pared in 43% yield from 3.41 g. (0.0153 mole) of 2-methyl-5-ethylpyridine-4-carboxaldehyde diethylacetal (X) and 3.75 g. (0.0153 mole) of 3,4-dimethoxyphenethyl bromide as described above for the preparation of XVIII.

Anal. Calcd. for $C_{23}H_{34}NO_4Br$: C, 58.97; H, 7.32; N, 2.99; Br, 17.06. Found: C, 59.05; H, 7.27; N, 3.27; Br, 16.94.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

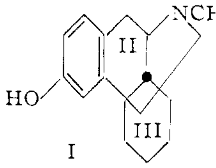
The Synthesis and Resolution of 3-Hydroxy-N-methylisomorphinan[1]

BY MARSHALL GATES AND WILLIAM GATEWOOD WEBB[2]

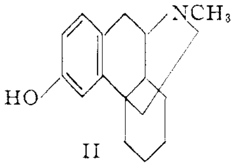
RECEIVED OCTOBER 1, 1957

3-Hydroxy-N-methylisomorphinan and 3-hydroxy-Δ^6-dehydro-N-methylisomorphinan have been synthesized and resolved. The *l*-enantiomorph of each exhibits powerful analgesic activity in animal screening tests.

The marked success of *l*-3-hydroxy-N-methylmorphinan[3] (I) (rings II/III *cis*) as an analgesic and the methyl ether of its enantiomorph as an antitussive[4,5] clearly suggest the desirability of examining the pharmacological properties of the C_{14}-epimers of these substances, and we have synthesized and resolved 3-hydroxy-N-methylisomorphinan (II) (rings II/III *trans*) as well as the corresponding Δ^6-dehydro derivative by the general method reported in earlier papers.[6]

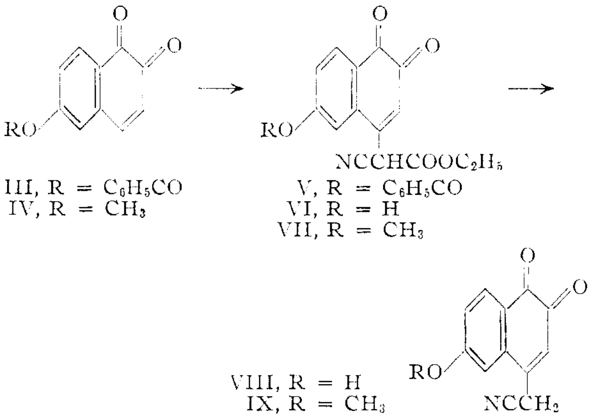


I



II

6-Benzoyloxy-1,2-naphthoquinone (III),[6b] readily prepared in three steps in 55% over-all yield from 2,6-dihydroxynaphthalene, and 6-methoxy-1,2-naphthoquinone (IV)[7] were both used as starting materials. Conversion of these to the 4-cyanomethylquinones VIII and IX through the intermediate cyanoacetates V, VI and VII by the methods developed earlier was successful, over-all yields of 40 and 49%, respectively, being obtained. During the condensation of III with ethyl cyanoacetate, some ethyl 6-hydroxy-1,2-naphthoquinonyl-4-cyanoacetate (VI) is formed by hydrolysis, and although V can readily be obtained, the best yields of VIII are obtained by cleaving the crude condensation product containing both V and VI with strong alkali. An alternative preparation of VII from 6-methoxy-2-naphthol entirely analogous to the preparation of ethyl 1,2-naphthoquinonyl-4-cyanoacetate from 2-naphthol by way of 1-nitroso-2-naphthol and 1-amino-2-naphthol-4-sulfonic acid,[8,9] was also investigated briefly. Comparable over-all yields were obtained. As in earlier examples[6a,b] the point of attachment of the cyanomethyl group in VIII was established by conversion to the known 5-methylbenzo[a]phenazine.[10]



III, R = C_6H_5CO
IV, R = CH_3

V, R = C_6H_5CO
VI, R = H
VII, R = CH_3

VIII, R = H
IX, R = CH_3

Both quinones VIII and IX condense readily with butadiene and with dimethylbutadiene to give the corresponding enolic diketones X, XI, XII and XIII in approximately 60% yield.

