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CONDENSATION OF NITROMETHANE WITH DIALDEHYDES

A thesis submitted in partial fulfilment

of the requirements of the degree of

Master of Science

Department of Chemistry

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Candidate

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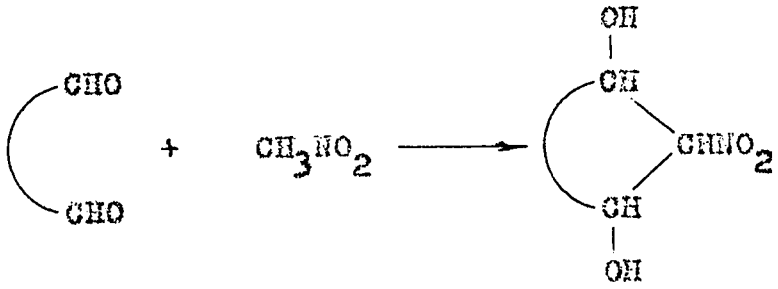
Research Supervisor

PREFACE

The nitromethane condensation with dialdehydes, leading to the formation of cyclic compounds proceeds according to the scheme:



This reaction has been used extensively in the field of carbohydrate chemistry. Examples of its application to simple dialdehydes are very few.

The present work, which is a part of the broader program of studies carried out in this laboratory, was undertaken with the purpose of studying further simple dialdehydes applicable to the cyclization reaction with nitromethane, with particular view of obtaining five- and seven-membered ring systems.

ACKNOWLEDGMENT

The author wishes to express her sincere gratitude to Professor Hans H. Baer for his guidance and patience as research director.

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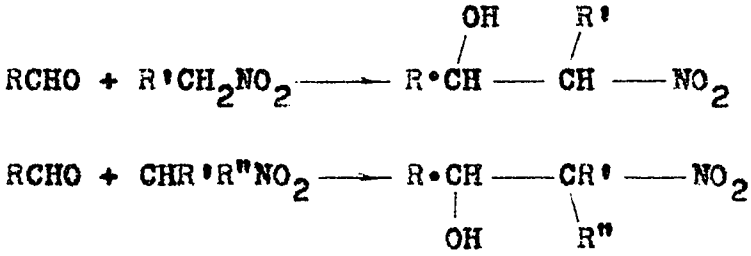
ABSTRACT

Phthalaldehyde was found to react with nitromethane, in methanolic solution and in the presence of sodium methoxide, to give the sodium salt of 2-aci-nitroindandiol-1,3. It was found that this salt, on acidification with ion exchange resin, afforded a mixture of 2-nitroindandiol-1,3 and 2-nitroindenol-3, which were separated by fractional crystallization. The structures of the compounds obtained were established by nuclear magnetic resonance spectroscopy. Hence, the applicability of phthalaldehyde in the condensation with nitromethane, to form a five-membered carbocyclic ring, was shown. On the other hand, when the reaction between phthalaldehyde and nitromethane was carried out without solvent, in the presence of sodium carbonate, the hemiacetal of 2-(1-hydroxy-2-nitroethyl)-benzaldehyde was exclusively formed. The structure of the latter was proved by means of chemical transformations leading to the isoquinoline system.

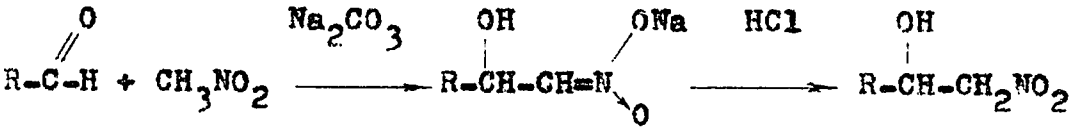
For the study concerning the closure of a seven-membered ring, adipic aldehyde was chosen. Under all conditions investigated, no formation of a seven-membered carbocyclic ring was noticed. It is believed that the failure was due to a more rapid formation of other compounds, namely 1,8-dinitrooctane-2,7-diol and the product of internal aldol condensation of adipic aldehyde, cyclopentene-1-aldehyde.

INTRODUCTION

Primary and secondary nitroparaffins, when allowed to react with aldehydes in the presence of basic catalysts, afford nitroalcohols:



The reaction was discovered in 1895 by Henry (1). He condensed nitromethane with acetaldehyde, propionaldehyde and isobutyraldehyde in the presence of sodium carbonate and obtained the sodium salts of the corresponding nitroalcohols which were liberated by acidification with mineral acid.



Later he extended the reaction using other nitroparaffins such as nitroethane and nitropropane (2).

The first condensation of nitromethane with an aromatic aldehyde and with the use of a basic catalyst* was performed by Thiele (3). He noticed the formation of the sodium salt (I) of a nitroalcohol (II) as in the case of aliphatic aldehydes, but acidification led directly to a dehydration product, the nitroolefin (III).

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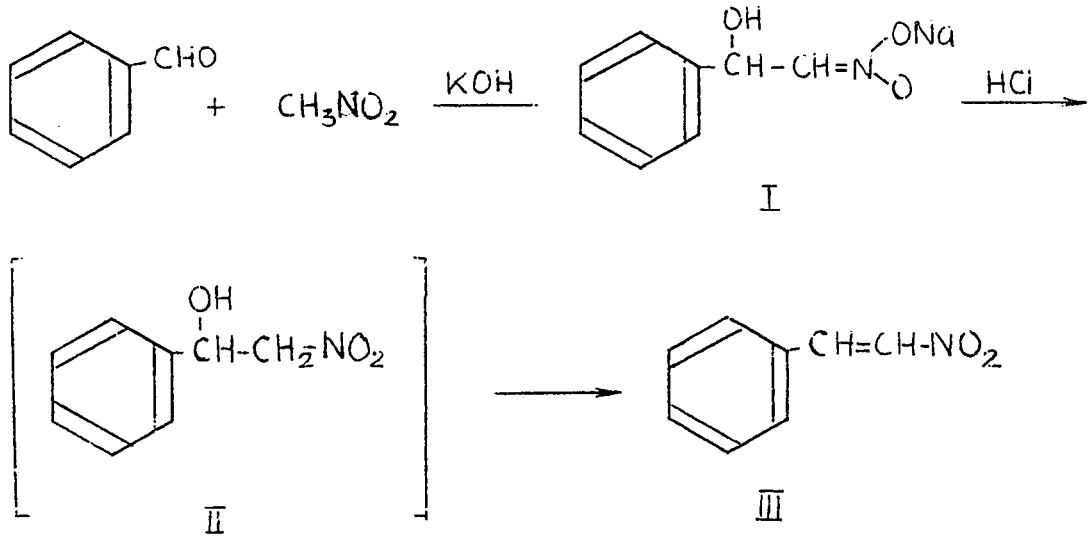
* Previously the same reaction had been done by Priebs (4), but at high temperature (160°) in a sealed tube and with $ZnCl_2$ as a catalyst.



The remarkable instability of nitroalcohols derived from aromatic aldehydes turned out to be one of their general properties, although, under gentle conditions of acidification, the isolation of aromatic nitroalcohols (II) was also possible (5).

Soon many other examples were studied, both for aliphatic (6,7,8) and aromatic (9,10,11) aldehydes, and in all cases the course of the reaction was as described above. It is worth mentioning that in aromatic aldehydes, substituents in the ring have a pronounced influence on the yield of the substituted nitrostyrene that is formed (16). Formaldehyde (12,13,14,15) provides a notable exception to the usual course of the nitromethane condensation, since more than one molecule of the aldehyde tends to condense with one molecule of nitromethane even in the presence of a large excess of the latter. When equimolar quantities of formaldehyde and nitromethane are allowed to react, the following

approximate percentages of the three possible condensation products are obtained (15):

$$CH_2O + CH_3NO_2 \longrightarrow \underset{9\%}{CH_2(OH)-CH_2NO_2} + \underset{13\%}{(CH_2OH)_2CHNO_2} + \underset{78\%}{(CH_2OH)_3CNO_2}$$

Even when a five molar excess of nitromethane is employed, the yield of 2-nitroethanol by this reaction is only about 40%. With homologs of either nitromethane or formaldehyde, the tendency for more than one molecule of aldehyde to condense with one molecule of nitroparaffin decreases sharply with increasing molecular weight or complexity of either component.

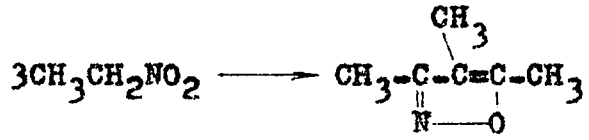
Many different basic catalysts have been used to promote the condensation reaction (17). They include sodium and potassium carbonate, sodium and potassium hydroxide in water and alcoholic solutions, calcium, barium, strontium hydroxides, rare earths, alkoxides and various secondary and tertiary amines.

The necessary conditions for a successful condensation reaction are invariably mild, since several competing reactions occur. The aldehyde component may undergo intermolecular aldol condensation or, as in case of formaldehyde and aromatic aldehydes, the Cannizzaro reaction. Nitroparaffins and particularly nitromethane are, moreover, sensitive to the action of alkali. Nitromethane forms successively

metazonic acid (IV) (18,19) and nitroacetic acid (V) (20), while its higher homologs yield trialkylisoxazoles (VI) (21,22,23).

IV

V



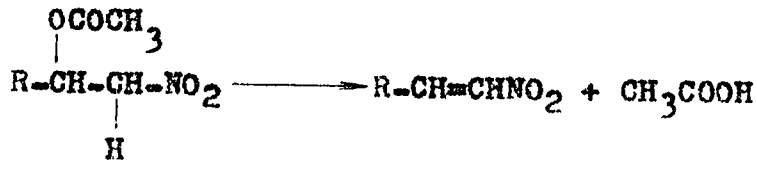
VI

Moreover, the condensation products are not stable in the presence of strong alkali since the condensation tends to be reversed by strong alkali, and even aliphatic nitroalcohols may undergo dehydration with the formation of nitroolefins. Vanderbilt and Hass (17) gave a useful summary of the reaction conditions, based on 27 examples of the condensation leading to the formation of nitroalcohols with yields of 88-98%.

