hydrogen (1H) appeared as a barely split peak at τ 4.83, the methyl in the ester group (3H) as a very sharp singlet at 6.5, the branching methyl (3H) as a doublet at 9.02 (J = 7 c.p.s.), and the remaining protons (11H) in a broad multiplet at 7.54–8.7.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.46; H, 9.95. Found: C, 71.77; H, 9.58.

Component B was characterized by its spectra as **methyl 4-cyclopentylidenepentanoate (X)**: absorption in the infrared at 5.77 μ (carbonyl); end absorption in the ultraviolet with ϵ 6200 at 200 mμ. In the n.m.r. spectrum there was no vinyl hydrogen, the methyl in the ester (3H) appeared as a very sharp singlet at τ 6.5, the allylic methylene hydrogens and α-hydrogens (8H total) as a broad multiplet at 7.6–8.1, and the remaining hydrogens (7H, ring methylenes and allylic methyl) in a broad multiplet at 8.1–8.6.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.46; H, 9.95. Found: C, 72.34; H, 9.85.

Methyl 4-Cyclopentylpentanoate.—A 1.52-g. sample of the unsaturated esters was hydrogenated in 15 ml. of 95% ethanol in presence of 0.12 g. of 83% platinum oxide on charcoal catalyst. Hydrogenation was continued for 48 hr., then the reaction was worked up as described in the hydrogenation of ionone. Gas chromatography of the product (10 ft. × 3/8 in. column, 20% NPGS; temperature 165°; He flow rate 120 cc./min.) showed two components: methyl 4-cyclopentylpentanoate, 86.4% of mixture, retention time 19.5 min.; unsaturated ester X, 13.6%, retention time 22.2 min. From the areas of the peaks in the tracing, it was estimated that about 22% of ester X had been hydrogenated during the 2-day period. The saturated ester, separated by gas chromatography, was used for analysis.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.68; H, 10.94. Found: C, 71.58; H, 10.89.

Methyl 5-Cyclopentylhexanoate.—A sample (0.748-g.) of methyl 4-cyclopentylpentanoate was saponified by heating with 15 ml. of 15% methanolic potassium hydroxide. After the cooled reaction mixture had been diluted with 20 ml. of water and acidified to pH 2 it was continuously extracted with ether for 3 hr. The residue remaining after removal of solvent from the dried extract was dissolved in 15 ml. of dry benzene and treated with 3 ml. of purified thionyl chloride. After the mixture had been heated under reflux, protected from atmospheric moisture, for 2 hr., solvent was removed by distillation through a 2-ft. column. A solution of the residual acid chloride in 6 ml. of anhydrous ether was added during about 5 min., at 5–10°, to a solution of diazomethane prepared from 1.5 g. of N-nitrosomethylurea. After the mixture had stood at room temperature overnight, solvent and any remaining diazomethane were removed at reduced pressure, and the residual diazo ketone was divided into two parts for preparation of ester and amide.

To a solution of 44% of the diazo ketone in 7 ml. of dry methanol there was added at room temperature a few drops of a solution of 0.43 g. of silver benzoate in 4 ml. of triethylamine, according to the procedure recommended by Newman and Beal.[22] Evolution of nitrogen set in promptly, as the mixture darkened. A new addition of silver benzoate solution was made when the evolution of nitrogen slackened, until a total of 1.2 ml. of the solution had been added during 2 hr. The mixture was finally heated under reflux for a few minutes, allowed to stand at room temperature for 2 hr., then filtered through a layer of Super Cel into 10 ml. of water. The product was extracted with ether, and the extracts were washed with water, 5% aqueous hydrochloric acid, water, 10% aqueous sodium carbonate solution, and finally water. Removal of solvent from the dried extract left 275 mg. (54%) of crude ester. An analytical sample was collected by gas chromatography (10 ft. × 3/8 in. column, 20% silicone SE-30; temperature 165°; He flow rate 150 cc./min.; retention time 19.3 min.).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.70; H, 11.18. Found: C, 72.59; H, 10.90.

5-Cyclopentylhexanamide.—A solution of 56% of the above-described diazo ketone in 7 ml. of purified dioxane was treated at room temperature with 7 ml. of concentrated ammonium hydroxide and 1.5 ml. of 10% aqueous silver nitrate solution. This mixture was heated at 70–80° for 1 hr., then a second 7 ml. of ammonium hydroxide was added and heating was continued for an additional hour. After the resultant reaction mixture had stood at room temperature for 1 hr. the precipitated solid was collected. Attempted crystallization of the product from ethanol was unsuccessful, but crystallization from hexane yielded 109 mg. (26.2%) of the amide, m.p. 71.5–73.0°.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.06; H, 11.55; N, 7.64. Found: C, 72.47; H, 11.05; N, 7.33.

The mass spectrum was determined under the conditions cited in the legend to Figure 3. The ions observed (per cent of base peak in parentheses) which were >2% of the base peak were m/e 37 (9), 38 (5), 39 (8), 39 (10), 41 (28), 42 (7), 43 (17), 44 (21), 53 (5), 55 (24), 59 (100), 60 (7), 67 (7), 68 (3), 69 (9), 71 (3), 72 (32), 73 (13), 81 (3), 86 (9), 97 (3), 100 (1), 114 (14), 122 (2.5), and 183 (1).

(22) M. S. Newman and P. F. Beal, III, *J. Am. Chem. Soc.*, **72**, 5163 (1950).