Reductive cyclization[6] of these diketones with copper chromite yielded the ketolactams XIV, XV, XVI and XVII, the yields ranging from 38 to 59%. The phenolic ketolactams XIV and XVI are, of course, easily methylated with dimethyl sulfate and alkali to XV and XVII, and if this methylation is carried out at 50° with a large excess of dimethyl sulfate, the corresponding N-methyketolactams are readily obtained.

The ketonic carbonyl group of XIV, XV, XVI and XVII is easily converted to methylene by Wolff–Kishner–Huang-Minlon reduction, although

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[1] Taken in part from the Ph.D. dissertation of William Gatewood Webb, the University of Rochester, 1954.

[2] Sherman Clark Fellow, 1951–1952; Beaunit Mills Fellow, 1952–1953.

[3] O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **34**, 2211 (1951); *cf.* R. Grewe, A. Mondon and E. Nollte, *Ann.*, **564**, 161 (1949).

[4] (a) W. M. Benson, P. L. Stafko and L. O. Randall, *J. Pharmacol. Exp. Therap.*, **109**, 189 (1953); (b) R. D. Hunt and F. F. Foldes, *New Engl. J. Med.*, **248**, 803 (1953).

[5] (a) B. Pellmont and H. Bachtold, *Schweiz. Med. Wochschr.*, **84**, 1368 (1954); (b) A. Hottinger, *ibid.*, **84**, 1372 (1954); (c) L. J. Cass and W. S. Frederick, *New Engl. J. Med.*, **249**, 132 (1953); (d) L. J. Cass and W. S. Frederick, *J. Lab. Clin. Med.*, **48**, 879 (1956).

[6] (a) M. Gates and W. F. Newhall, THIS JOURNAL, **70**, 2261 (1948); (b) M. Gates, *ibid.*, **72**, 228 (1950); (c) M. Gates, R. B. Woodward, W. F. Newhall and R. Künzli, *ibid.*, **72**, 1141 (1950); (d) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

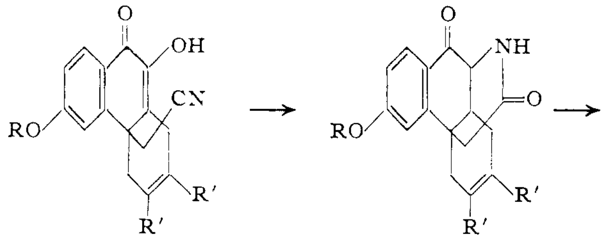
[7] H. E. French and K. Sears, *ibid.*, **70**, 1279 (1948). We were able to make substantial improvements (55% compared with 15% over-all from 2-naphthol) in the preparation of this substance by using aqueous alkali and copper-bronze to convert 6-bromo-2-methoxynaphthalene into 6-methoxy-2-naphthol and by using the corresponding nitroso compound rather than the azo compound in the conversion of this naphthol to the quinone.

[8] F. Sachs and M. Craveri, *Ber.*, **38**, 3685 (1905).

[9] E. L. Martin and L. F. Fieser, *Org. Syntheses*, **21**, 91 (1941); L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 42.

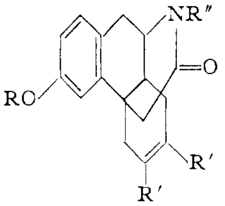
[10] L. F. Fieser and C. K. Bradsher, THIS JOURNAL, **61**, 417 (1939).

under the conditions used high yields (91 and 89%, respectively) were obtained only with the methyl ethers XV and XVII. The low yields (45%) obtained with the phenolic ketolactams XIV and XVI were recorded before it was realized that the conditions recommended by Huang-Minlon^{11} were much more vigorous than necessary in this series.^{6d} It seems likely that high yields may also be obtained with these compounds under more moderate conditions.



