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SYNTHESIS OF 6-DIMETHYLAMINO-4,4-DIPHENYLHEPTANE AND OTHER COMPOUNDS RELATED TO METHADONE

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Previous, unsuccessful attempts in this laboratory (1) to prepare 6-dimethylamino-4,4-diphenylheptane (IX) included the Wolff-Kishner or Clemmensen reduction of *dl*-methadone and the chlorination of α-*dl*-6-dimethylamino-4,4-diphenyl-3-heptanol (X) followed by hydrogenation of the resultant chloride.[1] The synthesis of IX has now been achieved by an indirect route starting from γ-dimethylamino-α,α-diphenylvaleraldehyde (II). Several other compounds related to methadone have also been synthesized for screening as analgesic agents and are reported in this paper.

The requisite II was initially prepared by Yandik and Larsen (3) in 28% yield by the lithium aluminum hydride reduction of γ-dimethylamino-α,α-diphenylvaleronitrile (I). By modifying the procedure of these authors somewhat we have obtained II in a yield of 80%.

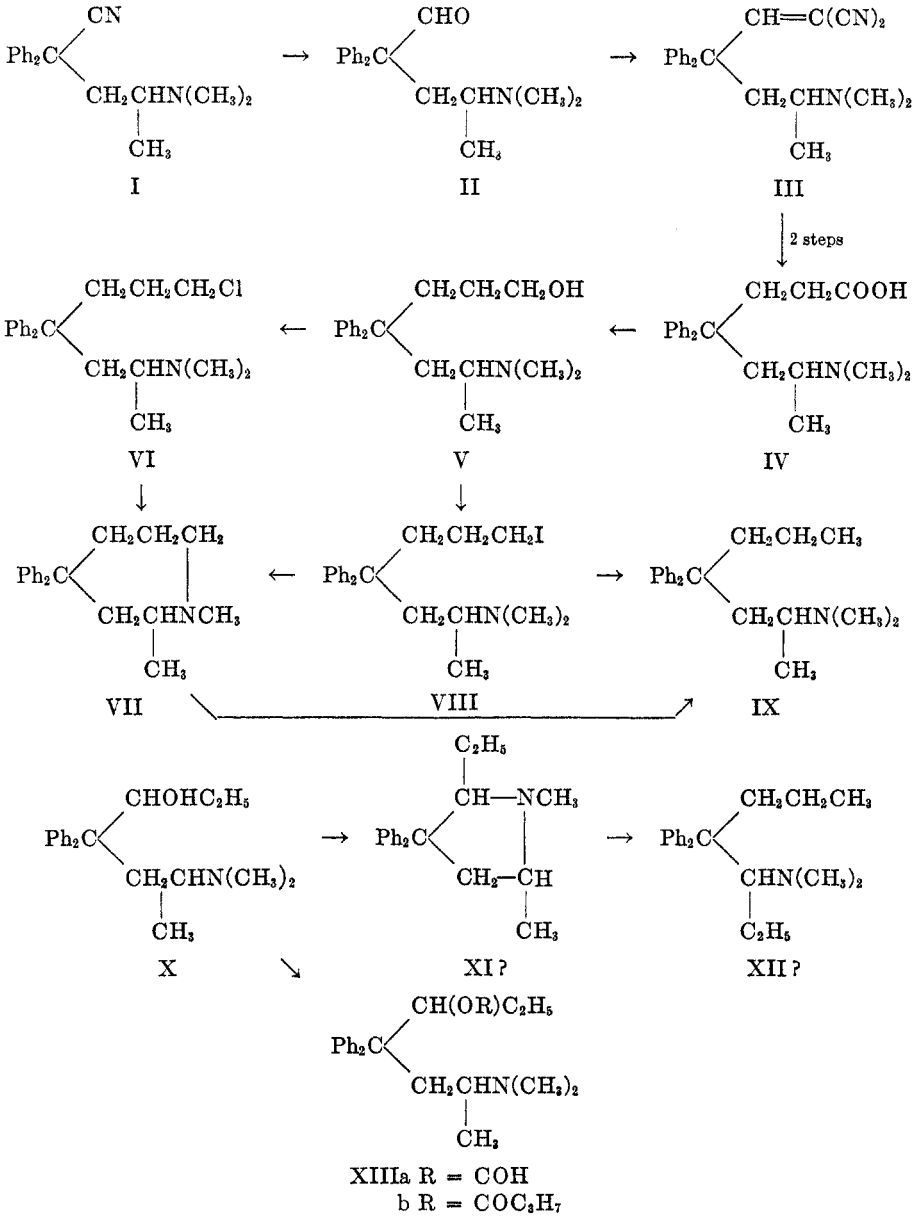
The Knoevenagel reaction of II and malononitrile as applied to 1-methyl-4-piperidone by McElvain and Lyle (4) readily gave the unsaturated dinitrile (III). Hydrogenation of III with platinum oxide, and acid hydrolysis-decarboxylation of the crude reduction product yielded 35–50% of the amino acid (IV). Reduction of IV with lithium aluminum hydride led to the alcohol (V) whose reaction with thionyl chloride produced the chloride (VI). Efforts to replace the chlorine of VI with hydrogen (platinum oxide or palladized charcoal) left the molecule intact. However, VI (as the free base) cyclized easily to the methochloride of the hexamethyleneimine derivative (VII) which could be converted to the desired product, IX, through exhaustive methylation and hydrogenation of the resultant, olefinic, tertiary amine.