The Derivation of Hydroaromatic Morphinans and Isomorphinans from Natural Sources*

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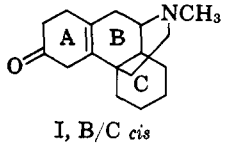
d-1,2,3,4-Tetrahydro-3-oxo-N-methylmorphinan and the corresponding isomorphinan, dihydro derivatives of the potent analgesic substances *l*-3-hydroxy-N-methylmorphinan and -isomorphinan, have been synthesized by Birch reduction of the corresponding methyl ethers, in turn prepared from natural sources by a new method. They showed little or no analgesic activity in the D'Amour–Smith test.

In spite of the intensity with which the relationship between structure and analgesic activity in the morphine and morphinan series has been studied, hydroaromatic derivatives of these systems have not been reported. We therefore planned to prepare and examine examples of such ring A hydroaromatic derivatives, not only simple cyclohexenones which might be expected to revert to the phenolic compounds in the organism, but also cyclohexenones with angular substituents not readily rearomatized. We report here two examples of the former type, *d*-1,2,3,4-tetrahydro-3-oxo-N-methylmorphinan (I) and the corresponding isomorphinan (II).

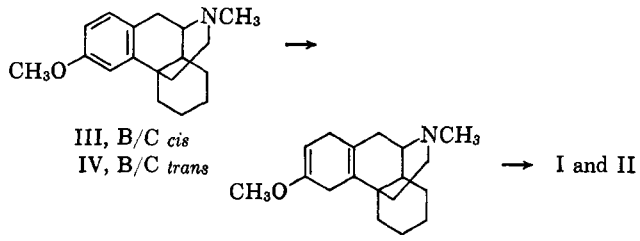


I, B/C *cis*
II, B/C *trans*

* To Professor Louis F. Fieser.

(1) National Science Foundation Predoctoral Fellow, 1961–1962, 1962–1963.

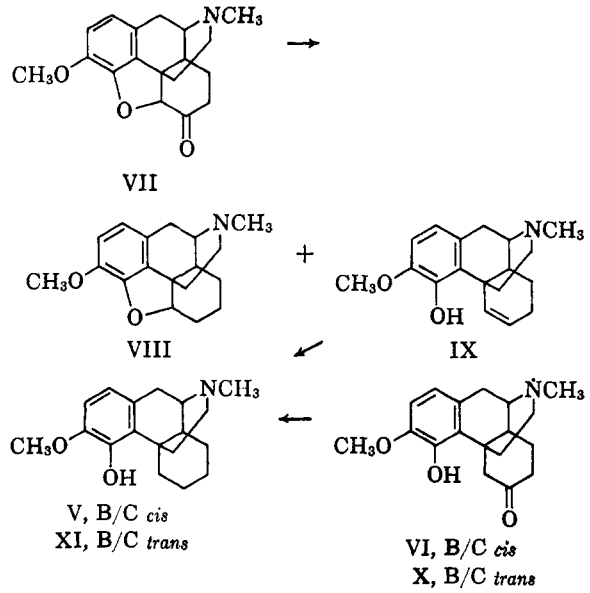
Both were prepared by Birch reduction of the corresponding 3-methoxy-N-methyl compounds and hydrolysis of the resulting enol ethers.



III, B/C *cis*
IV, B/C *trans*

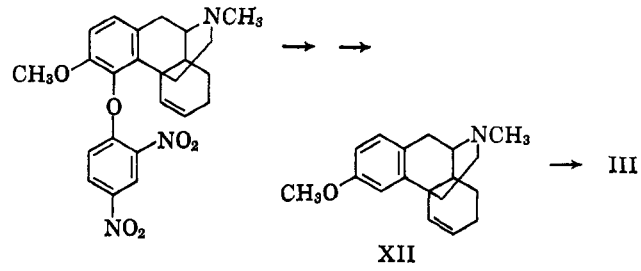
The *cis* methoxy compound (III) is readily prepared by methylation of the commercially available *l*-3-hydroxy-N-methylmorphinan (levorphanol) and some of our material was obtained this way. We wished, however, to develop a method for the preparation of the corresponding *trans* compound (IV) from natural sources in order to avoid a long and arduous synthesis and accordingly investigated as a model the removal of the phenolic hydroxyl group of *cis*-tetrahydrodesoxycodeine (*l*-3-methoxy-4-hydroxy-N-methylmorphinan, V). At the time this work was begun, III had not been obtained from natural sources.[2]

Tetrahydrodesoxycodeine (V) is the end product of the reduction of a number of codeine and thebaine degradation products.[3] Our samples were obtained by Wolf–Kishner or Clemmensen reduction[4] of *cis*-dihydrothebainone (VI) or by hydrogenation of *cis*-dihydrodesoxycodeine-C (IX), in turn obtained by Wolf–Kishner reduction of dihydrocodeinone (VII).[5]



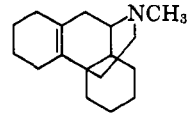
VII
VIII
IX
V, B/C *cis*
XI, B/C *trans*
VI, B/C *cis*
X, B/C *trans*

Arylation of V with 2,4-dinitrofluorobenzene in toluene–dimethylformamide using sodium hydride as catalyst gave the 2′,4′-dinitrophenyl ether in high yield. Catalytic hydrogenation to the 2′,4′-diamino ether followed by cleavage with sodium in liquid ammonia gave III in excellent over-all yield.[6] An analogous series of reactions starting with *trans*-dihydrothebainone (X) gave IV.[7] In this series, Wolf–Kishner reduction of X to XI proceeds smoothly and in high yield, in contrast to our experience with the corresponding *cis* ketone VI. The 2,4-dinitrophenyl ether of dihydrodesoxycodeine-C was likewise converted to *d*-3-methoxy-Δ^5-dehydro-N-methylmorphinan (XII),[8] the over-all yield being above 90%. The unsaturation in ring C is preserved during the hydrogenation of the dinitro ether, although XII is readily converted to III by hydrogenation.



