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SYNTHESIS OF 2-AMINO-1-PHENYL-1-PROPANOL AND ITS METHYLATED DERIVATIVES[1]

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Ephedrine is obtained commercially not only from extraction of the herb mahuang but also by a synthetic process (1) in which *l*-1-hydroxy-1-phenyl-2-propanone, obtained by action of benzaldehyde on fermenting sugar solutions, is allowed to react with methylamine, and the resulting Schiff base is reduced to *l*-ephedrine. This process has the advantage that no resolution is necessary.

Propadrine hydrochloride, also called Mydriatine, is a racemic mixture, melting at 190–194°. It is a mydriatic, diaphoretic, vasoconstrictor, and is used like ephedrine hydrochloride or ephedrine sulfate but its action is more prolonged.

In 1929, Nagai and Kanao (4) reported the synthesis of ephedrine from benzaldehyde and nitroethane. A similar series of reactions has been used in this work and offers a route to ephedrine.

(I) $C_6H_5CHO + C_2H_5NO_2 \rightarrow C_6H_5CHOHCHNO_2CH_3$ (Two Racemic Forms)

(II) $C_6H_5CHOHCHNO_2CH_3 + H_2 \xrightarrow{\text{Raney Ni}} C_6H_5CHOHCHNH_2CH_3$

(III) $C_6H_5CHOHCHNH_2CH_3 + HCHO$, then $+ H_2 \xrightarrow{\text{Raney Ni}} C_6H_5CHOHCH(NHCH_3)CH_3$

The nitro alcohol was obtained in good yield by the method of Vanderbilt and Hass (5), Kamlet (3), and Nagai and Kanao (4), but the method of Kamlet is particularly desirable because of the speed of the reaction. This method involves reaction between nitroethane and the sodium bisulfite addition product of benzaldehyde. It requires only a few hours whereas the other methods require several days.

The unmethylated amino alcohol was obtained by reduction of the nitro alcohol either with zinc and sulfuric acid, tin and hydrochloric acid, sodium amalgam and acetic acid, or by catalytic hydrogenation. Presumably many of the ordinary metal-acid reducing agents can be used provided the temperature is kept sufficiently low to prevent dehydration. There are, however, several by-products of the reduction. When catalytic hydrogenation was selected as the method, N-ethylbenzylamine was a by-product. It presumably forms by the following reactions:

(I) $C_6H_5CHOHCHNO_2CH_3 \rightleftarrows C_6H_5CHO + C_2H_5NO_2$

(II) $C_2H_5NO_2 + H_2 \xrightarrow{\text{Raney Ni}} C_2H_5NH_2$

(III) $C_6H_5CHO + C_2H_5NH_2 \rightarrow C_6H_5CH{:}NC_2H_5$

(IV) $C_6H_5CH{:}NC_2H_5 + H_2 \xrightarrow{\text{Raney Ni}} C_6H_5CH_2NHC_2H_5$

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This series of reactions postulates the formation of benzaldehyde and nitroethane by decomposition of 2-nitro-1-phenyl-1-propanol. It seemed logical to assume that this reaction was brought about by the catalytic effect of the basic (amine) reduction products. This hypothesis is supported by the fact that use of carbon dioxide in the Parr bomb reduces the yield of N-ethylbenzylamine to negligible quantities. Of those tested, the two best methods of reduction, from the standpoint of both simplicity and yield, are that using zinc and sulfuric acid, and that using acetic acid and sodium amalgam.

The amino alcohol which is an intermediate in the formation of Propadrine is easily methylated by adding an equimolecular amount of aqueous formaldehyde and then reducing catalytically.

Each step in the synthesis provides good yields. Efforts to separate the diastereoisomers were much less satisfactory. The method of Nagai and Kanao (4) for resolving the hydrochloride of 2-amino-1-phenyl-1-propanol, using absolute ethanol as the solvent, proved very inefficient, although enough of the desired diastereoisomer, *dl*-nor-ephedrine hydrochloride, was obtained for identification. The pressor action of these four stereoisomers has been studied by Jarowski and Hartung (2).

