the solution by 0.011, and this amount was subtracted from the first estimate of γ as obtained on the basis of the indices of the uncontaminated liquids.

White-light illumination, controlled by a doorbell switch to avoid prolonged heating of the slide, was supplemented in the more critical observations by sodium light.

The characteristics found are as follows: Habit (from ethanol): needles or long prisms, more or less flattened, with elongation parallel to Y (vibration direction for β). Refractive indices (sodium light): α, 1.618; β, 1.626; γ, 1.755. Optical character positive, shown decisively both by refractive indices and by the selenite plate. Sign of elongation variable, depending on the position at which the rolling needle comes to rest, since the lengthwise apparent index is β and the other may be either above or below. Optic axial angle calculated from refractive indices, 30°; agrees with Bertrand lens measurements within normal observational error. Extinction, in general, parallel to crystal length; thorough study of extinction angles complicated by marked tendency to twinning. Crystal system probably orthorhombic; which is in agreement with X-ray diffraction evidence reported by others.[2]

(2) G. L. Clark and F. W. Cagle, Jr., *Science*, **101**, 465–466 (1945)

BELTSVILLE, MD. RECEIVED AUGUST 4, 1945

The Reduction of Diethylstilbestrol Compounds[1]

BY WILLARD HOEHN AND HERBERT E. UNGNADE

The hydrogenation of diethylstilbestrol and its dimethyl ether in the presence of Raney nickel or other catalysts leads to the low-melting racemic dihydro compounds.[2] The phenolic rings are not affected unless the reaction is carried out under drastic conditions of temperature and pressure. Even then, the hydrogen uptake is slow.[3]

In view of the work of Docken and Spielman,[2] the perhydro compound of diethylstilbestrol is presumably derived from *racemic* dihydrostilbestrol which is first formed, during the reduction, and thus different from the perhydrohexestrol of Lane and Wallis[4] which was obtained by hydrogenation of the *meso*-dihydro isomer.

The results of the present investigation show that it is possible to perhydrogenate diethylstilbestrol in good yield in a relatively short time if rigorous conditions are used. A perhydro compound has been separated from the reaction mixture and characterized by its dibenzoate and by conversion to the corresponding diketone. The mixture also contains some octahydro compounds.

If the hydrogenation is interrupted before the required amount of hydrogen is absorbed, the product consists of a mixture of perhydro compound and a larger amount of octahydro compounds. The mixture remaining after removal of the perhydro compound is difficult to separate. Fractional crystallization has given two solids whose composition corresponds to octahydro compounds.

When one or both hydroxyl groups in diethylstilbestrol are methylated, the hydrogenation over nickel catalyst stops after absorption of one mole of hydrogen under the same conditions under which diethylstilbestrol is perhydrogenated. The dimethyl ether gives the racemic dihydro compound which has been identified by demethylation to *racemic*-dihydrodiethylstilbestrol. The monomethyl ether, on the other hand, gives a dihydro compound which can be demethylated to *meso*-hexestrol.

Experimental[5]

3,4-Di-(4-hydroxycyclohexyl)-hexane (I).—*trans*-Diethylstibestrol (50 g.) was dissolved in 100 cc. of methanol and reduced with hydrogen in the presence of 10 g. of Raney nickel under an average pressure of 265 atm. The temperature was maintained at 210° for seven and one half hours. After cooling, the methanol solution was filtered and the solvent removed by distillation. Ether and petroleum ether (1:1) (1000 cc.) were added to the residue, and the solid which precipitated was filtered and washed with three 25-cc. portions of ether. Crystallization of the solid from ethyl acetate yielded 16 g. of 3,4-di-(4-hydroxycyclohexyl)-hexane (I) melting at 188–188.5°.

Anal. Calcd. for $C_{18}H_{34}O_4$: C, 76.50; H, 12.13; mol. wt., 468. Found: C, 76.14; H, 12.11[6]; mol. wt., 490.

The dibenzoate of this compound melted at 137–138°.

Oxidation of the dihydric alcohol (I) in acetic acid by means of chromic acid resulted in a 95% yield of 3,4-di-(4-oxocyclohexyl)-hexane melting at 65–67°. Recrystallization from petroleum ether (b. p. 69°) raised the melting point to 75°.[7]

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.57; H, 10.86. Found: C, 78.08; H, 11.09.[8]

The disemicarbazone of the diketone melted at 180–182°.

