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β-PHENYLETHYLAMINES BY USE OF THE MANNICH REACTION

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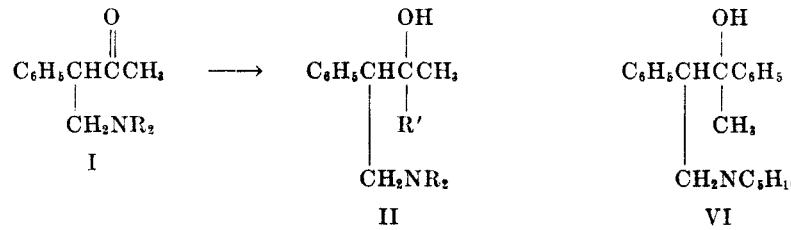
The Mannich reaction on phenylacetone involves the methylene group instead of the methyl group according to Wilson and Kyi (1) and Avison and Morrison (2). We have converted two Mannich bases from phenylacetone (I) to amino alcohols (II) by reduction and by the Grignard reaction. Since these substances are β-phenylethylamines, they are of potential pharmacological interest. Hydratropic aldehyde was also subjected to this series of reactions.



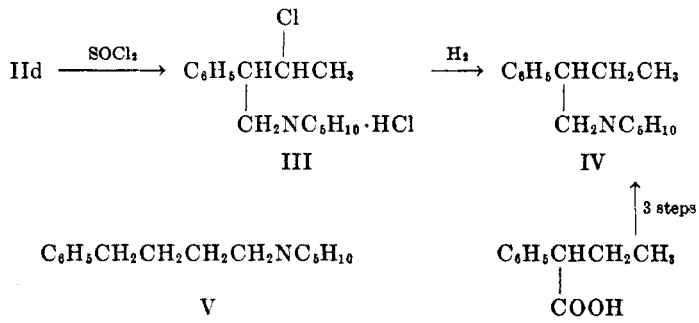
I II VI

(a) $R_2 = CH_3$ (a) $R = CH_3$, $R' = H$;
(b) $R_2 = (CH_2)_5$ (b) $R = CH_3$, $R' = C_2H_5$;
(c) $R = CH_3$, $R' = C_6H_{11}$;
(d) $R_2 = (CH_2)_5$, $R' = H$;
(e) $R_2 = (CH_2)_5$, $R' = C_6H_5$

The structure of the Mannich bases (I) was assigned by the previous workers (1, 2) on the basis of a positive iodoform test and the presence of a C methyl (Kuhn-Roth determination) in the pyrazoline obtained by the reaction of I with phenylhydrazine. In our experience, the iodoform test (3) gave an indefinite precipitate which, however, was not iodoform. We, therefore, sought another, more direct way of verifying the structure. Ib yielded acetic acid on oxidation with chromic acid. Further, Ib on reduction to the alcohol IId, successive conversion to the chloride (III), and catalytic reduction, yielded 1-(2-phenylbutyl)-piperidine (IV) rather than the isomeric V which would have resulted had the Mannich reaction occurred at the methyl group in phenylacetone. Authentic samples of IV and V were prepared by the following sequence: lithium aluminum hydride reduction of α-phenylbutyric and γ-phenylbutyric acids to the related alcohols, transformation of the alcohols to the corresponding bromides, and finally by reaction of the latter with piperidine.

Conversion of I to II should theoretically result in two diastereoisomers but in practice only one was isolated whether this transformation was brought about by reduction or by the Grignard reaction. This is another illustration of asymmetric addition to a carbonyl which is adjacent to an asymmetric carbon atom. The most recent discussion of this phenomenon is that by Cram and Elhafez (4). Both diastereoisomers of an amino alcohol may be obtained by the following procedures. Ib on reaction with phenylmagnesium bromide gave one diastereo-

isomer (IIe) while methylmagnesium iodide on 1,2-diphenyl-3-(1-piperidyl)-1-propanone gave the other (VI).



Pharmacological investigation of these compounds by Dr. Plummer in these laboratories revealed nothing of unusual interest.

We wish to acknowledge the advice of Dr. C. R. Scholz.

EXPERIMENTAL[1]

4-Dimethylamino-3-phenyl-2-butanol (IIa). Reduction of Ia hydrochloride (1) in aqueous ethanol over palladium on charcoal at atmospheric pressure failed to take place. Sodium borohydride reduction or hydrogenation of the free base over Raney nickel at 50 p.s.i. were successful, the former being more convenient for small quantities. To a solution of 3 g. of Ia hydrochloride in 25 ml. of water 0.5 g. of sodium borohydride (1 molar equivalent) was added over 5 min. After one-half hour at room temperature the excess borohydride was destroyed with hydrochloric acid. The solution was neutralized with 5 *N* sodium hydroxide and 5.3 ml. excess (2 molar equivalents) was added. The mixture was heated 15 min. on the steam-bath to hydrolize any borate esters. After concentration *in vacuo* to 5 ml., saturation with sodium carbonate, and extraction with ether, the oily base was obtained. The crystalline *hydrochloride* prepared in the usual manner by the addition of ethanolic hydrogen chloride and ether was recrystallized from ethanol-ether (1.9 g.), m.p. 140–141°. The m.p. of a mixture with the starting material was 120–130°.

