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STRUCTURES RELATED TO MORPHINE. I. 2-(2-DIMETHYLAMINOETHYL)-2-PHENYLCYCLOHEXANONE AND DERIVATIVES

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In the continuing search for an effective analgesic agent with minimal addiction liability and toxicity our attention has centered on simple derivatives of 2-phenylcyclohexanone (I), *e.g.*, 2-(2-dimethylaminoethyl)-2-phenylcyclohexanone (II). Such structures are of interest not only because of their simplicity but also because of their obvious chemical similarities to such outstanding analgesics as morphine, methadone, and Meperidine. Furthermore, II appeared to be a versatile starting material which could be utilized in the elaboration of compounds bearing a closer resemblance to morphine types (*cf.* the following paper).

The synthesis of II[1] was achieved in a yield of 21% by the reaction of 2-dimethylaminoethyl chloride, I, and sodamide in refluxing benzene; repeated attempts to improve this result were unsuccessful. That O-alkylation of the enol form of I is a competing reaction and therefore imposes a practical limitation on the yield of II was indicated by the isolation of an acid-labile, basic substance which gave I (60% recovery) and a water-soluble amine on mild, acid hydrolysis.[2] Treatment of II with benzaldehyde gave the benzylidene derivative (III) proving that alkylation had occurred at the 2-position.

The ketone II was readily reduced to the alcohol (IVa) with ethereal lithium aluminum hydride. Hydrogenation (platinum oxide) also gave IVa, one (and the same) diastereoisomer being obtained in each instance. Acetylation of IVa to IVb was effected in a pyridine-acetic anhydride medium.

Wolff-Kishner reduction (Huang-Minlon modification) of II yielded the deoxy compound (V). The latter has been synthesized in a different way, though apparently not evaluated as an analgesic agent, by Barltrop and Nicholson (3).

Preliminary screening of compounds II, III, IVa, IVb, and V in mice indicated that only V had significant analgesic action (about half that of Meperidine). However, it appeared to be much less toxic than Meperidine.[3]

EXPERIMENTAL[4]

2-(2-Dimethylaminoethyl)-2-phenylcyclohexanone (II) *hydrochloride.* To a stirred, refluxing mixture of 2.3 g. (0.06 mole) of commercial sodamide and 15 ml. of benzene was

[1] Previously (1) the N,N-diethyl-, and morpholino analogs of I were similarly prepared and found to be devoid of analgesic activity.

[2] Zaugg, Freifelder, and Horrom (2) report the isolation and identification of a stable enol ether in the β-tetralone series.

[3] We are indebted to Dr. Nathan B. Eddy for these results (unpublished).

[4] Microanalyses are by the Institutes service analytical laboratory under the direction of Dr. William C. Alford. Melting points are corrected (Hershberg-type apparatus, total-immersion thermometers).

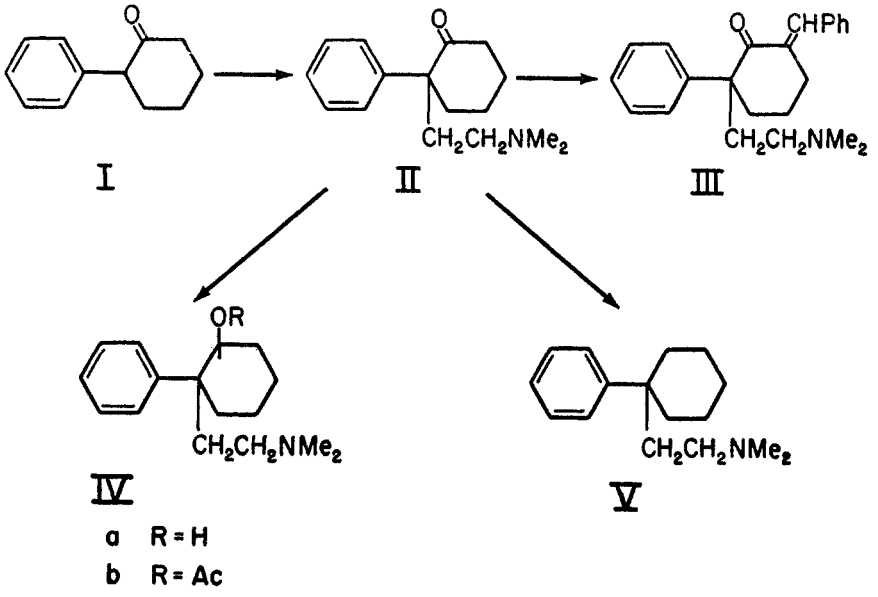

FIG. 1

added at such a rate as to avoid excessive foaming (*ca.* 5 minutes), 8.3 g. (0.05 mole) of I (4) in 15 ml. of benzene. After refluxing for one hour 5.1 g. (0.05 mole) of 2-dimethylaminoethyl chloride in 20 ml. of benzene was added and the mixture refluxed for 24 hours. The benzene solution was washed with water, dried, and evaporated. The 11.1 g. of residue was dissolved in ice-cold ether and extracted with 13.3 ml. of 3 *N* HCl. The ether layer gave 0.5 g. (6%) of I. The clear acid extract (pH *ca.* 6) was acidified to Congo Red and kept on the steam-bath for 5 minutes to give, on ether extraction, of the oil resulting, an additional 5.0 g. (60%) of I. The aqueous layer was then basified and the precipitated oil dried in ether. Acidification with alcoholic HCl and evaporation to dryness gave a sirup which crystallized from acetone;[5] yield 2.9 g. (21%), m.p. 187.5–189°. The analytical sample (rosettes) from alcohol-ether melted at 188.5–190°.