XII

Birch reduction of both III and IV proceeded smoothly, although it was necessary to use somewhat more rigorous conditions than those recommended by Wilds and Nelson[9] to achieve complete reduction. In each case the crude reduction product[10] was subjected to acid hydrolysis without purification, and each yielded, as the major product, the β,γ-unsaturated ketone (I and II, respectively) and in addition small amounts of a desoxo compound. The latter was assigned structures XIV and XV, respectively, on the basis of a lack of double-bond absorption in the infrared, end absorption in the ultraviolet (ϵ at 210 mμ, 8000), and,



XIV, B/C *cis*
XV, B/C *trans*

(2) We were later informed privately that Sawa and co-workers had effected the removal of the 4-hydroxyl group from a number of natural morphinan derivatives, including V, by a method similar to that described below, and this work has subsequently been published [Y. Sawa, N. Tsuji, and S. Meada, *Tetrahedron*, **15**, 144, 154 (1961)].

(3) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, p. 154.

(4) Y. Sawa, N. Tsuji, and S. Maeda, ref. 2.

(5) L. Small and R. Lutz, *J. Am. Chem. Soc.*, **56**, 1738 (1934). In our hands this method repeatedly gave dihydrodesoxycodeine-C in 55% yield and dihydrodesoxycodeine-D (VIII) in 21% yield, in contrast to the report of Small and Lutz, who found only a mixture of dihydrodesoxycodeine-B and -C.

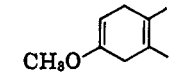
(6) This method of removal of phenolic hydroxyl groups closely resembles that of Sawa, *et al.*,[2] and is based on the diphenyl ether cleavages studied by F. J. Sowa [*ibid.*, **59**, 603, 1488 (1937); **60**, 94 (1938)]. It differs from that of Sawa in that the more easily prepared 2,4-dinitrophenyl ethers are used. Furthermore, the 2,4-diamino groups in the reduced ether assure cleavage in the desired sense and also improve solubility in liquid ammonia. The reaction appears to work well only in systems containing methoxyl or phenyl groups adjacent to the phenolic hydroxyl [*cf.* W. H. Pirkle and J. L. Zabriskie, *J. Org. Chem.*, **29**, 3124 (1964)].

(7) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).

(8) The double bond in dihydrodesoxycodeine-C, formerly assigned only on mechanistic grounds, and in XII can be placed at C-5 with confidence by n.m.r. analysis. The spectra of both show the vinyl proton at C-6 as the expected sextet centered at τ 4.35 and 4.30, $J_{5,6}$ = 11 c.p.s., $J_{6,7}$ = 3 c.p.s., respectively, and the vinyl proton at C-5 as the expected doublet centered at τ 3.35 and 3.90. The decreased shielding of the C-5 proton in dihydrodesoxycodeine-C seems to be associated with its nearness to the C-4 hydroxyl group, inasmuch as removal of this hydroxyl causes the doublet to move upfield to τ 3.90.

(9) A. L. Wilds and N. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

(10) The rules laid down by A. J. Birch [*Quart. Rev.* (London), **12**, 17 (1958)] predict XIII to be the principal product in both cases and the infrared



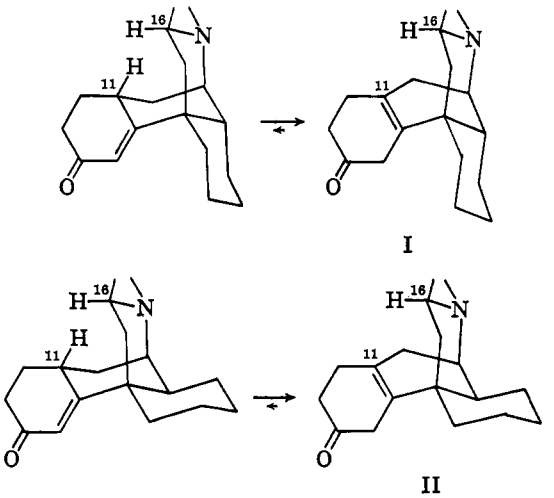
XIII, B/C *cis* and *trans*

spectra of the crude product shows the doublet (*cis* 1662 and 1710, *trans* 1660 and 1690 cm.$^{-1}$) characteristic of the 3,5-dihydroanisole system [G. Stork, *J. Am. Chem. Soc.*, **73**, 504 (1951)].

in the case of XIV, absence of vinyl protons in the n.m.r. spectrum. Confirmation of this assignment to XIV was obtained by pyrolysis of the methohydroxide of XIV to yield the desoxo base XVI whose ultraviolet spectrum [λ_{max} 268 mμ (ϵ 4000)] was characteristic of that of a homoannular conjugated diene (calcd. λ_{max} 273 mμ[11]). The formation of such desoxo compounds during Birch reductions is not without precedent, Wilds and Nelson[9] having found small amounts of $\Delta^{9,10}$-octalin among the products of the reduction of 2-methoxy-5,6,7,8-tetrahydronaphthalene.

