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SOME REACTIONS OF ISOAMIDONE

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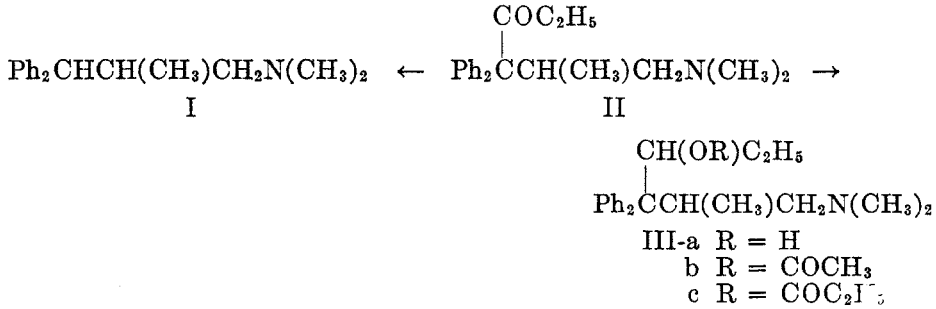
In a preceding publication (1) we reported that amidone (6-dimethylamino-4,4-diphenyl-3-heptanone), while resistant to reduction with aluminum isopropoxide or sodium amalgam, and to hydrogenation with Raney nickel, could be hydrogenated to the carbinol with platinum oxide. The O-acetyl and O-propionyl derivatives of this carbinol were found to have favorable analgesic properties, comparable to amidone. These investigations have now been extended to include the synthesis and pharmacological study of analogous acyl derivatives of 6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanol (III-a).

Unlike amidone, isoamidone (6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone) (II) did not absorb hydrogen in the presence of platinum oxide. Reduction to the carbinol III-a was ultimately achieved with lithium aluminum hydride, the excellent new reagent discovered by Finholt, Bond, and Schlesinger (2).[1] Likewise, amidone was converted to the corresponding carbinol more advantageously than with platinum oxide. In each instance, only one of the two possible diastereoisomers was encountered. Acylation of III-a to III-b and III-c was accomplished with acetic or propionic anhydride by the method of Houben (4) as described for 6-dimethylamino-4,4-diphenyl-3-heptanol (1).

Alkaline cleavage of the ethyl keto group of isoamidone did not proceed as readily as with amidone. After prolonged reaction, a product was obtained for which we postulate, by analogy (1) and on the basis of analytical data, the formula of 3-dimethylamino-1,1-diphenyl-2-methylpropane (I). The isolation of I was initially complicated by the fact that the picrates of I and II form a double compound, separable into its basic components *via* the hydrochloride salts. This difficulty was subsequently obviated by prolonging the reaction time and isolation of I as the hydrochloride rather than as the picrate salt.

Conversion of isoamidone to the carbinol III-a results in an almost complete loss of analgesic effect. Acetylation and propionylation of the hydroxyl group restore activity to one-half and one-fourth, respectively, that of isoamidone (N. B. Eddy) (5).



[1] *Cf.* Nystrom and Brown (3).

EXPERIMENTAL[2,3]

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanol (III-a). To 10 ml. of 1.4 *M* lithium aluminum hydride in ether and 25 ml. of dry ether was added during 15–20 minutes (stirring) the base of II (from 5 g. of hydrochloride)[4] in 50 ml. of dry ether. After another one-half hour, 10 ml. of water was added dropwise and the mixture stirred for ten minutes. The dried, ethereal solution was evaporated to dryness and the residue crystallized from ligroin (30–60°) to give 3.5 g. (75%) of prisms, m.p. 102–104°. They could be sublimed, or recrystallized from aqueous ethanol; m.p. 103–104.5°.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.9; H, 9.4.
Found: C, 80.7; H, 9.3.

Similarly, amidone was reduced to the carbinol, which was isolated from aqueous ethanol in a yield of 90%, m.p. 100–101°. A mixture with carbinol described previously (1) had the same m.p.

The hydrochloride of III-a crystallized from acetone-ether in needles, m.p. 198–200°.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.5; H, 8.7.
Found: C, 72.4; H, 8.7.

3-Acetoxy-6-dimethylamino-4,4-diphenyl-5-methylhexane (III-b) hydrochloride. To a stirred, ice-cooled solution of 1.5 g. of III-a in 20 ml. of dry ether was added slowly 18 ml. of 0.6 *M* ethereal ethylmagnesium bromide, then 1.5 ml. of acetic anhydride in 20 ml. of dry ether during five minutes. The mixture was refluxed for thirty minutes, shaken overnight, and stirred while adding slowly 10–20 ml. of water and 5 ml. of 10% potassium hydroxide. The ether was dried and acidified with 1.7 ml. of 15% alcoholic HCl to give 1.8 g. (95%) of hydrochloride, m.p. 129–132°. It crystallized from acetone-ether in plates (m.p. 129–132°)[5] or prisms, m.p. 220–222° (dec.). The prisms were analyzed.

