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Structures Related to Morphine. XV.[1] Stereochemical Control of Methyl-Metallo Additions to 9-Oxobenzomorphans

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Reaction of 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (I) with methylmagnesium iodide produces an 80% yield of α-9-hydroxy-2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan methiodide II which on pyrolysis in 1-nonanol gives the base VI. The stereochemistry of this addition is almost completely reversed by reaction of methylmagnesium iodide with the base V and is completely reversed by employing methyllithium and V, affording the β-isomer IX. That the hydroxyl group of II and VI was *cis* (equatorial for the hydroaromatic ring) to the *cis*-fused iminoethano system was proved by its conversion to the *cis*-fused furano compound (IV) in two Hofmann elimination reactions. Similar degradation of IX yielded what appears to be the *trans*-fused furan derivative (XIV). Spectral data were also consistent with th eVI, IX and XIV assignments. *O*-Demethylation of VI and IX produced the phenolic compounds VII and X, respectively, which may be considered as analogs of 14-hydroxydihydromorphinone (XVIIIb). Compound VI has also been converted to the corresponding phenolic *N*-phenethyl analog XI which along with VI, VII, IX, and X have been evaluated for analgesic effectiveness in mice.

In a previous communication[2] we reported that methylmagnesium iodide adds to the carbonyl group of 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide to yield only one of the two possible methyl carbinols in 80% yield. Such a reaction with the corresponding 2′-methoxy compound (I) would not only give benzomorphan analogs of the potent analgesics 14-hydroxydihydro-codeinone (XVIIIa)[3] and -morphinone (XVIIIb)[4] but would also provide an intermediate which might be useful for the synthesis of a neuropharmacologically promising benzomorphan derivative diastereoisomeric (at C-9) with XVII,[2] isolated in very low yield in the Grewe synthesis of XVII.[5] Furthermore, it was conceivable that the stereochemistry of addition to the ketonic function of I could be reversed by varying reagents or that appropriate equilibration of II or the base VI might produce some inversion at C-9 to give a diastereoisomer (IX) which would be of pharmacological and chemical interest. Results obtained in applying some of the above-mentioned thoughts are herein presented.

Reaction of the methobromide I with excess ethereal methylmagnesium iodide[6] afforded in 80% yield the methiodide II to the apparent exclusion of any diastereoisomer in agreement with our experience in the *de*-methoxy series.[2] Pyrolysis of II in boiling 1-nonanol gave VI which, with methyl iodide, could be reconverted nearly quantitatively to II. When the free base V and methylmagnesium iodide were brought to reaction only a 15% yield of VI resulted, the principal product (57% yield) being the diastereoisomer IX. The use of methyllithium instead of methylmagnesium iodide gave, as a characterizable product, only IX in 70% yield.

Degradation of II by two Hofmann elimination reactions according to Schöpf and Borkowsky[7] for XVIIIa afforded a nitrogen-free compound (70% yield from II) whose infrared, ultraviolet and NMR spectra and elemental analyses are accomodated by structure IV. Furthermore, hydrogenation of IV with the uptake of one molar equivalent of hydrogen gave a compound VIII showing only phenyl absorption in the ultraviolet and an infrared band at 9.34 μ characteristic of tetrahydrofurans.[8] These facts it seemed permitted the assignment of the hydroxyl group as *cis* (equatorial for the hydroaromatic ring) to the *cis*-fused iminoethano system inasmuch as molecular models indicated unfavorable geometry for a tetrahydrofuran ring *trans*-fused to the dihydronaphthalene moiety. However, identical double-Hofmann degradation of the isomer IX produced a nitrogen-free monomolecular compound (70% yield from the methiodide of IX) devoid of either a free hydroxyl or vinyl group as shown by infrared and NMR spectral determinations. Hydrogenation of this product resulted in the absorption of only one molar equivalent of hydrogen and disappearance of the 3,4-dihydro-6-methoxynaphthalene chromophore present in each IV and XIV. These findings of course cast doubt upon the validity of our assign-

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[1] Communication XIV, J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

[2] E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

[3] M. Freund and E. Speyer, *J. Prakt. Chem.*, [2], **94**, 135 (1916).