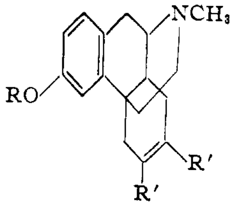
X, R = H, R' = H
XI, R = CH_3, R' = H
XII, R = H, R' = CH_3
XIII, R = CH_3, R' = CH_3

XIV, R = H, R' = H
XV, R = CH_3, R' = H
XVI, R = H, R' = CH_3
XVII, R = CH_3, R' = CH_3



XVIII, R = H, R' = H, R'' = H
XIX, R = CH_3, R' = H, R'' = H
XX, R = H, R' = CH_3, R'' = H
XXI, R = CH_3, R' = CH_3, R'' = H
XXII, R = CH_3, R' = H, R'' = CH_3
XXIII, R = CH_3, R' = CH_3, R'' = CH_3

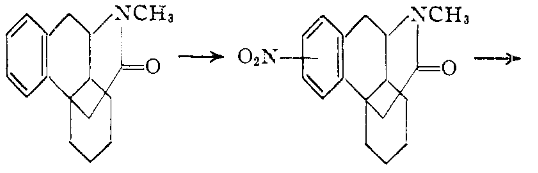
We had intended to convert the lactams XVIII and XX to the tertiary bases 3-hydroxy-Δ^6-dehydro-N-methylisomorphinan (XXIV) and 3-hydroxy-6,7-dimethyl-Δ^6-dehydro-N-methylisomorphinan (XXVI) by reduction with lithium aluminum hydride followed by methylation with formaldehyde–formic acid. This route was chosen so as to retain the 6,7-double bond, known^{12} to enhance analgesic activity in related substances. The reduction of these phenolic substances failed, however, owing to the precipitation of insoluble complexes. The corresponding N,O-dimethyl derivatives XXII and XXIII, produced by the action of sodium hydride and methyl iodide on XIX and XXI, were therefore used and led to excellent yields (85% as picrate) of the tertiary bases XXV and XXVII.



XXIV, R = H, R' = H
XXV, R = CH_3, R' = H
XXVI, R = H, R' = CH_3
XXVII, R = CH_3, R' = CH_3

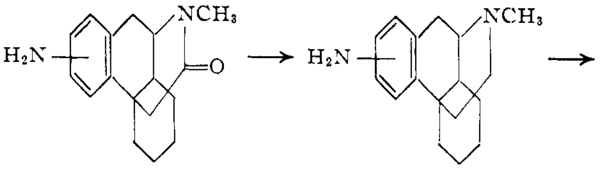
Demethylation with potassium hydroxide^{6d} then gave the 3-hydroxy derivatives XXIV and XXVI, and catalytic hydrogenation of the former yielded 3-hydroxy-N-methylisomorphinan (II).

Another route to II, reminiscent of that used by Schnider and Grüssner^{13} to prepare 3-hydroxy-N-methylmorphinan (I), was also studied. 16-Oxoisomorphinan^{6c,14} was methylated with sodium hydride and methyl iodide to give XXVIII, and this substance was nitrated. Fractional crystallization of the resulting mixture of nitro compounds yielded three pure isomers. That present in largest amount (50% yield) was shown (*vide infra*) to be the 3-nitro compound, and the other two, obtained in 16 and 10% yields, were shown less conclusively to be the 2- and 1-nitro compounds, respectively.^{15} All three were carried through the series of transformations necessary to convert the nitro group to a phenolic hydroxyl group and the lactam carbonyl to a methylene group, *viz.*, reduction with Raney nickel and hydrazine hydrate, reduction with lithium aluminum hydride, diazotization of the amino group and hydrolysis of the diazonium salt. In each case this sequence led to the phenolic tertiary amine, one of which, that from the nitro compound, produced in largest amount, was found to be identical with the 3-hydroxy compound II produced by the method described above. Yields were only moderate with the 1-



XXVIII

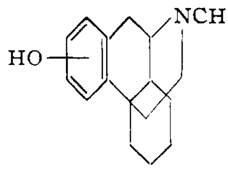
XXIX, 3-isomer
XXX, 2-isomer
XXXI, 1-isomer



XXXII, 3-isomer
XXXIII, 2-isomer
XXXIV, 1-isomer

XXXV, 3-isomer
XXXVI, 2-isomer
XXXVII, 1-isomer

II, 3-isomer
XXXVIII, 2-isomer
XXXIX, 1-isomer



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(11) Huang-Minlon, This Journal, **68**, 2487 (1946).

