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STRUCTURES RELATED TO MORPHINE. IV.[1] *m*-SUBSTITUTED PHENYLCYCLOHEXANE DERIVATIVES

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The introduction of a hydroxyl group into the 3-position of N-methylmorphinan to give racemorphan (Dromoran) (2–5) results in a ten- to twenty-fold increase in analgesic activity. We wish to report the chemistry relevant to an identical modification of the structures of 1-(2-dimethylaminoethyl)-1-phenylcyclohexane (6) and 2-methyl-5-phenylmorphan (7) (two compounds with about one-half the effectiveness of meperidine) and the effect of such a change on analgesic potency and toxicity.

The schemes employed in the synthesis of 1-(2-dimethylaminoethyl)-1-(*m*-methoxyphenyl)cyclohexane (III-a) and 5-(*m*-methoxyphenyl)-2-methylmorphan (IV-a) were the same as those used previously (6, 7) in the deoxy series. 2-(*m*-Methoxyphenyl)cyclohexanone (I), when alkylated with 2-chloro-N,N-dimethylethylamine in the presence of sodamide, like 2-phenylcyclohexanone gave a 20–25% yield of the desired C-alkyl, 2-(2-dimethylaminoethyl)-2-(*m*-methoxyphenyl)cyclohexanone (II) and at least a 60% yield of enol ether from which the I was readily regenerated in a relatively pure state. Wolff-Kishner reduction of II yielded III-a (80%) while bromination of II hydrobromide gave 6-bromo-2-(2-dimethylaminoethyl)-2-(*m*-methoxyphenyl)cyclohexanone hydrobromide, the base of which underwent ring closure at room temperature giving 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan methobromide. Dry distillation of this methobromide followed by Wolff-Kishner reduction of the distillate, (purified through the hydrochloride) produced IV-a. Demethylation of both III-a and IV-a to the phenolic compounds III-b and IV-b was effected in 80% yield with 48% hydrobromic acid and the acetyl derivatives III-c and IV-c were prepared by treating the corresponding phenolic compounds with acetic anhydride in pyridine. As was true in the deoxy series (7) only one of the two possible diastereoisomers of IV was encountered.[2]

As indicated in Table I the introduction of a methoxyl group into the *m*-position of 1-(2-dimethylaminoethyl)-1-phenylcyclohexane does not have a pronounced effect on either analgesic effectiveness or toxicity while a hydroxyl or acetoxyl decreases both, three to four fold. Likewise a methoxyl group introduced into the *m*-position of 2-methyl-5-phenylmorphan does not materially alter activity or toxicity. However, similar substitution of either a hydroxyl or acetoxyl radical not only increases activity eight to ten fold (subcutaneous administration) but *reduces* toxicity more than fifty per cent. Thus, 5-(*m*-hydroxyphenyl)-2-methylmorphan (IV-b) and its O-acetyl derivative (IV-c) are as potent as morphine, with the Straub reaction not appearing in mice until

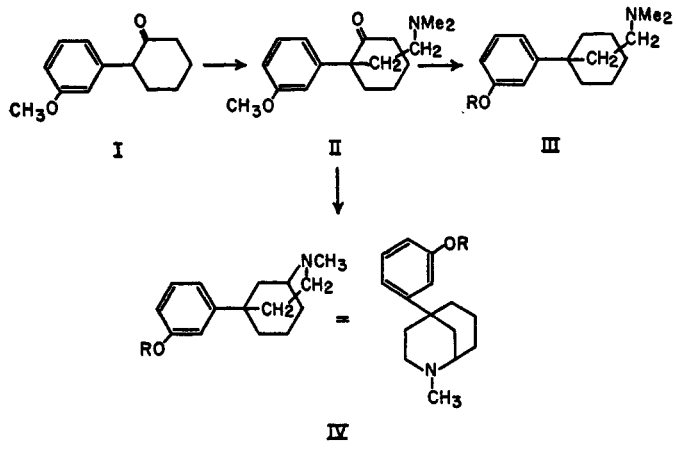
[1] *Cf.* reference 1 for the previous paper.

[2] A *trans* ring-closure of II is highly improbable on steric grounds.

