methyl series was applied to 2,9-dimethyl-5-ethyl-2′-hydroxy-6,7-benzomorphan. Acetylation proceeded in 92–97% yields. The crude sirup or crystalline product was treated with cyanogen bromide in chloroform in the usual manner. A solution of 30.5 g. of the O-acetyl-N-cyano intermediate in 250 ml. of 7% hydrochloric acid was refluxed for 17 hr., concentrated to a small volume, and diluted with water. Ether was added, at which point the nor-base hydrochloride started to precipitate. It was recovered by filtration to give 16.9 g. as a first crop. Cooling the mother liquor gave 4.1 g. more, m.p. 125–128° dec. The first crop was converted to the base by dissolving in approximately 100 ml. of boiling water, treating with charcoal, filtering, and adding excess ammonium hydroxide to give 12.7 g. of off-white nor-base, m.p. 261–265°.

Anal. Calcd. for $C_{15}H_{21}NO$: N, 6.06. Found: N, 5.86.

2-Allyl-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan (20). C.—A mixture of 6.2 g. of 5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan, 3.2 g. of allyl bromide, 80 ml. of dimethylformamide, and 3.2 g. of sodium bicarbonate was stirred and refluxed for 4 hr., filtered, the filter cake washed with ethanol, and the combined filtrates concentrated *in vacuo*. The crystalline residue was extracted with chloroform until the remaining residue was all water-soluble. The chloroform solution was concentrated to a small volume, ether was added, and the solution was chilled to give 5.9 g. (81%) of product melting at 165.5–168°. Experiments on a larger scale gave yields of 82–84%.

2-Cyclopropylmethyl-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan (22). D.—A solution of 9.4 g. of 5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan in 235 ml. of hot pyridine was cooled to room temperature and 10.4 g. of cyclopropylcarbonyl chloride added with stirring. After an additional hr. at room temperature, the pyridine was removed *in vacuo* and the residue partitioned between water and ether. The ether layer was washed with dilute hydrochloric acid and water, dried, and concentrated to give 14.0 g. of 2,2′-bis(cyclopropylcarbonyl)-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan as a light orange sirup. This was reduced in tetrahydrofuran with 5 g. of lithium aluminum hydride to give 8.6 g. of crude product, which, when dissolved in ether, gradually deposited crystals of product, m.p. 181–183°. The yield was 55%.

Acknowledgment.—We wish to thank Dr. Leonard Grumbach for carrying out some of the early pharmacological work and Mrs. Hattie Lawyer for technical assistance. It is a pleasure to acknowledge the aid of Dr. Nathan B. Eddy, Executive Secretary, Committee on Drug Addiction and Narcotics, in arranging for some of the trials in man.

Some Potent Morphine Antagonists Possessing High Analgesic Activity[1]

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The synthesis of a number of N-cyclopropylmethylmorphinan and morphine derivatives and one N-cyclobutylmethylmorphinan derivative is described. Very powerful morphine antagonism is exhibited by certain of these, and at least one, 3-hydroxy-N-cyclopropylmethylmorphinan, appears to be a very potent, presumptively nonaddicting analgesic of potential clinical utility.

The highly significant observation of Lasagna and Beecher,[3] confirmed and extended by Keats and coworkers,[4] that nalorphine (N-allylnormorphine), a powerful morphine antagonist which has been shown to be nonaddicting,[5] is a potent analgesic in man even though its analgesic activity is not detectable in the D'Amour–Smith rat tail-flick test suggested that clinically useful potent analgesics devoid of addiction liability might be uncovered among the group of morphine antagonists. Nalorphine itself is not acceptable for clinical use because of a high incidence of undesirable, sometimes bizarre, psychotic effects attending its use.

The relationship between structure and morphine antagonism in substances structurally related to morphine has been studied at length by Clark and coworkers,[6] who found that the substitution of allyl, *n*-propyl, methallyl, or isobutyl for the N-methyl group of morphine or its close relatives produces morphine antagonists. No significant morphine antagonism resulted from the substitution of a number of other groups, both closely and distantly related to these, for the N-methyl group.

We were led to a consideration of the cyclopropylmethyl group as a possible N-substituent which might confer morphine antagonism and analgesic activity at the same time by the well known[7] close similarity of the

(1) Taken in part from a Ph.D. dissertation submitted to the University of Rochester, 1962.

(2) Charles Pfizer Fellow 1959–1960, American Cyanamid Fellow 1960–1961, National Science Foundation Fellow, summer, 1961.

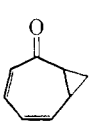
(3) L. Lasagna and H. K. Beecher, *J. Pharmacol. Exptl. Therap.*, **112**, 356 (1954).

(4) A. S. Keats and J. Telford, *ibid.*, **117**, 190 (1956). J. Telford, C. N. Papadopoulos, and A. S. Keats, *ibid.*, **133**, 106 (1961).