The ketones I and II were purified through their crystalline perchlorates. They show only the expected weak absorption characteristic of the unconjugated carbonyl group and end absorption [λ_{max} 280 mμ (ϵ 58), λ_{max} 210 mμ (ϵ 3800) in in the case of I] in the ultraviolet and unconjugated carbonyl absorption in the infrared (I, 1695 cm.$^{-1}$ (perchlorate); II, 1710 cm.$^{-1}$). The n.m.r. spectrum of I shows no vinyl protons.

All attempts, whether by acid, base, or activated carbon,[12] to isomerize I and II to the corresponding α,β-unsaturated ketones failed and the conclusion seems inescapable that in this series the β,γ forms are favored over the α,β forms at equilibrium. What appears to us to be an entirely adequate explanation of this is to be found in the very large nonbonded interactions of the



I

II

hydrogen at C-11 with the axial hydrogen at C-16,[13,14] which is clearly more than enough to reverse the usual position of equilibrium.[15]

The series of reactions III → → I were carried out not only with the *l* isomer but also with the *d* isomer of III and led analogously to the enantiomorph of I.

Only one of the two possible epimers is produced from I on reduction with sodium borohydride and the same epimer is also produced from the perchlorate of I by the action of Raney nickel. Sodium borohydride reduction of II yields a glass of unknown epimeric composition.

Analgesic Tests.—Samples of I and II as well as the secondary alcohol obtained by reduction of I were screened for analgesic activity by the D'Amour–Smith technique.[16,17] I showed questionable analgesic activity eliciting only 8 and 12% of the maximum effect at doses of 60 and 120 mg./kg., respectively. II showed analgesic activity but was much more toxic than I; at a dosage level of 15 mg./kg. analgesic response was 67% of the maximum but 3 of 6 animals died. The secondary alcohol corresponding to I was weakly active, producing 72% of the maximum response at 60 mg./kg.

Experimental[18]

Clemmensen Reduction of Dihydrocodeinone. Dihydrodesoxycodeines-C (IX) and -D (VIII).—The reported conditions[5] applied to 4.25 g. of dihydrocodeinone gave 2.25 g. (56%) of crude **dihydrodesoxycodeine-C (IX)**, m.p. 103–106°, which after crystallization from dilute alcohol had m.p. 107–113° (lit.[5] m.p. 109–111°), $[\alpha]^{27}D$ +5.2° (*c* 1.8, alcohol) (reported $[\alpha]^{24}D$ +5.6°), and 1.5 g. (25%) of dihydrodesoxycodeine-D L-(+)-bitartrate, m.p. 123–128° or 154–155°, depending on the rate of heating (lit.[19,20] m.p. 123–125° and 154–154.5°). **Dihydrodesoxycodeine-D**, m.p. 107–108° (lit.[19] m.p. 106–107°), was recovered from the bitartrate. Its picrate melted at 225–226° (lit.[21] m.p. 207°).

Catalytic hydrogenation of dihydrodesoxycodeine-C in alcohol over platinum gave **tetrahydrodesoxycodeine** (*l*-**3-methoxy-4-hydroxy-N-methylmorphinan, V**) (95% yield) as its hemihydrate, m.p. 141–147°, which on sublimation gives the anhydrous base, m.p. 123–124° (lit.[19] m.p. 141–147° for the hemihydrate, 123–124° for the anhydrous base).

Preparation and Cleavage of the 2,4-Dinitrophenyl Ether of *l*-3-Methoxy-4-hydroxy-N-methylmorphinan.—A mixture of 1.94 g. of sublimed V, 0.48 g. of 50% sodium hydride–mineral oil dispersion, and 20 ml. of dry xylene was stirred under nitrogen. When hydrogen evolution had ceased, 1.95 g. of 2,4-dinitrofluorobenzene in 12 ml. of xylene was added followed by 7 ml. of dry dimethylformamide. The solution warmed, frothed, and lightened in color, and was then heated under reflux for 15 min., cooled, diluted with 75 ml. of benzene, and washed with 25-ml. portions of 5% sodium hydroxide solution until the washings became almost colorless. The benzene solution was extracted with four 100-ml. portions of hot 0.1 *N* hydrochloric acid, the combined extracts were back-extracted with benzene, and the acid solution was stripped briefly *in vacuo* to remove traces of benzene. The clear yellow solution was slowly made basic with 15 *N* ammonium hydroxide to precipitate a light yellow, finely divided solid which was collected and air dried (3.13 g., 102% of theory). Recrystallization from ethanol gave small pale yellow crystals of **tetrahydrodesoxycodeine 2,4-dinitrophenyl ether** of m.p. 202.0–202.5°, $[\alpha]^{28}D$ −142° (*c* 2.26, benzene), $[\alpha]^{27}D$ −44.5° (*c* 1.1, chloroform).

Its infrared spectrum is compatible with the assigned structure, the lack of a hydroxyl band showing that O-arylation rather than C-arylation has occurred.

Anal. Calcd. for $C_{24}H_{27}N_3O_6$: C, 63.56; H, 6.00. Found: C, 63.71; H, 6.00.