TABLE I

PHARMACOLOGICAL RESULTS (2)

Compound	Toxicity LD_{50}, Mice		Analgesic Effect ED_{50}, Mice	
	Orally	Subcutaneously	Orally	Subcutaneously
Morphine sulfate	1229	700	3.9	2.1
dl-Methadone	95	44	9	1.6
Meperidine	181	154	55	10
1-(2-Dimethylaminoethyl)-1-phenyl-cyclohexane (6)		270		25
m-Methoxy (III-a)		168		39
m-Hydroxy (III-b)		1150		89
m-Acetoxy (III-c)		>600		83
2-Methyl-5-phenylmorphan (7)		43		21
m-Methoxy (IV-a)	—	74	53	28
m-Hydroxy (IV-b)	348	95	59	2.7
m-Acetoxy (IV-c)	471	90	58	2.1



a) R = CH_3; b) R = H; c) R = $COCH_3$

ten times the analgesic dose of IV-b is reached. Furthermore, the oral effectiveness of IV-b and IV-c is comparable to that of meperidine; their oral toxicity is one-half to one-third that of meperidine.

It should be borne in mind that the synthetic compound IV-b is a racemate while morphine is levorotatory and meperidine optically inactive. If the usual pattern is followed of most or all of the analgesic activity being resident in the *levo*-antipode (methadone, isomethadone, racemorphan) (3) the *levo*-isomer of IV-b should be about twice as effective as the racemate and therefore *more* potent than morphine. The racemate IV-b has been selected for addiction studies in monkeys.

EXPERIMENTAL

All compounds except morphine were tested either as hydrochlorides or hydrobromides. The method of determining analgesic effect was that described by Eddy, *et al.* (8). All doses are in mg./kg. as administered and are the result of probit analysis of the experimental data.

Melting points were taken in a Hershberg apparatus using Bureau-of-Standards-calibrated, total-immersion thermometers. Microanalyses are by the Institute's service analytical laboratory under the direction of Dr. William C. Alford.

2-(m-Methoxyphenyl)cyclohexanone (I). The reaction sequence described by Wildman and Wildman (9) was used. Inasmuch as their procedure for the Nef reaction used in this method had to be modified for adaptation to moderate-sized preparations, details are given for this reaction and the subsequent hydrogenation. A mixture of 14 g. of 2-(*m*-methoxyphenyl)-1-nitro-Δ^1-cyclohexene (9),[3] 105 ml. of 95% ethanol, and 90 ml. of alcoholic sodium ethoxide (containing 3 g. of sodium) was stirred under nitrogen for one hour and added during 40 minutes to 240 ml. of water, 180 ml. of 95% ethanol, and 72 ml. of conc'd HCl (−5° to 0°, stirring, nitrogen atmosphere). The mixture was stirred for another hour at 0° and for 30 minutes without cooling, poured into about 1200 ml. of ice-salt-water, and extracted quickly with three portions of ether (total volume of extracts *ca.* 150 ml.). The ether was washed with cold, saturated sodium bicarbonate, then cold water, dried over sodium sulfate at 5°, and evaporated *in vacuo* under nitrogen. The residue (12.2 g.), 25 ml. of methanol, and 3.0 g. of 5% palladium-barium sulfate, absorbed 0.9 molecular equivalent of hydrogen in 40 minutes when reaction ceased. The mixture was filtered through Super-Cel (suction) and evaporated to dryness *in vacuo* under nitrogen. Distillation of the residue at 0.02 mm. (air-bath temperature 135–145°) gave 10.1 g. (83% based on nitro compound) of I, n_D^{20} 1.5497; lit. (9), 1.5496. This procedure appears to be applicable to the preparation of I in almost any amount desired.

2-(2-Dimethylaminoethyl)-2-(m-methoxyphenyl)cyclohexanone (II) *hydrochloride.* To a stirred, refluxing mixture of 1.7 g. of sodamide and 40 ml. of benzene (dried over sodium) was added during 5–10 minutes 8.8 g. of I in 60 ml. of benzene. The mixture was refluxed 30–60 minutes and treated, during 30–45 minutes, with 4.8 g. of 2-chloro-N,N-dimethylethylamine in 60 ml. of benzene. After 20 hours of refluxing and stirring, the mixture was extracted twice with water, then twice with dilute HCl in excess. The acid extracts were warmed slightly (to hydrolyze remaining enol ether), washed with ether, basified with NH_4OH, and the liberated base was dried in ether. Evaporation left 4.6 g. of oil which was acidified in ether with dry HCl. The resultant hydrochloride partially crystallized overnight at 5° and after decantation and ether washing was triturated with 10 ml. of acetone to give, after cooling at 0°, 2.5 g. of II hydrochloride, m.p. 165–166°. The filtrate was evaporated to dryness *in vacuo*, and the residual, oily hydrochloride was converted to the base which was distilled at 0.05 mm. (bath temperature 130–140°). From the distillate was obtained as described above an additional 0.7 g. of hydrochloride; total yield 3.2 g. (24%); irregular prisms from acetone-ether, m.p. 165.5–166.5°.