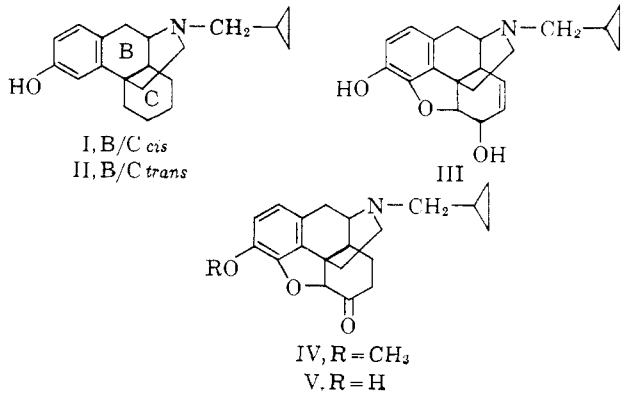
(5) H. Isbell, *Federation Proc.*, **15**, 442 (1956); *J. Am. Med. Assoc.*, **161**, 1254 (1956).

(6) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **75**, 4963 (1953).

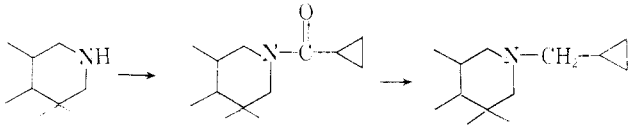
(7) Although an exhaustive review of these similarities, both theoretical and experimental, would be inappropriate here, the interested reader is referred to A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949); C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, **40**, 1 (1949); J. E. Kilpatrick and R. Spitzer, *J. Chem. Phys.*, **14**, 463 (1946); and J. F. Music and F. A. Matsen, *J. Am. Chem. Soc.*, **72**, 5256 (1950), for discussions of the theoretical similarities. Diverse physical measurements such as dipole moments (M. T. Rogers and J. D. Roberts, *ibid.*, **68**, 843 (1946); M. T. Rogers, *ibid.*, **69**, 2544 (1947)); ultraviolet absorption spectra (L. I. Smith and E. R. Rogier, *ibid.*, **73**, 3840 (1951); R. H. Eastman and S. K. Freeman, *ibid.*, **77**, 6642 (1955)); and molar refractions (V. A Slabey, *ibid.*, **76**, 3603 (1954)) also suggest the double-bond character and conjugative ability of the cyclopropyl group. There is also much chemical evidence for the unsaturated nature of the cyclopropyl group. Among recent observations may be cited the interesting findings of J. L. von Rosenberg, Jr., J. E. Mahler, and R. Pettit, *ibid.*, **84**, 2842 (1962); J. D. Holmes and R. Pettit, *ibid.*, **85**, 2531 (1963), that both the homotropyl cation and homotropone exhibit aromatic sextet stabilization.



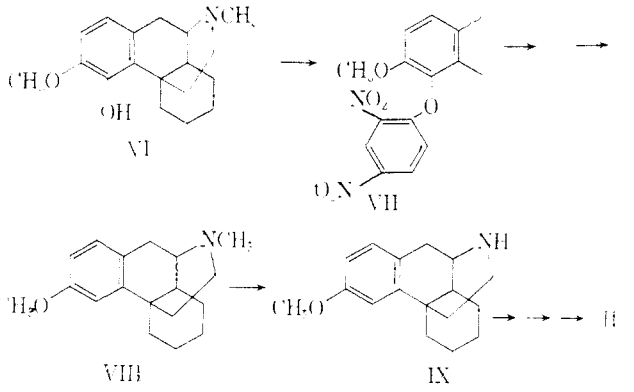
cyclopropyl group and the ethylenic double bond. It seemed possible that the cyclopropylmethyl group might resemble the allyl group so closely that similar physiological properties might be observed in substances carrying these substituents on nitrogen. Accordingly, we undertook the preparation of a number of N-cyclopropylmethyl derivatives and report here the synthesis of (−)-3-hydroxy-N-cyclopropylmethylmorphinan (I) (rings B/C *cis*) and -isomorphinan (II) (rings B/C *trans*), N-cyclopropylmethylnormorphine (III), and N-cyclopropylmethyldihydronorcodeinone (IV) and -morphinone (V). (−)-3-Hydroxy-N-cyclobutylmethylmorphinan[8] and (−)-3-hydroxy-N-(1-phenylcyclopropyl)methylmorphinan were also synthesized.



The N-cyclopropylmethyl group was introduced into the appropriate nor intermediate in the case of I, II, III, and IV by acylation with cyclopropylcarbonyl chloride and reduction with lithium aluminum hydride. Demethylation of the dihydronorcodeinone derivative (IV) yielded N-cyclopropylmethyldihydronormorphinone (V); N-cyclopropylmethylnormorphine (III) could also be obtained by demethylation of N-cyclopropylmethylnorcodeine.[9]



The required nor (N-demethylated) derivatives have, with the exception of (−)-3-hydroxyisomorphinan, all been reported previously. Although a well-defined synthetic route to 3-hydroxyisomorphinan (or to its N-cyclopropylmethyl derivative) exists,[10] the availability of a quantity of *trans*-tetrahydrodesoxycodeine [(−)-4-hydroxy-3-methoxy-N-methylismorphinan, VI[11]] and the development of an excellent method for the removal of the 4-hydroxyl group in high yield[12] suggested the preparation of this substance from natural sources. Accordingly, the 2,4-dinitrophenyl ether (VII) of *trans*-tetrahydrodesoxycodeine was reduced catalytically to the diamino derivative which was cleaved by sodium in liquid ammonia to (−)-3-methoxy-N-methylisomorphinan (VIII). N-Demethylation by standard methods yielded (−)-3-methoxy-



isomorphinan (IX) which was converted to II by N-acylation, reduction, and final O-demethylation.[13]