3-(4-Hydroxyphenyl)-4-(4-hydroxycyclohexyl)-hexane (II).—The filtrate from the preparation of the perhydro compound (I) was extracted with three 50-cc. portions of 2 *N* sodium hydroxide solution. The solvent layer was washed with water. The combined alkaline extracts and washings were acidified with dilute hydrochloric acid and extracted with ether. The extract was dried over sodium sulfate and distilled to remove the solvent. The residue was dissolved in three times its weight of benzene. The material which separated was filtered, recrystallized from benzene and dried. It melted at 60–61°. Recrystallization from cyclohexane raised the melting point to 92–94° (II).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21 Found: C, 78.52; H, 9.64.[6]

Benzoylation of this compound (II) with benzoyl chloride in the presence of pyridine yielded a dibenzoate which melted at 113–114°. *Anal.* Calcd. for $C_{32}H_{36}O_4$: mol. wt., 484. Found: mol. wt., 478.

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(1) This paper was presented before the Organic Division of the 105th Meeting of the American Chemical Society held in Detroit, Michigan, April 11–16, 1943.

(2) Docken and Spielman, THIS JOURNAL, **62**, 2163 (1940).

(3) Major, Christman and Folkers, U. S. Patent 2,350,361 (1944).

(4) Lane and Wallis, THIS JOURNAL, **65**, 994 (1943).

(5) All melting points are uncorrected. Molecular weights were determined by the Rast method.

(6) Semimicro analysis by E. Milberger, University of Missouri.

(7) Later work by Ungnade and Ludutsky (*J. Org. Chem.*, in press) indicates that the diketone exists in polymorphic forms.

(8) Microanalysis by Arlington Laboratories.

Benzoylation of (II) according to Schotten–Baumann yielded a monobenzoate, m. p. 123–124°. *Anal.* Calcd. for $C_{25}H_{32}O_3$: mol. wt., 380. Found: mol. wt., 370.

3-(4-Hydroxyphenyl)-4-(4-hydroxycyclohexyl)-hexane (III).—The benzene filtrate from the preparation of (II) was evaporated to one third of the original volume and cooled to 15°. The solid which crystallized melted at 125–126°, yield 130 mg. Three crystallizations from benzene and petroleum ether (2:1) yielded a product that melted at 132–133°. The melting point could be raised to 144–145° by further crystallization from aqueous methanol and drying under reduced pressure at 100°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.12, 78.52; H, 9.60, 9.70.[8]

***dl*-Dihydrodiethylstilbestrol.**—The reduction of the dimethyl ether of *trans*-diethylstilbestrol with Raney nickel catalyst led to the dimethyl ether of *dl*-dihydrodiethylstilbestrol. Demethylation of this ether according to the method of Bernstein and Wallis[9] yielded *dl*-dihydrodiethylstilbestrol[10] which melted at 126–129°. *Anal.* Calcd. for $C_{18}H_{22}O_2$: mol. wt., 270. Found: mol. wt., 263.

***meso*-Hexestrol.**—The monomethyl ether of *meso*-hexestrol[11] was isolated in 13% yield from the reduction products of the monomethyl ether of *trans*-diethylstilbestrol (0.036 mole) in 100 cc. of methanol with 3 g. of Raney nickel at 210° (265 atm.).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.26; H, 8.51. Found: C, 80.16; H, 8.51.[8]

The remaining reduction products were crystallized from methanol and melted at 74–76°. When this mixture was demethylated according to the method of Bernstein and Wallis,[9] it gave a 60% yield of *meso*-hexestrol, m. p. 184–185°, mixed melting point with an authentic specimen (m. p. 186°) 184–186°.

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(9) Bernstein and Wallis, THIS JOURNAL, **62**, 2871 (1940).

(10) Wessely and Welleba, *Ber.*, **74B**, 777 (1941).

(11) Foldi and Demjen, *ibid.*, **74B**, 930 (1941).

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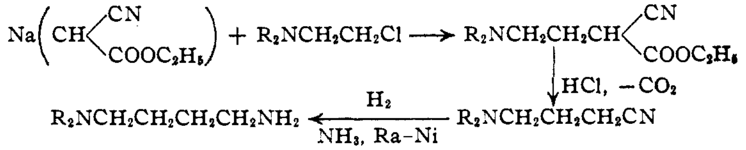
Some Dialkylaminoalkylamines

BY WOLFGANG HUBER, R. O. CLINTON, W. BOEHME AND MARY JACKMAN

The synthesis of 4-dialkylaminobutylamines usually involves the preparation of a 4-dialkylaminobutyronitrile *via* the intermediate 4-chloro- or bromobutyronitrile,[1] The over-all yields by this method are usually quite low. In the present work a new synthesis for this type of compound has been developed, based upon a modification of the method of Magidson and Strukov.[2]



$$Na\left(CH\begin{matrix}CN\\COOC_2H_5\end{matrix}\right) + R_2NCH_2CH_2Cl \longrightarrow R_2NCH_2CH_2CH\begin{matrix}CN\\COOC_2H_5\end{matrix} \xrightarrow{HCl,\ -CO_2} R_2NCH_2CH_2CH_2CN \xrightarrow[NH_3,\ Ra-Ni]{H_2} R_2NCH_2CH_2CH_2CH_2NH_2$$

It was possible by this method markedly to increase the yield of 4-diethylaminobutylamine; in the case of the dimethyl homolog the method does not appear to offer distinct advantages over the usual synthesis.

