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STRUCTURES RELATED TO MORPHINE. III. SYNTHESIS OF AN ANALOG OF N-METHYLMORPHINAN

EVERETTE L. MAY AND JAMES G. MURPHY

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The synthesis (1) and subsequent pharmacological evaluation (2, 3) of N-methylmorphinan (XV) have shown that morphine may be stripped of its peripheral groups with retention of pronounced morphine-like action. Moreover, the emergence of dromoran (XVI) (4, 5) as a more potent, longer-acting analgesic (6) than morphine further demonstrated that of the functional groups (other than the tertiary amino) present in morphine only the phenolic hydroxyl is necessary for the production of profound analgesia. To determine whether still more of the morphine molecule might be eliminated without adversely affecting activity and with perhaps beneficial results regarding addiction liability and other side-reactions we have projected the synthesis of analogs of XV and XVI in which a methyl group at the site of the quaternary carbon would replace the entire third ring of the phenanthrene skeleton. The present report deals with the first phase of this project, namely, the synthesis of 2,5-dimethyl-6:7-benzmorphan (VIII)[1] a model compound corresponding to XV.

The shortest and most obvious approach to VIII appeared to be one utilizing β-tetralone as a starting point. Such a synthesis was investigated briefly by Barltrop (7) who obtained in very low over-all yield, the ethobromide of 2-ethyl-5-methyl-9-oxo-6:7-benzmorphan. In the same general scheme employed by Barltrop, we have alkylated 3,4-dihydro-1-methyl-2(1*H*)-naphthalenone (XII) with 2-chloro-N,N-dimethylethylamine, brominated the resultant XIII, and cyclized the bromo ketone (XIV). Dry distillation of the methobromide of XI thus produced, yielded the morphan derivative (XI) which was converted to VIII by the Wolff-Kishner reduction, Huang-Minlon modification.

As noted in Figure 1 the yields in the reaction sequence just described are generally low. This route to VIII was therefore abandoned, as a preparative method, in favor of a longer but what proved to be a more satisfactory one involving hydratroponitrile (I) as the starting material. Proceeding as outlined in Figure 1, I was alkylated with 2-chloro-N,N-dimethylethylamine to give the amino nitrile (II) which was reduced to the aldehyde (III) with lithium aluminum hydride. The reaction of III and methyl cyanoacetate (Knoevenagel) took place readily, and double-bond hydrogenation of the product (as the hydrochloride) was effected with platinum oxide. Acid hydrolysis-decarboxylation of the saturated nitrile-ester resulting gave the amino acid (VI) which was cyclized with polyphosphoric acid to the α-tetralone derivative (V). It was unnecessary to purify any of the intermediates from III to V; the over-all yield was 61%. Having fashioned the tetrahydronaphthalene portion of VIII with an oxo group

[1] The nomenclature proposed by Barltrop (7) has been used in naming this and analogous compounds.

