hours the solvent was removed by distillation under diminished pressure. The white solid residue was washed thoroughly with ice-cold water while being filtered with suction. The crude product (11.0 g.) was crystallized from benzene, yield 9.4 g. (85%), m. p. 141–142°.

5-Alkyl-5-β-mercaptoethylbarbituric Acids.—Typical experiments were made using the crude 5-*n*-amyl-5-(β-ethylxanthoethyl)-barbituric acid made from 15.3 g. (0.050 mole) of the bromo acid.

Procedure A.—The crude xanthoethylbarbituric acid was dissolved in 70 cc. of 10% sodium hydroxide and kept at 45–50° for one and one-half hours. The solution was cooled and acidified to congo red by careful addition of hydrochloric acid. The precipitated oil was stirred vigorously while it crystallized. The product (11.5 g.) was crystallized from a mixture (2:1) of benzene and toluene, yield 9.0 g., m. p. 129–132°. Two recrystallizations raised the melting point to 133–134°.

Procedure B.—To a solution of the crude xanthoethylbarbituric acid in 20 cc. of 10% sodium hydroxide 50 cc. of aqua ammonia (0.90) were added with stirring. After standing seven hours at room temperature the solution was extracted with chloroform and the aqueous layer was made acid to congo red with hydrochloric acid. The precipitated oil crystallized when cooled in an ice-bath with vigorous stirring, yield 12 g. One recrystallization from the benzene–toluene mixture gave 10.2 g. (79%) of the product, m. p. 130–132.5°. Another recrystallization raised the melting point to 133–134°.

All of the mercapto acids gave a positive test for a mercaptan in alkaline solution with sodium nitroprusside. These acids had not suffered oxidation to the disulfides as indicated by molecular weight determinations (Rast). Calcd. as mercaptan: ethyl deriv. 216, *n*-amyl deriv. 258. Calcd. as disulfide: ethyl deriv. 430, *n*-amyl deriv. 514. Found: ethyl deriv. 227, *n*-amyl deriv. 241.

α-Ethyl-α-carboxethyl-γ-thiobutyrolactone.—Ethyl β-bromoethylethylmalonate was prepared in the usual way and the fraction distilling at 101–114° (0.5 mm.) was employed. The analysis for bromine indicated that 97.6% of it was the desired product.

To a solution of 48 g. (0.30 mole) of freshly prepared potassium ethylxanthate in 650 cc. of ethyl alcohol was added 74 g. (0.25 mole) of ethyl β-bromoethylethylmalonate with good mixing. After heating at 50° for twelve hours and allowing to stand at room temperature for eleven hours the amount of potassium bromide removed by filtration corresponded to the amount expected. Removal of the solvent under diminished pressure left 82.5 g. (98%) of a yellow, viscous oil possessing a nauseating odor. It contained only a trace of bromine.

Eighty grams of the oil were heated in a bath at 200° (40 mm.) for one hour. Toward the end of this period, distillation of a more volatile material began to occur. The residue was then distilled (30–7 mm., bath 160–190°). Refractionation of the distillate gave 32.5 g. of crude thiolactone. The analysis for sulfur indicated that the thiolactone comprised 92.5% of the product. It was purified by two recrystallizations from petroleum ether at dry ice temperature, b. p. 115–116° (5 mm.), 123–125° (7 mm.); d^{20}_4 1.1377, d^{25}_4 1.1346; $n^{20}D$ 1.4887, $n^{25}D$ 1.4860; $[M]^{25}r$ 51.18 (Lorentz-Lorenz), $[M]^{25}r$ 51.21 (calcd. from Eisenlohr's values).

Anal. Calcd. for $C_9H_{14}O_3S$: S, 15.85. Found: S, 15.63.

Condensation of α-Ethyl-α-carboxethyl-γ-thiobutyrolactone with Urea.—To an ice-cold solution of sodium ethoxide prepared from 3.5 g. of sodium and 50 cc. of absolute alcohol was added 6.0 g. of urea and then dropwise with stirring 10.1 g. of α-ethyl-α-carboxethyl-γ-thiobutyrolactone. The urea dissolved after three hours. The reaction mixture remained as a viscous solution after forty hours at room temperature. The product obtained by distillation of the solvent and acidification in the usual way partially crystallized. After removal of the liquid with petroleum ether the crude solid product weighed 6 g. Crystallization from benzene, dissolution in aqueous sodium hydroxide, and precipitation with hydrochloric acid gave 2.8 g. of crystals, m. p. 146–148°. The melting point was not lowered when mixed with a sample of 5-ethyl-5-β-mercaptoethylbarbituric acid prepared from the bromo acid. Further work is in progress.

Summary

1. 5-Alkyl-5-β-mercaptoethylbarbituric acids have been prepared from 5-alkyl-5-β-bromoethylbarbituric acids.

2. An α-carboxethyl-γ-thiobutyrolactone is described. It has been condensed with urea to give a β-mercaptoethylbarbituric acid.

