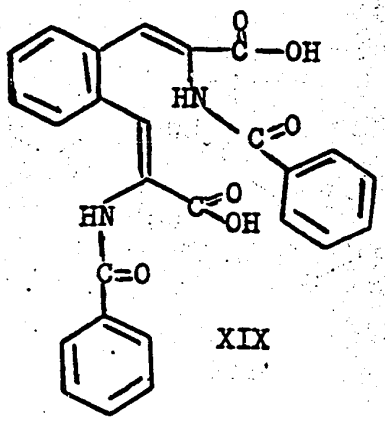


XVII

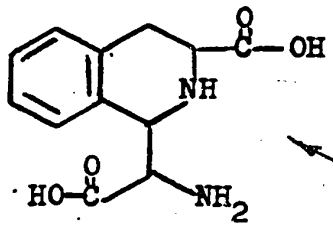
R = 



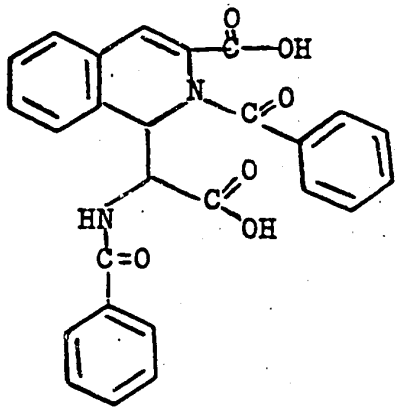
XVIII



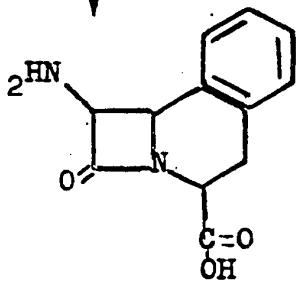
XIX



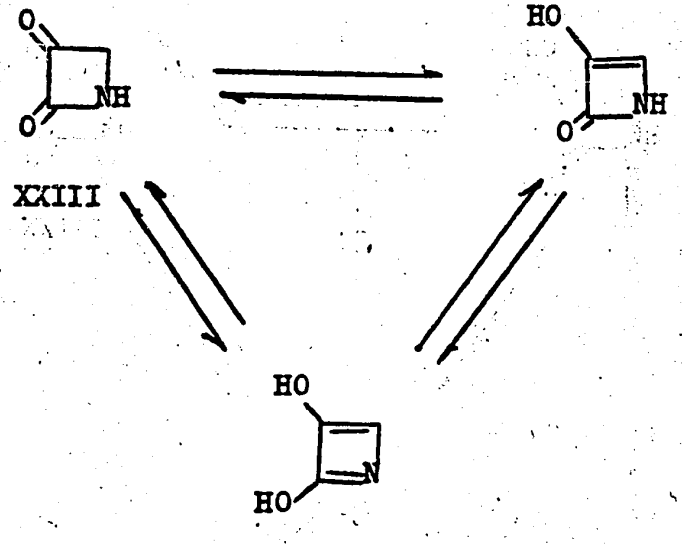
XXI



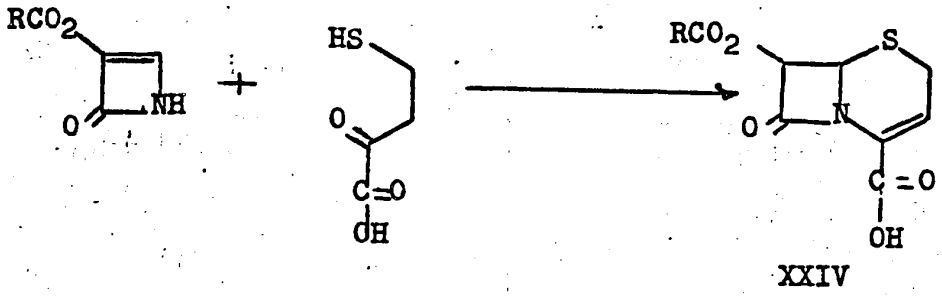
XX



XXII



XXIII



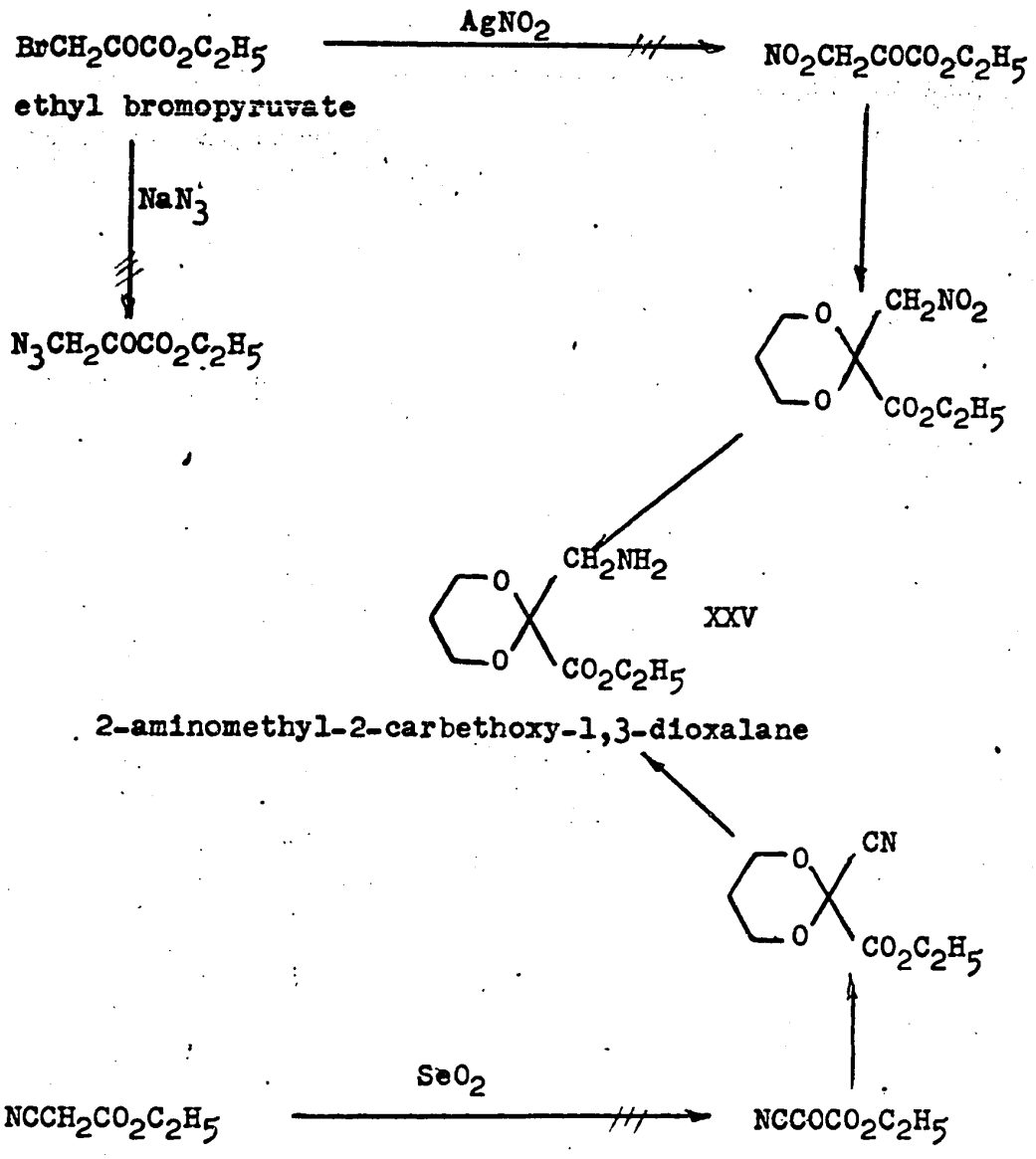