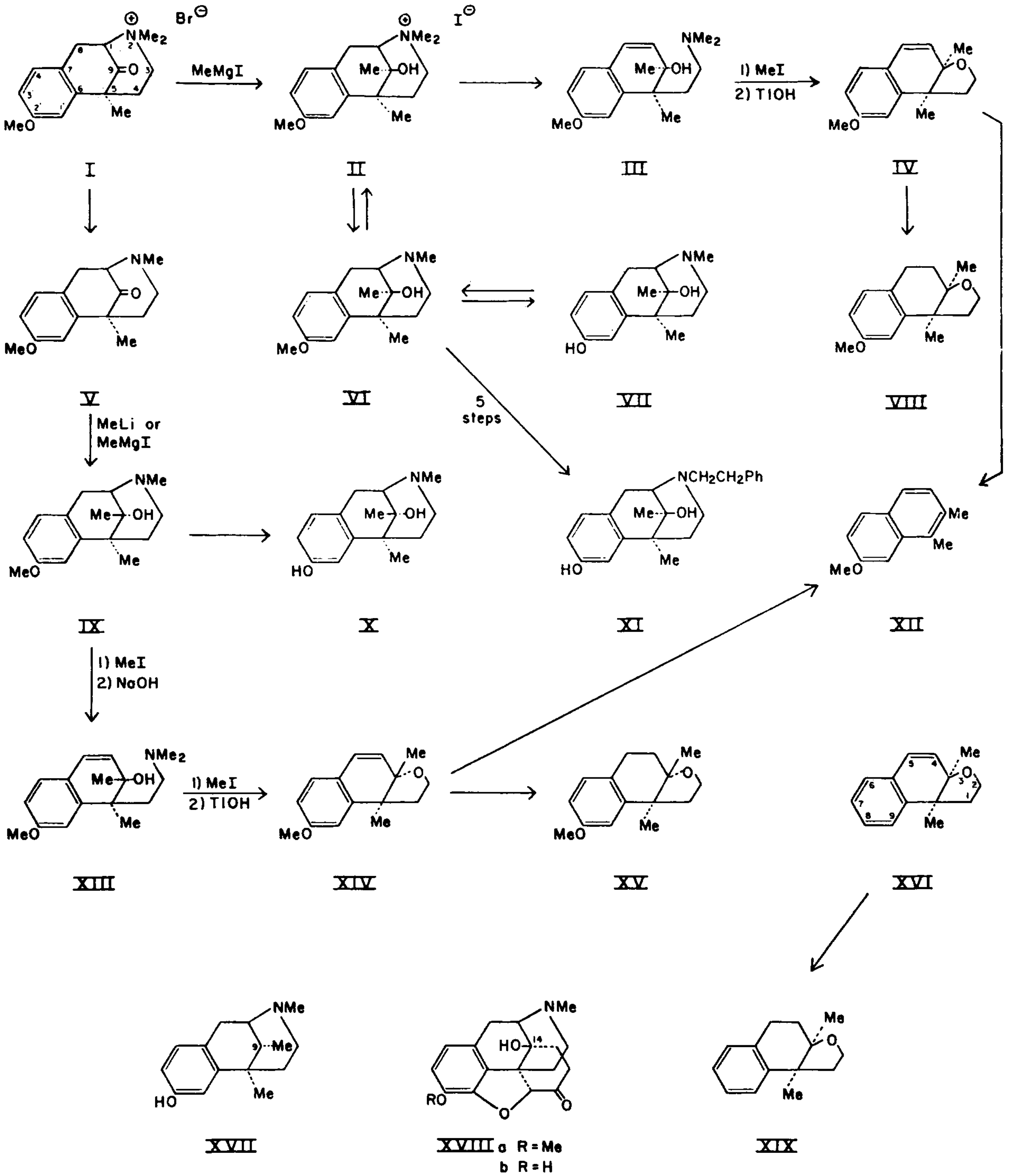
[4] (a) U. Weiss, *J. Am. Chem. Soc.*, **77**, 5891 (1955); (b) N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. World Health Orgn.*, **17**, 569 (1957). The international, nonproprietary names oxydocone and oxymorphone have been assigned to XVIIIa and XVIIIb respectively.

[5] E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

[6] Methyllithium and I gave only a low yield of VI after pyrolysis of the crude II first isolated) and no IX.

[7] C. Schöpf and F. Borkowsky, *Ann.*, **452**, 249 (1927).

[8] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 104.



I II III IV V VI VII VIII IX X XI XII XIII XIV XV XVI XVII XIX

XVIII a R = Me
b R = H

ments for VI and IX. To dispel this doubt the *de*-methoxy analog[2] of II was converted by the same series of reactions to the IV and VIII *de*-methoxy counterparts which proved to be identical with 1,2,3a,9b-tetrahydro-3a,9b-dimethylnaphtho (2,1-b) furan (XVI) and its hydrogenation product (XIX) synthesized by Fry[9] and almost certainly containing a *cis*-fused tetrahydrohydrofuran ring.[10]

Furthermore, examination of infrared spectra of VI and IX (the OH values for which were independent of dilution) determined in the Beckman IR-7 (carbon tetrachloride as solvent) revealed that VI exhibits a broad maximum at 3450 cm.$^{-1}$ typical of OH—N bonding,[11] while IX gave a weak but sharp maximum at 3622 cm.$^{-1}$ (free OH) and a

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(9) E. M. Fry, *J. Org. Chem.*, 22, 1710 (1957).

