Some Derivatives of Metamorphinan[1]

MARSHALL GATES AND DAVID ARTHUR KLEIN[2]

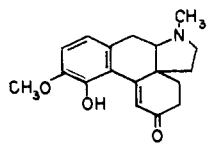
Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627

Received December 19, 1966

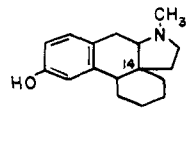
Several derivatives of a new isomer of morphinan, metamorphinan, have been prepared and screened for analgetic activity and morphine antagonism in small animals. A particularly straightforward test of one of the hypotheses as to the relationship between structure and analgetic activity put forward by Braenden, Eddy, and Halbach is provided by the results with 3-hydroxy-N-methylmetamorphinan, which exhibits no analgetic activity.

In reviewing evidence then available, Braenden, Eddy, and Halbach[3] concluded, *inter alia*, that a phenyl group (or phenyl isostere) directly connected to a quaternary carbon was a structural feature common to all potent analgetic agents.

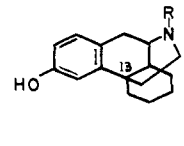
The ready availability (from thebaine) of metathebainone (I) coupled with the development[4] in these laboratories of a convenient method for the removal of phenolic hydroxyl groups from such substances has allowed a particularly straightforward test of this conclusion. Thus, we have prepared (−)-3-hydroxy-N-methylmetamorphinan[5] (II) for comparison with (−)-3-hydroxy-N-methylmorphinan (levorphanol, III) from which it differs only in the terminus of the ethanamine bridge (C-13, adjacent to the phenyl ring in III, C-14, one carbon removed from the phenyl ring in II).



I



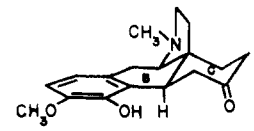
II



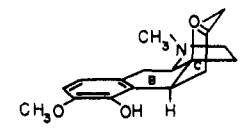
III R=CH$_3$
VIII R=CH$_2$-cyclopropyl

The reduction of thebaine in strongly acid solutions either by stannous chloride or more conveniently by hydrogen over palladium yields metathebainone (I) which in turn with sodium amalgam in dilute alkaline solution gives dihydrometathebainone (IV) in high yield.[6] Although IV is a well-known substance, its stereochemistry has not been ascertained nor indeed studied, and it seemed essential to establish the relationship between rings B and C before proceeding.

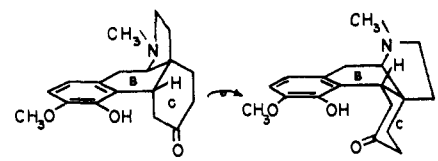
Of the three possible structures[7] for dihydrometathebainone (IVa–c), it seems possible to exclude IVc on the basis of the mode of formation of metathebainone from thebaine,[8] since the migration of the ethanamine chain from C-13 to C-14 presumably occurs in synchronous fashion, the new bond at C-13 forming on the same side of the molecule.



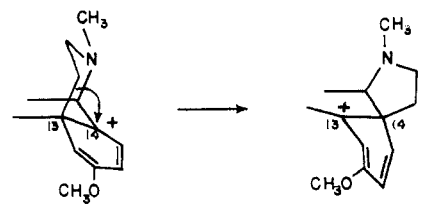
IVa
B/C TRANS



IVc
B/C cis



IVb
B/C cis



Stork and Darling[9] have shown that in the reduction of α,β-unsaturated ketones by lithium in ammonia, the proton is delivered to the β-carbon atom of the intermediate anion or anion radical in a direction axial to the ketonic ring and this principle applied to the sodium amalgam reduction of metathebainone (I) allows either IVa or IVb as product.[10]

Small and Meitzner[11] reported that a saturated ketone obtained in low yield from the hydrogenation of I over palladium was identical with the product of sodium amalgam reduction of I, dihydrometathebainone (IV). If true, this would allow the assignment of structure IVa (B/C *trans*) to dihydrometathebainone, inasmuch as models show clearly that a catalytic surface can be approached readily only from the side opposite the ethanamine chain of metathebainone (I). Hydrogenation from such a surface would give IVa. Unfortunately, the identity claimed by Small and Meitzner appears to us to be so insecure experimentally[12] as to require confirmation.