XXIV

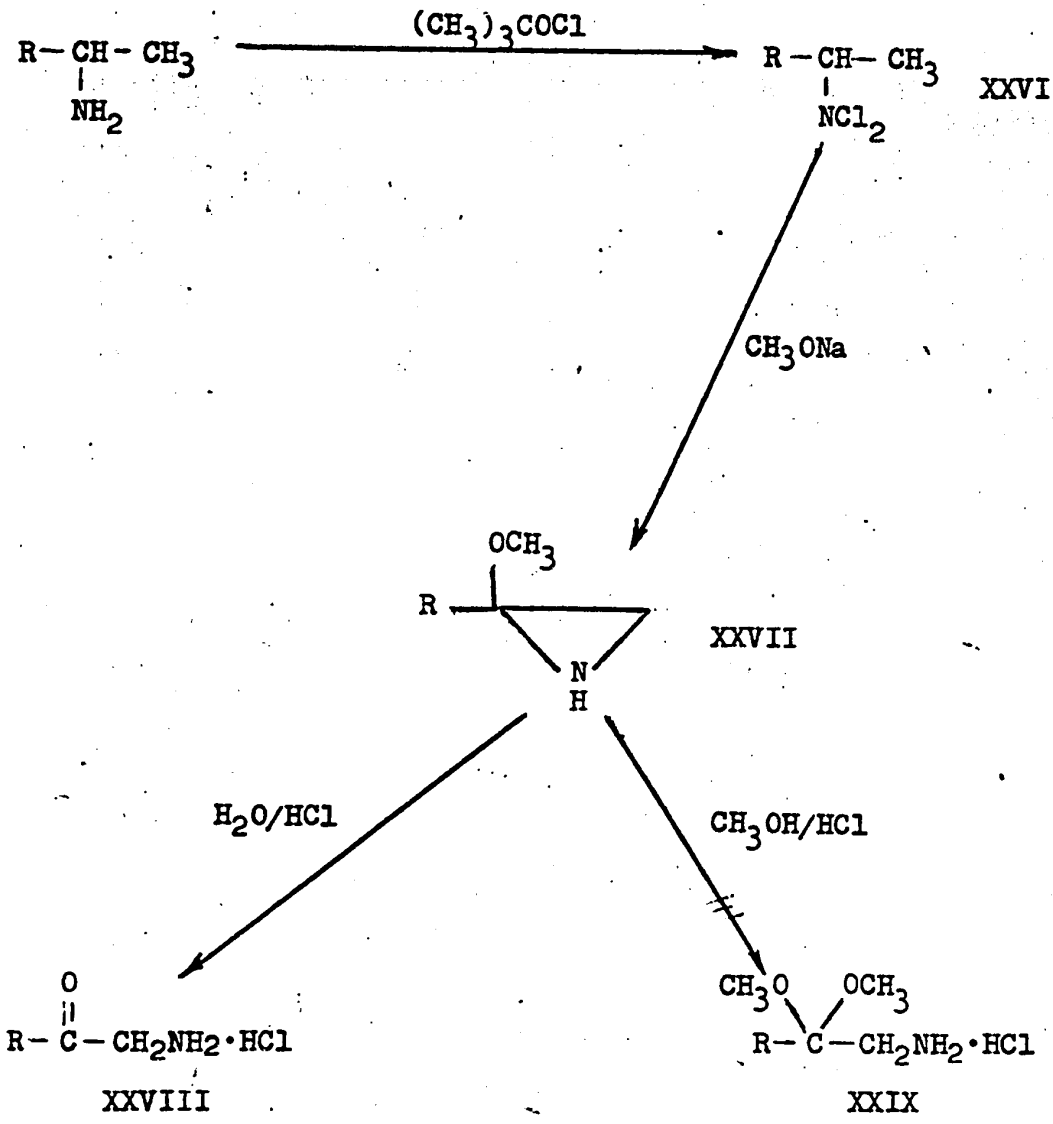
of mild hydrolytic conditions or better, an exchange dioxolanation reaction should serve to preserve the β -lactam ring while unmasking the α-keto function. Several potentially practical schemes for the synthesis of the required 2-aminomethyl-2-carbethoxy-1,3-dioxolane (XXV) have been explored.