NEWARK, DELAWARE RECEIVED AUGUST 6, 1949

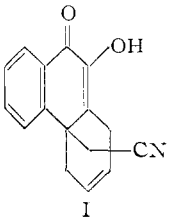
[CONTRIBUTION FROM THE MARIAN EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE AND THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Ring Systems Related to Morphine. IV. N-Methylisomorphinane*

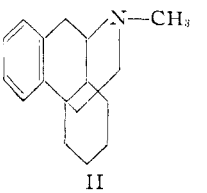
BY MARSHALL GATES, R. B. WOODWARD, WILLIAM F. NEWHALL AND ROSEMARIE KÜNZLI

The synthesis of 9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (I) and a preliminary account of its conversion to the tetracyclic tertiary base II which we now call N-methylisomorphinane, and which has, or is stereoisomeric with, the carbon–nitrogen skeleton present in morphine, have been the subjects of the first two papers of this series.[1a]

The present paper is concerned with a reinterpretation of the reaction path leading from I to II, with the detailed description of these reactions, and with an improved procedure for the preparation of I.



I



II

The adduct I on hydrogenation over copper–chromium oxide at moderate temperature and

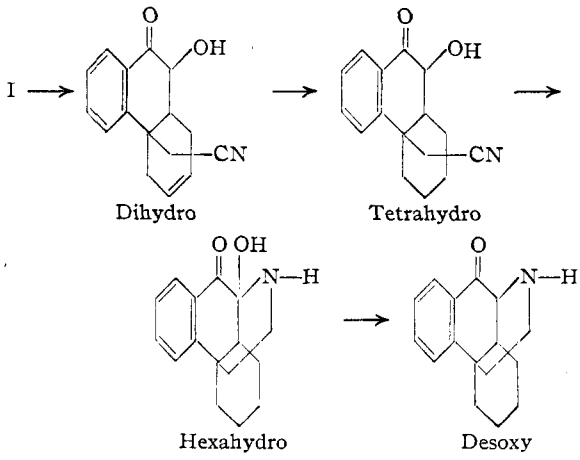
* Taken in part from a dissertation presented by William F. Newhall to the faculty of Bryn Mawr College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(1) (a) Gates and Newhall, THIS JOURNAL, **70**, 2261 (1948); (b) *Experientia*, **5**, 285 (1949).

pressure is converted in 50% yield into a dihydro compound which in contrast to I is insoluble in alkali. The dihydro compound forms an oxime and an acetyl derivative. Further reduction of the dihydro compound over Raney nickel at room temperature and atmospheric pressure results in the rapid absorption of one mole of hydrogen, and the further slow absorption of a second with the production in good yield of a feebly basic hexahydro derivative which forms a diacetyl derivative. If the hydrogenation is interrupted after one mole of hydrogen has been absorbed, a tetrahydro derivative can be isolated. That this tetrahydro derivative still contains a carbonyl group is shown by oxime formation. By further hydrogenation it is converted into the hexahydro derivative.

The action of hydriodic acid and red phosphorus on the hexahydro compound effects the quantitative removal of an hydroxyl group to yield a feebly basic desoxy compound which forms a monoacetyl derivative, but which does not yield an oxime.

This series of reactions was tentatively formulated as follows in an earlier publication,[1b,2] but when ultraviolet and infrared absorption spectra became available, a number of inconsistencies in this formulation became apparent. Thus, the above scheme requires that the dihydro, tetrahydro, hexahydro and desoxy compounds all show the high intensity absorption in the ultraviolet characteristic of a carbonyl group conjugated with an aromatic ring. The ultraviolet absorption spectra (Fig. 1) show that this is true of the dihydro and tetrahydro compounds, but that the hexahydro and desoxy compounds show only the moderate intensity absorption characteristic of an isolated benzene ring. In the infrared[3] (Fig. 2), the dihydro and tetrahydro compounds show no nitrile band, but they, as well as the hexahydro and desoxy compounds, show a strong band at 6.01μ, characteristic of *cyclic* amides,[4] and a band of moderate intensity at 2.94μ due to the



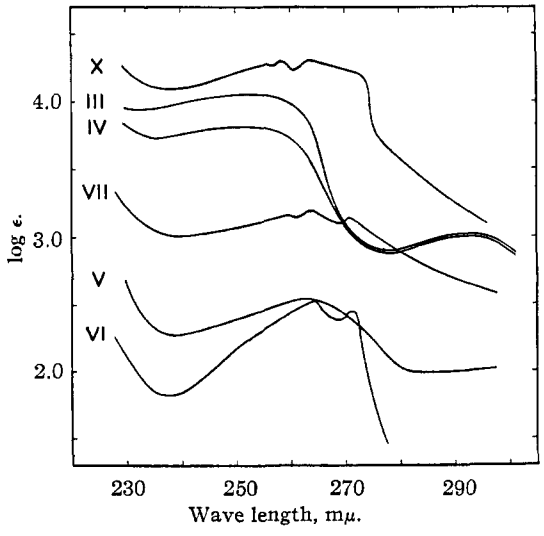


Fig. 1.—Ultraviolet absorption spectra: III, dihydro; IV, tetrahydro; V, isomeric tetrahydro; VI, hexahydro; VII, desoxy; X, desbase; 1 cm., approximately 10^{-4} M in methanol except for V, which was done in ethanol.