(1) Supported in part by funds supplied by the Hoffmann-La Roche Foundation.

(2) Union Carbide Fellow, 1964–1965.

(3) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

(4) W. H. Pirkle and J. L. Zabriskie, *J. Org. Chem.*, **29**, 3124 (1964). See also Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **15**, 144, 154 (1961).

(5) It seems appropriate to retain the prefix "meta" of metathebainone in naming these substances. Thus, metamorphinan bears the same structural relationship to morphinan as dihydrometathebainone does to dihydrothebainone.

(6) (a) R. Pschorr, A. Pfaff, and F. Herrschmann, *Ber.*, **38**, 3160 (1905); (b) J. M. Gulland and R. Robinson, *J. Chem. Soc.*, **123**, 998 (1923); (c) C. Schöpf and F. Borkowsky, *Ann.*, **458**, 148 (1927).

(7) The remaining B/C *trans* form and the conformationally flipped form of IVc would both require 1,3-diaxial *trans* ring junctions and are prohibited.

(8) G. Stork, *Alkaloids*, **2**, 194 (1952).

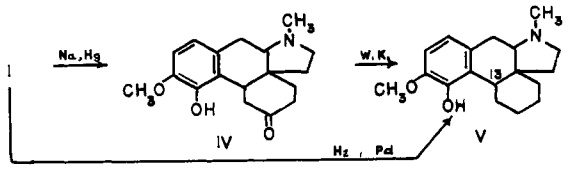
(9) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **82**, 1512 (1960); **86**, 1761 (1964).

(10) We assume that sodium amalgam and lithium ammonia reductions are mechanistically comparable.

(11) L. F. Small and E. Meitzner, *J. Am. Chem. Soc.*, **55**, 4602 (1933).

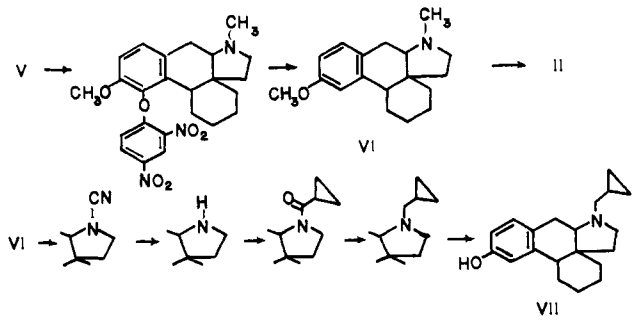
(12) Two semicarbazones, mp 217–218°, $[\alpha]^{25}D$ +88.4°, and mp 232°, $[\alpha]^{25}D$ +109.8°, were claimed to be identical on the basis of mmp 226°. The ketones themselves were not compared.

We find in contrast to earlier reports[13] that I readily absorbs 3 moles of hydrogen at atmospheric pressure to produce crystalline tetrahydrodeoxymetacodeine[14] (V) in good yield, and this substance is also produced by Wolff–Kishner reduction of IV. It is thus clear that the same configuration at C-13 results from either catalytic hydrogenation or sodium amalgam reduction of the 5–13 double bond of metathebainone and accordingly we assign structure IVa (B/C *trans*) to IV.



The removal of the phenolic group of V by the method of Pirkle and Zabriskie[4] was unexceptional and the conversion of the 3-methoxy-N-methylmetamorphinan (VI) so obtained to 3-hydroxy-N-methylmetamorphinan (II) and to 3-hydroxy-N-cyclopropylmethylmetamorphinan (VII) followed well-established routes.[15,16] Compound VII was prepared for examination as a morphine antagonist. These transformations are outlined in Scheme I.