Anal. Calc'd for $C_{17}H_{26}ClNO_2$: C, 65.5; H, 8.4.
Found: C, 65.6; H, 8.5.

The combined benzene and ether fractions above gave 5.2 g. of evaporatively distilled I, n_D^{20} 1.5494.

1-(2-Dimethylaminoethyl)-1-(m-methoxyphenyl)cyclohexane (III-a) *hydrobromide.* A mixture of 0.5 g. of II hydrochloride, 0.5 ml. of 95% hydrazine, 0.5 g. of KOH, and 5 ml. of triethylene glycol, heated during six hours from 180–210°, cooled, treated with water and ether, and the ether layer dried and acidified with 32% HBr-acetic acid gave 0.5 g. (90%) of III-a hydrobromide, m.p. 150–160°. It crystallized from acetone in prisms of m.p. 167–168.5°. For analysis it was dried *in vacuo* at 80°.

[3] The nitro-styrene precursor of this compound was prepared by the procedure of Shoesmith and Connor (10) except that the reaction mixture in ice-water was added to the acid for dehydration. Otherwise we obtained very low yields.

Anal. Calc'd for $C_{17}H_{28}BrNO$: C, 59.6; H, 8.2.
Found: C, 59.6; H, 8.2.

1-(2-Dimethylaminoethyl)-1-(m-hydroxyphenyl)cyclohexane (III-b) *hydrobromide.* Refluxing 0.6 g. of III-a hydrobromide and 2.5 ml. of 48% HBr for 30 minutes gave, after evaporation to dryness *in vacuo*[4] and crystallization of the sirup from acetone-ether, 0.5 g. (87%) of III-b hydrobromide, m.p. 178–179°; needles from alcohol-acetone-ether.

Anal. Calc'd for $C_{16}H_{26}BrNO$: C, 58.5; H, 8.0.
Found: C, 58.7; H, 7.9.

The *hydrochloride* (from alcohol-acetone-ether) melted at 191.5–193°; needles.

Anal. Calc'd for $C_{16}H_{26}ClNO$: C, 67.8; H, 9.2.
Found: C, 67.5; H, 9.3.

1-(m-Acetoxyphenyl)-1-(2-dimethylaminoethyl)cyclohexane (III-c) *hydrobromide.* Acetic anhydride (0.5 ml.), 0.5 g. of III-b hydrobromide, and 1.0 ml. of dry pyridine, left at 25° for one hour, diluted to incipient turbidity with ether, and kept at 5° overnight, gave 0.55 g. of III-c hydrobromide, m.p. 138–138.5°; needles from acetone-ether.

Anal. Calc'd for $C_{18}H_{28}BrNO_2$: C, 58.4; H, 7.6.
Found: C, 58.1; H, 7.5.

6-Bromo-2-(2-dimethylaminoethyl)-2-(m-methoxyphenyl)cyclohexanone hydrobromide. The hydrochloride of II (12 g.) was converted to the base which was dried in ether and the solution was acidified with 32% HBr-acetic acid to give 12.4 g. of crystalline hydrobromide. This in 140 ml. of refluxing acetic acid (stirring) was treated during 12–14 minutes with 6.0 g. of bromine in 50 ml. of acetic acid. The resultant solution, cooled to about 40°, was diluted to 500 ml. with dry ether (stirring) and kept at −6° overnight to give 14.5 g. of solid, m.p. 180–182°. Further ether dilution of the filtrate gave an additional 0.5 g.; total yield 90%. It crystallized from acetone in needles of m.p. 184–185°.

Anal. Calc'd for $C_{17}H_{25}Br_2NO_2$: C, 46.9; H, 5.8.
Found: C, 47.1; H, 5.7.

5-(m-Methoxyphenyl)-2-methyl-9-oxomorphan methobromide. To 14.5 g. of the bromo ketone hydrobromide above and 35 ml. of water was added dropwise (stirring) 4 ml. of conc'd NH_4OH. After 1–2 hours of stirring the crystalline mass was kept at −6° overnight, filtered, and the precipitate washed with a little ice-water to give 10.3 g. (90%) of methobromide; thick plates from methanol, m.p. 249–250° (dec.).