(2) The tetrahydro compound had not been characterized at the time of our earlier publication.[1b]

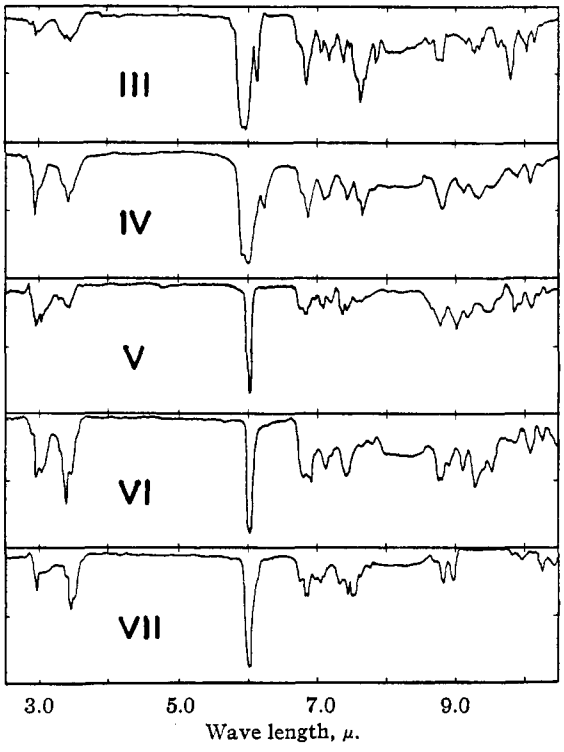


Fig. 2.—Infrared absorption spectra: III, dihydro; IV, tetrahydro; V, isomeric tetrahydro; VI, hexahydro; VII, desoxy; approximately 2% in chloroform.

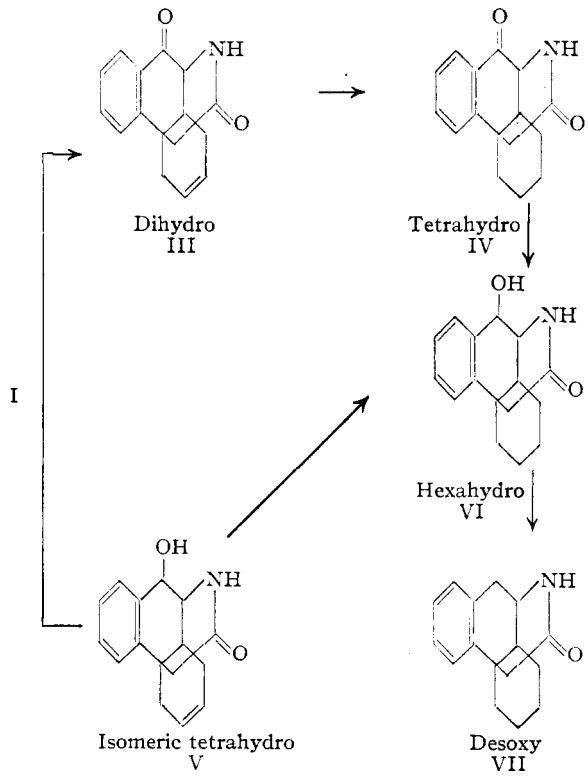
(3) We are indebted to Dr. Charles H. Schramm and to Dr. Gurbakhsh Singh for the determination of these spectra which were carried out on a Baird recording infrared spectrophotometer.

(4) The strong band in the region 6.45–6.65μ which accompanies the 6.0μ band in acyclic monosubstituted amides is not present in cyclic amides; *cf.* Monthly Progress Report, Contract OEMcmr-445, Shell Development Company, Sept. and Oct., 1945.

N–H grouping. Of these substances, only the di- and tetrahydro compounds exhibit absorption characteristic of a cyclic conjugated carbonyl group (5.96, 5.91μ, respectively), although the above formulation requires that all show this band. A second tetrahydro compound, isomeric with that mentioned above, and which, like its isomer, can be converted into the hexahydro compound by hydrogenation, can be obtained by varying the conditions of copper–chromium oxide hydrogenation of the adduct I. It forms a diacetyl derivative but does not react with hydroxylamine. The infrared spectrum (Fig. 2) of this isomeric tetrahydro compound shows the cyclic amide band but no carbonyl band, and exhibits both OH (3.01μ) and N–H (2.94μ) absorption, as does the hexahydro compound; the ultraviolet spectra of both (Fig. 1) show only benzenoid absorption.