SCHEME I



Physiological Results.—3-Hydroxy-N-methylmetamorphinan (II) and the corresponding N-cyclopropylmethylmetamorphinan (VII) have been screened in small animals for analgetic activity[17] by the D'Amour–Smith rat tail flick test, by the phenylquinone writhing test, and by the inflamed-paw test. Neither substance showed any analgetic activity in doses as high as 25 mg/kg in the D'Amour–Smith test using conditions under which morphine is effective at 5 mg/kg, and no significant activity was shown by either substance in the inflamed paw test. In the phenylquinone writhing test, II shows 0.09–0.12 times the activity of morphine, VII 0.06–0.07 times its activity. It would appear that II is less than $^1/_{50}$ as active as the corresponding 3-hydroxy-N-methylmorphinan (III, levorphanol) in the D'Amour–Smith test and perhaps $^1/_{100}$ as active in the phenylquinone writhing test. Compound VII is perhaps $^1/_{500}$ as active as the corresponding 3-hydroxy-N-cyclopropylmethylmorphinan (VIII, cyclorphan) in the phenylquinone writhing test and shows no morphine antagonistic activity in doses up to 25 mg/kg, whereas cyclorphan is a potent morphine antagonist (AD_{50} *vs.* meperidine, 0.034 mg/kg).

It seems clear that the shift in position of the ethanamine side chain from C-13 to C-14 in the metamorphinan derivatives II and VII has essentially obliterated the characteristic analgetic and antagonistic activity associated with the corresponding morphinans III and VIII.

Experimental Section

All melting points are corrected. Rotations were taken in 95% ethanol on a Rudolf Precision polarimeter. Infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer. Nmr spectra were taken on a Varian A-60 spectrometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Metathebainone (I) was prepared according to Gulland and Robinson[6b] and was obtained as the methanolate, mp 101–121°, gas evolution, $[\alpha]^{25}D$ −398° (*c* 2.04), lit. mp 115–118 °,[6a] $[\alpha]^{24}D$ −419° (*c* 1.966).[6b] Its infrared spectrum showed strong absorption at 1650 cm^{-1} (conjugated carbonyl). Its benzylidene derivative had mp 123–125° (lit.[6a] 120–123°).

Dihydrometathebainone (IV) was prepared according to Pschorr[6a] and was used as obtained for further transformations. For characterization it was purified through its **picrate,** mp 243–245° dec, after recrystallization from alcohol–dimethyl sulfoxide.

Anal. Calcd for $C_{24}H_{26}N_4O_{10}$: C, 54.34; H, 4.94; N, 10.56. Found: C, 54.19; H, 5.00; N, 10.55.

A sample of picrate (4.09 g) on distribution between 1% LiOH and $CHCl_3$ yielded 2.51 g of a colorless glass which on cooling in methanol gave heavy colorless prisms of the **methanolate,** 1.89 g, mp 58–69° (lit.[6b] 50–54°), ν_{max} 1705 cm^{-1} (carbonyl). On standing at room temperature for several days or on drying at 110°, unsolvated material of mp 140–141° (lit.[6b] 135–136°), $[\alpha]^{25}D$ +75.4° (*c* 1.67) (lit.[6b] +67.05°), was obtained. Its semicarbazone melted at 224–226° (gas evolution), lit.[6b] 217–218°.

Tetrahydrodeoxymetacodeine (V). A. By Hydrogenation of Metathebainone (I).—A solution of 2.00 g of I methanolate in 40 ml of 18% HCl was stirred under hydrogen over 1 g of 10% Pd–C. During 29 hr a total of 435 ml (96% of 3 moles) of hydrogen was absorbed, 335 ml within the first 2 hr. The solution was filtered from catalyst, made basic to excess with NH_3, and extracted four times with $CHCl_3$. The $CHCl_3$ extracts were dried, filtered, and concentrated. After pumping out, a residue of 1.73 g (100%) of a slightly pink glass which slowly crystallized, mp 58–81°, remained. This material was converted to the **picrate** in methanol, 2.67 g (86%), mp 261.5–263° dec. Two recrystallizations from dimethyl sulfoxide–methanol gave 1.98 g (64%), mp 264–265° dec.