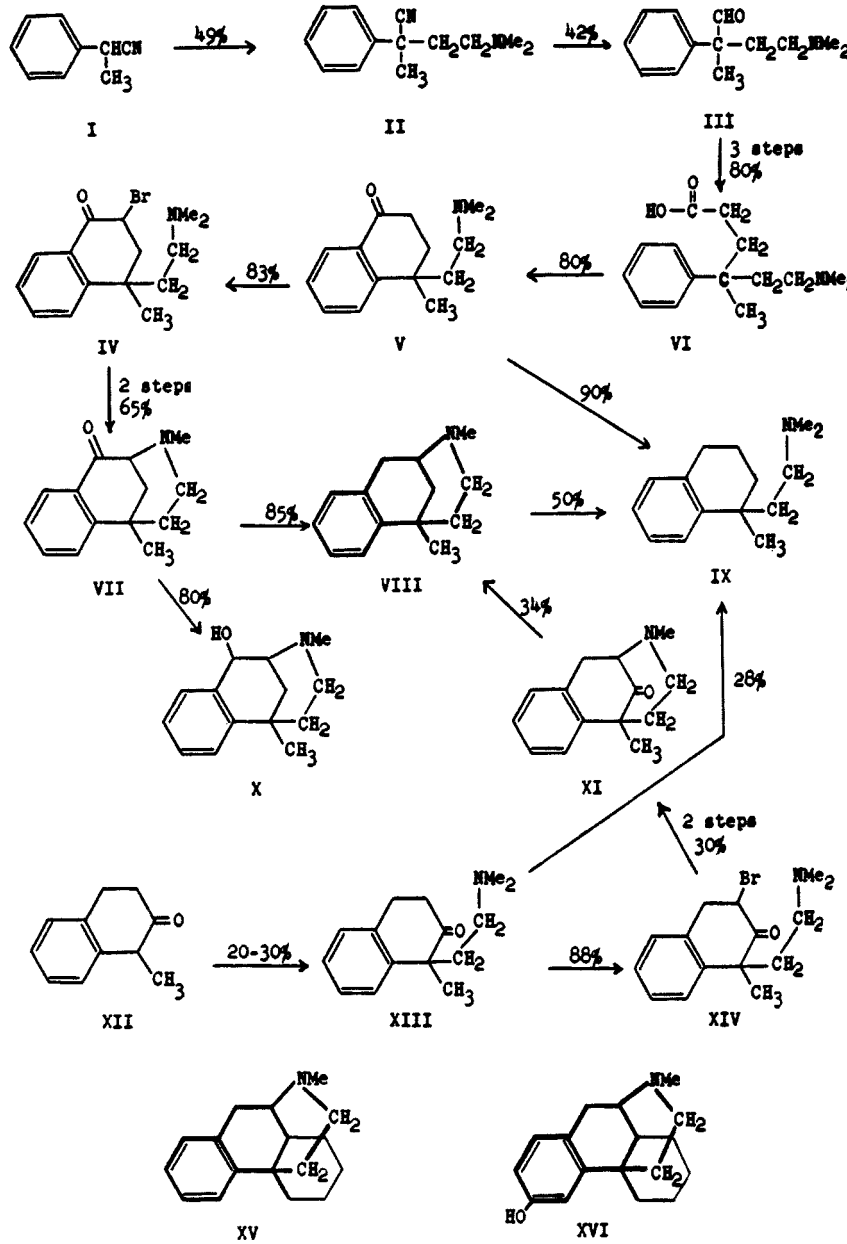

FIG. 1

in the 1-position and with the requisite basic side chain attached to the quaternary carbon atom, it was a relatively simple matter to form the N-methylpiperidine moiety by brominating V and allowing the free base of the thus-formed IV to cyclize to the methobromide of VII. Dry distillation (*in vacuo*) of this methobromide caused methyl bromide elimination to yield VII which, subjected

to Wolff-Kishner reduction, gave the N-methylmorphinan analog (VIII). An attempt to convert VII to VIII by hydrogenolysis using palladium-charcoal, acetic acid, and a catalytic amount of perchloric acid yielded only the alcohol (X) which also resulted from VII by platinum-oxide hydrogenation in methanol. In each instance only one and the same diastereoisomer was detected.

That VIII could be synthesized from either XII or I by the two schemes outlined, afforded unambiguous proof of *its* structure as well as that of XIII. Additional evidence that the 2-dimethylaminoethylation of XII had occurred at the 1-position arose from the fact that Wolff-Kishner reduction of XIII led to IX, a product obtained either by similar reduction of V or by the Hofmann degradation of VIII followed by hydrogenation of the olefin resulting. Furthermore, XIII could be converted to a benzylidene derivative whose ultraviolet spectrum accommodated a $C_6H_5C{=}C{-}C{=}O$ type of structure.

Compounds II, III, V, VII, VIII, IX, X and its O-acetyl derivative (Figure 1) were screened in mice with respect to analgesic potency and toxicity (2). Only VIII, IX, X and its O-acetyl derivative exhibited significant activity. The first was about half as active as XV (and demerol) although somewhat less toxic than either, while IX, X and its O-acetyl derivative were about one-third as effective and only one-half to one-fourth as toxic as XV and demerol when administered subcutaneously. Orally, VIII was one-half as active as subcutaneously but *more* effective than either XV or demerol by an oral route of administration.[2] Studies with *m*-phenolic compounds are underway.

