Cyclizations of Dialdehydes with Nitromethane. XII.[1] *o*-Phthalaldehyde[2]

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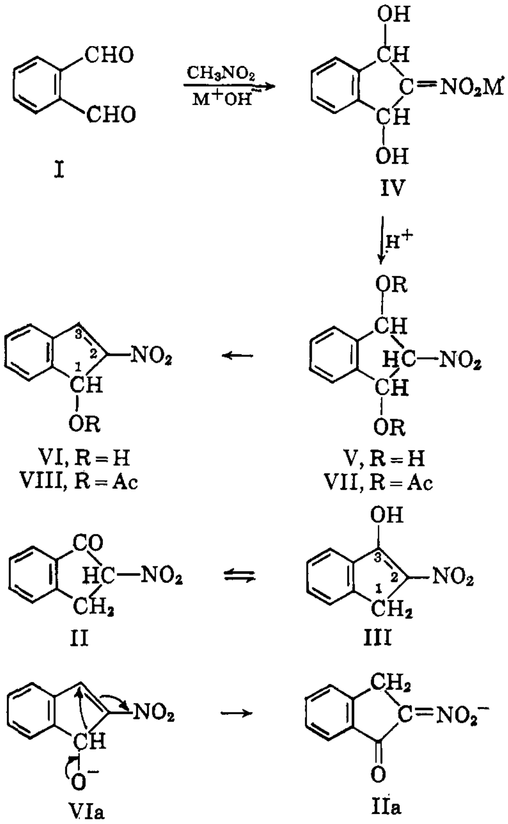
The condensation of *o*-phthalaldehyde (I) with nitromethane in methanolic solution in the presence of sodium or potassium hydroxide is shown to produce, as the only products detectable, the alkali nitronates (IV) of 1,3-dihydroxy-2-nitroindane (V). Acidification gives V and, by loss of water, 1-hydroxy-2-nitroindene (VI), rather than 3-hydroxy-2-nitroindene (III) as previously assumed. When I and nitromethane are condensed in the absence of hydroxylic solvent, the internal hemiacetal X of 2-(1-hydroxy-2-nitroethyl)benzaldehyde can be isolated in 80% yield. This product on treatment with alcoholic alkali is instantly converted into IV, whereas dichromate oxidation affords 3-phthalidylnitromethane (XIIa). Hydrogenation of XIIa leads, *via* the corresponding amine (XIIIa), to octahydroisocarbostyril (XVI) whose further reduction gives decahydroisoquinoline (XVII).

In 1910, Thiele and Weitz[3] condensed *o*-phthalaldehyde (I) with nitromethane in alcoholic solution in the presence of potassium hydroxide and obtained, upon acidification, a product to which they assigned the structure of 2-nitroindanone (II). An acetate and a methyl ether prepared from the compound were thought to be derived from the tautomeric form, 3-hydroxy-2-nitroindene (III). The structural assignment rested upon a conversion, by reduction with stannous chloride, of the presumed II into previously described 2-aminoindanone. No explanation was offered for the seemingly abnormal course of this Henry condensation leading to II until, almost 50 years later, the reaction was reinvestigated by Campbell and Pitzer.[4] These authors found that the product obtainable according to the earlier directions[3] was not uniform; this they ascribed to its being a tautomeric mixture of II and III, with the latter reverting rather slowly to the former. Realizing that one would normally expect I and nitromethane to yield, *via* IV and V, 1-hydroxy-2-nitroindene (VI) rather than II or III, the workers[4] proposed a mechanism which evidently implied that VI is engendered, as its anion VIa, in the alkaline medium of the condensation reaction. The anion VIa would then undergo a hydranion migration with accompanying electron shift to form the anion IIa. (See Scheme I.)

SCHEME I



Such course of reaction appeared to us to be at variance with the established pattern of the many dialdehyde–nitromethane cyclizations that have been investigated[5] in recent years on the inducement by H. O. L. Fischer. Admittedly, these newer experiences were limited to the aliphatic series; therefore, we have sought to clarify whether the aromatic dialdehyde, I, does in fact give rise to II (or III), or which other products, if any, may be obtained from it under a variety of conditions.

Reaction of I with nitromethane in alcoholic solution in the presence of potassium hydroxide leads to the precipitation of a salt which was acidified without isolation by the earlier authors.[3,4] We have isolated this colorless, crystalline potassium salt and have found its composition to correspond to IV.[6] It showed ultraviolet absorption peaks at 256, 268.5, and 275 mμ (Fig. 1), but no absorption at longer wave lengths such as would be expected for a compound containing a β-nitrostyrene or an α-nitroacetophenone chromophore.[7] The mother liquor likewise did not exhibit long wave-length absorption. These observations are in accord with the formulation of the salt as potassium 1,3-dihydroxy-2-*aci*-nitroindane (IV) and disprove the hypothesis of its dehydration to VIa and rearrangement to IIa in the alkaline reaction medium.

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[1] Paper XI in this series: H. H. Baer and A. Ahammad, *Can. J. Chem.*, **41**, 2931 (1963).

[2] (a) The results of this work are taken in part from the M.S. Thesis of B. Achmatowicz (University of Ottawa, 1963) and were included in a paper presented by H. H. Baer before the International Symposium on Nitro Compounds at Warsaw, Poland, Sept. 18-20, 1963. (b) Preliminary communication: H. H. Baer and B. Achmatowicz, *Angew. Chem.*, **76**, 50 (1964); in that communication the derivatives of *indene* were named according to the *Beilstein* system of numbering used in German publications. In the present paper the *Chemical Abstracts* system is applied, with the somewhat unfortunate consequence that for a comparison of the two papers the names of compounds III and VI will have to be interchanged.

[3] J. Thiele and E. Weitz, *Ann.*, **377**, 1 (1910).