The first approach used ethyl bromopyruvate as starting material. This involves the displacement of the bromo function in ethyl bromopyruvate by an azide ion or by a nitro function which may then be reduced to an amino function at a later stage. The displacement product should react with 1,3-propanediol to give the cyclic ketal (XXV).

A second approach involves at first the oxidation of cyanoacetate to ethyl α-ketocyanoacetate followed by a condensation of the product with 1,3-propanediol and reduction of the cyano function to amine.

The third approach involves a rather unconventional method for the preparation of α-ketoamines. This method was found to be effective in converting α-phenylethylamine and other aliphatic amines to their respective α-ketoamines[43]. It consists in converting the amine to the NN-dichloride (XXVI), followed by treatment with sodium methoxide to give the aminoketal (XXVII) which is then hydrolyzed to the α -ketoamine (XXVIII) Methyl α -aminopropionate was converted into its dichloride. Instead of hydrolyzing the presumed intermediate ketal to the ketoamine, methanolysis was carried out with the hope of obtaining the αα-dimethoxy- β -aminoproprionate (XXIX). Dimethoxy- β -aminoproprionate could be used directly to form the desired β -lactam or it could undergo exchange dioxolanation to give α-amino methyl-2-carbethoxy-1,3-dioxolane.


BrCH2COCO2C2H5
AgNO2
NO2CH2COCO2C2H5
ethyl bromopyruvate
NaN3
N3CH2COCO2C2H5
CH2NO2
CO2C2H5
CH2NH2
CO2C2H5
XXV
2-aminomethyl-2-carbethoxy-1,3-dioxalane
CN
CO2C2H5
SeO2
NCCH2CO2C2H5
NCCOCO2C2H5
ethyl cyanoacetate



R = C_6H_5 or $CO_2C_2H_5$

EXPERIMENTAL

The condensation of o-phthalaldehyde with hippuric acid was carried out as described by Wineman, Scott and Kingdon[44]. The yield of the expected bisazlactone was 11%; (IR spectrum 9) m.p. 266°-268°C with decomposition. (Literature 268°-270°C with decomposition).

Of special interest was the observation that the bisazlactone is extremely photo-sensitive either in solution or in the crystalline state. The deep orange colored bisazlactone is readily converted to a yellow compound after brief exposure to day light (IR spectrum 10). This photo-compound is readily converted back to the orange colored bisazlactone when heated to about 180°C. (IR spectrum 11). The interconversion is completely reversible.

Hydrolysis of the bisazlactone (XVIII)[45]. In a 500ml. flask fitted with a reflux condenser, 1.0 g. of the bisazlactone (0.0024 mole) was suspended in 200ml. of methanol. To this suspension, 5.0ml. 1 M sodium hydroxide solution was added and the contents heated under reflux for 2 hrs. (or allowed to stand overnight at room temperature). The resulting clear solution was taken to dryness in a flash evaporator at room temperature. The residue was dissolved in 10 ml. of water and the solution extracted with ether. The ether extract was found to contain methyl benzoate as ascertained by a comparison of the infrared spectrum with that of an authentic sample. The aqueous layer was acidified with hydrochloric acid (10%) whereupon a white solid separated out. It was collected and recrystallized from methanol to give 400 mg. of white crystals with m.p. 205°C (decomp.) and (IR spectrum 12). The aquous filtrate from the crystallization was taken to dryness in vacuum and the residue (410 mg.) was identified as hippuric acid by infrared

spectroscopy and m.p. behavior.

Aminolysis of the bisazlactone (XVIII). To a flask containing 4.0 g. of bisazlactone in 400 ml. of chloroform, dry amonia gas was bubbled in for one hour.. A white fine powder precipitated out and was collected and recrystallized from acetone; yield 3.5 g. m.p. 242°-243°C, (IR spectrum 13).

Anal. Calcd. for $C_{26}H_{22}O_4N_4$:

	C, 68.71	H, 4.88	N, 12.33
Found:	C, 68.02	H, 5.23	N, 12.89

Upon heating under reflux in excess hydrochloric acid overnight on a steam bath, this white crystalline amide gave a quantitive yield of benzoic acid and glycine as ascertained by melting point and infrared spectrum comparisons. No effort was made to characterize the other fragment which should consist of 2-isoquinoline carboxylic acid.

Catalytic hydrogenation of the unsaturated amide (XXX or XXXI) was next attempted with the hope that the expected reduction product (XXXII or XXXIII) would not suffer fragmentation upon acid hydrolysis. The amide was found to be soluble only in dimethyl formamide and also appeared to poison the various common catalysts. Moreover, DMF was observed to absorb hydrogen slowly, thus, complicating the interpretation of hydrogenation data. Catalysts such as pallodium on charcoal, freshly reduced platinum oxide, and rhodium on charcoal were tried without success.

Catalytic hydrogenation of the bisazlactone XVIII was also attempted; however, it was soluble in ethylacetate only to the extent of 0.05%. More polar solvents caused fragmentation of the

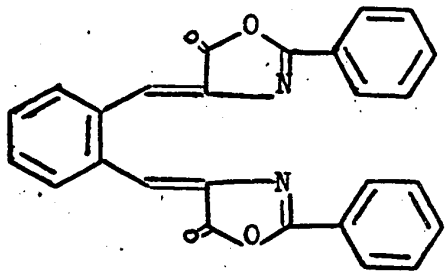
molecule with elimination of hippuric acid.

Reduction of the double bonds in the bisazlactone XVIII with sodium analgam in ethanol, a method which is successful in the case of benzazlactone,[46] was also attempted. However, only products resulting from hydrolysis and fragmentation appeared to be produced under these conditions.

Ethyl bromopyruvate was synthetized from pyruvic acid according to the procedure of Archer and Pratt[47] in 53% overall yield; b.p. 103°-107°C 8-9 mm. (Literature b.p. 116°-121°C 27 mm).