Proof that the ring cleavage of VII had occurred as depicted to give IX[2] rather than the alternative 7-dimethylamino isomer consisted in the conversion of V to the iodide (VIII) and zinc-hydrochloric acid reduction of VIII, a reaction sequence which afforded the same compound IX as obtained from VII. The iodide (VIII) like the corresponding chloride was unaffected by catalytic reduction, but cyclized spontaneously, as the free base, to give the methiodide of VII. This methiodide could also be prepared by hydriodic acid treatment of the methochloride.

On reaction of X in ethyl acetate with either mesyl or tosyl chloride, a substance (XI) isomeric with VII separated as the methochloride in a yield of 25%; none of the desired esters could be isolated. Hydrogenation of the olefinic mate-

[1] Recently (2) it has been shown that the chlorination of X gives 4-chloro-6-dimethylamino-3,4-diphenylheptane, instead of the normal chlorination product.

[2] Attempts to convert the "cyclic amidone" described by Blicke and Krapcho (5) and by Easton, *et al.* (6) to 4,4-diphenyl-1,2,6-trimethylpiperidine, a substance which would lead unambiguously to IX, failed.



rial resulting from exhaustive methylation of XI gave an isomer (XII) of IX. These results are consistent with a formulation of 1,5-dimethyl-3,3-diphenyl-2-ethylpyrrolidine for XI and of 5-dimethylamino-4,4-diphenylheptane for XII.[3]

For pharmacological comparison with the analgesically active O-acetyl and O-propionyl derivatives of X (1, 8–10), the formyl (XIIIa) and butyryl (XIIIb)

[3] Alternative ring opening of XI to give IX would be counter to Hofmann's rule (7).

esters were prepared using formic-acetic anhydride and butyric anhydride-pyridine respectively. Also prepared were the O-acetyl derivative of V (acetic anhydride-pyridine) and the methyl ester of IV (diazomethane). Finally the Wolff-Kishner reduction of II gave 2-dimethylamino-4,4-diphenylpentane, a 2-carbon-lower homolog of IX.

Analgesic tests in mice showed that the order of activity of the esters of X administered subcutaneously was acetyl > propionyl > formyl > butyryl (ED_{50} 1.2–6.4 mg./kg.) while the toxicity order was acetyl > formyl > propionyl > butyryl (LD_{50} 60–380 mg./kg.). Administered orally, activity decreased with increasing chain length (ED_{50} 3.2–9.5). All of these acyl derivatives are characterized by slow onset and long duration of action (11). Of the remainder of the compounds screened (III, V and its O-acetyl derivative, IX, XII, the methyl ester of IV, and 4-dimethylamino-2,2-diphenylpentane) V exhibited analgesic effect of a very low order; its O-acetyl derivative was somewhat more effective. Still somewhat more effective (ED_{50} 60–80) were III and 4-dimethylamino-2,2-diphenylpentane.