(10) The results of the degradation of the *de*-methoxy analog of II will appear in a later paper.

(11) Compare these results with those of R. E. Lyle, *J. Org. Chem.*, 22, 1280 (1957), B. L. Zenitz, C. Martini, M. Priznar, and F. Nachod, *J. Am. Chem. Soc.*, 74, 5564 (1952), and E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, 75, 68 (1953).

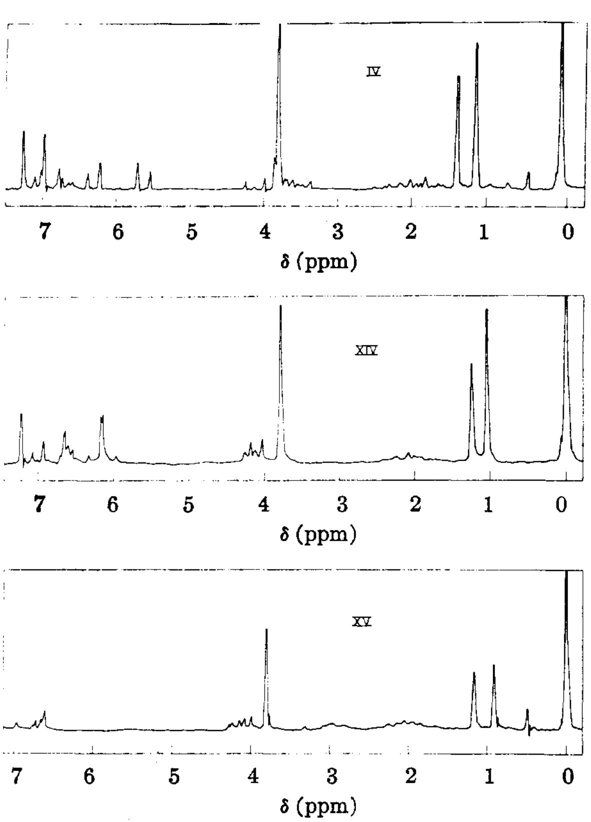

Fig. 1. Nuclear magnetic resonance spectra (deuterochloroform as solvent, tetramethylsilane as internal 0 reference) at 60 Mc.

much stronger broader band at 3586 cm.$^{-1}$ characteristic of OH—π bonding.[12] Molecular models indicate the plausibility of such bonding. These results combined with the degradative experiments outlined above leave little doubt about the stereochemical correctness of the VI and IX assignments.

All data that we have accumulated to date appear to be consistent with the formulation of XIV as a *trans*-fused tetrahydrofurano compound. (i) The yield of XIV from XIII (84%), comparable to that in going from III to IV, would indicate participation by a fairly acidic hydrogen, implicating the hydroxyl as the proton donor.[13] (ii) The ultraviolet absorption spectrum of IV shows a maximum at 270 mμ compared with 279 mμ for XIV which might be interpreted as a bathochromic shift due to conjugation of the 6-methoxy-3,4-dihydronaphthalene chromophore of XIV with a strained,[14] *trans*-fused tetrahydrofuran ring, which, according to molecular models, lies in essentially the same plane[15] as this chromophore; in the *cis*-fused furan (IV) there appears to be little if any strain in the oxygen-containing ring which lies well out of the plane of the principal chromophore. A similar effect was noted in the NMR spectra as described below. The ultraviolet spectra of the reduced compounds VIII and XV are virtually identical. (iii) Infrared and NMR data are entirely consistent with structures XIV and XV assigned to the products arising from XIII and incompatible with other possible formulations. (iv) Palladium-charcoal aromatization of either IV or XIV gave 7-methoxy-1,2-dimethylnaphthalene (XII) while treatment of either with acetic anhydride–sulfuric acid mixture afforded in each instance an oily, monoacetoxy derivative characterized only by its infrared spectrum.

Regarding the NMR spectra[16] of IV, XIV, and XV, each gives a sharp intense line at 3.78–3.82 p.p.m. due to CH_3O. Intense lines in the high-field region are unquestionably assigned to $CH_3C\!\!<\!\!{-}$ groups (not $CH_3CH\!\!<$ or $CH_3\overset{|}{C}{=}$) on the basis of intensity, chemical shift, and absence of spin splitting. The lower-field line (at 1.38) in IV is assigned to the CH_3 adjacent to the $>\!C{-}O{-}$ and $C{-}C{=}C$ groups. The difference between IV and XIV could arise from change of configuration (*e.g.*, crowding of methyls seems to cause a shift to low field in 6-methyl steroids).[17] The shift of these lines on reduction of XIV is reasonable. The nonequivalence quartet in IV arises from styrene type protons (δ = 5.65 and 6.32). On the basis of comparison with *cis*-propenylbenzene,[18] 6.32 is α to the benzene ring, 5.65 β. In XIV the pattern has changed, indicating a barely resolved nonequivalence quartet with components centered at 6.13 and 6.25, the spin-coupling remaining at 10 c.p.s., reasonable for *cis*-olefinic protons. The line due to the proton farther from the benzene ring (β) has thus been shifted to be nearly coincident with the nearer proton line (α).[19] In XV, of course, there is no absorption in this region. Absorption in the region 6.5–7.2 p.p.m. is