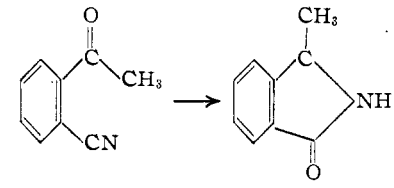
These inconsistencies are more than sufficient to eliminate the reaction course formulated above from further consideration, but in addition a number of chemical inconsistencies were uncovered.

Among these are the failure of the dihydro compound to reduce periodic acid or to give an azine with *o*-phenylenediamine, the very low basicity of the hexahydro and desoxy compounds,[5] the failure of the hexahydro compound, formulated above as a carbinolamine, to undergo ready ether formation, the failure of the desoxy compound to form an oxime, to be reduced by the Wolff–Kishner technique or to undergo methylation either with methyl iodide or with formaldehyde–formic acid and, finally, the complete removal of oxygen from the desoxy compound by means of lithium aluminum hydride.



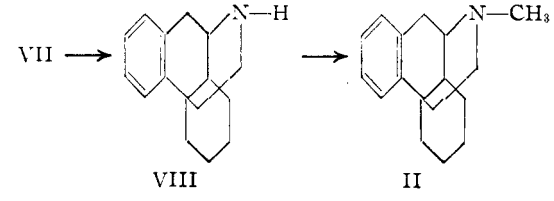
The new formulation just shown is consistent with all of the available evidence.

The remarkable conversion of the adduct I to the cyclic amide III finds a close analogy in the conversion, by hydrogenation under acid conditions over palladium, of *o*-cyanoacetophenone to 3-methylphthalimidine.[6]



It is now clear that the tetracyclic carbon–nitrogen ring system present in the morphine alkaloids can be assembled in *three* steps, since I can now be obtained (*vide infra*) in two steps from 1-amino-2-naphthol-4-sulfonic acid.

The desoxy compound VII loses its final oxygen atom by hydrogenation over copper chromite at 200–225° and 140–150 atmospheres, or by the action of excess lithium aluminum hydride,[7] to yield an oily oxygen-free base (VIII) which was not characterized as such but was methylated by the action of formaldehyde and formic acid to give N-methylisomorphinane (II), whose



picrate can be obtained in 79% yield from VII. The over-all yield of II from 1-amino-2-naphthol-4-sulfonic acid in the seven-step process approximates 15%.

The methylated base II, regenerated from its picrate and distilled, is a colorless oil which is saturated to Adams catalyst. It is isomeric, presumably at C_{14}, with Grewe's N-methylmorphinane,[8] and is identical with a substance obtained in small amounts as a by-product (*cf.* pikrat A, *Ber.*, **81**, 285 (1948)) in Grewe's elegant

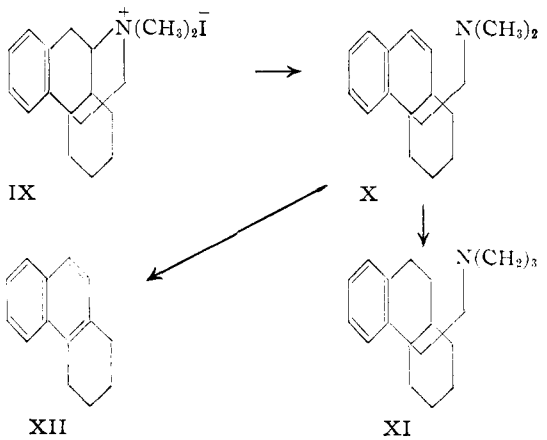
(5) VI and V are more soluble in hydrochloric acid than are III and IV, although all of these substances show weakly basic properties (see experimental section). This behavior may be due not so much to inherently different basicities as to different water solubilities (VI and V contain hydroxyl groups).

(6) Helberger and von Rebay, *Ann.*, **539**, 187 (1939).

(7) Uffer and Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948), have shown that amides can be converted to amines smoothly by this reagent.

(8) R. Grewe (a) *Naturwissenschaften*, **33**, 333 (1946); (b) *Z. angew. Chem.*, **A59**, 194 (1947); (c) Grewe and Mondan, *Ber.*, **81**, 279 (1948).

synthesis.[9] Its methiodide (IX) on short boiling with strong alkali yields an unsaturated oily desbase (X) which on hydrogenation over Adams catalyst yields an oily dihydrodesbase (XI) and on distillation with zinc dust yields 1,2,3,4-tetrahydrophenanthrene (XII).



The desbase has been assigned the methine structure X rather than the alternative isomethine structure with the double bond in the side chain on the basis of its absorption spectrum in the ultraviolet (Fig. 1).

Degradative work designed to ascertain the stereochemical nature of the ring juncture at carbon atoms 13 and 14 is in progress.