EXPERIMENTAL[4]

γ-Dimethylamino-α,α-diphenylvaleraldehyde (II) *(3) nitrate.* To a stirred, refluxing solution of 56 g. (0.2 mole) of I (8, 12) in 200 ml. of dry ether was added during one hour, 40 ml. (0.06 mole) of 1.5 *M* ethereal lithium aluminum hydride. The mixture was refluxed for another hour and was treated gradually with 24 ml. of water. Decantation and evaporation of the ether left a residue to which was added 2.5 *N* nitric acid to Congo-Red acidity. The precipitated nitrate of II weighed 56.3 g. (82%), m.p. 186–188°. Recrystallized from water it melted at 188–190°.

Anal. Calc'd for $C_{19}H_{24}N_2O_4$: C, 66.3; H, 7.0; N, 8.1.
Found: C, 66.2; H, 7.0; N, 8.0.

The *base* (from ligroin, b.p. 30–60°) melted at 77–78°.

Anal. Calc'd for $C_{19}H_{23}NO$: C, 81.1; H, 8.2.
Found: C, 81.4; H, 8.1.

The *2,4-dinitrophenylhydrazone hydrochloride* (from dilute HCl) was dried *in vacuo* at 77° for analysis; m.p. 170–172°.

Anal. Calc'd for $C_{25}H_{28}ClN_5O_4$: C, 60.3; H, 5.7.
Found: C, 60.4; H, 5.9.

4-Dimethylamino-2,2-diphenylpentylidenemalononitrile (III). Malononitrile (4 g.), 14 g. of II, 2 g. of ammonium acetate, 4 ml. of acetic acid, and 20 ml. of benzene were refluxed vigorously[5] for 40 minutes, the water formed being collected in a Stark-Dean trap. The mixture was kept at 5° for 1–2 hours to give 10.4 g. (63%) of III, m.p. 163–165°; prisms from alcohol, m.p. 167–168°.

Anal. Calc'd for $C_{22}H_{23}N_3$: C, 80.2; H, 7.0.
Found: C, 80.2; H, 7.0.

The *hydrochloride* crystallized from acetone-ether as the hemihydrate; needles, m.p. 187–192° (dec.).

Anal. Calc'd for $C_{22}H_{24}ClN_3 \cdot \frac{1}{2}H_2O$: C, 70.5; H, 6.7.
Found: C, 70.6; H, 6.8.

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[4] Melting points were taken in a Hershberg-type apparatus with total-immersion thermometers. Microanalyses are from the Institutes' service analytical laboratory under the direction of Dr. William C. Alford.

[5] For satisfactory results the level of the heating medium must be below that of the reaction mixture.

ε-Dimethylamino-γ,γ-diphenylenanthic acid (IV) *hydrochloride.* A mixture of 10 g. of III hydrochloride, 0.3 g. of platinum oxide, and 150 ml. of methanol was shaken under hydrogen until 1.1–1.2 moles were absorbed (1.5–4 hours). The reaction was interrupted, and the mixture was shaken with charcoal, filtered through Filter-Cel, and evaporated to dryness *in vacuo*. To the residue was added 70 ml. of 20% HCl and the solution was refluxed for 4 hours or kept on the steam-bath for 24 hours. The hydrochloride of IV, which usually separated during the heating, was filtered; yield 3.5–5.0 g. (35–50%),[6] m.p. 265–268°. It was recrystallized from water or 80% aqueous alcohol-ether; rectangular plates, m.p. 267–269° (dec.).

Anal. Calc'd for $C_{21}H_{28}ClNO_2$: C, 69.7; H, 7.8.

Found: C, 69.5; H, 7.9.

The *methyl ester* (*nitrate salt*) was prepared by mixing at 5°, IV hydrochloride and excess ethereal diazomethane containing a little methanol and treatment of the gum resulting from evaporation of the solution to dryness with aqueous nitric acid. It crystallized from ethanol in a yield of 81%, m.p. 190.5–191.5°.

