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SYNTHESIS OF COMPOUNDS RELATED TO THE METHADOLS

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In an extension of synthetic experiments in the methadone (I) and methadol (1) series, it seemed advisable to prepare diphenylalkanolamines of types II, III and IV, acyl derivatives of these types, and various other related substances for screening as analgesic agents.

$Ph_2C(COC_2H_5)CH_2CH(CH_3)N(CH_3)_2$ I

$Ph_2C(OH)CH_2CH(CH_3)N(CH_3)_2$ II

$Ph_2C(OH)CH(CH_3)CH_2N(CH_3)_2$ III

$Ph_2C(OH)C(CH_3)_2N(CH_3)_2$ IV

3-Dimethylamino-1,1-diphenyl-1-butanol (II)[1] was prepared in about 80% yield by the reaction of phenylmagnesium bromide or phenyllithium with ethyl or methyl β-dimethylaminobutyrate. Acylation of II with acetic anhydride-pyridine or with propionic anhydride-methyllithium[2] gave the corresponding acetyl and propionyl derivatives in yields of 40 and 90% respectively.

Dehydration of II was effected by heating it with concentrated hydrochloric acid. The resultant 3-dimethylamino-1,1-diphenyl-1-butene (V) was hydrogenated with palladium-charcoal to 3-dimethylamino-1,1-diphenylbutane (VI), previously obtained by May and Mosettig (5) in the drastic alkali treatment of I.

$Ph_2C{=}CHCH(CH_3)N(CH_3)_2$ V

$Ph_2CHCH_2CH(CH_3)N(CH_3)_2$ VI

3-Dimethylamino-1,1-diphenyl-2-methyl-1-propanol (III) was readily obtained by the reaction of phenylmagnesium bromide with either methyl β-dimethylaminoisobutyrate or β-dimethylaminoisobutyrophenone.[3] By the action of the appropriate anhydride and methyllithium (4), II afforded the acetyl and propionyl derivatives in 60–70% yields respectively.

The carbinol (IV) was previously prepared by Eidebenz (6) from α-dimethylaminoisobutyrophenone (VII). We were unable to acetylate IV by the method of Houben (4) using acetic anhydride or acetyl chloride or with acetyl chloride and pyridine.

The requisite VII was prepared by an improved method starting with acetone cyanohydrin. Reaction of the latter with dimethylamine gave α-dimethylaminoisobutyronitrile which, with phenyllithium yielded VII, but with phenylmagnesium bromide led to 2-phenyl-2-dimethylaminopropane (7). Reduction of VII with lithium aluminum hydride yielded the expected secondary alcohol.

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[1] This compound has been prepared in other ways by Archer and Auerbach (2) and by Bockmühl and Ehrhart (3).

[2] *Cf.* Houben (4).

[3] This compound has been reported by Bockmühl and Ehrhart without experimental details of its preparation.

All compounds designated by NIH numbers in the experimental section have been tested by Dr. N. B. Eddy of this Institute for their analgesic effect in mice. The acetyl and propionyl derivatives of II (NIH 4662 and 4665) were effective at a dosage of 20 mg. per kg., almost as active as meperidine.

The others were not significantly active. It is noteworthy that 3-dimethylamino-1,1-diphenyl-1-butene which is isosteric with the potent dithienylbutenes of Adamson and Green (8), is devoid of activity.

EXPERIMENTAL[4]

Methyl β-dimethylaminobutyrate. Methyl crotonate (100 g.) in 100 ml. of methanol was stirred (ice-cooling) during the rapid addition of 55 g. of dimethylamine. After standing for 24 hours at room temperature, the mixture was refluxed for 6 hours and concentrated *in vacuo* to the boiling point 40° at 25 mm. Fractional distillation of the residual product gave 126.7 g. (86%), of ester, b.p. 82–84°/40 mm., n_D^{20} 1.4282.

The *methiodide* melted at 168.2°.

Anal. Calc'd for $C_8H_{18}INO_2$: C, 33.46; H, 6.32; N, 4.88.
Found: C, 33.64; H, 6.03; N, 4.87.

The *chloroplatinate* melted at 158.5–158.8°.

Anal. Calc'd for $C_{14}H_{32}Cl_6N_2O_4Pt$: C, 24.01; H, 4.61; Pt, 27.87.
Found: C, 24.20; H, 4.32; Pt, 27.59.

The *hydrochloride* melted at 112.4–113.2°.