Pharmacological Results.—The ability of a number of these substances to antagonize the effect of merperidine in mice has been evaluated,[14] and the results are summarized in Table I. It has also been found[14] that that morphine-induced behavior and respiratory depression in dogs is effectively normalized by (−)-3-hydroxy-N-cyclopropylmethylmorphinan (I) at doses substantially lower than those of nalorphine required for the same effect.

N-Cyclopropylmethylnormorphine (III) powerfully antagonizes morphine analgesia in rats (D'Amour-Smith tail-flick test) and, in addition, at very high doses (32 mg./kg.) produces some analgesia.[15]

Both I and III are potent morphine antagonists capable of precipitating withdrawal symptoms of maximum intensity in addicted monkeys at doses in the range 0.04–0.25 mg./kg. and are distinguished by a remarkable duration of action (24 hr.).[16] Such precipitation of withdrawal symptoms in addicted monkeys has been taken as evidence in the past that a drug may be assumed to be nonaddicting in man.

Preliminary clinical studies with I by Lasagna, Pearson, and DeKornfeld[17] indicate that in post-operative patients, the dose equivalent to 10 mg. of morphine in analgesic effect is substantially below 0.5 mg. At 0.5 mg., analgesia superior to that produced by 10 mg. of

(8) We are very grateful to Miss Pamela Taylor for the preparation of this substance.

(9) J. von Braun, M. Kuhn, and S. Siddiqui, *Ber.*, **59**, 1081 (1926), reported the preparation of this substance by alkylation of norcodeine with cyclopropylcarbinyl bromide, but it is now known (*cf.* J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951)) that their preparation of the bromide (*Ann.*, **445**, 201 (1925)) cannot be expected to yield homogeneous material, nor can the subsequent alkylation of norcodeine, and it seems likely that their product was of questionable identity. Our sample was prepared by the acylation-reduction sequence.

(10) By appropriate modification of the method described by M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).

(11) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956). Our sample was prepared by Wolff-Kishner reduction of *trans*-dihydrothebainone.

(12) This method, developed by Dr. Wm. H. Pirkle of these laboratories, is closely related to the prior one of Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **15**, 144, 154 (1961), but offers several advantages in convenience. A description of the method will be published elsewhere.

(13) O-Demethylation of VIII provided a sample of (−)-3-hydroxy-N-methylisomorphinan of natural origin with which the synthetic sample described in ref. 10 could be identified. This identification confirms by independent synthesis the structural assignments originally made by the identification of synthetic and natural β-Δ⁶-dihydrodesoxycodeine methyl ether (*cf.* ref. 11).

(14) The method used is outlined in the accompanying paper by S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

(15) C. Winter, Merck Institute for Therapeutic Research, private communication.

(16) M. H. Seevers and G. A. Deneau, University of Michigan, private communication.

(17) L. Lasagna, private communication.

TABLE I

MEPERIDINE ANTAGONISM OF N-CYCLOPROPYLMETHYLMORPHINAN AND NORMORPHINE DERIVATIVES

Name	No.	AD_{50} mg./kg. vs. Meperidine	Potency relative to nalorphine
(−)-3-Hydroxy-N-cyclopropylmethylmorphinan	I	0.034	4
(−)-3-Hydroxy-N-cyclopropylmethylisomorphinan	II	.019	7
N-Cyclopropylmethylnormorphine	III	.046	3
N-Cyclopropylmethyldihydronormorphinone	V	.0135	10
(−)-3-Hydroxy-N-(1-phenylcyclopropyl)methylmorphinan		inactive	
N-Allylnormorphine (nalorphine)		.13	1.0
(−)-3-Hydroxy-N-allylmorphinan (levallorphan)		.052	2.6

morphine was observed. There was much sedation, but untoward side effects occurred only infrequently, and the drug appeared to be well tolerated. At 0.1 mg., analgesia somewhat inferior to that produced by 10 mg. of morphine was observed and sedation was not prominent.

In summary, the cyclopropylmethyl compounds described herein have proved to be unexpectedly powerful morphine antagonists and are among the most potent such substances known. At least one, (−)-3-hydroxy-N-cyclopropylmethylmorphinan, has been shown to be a highly potent analgesic in man, and it is perhaps not too much to hope that among such substances or their close relatives will be found the long-sought, nonaddicting, powerful analgesic.

Experimental

Unless otherwise stated, melting points are corrected. Rotations were taken in 95% alcohol unless otherwise specified. Infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer. Microanalyses were performed either by V. Landeryou of this laboratory, Micro-Tech Laboratories, Skokie, Ill., or F. Pascher, Bonn, Germany.