Since the universality of the reaction of nitroparaffin with aldehyde was established and because of high yields and preparative simplicity, it finds numerous applications in synthetic work:

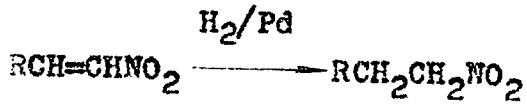
(a) Preparation of β-nitroalcohols.

(b) Preparation of nitroolefins. In the aromatic series, unsaturated compounds are the main products. The nitro-alcohols derived from aliphatic aldehydes may be readily transformed into corresponding olefins (VIII) through their acetyl derivatives (VII) which readily lose the elements of acetic acid on treatment with sodium bicarbonate (Schmidt-Rutz reaction)(24).



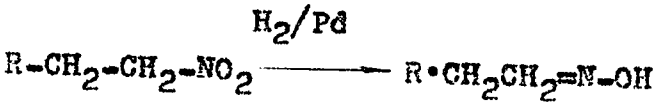
VII VIII

(c) Selective reduction of the double bond in a nitroolefin affords the corresponding nitroparaffin, which otherwise may not be easily accessible (25).



(d) Reduction of nitroparaffin or β-hydroxy-nitroparaffin is in turn the source of amines or β-hydroxyamines.

(e) Controlled catalytic hydrogenation of nitroparaffins may produce corresponding oximes.



(f) The primary and secondary nitroparaffins are typical

pseudo acids forming salts when treated with base.

$$RCH_2NO_2 + NaOH \longrightarrow RCH{=}NO_2Na$$

Acidification of these nitronic acid salts may lead to a variety of products, depending on the nature and strength of the acids employed.

1. Weak acids, such as acetic or carbonic acids, in general regenerate the nitroparaffins, although it has been reported (26), that Nef reaction (cf.4) may be caused even by weak acid.
2. Warm mineral acids hydrolyse the salts of primary aci-nitroparaffins to produce fatty acids and salts of hydroxylamine. The same reaction occurs when the primary nitroparaffins themselves are warmed with concentrated mineral acid (27).

$$R\text{-}CH{=}N\begin{matrix}\nearrow ONa \\ \searrow O\end{matrix} \xrightarrow[H_2O]{H_2SO_4} RCOOH + NH_2OH{\cdot}H_2SO_4$$

3. Under controlled conditions, intermediate hydroxamic acids are produced (28,29).

$$R\text{-}CH{=}NO_2H \xrightarrow{H_2SO_4} RCOH{=}NOH \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}OH$$

4. Great attention has been gained by the Nef reaction (30),

named so after its discoverer*. When the nitronates of primary and secondary nitroparaffins are decomposed by acids, there are produced aldehydes and ketones, respectively. The yield may be as high as 85-90%.

$$2RCH{=}NO_2Na + 2H_2SO_4 \longrightarrow 2RCHO + 2NaHSO_4 + N_2O + H_2O$$

$$2R'R''C{=}NO_2Na + 2H_2SO_4 \longrightarrow 2R'R''CO + 2NaHSO_4 + N_2O + H_2O$$

The Nef reaction was used to obtain simple aldehydes and ketones (30,33,34) and has achieved considerable importance in carbohydrate chemistry as a result of the work of Sowden and Fischer (cf.p.8).

5. Recently, an effective general method was developed for the oxidation of salts of mononitro compounds with neutral permanganate to aldehydes or ketones (35).

$$3R'R''C{=}NO_2K + 2KMnO_4 + H_2O \longrightarrow R'R''C{=}O + 2MnO_2 + 3KNO_2 + 2KOH$$

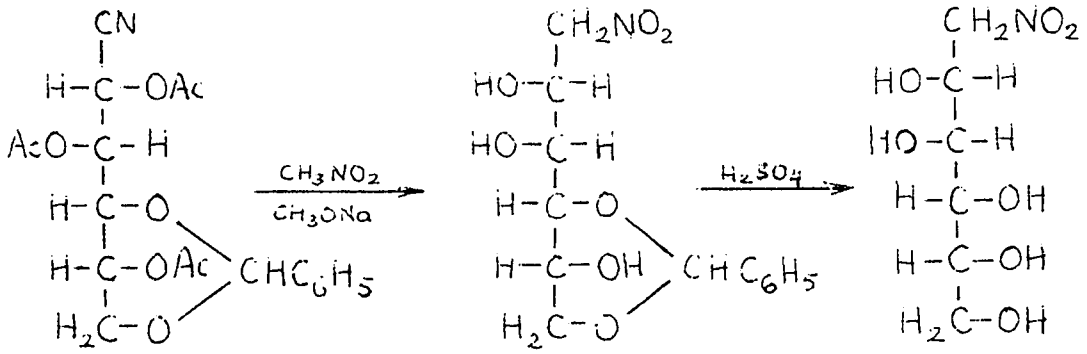
This reaction has the advantage that it may be successfully applied to those nitrocompounds which are stable under the conditions of the Nef reaction.

---

* In 1893 (31,32) Konovalov, on treatment of potassium-1-phenyl-nitromethane with dilute sulphuric, nitric and acetic acid, or even passing CO_2 into an alcoholic solution of the potassium salt, obtained a mixture of the desired 1-phenyl-nitromethane and acetophenone. It was Nef, however, who studied and established the generality of the reaction.

The Nitromethane Synthesis in Sugar Chemistry

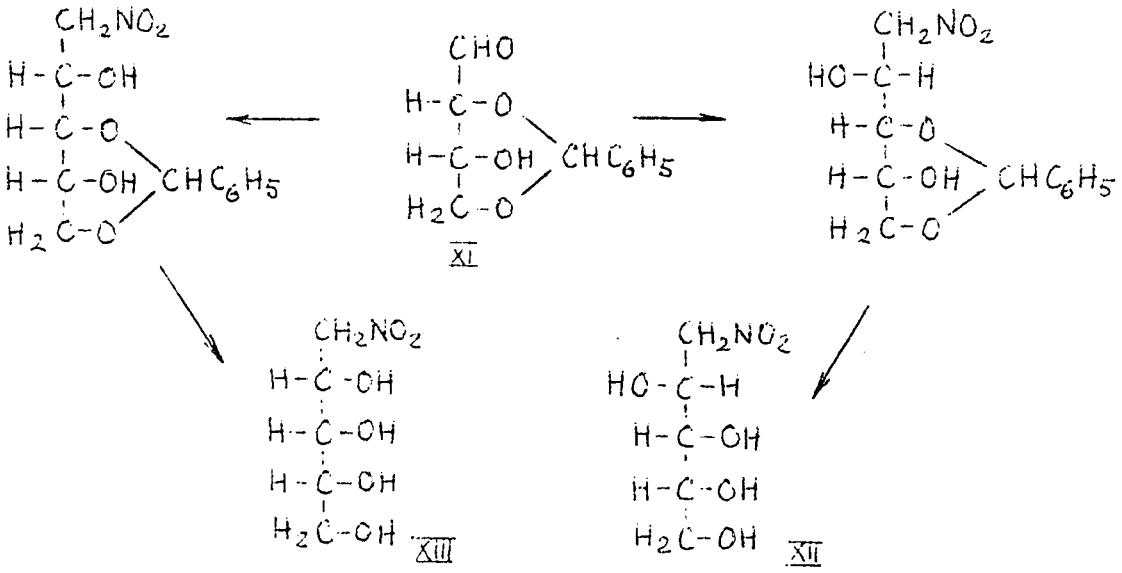
The nitromethane condensation with aldehydes has found wide application in sugar chemistry. The first attempt to produce higher-carbon sugar alcohols by means of nitromethane synthesis was done in 1921 by Pictet and Barbier (36), but their experiments did not demonstrate that nitromethane-aldose sugar condensation had been achieved. As a first successful example may be quoted the reaction performed by Sowden and Fischer (37), in which 4,6-benzylidene-2,3,5-triacetyl-D-gluconononitrile (IX) was treated with sodium methoxide in methanol solution, in the presence of nitromethane, to give finally 1-nitro-1-desoxy-D-mannitol (X).



IX X

Soon it was shown that substituted aldoses with free reducing groups as well as unsubstituted aldose sugars will undergo nitroparaffin condensations (38). This, in combination with

the Nef reaction, has become a key method for the lengthening of aldose chains. For instance, Sowden (39) prepared 1-nitro-1-desoxy-D-arabitol (XII) and 1-nitro-1-desoxy-D-ribitol (XIII), starting from 2,4-benzylidene-D-erythrose (XI) in the sequence of reactions outlined below. The nitro sugar alcohols were then converted into pentoses by Nef reactions (41,42).