An attempt was made to replace the bromine function in ethyl bromopyruvate by an azide group using sodium azide in dimethyl sulfoxide as the solvent. Under these conditions, a gas was rapidly evolved. Similar results were obtained when ethanol was used as the solvent. However, the addition of sodium azide to the solvent alone did not produce a gas. The gas was probably nitrogen resulting from the decompostion of the organic azide that was being formed. The desired compound could not be obtained by these procedures.

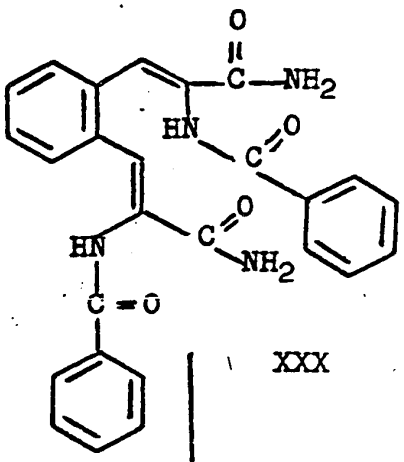
The synthesis in good yield of α-nitro esters from α-bromoesters and silver nitrite in absolute ethyl ether at room temperature has been reported.[48] However, with ethyl α-bromopropionate the reaction was found to be too slow to be practical. A good yield of ethyl α-nitropropionate was reported when ethyl α-iodopropionate was used instead of ethyl α-bromopropionate. Ethyl α-iodiopropionate can be obtained from ethyl α-bromopropionate in 80% yield by treatment with sodium iodide in dry acetone at room temperature for 12 hours. A similar method was used for the attempted preparation of ethyl nitropyruvate but unfortunately, treatment with sodium iodide in dry acetone on ethyl



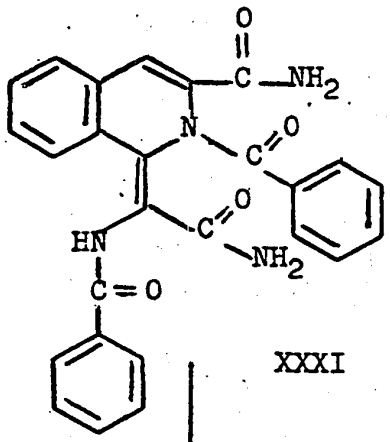
XVIII

NH_3

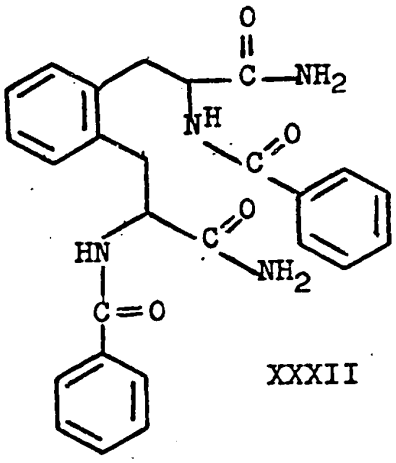
or



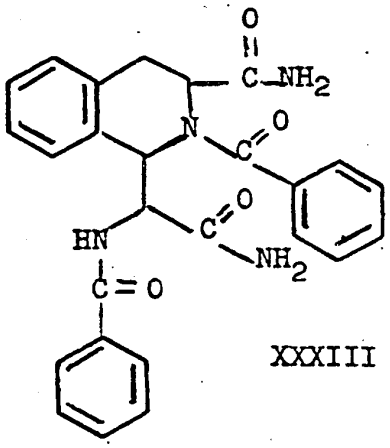
XXX



XXXI



XXXII



XXXIII

bromopyruvate was complex and did not result in the formation of the desired ethyl iodopyruvate.

Active methylene groups can generally be oxidized to carbonyl functions by selenium dioxide. Malonic ester was reported to be oxidized to the corresponding ketone in about 40% yield by selenium dioxide using benzene as the solvent[49]. A similar method failed for the oxidation of ethyl cyanocetate by selenium dioxide; instead, a red compound was formed which, on long standing broke down partly into the starting material.

Methyl α-aminopropionate was prepared by a modification of Fischer's method[50]. The aminoester hydrochloride was converted to the free amine by treatment with silver carbonate in dry methanol. The overall yield was 80%.

The procedure for the attempted synthesis of methyl dimethoxy β-aminopropionate was the same as that described for the conversion of α-phenethylamine to its α-keto analog. Instead of hydrolyzing the presumed intermediate ketal to the ketoamine, anhydrous hydrogen chloride was passed into the benzene solution followed by the addition of an excess of dry methanol. The mixture was allowed to stand over-night at room temperature and a white solid was removed; its properties indicated that this material was not organic. Evaporation of the benzene filtrate left a negligeable liquid residue.