Anal. Calc'd for $C_{12}H_{19}NO.HCl$: C, 62.73; H, 8.78.

Found: C, 62.53; H, 8.79.

3-Dimethylamino-2-methyl-2-phenyl-1-propanal. A mixture of 50 g. of hydratropic aldehyde, 31 g. of dimethylamine hydrochloride, and 30.6 g. of 36% aqueous formaldehyde was refluxed six hours in 100 ml. of ethanol. Ether was added to precipitate an oily hydrochloride. The oil was dissolved in the minimum amount of water, the solution carefully made basic with 10% sodium hydroxide, and the resulting organic base extracted into ether. After removal of ether, the basic mixture (43 g.) was distilled at 15 mm. The fraction boiling at 130–137° (25 g.) was converted to the *hydrochloride* by the addition of ethanolic hydrogen chloride and ether. After recrystallization from the same solvents the purified Mannich base hydrochloride was obtained, m.p. 164–165°.

Anal. Calc'd for $C_{12}H_{17}NO.HCl$: N, 6.15; Cl, 15.57.

Found: N, 6.19; Cl, 15.67.

The *methiodide* (from ethanol-ethyl acetate) melts at 210–213° (dec.).

Anal. Calc'd for $C_{13}H_{20}INO$: N, 4.20; I, 38.09.

Found: N, 4.10; I, 38.78.

3-Dimethylamino-2-methyl-2-phenyl-1-propanol. 3-Dimethylamino-2-methyl-2-phenyl-1-

[1] All melting points reported here are uncorrected.

propanal was reduced with sodium borohydride as described above to give the *hydrochloride* of the alcohol in similar yield, m.p. 133–134°.

Anal. Calc'd for $C_{12}H_{19}NO.HCl$: N, 6.10; Cl, 15.43.

Found: N, 6.06, Cl, 15.48.

1-Dimethylamino-2-phenyl-3-methyl-3-pentanol (IIb). A solution of the base from 6 g. of Ia hydrochloride in 50 ml. of anhydrous ether was added dropwise with stirring to the Grignard reagent (3 molar equivalents) prepared from 6.5 ml. of ethyl iodide, 1.9 g. of magnesium, and 100 ml. of ether. The mixture was refluxed for two hours and decomposed at ice-bath temperature with 2% hydrochloric acid. The aqueous extract was made basic with ammonia and extracted thoroughly with ether. The *hydrochloride* of IIb was recrystallized from ethanol-ether (2.7 g.), m.p. 178–179°.

Anal. Calc'd for $C_{14}H_{23}NO.HCl$: N, 5.43; Cl, 13.75.

Found: N, 5.36; Cl, 13.79.

2-Cyclohexyl-4-dimethylamino-3-phenyl-2-butanol (IIc). By reaction with cyclohexylmagnesium bromide as described above Ia gave IIc *hydrochloride* in a similar yield, m.p. 210–211°.

Anal. Calc'd for $C_{18}H_{29}NO.HCl$: N, 4.49; Cl, 11.37.

Found: N, 4.46; Cl, 11.84.

2,3-Diphenyl-4-(1-piperidyl)-2-butanol (IIe) (*α series*). Ib (1) by reaction with phenylmagnesium bromide as described above gave IIe as an oily base. The *hydrochloride* melted at 212–215°.

Anal. Calc'd for $C_{21}H_{27}NO.HCl$: N, 4.05; Cl, 10.25.

Found: N, 3.97; Cl, 10.31.

2,3-Diphenyl-4-(1-piperidyl)-2-butanol (VI) (*β-series*). 1,2-Diphenyl-3-(1-piperidyl)-1-propanone (5) was reacted in the usual manner with methylmagnesium iodide to yield the diastereoisomeric amino alcohol (VI), m.p. 102–103°.

Anal. Calc'd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53.

Found: C, 81.34; H, 8.64; N, 4.34.

The *hydrochloride* melted at 182–184° and the m.p. of a mixture of the two diastereoisomeric hydrochlorides (IIe and VI) was 165–175°.

Anal. Found: N, 4.09; Cl, 10.25.

Acetic acid from Ib. Chromic acid (40 g.) was added over two hours to a refluxing solution of 2 g. of Ib and 40 ml. of sulfuric acid in 200 ml. of water. Distillation was then begun. Water was added to keep the volume constant until the end of the distillation as 500 ml. of distillate was collected. The distillate was brought to neutrality by the addition of 8.0 ml. of 1 *N* sodium hydroxide (theory 8.7 ml.) and concentrated *in vacuo* to dryness. The sodium salt was converted to the *p*-phenylphenacyl ester of acetic acid (6), m.p. 108–110°. Identity with an authentic sample was confirmed by infrared spectra and by the melting point of a mixture of the two substances.