(12) H. D. Brown, I. M. Rasmussen, G. B. Payne and K. Pfister, III, *ibid.*, **75**, 6238 (1953).

(13) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949). Their nitration was, however, carried out on the tertiary base N-methylmorphinan (R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948)).

(14) Our sample was, however, prepared by Wolff–Kishner–Huang-Minlon reduction of the corresponding ketolactam^{6c} to yield 16-oxo-Δ^6-dehydroisomorphinan, followed by hydrogenation rather than by the method described in ref. 6c.

(15) The isomer distribution in this nitration is qualitatively about that expected. The 3-position is strongly favored by hyperconjugation over the equally unhindered 2-position, whereas positions 1 and 4 are hindered, the latter very strongly so.

and 2-isomers, but were unusually good (88.5% over-all from XXIX to II) with the 3-isomer.[16]

The four possible isomers producible by this method fall into two groups, *i.e.*, 1,2,3-trisubstituted benzenes (1- and 4-hydroxy-N-methylisomorphinans) and 1,2,4-trisubstituted benzenes (2- and 3-hydroxy-N-methylisomorphinans), and thus their infrared spectra should likewise fall into two groups.[17] The infrared spectra of 3-hydroxy-N-methylisomorphinan and one of the other isomers produced are very similar and quite different from that of the third. They show three bands between 13.5 and 14.5 μ resembling the three bands in this region exhibited by 1,3,4-xylenol[18] and also show a band at 12.5 μ shown by this substance. The third isomer shows prominent bands at 12.85 and 14.1 μ, the first of which is similar to that at 12.9 μ shown by 1,2,3-xylenol.[18] On this basis the isomer whose spectrum resembles that of II must be 2-hydroxy-N-methylisomorphinan (XXXVIII). The remaining isomer could be 1- or 4-hydroxy-N-methylisomorphinan and has been assigned the former structure since both steric and electronic effects favor substitution at position 1 over position 4.

Both 3-hydroxy-N-methylisomorphinan (II) and 3-methoxy-Δ^6-dehydro-N-methylisomorphinan (XXV) were resolved with the enantiomorphic dibenzoyltartaric acids, and in both cases both enantiomorphic bases were obtained in high yield. The optically active methoxy bases were cleaved by potassium hydroxide to the corresponding optically active 3-hydroxy-Δ^6 compounds (XXIV).

Pharmacological Results

A number of these new isomorphinan derivatives have been screened for analgesic activity in rats by the D'Amour-Smith tail-flick method[19] by Dr. P. D. Orahovats of the Merck Institute for Therapeutic Research through the courtesy of Dr. Karl Pfister and by Dr. A. C. Osterberg and his associates of Lederle Laboratories Division, American Cyanamid Co., through the courtesy of Dr. R. A. Hardy, Jr. *l*-3-Hydroxy-N-methylisomorphinan is about 8 to 10 times as active as morphine in this test and thus ranks among the most potent analgesics yet prepared. Its enantiomorph is inactive in doses up to 32 mg./kg. *l*-3-Hydroxy-Δ^6-dehydro-N-methylisomorphinan is also highly active, possibly slightly less so than the saturated compound. Its enantiomorph exhibits low activity, perhaps one-fourth that of morphine. Racemic 3-hydroxy-6,7-dimethyl-Δ^6-dehydro-N-methylisomorphinan (XXVI) exhibits about 6 times the activity of morphine. The racemic 1- and 2-hydroxy-N-methylisomorphinans (XXXIX and XXXVIII) show no analgesic activity, although the latter was too toxic to test above 16 mg./kg.