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[12] *Cf.* M. St. C. Flett, *Spectrochim. Acta*, **10,** 21 (1957); H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82,** 197 (1960). We gratefully acknowledge the aid and counsel of Drs. Fales and Wildman in these spectral determinations on VI and IX.

[13] Inversions during the degradations in both series appear unlikely because of the excellent yields of homogeneous products obtained in both steps.

[14] L. Dorfman, *Chem. Rev.*, **53,** 51 (1953); W. W. Robertson, J. F. Music, and F. A. Matsen, *J. Am. Chem. Soc.*, **72,** 5260 (1950); R. N. Moore and G. S. Fisher, *J. Am. Chem. Soc.*, **78,** 4362 (1956).

[15] W. J. Bailey and W. B. Lawson, *J. Am. Chem. Soc.*, **77,** 1606 (1955).

[16] We are greatly indebted to Mr. Robert Bradley and Dr. Edwin Becker of this Institute for the determination and complete analysis and interpretation of these spectra.

[17] G. Slomp, Jr., and B. R. McGarvey, *J. Am. Chem. Soc.*, **81,** 2200 (1959).

[18] J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-Resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, Toronto, London, 1959, p. 238.

[19] Such a shift to nearer equivalence of the vinyl protons of XIV than those of IV appears to be in harmony with the ultraviolet spectral differences noted and due to strain in XIV.

due to the three aromatic protons. The detailed pattern depends upon the nonequivalence of these protons due to substituents on the ring and spin coupling (differing for *o*, *m*, and *p* positions of the protons in relation to each other). The changes in pattern between compounds reflects small changes in the chemical environment of some of the protons. For example, reduction of the double bond will almost certainly cause a shift of the proton *ortho* to that double bond; and in IV one of the methyl groups appears to interfere sterically with one of the aromatic protons, probably causing a shift to low field relative to an unhindered proton (*e.g.*, that in the *trans*-compound XIV).[20] A more detailed interpretation of the aromatic pattern is not feasible. The group of lines centered ~3.82 in IV and ~4.20 in XIV and XV must arise from the CH_2O group spin-coupled to the adjacent CH_2 group. The patterns are complex—evidently because the two protons of one or both of the CH_2 groups are nonequivalent. The groups of lines in all three compounds 1.7–2.3 arise from the remaining CH_2 group. Of course XV has one additional CH_2 group in this region and one at 3.0 due to reduction of the double bond of XIV. Overall the spectra of XIV and XV are entirely consistent with the proposed structure involving the *trans* ring closure.

The Grignard reactions described in this paper constitute, we believe, a special case of stereochemical control of assymmetric induction[21] in which, with relatively small radicals involved, the electrical environment (charge on a neighboring heterocyclic nitrogen) appears to play a major role in the direction of addition to a carbonyl function. Further support of this view will be presented in the following paper dealing with the addition of hydrogen to the carbonyl group of I and V.

Conversion of VI and IX to the phenolic analogs VII and X respectively was effected in 65–70% yield with boiling 48% hydrobromic acid. Methylation of VII with diazomethane regenerated VI proving no inversion at C-9. The base VI was also converted by standard reactions[22] to the *N*-phenethyl compound XI. Deliberate attempts to convert II to the methiodide of IX by equilibration in 0.5*M* perchloric acid[23] gave only unchanged II and decomposition products. There was no indication of inversion.

Compounds VI, VII, IX, X, and XI have been tested in mice for analgesic effectiveness.[24] The phenolic compounds VII[25] and X lie between morphine and meperidine in analgesic potency, are half as active as XVII, and vastly inferior to XVIIIb. The methyl ether, VI, was comparable to codeine by parenteral administration but about three times more potent than codeine by the oral route. Diastereoisomer IX had little activity at subtoxic doses. The *N*-phenethyl derivative XI, surprisingly, was slightly less potent than the *N*-methyl counterpart VII.

A more detailed report on the pharmacology of these compounds will be published later.