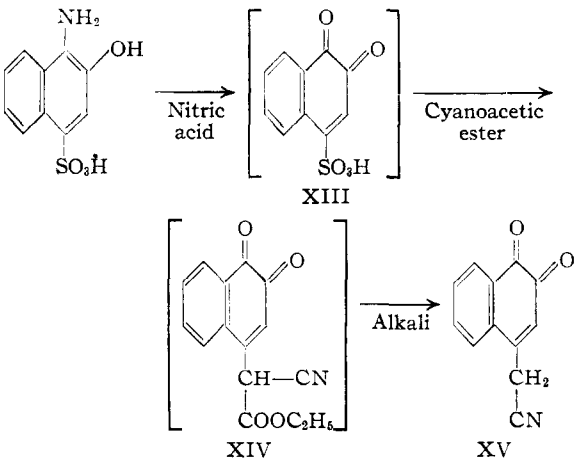
N-Methylisomorphinane has been found to exhibit a marked degree of analgetic activity on preliminary test by the D'Amour–Smith rat-tail method.[10]

We also wish to report briefly a substantial improvement in the synthesis of I. 4-Cyanomethyl-1,2-naphthoquinone (XV) may now be obtained in essentially one laboratory step from commercially available 1-amino-2-naphthol-4-sulfonic acid if the solution containing crude 1,2-naphthoquinone-4-sulfonic acid (XIII) resulting from nitric acid oxidation of the aminonaphthol is treated with cyanoacetic ester and an excess of alkali. The cyanoacetic ester condensation product (XIV) is rapidly cleaved by strong alkalies even at room temperature and XV is obtained in 61% over-all yield.[11] A slight change in the conditions of the condensation of XV with butadiene has raised the yield of I to 83% from XV, or 50.5% in a two-step process from 1-amino-2-naphthol-4-sulfonic acid.

(9) Professor Grewe very kindly supplied us with samples of his "pikrat A" and the corresponding desbase and dihydrodesbase picrates with which we were able to compare our samples.

(10) We are indebted to Mr. E. Macko of the Research Division, Smith, Kline and French Laboratories for this preliminary information.

(11) In paper I of this series the condensation of ammonium 1,2-naphthoquinone-4-sulfonate with cyanoacetic ester was reported to give XIV in 91% yield. This was an exceptional experiment, and we have been unable consistently to obtain yields this high. Large-scale runs averaged about 65%.



We wish gratefully to acknowledge the help of a Frederick Gardner Cottrell Special grant-in-aid from the Research Corporation with which a part of the expense of this work was defrayed.

Experimental[12]

4-Cyanomethyl-1,2-naphthoquinone (XV).—1-Amino-2-naphthol-4-sulfonic acid (100 g., technical product, washed thoroughly with alcohol and dried) was oxidized to the corresponding 1,2-quinone[13] and the thick paste of free sulfonic acid was dissolved in 1.3 liters of water, cooled to 10°, and treated with a solution of 63 g. of ethyl cyanoacetate in 850 cc. of methanol. One hundred and seventy cc. of 25% sodium hydroxide was then added and the deep purple solution was stirred for two or three minutes. The temperature was held below 20° by the addition of small amounts of ice. At the end of this period the solution was diluted with 500 cc. of methanol, cooled to 10° with ice, and then treated with a cooled solution of 250 g. of sodium hydroxide in 2 l. of water. Stirring was continued for about five minutes during which the deep purple solution changed gradually to a deep crimson with no bluish tinge, and the mixture was then acidified to congo red after cooling to 10°. The quinone separates as yellow microcrystalline needles, 51.0 g. (16%), air-dried, m. p. 199.5–204°[14] with decomposition.

The yield of **9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene** (I) from XV (15 g.) and butadiene (45 cc.) has been raised to 83% from 56% by working in absolute dioxane (40 cc.) and increasing the reaction period to forty-eight hours. The product (11.5 g., m. p. 182.5–185°) was obtained by removing the volatile material completely and crystallizing the residue from methanol with the aid of decolorizing black.

The dihydro compound III was prepared by hydrogenation of the adduct I (5.00 g.) in 75 cc. of absolute alcohol at 135° and 1000–1400 lb. pressure (cold) over 600 mg. of copper-chromium oxide for one hour. The adduct is sparingly soluble in cold alcohol and it is advantageous to wait at least ten minutes after the bomb has reached 135° before beginning agitation. After removal of the catalyst, the dark brown solution was decolorized twice and thoroughly concentrated to yield 2.35 g. (50%) of III as light green prisms, m. p. 250–251°. A small sample was

(12) All melting points are corrected, unless otherwise stated. All analytical samples were dried at 78° and 10^{-4} mm. unless otherwise indicated.

(13) Fieser, "Org. Synthesis," **21**, 91 (1941).

(14) In paper I of this series this quinone was described as having m. p. 191–194° with decomposition. We have subsequently had samples which melt as high as 208°. The decomposition at the melting point is extensive, and the m. p. is not a good criterion of purity.

purified for analysis by several crystallizations from methanol to give colorless prisms, m. p. 252.5–254°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.86; H, 5.96. Found: C, 75.73; H, 6.08.