[4] R. D. Campbell and C. L. Pitzer, *J. Org. Chem.*, **24**, 1531 (1959).

[5] For literature see ref. 1 and the preceding papers of this series; see also F. W. Lichtenthaler, *Ber.*, **96**, 845 (1963); *Angew. Chem.*, **75**, 93 (1963); A. C. Richardson, *J. Chem. Soc.*, 2758 (1962).

[6] The sodium salt was obtained similarly, by substituting sodium methoxide for potassium hydroxide.

[7] R. D. Campbell and F. J. Schultz [*J. Org. Chem.*, **25**, 1877 (1960)] reported strong peaks for β-nitrostyrene at 311 mμ and for the anion of α-nitroacetophenone at 352 mμ.

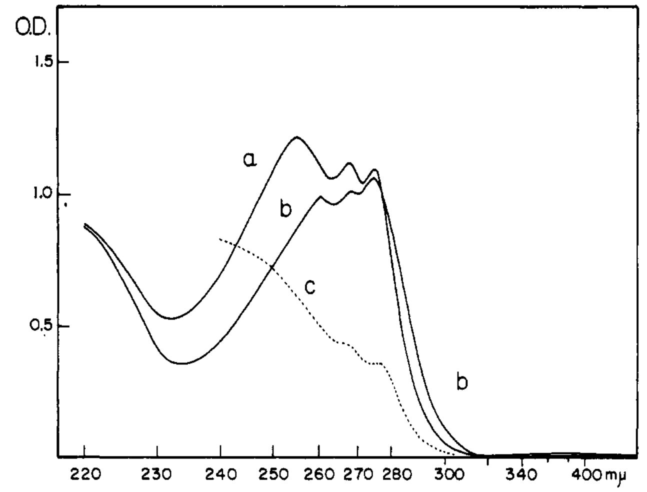


Fig. 1.—Ultraviolet spectra of 1,3-dihydroxy-2-*aci*-nitroindane sodium (IV): a, 10^{-4} *M* solution in 0.01 *N* aqueous NaOH; b, 10^{-4} *M* solution in 0.01 *N* ethanolic (95%) NaOH; c, mother liquor from preparation of IV, diluted.

Acidification of the above condensation product (IV) with aqueous hydrochloric acid furnished, in agreement with the previous reports, a yellow, crystalline compound $C_9H_7HO_3$[3,4] melting[4,8] at 148°. When, however, IV was treated with cation-exchange resin in methanolic suspension, there was obtained, in addition to the same yellow product, a colorless compound melting at 166–168° and analyzing as $C_9H_9NO_4$. Evidence is presented in the following that the new, colorless compound is 1,3-dihydroxy-2-nitroindane (V), and that the yellow compound is 1-hydroxy-2-nitroindene (VI) and not, as previously assumed, 3-hydroxy-2-nitroindene (III).

Compound V displayed a spectrum without high-intensity absorption in the near-ultraviolet and visible range (Fig. 2). The same was true for the acetyl derivative (VII, m.p. 93–94°) obtained from V. In the infrared, V had no carbonyl absorption, and the asymmetrical nitro modes of both V and its acetate appeared at 1550 cm.$^{-1}$. This evidence along with the elemental analyses supported the assigned structures. Unequivocal proof was provided by the n.m.r. spectrum of VII, which revealed the presence in the molecule of four kinds of protons in the proportion 4:2:1:6 (Fig. 3). The singlet at τ 2.57 (4H) accounts for the aromatic protons. The doublet at τ 3.38 (2H), with a splitting of 5–6 c.p.s., corresponds to the protons at C-1 and C-3, and its multiplicity proves the presence of one proton at C-2. The triplet at τ 4.83 (1H) with a splitting of 5–6 c.p.s. is due to the C-2 proton. A sharp singlet at τ 7.83 (6H) is caused by the six protons of the two acetyl groups. From these features formula VII clearly follows for the diacetate of the newly isolated V. It also appears from the spectrum that both acetoxy groups have identical steric dispositions in relation to the nitro group, *i.e.*, that the compound possesses either a *trans-trans* (A) or a *cis-cis* (B) configuration. This can be concluded from the identical chemical shifts of the acetoxy groups, and from the splitting of the C-2 proton signal into a triplet of the intensity ratio 1:2:1 which must be due to two like protons at C-1 and C-3. A decision between the two configurational possibilities A and B cannot be made at present.

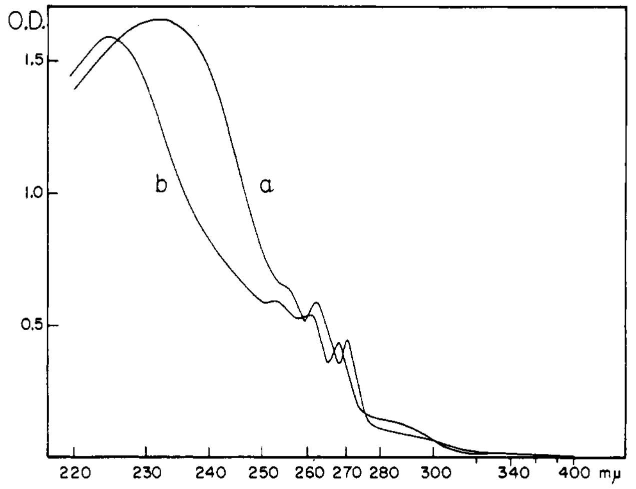


Fig. 2.—Ultraviolet spectra of 1,3-dihydroxy-2-nitroindane (V, a, 10^{-3} *M* in ethanol) and 2-(1-hydroxy-2-nitroethyl)benzaldehyde lactol (X, b, 10^{-3} *M* in ethanol).