N-(2-Aminoethyl)-di-*n*-hexylamine and 2-amino-4-morpholinobutane have been prepared by the Ing and Manske modification of the Gabriel method from N-(2-chloroethyl)-di-*n*-hexylamine and 2-chloro-4-morpholinobutane, respectively.

Experimental[3]

Ethyl 2-Cyano-4-diethylaminobutyrate.—A mixture of 120 g. of ethyl sodiocyanoacetate[4] (84% pure) and 250 ml. of distilled ethyl cyanoacetate (the ester acts as a solvent) was heated with stirring on the steam-bath and treated during one hour with a solution of 83.4 g. of 2-chlorotriethylamine in 250 ml. of dry benzene. When the addition of the halogen compound was complete, the mixture was heated and stirred for an additional one and one-half hours. After cooling, the sodium chloride precipitate was removed by filtration and washed with benzene until the filtrate ran colorless. The filtrate was evaporated at 55° and 12 mm., and the residual yellow oil was fractionated *in vacuo*, yielding 109.3 g. (68.7%) of colorless product, b. p. 125–127° at 3 mm.

Anal. Calcd. for $C_{11}H_{20}O_2N_2$: C, 62.26; H, 9.43; N, 13.20; neut. equiv., 212. Found: C, 62.38; H, 9.45; N, 13.15; neut. equiv., 214.

4-Diethylaminobutyronitrile.—A mixture of 127 g. of the above ester and 300 ml. of 10% aqueous hydrochloric acid was stirred at room temperature for two hours. Excess hydrochloric acid was removed at 40° and 12 mm. and the oily residue was evaporated *in vacuo* four times with 300-ml. portions of water to remove the hydrogen chloride insofar as possible. The crude 2-cyano-4-diethylaminobutyric acid hydrochloride (often crystalline) was then immersed in a bath preheated to 150° and, when carbon dioxide evolution had begun, the temperature was raised to 160° and held at this point for two hours. The cooled residue was covered with ether and treated with concentrated aqueous potassium carbonate solution. After separation of the ether layer, the aqueous layer was further extracted twice with ether, and the combined ethereal extracts were dried over anhydrous potassium carbonate. After removal of the ether the residual oil was fractionated *in vacuo*, yielding 70.1 g. (83%) of colorless product, b. p. 89–89.5° at 9 mm. (lit.[5] b. p. 101–103° at 21 mm.).

The **picrate** had m. p. 68–68.5° (lit.[5] m.p. 69–70°). The reduction of the nitrile to **4-diethylaminobutylamine** has been previously reported.[6]

Ethyl 2-Cyano-3-dimethylaminobutyrate.—Prepared from 2-dimethylaminoethyl chloride (obtained in 68% yield from 2-dimethylaminoethanol and thionyl chloride) and ethyl sodiocyanoacetate in 39% yield, the pure compound had b. p. 106° at 12 mm.

Anal. Calcd. for $C_9H_{16}O_2N_2$: C, 58.69; H, 8.69; N, 15.12. Found: C, 58.76; H, 8.47; N, 15.52.

Hydrolysis and decarboxylation gave a 64% yield of **4-dimethylaminobutyronitrile**, b. p. 44–47° at 1.5 mm. The **picrate** had m. p. 119–120° (lit.[10] m. p. 120°). The nitrile was also prepared in 39% yield from alcoholic dimethylamine and 4-chlorobutyronitrile. Reduction of the nitrile by the procedure of Huber[6] gave a 58% yield of **4-dimethylaminobutylamine**, b. p. 74–75° at 45 mm. The **chloroaurate** had m. p. 175° (lit.[10] m. p. 175°).

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(1) *Cf.* (a) Strukov, *Khim. Farm. Prom.*, 332 (1933); *Chem. Abs.*, **28**, 3714 (1934)); (b) Utermohlen and Hamilton, THIS JOURNAL, **63**, 156 (1941); (c) Keil, *Z. physiol. Chem.*, **171**, 242 (1927).

(2) Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

(3) All melting points and boiling points are uncorrected. The microanalyses were made by the Misses Esther Bass, Alice Rainey and Patricia Curran.

(4) Prepared by the method of Thorpe, *J. Chem. Soc.*, **77**, 923 (1900). The crude sodium salt obtained usually analyzed 83-90% pure. The chief impurities are ethyl cyanoacetate and ethanol

(5) Whitmore, *et al.*, THIS JOURNAL, **66**, 725 (1944).

(6) Huber, *ibid.*, **66**, 876 (1944).