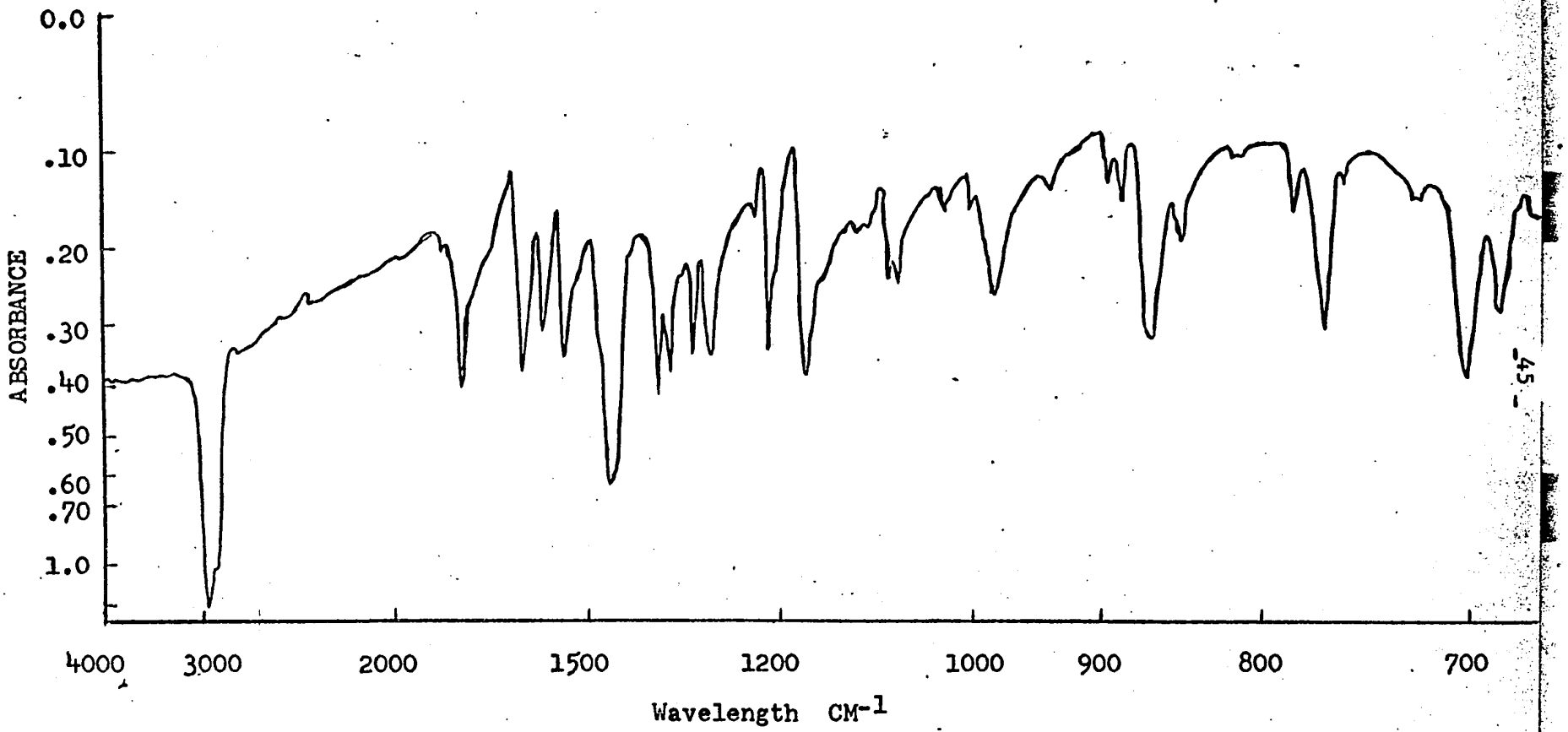


Fig.9. Infrared spectrum (nujol mull) of unphotolized bis-azlactone of σ-phthaldehyde.

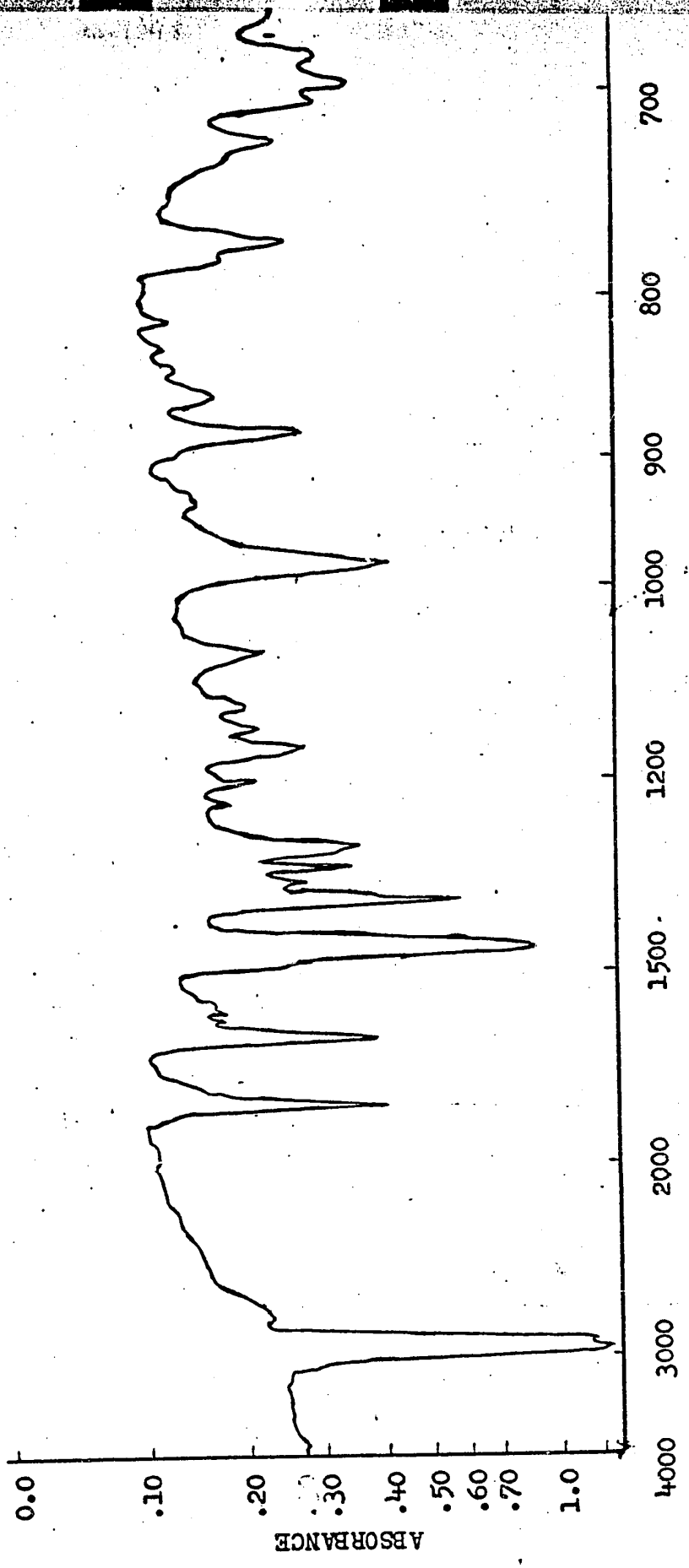


Fig.10. Infrared spectrum (nujol mull) of photolized bis-azlactone of σ-phthaldehyde.

