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THE ISOMETHADOLS[1] AND THEIR ACETYL DERIVATIVES

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Recent investigations have shown that the platinum oxide hydrogenation or lithium aluminum hydride reduction of *dl*-methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) (1, 2, 3) and of its optical isomers (3) gives consistently only one of the two possible isomeric alcohols. These have been designated as α-methadols (3, 4). Furthermore, reduction of *dl*-isomethadone (I) with lithium aluminum hydride[2] has similarly produced only one diastereoisomer, α-*dl*-isomethadol (II) (1b, 2).[3] If, however, reduction of the keto group of methadone to carbinol is effected with sodium and propanol (4, 5) the other possible (β) form is obtained in predominance, along with appreciable amounts of the α-alcohol.

While the α- and β-alcohols derived from methadone (except α-*l*-methadol) and the α-alcohol from *dl*-isomethadone exhibit only weak analgesic action, all of their O-acetyl derivatives have even greater analgesic potency than the corresponding parent ketones (1–4).

These studies have now been extended to include the α-alcohols derived from *d*- and *l*-isomethadones, the β-alcohols[3] from *dl*-, *l*-, and *d*-isomethadones, and the acetyl derivatives of both the α- and β-alcohols.

$$\underset{\text{dl-isomethadone (I)}}{Me_2N\overset{*}{C}H_2CH(CH_3)CPh_2COC_2H_5} \longrightarrow \underset{\alpha\text{-dl-isomethadol (II)}}{Me_2NCH_2\overset{*}{C}H(CH_3)CPh_2\overset{*}{C}HOHC_2H_5}$$

Reduction of the optical isomers of isomethadone with lithium aluminum hydride gave the α-alcohols to the exclusion of the β-isomers in concordance with results obtained previously with the *dl*-form (1b, 2). With sodium and propanol as the reducing medium, I and the enantiomorphs afforded from 30–40% yields of the β-alcohols and from 10–20% yields of the α-forms. A separation of the α and β racemic alcohols was achieved primarily by fractional crystallization of their hydrochlorides, while the mixture of alcohols resulting from the optical isomers of I could be more advantageously separated *via* the free bases. Acetylation of these amino alcohols was effected with a pyridine-acetic anhydride mixture at 65°.

In contrast to findings in the methadone series (3, 4) reduction of the isomethadones with lithium aluminum hydride did not change the sign of rotation,[4] but reduction with sodium and propanol gave isomethadols whose rotation was

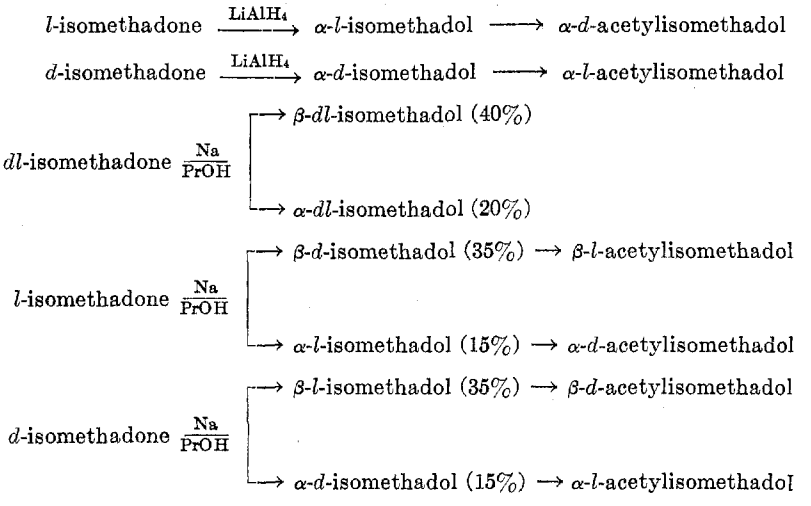
[1] For convenience all of the alcohols obtained from the isomethadones will be referred to as isomethadols.

[2] *dl*-Isomethadone resists hydrogenation with platinum oxide (1b).

[3] In conformity with the scheme established previously the isomethadols prepared by lithium aluminum hydride reduction will be termed α-isomers while the predominant ones obtained with sodium and propanol will be designated as β (3, 4) without knowledge of their configuration. Furthermore the letters *d* and *l* refer only to the observed sign of rotation.