Anal. Calc'd for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88; N, 7.71.
Found: C, 46.36; H, 8.90; N, 7.58.

Ethyl β-dimethylaminobutyrate. Ethyl crotonate (195.5 g.) in 200 ml. of methanol was stirred and kept at 10–15° while adding 80 g. of dimethylamine during 15 minutes. After 24 hours the mixture was refluxed for 5 hours and distilled, yielding 253.5 g. (92%) of product, b.p. 92–95°/40 mm., n_D^{20} 1.4268; lit., b.p. 69.5°/12 mm., n_D^{20} 1.4264.

The *methiodide* melted at 127.3–128.8° (lit. 127–128°).

The *chloroplatinate* melted at 166.0–166.3°.

Anal. Calc'd for $C_{16}H_{36}Cl_6N_2O_4Pt$: C, 26.38; H, 4.98; N, 3.84; Pt, 26.80.
Found: C, 26.23; H, 4.88; N, 3.69; Pt, 26.37.

This chloroplatinate was previously reported to melt at 178–179°.

3-Dimethylamino-1,1-diphenyl-1-butanol (II).[1] Methyl β-dimethylaminobutyrate (14.5 g.) was added dropwise to 145 ml. of 1.83 *N* phenylmagnesium bromide in ether. Decomposition of the complex by ammonium chloride solution yielded 20.9 g. (78%) of a yellow oil which soon crystallized. After recrystallization from ether, the m.p. was 123.5–124.3°.

Anal. Calc'd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.21.
Found: C, 80.08, 80.50; H, 8.17, 8.15; N, 5.12.

The *hydrochloride* (NIH 3085), prepared by adding aqueous hydrochloric acid to the base, was recrystallized from alcohol; m.p. 208.7–209.0°.

Anal. Calc'd for $C_{18}H_{24}ClNO$: C, 70.68; H, 7.91; N, 4.55.
Found: C, 70.79; H, 7.67; N, 4.44.

The *methiodide* formed very slowly. After recrystallization from aqueous alcohol, the m.p. was 249.5–250.5°.

Anal. Calc'd for $C_{19}H_{26}INO$: C, 55.48; H, 6.37.
Found: C, 55.55; H, 6.36.

The *perchlorate*, from ethanol, melts at 92° and at 150–151° after drying *in vacuo* at 56°. For analysis, the compound was dried *in vacuo* at 100°.

Anal. Calc'd for $C_{18}H_{24}ClNO_5$: C, 58.45; H, 6.54.
Found: C, 58.74; H, 6.40.

II was also prepared from ethyl β-dimethylaminobutyrate and phenylmagnesium brom-

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[4] All melting points are uncorrected.

ide and from methyl β-dimethylaminobutyrate and phenyllithium. The results were substantially the same in each experiment.

1-Acetoxy-3-dimethylamino-1,1-diphenylbutane (NIH 4662). Warming a mixture of II (1.35 g.), 22 ml. of pyridine, and 3 ml. of acetic anhydride for 16 hours on the steam-bath, and isolation of the acetyl compound *via* the water-insoluble perchlorate gave 0.75 g. of an oil which soon crystallized. After recrystallization from petroleum ether (b.p. 30–60°), the product melted at 65–65.5°.

Anal. Calc'd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09.
Found: C, 77.34; H, 7.91.

The *perchlorate*, from aqueous ethanol, melted at 154°.

Anal. Calc'd for $C_{20}H_{26}ClNO_6$: C, 58.32; H, 6.36.
Found: C, 58.12; H, 6.18.

The *hydrobromide* was crystallized from ethanol by overlaying with ether; m.p. 177–182°.

Anal. Calc'd for $C_{20}H_{26}BrNO_2$: C, 61.22; H, 6.68.
Found: C, 61.28; H, 6.73.

Hydrolysis of the acetyl compound with alcoholic KOH gave II.

3-Dimethylamino-1,1-diphenyl-1-propionoxy-1-butanol. Addition of 125 ml. of *N* ethereal methyllithium to 13.5 g. of II in ether followed by addition of 50 ml. of acetic anhydride (ice-cooling) gave, after refluxing for 15 hours, 94% of crude ester, n_D^{20} 1.5426. After distillation at 1 μ it had n_D^{20} 1.5415.

Anal. Calc'd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36.
Found: C, 77.77; H, 8.50.

The *nitrate* (NIH 4665), from water, melted at 160–161°. For analysis it was dried for 2 hours *in vacuo* at 56°.