Experimental[20]

Ethyl (6-Benzoyloxy-1,2-naphthoquinonyl-4)-cyanoacetate (V).—6-Benzoyloxy-1,2-naphthoquinone[6b] (20.0 g.), suspended in 600 cc. of alcohol, was treated with 9 cc. of ethyl cyanoacetate and 22 cc. of triethylamine. A deep purple color was produced immediately, and on short swirling the quinone dissolved completely. The mixture was then treated with 170 cc. of 10% sodium carbonate solution and 200 cc. of water followed by a solution containing 52.5 g. of potassium ferricyanide in 200 cc. of water, swirled briefly, and then filtered rapidly through diatomaceous filter aid and acidified with 250 cc. of 6 *N* hydrochloric acid. The crude product separated on short standing as a yellow-brown solid. Collected and air-dried, it weighed 22.7 g. (81%) and melted at 112-126°. It contains an appreciable amount of the corresponding 6-hydroxy compound formed by hydrolysis. Recrystallization from ethyl acetate gave two crops totaling 10.1 g. (36%), m.p. 160-162°. The crude product, however, may be used as such for further reactions. Several recrystallizations from ethyl acetate gave orange prisms of m.p. 162.6-163.4°. Its solutions in weak bases are deep purple. In aqueous carbonate, it produces a deep purple color which gradually changes to dark green. In dilute alkalies, it gives a dark green color immediately.

Anal. Calcd. for $C_{22}H_{15}O_6N$: C, 67.86; H, 3.88. Found: C, 68.04; H, 3.95.

Ethyl (3-Benzoyloxybenzo[a]phenazinyl-5)-cyanoacetate.—The azine of V was prepared by short refluxing of 500 mg. of the quinone and 140 g. of *o*-phenylenediamine in 15 cc. of glacial acetic acid. Dilution of the reaction mixture gave a yellow solid which was recrystallized several times from glacial acetic acid; 262 mg. of long yellow needles, m.p. 200.6-201.4°, was obtained.

Anal. Calcd. for $C_{28}H_{19}O_4N_3$: C, 72.87; H, 4.15. Found: C, 72.72; H, 4.33.

3-Hydroxy-5-methylbenzo[a]phenazine.—The above azine was hydrolyzed by refluxing 215 mg. for 11 hours with 2 cc. of water, 13 cc. of glacial acetic acid and 2 cc. of concentrated sulfuric acid. The cooled reaction mixture was diluted, made alkaline with aqueous sodium hydroxide and filtered. The filtrate was carbonated and the precipitated azine was collected and recrystallized from pyridine to yield 130 mg. of a bright yellow powder, dec. 316-320° (uncor.) with sintering at 275°.

Anal. Calcd. for $C_{17}H_{12}ON_2$: C, 78.44; H, 4.65. Found: C, 78.75; H, 5.10.

Its acetate was prepared by recrystallizing a small amount from acetic anhydride containing a trace of sodium acetate. Several further recrystallizations from acetic acid gave **3-acetoxy-5-methylbenzo[a]phenazine** as long pale yellow needles of m.p. 198.2-199.6°.

Anal. Calcd. for $C_{19}H_{14}O_2N_2$: C, 75.48; H, 4.67. Found: C, 75.28; H, 4.96.

5-Methylbenzo[a]phenazine.—3-Hydroxy-5-methylbenzo[a]phenazine (34 mg.) was sublimed (bath 400-460°) with zinc dust. The yellow sublimate (9 mg.) was crystallized from alcohol to give 4 mg., m.p. 170-172.5°. Its mixed melting point with an authentic sample[10] of m.p. 172-173.5° was 172-174°.