A solution of 504 mg. of this dinitro ether in 50 ml. of methanol was hydrogenated over 100 mg. of platinum at atmospheric pressure. Six molar equivalents of hydrogen was consumed rapidly. The catalyst was removed by filtration through a

(11) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 17.

(12) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).

(13) We are grateful to Dr. Robert L. Autrey for this suggestion and for other helpful discussions.

(14) In the α,β forms the H at C-11 must, of course, be axial to ring B.

(15) Examination of Dreiding models suggests that the centers of these two hydrogens would be only about 1.2 Å. apart. If ring D (that containing the N atom) assumes the boat form, this interaction is relieved in the B/C *cis* series (but not in the B/C *trans* series) and if ring B becomes a boat (necessitating epimerization at C-11) the interaction is also relieved, but both of these expedients are energetically grossly unfavorable compared with the α,β–β,γ shift. The equilibrium between the α,β and β,γ forms of 2-octalone favors the α,β 3 to 1 [G. Stork, *et al.*, *J. Am. Chem. Soc.*, **85**, 207 (1963); see also D. J. Baisted and J. S. Whitehurst, *J. Chem. Soc.*, 4089 (1961)] corresponding to a difference in free energy of only 0.7 kcal./mole.

(16) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 75 (1941).

(17) We are grateful to Dr. Sydney Archer and Dr. L. S. Harris of the Sterling-Winthrop Research Institute for arranging for these assays.

(18) All melting points are corrected. Elemental analyses were carried out by Micro-Tech Laboratories, by T. Montzka, V. Landeryou, or A. Revilla. Infrared spectra were recorded on Perkin-Elmer Model 21 or 421 spectrometers. Ultraviolet spectra were recorded on a Cary Model 11MS spectrometer. N.m.r. spectra were recorded on a Varian Associates HR 60 spectrometer by Dr. Lawrence Colebrook.

(19) L. Small and F. Cohen, *J. Am. Chem. Soc.*, **54**, 802 (1932).

(20) L. Small and D. Morris, *ibid.*, **55**, 2874 (1933).

(21) C. Mannich and H. Löwenheim, *Arch. Pharm.*, **258**, 295 (1920).

glass-wool plug and the filtrate was taken to dryness at reduced pressure. The light brown glassy residue was taken into 50 ml. of dry ether and diluted to about 200 ml. with liquid ammonia. Small pieces of clean sodium were added, with stirring, until a permanent blue color was developed. After short standing a few drops of alcohol were added to destroy any remaining sodium and the ammonia was evaporated under an air stream. The dark residue was taken into 100 ml. of water and extracted with three 25-ml. portions of ether. The ether extracts were dried with brine and anhydrous sodium sulfate and the ether was removed under diminished pressure. The slightly yellow oil thus obtained (311 mg., 103% of theory) crystallized on standing. Chromatography of this material upon Woelm activity I neutral alumina gave *l*-**3-methoxy-N-methylmorphinan (III)** of m.p. 108–109° in 93% yield. After recrystallization from ethanol–water, the melting point was raised to 109.5–110.0°, $[\alpha]^{23}D$ −48.4° (*c* 0.86, 95% ethanol); lit.[22] m.p. 108–111°, $[\alpha]D$ −49.3° (*c* 3, ethanol). The material exhibits the ultraviolet spectrum [$\lambda_{max}^{ethanol}$ 227 mμ (ε 7550), 280 (2360), and 288 (2140)] expected of a substituted anisole.

Its **methiodide** melts at 240–242°; $[\alpha]^{26}D$ −21.2° (*c* 1.0, 95% ethanol), lit.[22] m.p. 239–240°.

Its **hydriodide** was prepared by adding saturated potassium iodide solution to a solution of the base in dilute aqueous acetic acid. The salt was recrystallized from water as colorless needles of m.p. 120° (lit.[22] m.p. 125–127°).

Preparation and Cleavage of the 2,4-Dinitrophenyl Ether of 3-Methoxy-4-hydroxy-Δ⁵-dihydro-N-methylmorphinan.—When dihydrodesoxycodeine-C (2.95 g.) was subjected to arylation as described above, a total of 4.55 g. (95%) of recrystallized **dihydrodesoxycodeine-C 2,4-dinitrophenyl ether**, m.p. 167.5–168.5°, $[\alpha]^{28}D$ −7.5° (*c* 0.86, benzene), $[\alpha]^{27}D$ −135° (*c* 0.9, chloroform), was obtained.

Anal. Calcd. for $C_{24}H_{25}N_3O_6$: C, 63.85; H, 5.58. Found: C, 63.85; H, 5.94.

Hydrogenation of 606 mg. of this dinitro ether over platinum ceased after 6 molar equiv. of hydrogen had been absorbed. Cleavage of the crude 2,4-diamino ether by sodium in liquid ammonia as described above yielded 322 mg. (92%) of *d*-**3-methoxy-Δ⁵-dihydro-N-methylmorphinan (XII)**, m.p. 89.0–91.5°. The analytical sample was crystallized several times from methylcyclohexane and sublimed: m.p. 89.5–91.5°; $[\alpha]^{25}D$ +7.5° (*c* 0.8, ethanol); $\lambda_{max}^{ethanol}$ 228 mμ (ε 7220), 280 (2220), 288 (2070). Its n.m.r. spectrum ($CDCl_3$) showed two vinyl hydrogens, τ 3.90 (d, C-5 H) and 4.30 (pair of triplets, C-6 H), 6.24 (O-CH_3), 7.58 (N-CH_3).