Anal. Calc'd for $C_{17}H_{24}BrNO_2$: C, 57.6; H, 6.8.
Found: C, 57.9; H, 6.8.

5-(m-Methoxyphenyl)-2-methyl-9-oxomorphan hydrochloride. Dry distillation (210–225°, 0.5 mm.) of 10.2 g. of the above methobromide gave 7.2 g. of viscous distillate which, in 70 ml. of acetone, was acidified with dry HCl to give, after cooling to −7°, 7.4 g. (89%) of hydrochloride of m.p. 203–205° (dec.); plates from acetone.

Anal. Calc'd for $C_{16}H_{22}ClNO_2$: C, 65.0; H, 7.5.
Found: C, 64.7; H, 7.3.

5-(m-Methoxyphenyl)-2-methylmorphan (IV-a) *hydrobromide.* Triethylene glycol (50 ml.), 7 ml. of 95% hydrazine, 7 g. of KOH, and 7.7 g. of the preceding compound, kept at 170–175° (bath temperature) for 5.5 hours then heated to 190° during 0.5 hour, gave on isolation as described for III-a, 7.7 g. (90%) of IV-a hydrobromide, m.p. 160–164°. It crystallized from acetone in oblong plates, m.p. 165–167°.

Anal. Calc'd for $C_{16}H_{24}BrNO$: C, 58.9; H, 7.4.
Found: C, 59.0; H, 7.5.

5-(m-Hydroxyphenyl)-2-methylmorphan (IV-b) *hydrobromide.* Essentially as described in the preparation of III-b, 7.7 g. of IV-a hydrobromide and 30 ml. of 48% HBr gave 5.8 g. (80%) of IV-b hydrobromide; prisms from absolute alcohol (Norit), m.p. 171–172°.

Anal. Calc'd for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1.
Found: C, 57.5; H, 7.4.

[4] Repeating the evaporation 2–3 times with acetone proved advantageous.

The *base*, prepared from the hydrobromide with dilute NH_4OH, gave crusts from methanol-water, m.p. 156–157.5°.

Anal. Calc'd for $C_{15}H_{21}NO$: C, 77.9; H, 9.2.
Found: C, 77.8; H, 9.2.

5-(m-Acetoxyphenyl)-2-methylmorphan (IV-c) *hydrobromide.* The hydrobromide of IV-b (1.0 g.), 1.0 ml. of acetic anhydride, and 2.0 ml. of dry pyridine, left at 25° for one hour and diluted to incipient turbidity with ether, gave 1.1 g. (100%) of IV-c hydrobromide, m.p. 160–162°; small prisms from acetone-ether, m.p. 162–163.5°.

Anal. Calc'd for $C_{17}H_{24}BrNO_2$: C, 57.6; H, 6.8.
Found: C, 57.9; H, 7.1.

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SUMMARY

The synthesis of 1-(2-dimethylaminoethyl)-1-(*m*-hydroxyphenyl)cyclohexane (III-b) and of 5-(*m*-hydroxyphenyl)-2-methylmorphan (IVb) from 2-(*m*-methoxyphenyl)cyclohexanone is described.

Administered subcutaneously in mice III-b is only about one-fourth as effective an analgesic agent as the deoxy analog. On the other hand the racemate IV-b is eight times as potent as the parent deoxy compound and is comparable to morphine by a subcutaneous route of administration.

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REFERENCES

(1) MAY AND MURPHY, *J. Org. Chem.*, **20**, 257 (1955).
(2) EDDY, Private Communication.
(3) BECKETT, *J. Pharm. and Pharmacol.*, **4**, 425 (1952).
(4) GREWE, *Z. angew. Chem.*, **59**, 194 (1947).
(5) SCHNIDER AND GRÜSSNER, *Helv. Chim. Acta*, **32**, 821 (1949).
(6) MURPHY AND MAY, *J. Org. Chem.*, **19**, 615 (1954).
(7) MAY AND MURPHY, *J. Org. Chem.*, **19**, 618 (1954).
(8) (a) EDDY, TOUCHBERRY, AND LIEBERMANN, *J. Pharmacol. Exptl. Therap.*, **101**, 121 (1950); (b) EDDY AND LEIMBACH, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).
(9) WILDMAN AND WILDMAN, *J. Org. Chem.*, **17**, 581 (1952).
(10) SHOESMITH AND CONNOR, *J. Chem. Soc.*, 2230 (1927).