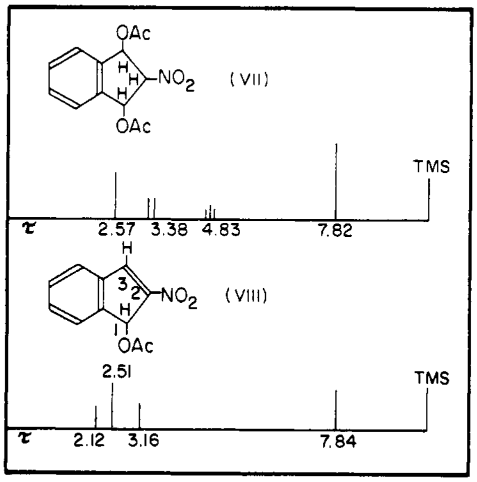
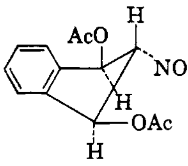
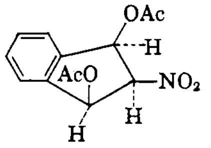


Fig. 3.—Schematic representation of n.m.r. spectra of VII and VIII in $CDCl_3$, with tetramethylsilane as internal standard. A 60-Mc. instrument, Varian V-4302B, was used, and the relative intensities of the signals were obtained by integration.



A



B

The yellow condensation product, VI, gave an infrared spectrum lacking carbonyl absorption.[9] Since in conjugated nitro olefins the asymmetric nitro mode may occur[10] at wave numbers as low as 1500 cm.$^{-1}$, we assigned a strong band at 1505 cm.$^{-1}$ to that vibration; one or possibly both of the strong bands in the region 1355–1325 cm.$^{-1}$ must be assigned to the symmetric NO_2 mode. Acetylation of VI afforded the previously described,[3,4] yellow monoacetate. The position of its carbonyl band, at 1740 cm.$^{-1}$, agrees with formula VIII better than with an acetate derived from III, as in a vinylic type acetate the corresponding band should be found[11] in the region 1800–1770 cm.$^{-1}$. The

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(8) O. Schales and H. A. Graefe, *J. Am. Chem. Soc.*, **74**, 4486 (1952).

(9) No carbonyl band occurred with a fresh sample, nor with one that had been stored at room temperature for over a year. In ref. 4 was reported a slow appearance of C=O absorption during the course of several weeks.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 297-301.

(11) *Cf.* ref. 10, p. 179.

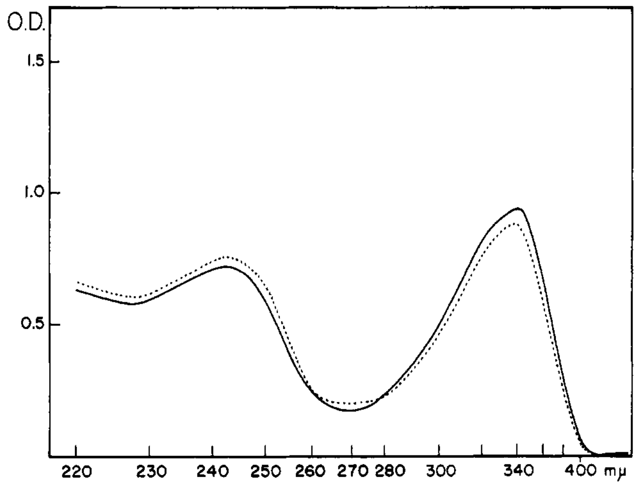


Fig. 4.—Ultraviolet spectra of 1-hydroxy-2-nitroindene VI (solid curve) and its acetate VIII (dotted curve); 10^{-4} *M* solutions in ethanol.

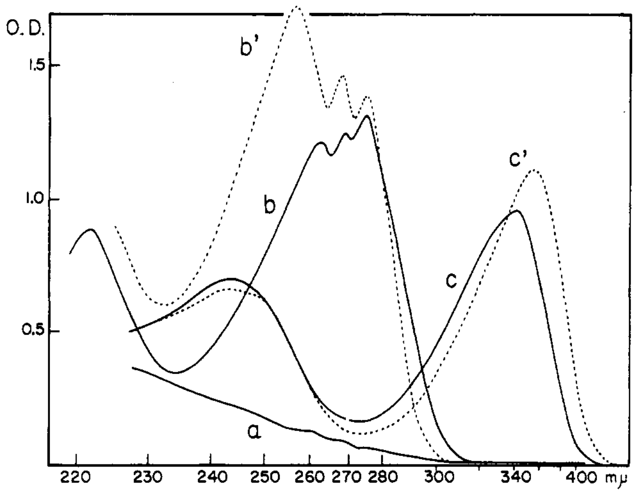


Fig. 5.—Spectroscopic demonstration of the conversion of the lactol X *via* the nitronate IV into 1-hydroxy-2-nitroindene (VI): a, 10^{-4} *M* solution of X in ethanol; b, the same, in 0.01 *N* ethanolic (95%) NaOH; c, the ethanolic, alkaline solution acidified with 1 *N* hydrochloric acid (1 drop/ml.). The dotted curves b' and c' represent an analogous experiment using *aqueous* NaOH.