The dihydro compound is insoluble in aqueous alkali. It is sparingly soluble in methanol or ethanol and only slightly soluble in cold benzene. Its solution in concentrated sulfuric acid is very pale yellow. It dissolves readily in cold 12 *N* hydrochloric acid and this solution on scratching deposits a crystalline hydrochloride which on dilution with water is hydrolyzed to III. It is only partially soluble in 6 *N* hydrochloric acid. It is unattacked by an aqueous methanol solution of periodic acid, and can be recovered unchanged after refluxing with *o*-phenylenediamine in acetic acid for one hour. Its **oxime**[15] was prepared in pyridine solution and crystallized from pyridine to give colorless material, m. p. 280–281°, soluble in aqueous alkalies.

Anal. Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.02. Found: C, 71.75; H, 6.36.

The **acetyl derivative** of III was prepared by refluxing in acetic anhydride containing sodium acetate and was purified by crystallization from dilute acetic acid; heavy colorless prisms, m. p. 176–178° when heated slowly The m. p. may begin as low as 168° if it is taken rapidly. This behavior may be due to polymorphism. On boiling with aqueous alcoholic alkali, the acetyl compound is hydrolyzed to III, m. p. 251–253.5°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80. Found: C, 73.33; H, 5.95.

A second dihydro compound of undetermined structure can be obtained in low yield (200 mg. (4%), m. p. 269–275° with decomposition) from the alcoholic filtrate from the preparation of III. Several crystallizations from methanol gave colorless material, m. p. 286.5–288.5° with decomposition. Like III, it is insoluble in cold benzene but somewhat more soluble in methanol and ethanol than III. Its solution in sulfuric acid is very pale yellow.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.86; H, 5.96. Found: C, 75.91; H, 6.05.

The Hexahydro Compound VI.—Hydrogenation of the dihydro compound III (2.0 g.) in methanol over fresh Raney nickel at atmospheric pressure and room temperature yielded, with the rapid uptake of one mole of hydrogen followed by the slow (sixteen hours) uptake of a second mole of hydrogen, VI, isolated by removal of the catalyst and concentration of the colorless filtrate. Colorless prisms, 1.6 g. (78%), m. p. 231–241°, sufficiently pure for use in the next step, were obtained. A small sample was crystallized several times from methanol for analysis, m. p. 242–243.5°.

Anal. Calcd. for $C_{16}H_{19}O_2N$: C, 74.67; H, 7.44. Found: C, 74.47; H, 7.29.

The substance is sparingly soluble in cold benzene, moderately soluble in methanol or ethanol. It is not soluble in moderate amounts of 2 *N* but dissolves in 6 *N* hydrochloric acid from which it can be recovered by diluting with water or by making alkaline. Its solution in concentrated sulfuric acid is colorless. Its **diacetyl derivative** was prepared by the action of refluxing acetic anhydride containing sodium acetate and purified by crystallization from aqueous methanol; colorless blades, m. p. 137–139°. It is insoluble in dilute acids, readily soluble in both methanol and benzene.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 70.35; H, 6.78. Found: C, 70.10; H, 6.71.

In one hydrogenation of III (540 mg.) the reaction was interrupted after the rapid absorption of one mole of hydrogen (53.5 cc., six minutes). Removal of the catalyst and concentration of the filtrate yielded 380 mg. of crude **tetrahydro compound** IV, m. p. 218–221°, which was recrystallized several times from benzene–ethanol to yield small colorless prisms, m. p. 226–227.5°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 75.23; H, 7.16.

It is partially soluble in 6 *N* hydrochloric acid, is insoluble in aqueous alkali, and is sparingly soluble in both benzene and ethanol. Its solution in concentrated sulfuric acid is a very pale yellow. Its **oxime** was prepared in pyridine and crystallized from ethanol to give small prisms, m. p. 256–258° with decomposition, soluble in aqueous alkalies.

Anal. Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.09; H, 6.71. Found: C, 70.63; H, 6.81.

The tetrahydro compound IV (98 mg.) on hydrogenation for five hours over Raney nickel yields the hexahydro compound VI (59 mg., m. p. 240–243°) as colorless prisms which after one recrystallization melted at 241–242.5° and did not depress the melting point of VI prepared directly from III.

The isomeric tetrahydro compound[16] V was obtained from I (30.0 g.) by hydrogenation at 165° and 1200 lb. over copper–chromium oxide in 500 cc. of absolute alcohol. During two and one-half hours hydrogen corresponding to two moles was absorbed. After removal of the catalyst, the filtrate on concentration under diminished pressure yielded 17.5 g. of pale yellow crystalline material. Recrystallization from alcohol in which it is rather sparingly soluble afforded 15.0 g. (49.2%) of colorless prisms, m. p. 282–283°.

Anal.[17] Calcd. for $C_{16}H_{17}O_2N_2$: C, 75.27; H, 6.71. Found: C, 75.35; H, 6.70.