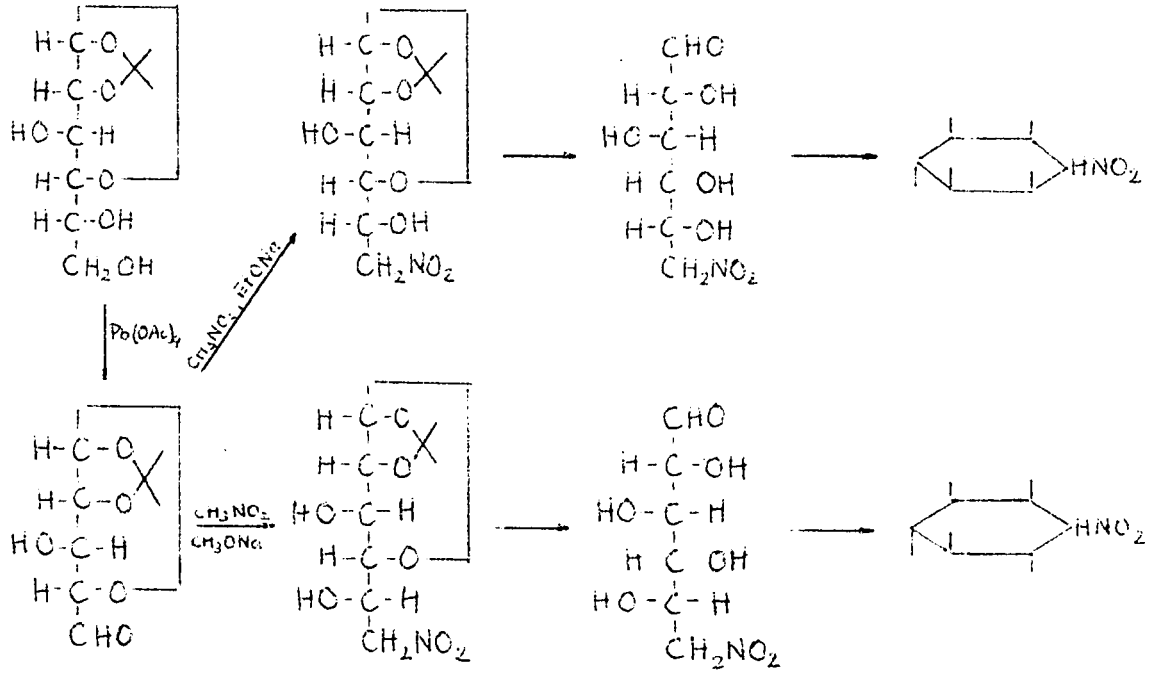
It is important to note that nitromethane condensations, apart from the good yields, generally afford both epimers, although in varying ratios. The ratio of isomers produced has, in some cases, been found to differ considerably from that produced in the Kiliani cyanohydrin synthesis of sugars (40), so that the two methods may be regarded as complementary.

Another aspect of the nitromethane synthesis in the field of carbohydrates is the preparation of 1-C^{14} sugars. Isotopically labelled compounds are finding extensive appli-

cation in the elucidation of both biological and chemical processes, and for such purposes the nitromethane synthesis has opened a new route for introducing C^{14} into sugar molecules. It was possible, for instance, to obtain 1-C^{14}-glucose (43,44), 1-C^{14}-D-mannose (43,44) and 1-C^{14}-D-xylose (45).

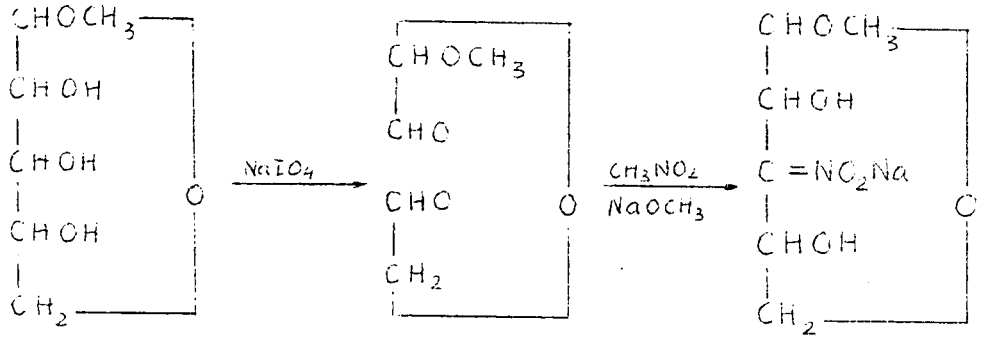
The Cyclization of Sugar Dialdehydes with Nitromethane

In 1948, Grosheintz and Fischer (46,47) were able to prepare nitrodesoxyinositols from 6-nitrodesoxyaldohexoses, as illustrated by the following reaction scheme.



A new application of the nitromethane condensation was found by Baer and Fischer (48,49). They achieved one-step condensa-

tions between sugar dialdehydes and nitromethane with formation of pyranoside ring structures. As starting materials were used methyl pentopyranosides (XVII), which were oxidized with two moles of periodate, giving the corresponding dialdehyde (XVIII), which in turn, on treatment with nitromethane, in the presence of sodium methoxide, formed salts of cyclic aci-nitrocompounds (XIX).



XVII XVIII XIX

The salts (XIX), on acidification, yielded free nitroglycosides, which were readily hydrogenated catalytically to the corresponding amino glycosides.

Thus, the new reaction opened the possibility of synthesizing not only 3-nitro, but also 3-amino sugars. The latter class of compounds is of considerable biological significance, since many 3-amino sugars have been discovered to be constituents of antibiotics. No facile and general methods for their synthesis had been available previously.

Since then, the nitromethane cyclization was studied

on many other dialdehydes derived from sugars, and its general applicability was established.

Application of the method made possible the synthesis of 3-nitro and 3-amino derivatives of D- and L-ribose (49), D- and L-xylose (49), D- and L-arabinose (50), D-mannose, D-glucose, D-galactose, D-talose (51,52,53), as well as nitrogenous derivatives of various 2,7-anhydro-β-D-heptulopyranoses (54). Of particular interest was the facile preparation, by this method, of 3-amino-3-deoxy-D-ribose (49), 3-amino-3-deoxy-D-glucose (55) and 3-amino-3,6-dideoxy-D-glucose (56), which are components of the antibiotics puromycin, kanamycin (57,58) and magnamycin.

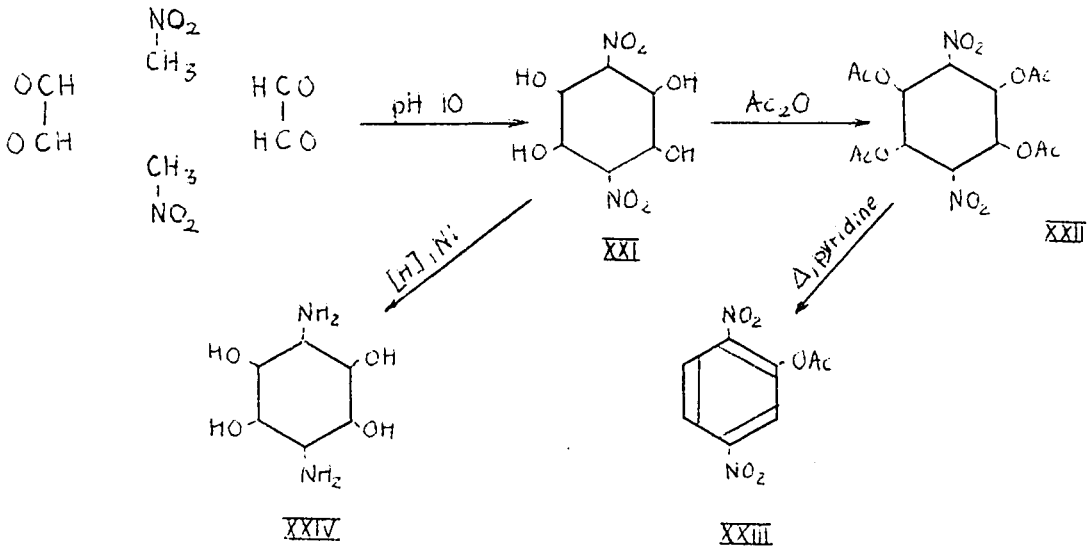
Apart from the synthesis of 3-amino sugars, the new reaction may lead to labelling sugars with C^{14} in the 3-position.

Cyclization with Nitromethane of Simple Dialdehydes

Whereas the nitromethane cyclization of dialdehydes has been used successfully in numerous cases in carbohydrate chemistry, there have been known only three examples of its application to the "simple" dialdehydes.

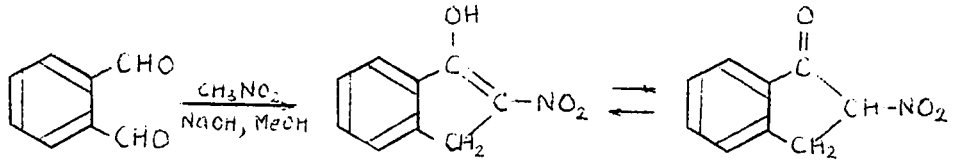
Recently, Lichtenthaler and Fischer (59) prepared a mixture of stereoisomers of 1,4-dinitro-tetrahydroxycyclohexane (XXI) by condensing two moles of glyoxal with two moles of nitromethane. The acetyl derivative (XXII) was readily

aromatized by heating in pyridine to give the acetate of 2,5-dinitrophenol (XXIII). This proved the cyclic structure of compound (XXI). Reduction with Raney nickel in dimethyl formamide-acetic acid solution of (XXI) gave, in excellent yield (90%), diamine (XXIV).



XXI XXII XXIII XXIV

Thiele and Weitz, in 1910, condensed phthalaldehyde with nit omethane and claimed to have obtained compound (XX) (9).

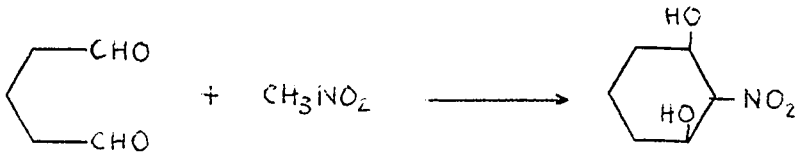


XX

The structure proposed is difficult to reconcile with the well-established general pattern of the nitromethane cyclization (see Discussion).

Finally, in 1961, Lichtenthaler obtained, from

glutaric aldehyde and nitromethane in water solution at pH 10, a mixture of 2-nitro-cyclohexanediols-1,2, from which he isolated the isomer (XXV) in 44% yield.