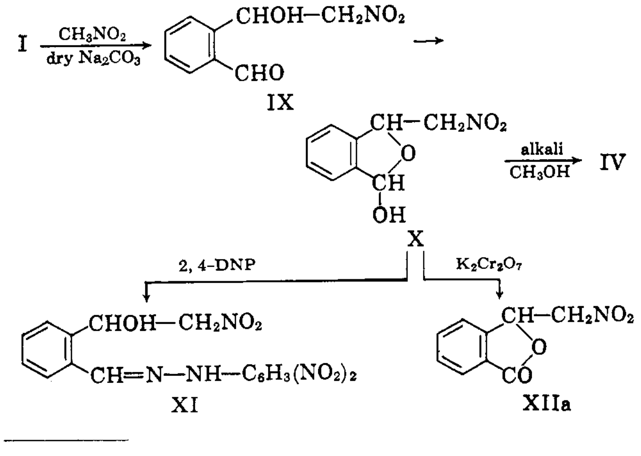
ultraviolet spectra of VI and VIII (Fig. 4) are depicted for comparison with that of the indane derivative V (and X); the peaks at 340 and 338 mμ, respectively, reveal the presence of a conjugated nitro olefin structure (*cf.* 2-nitroindene,[4] λ_{max} 337 mμ), although they do not afford a decision as to the location of the hydroxyl (acetoxyl) group. This decision was furnished, however, by the n.mr. spectrum of the yellow acetate, which confirmed formula VIII unambiguously. There were four kinds of protons giving singlets of the intensity ratio 1:4:1:3 (Fig. 3). The signal at τ 2.11 (1H) is attributed to the olefinic proton at C-3; the signal of the aromatic protons appeared at τ 2.51 (4H); the hydrogen at C-1 produced the signal at τ 3.16 (1H); the acetyl hydrogens gave a signal at τ 7.84 (3H). This pattern is in conformity only with VIII; an acetate of III would be lacking an olefinic proton and should be expected, instead, to produce an upfield signal for two protons at C-1.[12]

The observed[3,4] solubility of the yellow compound in aqueous sodium hydroxide is not in contradiction with formula VI since α-nitro olefins are known to be capable of adding base. In fact, the characteristic ultraviolet spectrum of the *aci*-nitro salt IV (Fig. 1, curve a) is instantly produced when VI is alkalized with an excess of dilute aqueous sodium hydroxide. If formula III rather than VI applied, the high intensity absorption in the 350-mμ region, which is lost, should be retained as is the case[7] with α-nitroacetophenone.

It follows, then, that under the conditions employed[3,4] the nitromethane cyclization of *o*-phthalaldehyde is indeed represented by the sequence I → IV → V → VI. One must assume, however, that the nitronate IV arises *via* an intermediate primary addition product, *o*-(1-hydroxy-2-nitroethyl)benzaldehyde (IX), that cyclizes too fast for isolation. We have found that, when I and nitromethane are allowed to react in the absence of hydroxylic solvents, the intermediate IX becomes stabilized as an internal hemiacetal (X) which can be isolated in crystalline form (m.p. 122–124°, *cf.* also Experimental) in about 80% yield. When treated with 1 equiv. of potassium hydroxide in alcohol, X is instantly converted into a salt which was identified as IV by isolation and spectroscopy (Fig. 5).

The structure of the 2-(1-hydroxy-2-nitroethyl)-benzaldehyde lactol (X) was established on the basis of the following evidence. The compound was colorless, and its ultraviolet spectrum (Fig. 2) did not indicate a nitrostyrene grouping. The infrared spectrum lacked carbonyl absorption but exhibited bands expected for the hydroxyl (3320 cm.$^{-1}$) and nitroalkane (1545 cm.$^{-1}$) groups. The presence of a potential carbonyl (masked as hemiacetal) was suggested by the production of a 2,4-dinitrophenylhydrazone, the analysis of which fitted formula XI. Oxidation of X, with potassium dichromate, furnished in 80% yield a crystalline lactone (XIIa) of m.p. 130–131° which proved to be identical with 3-phthalidylnitromethane prepared from *o*-phthalaldehydic acid and nitromethane.[13]

The production, in nitroalkane condensations of aromatic *o*-carboxyaldehydes, of lactones of type XII rather than of *o*-carboxy-β-nitrostyrenes had already been assumed by early workers;[14] rigorous proof



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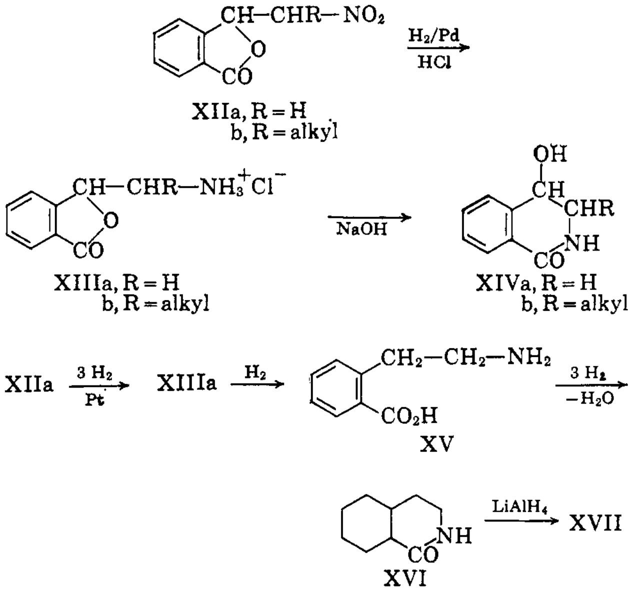
(12) In an independent n.m.r. study concerning the structure of Thiele and Weitz's compound, F. W. Lichtenthaler [*Tetrahedron Letters*, **775**, (1963)] arrived at the same result; he reported, in addition, that an analogous product is obtainable from 2,3-naphthalenedialdehyde. We became aware of his communication after the conclusion of our own work.

(13) B. B. Dey and T. K. Srinivasan, *Arch. Pharm.*, **275**, 397 (1937); T. Széki, *Ber. ungar. pharm. Ges.*, **13**, 680 (1937) [*Chem. Abstr.*, **31**, 6644 (1937)].

therefore was furnished by American investigators[15] who, with palladium catalyst, hydrogenated XIIa and a large number of alkyl substitution products (XIIb) and obtained the corresponding 3-phthalidylalkylamines (XIIIa and XIIIb). The latter were subsequently rearranged by alkali to give 4-hydroxy-3,4-dihydroisocarbostyrils (XIVa and XIVb).