Anal. Calcd for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46; N, 10.85. Found: C, 56.07; H, 5.39; N, 11.18.

Distribution of this picrate (1.98 g) between 1% LiOH and $CHCl_3$ gave 1.12 g (100%), mp 75–88°, of base after washing, drying, filtering, and concentrating the $CHCl_3$ solution. After three crystallizations from 30–60° petroleum ether, 0.56 g, mp 90–92°, $[\alpha]^{25}D$ +18.8° (*c* 1.65), of massive colorless prisms was obtained.

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22, H, 8.77; N, 4.87. Found: C, 75.23; H, 8.87; N, 4.82.

Its **hydriodide,** colorless needles, prepared in and crystallized from methanol, had mp 212–214.5°, gas evolution, after partial melting and resolidifying at 130–140°.[18]

Tetrahydrodeoxymetacodeine (V). B. By Wolff–Kishner Reduction of Dihydrometathebainone.—A mixture of 18 g of crude IV, 50 g of 85% KOH, 25 ml of 95% hydrazine hydrate, and 300 ml of diethylene glycol was refluxed for 2 hr, distilled until the temperature of the mixture reached 175°, and refluxed for an additional 3 hr. The reaction mixture was cooled, diluted

(13) The 5–13 double bond of metathebainone has been reported to be resistant to hydrogenation (H. Hock, Dissertation, Munich, 1926), quoted by Small and Meitzner[11] who also observed little hydrogenation at this position.

(14) Tetrahydrodeoxymetacodeine was prepared as an amorphous solid but not characterized by Small and Meitzner.[11] A crystalline hydriodide, melting point not recorded, was described.

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

(16) W. H. Pirkle and M. Gates, *J. Org. Chem.*, **30**, 1769 (1965).

(17) We are greatly indebted to Dr. A. C. Osterberg, Lederle Laboratories, American Cyanamid Co., to Dr. Harold Blumberg, Endo Laboratories, and to Dr. Charles A. Winter, Merck Institute for Therapeutic Research, through whose courtesy these tests were carried out.

(18) This substance was prepared and analyzed by Small and Meitzner,[11] but its melting point was not recorded.

to 1400 ml with water, almost neutralized with concentrated HCl, and extracted with ether. Drying and evaporation of the ether gave a brown oil which was eluted through a column of 100 g of grade I neutral alumina in ether. The resulting 15 g of light yellow oil solidified to a waxy solid, mp 83–86°. Its infrared spectrum showed no absorption in the carbonyl region. A small sample, recrystallized twice from 30–60° petroleum ether, had mp 88–91°, undepressed by V prepared by hydrogenation of I. The infrared spectra of these samples were indistinguishable. The picrate and hydriodide were indistinguishable (melting point and infrared spectra) from those described under method A.

Tetrahydrodeoxymetacodeine 2,4-Dinitrophenyl Ether.—A mixture of sodium hydride (3.4 g, 50% dispersion in mineral oil), 3.9 g of V, and 100 ml of benzene was stirred for 0.5 hr at room temperature until hydrogen evolution had ceased. A solution of 8 g of 2,4-dinitrofluorobenzene in 40 ml of benzene was added slowly, and the mixture was stirred for 1 hr at room temperature. Purified dimethylformamide (20 ml) was added, and the solution was refluxed for 1 hr, cooled, and thoroughly washed with 10% NaOH. The benzene was removed under reduced pressure and the residue, in ether, was extracted with 0.2 *N* HCl. The combined acid extracts were neutralized with concentrated NH_4OH, and the product was taken into ether. Elution through 100 g of grade I Merck acid-washed alumina in ether afforded 6 g of yellow amorphous solid. It did not crystallize or form a crystalline picrate or methiodide. Its infrared spectrum showed absorption at 1520 and 1345 cm^{-1} but no absorption in the 3100–3600-cm^{-1} region.

