[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

CHEMISTRY AND PHARMACOLOGY OF THE METHADOLS[1] AND ACETYLMETHADOLS[2]

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Previous investigations (1, 2) have shown that platinum oxide hydrogenation or lithium aluminum hydride reduction of *dl*-methadone (I) gives only one of the two possible racemic alcohols.

$$(CH_3)_2\overset{*}{N}CH(CH_3)CH_2CPh_2COC_2H_5 \rightarrow (CH_3)_2\overset{*}{N}CH(CH_3)CH_2CPh_2\overset{*}{C}HOHC_2H_5$$

dl-methadone (I) — *α-dl*-methadol (II)

These results were subsequently substantiated by Pohland, Marshall, and Carney (3) who hydrogenated I and the optical isomers with platinum oxide and designated the products obtained thereby as α-isomers.

In an earlier publication by Bockmühl and Ehrhart (4) describing I and several analogs, a brief account of the preparation of an alcohol obtained by the sodium-propanol reduction of I was included. The melting point reported for this amino alcohol was 26° higher than that found for the α-isomer (II) (1, 2). No yields or pharmacological data were given by the German authors for their alcohol and its O-acetyl derivative.

Because of the presently increased interest in synthetic analgesics and the favorable activity exhibited by the acetates of the α-alcohols (1–3, 5), a thorough study of the sodium-propanol reduction of I and of the optical isomers has been made. The resulting alcohols and their O-acetyl derivatives have been evaluated and compared with the α-isomers with respect to analgesic activity and toxicity.

The predominant product isolated (65% yield) when I was subjected to this type of reduction proved to be diastereoisomeric (β-isomer) with II. Concomitantly about 10% of II was produced. Owing to the difference in solubility of the hydrochlorides of the two racemates a separation could be readily effected. Similar reaction of *d*-methadone gave about 40% of β-*d*-methadol,[3] 5–10% of α-*l*-methadol, and 5% of *l*-3-dimethylamino-1,1-diphenylbutane which resulted from cleavage of the ethyl keto group. Approximately the same yields respectively of β-*l*-methadol, α-*d*-methadol, and *d*-3-dimethylamino-1,1-diphenylbutane were obtained from *l*-methadone.

The separation of the reduction products from *d*- and *l*-methadone presented some difficulties initially but was finally achieved in the following manner. Acidification of the ethereal solution of the mixture of bases with alcoholic

[1] For convenience the name methadol is used to denote the alcohols derived from the methadones.

[2] Presented before the XIIth International Congress of Pure and Applied Chemistry in New York, September 1951.

[3] The letters *l*- and *d*- refer only to the sign of rotation.

hydrogen chloride gave a precipitate (A) of the α- and β-alcohol hydrochlorides. From this filtrate 3-dimethylamino-1,1-diphenylbutane gradually crystallized. Fractional crystallization of A proved impractical,[4] but its conversion to the bases with aqueous alcoholic ammonia ultimately gave the pure crystalline β-alcohol, the α-form showing no tendency to crystallize under these conditions. The material from this filtrate afforded the pure α-alcohol as its hydrochloride.

The structure of the cleavage products was determined by recrystallizing together equal amounts of the hydrochlorides of the two enantiomorphs; the compound resulting was identical with *dl*-3-dimethylamino-1,1-diphenylbutane obtained in the drastic alkali treatment of *dl*-methadone (1).

Pohland, Marshall, and Carney (3) have already noted that the α-methadols exhibit optical rotation values that are opposite in sign to the parent ketone.

TABLE I

d,l-methadone	β-*d,l*-methadol (70%)
	α-*d,l*-methadol (10%)
d-methadone	β-*d*-methadol (40%)
	α-*l*-methadol (5–10%)
	l-3-dimethylamino-1,1-diphenylbutane (*ca.* 5%)
l-methadone	β-*l*-methadol (40%)
	α-*d*-methadol (10%)
	d-3-dimethylamino-1,1-diphenylbutane (*ca.* 5%)

Noteworthy also is the fact that replacement of the ethyl keto group by hydrogen (cleavage product formation) changes the sign of rotation. The present (β) alcohols, on the other hand, rotate polarized light in the same direction as, but to a lesser degree than, the precursor ketone.