When we hydrogenated XIIa using a platinum catalyst in aqueous acetic acid, the hydrogenation proceeded beyond the stage of phthalidylmethylamine (XIIIa), although this product could be isolated upon interruption of the reaction after an initial uptake of 3 moles of hydrogen. Prolonged hydrogenation (24 hr.) resulted in consumption of 7 moles of hydrogen. Examination by thin layer chromatography showed the hydrogenated material to be not uniform; however, on heating to 130–140° followed by vacuum sublimation, it yielded 57% of octahydroisocarbostyril (XVI), presumably as a *cis-trans* mixture.[16] On further reduction with lithium aluminum hydride, XVI afforded decahydroisoquinoline (XVII), the *cis* isomer[17] of which crystallized as the picrate.

The formation of XVI from XIIa is explained adequately by hydrogenolytic cleavage of the benzylic lactone ring in the first reduction product, XIIIa, followed by further hydrogenation and ring closure of intermediate 2-(β-aminoethyl)benzoic acid (XV).[18]

Experimental[19]

1,3-Dihydroxy-2-*aci*-nitroindane Salts (IV). **A. Sodium Salt.**—*o*-Phthalaldehyde (670 mg., 5 mmoles) and nitromethane (305 mg., 5 mmoles) were dissolved in 15 ml. of methanol. To the ice-cold solution was added with swirling a chilled sodium methoxide solution (105 mg. of sodium in 4 ml. of methanol) at a fairly rapid drop rate. The colorless, crystalline precipitate that appeared immediately was isolated within 10 min., washed with cold methanol, and dried in a desiccator; 630 mg. From the mother liquor further salt crops were obtained within 0.5 hr. (250 mg.) and after 1 day at 0° (80 mg.). Thus the total yield was 88%. The various crops were identical with respect to their ultraviolet and infrared spectra. Also, they showed identical behavior on heating: the material underwent a gradual change in texture between *ca.* 100 and 200°, with browning above 150°, and ended in thorough decomposition without melting. It had λ_{max} in water, 256, 268.5, and 275 mμ (ε 8600, 7900, and 7700); in aqueous 0.01 *N* NaOH, 256, 268.5, and 275 mμ (ε 12,200, 11,200, and 10,900); and in 95% ethanolic 0.01 *N* NaOH, 261, 269, and 275 mμ (ε 9900, 10,100, and 10,600).

Anal. Calcd. for $C_9H_8NNaO_4$ (217.2): N, 6.45; Na, 10.60. Found: N, 6.37; Na, 10.56.

One hour after the start of the above experiment the colorless mother liquor was examined by ultraviolet spectroscopy. Neither in methanol nor in 0.1 *N* NaOH (aqueous) was there any absorption in the region of 300 mμ and above. A green discoloration, though, developed within 2 days.

B. Potassium Salt.—Thiele and Weitz's procedure[3] was followed up to the point where the reaction mixture became a colorless slurry. The solid was filtered off with suction, washed thoroughly with ice-cold methanol, and dried in a desiccator, yielding 84% of the salt. The ultraviolet spectra were the same as those of the sodium salt.

Anal. Calcd. for $C_9H_8KNO_4$ (233.3): K, 16.76; N, 6.00. Found: K, 16.65; N, 5.97.

1-Hydroxy-2-nitroindene (VI).[2b]—The procedure for the preparation of the presumed[3] 2-nitrohydrindone (II) was found reproducible, although the crude product obtained melted at 135–140°. After one to two recrystallizations from petroleum ether (b.p. 80–100°) or, better, from benzene–cyclohexane, the yellow needles of VI showed m.p. 148° dec., in agreement with the reported[4,8] value. Vacuum sublimation[4] did not appear to be needed for purification. The compound was readily soluble in cold alcohols, moderately soluble in cold and fairly soluble in hot chloroform and benzene, and sparingly soluble in petroleum ether and water. It had λ_{max}^{EtOH} 242.5 and 340 mμ (ε 7200 and 9300); $\lambda_{max}^{H_2O}$ 244 and 355 mμ.

Anal. Calcd. for $C_9H_7NO_3$ (177.2): N, 7.91. Found: N, 7.78.

1-Acetoxy-2-nitroindene (VIII).[2b]—This compound was prepared by acetylation[3,4] of 100 mg. of VI in 1.2 ml. of acetic anhydride containing a droplet of sulfuric acid. The acetylation mixture was heated on a steam bath for 15 min., cooled, and decomposed with ice and sodium bicarbonate. The solid acetate, which tended to discolor when impure, was quickly taken up in chloroform, and the aqueous phase was extracted three times with chloroform, too. The combined chloroform solutions were washed with ice-cold sodium bicarbonate solution, dried over magnesium sulfate, treated with activated charcoal, and evaporated. The brownish yellow residue crystallized on scratching. The crude product (100 mg., 81%, m.p. 125–130 dec.) was purified by dissolving in boiling cyclohexane and treating with activated charcoal for 3 min. From the filtrate, pale yellow crystals of VIII, m.p. 128–130° dec., were deposited on standing overnight. The melting point (lit. above 120°,[3] 130–131°[4]) remained unchanged upon further recrystallization. VIII had λ_{max}^{EtOH} 243 and 338 mμ (ε 7500 and 8600).