Anal. Calc'd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.26.
Found: C, 64.72; H, 7.24.

The *perchlorate*, from ethanol, melted at 149–152°. Analysis indicated one-third mole of hydrate water.

Anal. Calc'd for $C_{21}H_{28}ClNO_6 \cdot 1/3H_2O$: C, 58.39; H, 6.69.
Found: C, 58.24, 58.49; H, 6.70, 6.75.

Hydrolysis of the propionoxy derivative with alcoholic KOH gave II.

3-Dimethylamino-1,1-diphenyl-1-butene (V) *hydrochloride* (NIH 4756). Compound II hydrochloride (10 g.) and 100 ml. of conc'd hydrochloric acid were warmed on the steam-bath overnight. Most of the water was removed *in vacuo*. The resultant gum was dissolved in ethanol and precipitated with ether. The product, 9.0 g., had m.p. 162–163°, unchanged by recrystallization from alcohol-ether. For analysis, the material was crystallized from ethyl acetate and dried *in vacuo* at 76°.

Anal. Calc'd for $C_{18}H_{22}ClN$: C, 75.11; H, 7.71.
Found: C, 75.23; H, 7.57.

Analysis of an air-dried sample indicated 1.5 moles of hydrate water.

Anal. Calc'd for $C_{18}H_{22}ClN \cdot 1.5H_2O$: Cl, 11.26. Found: Cl, 11.32, 11.19.

The *base*, liberated from the hydrochloride, boiled at 112°/0.5 mm.; n_D^{20} 1.5777.

Anal. Calc'd for $C_{18}H_{21}N$: C, 86.00; H, 8.42.
Found: C, 86.22; H, 8.46.

The *picrate* crystallized from aqueous alcohol in prismatic rods, m.p. 196–197°.

Anal. Calc'd for $C_{24}H_{24}N_4O_7$: C, 59.99; H, 5.03; N, 11.66.
Found: C, 60.14; H, 4.97; N, 11.74.

Thionyl chloride and II also gave V but this preparation is less convenient than the one I describe.

3-Dimethylamino-1,1-diphenylbutane (VI). Hydrogenation of V hydrochloride in ethanol (room temperature, 750 mm.) with 5% palladium-charcoal required about 95 minutes. After removal of catalyst and solvent the product was dissolved in water and the solution was divided into three portions. The first with potassium nitrate gave the *nitrate* salt of VI, m.p. 118–120° after two recrystallizations from water. The second with aqueous picric acid gave the *picrate*, flat plates from ethanol, m.p. 142–144°. The third, with aqueous magnesium perchlorate, gave the perchlorate, m.p. 165–166° (from ethanol). These salts of VI were found to be identical with those prepared from VI which was obtained by the alkaline degradation of I (5).

Methyl β-dimethylaminoisobutyrate. To 100 g. of methyl methacrylate[5] in 100 ml. of methanol was added the dimethylamine generated from 97 g. of its hydrochloride, while the reaction mixture was stirred and cooled. After 20 hours at 30°, the solution was refluxed for 4 hours. Fractional distillation yielded 125.5 g. (86%), b.p. 73°/40 mm., n_D^{20} 1.4188.

The *methiodide* melted at 110.4–110.8° (acetone).

Anal. Calc'd for $C_8H_{18}INO_2$: C, 33.46; H, 6.32; N, 4.88.
Found: C, 33.51; H, 6.20; N, 4.63.

The *hydrochloride*, from alcohol-ether, had m.p. 124–127.5°.

Anal. Calc'd for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88; N, 7.71.
Found: C, 46.37; H, 8.69; N, 7.69.

The *chloroplatinate* had the m.p. 162–163.5°.

Anal. Calc'd for $C_{14}H_{32}Cl_6N_2O_4Pt$: C, 24.01; H, 4.61; Pt, 27.87.
Found: C, 24.16; H, 4.59; Pt, 27.70.

Titration of the base with 1.00 *N* HCl with Bromphenol Blue indicator gave an equivalent weight for the compound of 146.0; theory, 145.2.

3-Dimethylamino-1,1-diphenyl-2-methyl-1-propanol (III). (a) *From methyl β-dimethylaminoisobutyrate.* Methyl β-dimethylaminoisobutyrate (14.5 g.) was added dropwise to 180 ml. of 1.85 *M* ethereal phenylmagnesium bromide. After the spontaneous reaction had subsided, the reaction mixture was decomposed with aqueous ammonium chloride, and the amine fraction isolated. The resultant III (almost a quantitative yield), crystallized from ether or petroleum ether, had m.p. 92.8–93.3°.