Anal. Calc'd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55.

Found: C, 75.68; H, 5.59.

1-(2-Phenylbutyl)piperidine (IV) *from* Ib. Ib was hydrogenated over Raney nickel at 50 p.s.i. in ethanol to yield IId (b.p. 180–186° at 15 mm.). Thionyl chloride (6.6 ml.) was added dropwise to a stirred solution of 20 g. of IId in 100 ml. of benzene held at room temperature by external cooling. The mixture was refluxed one-half hour and the benzene was removed. The gummy residue could be crystallized in part by trituration with 1:4 ethanol-ethyl acetate to yield 7 g. of 1-(2-phenyl-3-chlorobutyl)piperidine hydrochloride (III). Three recrystallizations from ethanol-ethyl acetate containing hydrogen chloride gave a product, m.p. 196–197°, still somewhat low in total chlorine but suitable for further reaction.

Anal. Calc'd for $C_{15}H_{22}ClN.HCl$: N, 4.86; Cl (ionic), 12.31; Cl (total) 24.65.

Found: N, 4.95; Cl (ionic), 12.25; Cl (total), 22.87.

When distillation of the free base of III was attempted at a bath temperature of about 180°, reaction took place to yield what apparently is a quaternary salt, m.p. 197–199°. The ring size of this substance is unknown.

Anal. Calc'd for $C_{15}H_{22}ClN$: N, 5.56; Cl, 14.08.
Found: N, 5.66; Cl, 13.76.

III (2 g.) in ethanol was reduced over Raney nickel at 50 p.s.i. Hydrogen uptake was slow, 18 hours being required for completion of the dehalogenation. The ethanol was distilled off, and the residue was dissolved in water, made alkaline, and the free base extracted with ether. The hydrochloride prepared by the addition of ethanolic hydrogen chloride was precipitated (0.5 g.) and after two recrystallizations from an ethanol-ethyl acetate-isopropyl ether mixture 1-(2-phenylbutyl)piperidine *hydrochloride* (IV) was obtained, m.p. 175–177°. The m.p. of the mixture with an authentic sample of IV hydrochloride (m.p. 173–175°) prepared as described below was 173–175°.

Anal. Calc'd for $C_{15}H_{23}N.HCl$: N, 5.52; Cl, 13.97.
Found: N, 5.51; Cl, 13.72.

IV from α-phenylbutyric acid. A 0.6 *M* lithium aluminum hydride solution (192 ml.) in ether was added with stirring and cooling to 25 g. of α-phenylbutyric acid in 200 ml. of anhydrous ether. The mixture was refluxed one hour and the excess lithium aluminum hydride was decomposed with ethyl acetate. Water was carefully added to produce granular lithium aluminate. After filtration, the alcohol (18 g.) was obtained by removal of the solvent. An equal weight of phosphorus tribromide was added cautiously with cooling to the alcohol. After one-half hour on the steam-bath, the mixture was decomposed with ice-water. The crude bromide (20 g.) was then refluxed directly with 30 ml. of piperidine in 100 ml. of ethanol for 12 hours. Most of the alcohol was distilled off, aqueous sodium hydroxide was added, and the bases were extracted with ether. IV distilled at 148–149° at 15 mm., yield 11 g.

The *hydrochloride* which was obtained in the usual way melted at 173–175°. After three additional recrystallizations from ethanol, the melting point was 178–180°.

Anal. Found: N, 5.67; Cl, 13.52.

The *methiodide* from ethanol melted at 239–240° (dec.).

Anal. Calc'd for $C_{16}H_{26}NI$: C, 53.48; H, 7.29; N, 3.90.
Found: C, 53.69; H, 7.52; N, 3.82.

1-(4-Phenylbutyl)piperidine (V). Reduction of γ-phenylbutyric acid (7) followed by the subsequent transformations as described for IV yielded the straight chain isomeric piperidine derivative. It distilled at 166–167° at 15 mm.

The *hydrochloride* melted at 148–149°. The melting point of the mixture with the isomeric branched chain compound was 124–134°.

Anal. Calc'd for $C_{15}H_{23}N.HCl$: Cl, 13.97. Found: Cl, 14.09.

The *methiodide* melted at 165–166°.

Anal. Calc'd for $C_{16}H_{26}NI$: C, 53.48; H, 7.29; N, 3.90.
Found: C, 53.77; H, 7.79; N, 3.79.

SUMMARY

Mannich bases derived from phenylacetone and hydratropic aldehyde were converted to alcoholic β-phenylethylamines by reduction or by the Grignard reaction. The structure of the Mannich bases obtained from phenylacetone was confirmed by removal of the carbonyl to give an oxygen-free amine which was synthesized by an unambiguous route.

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