3-Cyclopropylcarbonyloxy-N-cyclopropylcarbonylmorphinan.—A mixture of 1.9 g. of (−)-3-hydroxymorphinan,[18] 80 ml. of methylene chloride, 14 ml. of triethylamine, and 2.1 g. of cyclopropylcarbonyl chloride was refluxed for 12 hr. The reaction mixture was cooled, washed with dilute hydrochloric acid, then with water, dried over potassium carbonate, and evaporated to give 3.0 g. of amorphous material. A portion of this was purified by short path distillation to give a colorless amorphous solid, $[\alpha]^{30}D$ −164° (*c* 2.15).

Anal. Calcd. for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70. Found: C, 75.91; N, 7.82.

(−)-3-Hydroxy-N-cyclopropylmethylmorphinan (I).—A solution of 2.65 g. of the above biscyclopropylcarbonyl derivative in 70 ml. of purified tetrahydrofuran was added to 0.6 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 20 hr. and then the excess hydride was decomposed with 6 ml. of ethyl acetate. Saturated ammonium tartrate (125 ml.) was then added and the mixture was stirred for 1 hr. The tetrahydrofuran layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and evaporated to give 2.07 g. of crystalline material which was recrystallized from ethyl acetate, m.p. 187.5–189°, $[\alpha]^{30}D$ −120° (*c* 2.26). Its infrared spectrum shows cyclopropane absorption at 1016 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.52; H, 9.13; N, 4.72.

(−)-3-Hydroxy-N-cyclobutylmethylmorphinan.[8]—A mixture of 1.40 g. of (−)-3-hydroxymorphinan, 1.75 g. of cyclobutylcarbonyl chloride, and 9.8 ml. of triethylamine in 75 ml. of methylene chloride was heated under reflux for 12 hr. The solution was washed with 3 *N* hydrochloric acid, then with water, and dried and concentrated to give 2.29 g. (97.5%) of the biscyclobutylcarbonyl derivative of (−)-3-hydroxymorphinan. The material absorbed strongly at 1730–1750 and at 1610–1630 cm.$^{-1}$ in the infrared, but was amorphous and was used without further characterization or purification.

A solution of 2.28 g. of the above biscyclobutylcarbonyl derivative and 0.5 g. of lithium aluminum hydride in 120 ml. of purified tetrahydrofuran was heated under reflux for 21 hr. The excess hydride was decomposed by the addition of ethyl acetate, and the mixture was treated with 125 ml. of saturated ammonium tartrate solution, stirred for 1 hr., and extracted several times with methylene chloride. The washed, dried, and concentrated methylene chloride yielded 1.86 g. of crude material, m.p. 216.5–219.5°, which after several crystallizations from ethyl acetate gave 1.09 g. (65.4%) of colorless (−)-3-hydroxy-N-cyclobutylmethylmorphinan, m.p. 219.2–219.8°, $[\alpha]^{28}D$ −92 ± 1° (*c* 1.03, pyridine).

Anal. Calcd. for $C_{21}H_{29}NO$: C, 80.98; H, 9.39. Found: C, 80.78; H, 9.28.

Its **methiodide,** prepared in methanol and crystallized from 50% aqueous methanol, melted at 256–257°, dec.

Anal. Calcd. for $C_{22}H_{32}INO$: C, 58.27; H, 7.11. Found: C, 57.59; H, 7.36.

(−)-3-Hydroxy-N-(1-phenylcyclopropyl)methylmorphinan.—To a suspension of 2.0 g. of (−)-3-hydroxymorphinan in 65 ml. of methylene chloride and 15 ml. of triethylamine was added 3.6 g. of 1-phenylcyclopropanecarbonyl chloride in 20 ml. of methylene chloride. The mixture was refluxed gently for 19 hr., then washed with dilute hydrochloric acid and dilute sodium carbonate, and dried over sodium sulfate. The residue (4.48 g.), after evaporation of the solvent, was put on a column of 50 g. of Grade I neutral alumina in ether. Elution of the column gave 2.38 g. of a glass, presumably the bis(1-phenylcyclopropyl)carbonyl derivative, which did not crystallize or sublime readily. Its infrared spectrum showed carbonyl absorption bands at 1735 and 1625 cm.$^{-1}$ but showed no hydroxyl absorption. Further elution of the column with chloroform gave 1.16 g. of **(−)-3-hydroxy-N-(1-phenylcyclopropyl)carbonylmorphinan** as a colorless amorphous solid. The material could not be induced to crystallize but readily sublimed at 135° (2–5 × 10^{-3} mm.) to give an amorphous solid, $[\alpha]^{26}D$ −119° (*c* 0.80).

Anal. Calcd. for $C_{26}H_{29}NO_2$: C, 80.58; H, 7.54; N, 3.61. Found: C, 80.34; H, 7.72; N, 3.74.

Its infrared spectrum showed hydroxyl absorption at 3530 and 3200 cm.$^{-1}$, a very slight impurity of II by a very small band at 1735 cm.$^{-1}$, and a strong amide band at 1620 cm.$^{-1}$.