EXPERIMENTAL

Melting points were taken in a capillary (Hershberg apparatus, total-immersion thermometers). Microanalyses are by Paula Parisius, Elizabeth Fath, Evelyn Peake, and Byron Baer of the Institute's service analytical laboratory, Harold McCann, director, and infrared determinations (Perkin-Elmer, 21) are by Harold K. Miller, Richard Brown, and Ann Wright of this Institute unless otherwise noted.

α-9-Hydroxy-2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan methiodide (II).[26] Five grams of I[1] was covered with dry ether and treated rapidly (stirring) with 50 ml. of 1.7*M* ethereal methylmagnesium iodide. Stirring was continued until all solid had disappeared. The ether was then distilled. Water was added gradually to the sirup (ice-cooling, nitrogen atmosphere), followed by 15 ml. of 6*N* hydrochloric acid, and 5.0 g. of potassium iodide in 10 ml. of water. After stirring for 2 additional hr. 4.4 g. (74%) of II, m.p. 217–224° was obtained; plates from alcohol-acetone, m.p. 233–235°, λ_{max}^{nujol} 3.0 μ.

Anal. Calcd. for $C_{17}H_{26}INO_2$: C, 50.63; H, 6.50. Found: C, 50.58; H, 6.47.

When methyllithium was used instead of methylmagnesium iodide the yield of II was only 20%; no other identifiable products could be isolated. The II thus obtained could not be readily purified but was converted to the easy-to-purify VI as described below.

α-9-Hydroxy-2'-methoxy-2,5,9-trimethyl-6,7-benzomorphan (VI) *picrate.* 1-Nonanol (8 ml.) and 1.4 g. of II were refluxed for 10–15 min., cooled under nitrogen, and extracted thrice with 5% hydrochloric acid. The combined extracts were made alkaline (ammonium hydroxide) and extracted with ether. The dried ether extracts were evaporated giving an oil, which with 8 ml. of alcohol and 1.0 g. of picric acid, yielded 1.4 g. (82%) of VI picrate, m.p. 195–199°; yellow rods from alcohol-acetone, m.p. 197–199°, λ_{max}^{nujol} 2.9 μ.

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34. Found: C, 53.60; H, 5.39.

The hydrochloride of VI crystallized from alcohol-ether in prisms apparently as the monohydrate, m.p. 160–163° (after drying at 40°/75 mm.).

Anal. Calcd. for $C_{16}H_{24}ClNO_2:H_2O$: C, 60.84; H, 8.30. Found: C, 60.87; H, 8.20.

In carbon tetrachloride (Beckman IR.7),[12] VI showed a broad maximum of medium intensity at 3450 cm.$^{-1}$

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(20) Molecular models clearly demonstrate that in IV the 1' proton and 9b methyl are very close together and much farther apart in XIV.

(21) For leading references on assymmetric induction *cf.* D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); N. H. Cromwell, *J. Am. Chem. Soc.*, **81**, 4702 (1959).

(22) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(23) C. A. Bunton, A. Konasiewicz, and D. R. Llewellyn, *J. Chem. Soc.*, 604 (1955).

(24) N. B. Eddy, Chief, Section on Analgesics of this Institute and staff by a method previously described; *cf.* N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). Statistical analysis of the data are by Wendy Ness.

(25) The diacetoxy derivative of VII has twice the potency of morphine and shows relatively low (if any) physical dependence capacity in the monkey (private communication from Dr. G. Deneau, University of Michigan).

(26) This compound was first synthesized by J. Harrison Ager of this Institute. The α (OH *cis*- to iminoethano system) and β-designations were chosen arbitrarily.

which was independent of concentration (OH—N bonding)[11] and no free OH absorption.

Treatment of VI in warm alcohol with excess methyl iodide regenerated II almost quantitatively.

β-9-Hydroxy-2′-methoxy-2,5,9-trimethyl-6,7-benzomorphan (IX) *picrate*. V (0.8 g.)[1] in 10 ml. of dry ether was treated (stirring) during 2–5 min. with 7.0 ml. of 1.3*M* ethereal methyl lithium. The mixture was refluxed for 20 min. and poured into ice water. The dried ether layer was evaporated and the residue treated with 15–20 ml. of alcohol and 1.0 g. of picric acid. On heating to homogeneity and cooling to 5°, 1.1 g. (70%)[27] of the picrate of IX, m.p. 210–213°, was obtained as the sole product; yellow cubes from alcohol-acetone, m.p. 213–214° dec., λ_{max}^{nujol} 2.93 μ.

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34. Found: C, 54.02; H, 5.34.

The *hydrobromide* of IX crystallized from 95% ethanol in prisms of m.p. 259–260° dec.

Anal. Calcd. for $C_{16}H_{24}BrNO_2$: C, 56.14; H, 7.07. Found: C, 55.96; H, 7.18.