EXPERIMENTAL

Preparation of 2-nitro-1-phenyl-1-propanol. (a) Method of Vanderbilt and Hass (5). Benzaldehyde (13.25 g., 0.125 mole), nitroethane (9.38 g., 0.125 mole), and 50 ml. of 95% ethanol were mixed, and 2 ml. of sodium hydroxide (25% solution) was added with cooling. After allowing the mixture to stand for four days, the sodium hydroxide was neutralized and most of the alcohol was removed under reduced pressure. The residue was dissolved in ether, extracted with sodium bisulfite solution to remove unreacted benzaldehyde, and then distilled (b.p. 120–130° at 2 to 4 mm.) conversion 28 g. (62%). Based on the benzaldehyde that reacted, the yield was almost quantitative.

(b) Method of Nagai and Kanao (4). Benzaldehyde (106 g., 1 mole), nitroethane (75 g., 1 mole), and 50 ml. of saturated sodium bicarbonate solution were vigorously stirred for one week at room temperature (25–30°). The organic and aqueous layers were separated, the organic layer was washed with sodium bisulfite solution and distilled (b.p. 120–130° at 2 to 4 mm.), 90.5 g. resulted, conversion 50%, yield, based on benzaldehyde which reacted, 90%.

(c) Method of Kamlet (3). Benzaldehyde (106 g., 1 mole) was vigorously agitated with sodium bisulfite (110 g., 1.06 mole) in 500 ml. of water until the formation of the addition compound was complete. Simultaneously, nitroethane (82.5 g., 1.10 mole) was dissolved in a solution made from sodium hydroxide (45 g., 1.125 moles) dissolved in 200 ml. of water. This solution was gradually added, with agitation and at room temperature, to the addition product of benzaldehyde and sodium bisulfite. After stirring for a half hour, the mixture was allowed to stand overnight. The lower layer was discarded and the upper layer was dissolved in ether and washed with sodium bisulfite solution. The ethereal solution was dried over Drierite, and after removal of ether, distilled (b.p. 120–130° at 2–4 mm.) The usual conversion is 90–100 g. (50–55%) and the yield, based on benzaldehyde which reacts, is nearly quantitative.

Preparation of 2-amino-1-phenyl-1-propanol. (a) With zinc and sulfuric acid. Sulfuric acid (375 g. of 30% acid) was added with stirring to a mixture of 2-nitro-1-phenyl-1-propanol (54.3 g., 0.3 mole), zinc dust (90 g., 1.37 mole of 80 mesh zinc), and 100 ml. of 95% ethanol. The acid was added at such a rate that the temperature remained at 45° or below. Usually 10 to 12 hours were required. Agitation was continued for 1–2 hours after completing the

addition of acid, then after extracting the acidic solution with ether to remove non-basic materials, a large excess of sodium hydroxide (as 50% solution) was added. The product which was freed was extracted with ether. Three extractions, with a total of 500 ml. of ether, sufficed. The ether solution was dried, ether was removed, and the product was distilled (b.p. 122° at 4 to 5 mm.); 29–32 g. resulted (yield 65 to 70%). The viscous liquid solidified on standing, and m. 46–50°.

Anal. Calc'd for $C_9H_{14}ClNO$: Cl, 18.91. Found: Cl, 18.88.

(b) With sodium amalgam and acetic acid. Glacial acetic acid (160 g., 2.66 moles) and 3% sodium amalgam (1924 g., 2.5 moles) were added in small portions and with good agitation to a solution of 2-nitro-1-phenyl-1-propanol (36.2 g., 0.2 mole) in 300 ml. of absolute alcohol. Acetic acid was introduced at a rate sufficient to maintain an acidic reaction. The rate of adding the amalgam was such that the temperature was maintained at 45° or less. At the end of the reaction mercury was separated, water was added to dissolve the sodium acetate, and the mixture was heated to remove the alcohol and concentrate the solution. The cooled solution was extracted with ether to remove non-basic material and then treated with excess sodium hydroxide (as 50% solution), and the product was taken up in ether. After removing the ether and distilling, 18–21 g. of product resulted (b.p. 112° at 2 to 3 mm.).