Anal. Calc'd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.21.
Found: C, 80.40; H, 8.35; N, 5.16.

The *hydrochloride* (NIH 3017), recrystallized from alcohol-ether, melted sharply at 242.5°.

Anal. Calc'd for $C_{18}H_{24}ClNO$: C, 70.68; H, 7.91; N, 4.58; Cl, 11.59.
Found: C, 70.76; H, 7.65; N, 4.55; Cl, 11.61.

The *perchlorate* crystallized from ethanol in long needles and small rosettes; m.p. 160–161.5°. For analysis, the material was dried one hour at 78° *in vacuo*.

Anal. Calc'd for $C_{18}H_{24}ClNO_5$: C, 58.45; H, 6.54.
Found: C, 58.69; H, 6.48.

In a similar manner, using phenyllithium in place of phenylmagnesium bromide, carbinol III was prepared in 92% yield; m.p. 93–94°.

(b) *From propiophenone.* Propiophenone (12.5 g.), 7.7 g. of dimethylamine hydrochloride, 3.1 g. of trioxane, 20 ml. of benzene, and 20 ml. of nitrobenzene were heated 20 minutes under reflux, the liberated water being collected in a Dean and Starke moisture trap. The non-volatile base was isolated in the usual manner, and carefully dried. This crude β-dimethylaminoisobutyrophenone was added directly to a large excess of phenylmagnesium bromide in ether. The resultant III[3] had the m.p. 92.3–92.8° and was found to be identical with the III described in section (a).

1-Acetoxy-3-dimethylamino-1,1-diphenyl-2-methylpropane hydrochloride (NIH 3072). To 1.4 g. of III in 50 ml. of dry ether (ice-cooled, nitrogen atmosphere, stirring) was added 13 ml. of *M* methyllithium, then 5 ml. of acetic anhydride in 25 ml. of ether. After 0.5 hour the mixture was refluxed for 15 hours. The ether solution was washed with water, dried, and acidified with dry hydrogen chloride to give 1.1 g. of a hydrochloride which crystallized from alcohol-ether in large rosettes (m.p. *ca.* 180°) which gradually changed to prisms (m.p. *ca.* 188–189°).[6] Recrystallization from alcohol-ethyl acetate gave crystals of m.p. 196–197°.

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[5] A generous quantity of this chemical was supplied by the Rohm and Hass Chemical Company.

[6] The two forms were interconvertible. Furthermore, slow heating gave a m.p. of 200°.

Anal. Calc'd for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53.
Found: C, 69.13; H, 7.53.

Refluxing this ester for 2 hours with alcoholic KOH gave III, m.p. 94°, alone or in mixture with authentic III.

3-Dimethylamino-1,1-diphenyl-2-methyl-1-propionoxypropane. This compound was prepared as described for the foregoing acetoxy derivative (propionic anhydride was used); yield 66%, n_D^{20} 1.5433 after distillation at 70° and 1 μ.

Anal. Calc'd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36.
Found: C, 77.43; H, 8.21.

The *hydrochloride* (NIH 4753) from alcohol-ether, melted at 177° (sealed tube). For analysis, this was dried 2 hours *in vacuo* at 25°.

Anal. Calc'd for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80.
Found: C, 69.73; H. 7.86.

The *picrate*,[7] from aqueous alcohol, had m.p. 142–143°.

Anal. Calc'd for $C_{27}H_{30}N_4O_9$: C, 58.47; H, 5.45.
Found: C, 58.76; H, 5.43.

α-Dimethylaminoisobutyrophenone (VII) *hydrochloride.* Acetone cyanohydrin[5] (199 g. of 97% purity) and 1500 ml. of methanol were saturated with dimethylamine and kept at 30° for 15 hours. The methanol was distilled at 760 mm. through a Widmer column. Fractional distillation of the residue gave 167 g. (66%) of *α-dimethylaminoisobutyronitrile* (9–11),[8, 9] b.p. 51°/20 mm., n_D^{28} 1.4188. To 5.2 g. of this nitrile in 100 ml. of dry ether was added 230 ml. of 0.48 *M* phenyllithium during one hour. After refluxing for an additional two hours the basic fraction gave 9.2 g. of an oil which, after fractionation, weighed 5 g., b.p. 87°/3 mm. The *hydrochloride* (NIH 3771), from acetone, melted at 189.5–192°.