The results of the sodium-propanol reduction (average yields) are shown schematically in Table I.

The pharmacological results obtained with the methadols and acetyl methadols in comparison with the parent ketones, methadone and its optical isomers, are shown in Table II.

Both *d,l*-methadols (α and β) were less toxic, and had less analgesic effect, orally or subcutaneously than *d,l*-methadone. The acetyl derivatives, on the other hand, were similar to *d,l*-methadone in toxicity, but had greater analgesic effectiveness. Morphine, *d,l*-methadone, the *d,l*-methadols and acetyl derivatives, with the exception of α-*d,l*-methadol, are less effective orally than sub-

[4] The mixture could be enriched with respect to the β-isomer thereby.

cutaneously. There was, however, good agreement in onset of effect with each route of administration, indicating good absorption from the gastrointestinal tract. The duration of effect was longer after oral doses.

With the compounds obtained from *l*-methadone similar results were obtained. The alcohols (*α-d*, *β-l*) were less toxic and less effective, and the acetates more effective than the ketone. All compounds of this group were less effective orally than subcutaneously.

In the series of compounds obtained from *d*-methadone a number of differences were noted. Both *α-l*- and *β-d*-methadol were less toxic than the ketone or the

TABLE II

PHARMACOLOGICAL RESULTS

NIH NO.	COMPOUND	LD_{50}, MICE		ANALGESIC EFFECT, ED_{50}, MICE	
		Orally	Subcutaneously	Orally	Subcutaneously
	Morphine sulfate		700.0	3.7	2.3
2300	*dl*-Methadone	95.4	43.5	9.2	1.6
2933	*α-dl*-Methadol	266.0	137.0	10.9	18.9
4543	*β-dl*-Methadol	272.3	164.0	67.3	7.3
2953	*α-dl*-Acetylmethadol	118.3	61.0	4.0	1.2
4547	*β-dl*-Acetylmethadol	80.2	42.0	2.6	0.8
2887	*l*-Methadone	97.3	35.5	8.0	0.8
4586	*α-d*-Methadol	345.6	200.0	61.8	24.7
4549	*β-l*-Methadol	340.8	175.0	36.7	7.6
4544	*α-d*-Acetylmethadol	130.4	72.2	1.6	0.3
4596	*β-l*-Acetylmethadol	86.9	41.9	2.0	0.4
2886	*d*-Methadone		90.0	89.3	25.7
4552	*α-l*-Methadol	181.6	121.0	3.8	3.5
4603	*β-d*-Methadol	*ca.* 200.0	161.0	70.0	63.7
4539	*α-l*-Acetylmethadol	172.8	110.0	1.1	1.8
4607	*β-d*-Acetylmethadol	81.5	56.4	5.1	4.1

All compounds except morphine were tested as hydrochlorides. For method of determining analgesic effect see (5). All doses are in mg./kg. of substance as administered and are the result of statistical analysis of the data.

acetyl Methadols. *β-d*-Methadol had a very weak analgesic action. *α-l*-Methadol was a striking exception. By either route of administration, and in the rat as well as in the mouse, its analgesic effect was much greater than that of *d*-methadone. Although *d*-methadone was much less effective orally than subcutaneously, the oral doses for the methadols and acetyl methadols derived from it were very close to the subcutaneous doses. In one instance, i.e. with *α-l*-acetyl methadol the oral analgesic dose was significantly less than the subcutaneous. The difference in the two doses was more than five times the standard error of either. Another characteristic of the compounds obtained from *d*-methadone was their slower onset and longer duration of action.

It is of practical significance that the most interesting compounds in the

methadone series are derived from the relatively inactive *d*-methadone; namely, *α-l*-methadol, *α-l*- and *β-d*-acetylmethadol. They are being tried clinically and may be important both for high oral effectiveness and for long duration of action.