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.25; H, 8.61. Found: C, 80.09; H, 8.58.

Its **methiodide**, crystallized from ethanol–ether, melts at 225–227°; $[\alpha]^{28}D$ +21.8° (*c* 1.94, 50% ethanol).

Anal. Calcd. for $C_{19}H_{26}INO$: C, 55.48; H, 6.37. Found: C, 55.44; H, 6.40.

Hydrogenation of this Δ⁵ compound (XII, 669 mg.) over platinum in methanol gave 660 mg. of *l*-3-methoxy-N-methylmorphinan (III), m.p. 109–110.5°.

Birch Reductions. A. *l*-3-Methoxy-N-methylmorphinan.—A solution of 80.4 g. of *l*-3-methoxy-N-methylmorphinan (III) in 1250 ml. of 1:4 dry ether–anhydrous ammonia was treated with 20 g. of clean lithium shot. After stirring for 15 min., the deep blue solution was treated dropwise with 180 ml. of absolute ethanol (frothing). The ammonia was then allowed to evaporate and the residue was taken up in 1 l. of water and extracted with three 100-ml. portions of ether. The extracts were washed with water, dried with brine and anhydrous sodium sulfate, and stripped to dryness under diminished pressure. The infrared spectrum of the residual oil showed the doublet at 1662 and 1710 $cm.^{-1}$ characteristic of 2,5-dihydroanisole systems.[23] Its ultraviolet spectrum indicated that less than 5% of aromatic material remained. The oil was taken up in 50 ml. of 2.4 *N* hydrochloric acid and heated on a steam bath for 15 min. The acid solution was washed with ether, made basic with ammonia, and extracted with three 50-ml. portions of methylene chloride; the extract, after drying with brine and anhydrous sodium sulfate, was concentrated under diminished pressure. The colorless oil (7.52 g.) was taken into 50 ml. of warm 20% L-(+)-tartaric acid solution and allowed to stand. The long needles which soon formed were collected and washed with 10 ml. of cold water (3.39 g. after drying). No additional crystalline material could be obtained from the mother liquors. Recrystallization from water yielded 3.02 g. of *d*-**1,2,3,4-tetrahydro-N-methyl-morphinan L-(+)-bitartrate sesquihydrate** melting at 146–147°; $[\alpha]^{25}D$ +51.8 (*c* 1.3, 95% ethanol).

Anal. Calcd. for $C_{21}H_{33}NO_6 \cdot 1.5H_2O$: C, 59.69; H, 8.59. Found: C, 59.82; H, 8.56.

A sample dried 8 hr. at 55° and 0.3 mm. suffered a 4.7% weight loss; calcd. water content of sesquihydrate, 6.4%.

A portion (1.63 g.) of this bitartrate was converted to the free base by partitioning between 100 ml. of dilute ammonium hydroxide and four 25-ml. portions of methylene chloride. The combined extracts were dried with brine and anhydrous sodium sulfate and concentrated to give crystalline *d*-**1,2,3,4-tetrahydro-N-methylmorphinan (XIV)**. Crystallization from ligroin gave clusters of fine needles (513 mg. in two crops) of m.p. 58.4–59.4°. Sublimation gave white rhomboids of m.p. 59.0–60.0°, $[\alpha]^{20}D$ +71.0° (*c* 1.9, 95% ethanol). Its infrared spectrum shows no double-bond absorption and its n.m.r. spectrum shows no vinyl hydrogens. However, the ultraviolet spectrum shows end absorption [210 mμ, (ε 7790)] indicating the presence of a tetrasubstituted double bond.

Anal. Calcd. for $C_{17}H_{27}N$: C, 83.20; H, 11.09. Found: C, 83.36; H, 11.13.

Its **picrate**, prepared in and recrystallized from ethanol, melts at 185.5°; $[\alpha]^{27}D$ +25° (*c* 1.2, chloroform).

Anal. Calcd. for $C_{23}H_{30}N_4O_7$: C, 58.21; H, 6.37. Found: C, 58.39; H, 6.54.

Its **methiodide**, prepared in neat methyl iodide and recrystallized from ethanol–ether, melts at 275–276°; $[\alpha]^{20}D$ +57.5° (*c* 1.2, 95% ethanol).

Anal. Calcd. for $C_{18}H_{30}IN$: C, 55.81; H, 7.81. Found: C, 55.95; H, 7.90.

The mother liquors from the bitartrate crystallization were diluted to 100 ml. with water, made basic with 15 *N* ammonium hydroxide, and extracted with four 25-ml. portions of methylene chloride. These extracts were dried with brine and anhydrous sodium sulfate and concentrated to yield a yellow oil which crystallized on standing. Treatment with activated carbon and recrystallization from ligroin (b.p. 30–60°) gave tan platelets of *d*-**1,2,3,4-tetrahydro-3-oxo-N-methylmorphinan** (I, 4.06 g., 51% yield) of m.p. 110–113°. After another recrystallization, the base melted at 115–118°; $[\alpha]^{23}D$ +50.8° (*c* 2.4, 95% ethanol), infrared carbonyl adsorption 1708 $cm.^{-1}$. The n.m.r. spectrum shows no vinyl hydrogens.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.72. Found: C, 78.71; H, 9.77.