1,3-Dihydroxy-2-nitroindane (V).—Freshly prepared sodium salt IV (1.0 g.) was suspended in methanol (50 ml.) and stirred magnetically with 15 ml. of methanol-washed cation-exchange resin, Rexyn RG-50(H^+) or Amberlite IR-120(H^+). Within 10 min. the salt dissolved and the solution turned light yellow. The resin was filtered off and washed with 10 ml. of methanol; the filtrate was carefully evaporated to yield a pale yellow solid weighing 792 mg. On examination by thin layer chromatography on silica gel, with cyclohexane–chloroform–acetone mixtures (5:4:1 or 4:4:2) as running media, the product was found to contain two compounds. The faster moving component was

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(14) P. Freundler, *Bull. soc. chim. France*, [4] **15**, 470 (1914); W. Rodionow and S. Kagan, *Ber.*, **57**, 1442 (1924).

(15) G. E. Ullyot, J. J. Stehle, C. L. Zirkle, R. L. Shriner, and F. J. Wolf, *J. Org. Chem.*, **10**, 429 (1945); J. W. Wilson, III, C. L. Zirkle, E. L. Anderson, J. J. Stehle, and G. E. Ullyot, *ibid.*, **16**, 792 (1951); J. W. Wilson, III, E. L. Anderson, and G. E. Ullyot, *ibid.*, **16**, 800 (1951).

(16) The melting point was 145-148°; the amide band I in the infrared spectrum occurred as a doublet with the main peak at 1645 and a shoulder at 1670 cm.$^{-1}$. E. Ochiai and Y. Kawazoe [*Pharm. Bull.* (Tokyo), **5**, 606 (1957)] reported m.p. 147° for XVI but did not state the configuration of their product.

(17) B. Witkop, *J. Am. Chem. Soc.*, **70**, 2617 (1948).

(18) E. Bamberger and W. Dieckmann [*Ber.*, **26**, 1219 (1893)] converted XV into 3,4-dihydroisocarbostyril by heating.

(19) Unless otherwise indicated, the evaporations were done *in vacuo* at 35–40° (bath temperature), the melting points were taken in capillary tubes with an electrically heated, aluminum-block apparatus, the ultraviolet spectra were recorded with a Beckman DK-2 recording spectrophotometer, and the infrared data were obtained by the Nujol mull technique with a Perkin-Elmer Infracord instrument.

identified as VI, whereas the more slowly migrating component represented V. The crude reaction product was triturated three times with 10 ml. of benzene, with gentle warming. This operation resulted in a yellow benzene extract and an undissolved residue (426 mg.) that was almost colorless. The residue on recrystallization from ethanol–chloroform formed colorless, hexagonal prisms of m.p. 164–166° dec., raised to 166–168° dec. by a second recrystallization. It was 1,3-dihydroxy-2-nitroindane (V): $\lambda_{\max}^{\text{EtOH}}$ 232, 255, 262, and 270.5 mμ (ϵ 1650, 650, 600, and 450).

Anal. Calcd. for $C_9H_9NO_4$ (195.2): C, 55.38; H, 4.65; N, 7.18. Found: C, 55.17; H, 4.79; N, 7.08.

To the yellow benzene extract obtained above there was added cyclohexane to incipient cloudiness. A small amount of impure crystalline material, which was discarded, separated slowly. The supernatant liquor was evaporated and the residue recrystallized several times from benzene–petroleum ether (with 1 or 2 drops of methanol added) and from water containing a little ethanol. The product so obtained was identified as 1-hydroxy-2-nitroindene (VI) by its infrared and ultraviolet spectra and by a mixture melting point, 145–146° dec.

1,3-Diacetoxy-2-nitroindane (VII).—Compound V (64 mg.) was dissolved in 1.1 ml. of acetic anhydride containing 1 drop of sulfuric acid, allowed to stand at room temperature for 30 min., and then heated on the steam bath for 5 min. After cooling, the excess anhydride was destroyed by the addition of 1 ml. of ethanol. The mixture was poured onto crushed ice and neutralized with sodium bicarbonate. The diacetate VII separated as a white solid that was washed with water, dried in a desiccator (yield, 86 mg., 96%, m.p. 68–73° dec.), and recrystallized twice from cyclohexane. The yield of purified, colorless prisms melting at 80–91° was 60 mg. (from the mother liquor big plates of m.p. 93–94° were slowly deposited). Since prolonged heating caused discoloration, the analytical sample was dried at room temperature at 10^{-2} mm. VII deteriorated on storage.

Anal. Calcd. for $C_{13}H_{13}NO_6$ (279.2): C, 55.91; H, 4.69. Found: C, 56.32; H, 4.68.

2-(1-Hydroxy-2-nitroethyl)benzaldehyde Lactol (X).—A solution of *o*-phthalaldehyde (500 mg.) in nitromethane (10 g.) was magnetically stirred overnight at 25–30° in the presence of 1 g. of anhydrous sodium carbonate and with exclusion of moisture. The inorganic solid was filtered off and the solution was evaporated with several additions of dry benzene. The dry, crystalline residue (580 mg., 80%) was recrystallized from about 10 ml. of chloroform, furnishing 489 mg. of colorless needles in two fractions of m.p. 121–123° dec. and 122–124° dec. Further recrystallization from the same solvent or from benzene did not raise the melting point. The product (X) was readily soluble in ethanol and moderately soluble in chloroform and benzene. X had $\lambda_{\max}^{\text{EtOH}}$ 253.5, 261, and 268 mμ (ϵ 600, 540, and 430).

Anal. Calcd. for $C_9H_9NO_4$ (195.2): C, 55.38; H, 4.65; N, 7.18. Found: C, 55.10; H, 4.50; N, 7.10.

In one repetitive experiment for which, inadvertently, one-tenth of the above-mentioned amount of nitromethane had been used, the reaction mixture solidified overnight. Dilution with nitromethane and work-up as described resulted in a comparatively poor yield of crystals (132 mg.) which after two recrystallizations from chloroform melted at 133–134°. As judged from the higher melting point, a different appearance of the crystals, and a somewhat greater solubility in chloroform, this product was not the same as X that has been obtained in several runs before and afterwards. On the other hand, no differences were found in the infrared and ultraviolet spectra. Allomorphism seems unlikely since either modification persisted on identical recrystallization and seeding with the other. Possibly, the two forms are diastereoisomers.