[4] Rotations were, however, considerably decreased thereby.

opposite in sign to that of the parent ketone. Since, however, acetylation of the α- and β-isomethadols[3] did in both instances reverse the sign of rotation, the net result of the series of reactions in which *d*-isomethadone yields α-*l*-acetylisomethadol and β-*d*-acetylisomethadol, is the same as that observed in the methadone series (see below).



dl-Isomethadone and its optical isomers are less toxic and less effective analgesic agents than methadone and its isomers. The isomethadols and acetylisomethadols have been evaluated for analgesic potency, and almost all of them are less effective whether administered orally or subcutaneously than the corresponding members of the methadone series. (See Table I). In most instances the methadone derivative is one and one-half to two times more effective than the isomethadone. The methadone derivatives are also more toxic, but generally the difference in toxicity between corresponding methadone and isomethadone derivatives is less than the difference in analgesic effectiveness. Details of the pharmacology of the two series of compounds will be published elsewhere.

Acknowledgment: We are indebted to Merck & Co., Inc. for generously supplying the isomethadones used. The microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

EXPERIMENTAL[5]

α-l-6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanol (α-l-isomethadol).[1, 3] The base from 5.0 g. of *l*-isomethadone hydrochloride[6] in 40 ml. of dry ether was treated during five minutes (stirring) with 20 ml. of *M* ethereal lithium aluminum hydride. After stirring for 0.5 hour, 10 ml. of water was added gradually and the mixture was stirred an additional 0.5 hour. Decanting, drying, and evaporating the ether gave 3.8 g. (84%) of α-*l*-isomethodol, m.p. 122–124°; prisms from alcohol-water, m.p. 125–126°, $[\alpha]_D^{20}$ −19.7° (*c*, 1.43).

[5] Melting points are uncorrected; rotations were taken in a 1-dm. tube with water as a solvent for the hydrochloride salts and 95% alcohol for the free bases.

[6] Supplied by Merck & Co., Inc. as the monohydrate.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.96; H, 9.38.
Found: C, 80.71; H, 9.15.

The *hydrochloride* crystallized from acetone as the hemihydrate in rectangular plates, m.p. 202–204°, $[\alpha]_D^{20}$ − 9.6° (*c*, 2.93).

Anal. Calc'd for $C_{21}H_{30}ClNO \cdot 1/2H_2O$: C, 70.67; H, 8.76.
Found: C, 70.95; H, 8.70.

α-d-Isomethadol. This alcohol, obtained from *d*-isomethadone as described above, melted at 124.5–125.5° and had $[\alpha]_D^{20}$ +19.1° (*c*, 0.63).

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.96; H, 9.38.
Found: C, 81.02; H, 9.19.

TABLE I

PHARMACOLOGICAL RESULTS

NIH No.	COMPOUND	LD_{50}, Mice	ANALGESIC EFFECT, ED_{50}, Mice	
		Subcutaneously	Orally	Subcutaneously
2880	*dl*-Isomethadone	67.7	23.0	2.5
3140	*α-dl*-Isomethadol	143.0	[a]	66.8
4757	*β-dl*-Isomethadol	177.7	30.3	12.3
3157	*α-dl*-Acetylisomethadol	172.8	11.2	4.8
5120	*β-dl*-Acetylisomethadol	191.7	55.4	17.4
2961	*l*-Isomethadone	56.8	24.4	1.2
4745	*α-l*-Isomethadol	260.2	131.6	91.7
5234	*β-d*-Isomethadol	204.7	40.7	6.2
4754	*α-d*-Acetylisomethadol	110.5	10.4	2.7
5233	*β-l*-Acetylisomethadol	163.4	35.0	10.9
2962	*d*-Isomethadone	137.1	[b]	49.8
4733	*α-d*-Isomethadol	80.6	[c]	60.7
5228	*β-l*-Isomethadol	214.1	93.9	58.7
4755	*α-l*-Acetylisomethadol	152.9	104.1	62.7
5230	*β-d*-Acetylisomethadol	223.5	164.0	70.6

All compounds tested as hydrochlorides. For the method of determining analgesic effect, see (6). All doses are in mg./kg. of substance as administered and are the result of statistical analysis of the data.

[a] Maximum effect = 3 of 10 at 250 mg./kg., a convulsant dose, fatal for 4 of 10 within 30 minutes. [b] No analgesic effect up to 200.0 mg./kg., a convulsant dose, ⅔ of the oral LD_{50}. [c] No analgesic effect up to 150.0 mg./kg., a convulsant dose, fatal for 1 of 10 within 30 minutes.

The *hydrochloride* crystallized from acetone as the hemihydrate;[7] m.p. 202–204°, $[\alpha]_D^{20}$ +10.1° (*c*, 1.89).