In the light of the knowledge available at the beginning of the present work and delineated in this Introduction, it appeared to be of interest to investigate the following problems:

1. All the nitromethane cyclizations of dialdehydes, with the one exception of phthalic aldehyde, have led to six-membered ring systems. Before any more thorough studies of the synthesis of five-membered ring systems could be undertaken, it was desirable to reinvestigate the nitromethane condensation of phthalic aldehyde with view of some justifiable doubts that existed in the structure of the product.
2. The possibility of cyclizing dialdehydes to form seven-membered rings was to be studied with adipic aldehyde as the simplest compound available for this purpose.

EXPERIMENTAL*

General

Nitromethane and phthalic aldehyde were reagent grade and were used without further purification. Adipic aldehyde was freshly prepared for each experiment from trans-1,2-cyclohexanediol obtained according to the procedure described in Organic Syntheses, Vol. III, p. 217. For thin layer chromatography (T.L.C.), silica gel G (according to Stahl) was used. The procedure was as follows. The plates were covered with a layer (about ½ mm.) of a slurry made from silica and water (1:2), dried in the air and activated for two hours at 80°C. As developing solvent systems, cyclohexane-chloroform-acetone mixtures (5:4:1; 6:3:2; 4:4:2) were applied. The positions of the spots on the plates were found by spraying the plates with 1% cerium sulphate solution in 10% sulphuric acid and heating for 10-20 minutes in the oven at 120°. Because of unreproducibility of R_F values in thin layer chromatography, the mobilities of the compounds were examined only by direct comparison with samples of reference. Catalyst for the hydrogenations was freshly prepared before each reaction by shaking PtO_2 in a hydrogen atmosphere. The hydrogen uptake was recalculated for normal conditions. Melting points were measured in capillary tubes and are uncorrected. Infrared spectra were taken in nujol mull on Perkin-

*The Roman numerals of the compounds described relate to the Discussion, not the Introduction.

Elmer Infracord spectrophotometer Model 137. Nuclear magnetic resonance spectra were measured on the Varian HR-60 instrument in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in parts per million (τ values) (63).

A. Condensation of Nitromethane with Phthalaldehyde

Method 1

2-Nitroindenol-3 (I)

A methanolic solution (17 ml.) of phthalaldehyde (1.0 g., 7.5 mmoles) and nitromethane (2.0 g., 33 mmoles) was cooled in ice water and 30% ethanolic potassium hydroxide (1.7 ml.) was added dropwise. The mixture, when stirred, solidified to a colorless gel. Then crushed ice (60 g.) was added and triturated with the gel. The reaction mixture still containing some ice was made acidic with 1N hydrochloric acid (60 ml.). The solution almost immediately turned greenish and after a short time, yellow needles separated. They were filtered off, washed with water on the suction funnel, and dried in a vacuum dessicator. The crude product (0.84 g., 77.8%) melted at 135-140°(dec.); it appeared to be homogeneous in thin layer chromatography. Recrystallization from benzene-petroleum ether (b.p. 80-100°) afforded an analytical sample of m.p. 140-141°C. The yellow needles were soluble in cold alcohol, chloroform, and benzene, sparingly soluble in petroleum ether, and almost insoluble in water.

Analysis:

Calculated for $C_9H_7O_3N$ (177): C, 61.01%; H, 3.95%; N, 7.91%.

Found: C, 60.05%; H, 3.71%; N, 7.72%.

Acetylation of 2-nitroindenol-3 (I)

2-Nitroindenol-3-acetate (III)

2-Nitroindenol-3 (100 mg.) was dissolved in acetic anhydride (1 ml.) and a small drop of sulphuric acid was added. The mixture was heated on the steam bath for 15 minutes. After cooling, ethanol (1 ml.) was added and the resulting mixture put aside for ½ hour in order to decompose the excess of acetic anhydride. Then it was poured on crushed ice, made alkaline with sodium carbonate, and extracted four times with chloroform. The combined chloroform extracts (60 ml.) were dried with magnesium sulphate, filtered and evaporated under reduced pressure. The residue consisted of a yellow crystalline solid (100 mg., 81%), m.p. 125-130°. The crude 2-nitroindenol-3-acetate was dissolved in cyclohexane and heated with activated charcoal on the steam bath for 3 minutes, then filtered while hot. On cooling, the solution deposited yellowish needles, m.p. 126-130°. Further recrystallization did not change the melting point.

Method 2

Sodium Salt of 2-Nitroindanediol-1,3 (V)

Phthalaldehyde (670 mg., 5 mmoles) was dissolved in methanol (15 ml.) and nitromethane (305 mg., 5 mmoles) was added at once. To the ice-cold mixture, a solution of sodium methoxide (prepared by dissolving 105 mg. of sodium in 4 ml. of methanol) was added dropwise. A white, crystalline precipitate appeared immediately, which was filtered off and washed with ice cold ethanol. All attempts at recrystallization led to decomposition of the product. It was unstable on heating at 80° for a few hours, and on rapid heating decomposed without melting from ~ 150°. For analysis, the sodium salt (V) was dried in a vacuum dessicator over phosphorus pentoxide at room temperature.

Analysis:

Calculated for $C_9H_8O_4NNa$ (217):

C, 49.76%; H, 3.69%; N, 6.45%; Na, 10.6%.

Found: C, 48.37%; H, 4.08%; N, 6.24%; Na, 9.44%.

Acidification of Sodium Salt (V) with Ion Exchange Resin. 2-Nitroindanediol-1,3 (VI)

Freshly prepared sodium salt (V) (1.00 g.) was suspended in methanol (50 ml.) and 10 ml. of ion exchange resin, Rexyn RG-50(H^+), was added. The mixture was then stirred for 10 minutes. The crystals of the salt dissolved

and the solution turned yellow. The resin was filtered off, washed with methanol (10 ml.), and the combined methanol solutions were evaporated to dryness. The resulting crystalline product (700 mg.) was examined by thin layer chromatography. It showed the presence of two compounds, one of them having a mobility identical with that of 2-nitroindenol-3 (I). 2-Nitroindanediol-1,3 (VI) appeared as a slower spot. A crude separation of both compounds was achieved by means of their different solubilities in benzene, 2-nitroindenol-3 being easily soluble. Final purification was performed by recrystallization: 2-nitroindanediol-1,3 (300 mg.), after several crystallisations from ethanol-chloroform, separated as colorless needles of m.p. 162-5°(dec.), It gave a single spot in thin layer chromatography.

Analysis:

Calculated for $C_9H_9O_4N$ (195): C, 55.39%; H, 4.61%.

Found: C, 55.17%; H, 4.79%.

2-Nitroindenol-3 (390 mg.) crystallized from cyclohexane-benzene mixture as yellow needles, m.p. 140-141°. It was identical in all respects with that prepared in the previous experiment (m.p., mixed m.p., mobility in thin layer chromatography, infrared spectra).

Acetylation of 2-Nitroindanediol-1,3 (VI)

2-Nitroindanediol-1,3-diacetate (VII)

2-Nitroindanediol-1,3 (50 mg.) was dissolved in

acetic anhydride (1 ml.) with a small drop of sulphuric acid. The mixture was heated on the steam bath for ½ hour, cooled to room temperature and after addition of ethanol (1 ml.) was allowed to stand for ½ hour. The solution was poured on crushed ice and neutralized with sodium bicarbonate. A crystalline precipitate separated and was filtered off and washed with cold water on the suction funnel. After drying in a vacuum dessicator, 2-nitroindanediol-1,3-diacetate (60 mg.) formed fine, colorless needles melting at 82-5°. An analytical sample was prepared by two recrystallizations from cyclohexane and drying at 10^{-2} mm. at room temperature*. It showed m.p. 90-91°.

Analysis:

(279.2)

Calculated for $C_{13}H_{13}NO_6$: C, 55.91%; H, 4.70%.

Found: C, 56.62%; H, 4.80%.

Method 3

Hemiacetal of 2-(1-Hydroxy-2-nitroethyl)-benzaldehyde (IX)

To the mixture of phthalaldehyde (100 mg., 0.75 mmoles) and nitromethane (~~200~~ 2 mL mg., ~~3.3 mmoles~~), powdered anhydrous sodium carbonate (200 mg., 1.9 mmoles) was added. The reaction mixture was stirred overnight at room temperature. Sodium carbonate was filtered off and the excess of

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* After drying overnight at room temperature, the crystals turned from colorless into brown-purple color.

nitromethane evaporated under reduced pressure on the water bath (40°C). The residue (110 mg.) was recrystallized several times from benzene. The hemiacetal (IX) formed colorless needles of m.p. 120-123°, which were readily soluble in alcohol, but only moderately soluble in chloroform and benzene.

Analysis:

Calculated for $C_9H_9O_4N$ (195): C, 55.4%; H, 4.61%; N, 7.2%.
Found: C, 55.1%; H, 4.50%; N, 7.1%.

2,4- Dinitrophenylhydrazone (VIIIa) of 2-(1-Hydroxy-2-nitroethyl)-benzaldehyde (VIII)

Hemiacetal (IX) (100 mg.) was added to the solution of 2,4-dinitrophenylhydrazine (105 mg.) in methanol (5 ml.) with sulphuric acid (0.2 ml.). The mixture was heated on the steam bath for five minutes and then cooled to room temperature. Immediately, red crystals precipitated which were filtered and washed thoroughly with ethanol. The crude product (200 mg.) had m.p. 198-200°. Recrystallization from chloroform-dimethylformamide mixture afforded an analytical sample of m.p. 205-208°C. The red prisms were hardly soluble in all common solvents except dimethylformamide.

Analysis:

Calculated for $C_{15}H_{13}O_7N_5$ (375): N, 18.6%. C, 48.0, H 3.49
Found: N, ~~18.4%~~ 18.54. C 48.04, H 3.53
Bernhardt (1931)

Catalytic Hydrogenation of Hemiacetal (IX).