Ethyl (6-Hydroxy-1,2-naphthoquinonyl-4)-cyanoacetate (VI).—Crude ethyl (6-benzoyloxy-1,2-naphthoquinonyl)-4-cyanoacetate (V) (20.7 g.) obtained from 20 g. of 6-benzoyloxy-1,2-naphthoquinone was dissolved in 200 cc. of alcohol by warming and treated with 240 cc. of 10% aqueous sodium carbonate. The deep purple solution was swirled for 30 minutes during which the purple color gradually changed to a dark green, and then filtered through a mat of diatomaceous filter aid. The filtrate was acidified with 240 cc. of 6 *N* hydrochloric acid. The product separated on short

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(16) The yield in the diazotization and hydrolysis (90%) is especially noteworthy since this reaction often is characterized by moderate to poor yields.

(17) N. B. Colthup, *J. Optical Soc. Am.*, **40**, 397 (1950), has shown that the out-of-plane CH deformation bands in the 10-15 μ region in substituted benzenes are determined by the number of adjacent hydrogen atoms remaining on the ring.

(18) R. A. Friedel, L. Pierce and J. J. McGovern, *Anal. Chem.*, **22**, 418 (1950).

(19) F. E. D'Amour and D. M. Smith, *J. Pharmacol. Exp. Therap.*, **72**, 74 (1941).

(20) Melting points are corrected unless otherwise specified. Analyses were carried out by Miss Claire King, Miss Viola Williams, Miss Annette Smith and by Microtech Laboratories. Infrared spectra were determined by Mr. Carl Whiteman on a Perkin-Elmer spectrophotometer, model 12c or model 21. Ultraviolet spectra were determined on a Beckman ultraviolet spectrophotometer, model DU, cell 1 cm. in alcohol. Rotations were observed in alcohol at concentrations of 1-2 g./100 cc. in a 1-dm. tube.

standing as orange-red needles. Collected, washed thoroughly with water and air-dried, it weighed 14.9 g., m.p. 188–193° dec. Recrystallization from glacial acetic acid gave a total of 10.0 g. (49% based on 6-benzoyloxy-1,2-naphthoquinone) in two crops, m.p. 205–208° dec. A small sample, recrystallized several times from glacial acetic acid for analysis, gave long orange-red needles of m.p. 210.2–212.6° dec. It dissolves in aqueous alkalies and alkali carbonates with a dark green color.

Anal. Calcd. for $C_{15}H_{11}O_5N$: C, 63.16; H, 3.89. Found: C, 63.15; H, 4.15.

6-Hydroxy-4-cyanomethyl-1,2-naphthoquinone (VIII).—Ten grams of ethyl (6-hydroxy-1,2-naphthoquinonyl-4)-cyanoacetate (VI) dissolved in 60 cc. of alcohol was treated with 200 cc. of 10% sodium hydroxide and stirred for 30 minutes, during which the color gradually changed from dark emerald green to crimson red. (The color change was essentially complete in 12 to 15 minutes). At the end of this period, the reaction mixture was filtered with suction and the deep red filtrate acidified with 100 cc. of 6 *N* hydrochloric acid. On short standing, the cyanomethyl compound crystallized as fine, golden-yellow needles. Collected, washed thoroughly with water and air-dried, it weighed 6.95 g. (93% crude), dec. 265–275° without melting. Recrystallization from a large volume of methanol–glacial acetic acid gave 6.10 g. (82%) of orange-yellow needles, dec. 265–270°. A small sample was recrystallized several times from glacial acetic acid for analysis, dec. 265–270° without melting. It dissolves readily in dilute aqueous alkalies or alkali carbonates with the production of a bright crimson-red color.

Anal. Calcd. for $C_{12}H_7O_3N$: C, 67.60; H, 3.31. Found: C, 67.34; H, 3.19.

3-Hydroxy-5-cyanomethylbenzo[a]phenazine.—A solution of 500 mg. of VIII and 280 mg. of *o*-phenylenediamine in 25 cc. of ethanol and 4 cc. of concentrated hydrochloric acid was refluxed for 30 minutes, cooled, and the red hydrochloride which had separated was collected and hydrolyzed to the free base by recrystallization from dilute pyridine to give material which decomposed at 271.6–276° without melting. It dissolves in concentrated sulfuric acid with the production of a deep purple color.