To a stirred suspension of 2.0 g. of lithium aluminum hydride in 30 ml. of purified tetrahydrofuran was slowly added a crude mixture of the mono- and bis-1-phenylcyclopropylcarbonyl derivatives (9.1 g.) in 170 ml. of tetrahydrofuran. The mixture was stirred for 12 hr., then 10 ml. of ethyl acetate was added followed by 200 ml. of saturated ammonium tartrate. The aqueous layer was separated and extracted twice with ethyl acetate. Washing the organic layers with saturated sodium chloride followed by drying over sodium sulfate and evaporation yielded 9.1 g. of a crude yellow gum which could not be induced to crystallize. An attempt to purify the substance by extracting an ether solution with dilute hydrochloric acid failed as the hydrochloride formed an oil. A stubborn impurity was present which showed a very strong band at 1710 cm.$^{-1}$ in the infrared. A small portion was very carefully fractionally sublimed twice to give a colorless amorphous solid which did not absorb in the 1710-cm.$^{-1}$ region of the infrared, $[\alpha]^{25}D$ −68° (*c* 0.88).

Anal. Calcd. for $C_{26}H_{31}NO$: C, 83.60; H, 8.37; N, 3.75. Found: C, 83.50; H, 8.41; N, 3.57.

It did not give a crystalline methiodide, hydrochloride, hydrobromide, hydriodide, or tartrate.

(−)-3-Methoxy-N-methylisomorphinan (VIII).—Sodium hydride (3.4 g., 49% dispersion in mineral oil), 4.0 g. of (−)-4-hydroxy-3-methoxy-N-methylisomorphinan hemihydrate (VI) (*trans*-tetrahydrodesoxycodeine, β-tetrahydrodesoxycodeine),[11]

(18) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **34**, 2211 (1951).

and 100 ml. dry toluene were stirred for 0.5 hr. until hydrogen evolution had ceased. To this was added slowly 8.0 g. of 2,4-dinitrofluorobenzene in 40 ml. of toluene followed by 20 ml. of purified dimethylformamide. The mixture was stirred at room temperature for 1 hr., then refluxed for 1 hr. The resulting dark brown solution was thoroughly washed with 10% sodium hydroxide. After evaporation of the toluene the residue was taken into ether, extracted with several portions of 0.1 *N* hydrochloric acid, and re-extracted into ether after making the aqueous layer basic with ammonia. Evaporation of the ether gave 11–12 g. of residue which was eluted through a column of 100 g. of Grade I Merck alumina in ether to yield 10.6 g. of VII as a light yellow foam. It did not crystallize or form a crystalline picrate or hydrochloride, and was used without further purification.

A mixture of 650 mg. of platinum oxide (prereduced in 50 ml. of ethanol) and 10.6 g. of the crude dinitrophenyl ether (VII) in 350 ml. of absolute ethanol was shaken with hydrogen at atmospheric pressure until no more uptake was observed (*ca.* 15 hr.). The initial uptake was extremely rapid. Total uptake was *ca.* 3.4 l. (3.2 l. theoretical). The catalyst was removed by rapid filtration, and the ethanol was removed under diminished pressure. The solution, on exposure to air, rapidly turns red. The red-brown residue, crude (−)-4-hydroxy-3-methoxy-*N*-methylisomorphinan 2,4-diaminophenyl ether, used quickly in the next reaction without purification or characterization, was dissolved in 75 ml. of purified tetrahydrofuran and the solution diluted with 400 ml. of liquid ammonia; sodium was then added in small lumps with swirling until a deep blue color persisted for 2 min. About 10 ml. of ethanol was added to decompose the excess sodium. After allowing the ammonia to evaporate and the flask to come to room temperature, the very dark residue was partitioned between ether and 10% sodium hydroxide. After thorough washing of the ether layers with 10% sodium hydroxide, they were dried over potassium carbonate and evaporated under diminished pressure to yield 6.2 g. of brown oil. Elution of this brown oil through 70 g. of Grade I neutral alumina with benzene–ether gave 5.6 g. of colorless oil. Purification through its picrate followed by molecular distillation at 93–97° ($1–3 \times 10^{-3}$ mm.) gave pure VIII, $[\alpha]^{27}D$ −45° (*c* 1.51).

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.42; H, 9.32; N, 5.46.

It forms a crystalline **picrate**, m.p. 203–214° (acetone).

Anal. Calcd. for $C_{18}H_{25}NO \cdot C_6H_3N_3O_7$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.98; H, 5.86; N, 11.66.

(−)-3-Hydroxy-N-methylisomorphinan.—A mixture of 113 mg. of (−)-3-methoxy-*N*-methylisomorphinan and 0.8–1.0 g. of pyridine hydrochloride was heated at 207–218° under nitrogen for 15 min. The reaction was diluted with 20 ml. of water and made basic with dilute sodium carbonate. Thorough extraction with chloroform, followed by removal of the chloroform under vacuum, gave a brown oil which was chromatographed on a column of 6 g. of Grade I neutral alumina. Elution with chloroform removed pyridine and traces of starting material. Further elution with acetone gave 103 mg. of colorless crystalline material which rapidly turned pink on standing in air. Two crystallizations from benzene followed by crystallization from ethyl acetate gave colorless crystalline material, m.p. 171.5–173.5°, lit.[11] m.p.[10] 171–173°; $[\alpha]^{30}D$ −59° (*c* 1.65), lit.[1] $[\alpha]^{25}D$ −54°. Its mixture melting point with the levo isomer was not depressed; their infrared spectra were essentially superimposable.