3-Methoxy-N-methylmetamorphinan (VI).—A mixture of 0.5 g of PtO_2 and 7 g of the dinitrophenyl ether in 250 ml of anhydrous methanol was stirred under hydrogen until absorption ceased (about 20 hr). The initial uptake was extremely rapid, and total uptake was about 2.7 l. (2.1 l., theoretical). The methanol was removed under reduced pressure, and residue was dissolved in 40 ml of purified tetrahydrofuran. Liquid NH_3 (400 ml) was added, and the resulting solution was treated with chunks of sodium until a deep blue color persisted for 5 min. Methanol was added dropwise to decompose the excess sodium and the NH_3 was allowed to evaporate. The residue was partitioned between ether and 10% NaOH. After thorough washing with 10% NaOH, the organic layer was dried and concentrated at reduced pressure to give 3.8 g of light brown oil. Elution through 100 g of grade I neutral alumina in ether gave 3.5 g of colorless oil which crystallized on standing. Recrystallization from ether (cooling to Dry Ice temperature) afforded 3.3 g of colorless crystals, mp 82.3–84.0°, $[\alpha]^{24}D$ +20.7° (*c* 1.161).

Anal. Calcd for $C_{18}H_{29}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.58; H, 9.28; N, 5.23.

It formed a crystalline **picrate**, mp 229–231°, and **methiodide**, mp 180.5–181.5°.

Anal. Calcd for $C_{18}H_{29}NO \cdot C_6H_3N_3O_7$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.65; H, 5.86; N, 11.19.

Anal. Calcd for $C_{18}H_{29}NO \cdot CH_3I$: C, 55.21; H, 6.78; N, 3.39. Found: C, 55.25; H, 6.97; N, 3.34.

3-Hydroxy-N-methylmetamorphinan (II).—Pyridine hydrochloride (10 g) at 250° was poured onto 0.5 g of VI, and the mixture was heated at 207–220° for 15 min. The cooled reaction mixture was dissolved in 50 ml of water, neutralized with Na_2CO_3, and extracted with $CHCl_3$, and the $CHCl_3$ was dried and concentrated under reduced pressure. The residual brown oil was chromatographed on 20 g of grade I neutral alumina. Elution with $CHCl_3$ removed pyridine. Further elution with 9:1 ether–methanol gave colorless crystalline material which on recrystallization from acetone (cooled to Dry Ice temperature) yielded 0.4 g of crystals, mp 231–232°, $[\alpha]^{28}D$ −7° (*c* 1.133).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.01; H, 9.11; N, 5.96.

3-Methoxy-N-cyanometamorphinan.—A cooled, stirred solution of 3 g of cyanogen bromide in 25 ml of $CHCl_3$ was treated with 4.6 g of VI in 55 ml of $CHCl_3$. The reaction mixture was stirred with cooling for 1 hr, then gently refluxed for 2 hr. After washing with water, dilute HCl, and dilute Na_2CO_3, the $CHCl_3$ was dried and concentrated under reduced pressure. Elution through 100 g of grade I neutral alumina with benzene–ether afforded 2.9 g of yellow viscous oil whose infrared spectrum showed strong absorption at 2200 cm^{-1} (N-cyano). An analytical sample was prepared by molecular distillation at 135–140° (0.05 mm), $[\alpha]^{28}D$ −129.5° (*c* 1.359).

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.66; H, 8.01; N, 10.19.

3-Methoxymetamorphinan.—A suspension of 2.1 g of 3-methoxy-N-cyanometamorphinan and 250 ml of 6% HCl was refluxed for 21 hr. The resulting yellow solution was neutralized with concentrated NH_4OH, and the product was extracted into ether. Extraction into dilute HCl, neutralization with NH_4OH, and reextraction into ether afforded 1.7 g of colorless oil which was purified by molecular distillation at 140–147° (0.5 mm), $[\alpha]^{25}D$ +45° (*c* 2.973).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.45. Found: C, 78.64; H, 9.27; N, 5.66.

The oil readily absorbs CO_2 to form a solid carbonate. Its **picrate** crystallized readily from 95% ethanol: mp 223–225°.