Anal. Calc'd for $C_{21}H_{30}ClNO \cdot 1/2H_2O$: C, 70.67; H, 8.76.
Found: C, 71.09; H, 8.88.

β-dl-Isomethadol. The base from 4.0 g. of the hydrochloride of I[8] in 70 ml. of propanol was treated during 30–40 minutes with 4 g. of sodium with the application of sufficient heat to cause vigorous refluxing. After all sodium had dissolved the cooled solution was treated with water and benzene. The benzene layer was washed twice with water, dried, (sodium sulfate), and evaporated to dryness *in vacuo*. The residual oil, in ether, was acidified (to Congo Red)

[7] The bound water was indeterminate by weight-loss at 100° *in vacuo* due apparently to sublimation.

with alcoholic HCl. Cooling at 5° gave 3.6 g. of a mixture which was dissolved in 20 ml. of commercial absolute alcohol and the solution concentrated to *ca.* 15 ml. After 15 hours at 25° and five days at 5°, 1.5 g. of *β-dl*-isomethadol hydrochloride (diamond plates) of m.p. 248–251° was obtained. The filtrate was evaporated to dryness and the residue dissolved in a little alcohol. Addition of conc'd NH_4OH to slight excess, then water to incipient turbidity and seeding[8] gave after five hours at 25° and 15 hours at 5°, 0.2 g. of *β-dl*-isomethadol (total yield 43%), m.p. 102–105°. It crystallized from water-ethanol in prisms, m.p. 107–108.5°.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.96; H, 9.38.

Found: C, 80.77; H, 9.38.

The *hydrochloride* melted at 252–254° after a recrystallization from ethanol-ether.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69.

Found: C, 72.55; H, 8.98.

The filtrate from the 0.2 g. of *β-dl*-isomethadol above was diluted slightly with water and seeded with *α-dl*-isomethadol (II) to give, after 40 hours at 5°, 0.7 g. (20%) of II, m.p. 100–102.5° alone or in mixture with that prepared previously (1b). Further, it gave a hydrochloride of m.p. 231–233° (sinters at 200°) identical with that prepared previously.[9]

β-d-Isomethadol. The sodium-propanol reduction of the *l*-isomethadone from 10 g. of the hydrochloride[6] as described for I gave 8.5 g. of a mixture (m.p. 195–205°) of hydrochlorides which was dissolved in 40 ml. of warm alcohol. Addition of 12 ml. of conc'd NH_4OH and 12 ml. of water gave, after warming to solution, cooling to 30–35°, seeding,[10] cooling to 5° during 2–3 hours, and keeping at 5° for 3–4 hours, 2.7 g. of *β-d*-isomethadol (an additional 0.5 g. was obtained as described below; total yield 35%), m.p. 93–95°. Recrystallized from alcohol-water it melted at 94–95° and had $[\alpha]_D^{20}$ +13.3° (*c*, 1.65); slim rods.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.96; H, 9.38.

Found: C, 80.94; H, 9.43.

The *hydrochloride* crystallized from ethanol-ether in thin prisms, m.p. 241–243°, $[\alpha]_D^{20}$ +13.5° (*c*, 1.78).

Anal. Calc'd for $C_{21}H_{30}Cl1NO$: C, 72.49; H, 8.69.

Found: C, 72.63; H, 8.72.

The filtrate from the 2.7 g. of *β-d*-isomethadol was seeded with *α-l*-isomethadol to give, after four days at 5°, 3.2 g. of a precipitate, m.p. 85–113°. It was dissolved in 4.0 ml. of warm alcohol to give, on seeding the solution with *α-l*-isomethadol and keeping at 15–20° overnight and at 5° for two hours, 1.3 g. (14%) of *α-l*-isomethadol, m.p. 121–123°, identical with that prepared by the lithium aluminum hydride reduction of *l*-isomethadone. The filtrate from the 1.3 g., on slight dilution with water and seeding gave an additional 0.5 g. of *β-d*-isomethadol, m.p. 92–94°.

β-l-Isomethadol. This amino alcohol was prepared from *d*-isomethadone[11] as described for *β-d*-isomethadol above. The *l*-isomer melted at 93.5–94.5° and had $[\alpha]_D^{20}$ −13.8° (*c*, 1.09).

Anal. Calc'd for $C_{21}H_{29}NO$: C, 80.96; H, 9.38.

Found: C, 80.83; H, 9.51.

The *hydrochloride* melted at 241–243° and had $[\alpha]_D^{20}$ −13.5° (*c*, 1.56).

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69.

Found: C, 72.55; H, 8.78.