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EXPERIMENTAL[5]

β-dl-6-Dimethylamino-4,4-diphenyl-3-heptanol (β-dl-methadol) hydrochloride. To 3.6 g. of *dl*-methadone in 70 ml. of propanol was added during 15–20 minutes 3.6 g. of sodium with application of enough heat to cause gentle refluxing. After an additional 15–20 minutes of refluxing, the cooled solution was diluted with water and benzene. The benzene layer was washed twice with water, dried, and evaporated *in vacuo*. The residue was acidified to Congo Red with alcoholic HCl, diluted to 100 ml. with dry ether, and kept at 5° overnight to give 2.5 g. of hydrochloride, m.p. 210–212°. It crystallized from acetone in rods.

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

Found: C, 72.7; H, 8.8.

The *free base* (4) melted at 127–128°.

The filtrate from the 2.6 g. of *β*-hydrochloride was evaporated to dryness. The sirupy residue gave, from acetone-ether, 0.4 g. of *α*-hydrochloride identical with that obtained in the platinum oxide or lithium aluminum hydride reduction of *dl*-methadone (1–3).

β-d-Methadol. Reduction of 2.0 g. of *d*-methadone as described above gave, after alcoholic-HCl acidification of the reduction products in ether and cooling for 2–3 hours at 5°, 1.4 g. of a mixture (A) of hydrochlorides of m.p. 197–202°. This was dissolved in 5–7 ml. of alcohol and the solution treated with 2 ml. of conc'd NH_4OH and 1 ml. of water. Seeding[6] and cooling gradually to 5° gave, after fifteen hours at 5°, 0.8 g. of *β-d*-methadol, m.p. 106–107°; prisms from alcohol-water, $[\alpha]_D^{20}$ +178° (*c* in 95% ethanol, 0.63).

Anal. Calc'd for $C_{21}H_{29}NO$: C, 81.0; H, 9.4.

Found: C, 81.4; H, 9.4.

The *hydrochloride* crystallized from acetone-ether in plates, m.p. 206–208°, $[\alpha]_D^{25}$ +73.9° (*c* in water, 0.69).

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

Found: C, 72.5; H, 8.8.

The filtrate from the 0.8 g. of *β-d*-methadol was diluted with water and ether. The ether layer was washed once with water, dried, and acidified to Congo Red with alcoholic HCl to give after sixty hours at 5°, 0.12–0.2 g. of *α-l*-methadol hydrochloride m.p. 93–97°.[7] Occasionally an additional 0.1 g. of *β-d*-methadol hydrochloride could be obtained from this filtrate.

l-3-Dimethylamino-1,1-diphenylbutane hydrochloride. The filtrate from the 1.4 g. of A above gave 0.15 g. of a crude hydrochloride on standing at 5°. This was recrystallized from acetone to give rods of m.p. 180–182°, $[\alpha]_D^{20}$ −43.3° (*c* in water, 1.04).

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[5] Melting points observed in a capillary are uncorrected; rotations were taken in a 1-dm. tube.

[6] Seed crystals were obtained by making ammoniacal an aqueous solution of A and allowing the mixture to stand at 5° for several days.

[7] This represents another modification of the *α*-hydrochloride. On recrystallization from acetone-ether it was converted to the higher-melting (169–171°) form described previously (3).

Anal. Calc'd for $C_{18}H_{24}ClN$: C, 74.6; H, 8.4.
Found: C, 74.4; H, 8.4.

β-l-Methadol. Reduction of *l*-methadone as described for *d*-methadone gave this base[8] in a yield of 40%; prisms, m.p. 105–107°, $[\alpha]_D^{20}$ −178° (*c* in 95% ethanol, 1.04).

Anal. Calc'd for $C_{21}H_{29}NO$: C, 81.0; H, 9.4.
Found: C, 80.7; H, 9.5.

The *hydrochloride* melted at 206–208° and had $[\alpha]_D^{20}$ −74.2° (*c* in water, 0.94).

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.5; H, 8.7.
Found: C, 72.5; H, 8.6.

d-3-Dimethylamino-1,1-diphenylbutane hydrochloride. This hydrochloride was isolated as its enantiomorph above; m.p. 179–181°, $[\alpha]_D^{29}$ +43.1° (*c* in water, 0.53).