To the suspension of platinum catalyst (100 mg. of PtO_2, prehydrogenated) in acetic acid-water mixture (10 ml. + 10 ml.), hemiacetal (IX) (390 mg., 2 mmoles) was added. The hydrogenation was stopped as soon as 3 molar equivalents of hydrogen were absorbed. The catalyst was filtered off and washed with water. The ninhydrin-positive filtrate was evaporated to dryness under reduced pressure. The residue (300 mg.) after trituration with benzene crystallized partially. Recrystallization from ethanol-ether gave colorless crystals of m.p. 150-151°, which showed a negative ninhydrin test. The product was presumed to be (Xa).

Picrate:

To an ethanolic solution of 25 mg. of the above product, picric acid in ethanolic solution was added in slight excess. The mixture was heated on the steam bath for three minutes and then put aside. On cooling, yellow prisms separated (30 mg.) which, after recrystallization from ethanol, melted at 169-171°. The nitrogen content of the material was in agreement with formula $C_{15}H_{12}O_8N_4$ of a 4-hydroxy-dihydroisoquinoline picrate. Calc. 14.88%, found, 14.79%.

Oxidation of Hemiacetal (IX). Lactone of 2-(1-Hydroxy-2-nitroethyl) benzoic acid (XI)

Potassium dichromate dihydrate (600 mg.) was

dissolved in water (3 ml.) and concentrated sulphuric acid (0.5 g.) was added. Into this solution, 600 mg. of powdered hemiacetal (IX) was introduced in small portions. The reaction mixture was heated at 80° with stirring for 1 hour. Then the crystalline precipitate was filtered off and washed with water. After drying, the crude product (470 mg., m.p. 131-132°) showed a single spot in thin layer chromatography. Recrystallization from ethanol gave colorless prisms of (XI) showing m.p. 132°C.

Analysis:

Calculated for $C_9H_7O_4N$ (193): C, 55.9%; H, 3.6%; N, 7.2%.

Found: C, 56.1%; H, 3.7%; N, 7.0%.

Partial Catalytic Hydrogenation of Lactone (XI). Lactone of 2-(1-Hydroxy-2-aminoethyl)-benzoic Acid Hydrochloride (XII)

To the suspension of platinum catalyst (50 mg.) in an acetic acid-water mixture (5 ml. + 5 ml.) was added 100 mg. of the lactone (XI). The hydrogenation was stopped as soon as 3 molar equivalents (85 ml.) of hydrogen were consumed. The catalyst was filtered off and washed with water. The combined filtrates were treated with sodium carbonate until the solution became alkaline. Then the amine was extracted with chloroform and dried with sodium carbonate. After evaporation of solvent, the amine did not crystallize. Concentrated hydrochloric acid (0.1 ml.)

was added to the syrup and thus a crystalline precipitate was obtained (50 mg.), which after recrystallization from ethanol gave colorless needles of m.p.~ 260°C.

Analysis:

Calculated for $C_9H_9O_2N \cdot HCl$ (199): C, 54.4%; H, 5.02%; N 7.0%; Cl 17.8

Found: C, 53.8%; H, 5.06%.

Bernhard: 54.54; H, 5.19; N, 7.20; Cl 17.84

Exhaustive Catalytic Hydrogenation of Lactone (XI). Octahydroisocarbostyrile (XIII).

To the suspension of platinum catalyst (150 mg.) in acetic acid-water mixture (30 ml. + 15 ml.), the lactone (500 mg.) was added. The reduction was carried out exhaustively (24 hours) and 250 ml. of hydrogen was consumed. The catalyst was filtered off and washed with water. The combined filtrates after evaporation left a residue which on contact with ethanol crystallized partially to give 50 mg. of an unidentified product of m.p. 155°. The residual oil was a mixture of several compounds according to thin layer chromatography. The oil was suspended in water and made slightly acidic with 1N hydrochloric acid. Extraction with benzene resulted in a crystalline colorless product (150 mg.), m.p. 146-149°C., which was finally purified by sublimation at 120°C. and 9 mm. Hg. The product was octahydroisocarbostyrile (XIII).

Analysis:

Calculated for $C_9H_{15}NO$: C, 71.28%; H, 9.86%; N, 9.14

Bernhard: f. C 70.60; H 9.75; N, 9.30

(1952)

Found: C, 70.59%; H, 9.80%.

Reduction of Octahydroisocarbostyrile (XIII). Decahydroisoquinoline (XIV)

Octahydroisocarbostyrile (60 mg.) was dissolved in anhydrous tetrahydrofuran (10 ml.) and an excess of lithium aluminum hydride (100 mg.) was added. The mixture was refluxed with stirring for two hours under exclusion of moisture, then cooled in an ice-bath, and wet ether (130 ml.) was added dropwise with stirring. When the evolution of hydrogen had ceased, the inorganic material was filtered off and washed with chloroform. The combined solutions were evaporated to dryness under reduced pressure. The residue (72 mg.) was distilled (90-120°/20 mm. Hg) giving 38 mg. of a colorless oil.

Picrate of Trans-decahydroisoquinoline (XIVa).

The oil (38 mg.) obtained in the previous experiment was dissolved in a few drops of methanol and a hot solution of picric acid (100 mg.) in methanol (2 ml.) was added. To the warm mixture, water was added dropwise, until the solution became turbid. Upon scratching with a spatula there began crystallization. Crude picrate (65 mg.) was separated by decantation and recrystallized several times from methenol. It formed yellow prisms, m.p. 156-158°, which were easily soluble in metha-

nol and insoluble in water.

Hydrochloride of cis-Decahydroisoquinoline (XIVb)

The mother liquor from which the above picrate had been removed was passed over a small column containing an anion exchange resin in the chloride form (Dowex-1 (Cl^-)). The column was eluted with methenol. The nearly colorless effluent was concentrated and, on cooling with ice, deposited about 6 mg. of colorless needles melting at 175-178°.

Reaction of polyphosphoric acid on amino-lactone (XII)

The aminolactone (XII) (50 mg) was suspended in a water - ethanolic solution (10 ml.) of sodium hydroxide (135 mg) and refluxed for two hours. The mixture was evaporated to dryness in vacuo and excess of polyphosphoric acid was added carefully. The mixture was heated on the steam bath for ½ hour. Then water (20 ml) was added and the product was extracted with chloroform (6 x 20 ml). Evaporation of combined chloroform extracts gave an oily product (6 mg), which showed in IR, absorption at 1650 cm^{-1}.

B. Condensation of Nitromethane with Adipic Aldehyde

Preparation of Adipic Aldehyde

To an ice-cooled solution of sodium metaperiodate (2.1 g., 0.01 moles) in water (30 ml.), trans-1,2-cyclohexanediol (1.2 g., 0.01 moles) was added portion-

wise. The mixture was allowed to stand in the dark at room temperature, and the presence of periodate was examined with starch paper that was saturated with a water solution of potassium iodide and excess of sodium bicarbonate. When the test became negative (15 min.), the reaction mixture was extracted six times with ethyl acetate (200 ml.). The ethyl acetate extracts were combined and dried with magnesium sulphate. On evaporation under reduced pressure to dryness, they left a colorless oil (1.2 g.). Adipic aldehyde may be distilled at 91-94°C/ 8 mm. Hg. Usually it was used for the condensations freshly prepared without distillation. The product gave a crystalline bis-(2,4-dinitrophenylhydrazone) of m.p. 210-215°C.

Condensation I

To the mixture of adipic aldehyde (1.5 g., 13.1 mmoles) and nitromethane (0.8 g., 13.2 mmoles), cooled in ice, methanolic sodium methoxide (0.03 g. Na (1.3 mmoles) in 1 ml. of methanol) was added dropwise. The precipitate that appeared was dissolved by addition of methanol (10 ml.). The mixture was kept at 0°C., with stirring, for one hour, then it was diluted with methanol (25 ml.) and neutralized with an excess of the ion exchange resin (IR-120(H^+)). The resin was filtered off and washed with methanol. The combined methanolic solutions were evapo-

rated to dryness and left a yellowish oil (2.4 g.) which, when examined in T.L.C., showed the presence of 9 components. This mixture could not be induced to crystallize, nor could it be separated by distillation.

Condensation II

Preparation of 1,8-Dinitro-2,7-dihydroxyoctane

To a mixture of adipic aldehyde (1.5 g., 13.1 mmoles) and nitromethane (7.8 g., 130 mmoles), cooled in ice, a 3% methanolic sodium methoxide solution was added dropwise to adjust the pH to 8. The precipitate formed was dissolved by addition of methanol (5 ml.). The mixture was kept at room temperature for half an hour, then it was diluted with methanol (25 ml.) and neutralized with excess of ion exchange resin (IR-120(H^+)). The resin was filtered off and washed with methanol. The combined methanolic solutions were evaporated to dryness and left a yellowish oil (2.7 g.), which in T.L.C. showed the presence of one major spot accompanied by six minor spots. The oil partially crystallized when it was kept overnight in the refrigerator. The crystals were separated by washing with 2-propanol. Recrystallized three times from the same solvent, they formed colorless needles of m.p. 99-100°C. Further crops were obtained from the mother liquor, giving a total yield of 50% of 1,8-dinitro-2,7-dihydroxyoctane.

Analysis:

Calculated for $C_8H_{16}O_6N_2$ (236): C, 40.67%; H, 6.83%.

Found: C, 41.00%; H, 6.47%.

Acetylation of 1,8-Dinitro-2,7-dihydroxyoctane

1,8-Dinitro-dihydroxyoctane-2,7-diacetate

1,8-Dinitro-2,7-dihydroxyoctane (100 mg.) was dissolved in acetic anhydride (1 ml.) with a small drop of sulphuric acid. The mixture was heated on the steam bath for ½ hour, cooled to room temperature, and after addition of ethanol (1 ml.) was allowed to stand for ½ hour. The solution was poured into crushed ice and neutralized with sodium bicarbonate. The solution was extracted six times with chloroform. The combined chloroform extracts were dried with calcium chloride and evaporated to dryness, leaving a syrup which crystallized on scratching. The colorless prisms (105 mg.) were recrystallized twice from cyclohexane-chloroform and then melted at 110-112°C.