α-l-3-Acetoxy-6-dimethylamino-4,4-diphenyl-5-methylhexane (*α-l-acetylisomethadol*) *hy-*

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[8] Seed crystals were obtained by basifying with conc'd NH_4OH an aqueous solution of the pure *β*-hydrochloride and keeping the mixture at 5° for a few days.

[9] This hydrochloride as originally reported melted at 198–200° (1b) but changed to the higher-melting modification on standing or recrystallization.

[10] Repeated recrystallizations of the original hydrochloride mixture from absolute ethanol gave in low yield the pure *β*-hydrochloride from which seed crystals were obtained as described in footnote 8.

[11] In addition a 15% yield of *α-d*-isomethadol was isolated as described in the previous experiment.

drochloride. A mixture of 1.0 g. of *α-d*-isomethadol hydrochloride, 1.0 ml. of acetic anhydride, and 2.0 ml. of dry pyridine was kept at 65–70° for 17 hours, diluted to 30 ml. with ether, and cooled at 5° for 3–4 days to give 0.8 g. (70%) of hydrochloride. It crystallized from acetone-ether in plates, m.p. 112–115°, or needles, m.p. 170–172.5°. The needles analyzed for the monohydrate and had $[\alpha]_D^{20}$ −20.5° (*c*, 1.66).

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot H_2O$:[7] C, 67.70; H, 8.40.
Found: C, 67.90; H, 8.46.

The *picrate*, prepared from an aqueous solution of the hydrochloride with alcoholic picric acid, crystallized from alcohol in yellow plates of m.p. 206–208°.

Anal. Calc'd for $C_{29}H_{34}N_4O_9$: C, 59.78; H, 5.88.
Found: C, 59.86; H, 6.00.

α-d-Acetylisomethadol hydrochloride. This compound, prepared from *α-l*-isomethadol hydrochloride as described above, exhibited the same crystal-formation and melting-point phenomena as the *l*-isomer. The needles were analyzed; m.p. 170–172.5°, $[\alpha]_D^{20}$ +21.5° (*c*, 1.35).

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot H_2O$:[7] C, 67.70; H, 8.40.
Found: C, 68.07: H, 8.08.

The *picrate* melted at 207–209°.

Anal. Calc'd for $C_{29}H_{34}N_4O_9$: C, 59.78; H, 5.88.
Found: C, 59.69; H, 5.87.

β-dl-Acetylisomethadol hydrochloride. The acetylation of *β-dl*-isomethadol hydrochloride as described above (reaction time, 24 hours) gave this hygroscopic hydrochloride in a yield of 90%. It crystallized from acetone-ether in plates (dihydrate) of m.p. 218–220° after sintering at about 145°.

Anal. Calc'd for $C_{23}H_{32}ClNO_2 \cdot 2H_2O$: C, 64.84; H, 8.52.
Found: C, 65.25; H, 8.52.

The *base* crystallized slowly from alcohol-water; thin prisms, m.p. 78–79.5°.

Anal. Calc'd for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84.
Found: C, 78.27; H, 8.75.

β-d-Acetylisomethadol hydrochloride. The acetylation of *β-l*-isomethadol hydrochloride gave this dextrorotatory compound in a yield of 85%; clusters of needles from acetone-ether (charcoal), m.p. 205–208°, $[\alpha]_D^{20}$ +17.0° (*c*, 1.06).

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.83; H, 8.27.
Found: C, 70.68; H, 8.05.

The *base* (prisms from alcohol-water) melted at 128.5–129.5° and had $[\alpha]_D^{20}$ +25.0° (*c*, 0.32).

Anal. Calc'd for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84.
Found: C, 78.24; H, 8.80.

β-l-Acetylisomethadol hydrochloride. This levorotatory isomer (prepared from *β-d*-isomethadol) melted at 207–209.5° and had $[\alpha]_D^{20}$ −15.3° (*c*, 1.18).

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.83; H, 8.27.
Found: C, 70.45; H, 8.63.

The *base* melted at 128.5–129.5°, $[\alpha]_D^{20}$ −23.7° (*c*, 0.93).

Anal. Calc'd for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84.
Found: C, 77.88; H, 8.91.

SUMMARY

Reduction of *d*- and *l*-isomethadone with lithium aluminum hydride has given 84% yields of stereochemically pure alcohols (designated *α*-isomethadols), while reduction of *dl*-, *l*-, and *d*-isomethadone with sodium and propanol has given predominantly the other possible diastereomeric alcohols (*β*) along with 15–20% yields of the *α*-isomers.

These alcohols and their O-acetyl derivatives have been evaluated as analgesic agents.

BETHESDA 14, MD.

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