Conversion of X into IV and VI.—In a preliminary, spectroscopic experiment the lactol X was found to produce, instantaneously, the characteristic ultraviolet spectrum of IV when dissolved in aqueous sodium hydroxide solution (0.01 N): $\lambda_{\max}$ 256, 268.5, and 275 mμ (ϵ 12,600, 10,000, and 9200). This spectrum was at once changed into that of VI when the alkaline solution was acidified with hydrochloric acid.

The lactol X (100 mg., m.p. 121–123° dec.) was dissolved in 3 ml. of methanol, and to the solution that was cooled to 0° there was added 0.5 ml. of 1 N potassium hydroxide in ethanol. A copious precipitate of colorless crystals occurred instantly; it was isolated, washed with ethanol, and identified with the potassium salt IV by infrared and ultraviolet spectroscopy.

In a similar experiment the alcoholic reaction mixture was diluted with ice–water until the precipitate was dissolved. Acidification with cold, 1 N hydrochloric acid then produced 80 mg. (88%) of yellow needles that melted at 148° dec., even without recrystallization. The mixture melting point with VI was undepressed.

2-(1-Hydroxy-2-nitroethyl)benzaldehyde 2,4-Dinitrophenylhydrazone (XI).—A solution of 100 mg. of the lactol X, 105 mg. of 2,4-dinitrophenylhydrazine, and 0.2 ml. of sulfuric acid in 5 ml. of methanol was refluxed for 5 min. Upon cooling, red prisms separated quickly; they were isolated and washed well with ethanol. The crude hydrazone (200 mg., m.p. 198–200°) was recrystallized from dimethylformamide–chloroform, which raised the melting point to 205–207°. The compound (XI) was very difficultly soluble in the common solvents except dimethylformamide.

Anal. Calcd. for $C_{15}H_{13}N_5O_7$ (375.3): C, 48.00; H, 3.49; N, 18.66. Found: C, 48.04; H, 3.53; N, 18.54.

3-Phthalidylnitromethane (XIIa).—To a solution of potassium dichromate dihydrate (600 mg.) and sulfuric acid (500 mg.) in 3 ml. of water there was introduced 600 mg. of finely divided lactol X in small portions. The reaction mixture was then stirred at 80° for 1 hr. Upon cooling, the crystalline material was collected, washed thoroughly with water, and dried, yielding 490 mg. of XIIa melting at 130–131° as reported.[13,15] Recrystallization from ethanol afforded colorless prisms with m.p. 132°.

Anal. Calcd. for $C_9H_7NO_4$ (193.15): C, 55.96; H, 3.65; N, 7.25. Found: C, 56.1; H, 3.7; N, 7.03.

A sample of comparison of XIIa was prepared[13] from *o*-phthalaldehydic acid and nitromethane and was found to give an undepressed mixture melting point with the product obtained above as well as identical ultraviolet and infrared[20] spectra: $\lambda_{\max}^{\text{MeOH}}$ 273 and 280 mμ (ϵ 1500 and 1500).

3-Phthalidylmethylamine Hydrochloride (XIIIa).—The nitrolactone XIIa (100 mg.) was hydrogenated at room temperature and atmospheric pressure with 50 mg. of Adams catalyst in 10 ml. of 50% aqueous acetic acid. Hydrogen was taken up at a rapid rate; the reaction was interrupted as soon as 3 molar equiv. had been consumed. The filtrate from the catalyst was made alkaline by the addition of sodium carbonate solution and was extracted with chloroform. Drying of the extract with potassium carbonate followed by evaporation furnished a colorless oil that crystallized on trituration with 0.1 ml. of concentrated hydrochloric acid. Recrystallization from ethanol gave the amine hydrochloride XIIIa as colorless needles (50 mg.) of m.p. 260.5–261.5° dec. (lit.[13] m.p. 253°).

Anal. Calcd. for $C_9H_{10}NClO_2$ (199.6): C, 54.15; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 53.80; H, 5.06; Cl, 17.84; N, 7.20.

Octahydroisocarbostyril (XVI).—Nitrolactone XIIa (300 mg.) was hydrogenated with 150 mg. of prehydrogenated platinum oxide catalyst in a mixture of 20 ml. of glacial acetic acid and 10 ml. of water. At room temperature and ordinary pressure the hydrogen uptake was rapid initially but became sluggish after several hours. After 24 hr., 245 ml. of hydrogen (corrected volume; 7 molar equiv.) had been consumed and the solution was brought to dryness, the last traces of acetic acid being removed by codistillation with toluene. According to thin layer chromatography the residue was not uniform.[21] After thorough drying in a desiccator over phosphorus pentoxide and potassium hydroxide, the material, contained in a sublimation apparatus, was heated to 130° for 1 hr. without evacuation. A release of water was thereby observed. Then a vacuum of 10 mm. was applied and the temperature was slowly raised to 140° in the course of several hours. A sublimate of white crystals[16] was collected in three successive portions of 64, 50, and 23 mg. (total yield, 57.5%). The final fraction was slightly contaminated, evidenced by the infrared spectrum which showed some carbonyl absorption at 1770 cm.$^{-1}$ (this band was strong in the crude product before sublimation and also in the sublimation residue). Too rapid sublimation, or application of high vacuum, tended to increase the amount of contamination in the sublimate.

Anal. Calcd. for $C_9H_{15}NO$ (153.2): C, 70.55; H, 9.87; N, 9.14. Found: C, 70.60; H, 9.75; N, 9.30.

cis-**Decahydroisoquinoline (XVII).**—To a solution of 88 mg. of XVI in 12 ml. of anhydrous tetrahydrofuran was added 200 mg.