Analysis:

Calculated for $C_{12}H_{20}O_8N_2$ (320):

C, 45.01%; H, 6.25%; N, 8.7%.

Found: C, 44.83%; H, 6.65%; N, 8.2%

DISCUSSION

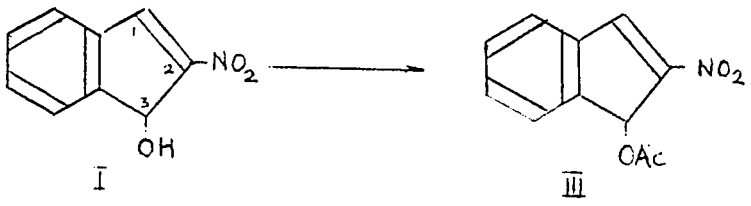
A Condensation of Phthalaldehyde with Nitromethane

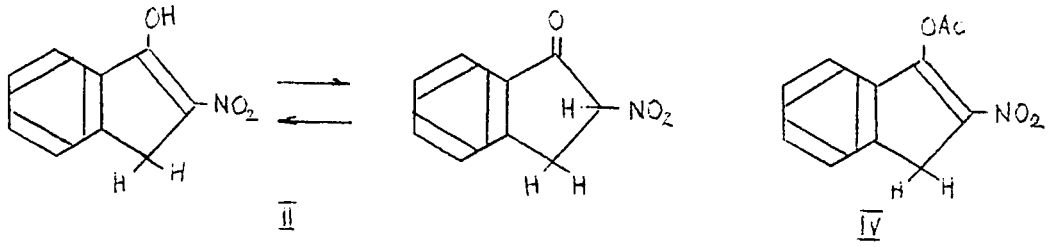
The choice of phthalaldehyde as an object of this study was made for the purpose of investigating the possibility of closing a five-membered ring in the nitromethane-dialdehyde condensation. Although this particular example had been reported long ago by Thiele and Weitz (9), it was felt that a reinvestigation was warranted for the following reasons: the structure of the condensation product, as given by the early authors, was at variance with that to be expected from the usual course of the reaction, which has been well established in the acyclic series. An explanation, involving a hydride shift, for the formation of the product, was offered by Campbell and Pitzer (60), but was not supported by experimental evidence. It was of interest, therefore, to prove or disprove the structure of Thiele and Weitz's product, and to investigate whether additional reaction products between nitromethane and phthalaldehyde are obtainable, and if so, to elucidate their structures.

The condensation reaction between phthalaldehyde and nitromethane was tried under several different conditions, involving changes of the molar proportions of reagents, of the solvent and the amount of catalyst. We will discuss here only three experiments that led to different products.

1. Formation of Five-membered Ring

At first we repeated the experiment described by Thiele and Weitz (9); that is, we carried out the reaction in methanolic solution and in the presence of potassium hydroxide. On acidification with 1N hydrochloric acid, we obtained a product which, judging from its melting point, was identical with that of Thiele and Weitz, but for which we established the structure of 2-nitroindenol-3 (I) instead of 2-nitroindenol-1 (II), as proposed by those authors.





Structure (I) follows from the evidence summarized below. The product, m.p. 140-141° (reported 142°), analyzed correctly for $C_9H_7O_3N$. It showed infrared absorption at 3350 $cm.^{-1}$ (OH), 1600 and 1500 $cm.^{-1}$ (arom. skeletal), 1550 and 1350 $cm.^{-1}$ (NO_2), and 770 $cm.^{-1}$ (arom. out-of-plane). Acetylation with acetic anhydride gave the monoacetyl deriva-

tive, m.p. 126-130° (reported 127°), which showed infrared absorption at 1740 $cm.^{-1}$ (C=O) and 1230 $cm.^{-1}$ (C-O of acetate) and lacked OH absorption, in agreement with structure (III). The absence of C=O absorption in compound (I), which has been previously noticed by Campbell and Pitzer (60), is not sufficient to reject formula (II), because one could well assume complete enolization. However, the carbonyl band in the acetate (III) is too low for a vinyl type ester such as (IV), for which the range 1770-1800 $cm.^{-1}$ was noted (61). Also, C-O stretching vibrations in enol acetates are near 1205 $cm.^{-1}$, that is, much lower than we found for acetate (III).

Conclusive evidence came from the NMR spectrum of compound (I) and its acetate (III). The spectrum of (I) (Table I) showed a singlet at 2.19 τ (1H), a multiplet centered at 2.49 τ (4H) and a broad singlet at 4.38 τ (1H). This accounts for all protons but one. Missing is obviously the hydrogen of the OH group, owing to the fast exchange with solvent.

The acetate (III) similarly has a singlet at 2.11 τ (1H), a singlet at 2.51 τ (4H), a singlet at 3.17 τ (1H) and a sharp singlet at 7.81 τ (3H), which again accounts for all protons present in the molecule.

The signals corresponding to 4H can immediately be assigned to the aromatic protons. The signal at lowest field in both spectra comes from the olefinic proton at C-1. Although the corresponding proton in indene appears at ~3.8 τ

TABLE I

NMR Data of Compound I

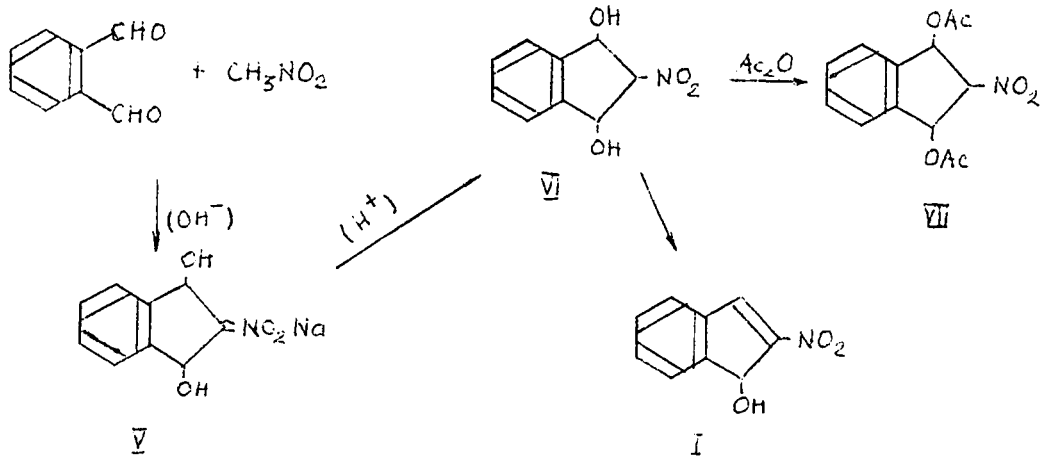
Position of proton	τ	Multiplicity	Intensity
C-1	2.19	singlet	1
aromatic	2.49	multiplet	4
C-3	4.38	singlet	1

NMR Data of Compound III

Position of proton	τ	Multiplicity	Intensity
C-1	2.11	singlet	1
aromatic	2.51	singlet	4
C-3	3.17	singlet	1
acetyl	7.81	singlet	3

(62), the downfield shift observed in our case may be expected because of an anisotropic effect of the nitro group. The absorption at 4.38 τ arises from the proton in α-position to the hydroxyl group which, in acetyl derivative is shifted downfield to 3.17τ, as it may be predicted (63). The signal corresponding to three protons in acetates is due to the hydrogens of the acetyl group. These findings fit formula (I); they are in disagreement with compound (II) which possesses no olefinic protons, but has two aliphatic protons in both the ketonic and the enolic form*.

2-Nitroindenol-3 (I) may be considered as arising from a dehydration of 2-nitroindandiol-1,3 (VI), that should be obtained as a primary product of condensation between phthalaldehyde and nitromethane.



* After the present work had been concluded, Lichtenthaler (64), in a preliminary communication reported the same structure for the cyclization product forwarding arguments similar to those presented in this thesis. He also obtained an analogous product from 2,3-naphthaldehyde.

Our next attempt was to isolate compound (VI) from the reaction mixture.

Upon condensation of phthalaldehyde with nitromethane in methanolic solution in the presence of sodium methoxide, the sodium salt (V) crystallized in form of fine, colorless needles, which were isolated, and without further purification analyzed correctly for $C_9H_8O_4NNa$.

When a suspension in ethanol of this sodium salt (V) was stirred with a cation exchange resin (Rexyn RG50 (H^+)), there was obtained in good yield a product which, according to thin-layer chromatography, consisted essentially of two components. These were separated by fractional crystallization from benzene and ethanol-chloroform mixtures.* The more soluble compound, which accounted for about 50% of the product, was revealed to be identical with previously obtained 2-nitroindenol-3. This was established by direct comparison of the melting points, infrared spectra and chromatographic mobilities. The second product was less soluble and less mobile in thin layer chromatography;

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* It is worth mentioning that application of column chromatography for the purpose of purification and isolation of the reaction products was impracticable in all cases, owing to the instability of the condensation products on contact with alumina or silica gel. Even fast runs on thin-layer chromatography plates suffered from some decomposition of product, although it was possible to use this technique for analytical purpose.

after crystallization from ethanol-chloroform mixtures it formed colorless needles of m.p. 162-5° (dec.) and showed the following infrared absorption peaks: 3400 cm.$^{-1}$ (OH), 1550 cm.$^{-1}$ and 1370 cm.$^{-1}$ (NO_2). It formed a diacetate that analyzed correctly for $C_9H_9O_4N$ and showed IR-absorption at 1720 cm.$^{-1}$ (C=O) and 1220 cm.$^{-1}$ (C-O), 1550 cm.$^{-1}$ (NO_2). No hydroxyl absorption was found. These data indicated structure (VI) for the less soluble product obtained from the salt (V), and structure (VII) for its diacetate. Final proof was furnished by means of NMR spectroscopy. The NMR spectrum of (VII) showed the presence in the molecule of four types of protons in the proportion 4:2:1:6 (Table 2). At lowest field there was a singlet at 2.57 τ (4H), which accounts for the aromatic protons. Then there was a doublet at 3.38 τ (2H) with splitting J 5-6 c.p.s. This signal corresponds to the hydrogens at C-1 and C-3.