EXPERIMENTAL

Melting points were taken in a Hershberg apparatus with Bureau of Standards calibrated, total-immersion, Anschütz thermometers. Microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

γ-Dimethylamino-α-methyl-α-phenylbutyronitrile (II) *nitrate.* To 14 g. (0.36 mole) of sodamide in 175 ml. of refluxing benzene was added (stirring) during *ca.* 5 minutes, 43 g. (0.33 mole) of I (8) in 75 ml. of benzene, then (after 30 minutes) 38.5 g. (0.36 mole) of 2-chloro-N,N-dimethylethylamine in 150 ml. of benzene during 30 minutes. The mixture was refluxed and stirred for an additional 8 hours, washed twice with water, and shaken with 2 portions of dilute HCl in slight excess. The combined acid extracts were basified (NaOH) to give 48 g. (after drying in ether) of oily base which was acidified with 21 ml. of conc'd HNO_3 in 25 ml. of ice-water; yield of nitrate, 42.5 g. (49%), m.p. 148–150°. Six grams of neutral material was recovered from the benzene. The nitrate crystallized from water in prisms, m.p. 149.5–150.5°.

Anal. Calc'd for $C_{13}H_{19}N_3O_3$: C, 58.9; H, 7.2; N, 15.8.
Found: C, 59.0; H, 7.0; N, 15.6.

The *hydrochloride* crystallized from methanol-ether in needles, m.p. 229–230° (dec.).
Anal. Calc'd for $C_{13}H_{19}ClN_2$: N, 11.7. Found: N, 11.9.

γ-Dimethylamino-α-methyl-α-phenylbutyraldehyde (III) *sulfate.* To 16.5 g. (0.08 mole) of II (base) in 75 ml. of dry ether was added with stirring during one hour, 14.0 ml. (0.09 equiv.) of 1.6 *M* ethereal lithium aluminum hydride. After stirring 3 hours longer and refluxing for 0.5 hour, 10 ml. of water was added gradually. The ether was decanted and extracted thrice with dilute HCl. The acid extracts were basified (NaOH), extracted with

[2] We are indebted to Dr. Nathan B. Eddy and staff for these results.

ether, and the ethereal extracts dried (Na_2SO_4) and acidified (ice-cooling) to Congo Red with *ca.* 6 ml. of conc'd H_2SO_4. After keeping at 5° overnight the ether was poured from a viscous sirup which was washed thrice with ether by decantation and dissolved in 30 ml. of warm propanol. Addition of 10–12 ml. of ether, gradual cooling to 3°, and keeping at 3° for 2–3 days gave 11.1 g. (42%) of the acid sulfate monohydrate of III; needles from acetone ether, m.p. 88.5–90°.

Anal. Calc'd for $C_{13}H_{21}NO_5S \cdot H_2O$: C, 48.6; H, 7.2.
Found: C, 48.6; H, 7.0.

The *picrate* crystallized from alcohol in yellow needles of m.p. 145–146.5°.

Anal. Calc'd for $C_{19}H_{22}N_4O_8$: C, 52.5; H, 5.1; N, 12.9.
Found: C, 52.4; H, 5.0; N, 12.8.

ε-Dimethylamino-γ-methyl-γ-phenylcaproic acid (VI) *hydrochloride.* The base III (5.4 g., from 8.0 g. of sulfate), 3.5 g. of methyl cyanoacetate, 1.5 g. of ammonium acetate, 1.6 ml. of acetic acid, and 12 ml. of benzene were refluxed vigorously (the water produced being collected in a Dean-Stark trap) for 50 minutes, diluted to 100 ml. with ether, acidified with dry HCl, and kept at 5° overnight. Solvents were decanted, the residue was washed twice with ether dissolved in 30 ml. of water and 30 ml. of alcohol, and the solution hydrogenated (0.3 g. of platinum oxide). After absorption of 1.2–1.3 moles of hydrogen, the rate of uptake was only about one-fourth the maximum rate, and the reaction was interrupted. The mixture was treated with Norit, filtered through Super-Cel, freed of alcohol *in vacuo* and the resultant solution refluxed for 4 hours with 30 ml. of conc'd HCl. Evaporation to dryness gave a residue which, digested with acetone containing a little alcohol, gave 1.5 g. of ammonium chloride. The filtrate, evaporated to dryness, yielded 8.7 g. of a sirupy hydrochloride which was subjected to ring-closure as described below. The VI hydrochloride could be obtained crystalline in low yield by extracting the sirup with two 50-ml. portions of boiling acetone, concentrating the combined extracts to 60 ml. and cooling; yield 1.4 g., m.p. 155–160°. A small sample was converted to the picrate (alcoholic picric acid); yellow prisms. Treatment of the picrate in acetone-ether with dry HCl gave again the hydrochloride which crystallized from acetone-ethanol-ether in small ellipsoids, which melted at 169–170° to a froth which was clear at 175°.