Anal. Calc'd for $C_{12}H_{18}ClNO$: C, 63.28; H, 7.97; N, 6.15.
Found: C, 63.59, 63.06; H, 7.53, 7.83; N, 6.00.

The *picrate*, from methanol, had the m.p. 189.5–190.5°; lit. (12), m.p. 153–155°.

Anal. Calc'd for $C_{18}H_{20}N_4O_8$: C, 51.43; H, 4.79; N. 13.35.
Found: C, 51.76; H, 4.83; N, 13.05.

2-Dimethylamino-2-phenylpropane hydrochloride. The reaction of α-dimethylaminoisobutyronitrile with phenylmagnesium bromide in refluxing ether for 24 hours yielded the base, b.p. 120–130°/20 mm., 52°/3 mm. The hydrochloride was recrystallized from propanol-acetone-ether; m.p. 211–212 °.

Anal. Calc'd for $C_{11}H_{18}ClN$: C, 66.15; H, 9.08; N, 7.02.
Found: C, 66.40; H, 9.16; N, 6.97.

The *methiodide*, from acetone, melted at 257–258°.

Anal. Calc'd for $C_{12}H_{22}IN$: C, 47.22; H, 6.60.
Found: C, 47.37; H, 6.68.

The *picrate* (from methanol or 90% ethanol) melted at 208–209°; lit. (7), m.p. 205°.

2-Dimethylamino-1,1-diphenyl-2-methyl-1-propanol (IV). The addition of 275 ml. of 1.16 *M* phenyllithium in ether to an ethereal solution of 43.9 g. of VII gave 59.2 g. (95%) of IV, m.p. 117–119°. After sublimation at 100° (1 μ) or after recrystallization from ethanol or petroleum ether, it melted at 118.5–119.5°.

Anal. Calc'd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20.
Found: C,80.02; H, 8.80; N, 5.09.

The *hydrochloride* (NIH 4608) had m.p. 225–226°; lit. (6) m.p. 224°.

Anal. Calc'd for $C_{18}H_{24}ClNO$: C, 70.68; H, 7.91.
Found: C, 70.42; H, 7.93.

The *chloroplatinate* had the m.p. 198–199° (dec).

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[7] The perchlorate (m.p. 106–107°, from ethanol-ether) was unstable and on repeated recrystallization or on standing for several days gave III and propionic acid.

[8] This reaction has been reported, without experimental details, by Jacobson (9).

[9] This compound is very irritating to the skin.

Anal. Calc'd for $C_{36}H_{48}Cl_6N_2O_2Pt$: C, 45.57; H, 5.10; Pt, 20.58.
Found: C, 45.77; H, 5.38; Pt, 20.38.

The *nitrate* melted at 228–229°, with gas evolution.

Anal. Calc'd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28.
Found: C, 64.98; H, 7.27.

The *perchlorate* had the m.p. 253–255°, dependent on the rate of heating.

Anal. Calc'd for $C_{18}H_{24}ClNO_5$: C, 58.45; H, 6.54.
Found: C, 58.25; H, 6.59.

The *acid sulfate* had the m.p. 218–222°.

Anal. Calc'd for $C_{18}H_{25}NO_5S$: C, 58.88; H, 6.86.
Found: C, 59.15; H, 6.77.

2-Dimethylamino-2-methyl-1-phenyl-1-propanol. An ethereal solution of VII was reduced with excess ethereal lithium aluminum hydride. The ether-soluble base was sublimed for analysis; m.p. 53.8–54.1°.

Anal. Calc'd for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.24.
Found: C, 74.71; H, 10.13; N, 7.26.

The *methiodide* (NIH 3777), m.p. 200.4–200.8°, was recrystallized from alcohol.

Anal. Calc'd for $C_{13}H_{22}INO$: C, 46.57; H, 6.62.
Found: C, 46.80; H, 6.64.

The *hydrochloride* (NIH 3772), from alcohol-acetone, melted at 220–221°.

Anal. Calc'd for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77.
Found: C, 62.70; H, 8.78.

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SUMMARY

3-Dimethylamino-1,1-diphenyl-1-butanol (II), 3-dimethylamino-1,1-diphenyl-2-methyl-1-propanol (III), and 2-dimethylamino-1,1-diphenyl-2-methyl-1-propanol (IV), have been synthesized. These amino alcohols, the acetyl and propionyl derivatives of III, and several closely related substances exhibited a low order of analgesic activity. The acetyl and propionyl derivatives of II were about as active as meperidine.

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