The *methiodide* of IX formed sluggishly with excess methyl iodide in acetone or refluxing alcohol; rosettes from absolute ethanol, m.p. 213–216°, λ_{max}^{nujol} 2.96 μ.

Anal. Calcd. for $C_{17}H_{26}INO_2$: C, 50.63; H, 6.50. Found: C, 50.43; H, 6.33.

The base (IX) crystallized from ligroin (30–60°) in prisms, m.p. 90–91°, $\lambda_{max}^{CHCl_3}$ 2.79 μ (3586 cm.$^{-1}$), $\nu_{max}^{CCl_4}$ (Beckman IR.7) 3622 cm.$^{-1}$ (weak, sharp), 3586 cm.$^{-1}$ (strong, broad, OH—π bonding).[12]

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.67; H, 8.97.

1,2-Dihydro-2-hydroxy-7-methoxy-cis-1,2-dimethyl-1-(2-dimethylaminoethyl)naphthalene (III). II (300 mg.) and 5 ml. of 10% sodium hydroxide were refluxed gently for 20 min. The liberated oil was dried in ether and distilled (bath temperature 140–150°) at 0.2 mm. to give 180 mg. (88%) of colorless, oily III, $\lambda_{max}^{C_2H_5OH}$ 275 mμ (ε 12,560) and showing associated hydroxyl absorption (chloroform) in the 3 μ region.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 74.01; H, 9.03.

1,2,3a,9b-Tetrahydro-8-methoxy-cis-3a,9b-dimethylnaphtho(2,1-b)furan (IV). III (170 mg.), 0.05 ml. of methyl iodide, and 2 ml. of methanol were refluxed for 1 hr. Distillation of solvent and washing the residue with ether left 220 mg. (86%) of white amorphous III methiodide which was dissolved in 2 ml. of hot water and treated with 2.3 ml. of 0.23*M* thallium hydroxide.[28] The mixture was digested on the steam bath for 20 min. and filtered from thallium iodide. The filtrate was evaporated to dryness at the water pump. The residual methohydroxide was dry-distilled at 110–120° (air bath temperature)/0.3 mm. Colorless needles of nitrogen-free product (IV) sublimed in a yield of 90 mg. (78%), m.p. 62.8–63.1°. Resublimation did not change the melting point and the material was chromatographically homogeneous. The infrared spectrum showed bands at 9.37, 9.79, and 11.42 μ (tetrahydrofuran characteristics)[8] and no hydroxy or vinyl group absorption; $\lambda_{max}^{C_2H_5OH}$ 271 mμ (ε 14,200).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.41; H, 8.11.

1,2,3a,4,5,9b-Hexahydro-8-methoxy-cis-3a,9b-dimethylnaphtho(2,1-b)furan (VIII). IV (80 mg.) 10 mg. of platinum oxide and 5 ml. of methanol absorbed rapidly 1 molar equivalent of hydrogen to give after distillation at 0.3 mm. (bath temperature 110–115°) 80 mg. of VIII, $\lambda_{max}^{CHCl_3}$ 9.28, 9.72, and 11.40 μ, $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 2680).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.75; H, 8.70.

1,2-Dihydro-2-hydroxy-7-methoxy-trans-1,2-dimethyl-1(2-dimethylaminoethyl)naphthalene (XIII). The methiodide of IX (0.8 g.) and 10 ml. of 10% sodium hydroxide were kept on the steam bath for 20–30 min. The liberated oil was dried in ether and distilled at 0.3 mm. (bath temperature 140–150°) giving 0.5 g. (88%) of colorless XIII, $\lambda_{max}^{CHCl_3}$ 2.8 μ,[29] $\lambda_{max}^{C_2H_5OH}$ 277 mμ (ε 8940).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.13; H, 9.15. Found: C, 73.25; H, 9.29.

1,2,3a,9b-Tetrahydro-8-methoxy-trans-3a,9b-dimethylnaphtho(2,1-b)furan (XIV). The methiodide of XIII (0.65 g. prepared in 94% yield as a noncrystalline powder as described for that of III above), 7.3 ml. of 0.23*M* thallium hydroxide, and 5 ml. of water gave 0.30 g. (80%) of pure XIV as described above; m.p. 63.4–64.2°, $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 12,080), $\lambda_{max}^{CHCl_3}$ 9.44, 10.09, 10.40, and 11.09 μ (no hydroxyl band).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88; M.W., 230.3. Found: C, 77.80; H, 7.76; M.W. (Rast), 216.