Anal. Calc'd for $C_{22}H_{30}N_2O_5$: C, 65.7; H, 7.5; N, 7.0.

Found: C, 65.4; H, 7.4; N, 6.9.

6-Dimethylamino-4,4-diphenyl-1-heptanol (V) *hydrochloride.* To a stirred suspension of 1.6 g. of IV hydrochloride and 50 ml. of dry ether was added 5 ml. of 1.5 *M* ethereal lithium aluminum hydride. The mixture was refluxed (stirring) for 4 hours and stirred overnight. After gradual addition of excess water, the ethereal solution was filtered, dried, and evaporated to give 1.3 g. of oily V. The hydrochloride (alcoholic HCl-acetone-ether) weighed 1.3 g. (87%), m.p. 197–199°. The analytical sample (from ethanol) melted at 199–200°.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.5; H, 8.7; N, 4.0.

Found: C, 72.7; H, 8.6; N, 4 2.

The *O-acetyl derivative* (*hydrochloride*), prepared from V hydrochloride and pyridine-acetic anhydride (intermittent steam-bath warming for one hour) crystallized from ethyl acetate; m.p. 155–156°.

Anal. Calc'd for $C_{23}H_{33}ClNO_2$: C, 70.7; H, 8.5.

Found: C, 70.9; H, 8.7.

1-Chloro-6-dimethylamino-4,4-diphenylheptane (VI) *nitrate.* To an aqueous solution of 1.3 g. of V hydrochloride was added excess sodium hydroxide. The liberated base was extracted and dried azeotropically with benzene. The solution resulting and 0.4 ml. of thionyl chloride were refluxed for one hour to give a precipitate of VI hydrochloride which, in water, was converted to the nitrate with excess sodium nitrate. Recrystallization of this nitrate from 90% ethanol gave 1.2 g. (84%), m.p. 167–168° (Kofler).

Anal. Calc'd for $C_{21}H_{29}ClN_2O_3$: C, 64.2; H, 7.4; N, 7.1.

Found: C, 64.4; H, 7.5; N, 7.4.

1,7-Dimethyl-4,4-diphenylhexamethyleneimine (VII) *methiodide.* (*a*) *From* VI. Finely divided VI nitrate (1.0 g.) was converted to the base (dilute NH_4OH-ether). After brief drying the ether was evaporated. The resultant oil and 5 ml. of absolute ethanol were refluxed for 2 hours, diluted to incipient turbidity with ether, and cooled to 5° to give 0.7 g. (84%) of the methochloride of VII, m.p. 265–267° (dec.). It was warmed with 0.6 ml. of 47% hydriodic acid in acetone, and the solution was diluted with ether to give 0.6 g. of the methiodide of VII; oblong plates from acetone-ether, m.p. 234–236°.

Anal. Calc'd for $C_{21}H_{28}IN$: C, 60.0; H, 6.7.

Found: C, 60.0; H, 6.9.

(*b*) *From* V *via* VIII. Refluxing 0.5 g. of V hydrochloride and 5 ml. of 47% hydriodic acid for one hour, cooling at 5°, and decanting gave a sirup which was washed with ether, then

[6] After this manuscript was submitted for publication, we found that methyl cyanoacetate would condense readily with II. Reduction of the sirupy hydrochloride of the resultant product in 50% ethanol followed by hydrolysis-decarboxylation as described, gave a 62% over-all yield of IV based on aldehyde.

ligroin (30–60°), and crystallized with acetone containing a little ligroin. The 0.5 g. of VIII hydriodide (m.p. 199–200°) resulting was quickly partitioned between dilute NaOH and ether. The briefly dried ether layer was evaporated to dryness. The residue and 3 ml. of absolute ethanol were refluxed for 15–30 minutes to give, after ether dilution, 0.3 g. (50% based on V) of the methiodide of VII identical with that prepared from the methochloride.