Anal. Calc'd for $C_{15}H_{24}ClNO_2$: C, 63.0; H, 8.5.
Found: C, 62.9; H, 8.7.

3,4-Dihydro-4-(2-dimethylaminoethyl)-4-methyl-1(2H)-naphthalenone (V) *hydrochloride.* The 8.7 g. of sirupy VI hydrochloride above and 80 g. of polyphosphoric acid were kept on the steam-bath for 3 hours, cooled, dissolved in ice-water, and the solution added slowly to 120 g. of KOH in ice-water. The liberated V was dried in ether, evaporatively distilled at 110–120° (0.5 mm.), and converted to the hydrochloride (acetone-dry HCl); yield 4.3 g. (over-all from III, 61%), m.p. 204–207°; plates from acetone, m.p. 206.5–208°.

Anal. Calc'd for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.3.
Found: C, 67.4; H, 8.3.

The *picrate* crystallized from alcohol in yellow rods of m.p. 160.5–162°.

Anal. Calc'd for $C_{21}H_{24}N_4O_8$: C, 54.8; H, 5.3.
Found: C, 54.9; H, 5.3.

2-Bromo-3,4-dihydro-4-(2-dimethylaminoethyl)-4-methyl-1(2H)-naphthalenone (IV) *hydrobromide.* The hydrochloride (2.7 g., 0.01 mole) of V was converted to the base (dilute NaOH) which, after drying in ether, was converted to the crystalline hydrobromide (33% HBr-acetic acid). This hydrobromide in 15 ml. of refluxing acetic acid was treated (stirring) during 20–25 minutes, with 1.6 g. (0.53 ml.) of bromine in 5 ml. of acetic acid. The solution was boiled without reflux for 5 minutes, and ether was added to incipient turbidity. Left at 3° overnight, 3.2 g. (83%) of hydrobromide, m.p. 179–181° (dec.), separated. It crystallized from either acetone-alcohol-ether (charcoal) or absolute ethanol in needles of m.p. 182–183°.

Anal. Calc'd for $C_{15}H_{21}Br_2NO$: C, 46.1; H, 5.4.
Found: C, 46.1; H, 5.5.

2,5-Dimethyl-8-oxo-6:7-benzmorphan (VII) *methobromide.*[1] To a magnetically stirred mixture of 3.4 g. of IV hydrobromide and 12 ml. of water was added dropwise 1.0 ml. of conc'd NH_4OH. The mixture was stirred for one hour and evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of boiling methanol to give, after cooling, finally at 3°, 2.0 g. (74%) of the methobromide of VI, m.p. 278–280° (dec.); flakes.

Anal. Calc'd for $C_{15}H_{20}BrNO$: C, 58.1; H, 6.5.
Found: C, 57.9; H, 6.5.

The *hydrochloride* of VII was prepared by slow distillation of 2 g. of the methobromide (air-bath temperature 230–240°, 0.5 mm.) and acidification of the resultant base in ether with dry HCl; yield 1.5 g. (90%), prisms from acetone-ether, m.p. 202–205° (dec).

Anal. Calc'd for $C_{14}H_{18}ClNO$: C, 66.8; H, 7.2.
Found: C, 66.5; H, 7.2.

2,5-Dimethyl-6:7-benzmorphan (VIII) *hydrochloride.* A mixture of 0.5 g. of VII hydrochloride, 0.5 ml. of 95% hydrazine, 0.5 g. of KOH, and 5 ml. of triethylene glycol was kept at 170–180° for 2 hours and at 180–190° for 3 hours (air condenser). Water and ether were added to the cooled mixture. The ether was dried and distilled to give an oil which, evaporatively distilled at 110–120° (0.5 mm.), yielded 0.4 g. of VIII. It was converted to the hydrochloride (ether-dry HCl) which crystallized from a small amount of acetone in prisms of m.p. 194–196°; yield 0.4 g. (85%). Occasionally a lower-melting form m.p. *ca.* 95° was encountered if acetone-ether was used. Digestion with a little acetone quickly converted it to the more stable modification.