The splitting into a doublet proves the presence of one hydrogen at C-2. The triplet at 4.83 τ is due to the hydrogen at C-2 (J 5-6 c.p.s.). At highest field there was a sharp singlet corresponding to 6 protons of the two acetyl groups. These features of the NMR spectrum proved structure (VII) for the acetate, from which follows structure (VI) for the product of condensation. It is also apparent from the NMR spectrum that both acetoxy groups must be on one side of the five-membered ring. This follows from the identical chemical

TABLE II

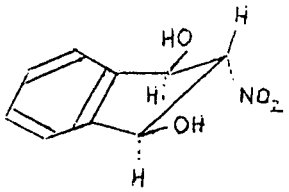
NMR Data of Compound VII

Position of proton	τ	multiplicity	Intensity	Splitting c.p.s.
aromatic	2.57	singlet	4	-
C-1, C-3	3.30	doublet	2	5-6
C-2	4.83	triplet	1	5-6
acetyl	7.83	singlet	6	-

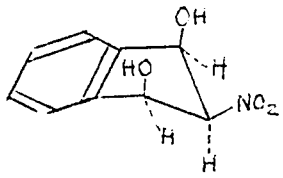
NMR Data of Compound XVIII

Position of proton	τ	multiplicity	Intensity	Splitting c.p.s.
C-2, C-7	4.50	multiplet	2	-
C-1, C-8	5.45	doublet	4	6
acetyl	7.95	singlet	6	-
methylene	7.9-8.8	multiplet	8	-

shifts of the acetoxy groups, and from the splitting of the hydrogen at C-2 into a triplet with an intensity 1:2:1, which must be due to two identical protons. Therefore, one can assign compound (VI) either the <u>all-trans</u> configuration (A) or the <u>all-cis</u> configuration (B). Although we cannot at present decide between these stereochemical possibilities, the configuration (A) would appear to be more likely because of the quasi-equatorial disposition of all bulky substituents.



A

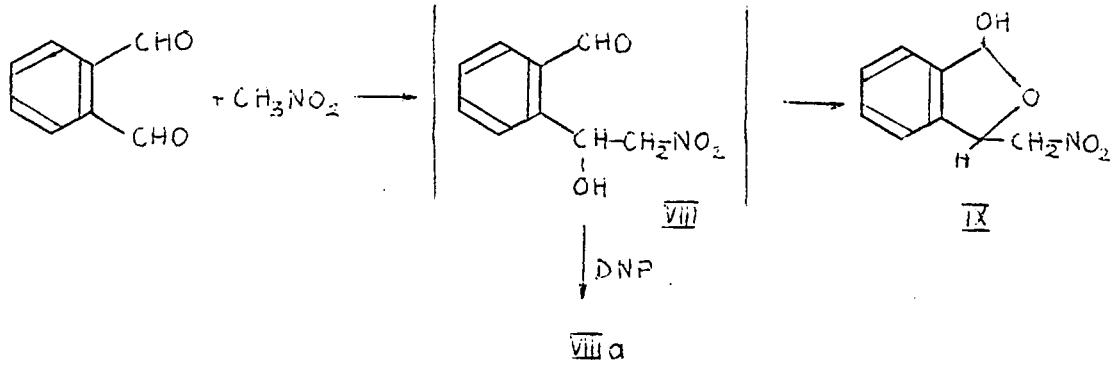


B

<u>Formation of Internal Hemiacetal of 2-(1-hydroxy-2-nitroethyl)-benzaldehyde</u>

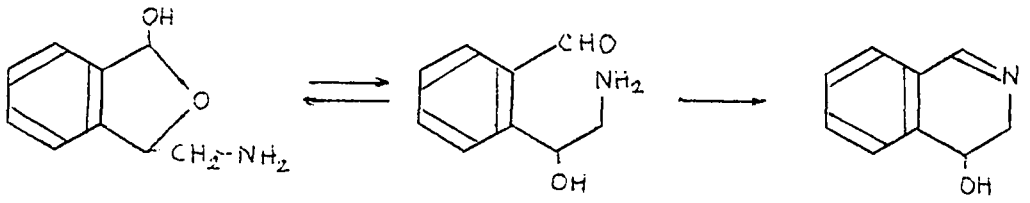
When a solution of phthalic aldehyde in nitromethane was stirred with solid sodium carbonate at room temperature for 12 hours, a condensation product different from (I) and (VI) was formed in 80% yield. It was isolated as colorless crystals melting at 120-123°. This product was shown, on the strength of the following evidence, to be the internal hemiacetal (IX) of 2-(1-hydroxy-2-nitroethyl)-benzaldehyde (VIII).

Product (IX) analyzed correctly for $C_9H_9O_4N$. Its infrared spectrum exhibited bands at 3300 $cm.^{-1}$ (OH), 1550 $cm.^{-1}$ (NO_2), 760 $cm.^{-1}$ (aromat.), but lacked carbonyl absorption. However, on treatment with 2,4-dinitrophenylhydrazine, it afforded a crystalline 2,4-dinitrophenylhydrazone whose analysis was in agreement with the assumed formula (VIIIa).



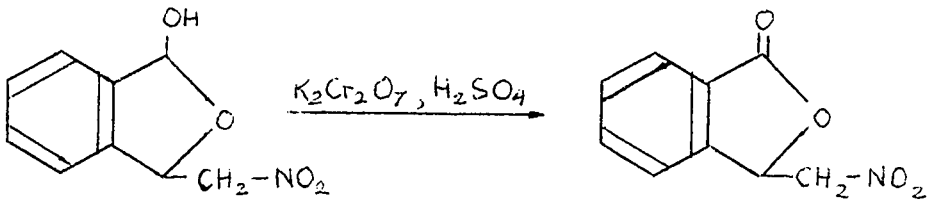
Catalytic hydrogenation of (IX) with platinum catalyst led to various products, depending on the reaction conditions. The solution became ninhydrin-positive, which suggested that the amine (X) was an initial product. However, a crystalline and ninhydrin-negative product melting at 150-151° was obtained upon work-up. Possibly this product was 4-hydroxy-3,4-dihyroisoquinoline (Xa), which is a Schiff base arising from the aldehyde form of (X). Although a crystalline picrate could be prepared from the presumed isoquinoline derivative (Xa), these hydrogenation experiments did not furnish conclusive evidence as to the structure of

the nitro compound (IX) because of unsatisfactory elemental analyses of (Xa).



X Xa

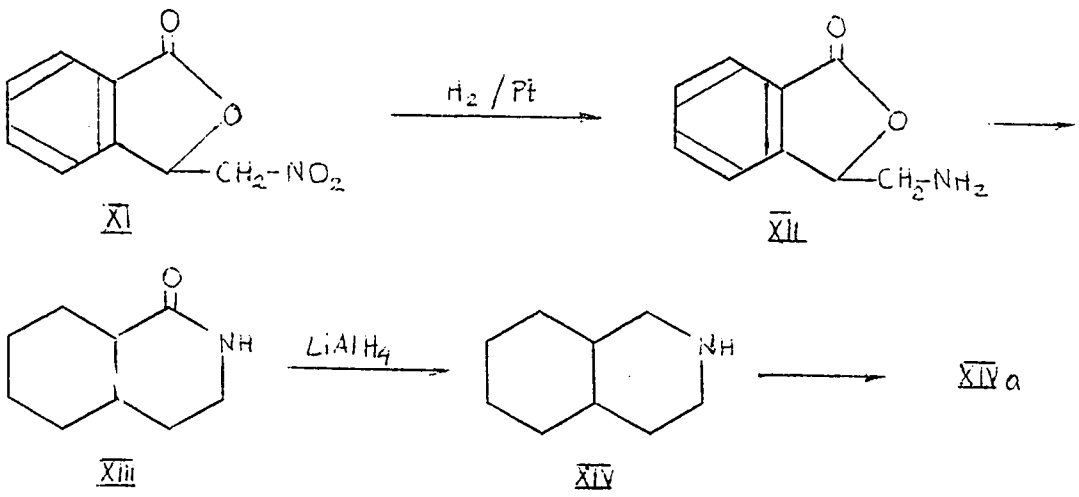
More successful was the oxidation of (IX) followed by hydrogenation. With potassium dichromate in sulphuric acid, (IX) gave a highly crystalline lactone (XI) in quantitative yield. The more important bands in the infrared were at 1750 $cm.^{-1}$ (γ -lactone, α , β -unsaturated), 1600 $cm.^{-1}$ (arom. skel.), and 1550 $cm.^{-1}$ (NO_2). On titration the lactone consumed 1.1 equivalents of alkali.