The base is best isolated and purified as its **perchlorate** which crystallizes readily when the crude base, in a small volume of 95% ethanol, is acidified (congo red paper) with 10% ethanolic perchloric acid. The perchlorate can be recrystallized from ethanol or from methylene chloride–ether and, when pure, melts at 217–218°; $[\alpha]^{20}D$ +40° (*c* 1.1, 95% ethanol), λ_{max}^{KBr} 1691 $cm.^{-1}$, $\lambda_{max}^{95\% \text{ ethanol}}$ 280 mμ (ε 58), end absorption ($\epsilon_{210\,m\mu}$ 3800).

Its **picrate**, prepared in and recrystallized from 95% ethanol as fine yellow needles, melts at 197.0–197.5°; $[\alpha]^{27}D$ +19° (*c* 1.5, chloroform).

Anal. Calcd. for $C_{23}N_{28}N_4O_8$: C, 56.55; H, 5.78; equiv. wt., 488. Found: C, 56.51; H, 5.73; equiv. wt., 481 (determined spectroscopically).

Its **methiodide** was prepared in neat methyl iodide and recrystallized from absolute ethanol–ether; m.p. 251–252° dec., $[\alpha]^{25}D$ +51.4° (*c* 2.1, 50% ethanol).

Anal. Calcd. for $C_{18}H_{28}INO$: C, 53.87; H, 7.03. Found: C, 53.10; H, 7.19.

Hofmann Degradation of I.—*d*-1,2,3,4-Tetrahydro-N-methylmorphinan methiodide (490 mg.) was converted to its methohydroxide using Dowex I X-4 anion-exchange resin, and the resulting aqueous solution was taken to dryness *in vacuo* at room temperature. The fluffy glass of methohydroxide was distilled under reduced pressure. *d*-**1,2,3,4-Tetrahydro-N-methylmorphinan methine** collected on the cold finger at 0.1 mm. and 85° as a colorless oil. The methine was redistilled to yield a sample which was homogeneous by g.l.c.; $[\alpha]^{20}D$ +262° (*c* 1.5, 95% ethanol), $\lambda_{max}^{ethanol}$ 268 mμ (ε 3980).

Anal. Calcd. for $C_{18}H_{29}N$: C, 83.55; H, 11.05. Found: C, 84.08; H, 11.34.

Its **picrate** was prepared in and recrystallized from 95% ethanol; m.p. 160–161°, $[\alpha]^{25}D$ +116° (*c* 1.7, chloroform).

(22) O. Schnider and A. Grussner, U. S. Patent 2,676,177 (1954).

(23) G. Stork, *J. Am. Chem. Soc.*, **73**, 504 (1951).

Anal. Calcd. for $C_{24}H_{32}N_4O_7$: C, 59.00; H, 6.60. Found: C, 58.86; H, 6.33.

Its **methiodide**, prepared in neat methyl iodide and recrystallized from 95% ethanol–ether, melts at 228–229°; $\lambda_{max}^{95\% \text{ ethanol}}$ 267 mμ (ε 4360) and 219 mμ (ε 14,650).

Anal. Calcd. for $C_{19}H_{32}IN \cdot 0.5H_2O$: C, 55.60; H, 8.11. Found: C, 55.64; H, 7.93.

B. ***d*-3-Methoxy-N-methylmorphinan**.—When this substance was reduced under the same reaction conditions used for its enantiomorph, ***l*-1,2,3,4-tetrahydro-N-methylmorphinan D(−)-bitartrate sesquihydrate** of m.p. 147–149°, $[\alpha]^{26}D$ −54.5° (*c* 1.4, 95% ethanol), was obtained in 19% yield and ***l*-1,2,3,4-tetrahydro-3-oxo-N-methylmorphinan perchlorate** of m.p. 218.5–219.5°, $[\alpha]^{26}D$ −38.2° (*c* 1.5, 95% ethanol), was obtained in 50% yield.

The bitartrate, after being dried at 80° (0.05 mm.) for 14 hr., melted at 136–137°. A synthetic racemic mixture of ***dl*-1,2,3,4-tetrahydro-N-methylmorphinan DL-bitartrate sesquihydrate** melted, after recrystallization from water, at 189.0–189.5°. Drying to constant weight at 100° (0.05 mm.) resulted in a 5.7% weight loss; calcd. weight loss for the sesquihydrate, 6.4%. The dried racemate melted at 187–188°, which suggests that water of hydration may be lost from the racemic sesquihydrate during the determination of its melting point.

***l*-1,2,3,4-Tetrahydro-3-oxo-N-methylmorphinan** was obtained from its perchlorate as cream-colored plates of m.p. 105–111°.