(−)-3-Methoxy-N-cyanoisomorphinan.—A cool, stirred solution of 1.9 g. of cyanogen bromide in 15 ml. of chloroform was treated rapidly with a solution of 3.9 g. of (−)-3-methoxy-*N*-methylisomorphinan in 40 ml. of chloroform. The solution was stirred while cooling for 1 hr. and gently refluxed for an additional 2 hr. Evaporation of the chloroform gave 5.5 g. of orange oil. The oil was taken into ether and washed with water, dilute hydrochloric acid, and dilute sodium carbonate. Drying and evaporation of the ether gave 3.8 g. of a very viscous orange oil. The oil was eluted through a column of 120 g. of Grade I neutral alumina with benzene–ether to yield 2.1 g. of a colorless viscous oil whose infrared spectrum showed strong absorption at 2200 cm.$^{-1}$ attributable to the N-cyano group. An analytical sample was prepared by molecular distillation at 120–124° (10^{-3} mm.), $[\alpha]^{30}D$ −161° (*c* 1.28).

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.47; H, 7.77; N, 9.91.

Further elution with ethyl acetate gave about 1 g. of a colorless oil which rapidly turned orange on standing. Its infrared spectrum also showed strong absorption at 2200 cm.$^{-1}$. This compound was not further investigated.

(−)-3-Methoxyisomorphinan (IX).—(−)-3-Methoxy-*N*-cyanoisomorphinan (2.1 g.) and 140 ml. of 6% hydrochloric acid were refluxed for 18 hr. The acid solution was made basic with ammonia and extracted with ether. The ether solution was extracted with dilute hydrochloric acid, the acid solution made basic with ammonia, and the basic solution extracted with ether. Drying and evaporation of the ether gave 1.7 g. of a yellow oil. This oil on standing readily absorbs atmospheric carbon dioxide to form a low melting solid. Purification through its picrate and recovery of the base followed by molecular distillation at 100–105° (10^{-4} mm.) gave an almost pure sample, $[\alpha]^{28}D$ −35° (*c* 1.99).

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 78.78; H, 9.00; N, 5.30.

The **picrate** readily crystallized from acetone, m.p. 225–228°.

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, 56.65; H, 5.51; N, 11.78.

The **L-(+)-tartrate** had m.p. 193.5–195.5°.

Anal. Calcd. for $C_{17}H_{23}NO \cdot C_4H_6O_6 \cdot H_2O$: C, 59.28; H, 7.34; N, 3.29. Found: C, 58.95; H, 7.36; N, 3.44.

(−)-3-Methoxy-N-cyclopropylcarbonylisomorphinan.—A solution of 3.8 g. of IX in 60 ml. of methylene chloride and 10 ml. of triethylamine was treated with 2.4 g. of cyclopropylcarbonyl chloride in 20 ml. of methylene chloride. The mixture was heated under reflux for 10 hr., washed with dilute acid until the washings were acid, and then washed with dilute sodium carbonate. The methylene chloride solution was passed through 10 g. of Grade I Merck alumina. Evaporation of the methylene chloride yielded 4.9 g. of a yellow glass. A small portion of this glass was distilled at 145–148° (10^{-3} mm.) to give a colorless glass, $[\alpha]^{26}D$ −178° (*c* 1.48).

Anal. Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.02; H, 8.16; N, 4.22; residue, 0.67%.

(−)-3-Methoxy-N-cyclopropylmethylisomorphinan.—A suspension of 0.7 g. of lithium aluminum hydride in 50 ml. of anhydrous ether was treated slowly with 4.8 g. of the above *N*-cyclopropylcarbonyl derivative in 75 ml. of ether and then stirred for 12 hr. at room temperature. The excess hydride was decomposed cautiously with 3 ml. of saturated sodium sulfate. After removal of the aluminum salts the ether solution was extracted with dilute hydrochloric acid. The acid solution was made basic with ammonia and extracted with ether. Drying and evaporation of the ether gave 4.2 g. of colorless oil. Molecular distillation of a small portion at 125–127° (10^{-3} mm.) gave an analytical sample, $[\alpha]^{26}D$ −90° (*c* 1.91).

Anal. Calcd. for $C_{21}H_{29}NO$: C, 80.98; H, 9.39; N, 4.50. Found: C, 80.71; H, 9.26; N, 4.58.

(−)-3-Hydroxy-N-cyclopropylmethylisomorphinan (II).—Pyridine hydrochloride (3 g.) and 1.0 g. of the above 3-methoxy-*N*-cyclopropylmethyl compound were heated together under a gentle stream of nitrogen at 215–220° for 16 min. The mixture was diluted with 30 ml. of water, made basic with ammonia, and extracted with chloroform. Drying and evaporation of the chloroform gave 1.1 g. of orange, viscous oil. The material could not be induced to crystallize. The **hydrochloride** was formed with 0.5 ml. of concentrated hydrochloric acid. Recrystallization from ethanol–water, after decolorizing, gave 0.6 g. of colorless crystalline material, m.p. 258–266° uncor., $[\alpha]^{25}D$ −83° (*c* 0.50).