It is fairly soluble in 6 *N* hydrochloric acid, from which it can be recovered by diluting with water or by making the solution alkaline. It does not form an oxime. Its **diacetyl derivative** was prepared by refluxing 291 mg. of the isomeric tetrahydro compound for one hour with 2 cc. of acetic anhydride and some sodium acetate. The oil resulting from the hydrolysis of excess anhydride readily crystallized and was recrystallized from dilute acetic acid; 328 mg., colorless prismatic needles, m. p. 170–172°. Two further crystallizations raised the m. p. to 172.5–174°.

Anal.[18] Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24. Found: C, 71.03; H, 5.81.

Hydrogenation[16] of the isomeric tetrahydro compound V over Raney nickel in methanol at atmospheric pressure yields, with the rapid absorption of 1 mole of hydrogen, the hexahydro derivative VI, m. p. 240–242°, mixed m. p. not depressed.

The Desoxy Compound VII.—One gram of VI was refluxed for seventeen hours in 47% hydriodic acid containing about 0.5 g. of red phosphorus. The cooled solution was filtered through a sintered glass funnel to remove phosphorus and diluted with sodium hydroxide solution until basic. The precipitated colorless solid was collected, washed with water and dried, 0.90 g. (98%) m. p. 206–209°. For analysis, a sample was crystallized several times from benzene to yield small colorless blades, m. p. 208–209°.

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.62; H, 7.93. Found: C, 79.57; H, 8.00.

If the hydriodic acid filtrate is diluted with water rather than alkali, a sparingly soluble hydriodide, m. p. (crude) 245–256° separates. This hydriodide was not characterized further.

The half-hydrochloride is easily prepared by dissolving the desoxy compound (137 mg.) in a small amount of warm methanol and diluting with 2 *N* hydrochloric acid. Colorless blades separate slowly, 122 mg., m. p. 252–260° with evolution of hydrogen chloride (silver chloride test). Repeated crystallization from chloroform–methanol or from 20% hydrochloric acid does not raise or sharpen the melting point. The substance is sparingly soluble in and partially hydrolyzed by water and yields the desoxy com-

(15) This substance was prepared and analyzed by Miss Cristel Kappes.

(16) This preparation was carried out by Dr. Charles H. Schramm.

(17) Analysis by Mr. S. M. Nagy.

(18) Analysis by Mrs. Shirley Golden.

pound VII on treatment with alkali. A suspension of 52.3 mg. of the half hydrochloride in distilled water exhibits a *p*H of 2.80, and its titration curve against 0.05 *N* sodium hydroxide closely resembles that of an equivalent quantity of hydrochloric acid.

Anal.[18] Calcd. for $C_{32}H_{39}O_2N_2Cl$: C, 74.03; H, 7.57. Found: C, 74.34; H, 7.57.

The desoxy compound does not form an oxime and attempts to reduce it by the Huang-Minlon modification of the Wolff-Kishner method resulted in nearly quantitative recovery of starting material. It is not methylated by methyl iodide in benzene or by formaldehyde-formic acid.

The monoacetyl derivative of VII was prepared by refluxing the desoxy compound (50 mg.) in acetic anhydride containing sodium acetate. Hydrolysis of excess acetic anhydride gave colorless plates, 38 mg., m. p. 134–137°. The material is insoluble in dilute acids and only moderately soluble in methanol. One further crystallization gave 22 mg., m. p. 135.5–137°.

Anal. Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47. Found: C, 76.57; H, 7.91.

N-Methylisomorphinane (II).—Two hundred and forty milligrams of desoxy compound VII was hydrogenated in 15 cc. of dioxane over 150 mg. of copper chromite for three hours at 210–225° and 2100 lb. The filtered solution was concentrated to dryness and the residual colorless oil was methylated by refluxing for twenty hours with a mixture of equal volumes of formaldehyde and formic acid. The solution was concentrated to dryness, the residue taken up in 20 cc. of methanol, filtered from insoluble formaldehyde polymers and treated with a methanol solution of 187 mg. of picric acid. **N-Methylisomorphinane picrate** separated at once as yellow blades, 299 mg. (70% from VII), m. p. 205–209° with decomposition. Several crystallizations from methanol, in which it is very sparingly soluble, afforded pure picrate, m. p. 210–212.5° with decomposition. A mixed melting point with Grewe's "pikrat A"[9] was not depressed.

Anal. Calcd. for $C_{23}H_{26}O_7N_4$: C, 58.71; H, 5.57. Found: C, 58.72; H, 6.05.

N-Methylisomorphinane can be obtained from VII by reduction with lithium aluminum hydride followed by methylation. One gram of VII, when refluxed with 1.0 g. of lithium aluminum hydride in 50 cc. of absolute ether for three days, yielded, after decomposition with alkali and methylation of the basic product as described above, 0.30 g. of picrate, m. p. 210–212°.[16]

Extraction of an ether suspension of the picrate (225 mg.) with successive portions of dilute alkali and concentration of the dried ether layer afforded 113 mg. (92.5%) of a colorless oil which was distilled in a microsublimer at 10^{-4} mm. and 180° (bath) to give N-methylisomorphinane as a colorless oil.