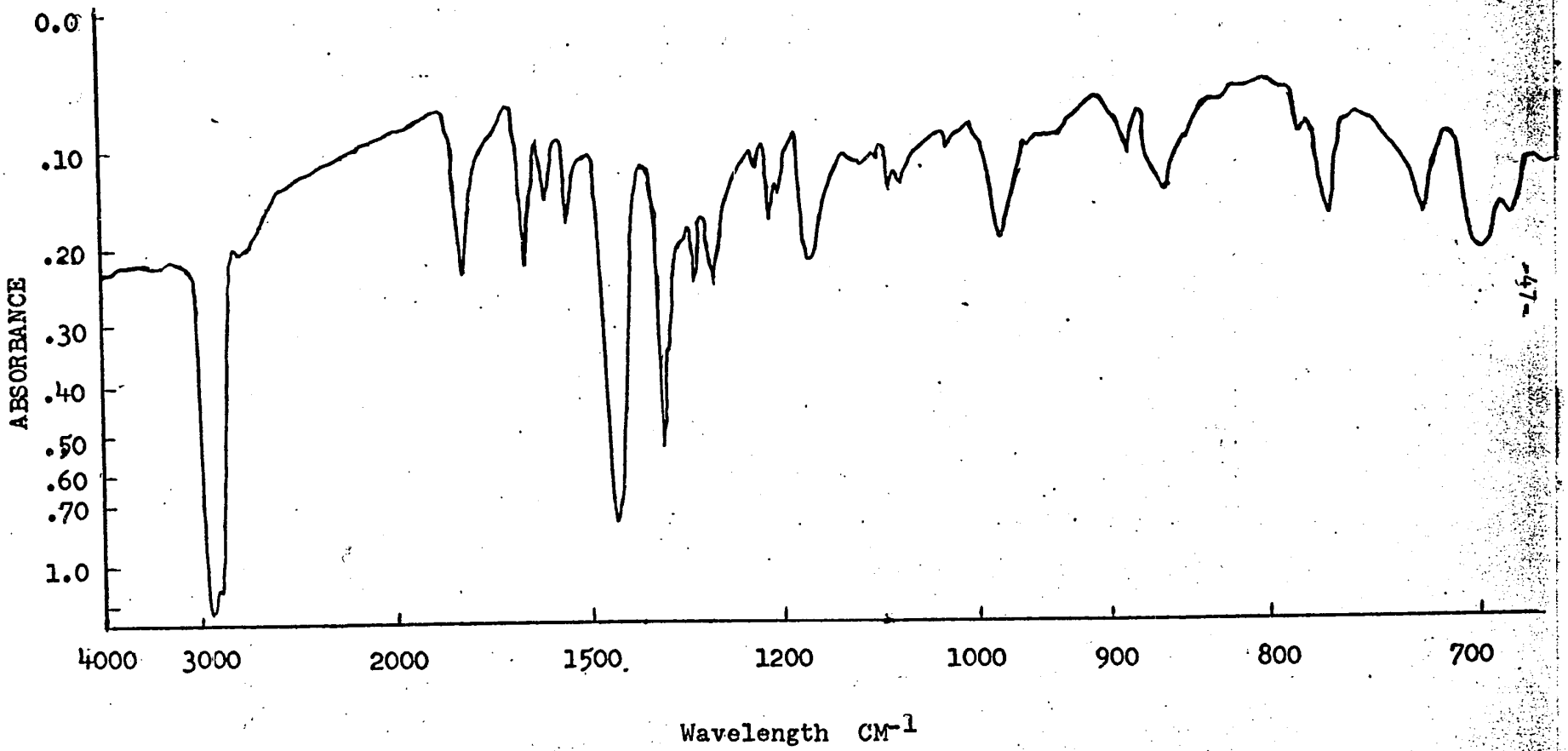


Fig.11. Infrared spectrum (nujol mull) of photolized bis-azlactone of o-phthaldehyde. (after heating).