Anal. Calcd. for $C_{20}H_{27}NO \cdot HCl$: C, 71.94; H, 8.45; N, 4.20. Found: C, 72.03; H, 8.46; N, 4.34.

N-Cyclopropylcarbonylnorcodeine.—A suspension of 1.0 g. of norcodeine in 50 ml. of anhydrous ether and 10 ml. of triethylamine was cooled in an ice bath and treated with 0.4 g. of cyclopropylcarbonyl chloride. The mixture was then refluxed for 2 hr. Processing as above with 9:1 ether–methanol elution yielded 1.14 g. of colorless, amorphous solid. A small portion of this was distilled at 170° (10^{-4} mm.) as an amorphous solid, $[\alpha]^{27}D$ −205° (*c* 1.04).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56. Found: C, 71.44; H, 6.77.

Its infrared spectrum shows a hydroxyl at band 3330 cm.$^{-1}$ and an amide band at 1640 cm.$^{-1}$, but no ester band.

N,6-Biscyclopropylcarbonylnorcodeine.—A suspension of 1.2 g. of norcodeine[19] in 50 ml. of anhydrous ether with 7 ml. of tri-

(19) J. von Braun, *Ber.*, **47**, 2312 (1914).

ethylamine and 2.0 g. of cyclopropylcarbonyl chloride was refluxed for 4 hr. The residue, after evaporation of the ether, was taken up in 1,2-dichloroethane, washed with dilute hydrochloric acid, then water, and chromatographed on a column of 30 g. of neutral alumina Grade I made up in ether. A colorless amorphous solid (1.3 g.) was eluted with ether. A small portion was distilled onto a cold finger at 160–170° (5×10^{-5} mm.) as an amorphous solid, $[\alpha]^{25}D$ −260° (*c* 1.11).

Anal. Calcd. for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46. Found: C, 71.47; H, 6.34.

Its infrared spectrum shows no hydroxyl band, but does show an ester band at 1725 and an amide band at 1640 cm.$^{-1}$.

Further elution with 9:1 ether–methanol yielded 0.2 g. of N-cyclopropylcarbonylnorcodeine.

N-Cyclopropylmethylnorcodeine.—Either the mono- or the biscyclopropylcarbonyl derivative was dissolved in a small amount of purified tetrahydrofuran and the solution added to a 25% excess of lithium aluminum hydride in diethyl ether. The reaction was stirred for 20–24 hr. at room temperature. The excess hydride was destroyed with the minimum amount of saturated sodium sulfate. The aluminum salts were removed and thoroughly washed with ethyl acetate. Drying over potassium carbonate and evaporation yielded a sticky glass which was purified by elution through a column of grade I neutral alumina with ethyl acetate; yield 85–95%, $[\alpha]^{22}D$ −153° (*c* 1.67). It forms a crystalline **hydriodide**, m.p. 245–253° (ethanol).

Anal. Calcd. for $C_{21}H_{25}NO_3 \cdot HI$: C, 53.97; H, 5.61; N, 3.00. Found: C, 54.10; H, 5.70; N, 3.02.

Its infrared spectrum shows cyclopropane absorption at 1015 cm.$^{-1}$.

N-Cyclopropylmethylnormorphine (III). (A) **From N-Cyclopropylmethylnorcodeine.**—A mixture of 861 mg. of N-cyclopropylmethylnorcodeine and 2.7 g. of pyridine hydrochloride was heated at 210–218° for 6 min. in a nitrogen atmosphere. The reaction mixture was cooled, diluted with water, adjusted to pH 6, and extracted continuously with methylene chloride while the pH was raised slowly to 10. The solvent was evaporated, and the residue was chromatographed on a column of 30 g. of Grade II alumina (100 g. Woelm neutral alumina activity I plus 3 g. of water) in methylene chloride and eluted with ethyl acetate to give 470 mg. of recovered starting material. Then III (180 mg.) was obtained by elution with 2:1 ethyl acetate–methanol and was crystallized from either methanol or ethyl acetate, m.p. 191.5–192.5°, $[\alpha]^{22}D$ −140° (*c* 1.19). Its infrared spectrum shows cyclopropane absorption at 1015 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.68; H, 7.34; N, 4.38.