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.8; H, 8.3.
Found: C, 70.6; H, 8.0.

The picrate, prepared from either the plates or the prisms with ethanolic picric acid, melted at 223–224° (dec.); yellow prisms.

Anal. Calc'd for $C_{29}H_{34}N_4O_9$: C, 59.8; H, 5.9.
Found: C, 60.1; H, 6.1.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-propionoxyhexane (III-c) picrate. The foregoing experiment was repeated (2 ml. of propionic anhydride). The dried ether layer, in this case, was evaporated to dryness and the base, in ethanol, was treated with 1.5 g. of picric acid in ethanol to give 2.5 g. (85%) of picrate, m.p. 213–214°, yellow prisms from acetone-alcohol.

Anal. Calc'd for $C_{30}H_{36}N_4O_9$: C, 60.4; H, 6.1.
Found: C, 60.4; H, 6.2.

The hydrochloride crystallized from acetone-ether in prisms, m.p. 197–199°.

Anal. Calc'd for $C_{24}H_{34}ClNO_2$: C, 71.4; H, 8.5.
Found: C, 71.2; H, 8.7.

3-Dimethylamino-1,1-diphenyl-2-methylpropane (I) hydrochloride. A mixture of 2.0 g. of II hydrochloride, 1.6 g. of potassium hydroxide, and 10 ml. of triethylene glycol was refluxed (bath temperature 220–230°) for 11–16 hours. Water and ether were added and the ether layer was dried and acidified with 2 ml. of alcoholic HCl. The oily hydrochloride crystallized from acetone-ether or ethyl acetate in prisms of m.p. 182–184°; yield 0.6–0.8 g. (35–50%).

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[2] All melting points given are uncorrected.

[3] The microanalyses are from the Institute service analytical laboratory under the direction of C. A. Kinser.

[4] This material was generously supplied by the Mallinckrodt Chemical Works.

[5] If the temperature rise is very slow from 120–130°, the plates merely sinter at 130° and melt at 220–222° (dec.). The plates are converted to the prisms either by recrystallization or by grinding.

Anal. Calc'd for $C_{18}H_{24}ClN$: C, 74.6; H, 8.4.
Found: C, 74.5; H, 8.3.

The picrate crystallized from ethanol in yellow prisms, m.p. 157.5–159°.

Anal. Calc'd for $C_{24}H_{26}N_4O_7$: C, 59.7; H, 5.4.
Found: C, 59.9; H, 5.4.

Double compound of the picrates of I and II. When the above reaction was carried out for 4–6 hours, an 80% yield of picrate of m.p. 169–171° was isolated. The same picrate was obtained on recrystallization (ethanol) of approximately equimolar amounts of the picrates of I and II.

Anal. Calc'd for $C_{27}H_{30}N_4O_8 \cdot C_{24}H_{26}N_4O_7$: C, 60.0; H, 5.5.
Found: C, 59.9; H, 5.5.

The double compound was converted to the bases (aqueous ammonia-ether). Fractional crystallization of the hydrochlorides of these basic products gave almost equal amounts of the hydrochlorides of I and II. Furthermore, the bases prepared from the double compound gave, as described above (alkali, triethylene glycol, 225°, ten hours), pure I hydrochloride in a yield of 50%.

SUMMARY

The reduction of isoamidone and amidone to the corresponding carbinols has been effected with lithium aluminum hydride.

Treatment of isoamidone in triethylene glycol with alkali at 220–230° gives 3-dimethylamino-1,1-diphenyl-2-methylpropane.

3-Acetoxy-6-dimethylamino-4,4-diphenyl-5-methylhexane and the propionoxy homolog have been prepared and evaluated as analgesic agents.

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REFERENCES

(1) MAY AND MOSETTIG, *J. Org. Chem.*, **13**, 459 (1948).
(2) FINHOLT, BOND, AND SCHLESINGER, *J. Am. Chem. Soc.*, **69**, 1199 (1947).
(3) NYSTROM AND BROWN, *J. Am. Chem. Soc.*, **70**, 1197 (1947).
(4) HOUBEN, *Ber.*, **39**, 1736 (1906).
(5) EDDY, Unpublished results.