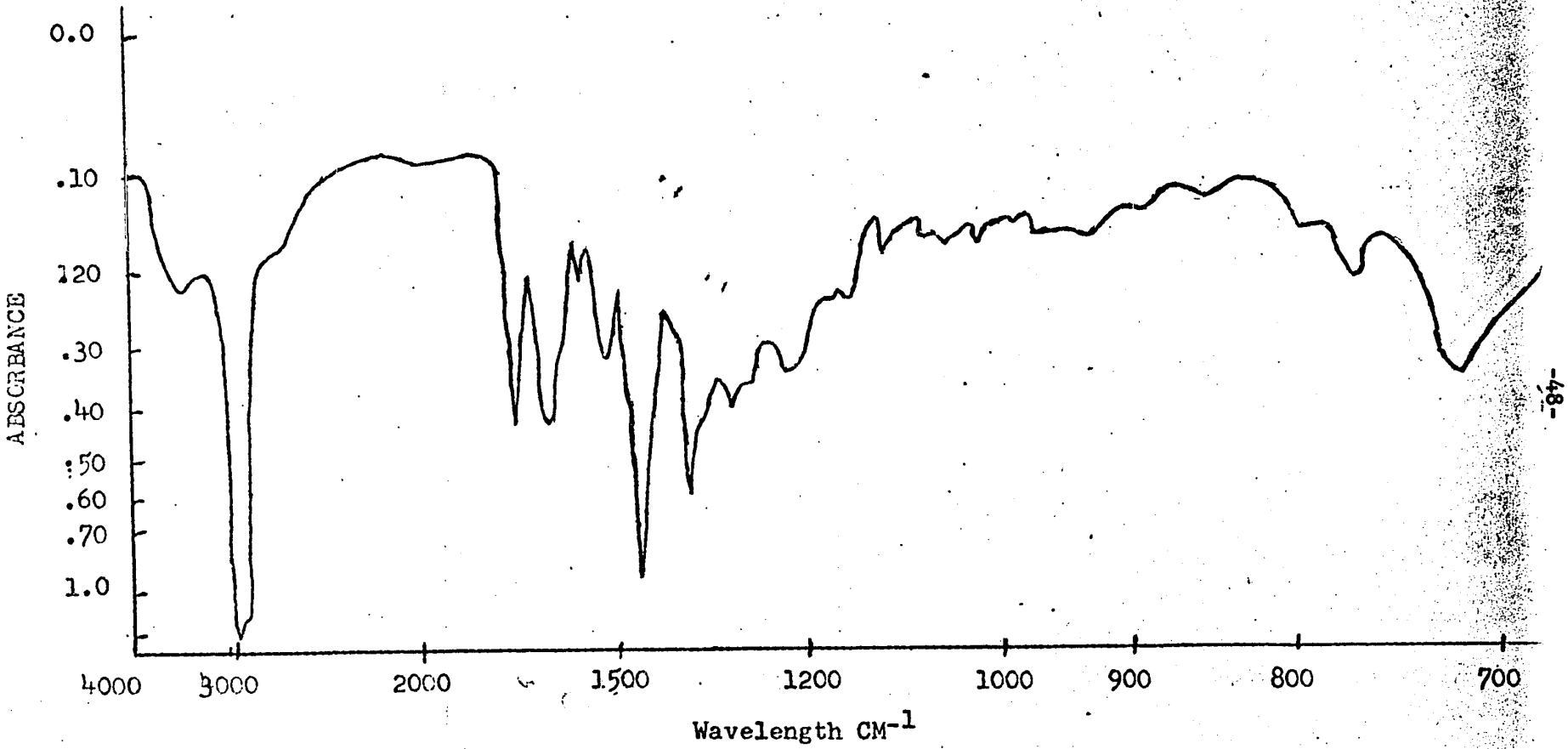


Fig. 12. Infrared spectrum (nujol mull) of the product from hydrolysis of o-benzabisazlactone

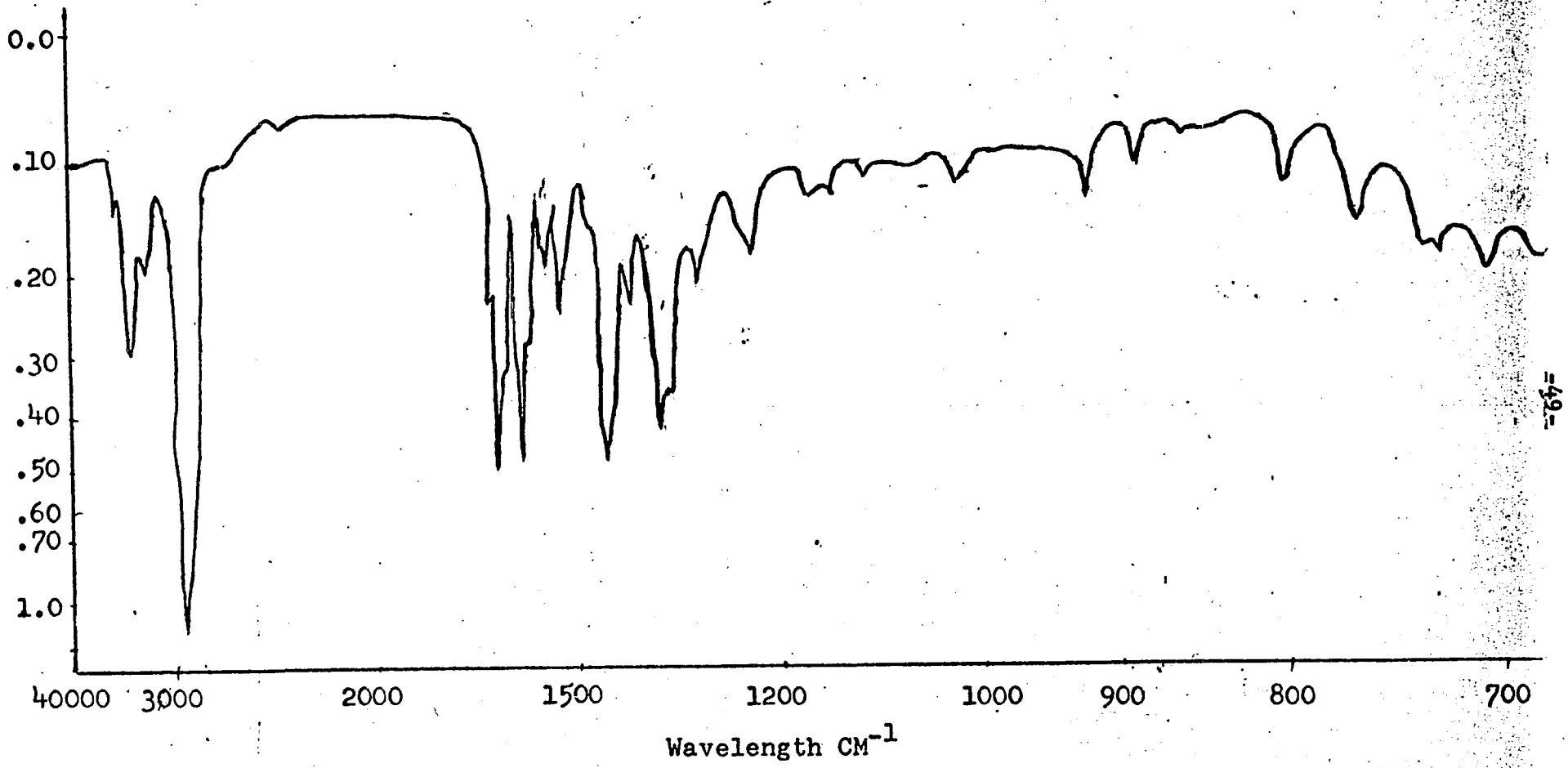


Fig. 13. Infrared spectrum (nujol mull) of the product from aminolysis of the bisazlactone of o-phthaldehyde (o-benzabisazlactone)

DISCUSSION

In the condensation of o-phthalaldehyde with hippuric acid, several modifications of this procedure were attempted including the use of sodium acetate as catalyst and longer reaction time. The condensation of o-phthalaldehyde directly with 2-phenyloxayl-5-one did not give a better yield[51]. The low yield is probably due to steric hindrance, since the corresponding paradialdehyde was found to give a bisazlactone in 97% yield[52].