Anal. Calc'd for $C_{14}H_{20}ClN$: C, 70.7; H, 8.5.
Found: C, 70.7; H, 8.5.

The *picrate* crystallized from alcohol in small yellow prisms of m.p. 181–183°.

Anal. Calc'd for $C_{20}H_{22}N_4O_7$: C, 55.8; H, 5.2.
Found: C, 55.6; H, 5.2.

2,5-Dimethyl-8-hydroxy-6:7-benzmorphan (X) *hydrochloride.* A mixture of 0.3 g. of VII hydrochloride, 50 mg. of platinum oxide, and 5 ml. of methanol absorbed one mole of hydrogen in 15 minutes. The filtered solution was concentrated and diluted with acetone-ether to give 0.25 g. (82%) of X hydrochloride; needles from acetone-alcohol-ether, m.p. 178–180° (dec.). It was dried *in vacuo* at 57° for analysis.

Anal. Calc'd for $C_{14}H_{20}ClNO$: C, 66.3; H, 7.9.
Found: C, 66.4; H, 7.8.

The O-acetyl derivative (hydrochloride) of IX, prepared with acetic anhydride and pyridine at room temperature crystallized from alcohol-acetone in plates of m.p. 257–259°.

Anal. Calc'd for $C_{16}H_{22}ClNO_2$: C, 65.0; H, 7.5.
Found: C, 64.8; H, 7.7.

In an attempt to convert VII to VIII using 5% palladium-charcoal, acetic acid, and a trace of perchloric acid, the same alcohol hydrochloride was obtained in 63% yield.

1-(2-Dimethylaminoethyl)-1-methyl-1,2,3,4-tetrahydronaphthalene (IX) *hydrochloride.* (a) *From V.* Reduction of V as described in the preparation of VIII from VII gave the IX hydrochloride in a yield of 90%; flakes from acetone, m.p. 211–212°.

Anal. Calc'd for $C_{15}H_{24}ClN$: C, 71.0; H, 9.5.
Found: C, 70.9; H, 9.3.

The *picrate* crystallized from 70% ethanol in yellow needles, m.p. 113–115°.

Anal. Calc'd for $C_{21}H_{26}N_4O_7$: C, 56.5; H, 5.9.
Found: C, 56.4; H, 5.6.

(b) *From XIII.* A mixture of 0.3 g. of XIII hydrobromide (see below), 0.3 ml. of 95% hydrazine, 0.3 g. of KOH, and 3 ml. of triethylene glycol was heated during 2 hours to 220° (air condenser) where it was kept for an additional 4 hours. The distilled base, isolated as described for VIII, was converted to an amorphous hydrochloride mixture (dry HCl, acetone, ether). Fractional crystallization of this from acetone-ether gave first a few milligrams of a hydrochloride of m.p. above 220°, then 30 mg. of crude IX hydrochloride, m.p. 205–209° and finally, on further ether dilution, 40 mg. of flakes (pure IX hydrochloride),

m.p. 209–211° alone or in mixture with that prepared from V; total yield 28%. A small specimen of the flakes gave a picrate of m.p. 113–115°, indistinguishable from that prepared from V.

(c) *From VIII.* The methiodide of VIII (0.2 g. prepared from VIII, methyl iodide, methanol and ether) and 5 ml. of 10% NaOH were kept on the steam-bath for one hour. The resultant oil was dried in ether and hydrogenated in methanol with 5 mg. of platinum oxide. The resultant hydrochloride (from acetone-ether, dry HCl) weighed 0.1 g. (67%) and melted at 209–212°. It was identical with the IX prepared from V (comparison of hydrochlorides and picrates).

3,4-Dihydro-1-(2-dimethylaminoethyl)-1-methyl-2(1H)-naphthalenone (XIII) *perchlorate.* The reaction of 4.9 g. of XII (9)[3] with 3.4 g. of 2-chloro-N,N-dimethylethylamine (1.4 g. of sodamide) was carried out as described in the preparation of II (reaction time 22 hours) to give 3.9 g. of impure XIII and 1.5 g. of neutral material, mainly XII. To the 3.9 g. was added slowly (ice-cooling) 2.0 ml. of 60% $HClO_4$. Addition of acetone-ether gave, after cooling at 5°, 0.7 g. (5%) of a perchlorate of m.p. 255–256° (dec.) of the formula $C_{18}H_{28}N_2O \cdot 2HClO_4$.[4] The hydrochloride salt (m.p. 245–247°, dec.) gave analyses also indicative of a formula $C_{18}H_{28}N_2O \cdot 2HCl \cdot H_2O$ and exhibited only phenyl group absorption in the ultraviolet. Ether dilution of the filtrate to incipient turbidity gave gradually, prisms. After about three days at 3° the yield of perchlorate was 2.1–3.1 g. (21–30%), m.p. 139–142°. It crystallized from water or preferably from absolute ethanol containing a little ether, in prisms, m.p. 143–144.5°. For analysis it was dried *in vacuo* at 57°.