6-Dimethylamino-4,4-diphenylheptane (IX) *hydrochloride.* (*a*) *From* VII. The methiodide of VII (0.5 g.), 0.5 g. of commercial silver oxide, and 10 ml. of water were kept on the steam-bath (frequent shaking) for 40 minutes, filtered, and evaporated to dryness *in vacuo*. Distillation of the residue at 110–125° (bath temperature) and 0.5 mm. gave 0.35 g. of liquid which absorbed one mole of hydrogen (0.01 g. of platinum oxide, 5 ml. of ethanol) during ten minutes. The hydrochloride of the resultant base, prepared with alcoholic HCl-ether, weighed 0.3 g. (76%) and melted at 185–187.5°. It crystallized from acetone-ether in broad needles of m.p. 186.5–188.5°.

Anal. Calc'd for $C_{21}H_{30}ClN$: C, 76.0; H, 9.1.
Found: C, 75.9; H, 9.2.

The *picrate* crystallized from ethanol in yellow rods, m.p. 149–151°.

Anal. Calc'd for $C_{27}H_{32}N_4O_7$: C, 61.8; H, 6.2.
Found: C, 61.9; H, 6.2.

Aqueous triethylene glycol and potassium hydroxide (130–140°) could also be used successfully in the ring opening of VII methiodide.

(*b*) *By reduction of* VIII. The hydriodide of VIII (0.5 g.), 1.5 g. of mossy zinc, 5 ml. of methanol, and 5 ml. of conc'd HCl were refluxed until the zinc was consumed. An additional 1 g. of zinc was added, and the reaction was continued three more hours. The mixture was partitioned between 25% sodium hydroxide and ether. The dried ethereal layer was evaporated and the residue was distilled (100–125°, 0.5 mm.). The distillate, treated with alcoholic HCl-acetone-ether, gave 0.08 g. (26%) of hydrochloride, m.p. 185–187° alone or in mixture with that prepared from VII. Further, the picrate was found to be identical with the picrate of IX which was obtained from VII.

1,5-Dimethyl-3,3-diphenyl-2-ethylpyrrolidine (XI?) *methochloride.* To 4.0 g. of X (1, 8–10) in 40 ml. of ethyl acetate was added during 5 minutes (shaking) 1.3 ml. of mesyl chloride or an equivalent amount of tosyl chloride. After 24 hours at 25°, filtration gave 1.5 g. of a mixture which was recrystallized from ethanol-ethyl acetate; yield of XI methochloride, 1.1 g. (26%), m.p. 260–263°. Further recrystallization from ethanol-ether gave rods of m.p. 267–268° (dec.).

Anal. Calc'd for $C_{21}H_{29}ClN$: C, 76.5; H, 8.6; Cl, 10.8.
Found: C, 76.5; H, 8.7; Cl, 10.6.

The *methochloroplatinate* of XI crystallized from *ca.* 90% ethanol; m.p. 221–222°.

Anal. Calc'd for $C_{42}H_{58}Cl_6N_2Pt$: C, 50.5; H, 5.9; Pt, 19.5.
Found: C, 50.6; H, 5.7; Pt, 19.6.

5-Dimethylamino-4,4-diphenylheptane (XII?) *hydrochloride.* Precisely as described in the preparation of IX from VII, this product was obtained from the methiodide of XI (prepared from the methochloride with 47% HI-acetone-ether) in a yield of 70%. It crystallized from acetone as octagonal prisms, m.p. 224–226° (dec.).

Anal. Calc'd for $C_{21}H_{30}ClN$: C, 76.0; H, 9.1.
Found: C, 75.8; H, 9.2.

The XII hydrochloride could be prepared equally well from XI methochloride and aqueous triethylene glycol-KOH, (130–140°, 3–4 hours, hydrogenation of the olefinic base resulting).

α-dl-6-Dimethylamino-4,4-diphenyl-3-formoxyheptane (XIIIa) *hydrochloride.* Formic-acetic anhydride (1.5 ml.) (13, 14) and 0.3 g. of X hydrochloride were kept at 20° for 50–60 hours and were diluted with 10 ml. of ether and 3 ml. of ligroin (30–60°) to give gradually 0.2 g. (55%) of bipyramidal crystals of m.p. 213–216°. The analytical sample (from acetone-ether) melted at 214–216°.