Anal. Calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60. Found: C, 84.12; H, 9.77.

The base is soluble in dilute acids and can be reprecipitated by alkalies. It is saturated to Adams catalyst. Its **methiodide** was prepared by heating a benzene solution of 180 mg. of II and excess methyl iodide at 100° in a sealed tube for seventeen hours. Colorless needles (259 mg., 90%) of the methiodide separated during the heating period, m. p. 231–236°. Crystallization from methanol–ether raised the melting point to 233–236° with slight decomposition.

Anal. Calcd. for $C_{18}H_{26}NI$: C, 56.39; H, 6.84. Found: C, 56.43; H, 7.15.

The methiodide (259 mg.) on warming with 30% potassium hydroxide solution, went into solution, and a colorless oil separated. The oil was taken into ether, washed with water and dried over anhydrous sodium sulfate. Removal of the ether left the desbase as a colorless oil (159 mg., 97%), which was taken into methanol and treated with a solution of 116 mg. of picric acid in methanol. The **desbase picrate** separated as yellow blades, m. p. 207.5–209.5°, mixed m. p. with N-methylisomorphinane picrate, 178–195°. It gave no melting point depression when mixed with a sample of the picrate of the desbase corresponding to the base of Grewe's "pikrat A."

Anal. Calcd. for $C_{24}H_{28}O_7N_4$: C, 59.49; H, 5.82. Found: C, 59.35; H, 6.09.

The **desbase** X was regenerated from its picrate (192 mg.) by extraction of an ether suspension of the picrate with dilute sodium hydroxide. Concentration of the washed and dried ether solution yielded 100 mg. of the desbase as a colorless oil. It was distilled under high vacuum in a microsublimer, bath temperature 180°.

Anal. Calcd. for $C_{18}H_{25}N$: C, 84.65; H, 9.87. Found: C, 84.09; H, 9.43.

It is soluble in dilute acids. Reduction of the desbase (100 mg.) over Adams catalyst in methanol (uptake 10.2 cc., theoretical 11.6 cc.) and removal of the solvent gave 100 mg. of **dihydrodesbase** XI as a colorless oil, which was distilled at 10^{-4} mm. in a microsublimer, bath temperature 180°.

Anal. Calcd. for $C_{18}H_{27}N$: C, 83.98; H, 10.57. Found: C, 84.48; H, 10.66.

The **dihydrodesbase picrate** was prepared in methanol from 80 mg. of the base and 58 mg. of picric acid; yellow blades (77 mg.) m. p. 190–192.5° separated at once. One crystallization from methanol gave 60 mg. of pure picrate, m. p. 191–192.5°. It gave no melting point depression when mixed with a sample of the picrate of the dihydrodesbase corresponding to the base of Grewe's "pikrat A."

Anal. Calcd. for $C_{24}H_{30}O_7N_4$: C, 59.25; H, 6.21. Found: C, 59.34; H, 6.30.

Zinc Dust Distillation of the Desbase.—The desbase (41 mg.) was intimately mixed with zinc dust and heated to 490° at atmospheric pressure for thirty minutes in a microsublimer. During this time a pale yellow oil appeared on the cold finger. The distillate was taken into ether and the ethereal solution was extracted three times with dilute acid, dried and concentrated to yield 18 mg. of neutral oil which solidified at 0°, m. p. 25–28° (m. p. of 1,2,3,4-tetrahydrophenanthrene, 33°). This oil was treated with picric acid (15 mg.) in methanol and recrystallization of the first crop yielded 5 mg. of picrate, m. p. 108–110°, whose mixed melting point with authentic 1,2,3,4-tetrahydrophenanthrene picrate of m. p. 108.5–111° was 108–110.5°. The picrate dissociates almost completely in 60–70° petroleum ether, and by passing the solution through a column of activated alumina the last traces of picric acid were removed. In this way several milligrams of the hydrocarbon were recovered and converted to the previously unreported **1,2,3,4-tetrahydrophenanthrene-trinitrobenzene complex**, m. p. 126–127.5° after several crystallizations. Its m. p. showed no depression when mixed with an authentic sample of m. p. 128–129° prepared from 1,2,3,4 - tetrahydrophenanthrene.[19] The authentic sample was crystallized several times from methanol-benzene.

Anal. Calcd. for $C_{20}H_{17}N_3O_6$: C, 60.75; H, 4.34. Found: C, 60.67; H, 4.96.

Summary

The conversion of 9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (I) into N-methylisomorphinane (II), which has, or is stereoisomeric with, the carbon–nitrogen skeleton of morphine, is described.

An improved synthesis of I is reported.

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(19) We are indebted to Dr. Ernst Berliner for a sample of γ-(2-naphthyl)-butyric acid from which our sample of 1,2,3,4-tetrahydrophenanthrene was prepared.