Anal. Calc'd for $C_{16}H_{24}ClNO$: C, 68.2; H, 8.6.
Found: C, 67.9; H, 8.6.

The *methiodide* crystallized from acetone[5] in blades, m.p. 223.5–224°.

Anal. Calc'd for $C_{17}H_{26}INO$: C, 52.7; H, 6.8.
Found: C, 52.6; H, 6.8.

6-Benzylidene-2-(2-dimethylaminoethyl)-2-phenylcyclohexanone (III) *hydrochloride.* Benzaldehyde (0.20 ml., 0.002 mole), 0.28 g. (0.001 mole) of II hydrochloride, 0.80 ml. (0.004 mole) of 5 *N* sodium hydroxide, and 4 ml. of ethanol were kept at 25° overnight, and diluted with 100 ml. of water. The resultant, viscous oil was taken up in ether and the solution extracted with 3 *N* HCl. The acid extract was basified, shaken with ether and the dried, ethereal solution was evaporated to dryness. The hydrochloride of the residue crystallized from alcohol-ether in tiny rosettes of m.p. 186–189°; yield 0.26 g. (70%). The analytical sample melted at 192–193°.

Anal. Calc'd for $C_{23}H_{28}ClNO$: C, 74.7; H, 7.6.
Found: C, 74.5; H, 7.8.

[5] It is necessary to dissolve the substance in a relatively large volume of refluxing solvent, concentrate to a small volume, and initiate crystallization from the resultant supersaturated solution.

2-(2-Dimethylaminoethyl)-2-phenylcyclohexanol (IVa) *hydrochloride.* The hydrochloride of II (0.28 g.), 0.1 g. of platinum oxide, and 25 ml. of methanol absorbed one mole of hydrogen during 50 minutes. The filtered solution was evaporated to dryness. The residue crystallized from acetone[5] in a yield of 0.22 g. (78%); blades of m.p. 179.5–180.5°.

Anal. Calc'd for $C_{16}H_{26}ClNO$: C, 67.7; H, 9.2.
Found: C, 67.6; H, 9.2.

The *picrate* (rhombic plates from aqueous ethanol), melted at 169.5–170°.

Anal. Calc'd for $C_{22}H_{28}N_4O_8$: C, 55.5; H, 5.9.
Found: C, 55.5; H, 6.1.

Reduction of II (base) with ethereal lithium aluminum hydride gave the hydrochloride of IVa in a yield of 83%; m.p. 179–180° alone or in mixture with that described above.

1-Acetoxy-2-(2-dimethylaminoethyl)-2-phenylcyclohexanone (IVb) *hydrochloride.* Acetic anhydride (0.2 ml.), 0.8 ml. of pyridine, and 0.2 g. of IVa hydrochloride were warmed to solution, kept at room temperature for 17 hours, and evaporated to dryness *in vacuo* to give, from acetone-ether, 0.18 g. (78%) of IVb hydrochloride, m.p. 179–180°. Further recrystallization for analysis gave rosettes of m.p. 174.5–175.5° (after drying at 100° in a high vacuum). On cooling, the melt solidified after which the m.p. was 181.5°. Apparently it is dimorphic.

Anal. Calc'd for $C_{18}H_{28}ClNO_2$: C, 66.3; H, 8.7.
Found: C, 66.1; H, 8.7.

1-(2-Dimethylaminoethyl)-1-phenylcyclohexane (V) *hydrochloride.* Triethylene glycol (10 ml.), 1.75 g. of II hydrochloride, 1.0 ml. of 95% hydrazine, and 2.0 g. of KOH were heated at 170–180° (bath temperature) for 7 hours. Water and ether were added, and the ether was dried (Na_2SO_4) and acidified with alcoholic HCl. Evaporation to dryness and crystallization of the residue (acetone-ether) gave 1.04 g. (63%) of the hydrochloride, m.p. 178–182°; it crystallized from ethyl acetate[5] in fine needles, m.p. 186.0–186.5°; lit. (3), m.p. 182–184°.

Anal. Calc'd for $C_{16}H_{26}ClN$: C, 71.7; H, 9.8.
Found: C, 71.9; H, 9.8.

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SUMMARY[6]

2-(2-Dimethylaminoethyl)-2-phenylcyclohexanone (II), the corresponding alcohol (IVa), and its O-acetyl derivative (IVb), and the deoxy compound (V) have been synthesized and screened for analgesic activity. Only V showed significant action.

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REFERENCES

(1) BROWN, COOK, AND HEILBRON, *J. Chem. Soc. Suppl. Issue*, **1**, 113 (1949).
(2) ZAUGG, FREIFELDER, AND HORROM, *J. Org. Chem.*, **15**, 1197 (1950).
(3) BARLTROP AND NICHOLSON, *J. Chem. Soc.*, 2524 (1951).
(4) NEWMAN AND FARBMAN, *J. Am. Chem. Soc.*, **66**, 1550 (1944).

[6] The contents of this and the following paper were presented by title at the September 1953 meeting of the American Chemical Society.