Anal. Calc'd for $C_{22}H_{30}ClNO_2$: C, 70.3; H, 8.1.

Found: C, 70.2; H, 8.2.

The *picrate* crystallized from acetone-water in yellow prisms, m.p. 200–202° (dec.).

Anal. Calc'd for $C_{28}H_{32}N_4O_9$: C, 59.1; H, 5.7.

Found: C, 59.0; H, 5.5.

The formylation of X with refluxing formic-acetic anhydride was recently described by Clark (15) whose XIIIa hydrochloride was obtained as the dihydrate, m.p. 115–120°. At temperatures above 50° we obtained only the O-acetyl derivative of X.

3-Butyroxy-6-dimethylamino-4,4-diphenylheptane (XIIIb) *hydrochloride.* A mixture of 1.7 g. of X hydrochloride, 1.7 ml. of butyric anhydride, and 3.5 ml. of dry pyridine were kept at 70 ± 2° for 48 hours, and diluted to 50 ml. with ether containing a little ligroin (30–60°). The hygroscopic hydrochloride which separated after 48 hrs. (last 8 hours at 5–10°) was recrystallized from acetone-ether to give 1.6 g. (71%), m.p. 148–152°. The analytical sample was recrystallized first from 1:1 ethyl acetate-ether then from ethyl acetate; fine needles, m.p. 151–154°.

Anal. Calc'd for $C_{25}H_{36}ClNO_2$: C, 71.8; H, 8.7.

Found: C, 71.8; H, 8.7.

The *picrate* crystallized from alcoholic picric acid-water as yellow ellipsoids of m.p. 168–170°. Recrystallization from alcohol or acetone-ligroin (30–60°) gave long prisms which melted at 166–168° to a turbid melt that was clear at 171–172°. Immersed in a bath preheated to 167° it melted instantaneously to a clear melt. It appears to be dimorphic.

Anal. Calc'd for $C_{31}H_{38}N_4O_9$: C, 61.0; H, 6.3.

Found: C, 61.2; H, 6.5.

4-Dimethylamino-2,2-diphenylpentane hydrochloride. The hydrochloride of II (2.0 g.), 1.0 ml. of 95% hydrazine, 2.0 g. of KOH, and 10 ml. of triethylene glycol were kept at 170–180° (bath temperature) for 7 hours and treated with water and ether. The dried ethereal layer was acidified to Congo Red with alcoholic-HCl to give 1.9 g. (95%) of monohydrated crystals, m.p. 151–155°; diamonds from acetone, m.p. 155–156°.

Anal. Calc'd for $C_{19}H_{26}ClN + H_2O$: C, 70.9; H, 8.8.

Found: C, 70.9; H, 8.6.

The *picrate*, yellow needles from ethanol, melted at 114–115°.

Anal. Calc'd for $C_{25}H_{28}N_4O_7$: C, 60.5; H, 5.7.

Found: C, 60.4; H, 5.9.

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SUMMARY

6-Dimethylamino-4,4-diphenylheptane (IX), the deoxy compound corresponding to methadone, has been synthesized from γ-dimethylamino-α,α-diphenylvaleraldehyde (II) *via* 1,7-dimethyl-4,4-diphenylhexamethyleneimine (VII). Zinc-hydrochloric acid reduction of 6-dimethylamino-4,4-diphenyl-1-iodoheptane (VIII) yielded the same compound (IX) proving that ring fission of VII had not occurred alternatively to give the 7-dimethylamino isomer.

Reaction of α-*dl*-6-dimethylamino-4,4-diphenyl-3-heptanol (X) with either mesyl or tosyl chloride, gave, in 25% yield, the methochloride of a heterocyclic compound isomeric with VII, provisionally assigned the structure of 1,5-dimethyl-2-ethyl-3,3-diphenylpyrrolidine (XI). Exhaustive methylation of XI followed by hydrogenation of the olefinic material yielded an isomer of IX, presumably 5-dimethylamino-4,4-diphenylheptane (XII).

The formyl and butyryl esters of X and 4-dimethylamino-2,2-diphenylpentane have also been prepared for screening as analgesic agents.

BETHESDA 14, MD.

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