The bisazlactone of o-phthalaldehyde was found to be sensitive to light. This could be due to free radical intramolecular rearrangement involving the double bonds which are held in a favourable position for this type of reaction. This is supported by the fact that the compound, after being exposed to day-light, changed from deep orange to light green. This change in color might be due to the loss of conjugation resulting from the loss of the two double bonds. Also, the fact that two absorption peaks at 1550 cm^{-1} and 1590 cm^{-1} in the infrared spectrum of the unphotolysed bisazlactone were not found in the infrared spectrum of the photolysed compound supports this view. Upon heating, the photolysed compound reverted back to the original bisazlactone (IR spectrum 9, 10, and 11). A similar phenomenon was observed in the case of 1,2,5 tri-t-butyl benzene[53] which changed to the Dewar structure when exposed to ultra-violet light and changed back to the normal benzene structure upon heating. It is unfortunate that this compound (possible structure XXXIV) is insoluble in organic solvents which made the determination of its molecular weight impossible.

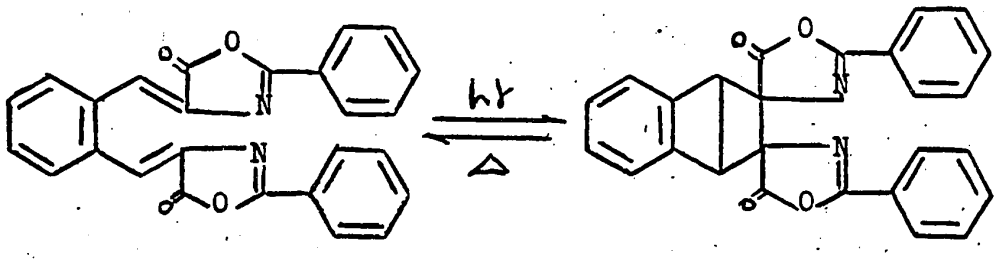
The products methylbenzoate and hippuric acid, recovered as fragments of the hydrolyzed bisazlactone, indicates that neither compound

XIX nor compound XX was obtained. As the main fragment from the hydrolysis could not be used as an intermediate for the synthesis of cephalosporin C related compounds, no attempt was made to characterize it. One possible explanation for the resulting products could be that one of the azlactone rings opened first, followed by ring-closure to an isoquinoline derivative and aromatization. This would result in the cleavage of a benzoyl group as methyl benzoate and a reversed condensation of the other azolactone ring to give hippuric acid.

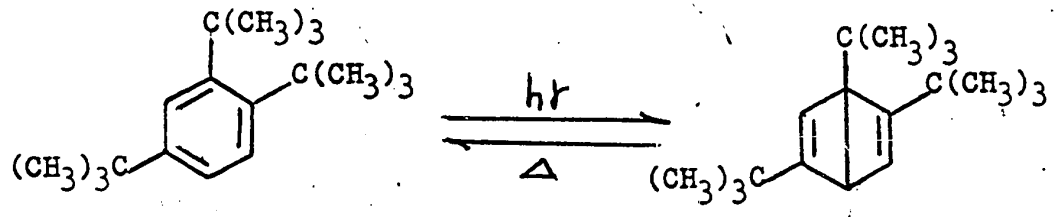
As there seems to be only one product resulting from the aminolysis of the bisazlactone, the side chains must be all intact. However, when acid hydrolysis was carried out to convert the amide to the corresponding acid, glycine was isolated thus, again making the product useless as intermediates for the synthesis of cephalosporin C related compounds. Attempts were made to hydrogenate the bisazlactone and thus keep the side chain intact. However, a suitable reduction method has not been found.

To synthesize α-ketopropionic β-lactam by the method of E. Testa and L. Fontanella, 2-aminomethyl-2-carbethoxy-1,3-dioxalane was required as an intermediate. The synthesis of a ketal derivative containing a primary amine function would be difficult because ketal synthesis usually requires an acid as catalyst and the amine function would react with the catalyst to form a salt. It would be desirable then to have groups such as azida, nitro and cyano which should be easily convertible to an amine function after formation of the ketal. The replacement of the bromide function in ethyl bromopyruvate by solvolytic reactions to give a azide and nitro derivatives were unsuccessful. This might be due to the unstable nature of the pyruvate system. The oxidation of ethyl cyanoacetate by selenium dioxide resulted in the formation of complex

products. The novel method which might convert DL alanine to the desired aminoketal was found to be ineffective even though this method has been used for the synthesis of many aliphatic ketoamines.



XXXIV



1,2,5 tributyl benzene

1,2,5 tributyl bicyclohexa-2,5-diene

(a derivative of Dewar benzene)

CLAIMS TO ORIGINAL RESEARCH

1. An excellent method of preparing pure *endo* norborn-5-ene-2-carboxylic acid by zinc reduction in acetic acid of the corresponding iodolactone has been developed. This acid was obtained previously by successive recrystallizations of *exo* and *endo* norborn-5-ene-2-carboxylic acid mixture.

2. Four peresters, *exo* and *endo* t-butyl norbornane-2-percarboxylate and *exo* and *endo* t-butyl norborn-5-ene-2-percarboxylate were synthesized from their respective acids via their acid chlorides.

3. Kinetic studies have been carried out on the thermal decomposition of *exo* and *endo* t-butyl norbornane-2-percarboxylate, and, *exo* and *endo* t-butyl norborn-5-ene-2-percarboxylate in chlorobenzene. Their respective first order rate constants have also been determined and compared.

4. A reversible photolysis reaction of the bis-azlactone of σ-phthaladehyde has been observed. Spectral evidence for this reaction is also presented.

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