Anal. Calcd for $C_{17}H_{23}NO \cdot C_6H_3N_3O_7$: C, 56.78; H, 5.39; N, 11.52. Found: C, 56.97; H, 5.69; N, 11.23.

3-Methoxy-N-cyclopropylcarbonylmetamorphinan. A solution of 1.0 g of 3-methoxymetamorphinan and 4 ml of triethylamine in 15 ml of CH_2Cl_2 was treated with 1 g of cyclopropanecarboxylic acid chloride in 10 ml of CH_2Cl_2. The mixture was refluxed for 10 hr, cooled, washed with dilute HCl until the washings were acid, then washed with dilute Na_2CO_3. Drying and evaporation of the CH_2Cl_2 followed by elution through 50 g of grade I neutral alumina with benzene–ether afforded 0.7 g of light yellow solid. Crystallization from benzene–ether gave colorless crystals: mp 150.0–152.4°; $[\alpha]^{27}D$ −235° (*c* 1.614); ν_{max} 3010, 1635, and 1420 cm^{-1}.

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.26; H, 8.38; N, 4.28.

3-Methoxy-N-cyclopropylmethylmetamorphinan. A slurry of 0.5 g of $LiAlH_4$ in 50 ml of purified THF was treated slowly with 0.6 g of 3-methoxy-N-cyclopropylcarbonylmetamorphinan in 50 ml of purified THF and stirred for 15 hr at room temperature. The excess hydride was cautiously decomposed with wet THF and the mixture was dissolved in a solution of KOH containing Rochelle salt. The precipitated product was taken into ether, then into dilute HCl. After neutralization with NH_4OH, the product was reextracted into ether. Drying and concentration of the ether, followed by elution through 50 g of grade I neutral alumina gave 0.5 g of colorless oil. Molecular distillation at 125–130° (10^{-3} mm) gave an analytical sample: $[\alpha]^{25}D$ −34° (*c* 1.699); ν_{max} 3085 and 1010 cm^{-1}, indicative of a cyclopropyl ring.

Anal. Calcd for $C_{21}H_{29}NO$: C, 80.98; H, 9.39; N, 4.50. Found: C, 80.71; H, 9.30; N, 4.39.

Its **picrate** crystallized from $CHCl_3$–ethyl acetate; mp 210–211.5°.

Anal. Calcd for $C_{21}H_{29}NO \cdot C_6H_3N_3O_7$: C, 59.99; H, 5.97; N, 10.37. Found: C, 59.87; H, 6.05; N, 9.91.

3-Hydroxy-N-cyclopropylmethylmetamorphinan (VII). Pyridine hydrochloride (5 g) at 250° was poured onto 575 mg of 3-methoxy-N-cyclopropylmethylmetamorphinan, and the mixture was heated at 207–220° for 12 min under a slow stream of nitrogen. After cooling, the reaction mixture was dissolved in 50 ml of water, neutralized with Na_2CO_3, and extracted with $CHCl_3$, and the $CHCl_3$ was dried and concentrated under reduced pressure. The resulting brown oil was chromatographed on 20 g of grade I neutral alumina. Elution with $CHCl_3$ removed pyridine. Further elution with 3:1 ether–methanol gave 325 mg of colorless solid. It did not crystallize well from any of a variety of solvents. Sublimation at 130–140° (10^{-3} mm) afforded 232 mg of colorless crystalline material, mp 172.6–173.8°, $[\alpha]^{27}D$ −42° (*c* 1.529).

Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.52; H, 9.15; N, 4.57.

Its **picrate** crystallized from ethanol–water; mp 196–198°.

Anal. Calcd for $C_{20}H_{27}NO \cdot C_6H_3N_3O_7$: C, 59.31; H, 5.74; N, 10.64. Found: C, 59.09; H, 5.80, N, 10.85.

Acknowledgment.—It is a pleasure to acknowledge generous financial aid from the Hoffmann-La Roche Foundation and generous gifts of thebaine from Merck and Co., Inc.