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(20) The infrared spectrum of XIIa has been discussed in detail by K. Nakanishi in "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p. 183.

(21) In one experiment a small amount of unidentified crystals, m.p. 155°, was isolated at this stage.

of lithium aluminum hydride. The mixture was refluxed for 2 hr. with magnetic stirring and under exclusion of moisture and then cooled in an ice bath; the excess reductant was destroyed by careful addition of tetrahydrofuran-water (10:1). The inorganic solid was removed and washed with chloroform, and the combined solutions were evaporated to furnish a colorless oil. The oil was taken up in 1 ml. of methanol, and picric acid (145 mg.) in hot methanol (3 ml.) was added. Dropwise addition of water to incipient turbidity and cooling produced yellow crystals that were isolated and washed with water-containing, cold methanol. After drying, the crude picrate of XVII, m.p. 143–146°, weighed 87 mg. (a second crop, of lesser purity, was obtained from the mother liquor). The crude picrate was triturated, in a centrifuge tube, with 0.3 ml. of warm methanol, decanted, and washed twice with 0.2 ml. of cold methanol, and then melted at 154–156°. Recrystallization from methanol raised the melting point to 156–157°.

In one experiment, the picrate of XVII which had remained in the mother liquor was converted into the hydrochloride by passage over a small column containing an anion-exchange resin, Dowex-1, in the chloride form. The hydrochloride of XVII formed colorless needles, m.p. 178°.

Witkop[17] reported m.p. 150° for the picrate, and m.p. 183° for the hydrochloride, of *cis*-decahydroisoquinoline, and m.p. 177° and 224°, respectively, for the corresponding *trans* derivatives.

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Stereochemistry and Mechanism of Lithium Aluminum Hydride and Mixed Hydride Reduction of 4-*t*-Butylcyclohexene Oxide[1]

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Lithium aluminum hydride reduction of *trans*-4-*t*-butylcyclohexene oxide gives only *trans*- (90%) and *cis*-3-*t*-butylcyclohexanol (10%). The *cis* epoxide affords only 4-ols, in a comparable ratio (90% *cis*, 10% *trans*). Deuterium distribution in the products derived from lithium aluminum deuteride reduction suggests that the minor product arises by a novel rearrangement to ketone which is subsequently converted to alcohols. In contrast, mixtures of lithium aluminum hydride and aluminum chloride give very stereospecific reduction, the product from each epoxide being essentially pure axial alcohol.

Epoxide ring-opening reactions involving numerous reagents have been studied, and this subject has been reviewed by Parker and Isaacs.[2] Lithium aluminum hydride has been widely used for the reduction of epoxides to alcohols; the steric effects observed when this reagent is applied to unsymmetrical epoxides,[2] and the general observation of inversion of configuration at the attacked carbon[3] support the view that reduction occurs through nucleophilic displacement of oxygen by a hydride-donor species. Stereochemical implications were further explored by Fürst and Plattner[4] with steroidal epoxides, where it was demonstrated that axial alcohols are formed in high yield by lithium aluminum hydride reduction. Inversion of configuration at the carbon attacked by hydride would thus correspond to formation of the new carbon–hydrogen bond in the axial position. The resultant "rule of diaxial opening"[5] appears to be a specific statement of the energetically favorable *trans*-coplanar transition state associated with both additions to olefins and the reverse elimination reactions. The opening of an epoxide ring may in fact be viewed as analogous to the latter stages of any addition reaction involving the intermediacy of a three-membered ring.

The purpose of the present study was to examine in detail, with the aid of modern analytical techniques, the nature of the products formed on reduction of a flexible cyclohexene oxide system (Table I). Extension of the rule of diaxial opening from conformationally frozen steroidal epoxides is not obvious; the limited data pertaining to this question involve for the most part reactions of anhydro sugars.[6–8] Results from these studies indicate that the major product is that arising from diaxial opening, but the alternate isomer is formed in varying amounts.[8] The process leading to the minor product has been the subject of speculation for some time, but at present the literature contains no data allowing a choice from among the several mechanistic alternatives.[9] Cookson[10] and Angyal[11] have suggested that the controlling feature is the conformation of the epoxide through which reaction occurs, and that the minor product is formed through the less stable, half-chair, cyclohexene oxide conformation. An alternate, and in many ways more attractive, explanation involves reaction through the most stable half-chair to give the minor product initially formed in the boat conformation. Both mechanisms allow for major and minor products to be formed by *trans*-diaxial opening of the epoxide ring. It was in the hope of distinguishing between these two possibilities that we undertook a study of the hydride reduction of *trans*- and *cis*-4-*t*-butylcyclohexene oxide. The former isomer is readily available in pure form,[12] and all four potential alcohol products are separable (as the acetates) by vapor phase chromatography.

An entirely unexpected result was obtained when *trans*-4-*t*-butylcyclohexene oxide was reduced with lithium aluminum hydride in ether. The major product,

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(1) Support by The Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(2) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(3) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).

(4) A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(5) A. Fürst and P. A. Plattner, Abstracts, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., 1951, p. 409.

(6) A. K. Bose, D. K. R. Chaudhuri, and A. K. Bhattacharyya, *Chem. Ind.* (London), 869 (1953).

(7) F. H. Newth, *ibid.*, 1257 (1953).

(8) W. G. Overend and G. Vaughn, *ibid.*, 995 (1955).

(9) This topic is discussed and the literature is summarized by E. L. Eliel, "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 130–134, and "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 230.

(10) R. C. Cookson, *Chem. Ind.* (London), 223 (1954); 1512 (1954).

(11) S. J. Angyal, *ibid.*, 1230 (1954).

(12) See reference in footnote *b*, Table I.