C. ***l*-3-Methoxy-N-methylisomorphinan**.—A solution of 2.50 g. of *l*-3-methoxy-N-methylisomorphinan (IV) in 600 ml. of 5:1 ammonia–ether was treated with 8 g. of ether-washed lithium shot. The blue color which appeared within a few seconds was allowed to persist for 20 min., then was destroyed by cautious addition of 35 ml. of absolute ethanol. When most of the ammonia had evaporated, the solution was diluted to 800 ml. with water and extracted with three 100-ml. portions of ether.[24] The combined extracts were washed with water, then extracted with three 30-ml. portions of 1 *N* hydrochloric acid. The colorless acid extracts were made basic with 15 *N* ammonium hydroxide and quickly extracted with three 30-ml. portions of methylene chloride. Concentration of the acid extracts gave 2.22 g. of light yellow oil. Treatment of this oil with 10% alcoholic perchloric acid yielded 1.98 g. (60% of theory) of crude ***d*-1,2,3,4-tetrahydro-3-oxo-N-methylisomorphinan perchlorate**, m.p. 246–250°. Recrystallization from 95% ethanol–ether gave long colorless needles, m.p. 253–254° with sintering at 246°, $[\alpha]^{30}D$ +23.6° (*c* 1.12, 50% ethanol), λ_{max}^{KBr} 1680 and 1690 cm.$^{-1}$ (sh). Although the infrared spectrum suggests that the carbonyl may be conjugated with the double bond, the ultraviolet spectrum (ethanol) shows no evidence of this. We believe that the infrared carbonyl absorption is abnormal and is a result of interaction with the potassium bromide matrix.

Anal. Calcd. for $C_{17}H_{26}ClNO_5$: C, 56.74; H, 7.28. Found: C, 56.85; H, 7.39.

Conversion of the purified perchlorate to the free base by partitioning between dilute ammonium hydroxide and methylene chloride gave, after drying the extract over anhydrous sodium sulfate and concentration, a yellow mobile oil which crystallized upon molecular distillation at 100° (0.01 mm.) to yield *d*-1,2,3,4-tetrahydro-3-oxo-N-methylisomorphinan (II) of m.p. 83–84°, $[\alpha]^{25}D$ +5.7 (*c* 1.1, 95% ethanol), λ_{max}^{KBr} 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.72. Found: C, 78.97; H, 9.81.

(24) Aliquots of the combined extract, when evaporated to dryness, gave an oil showing the infrared adsorption at 1690 and 1660 cm.$^{-1}$ characteristic of the unconjugated dihydroanisole system, but showing only traces of the band at 1610 cm.$^{-1}$ which is present in the aromatic starting material. The ultraviolet spectrum also indicated that only a few per cent of aromatic material remained.

Its **picrate** was prepared in and recrystallized from 95% ethanol as clusters of yellow needles, m.p. 214.5–216.5° with sintering at 211.5°, $[\alpha]^{27}D$ +5.4° (*c* 1.2, chloroform), λ_{max}^{KBr} 1708 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78. Found: C, 56.71; H, 6.12.

The mother liquors from the isolation of the perchlorate were taken into 25 ml. of water and excess potassium triiodide was added. After 18 hr., the solution was made strongly basic with 15% sodium hydroxide solution and extracted with three 25-ml. portions of ether. The ether extracts were combined, washed with water, and dried with brine and anhydrous sodium sulfate. Evaporation of the ether gave a yellow oil which showed no aromatic, carbonyl, or double-bond absorption in the infrared. This oil was chromatographed on Woelm activity III neutral alumina. The major fraction was treated with dilute acetic acid and saturated sodium iodide and gave 150 mg. of colorless needles of m.p. 193–194°. After recrystallization from water followed by thorough drying, an analytical sample of **1,2,3,4-tetrahydro-N-methylisomorphinan hydriodide** melting at 200–201°, sintering at 193–198°, was obtained.

Anal. Calcd. for $C_{17}H_{28}IN$: C, 54.69; H, 7.56. Found: C, 54.72; H, 7.69.

The remainder of the eluted oil was converted to ***d*-1,2,3,4-tetrahydro-N-methylisomorphinan picrate** by treatment with alcoholic picric acid. After recrystallization from ethanol–water, an analytical sample of m.p. 189–192°, $[\alpha]^{27}D$ +12.0° (*c* 1.1, chloroform), was obtained.

Anal. Calcd. for $C_{23}H_{30}N_4O_7$: C, 58.21; H, 6.37. Found: C, 58.31; H, 6.63.

***d*-1,2,3,4-Tetrahydro-3-hydroxy-N-methylmorphinan**.—A solution of 104 mg. of sodium borohydride in 10 ml. of isopropyl alcohol and 0.5 ml. of 2 *M* sodium hydroxide was treated with 1.07 g. of *d*-1,2,3,4-tetrahydro-3-oxo-N-methylmorphinan (I) perchlorate. The mixture warmed and evolved gas, and after 1 hr. was diluted with 50 ml. of 1.5 *N* sulfuric acid (foaming) and extracted several times with ether. The raffinate was made basic with 15 *N* ammonium hydroxide followed by extraction with three 20-ml. portions of methylene chloride to give, after drying with anhydrous sodium sulfate and removal of the methylene chloride, 735 mg. (84%) of pink sirup which crystallized spontaneously, m.p. 174–176°. Recrystallization from ethanol–water gave 635 mg. of white platelets of ***d*-1,2,3,4-tetrahydro-3-hydroxy-N-methylmorphinan** of m.p. 175–176°. After sublimation, the melting point was 175–175.5°, $[\alpha]^{24}D$ +64.5° (*c* 1.4, 95% ethanol).

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 78.47; H, 10.33.

The action of Raney nickel in refluxing alcohol on the perchlorate of I produced the same substance in lower yield. Paper chromatography of the mother liquors from both reductions failed to indicate the presence of another epimer.

***d*-1,2,3,4-Tetrahydro-3-hydroxy-N-methylisomorphinan**.—The similar treatment of II (456 mg.), after processing and chromatography on Woelm neutral alumina (activity I), gave 62% of a glass which was purified by molecular distillation.

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 77.41; H, 10.01.

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