Anal. Calc'd for $C_{15}H_{22}ClNO_5$: C, 54.3; H, 6.7.
Found: C, 54.3; H, 6.7.

The *benzal derivative (perchlorate)* was prepared in 33% yield from 0.2 g. of XIII, 0.2 ml. of benzaldehyde, 0.7 ml. of 10% NaOH, and 1.5 ml. of alcohol (25°, 28 hours). It crystallized from acetone-ether in plates of m.p. 167.5–169°. Its U.V. spectrum was typical of a PhCH=CH—CO=system.

Anal. Calc'd for $C_{22}H_{26}ClNO_5$: C, 62.9; H, 6.2.
Found: C, 62.9; H, 6.3.

3-Bromo-3,4-dihydro-1-(2-dimethylaminoethyl)-1-methyl-2(1H)-naphthalenone (XIV) *hydrobromide.* As described in the bromination of V the hydrobromide (1.7 g.) of XIII and 0.78 g. (0.9 mole) of bromine yielded, after addition of 50 ml. of ether to the reaction mixture and cooling (5°), 1.8 g. (88%) of solid hydrobromide, m.p. 132–140°. Two recrystallizations from acetone made the m.p. constant at 147–148.5°, small plates.

Anal. Calc'd for $C_{15}H_{21}Br_2NO$: C, 46.1; H, 5.4.
Found: C, 46.1; H, 5.3.

2,5-Dimethyl-9-oxo-6:7-benzmorphan (XI) *methobromide.* The hydrobromide (1.5 g., m.p. 132–140°) of XIV was cyclized as described for IV. The solid residue was digested with methanol (2 ml.)-acetone (25 ml.) to give 0.25 g. of NH_4Br. Evaporation of the filtrate to dryness and crystallization of the sirup from 10 ml. of absolute ethanol gave, after cooling, finally at 3°, 0.8 g. (66%) of solid, m.p. 186–191°. It crystallized from methanol in plates of m.p. 192–194°.

Anal. Calc'd for $C_{15}H_{20}BrNO$: C, 58.1; H, 6.5.
Found: C, 58.1; H, 6.3.

Transformation of XI methobromide to VIII. The methobromide (0.2 g., m.p. 186–191°) of XI in a distillation bulb under 0.5 mm. pressure was placed into a 250° air-bath. During 5–10 minutes an oil distilled. It was converted to the hydrochloride (dry HCl-ether); yield 70 mg. (47%), m.p. *ca.* 220° (dec.). Reduction of this hydrochloride (0.2 g.) as described for the reduction of XIII to IX gave, from acetone, 65 mg. (34%) of the hydrochloride of VIII m.p. 192–194.5° alone or in mixture with that prepared from VII. Furthermore, the picrate

[3] For a convenient preparation of β-tetralone see reference 10.

[4] This appears to be 1,1-*bis*-(2-dimethylaminoethyl)-3,4-dihydro-2(1H)-naphthalenone and indicates that the XII used was contaminated with a little β-tetralone.

prepared from this hydrochloride melted at 181–183° (after a recrystallization from alcohol) and was identical with that prepared from the VIII hydrochloride which was obtained from VII.

SUMMARY

The synthesis of 2,5-dimethyl-6:7-benzmorphan (VIII), an analog of N-methylmorphinan, from either hydratroponitrile in a ten-step reaction sequence or from β-tetralone in a six-step scheme is described.

Compound VIII and three other closely allied substances were found to be one-half to one-third as active, analgesically, as N-methylmorphinan and demerol in mice, but much less toxic than either by subcutaneous route of administration. Orally, VIII was also fairly effective, more so than demerol.

BETHESDA 14, MASS.

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