(c) Catalytic hydrogenation. A mixture of 2-nitro-1-phenyl-1-propanol (36.2 g., 0.2 mole), 100 ml. of absolute alcohol, and 4 g. of Raney nickel was placed in a Parr hydrogenation bomb. Sufficient solid carbon dioxide was added to produce a pressure of 300 lbs./sq. in., then hydrogen was introduced to bring the total initial pressure to 1800 lbs./sq.in. Approximately four hours was required for complete reduction. On distilling, N-ethylbenzylamine (5%) and 2-amino-1-phenyl-1-propanol (87%) were obtained. When no carbon dioxide was used, the yield of N-ethylbenzylamine approximated 45%.

N-ethylbenzylamine was identified by its boiling point (198°) and the melting point of the hydrochloride (184°) compared with an authentic sample prepared from benzaldehyde and ethylamine.

Identification of 2-amino-1-phenyl-1-propanol. The product was a very viscous, colorless liquid which solidified on standing, m.p. 46–50°. When dry hydrogen chloride was passed into an ether solution, a gelatinous precipitate resulted, which hardened on standing. This character of precipitate was attributed to the rather complex mixture of isomers, since an authentic sample of *l*-ephedrine yielded well formed crystals. A better product could be made from the base by treating it with concentrated hydrochloric acid to the end point of methyl red indicator, evaporating under reduced pressure, and recrystallizing from butanol-ether (50–50 mixture by volume). The white crystals (m.p. 134–137°) gave 18.87 and 18.89% chlorine by Fajan's method (theory 18.91%). The neutral equivalent of the free amine was 155 (theory 151). The material is therefore believed to be a mixture of *dl*-norephedrine and *dl*-norisoephedrine. These two compounds are diastereoisomers and have the following constants:

dl-norephedrine		*dl*-norisoephedrine	
Free base	m.p. 104–105°	Free base	m.p. 71°
Hydrochloride	m.p. 192°	Hydrochloride	m.p. 169°

After four fractional crystallizations from absolute alcohol it was possible to obtain a hydrochloride m.p. 192°. The melting point of a mixture of this compound and norephedrine hydrochloride was 192°. Thus, it is possible to separate the components of the mixture by fractional crystallization but the yield is low.

The method of Nagai and Kanao (4), which utilizes the greater solubility in ether of norisoephedrine to separate the isomers, was tried on the free base. After four crystallizations, the amino alcohol melted at 72–75°. Since the original base mixture melted at 46–50°, the difference in solubility is evidently not great.

The mixture of stereoisomers obtained in this synthesis was tested for physiological action by two manufacturers of pharmaceuticals who compared it with norephedrine hydro-

chloride and found it to have a similar effect on the blood pressure. The work of Jarowski and Hartung already has been mentioned (2).

Preparation of 2-methylamino-1-phenyl-1-propanol. Formaldehyde (0.3 mole of active material as 37% solution) was added, with cooling, to 2-amino-1-phenyl-1-propanol (45.3 g., 0.3 mole) dissolved in ethanol. After the mixture had stood for a half hour, the Schiff base was reduced in a Parr hydrogenation bomb. Raney nickel (4 g.) was used as a catalyst. Initial pressures of hydrogen from 600 to 1400 lbs./sq.in. were suitable. The product was recovered by distilling the alcoholic solution with a Podbielniak column. There was a small amount of material which boiled at 106° at 5 mm., but the main portion of the distillate was collected at 115–120° at 5 mm. The yield of the more high-boiling product was 40 g. (81%).

Anal. Calc'd for $C_{10}H_{15}NO$: N, 8.5. Found: N, 8.4.

This mixture presumably is norephedrine and norisoephedrine and their monomethylated derivatives. This type of alkylation usually results in the formation of primary, secondary, and tertiary amines. Knowing that they usually result in such mixtures, we assume that small amounts are present in spite of the good agreement of the percentage of nitrogen with that required for $C_{10}H_{15}NO$. Samples of this material were prepared for several laboratories which specialize in techniques for separating isomers, but as yet no satisfactory process has been devised.

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SUMMARY

The synthesis of 2-amino-1-phenyl-1-propanol and of 2-methylamino-1-phenyl-1-propanol has been effected in several ways, all utilizing economical intermediates as initial materials. The mixture of diastereoisomers can be obtained in good yield but the methods for separating the isomers are not yet entirely satisfactory.

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