(B) **From Normorphine.**—A solution of 11.4 g. of cyclopropylcarbonyl chloride in 50 ml. of chloroform was added slowly to a cooled solution of 9.92 g. of normorphine hemimethanolate in 200 ml. of chloroform and 30 ml. of triethylamine. The mixture was then refluxed 12 hr. The chloroform solution was washed with dilute hydrochloric acid and dilute sodium carbonate, dried with sodium sulfate, and concentrated to yield 17.5 g. of brown oil which crystallized on standing. This material (17.5 g.) without purification was dissolved in 350 ml. of purified tetrahydrofuran and added dropwise to a stirred slurry of 5 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. After stirring at room temperature for 20 hr. the excess hydride was cautiously decomposed with 15 ml. of ethyl acetate followed by 25 ml. of water. Saturated ammonium tartrate (300 ml.) was added and the mixture was stirred for 2 hr. The aqueous suspension of aluminum salts was separated and washed thoroughly with ethyl acetate. The combined organic layers were washed with saturated sodium chloride solution. Drying and evaporation of the solvent yielded 12.8 g. of a dark solid. This solid was purified by elution through 120 g. of Grade II neutral alumina with methanol and crystallization from ethyl acetate followed by crystallization from methanol to yield 7.6 g. of pure colorless N-cyclopropylmethylnormorphine, m.p. 190–192°.

Dihydronorcodeinone Ethylene Ketal.—A mixture of 80 ml. of toluene, 2.24 g. of dihydronorcodeinone hydrochloride,[6] 1.0 g. of ethylene glycol, and 0.5 g. of *p*-toluenesulfonic acid hydrate was refluxed in a flask fitted with a Dean–Stark trap for 16 hr. After concentration of the mixture the residue was treated with an excess of concentrated ammonia and diluted with water. Extraction with chloroform gave 2.3 g. of crystalline material which was recrystallized from acetone, 1.4 g., $[\alpha]^{23}D$ −156° (*c* 1.32). At 159.5–160° the material alters to another crystalline form which melts 164.0–165.0°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.35; H, 7.20; N, 4.21.

A 20–30% recovery of dihydronorcodeinone was obtained by dilute acid hydrolysis of the mother liquors.

N-Cyclopropylcarbonyldihydronorcodeinone Ethylene Ketal.—Dihydronorcodeinone ethylene ketal (8.69 g.), 15 ml. of triethylamine, 3.5 g. of cyclopropylcarbonyl chloride, and 175 ml. of chloroform were refluxed for 12 hr. The chloroform solution was thoroughly washed with dilute sodium carbonate, dried, and concentrated. Crystallization of the residue from acetone gave 9.3 g., m.p. 196.0–197.5°, $[\alpha]^{26}D$ −237° (*c* 0.58).

Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.39; H, 6.97; N, 3.52; residue, 0.43%.

N-Cyclopropylmethyldihydronorcodeinone Ethylene Ketal.—A solution of 9.4 g. of the above N-cyclopropylcarbonyl derivative in 275 ml. of purified tetrahydrofuran was added slowly to 1.2 g. of lithium aluminum hydride in 25 ml. of tetrahydrofuran, and the mixture was stirred at room temperature for 20 hr. The excess hydride was cautiously decomposed with the minimum of saturated sodium sulfate, and the aluminum salts were removed and thoroughly washed with chloroform. Drying and evaporation of the organic layers yielded a crystalline residue which was recrystallized from acetone to give 7.4 g. of colorless crystalline solid, m.p. 131.5–133°, $[\alpha]^{23}D$ −179° (*c* 1.27).

Anal. Calcd. for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.80; H, 7.67; N, 3.73.

N-Cyclopropylmethyldihydronorcodeinone (IV).—A solution of 6.0 g. of N-cyclopropylmethyldihydronorcodeinone ethylene ketal in 270 ml. of 6% hydrochloric acid was refluxed gently for 4 hr. and allowed to stand at room temperature overnight. The aqueous solution was made basic with ammonia and extracted with chloroform to yield 6.8 g. of yellow oil which was chromatographed on 40 g. of Merck Grade I alumina in chloroform to yield 5.4 g. of colorless oil. It formed a crystalline **hydrobromide** from 95% ethanol, m.p. 210–213°, $[\alpha]^{25}D$ −139° (*c* 0.70).

Anal. Calcd. for $C_{21}H_{25}NO_3 \cdot HBr \cdot H_2O$: C, 57.53; H, 6.44; N, 3.20. Found: C, 57.64; H, 6.63; N, 3.09.

It also forms a crystalline **methiodide**, m.p. 229–231°.

Anal. Calcd. for $C_{21}H_{25}NO_3 \cdot CH_3I$: C, 54.89; H, 5.86. Found: C, 54.65; H, 5.83.

N-Cyclopropylmethyldihydronormorphinone (V).—Pyridine hydrochloride (3–4 g.) and 1.1 g. of IV were heated together at 213–217° under a gentle stream of nitrogen for 10 min. The mixture was diluted with water and extracted continuously with ethyl acetate. During the extraction the pH was raised slowly to 9–10 with dilute ammonia. Drying and evaporation of the ethyl acetate gave 1.1 g. of dark foam. The foam was dissolved in ethanol, decolorized, filtered, and evaporated to give 1.0 g. of brown solid which on crystallization from methanol–water gave 0.6 g. of still-colored material. Several more crystallizations from ether–ethyl acetate–methanol–water or 95% ethanol gave an analytical sample of the hydrate, m.p. 113–116°, $[\alpha]^{25}D$ −182° (*c* 0.74).

Anal. Calcd. for $C_{20}H_{23}NO_3 \cdot H_2O$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.99; H, 7.12; N, 4.15.

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