1,2,3a,4,5,9b-Hexahydro-8-methoxy-trans-3a,9b-dimethylnaphtho(2,1-b)furan (XV). During 80 min. 200 mg. of XIV, 10 mg. of platinum oxide and 5 ml. of methanol absorbed 1 molar equivalent of hydrogen and reduction ceased. By distillation at 0.2 mm. (bath temperature 95–105°) 185 mg. of XV was obtained; $\lambda_{max}^{C_2H_5OH}$ 280 mμ (ε 2,450). In the infrared (chloroform) there were strong bands at 9.43, 9.98, 10.40, and 11.13 μ and no hydroxyl absorption.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.44; H, 8.59.

1,2,3a,9b-Tetrahydro-cis-3a,9b-dimethylnaphtho(2,1-b)furan (XVI).[9] By a series of reactions identical with those described in the preparation of IV from II, 9-hydroxy-2,5,9-trimethyl-6,7-benzomorphan methiodide (obtained in the reaction of methylmagnesium iodide with 2,5,9-trimethyl-9-oxo-6,7-benzomorphan methobromide)[3] yielded XVI, $\lambda_{max}^{C_2H_5OH}$ 263 (ε 9630) whose infrared spectrum was identical with that of the XVI synthesized by Fry.[9] The synthetic XVI almost certainly contains a *cis*-fused tetrahydrofuran ring.[10] Furthermore, hydrogenation of our XVI from degradation resulted in the absorption of one molar equivalent of hydrogen affording XIX, $\lambda_{max}^{C_2H_5OH}$ 272 mμ (ε 520) also identical in the infrared with the synthetic hydrogenation product.[9]

7-Methoxy-1,2-dimethylnaphthalene picrate. Either IV or XIV (0.2 g.) and 0.5 g. of 5% palladium charcoal were kept at 300–330° (bath temperature) for 20–30 min. and extracted with ether. Evaporation of the ether left an oil which gave 70 mg. (20%) of picrate (from alcoholic picric acid), m.p. 134–135° which proved to be identical with 7-methoxy-1,2-dimethylnaphthalene picrate described previously.[5] By the same procedure XVI afforded a 30% yield of 1,2-dimethylnaphthalene picrate.[3]

Acetic anhydride–sulfuric acid[30] *treatment of* VIII *and* XV. To 80 mg. of VIII in 2 ml. of acetic anhydride was added one drop of concd. sulfuric acid and the solution left at 25° overnight. After decomposition of the acetic anhydride with water and treatment with ammonium hydroxide the liberated oil was dried in ether and distilled at 0.2 mm. (bath temperature 130–140°); yield 30–40%, $\lambda_{max}^{CHCl_3}$ 5.75 μ. Similar treatment of XV likewise gave an oil which absorbed at 5.75 μ. Both products analyzed for one *O*-acetyl group (15.5 and 16.3%, calcd. 15.7%) based on the empirical formula $C_{17}H_{22}O_3$. The near identity of the infrared spectra indicate

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[27] When ethereal methylmagnesium iodide was used in place of methyllithium there was obtained a 57% yield of the less soluble IX picrate and a 15% yield of the picrate of VI.

[28] We are grateful to Dr. L. J. Sargent of this laboratory for suggesting thallium hydroxide which proved vastly superior to silver hydroxide; *cf.* L. J. Sargent and L. F. Small, *J. Org. Chem.*, 16, 1031 (1951).

[29] The hydroxyl of XIII is apparently π-bonded in contrast to the strongly intramolecularly associated (with nitrogen) hydroxyl of III.

[30] T. Kitagawa, S. Uyeo, and N. Yokoyama, *J. Chem. Soc.*, 3741 (1959).

that the monoacetoxy derivatives are the same compound or isomers.

α-2',9-Dihydroxy-2,5,9-trimethyl-6,7-benzomorphan. (VII). VI (0.75 g.) and 8 ml. of 48% hydrobromic acid were refluxed gently for 15 min., cooled, and made alkaline with ammonium hydroxide. Addition of sodium chloride and extraction of the mixture with 20 ml. of chloroform in five portions gave, after drying and evaporation of the solvent *in vacuo* and crystallization of the residue from 1 ml. of acetone and 1 ml. of ligroin (30–60°), 0.5 g. (70%) of VII, m.p. 155.5–157°; prisms, λ_{max}^{nujol} 2.9 μ (sharp, strong), shoulder at 2.83 μ, $\lambda_{max}^{CHCl_3}$ 2.78 (sharp, medium), 3.0 (broad, strong).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.55. Found: C, 72.84; H, 8.35.

The *hydrobromide* salt crystallized from absolute ethanol-ether in prisms of m.p. 238–240°, λ_{max}^{nujol} 2.78 (weak), 3.07 (strong), 3.21 μ (medium).

Anal. Calcd. for $C_{15}H_{22}BrNO_2$: C, 54.87; H, 6.76. Found: C, 54.89; H, 6.86.

Methylation of 50 mg. of VII in methanol with ethereal diazomethane regenerated VI, isolated as the picrate in 70% yield, showing no inversion at C-9 or rearrangement during the 48% hydrogen bromide treatment.