Anal. Calc'd for $C_{18}H_{24}ClN$: C, 74.6; H, 8.4.
Found: C, 74.7; H, 8.4.

dl-3-Dimethylamino-1,1-diphenylbutane hydrochloride. Proof of structure of the cleavage products. An equal mixture of the *l*- and *d*-3-dimethylamino-1,1-diphenylbutane hydrochloride was recrystallized from acetone ether to give prismatic rods of m.p. 151–155° alone or in mixture with the *dl*-3-dimethylamino-1,1-diphenylbutane hydrochloride obtained previously (1). Furthermore the *dl*-picrate prepared from these optical isomers melted at 137–139° alone or in mixture with that prepared from *dl*-methadone (1).

β-dl-3-Acetoxy-6-dimethylamino-4,4-diphenylheptane (β-dl-acetylmethadol) hydrochloride. The conditions employed for the α-alcohols (3) were used. A mixture of 1.5 g. of *β-dl*-methadol hydrochloride, 1.5 ml. of acetic anhydride, and 3 ml. of dry pyridine kept at 50° for fifteen hours, diluted to 40 ml. with dry ether, and cooled at 5° for six hours gave 1.3 g. (80%) of the acetyl derivative of m.p. 181–183.5°. It crystallized from acetic anhydride-ether as the hemihydrate;[9] rectangular plates, m.p. 186–188.5°.

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot \frac{1}{2}H_2O$: C, 69.3; H, 8.3.
Found: C, 69.2; H, 8.3.

From acetone-ether, this hydrochloride crystallized as the monohydrate, m.p. 142–146°.

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot H_2O$: C, 67.7; H, 8.4; H_2O, 4.0.
Found: C, 68.1; H, 8.4; Loss (150°),[10] 4.4.

The *free base* crystallized from water-ethanol in plates of m.p. 129–130° (4).

Anal. Calc'd for $C_{23}H_{31}NO_2$: C, 78.1; H, 8.8.
Found: C, 78.2; H, 8.8.

β-d-Acetylmethadol hydrochloride. *β-d*-Methadol was acetylated as described above to give this O-acetyl derivative as the monohydrate,[9] needles m.p. 158–160°, $[\alpha]_D^{20}$ +47.2° (*c* in water, 0.89).

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot H_2O$: C, 67.7; H, 8.4; Cl, 8.7.
Found: C, 68.2; H, 8.2; Cl, 8.7.

The *base* melted at 71–72°; prisms, $[\alpha]_D^{20}$ +90.7° (*c* in 95% ethanol, 0.43).

Anal. Calc'd for $C_{23}H_{31}NO_2$: C, 78.1; H, 8.8.
Found: C, 78.0; H, 8.7.

β-l-Acetylmethadol hydrochloride. This O-acetyl derivative crystallized from acetone-ether as the monohydrate, m.p. 159–161°, $[\alpha]_D^{20}$ −46.7° (*c* in water, 0.75).

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot H_2O$: C, 67.7; H, 8.4.
Found: C, 68.2; H, 8.5.

A sample dried at 100° partially sublimed; the residue analyzed for the anhydrous hydrochloride.

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.8; H, 8.3.
Found: C, 70.6; H, 8.4.

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[8] As described for the isolation of *α-l*-methadol hydrochloride, *α-d*-methadol hydrochloride was ultimately obtained from the filtrate of this base.

[9] Water of crystallization could not be determined by weight loss at 100°, due apparently to sublimation.

[10] Without a vacuum, instantaneous melting.

The *base* melted at 69.5–71° and had $[\alpha]_D^{20}$ −91.5° (*c* in 95% ethanol, 0.46).
Anal. Calc'd for $C_{23}H_{31}NO_2$: C, 78.1; H, 8.8.
Found: C, 78.2; H, 8.8.

SUMMARY

Reduction of *dl*-methadone with sodium and propanol has given a 7:1 mixture of *β-dl*-6-dimethylamino-4,4-diphenyl-3-heptanol and the previously described *α*-diastereoisomer. Similar reduction of the optical isomers has likewise given the *β*- and *α*-alcohols and approximately 5% of a cleavage product, 3-dimethylamino-1,1-diphenylbutane.

The compounds described have been evaluated pharmacologically in respect to toxicity and analgesic effectiveness.

BETHESDA 14, MD.

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