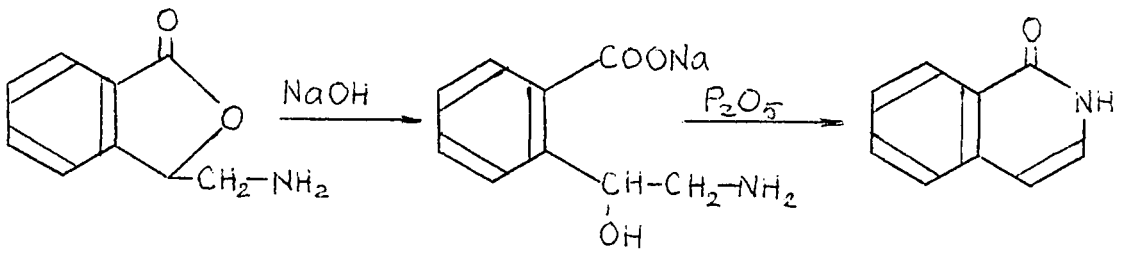
IX XI

The lactone (XI) was hydrogenated catalytically in the presence of a platinum catalyst. When the hydrogenation was interrupted after three moles of hydrogen had been consumed, an aminolactone (XII) was isolated that will be described further below. When, on the other hand, the hydrogenation was allowed to proceed to completion, the product was octahydroisocarbostyril (XIII). It was tentatively identified on the basis of its analytical data, melting point and infrared spectrum. The melting point recorded in the literature (65) for octahydroisocarbostyril is 147°C, whereas our product melted at 145-149°; it must have contained some of the cis isomer as became apparent from the subsequent experiment.

Since authentic samples of comparison of octahydroisocarbostyril were unavailable, the product was converted, by reduction with lithium aluminum hydride, into another known compound, decahydroisoquinoline (XIV). The reduction product consisted mainly of the trans isomer, which was characterized as its crystalline picrate of m.p. 156-158° (reported (66), m.p. 159-160°). From the mother liquor the cis isomer was isolated as a crystalline hydrochloride of m.p. 175-178°C (reported (66), m.p. 176°.



The aminolactone (XII) that was obtained as a primary product in the hydrogenation of the nitrolactone (XI) was characterized as a crystalline hydrochloride melting at 260°. The infrared spectrum revealed the presence of a γ-lactone grouping (1750 $cm.^{-1}$) and an amino group (3450 $cm.^{-1}$), and showed the absence of a nitro group. An attempt to convert this amino lactone into isocarbostyril (XVI) by treatment, first with alkali to produce the salt (XV), and then with polyphosphoric acid to achieve ring closure and dehydration to (XVI), did not result in the formation of an identifiable product, although the infrared spectrum of the product obtained showed an absorption at 1650 cm. which may correspond to a cyclic lactam.

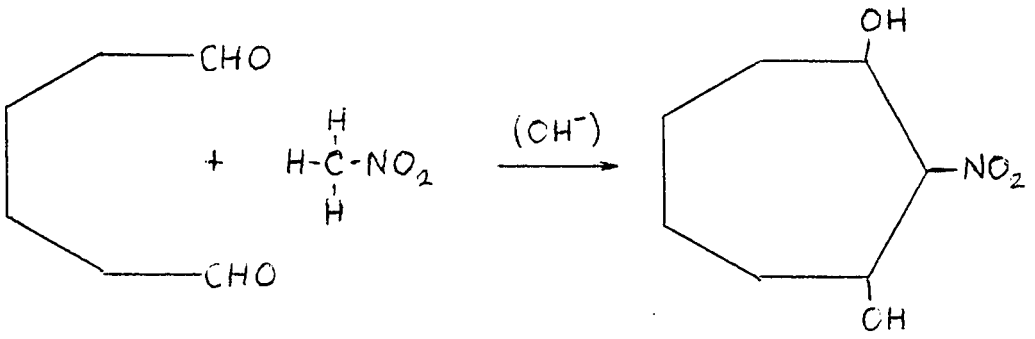


XI XV XVI

The sequence of reactions carried out with the phthalic aldehyde-nitromethane condensation product (IX), leading to the isoquinoline system, proves that only one aldehyde function of phthalic aldehyde had undergone Henry condensation with nitromethane, while the other remained available for a subsequent oxidation to the carboxylic acid stage. Reduction of the nitro group in (XI) to an amino group then made possible the closure of the lactam ring which constitutes part of the isocarbostyril derivative that was ultimately obtained. The fact that the second aldehyde group of phthalic aldehyde did not condense with nitromethane can be explained by a rapid formation and -- in the absence of hydroxylic solvents -- great stability of the internal hemiacetal (IX).

B. Condensation of Nitromethane with Adipic Aldehyde

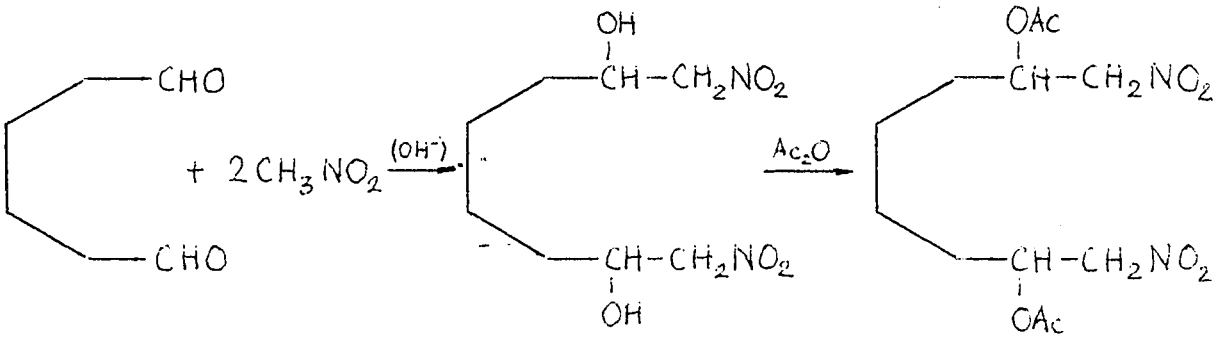
In our attempt to obtain a seven-membered cyclic condensation product of nitromethane with adipic aldehyde according to the reaction scheme given below, we investigated various reaction conditions which had been successful in the formation of five- and six-membered rings.



Using stoichiometric amounts of adipic aldehyde and nitromethane we obtained, regardless of solvent and kind and amount of catalyst, oily products which were revealed by thin layer chromatography to be mixtures of up to ten components. Judging from the intensities of the chromatographic spots these components arose in comparable quantities although some variation occurred with changing reaction conditions. No crystalline product could be isolated, and chromatography on a preparatory scale proved unsuccessful. The oils produced always seemed to contain a component which also arose when nitromethane was omitted from the reaction mixture: from its infrared spectrum as well as from its benzaldehyde-like smell

this substance appeared to be cyclopentene-1-aldehyde, being produced by an intramolecular aldol condensation of adipic aldehyde.

When adipic aldehyde was reacted with a tenfold excess of nitromethane, again there was produced a mixture of products, with one component being in preponderance. This chief product was isolated in crystalline form in 40% yield. It analyzed for $C_8H_{16}O_6N_2$ and showed hydroxyl and nitro bands in the infrared spectrum (3040 $cm.^{-1}$ (OH); 1535 $cm.^{-1}$ (NO_2)). The elemental composition of the product suggested that the dialdehyde had reacted with two nitromethane molecules to give 1,8-dinitrooctandiol-2,7 (XVII).



XVII XVIII

The structure of (XVII) was confirmed by the NMR spectrum of a crystalline diacetate (XVIII) that was obtained from it. The spectrum exhibited four groups of signals with intensities corresponding to 2, 4, 6, and 8 protons. There was an unresolved multiplet centered at 4,50τ(2H), being attributable to the hydrogens at C-2 and C-7; a sharp doublet at 5,45τ(4H)

with a spacing of $\mathcal{J}$ 6 c.p.s., corresponding to the hydrogens at C-1 and C-8; a sharp singlet at 7,95τ(6H) being due to the protons of the acetyl groups; and finally a broad signal around 7,9-8,8τ(8H) originating from the protons of the four methylene groups.

From the results of the experiments with adipic aldehyde it may be concluded that the nitromethane cyclization to form a seven-membered ring is a more difficult proposition than the synthesis of five- or six-membered rings, which is in keeping with general observations in organic chemistry. Possibly, the formation of seven-membered rings might be facilitated by using dialdehydes that are substituted in α, α'-position. Adipic aldehyde derivatives so substituted would be barred from undergoing internal aldol condensation, and it is known, moreover, that substitution generally tends to favor the cyclization of open-chain compounds.

CLAIMS TO ORIGINAL RESEARCH

1. The structure of a product of condensation between phthalaldehyde and nitromethane, which had been claimed by J. Thiele and E. Weitz to be 2-nitro-indenol-1, was established to be 2-nitro-indenol-3.

2. It was shown that the cyclization with nitromethane of phthalaldehyde proceeds in the normal way, giving rise to a primary product which was isolated and proved to be 2-nitro-indanediol-1,3. Elimination of water from this product then leads to 2-nitro-indenol-3, rather than to 2-nitro-indenol-1.

3. A third product of condensation between phthalaldehyde and nitromethane was obtained, and its structure was shown by a series of reactions leading to decahydroisoquinoline, to be that of an internal hemiacetal of 2-(1-hydroxy-2-nitroethyl)-benzaldehyde.

4. An attempted cyclization with nitromethane of adipic aldehyde failed to produce the desired seven-membered ring system but afforded, instead, hitherto unknown 1,8-dinitro-2,7-dihydroxyoctane.

5. The following compounds are described for the first time in this thesis:

   (a) 2-Nitroindanediol-1,3

(b) 2-Nitroindanediol-1,3-diacetate

(c) Hemiacetal of 2-(1-hydroxy-2-nitroethyl)-benzaldehyde

(d) 2,4-Dinitrophenylhydrazone of 2-(1-hydroxy-2-nitroethyl)-benzaldehyde

(e) Lactone of 2-(1-hydroxy-2-nitroethyl)-benzoic acid

(f) Lactone of 2-(1-hydroxy-2-aminoethyl)-benzoic acid

(g) 1,8-Dinitro-2,7-dihydroxyoctane

(h) 1,8-Dinitro-dihydroxyoctane-2,7-diacetate

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