α-2',9-Diacetoxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromide. VII (0.4 g.) and 3.5 ml. of acetic anhydride were refluxed for 2 hr. and evaporated to dryness *in vacuo*. The residue was treated with cold, dilute ammonium hydroxide and extracted with ether. Drying and evaporating the ether left an oil which was distilled at 0.2 mm. (bath temperature 165–175°). The 0.55 g. of distillate in 5 ml. of acetone was treated with 30% hydrobromic-acetic acids to Congo-Red acidity. The hydrobromide crystallized in a yield of 0.63 g. after overnight standing; wedges from absolute ethanol-ethyl acetate, m.p. 264–265° dec.

Anal.[31] Calcd. for $C_{19}H_{26}BrNO_4$: C, 55.34; H, 6.35; Br, 19.38. Found: C, 55.66; H, 6.57; Br, 19.07.

β-2',9-Dihydroxy-2,5,9-trimethyl-6,7-benzomorphan (X). This compound was prepared from IX (55% yield after sublimation at 0.1 mm., bath temperature 180°) as described above for VII; prisms from acetone, m.p. 194–195°, λ_{max}^{nujol} 3.03 μ (strong, broad).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.55. Found: C, 72.67; H, 8.58.

The *hydrobromide* crystallized from 95% ethanol in triangular plates, m.p. 258–260° (dec.), λ_{max}^{nujol} 2.99, 3.11 μ (strong, sharp).

Anal. Calcd. for $C_{15}H_{22}BrNO_2$: C, 54.87; H, 6.76; Br, 24.34. Found: C, 55.23; H, 6.52; Br, 24.30.

α-9-Hydroxy-2'-methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. VI (1.1 g.) in 7 ml. of chloroform was added during 30 min. to a stirred solution of 0.45 g. of cyanogen bromide in 4 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness at the water pump. The residual crude cyanamide derivative, and 20 ml. of 6*N* hydrochloric acid were refluxed for 7 hr. The cooled mixture was made alkaline with potassium carbonate, extracted with ether, and the extracts washed with water, dried, and evaporated leaving 1.05 g. of crude secondary amine. To this was added 15 ml. of methanol, 5 ml. of water and 0.8 g. of potassium carbonate. The mixture was stirred while adding 0.8 ml. of phenylacetyl chloride during 7 min., then stirred an additional 3 hr. Water and ether were added and after thorough shaking the ethereal layer was washed with dilute hydrochloric acid,[32] then aqueous sodium carbonate, dried and evaporated. To the resultant 1.1 g. of *N*-phenylacetyl compound in 20 ml. of dry ether was added carefully (stirring) 15 ml. of *M* ethereal lithium aluminum hydride. After stirring and refluxing for 6–8 hr. 2 ml. of water was added carefully and inorganic material filtered. The filtrate was extracted with dilute hydrochloric acid and these extracts made alkaline to give after extraction with ether 0.46 g. of crude XI methyl ether. In another identical run using 0.43 g. of the VI recovered above, 0.25 g. more XI methyl ether was obtained. The combined products in 5 ml. of acetone were treated with 30% hydrobromic-acetic acid to Congo-Red acidity and cooled to −5° to give 0.4 g. of the hydrobromide, m.p. 200–201°. Concentration of the filtrate and washings gave an additional 0.1 g.; pillars from absolute ethanol-ethyl acetate, m.p. 199–201°.

Anal. Calcd. for $C_{22}H_{30}BrNO_2$: C, 63.89; H, 6.98. Found: C, 63.99; H, 6.98.

α-2',9-Dihydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (XI) *hydrobromide.* The methyl ether of XI (0.48 g.) and 4 ml. of 48% hydrobromic acid were refluxed gently for 15 min. After vacuum distillation to dryness, the residue was washed several times with ether and triturated with acetone. Filtration gave 0.39 g. of XI hydrobromide, m.p. 261–263°, which was dissolved in hot ethanol. The solution was filtered, concentrated, and treated with Norit. The filtrate deposited 0.25 g. (55%) of colorless granules of pure XI hydrobromide, m.p. 265–267° (dec.).

Anal. Calcd. for $C_{22}H_{28}BrNO_2$: C, 63.16; H, 6.74. Found: C, 63.16; H, 6.82.

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[31] Sample dried for 6 hr. at 60°.

[32] On making these washings alkaline, 0.45 g. of VI, identified as the picrate, was recovered. Thus, the *N*-demethylation of VI was only about 50% complete indicating hindrance by the 9-hydroxy substituent. In the *N*-demethylation of the methyl ether of XVII [E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959)], by a similar procedure, only small yields of starting *N*-methyl compound were recovered.