Anal. Calcd. for $C_{18}H_{11}ON_3$: C, 75.78; H, 3.89· Found: C, 75.94; H, 3.92.

A solution of 277 mg. of the above azine in 15 cc. of glacial acetic acid, 2 cc. of concentrated sulfuric acid and 2 cc. of water was refluxed for ten hours, cooled, diluted with water and neutralized with dilute sodium hydroxide. The precipitated azine was collected and air-dried to give 254 mg., dec. 320–325° (uncor.). A small amount was converted to 3-acetoxy-5-methylbenzo[a]phenazine by recrystallizing from acetic anhydride containing a trace of sodium acetate. The material thus obtained had m.p. 198.6–200.2°, undepressed by admixture with the acetate obtained by hydrolysis and acetylation of ethyl 3-benzoyloxybenzo[a]phenazinyl-5-cyanoacetate.

3-Hydroxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (X).—One gram of 6-hydroxy-4-cyanomethyl-1,2-naphthoquinone (VIII) was suspended in 15 cc. of absolute dioxane and 10 cc. of butadiene and heated in a glass liner in an autoclave equipped with a steam jacket for 48 hours. At the end of this period, the cooled reaction mixture was decolorized (Norit), filtered and concentrated. The residue was crystallized from dilute acetone to give 0.73 g. (58%) of pale tan prismatic blades or needles of m.p. 283–285° dec. A small sample, recrystallized several times from ethanol, gave small colorless prismatic blades or rods, m.p. 287–288° dec. It dissolves readily in dilute alkalies with the formation of light yellow solutions.

Anal. Calcd. for $C_{16}H_{13}O_3N$: C, 71.90; H, 4.90. Found: C, 71.87; H, 4.96.

3-Hydroxy-6,7-dimethyl-9,10-dioxo-13-cyanomethyl-5,8,-9,10,13,14-hexahydrophenanthrene (XII).—A similar reaction of 6-hydroxy-4-cyanomethyl-1,2-naphthoquinone (VIII) (2.45 g.) with 3.00 g. of 2,3-dimethylbutadiene-1,3 gave, after heating for 72 hours, 2.54 g. of crude product, m.p. 269–274° dec. (uncor.). It was recrystallized from methanol to yield 2.08 g. (61%) of pale yellow, almost colorless, prisms of m.p. 271–274° dec. (uncor.). A small sample, recrystallized several times from methanol for analysis, yielded pale yellow prisms of m.p. 272–274° dec. (uncor.). It dissolves readily in dilute alkalies to give yellow solutions.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80. Found: C, 73.04; H, 5.91.

3-Hydroxy-Δ^6-dehydro-10,16-dioxoisomorphinan (XIV).—The phenolic butadiene adduct X (1.00 g.) was reduced in 25 cc. of absolute alcohol over 200 mg. of copper chromite[6d] at 153–160° and 13.5 atm. of hydrogen (cold) for two hours with agitation. The cooled bomb was washed out with small portions of alcohol and the reaction mixture was decolorized with Norit, filtered, concentrated and allowed to crystallize. Fine almost colorless prisms, 442 mg. (44%), m.p. 319–324° dec. (uncor.), were obtained. A small sample, recrystallized several times from methanol, gave colorless fine prisms of m.p. 311–314° dec. (uncor.); infrared maxima: 3.04, 6.01, 6.33 μ. It is not soluble in concentrated hydrochloric acid.

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61. Found: C, 71.40; H, 5.85.

3-Hydroxy-6,7-dimethyl-Δ^6-dehydro-10,16-dioxoisomorphinan (XVI).—The phenolic dimethylbutadiene adduct XII (1.19 g.) was reduced similarly to give 458 mg. (38%) of pale tan, almost colorless prisms, decomposition point 350–353° (uncor.). A small sample, recrystallized from alcohol for analysis, gave pale yellow prisms, dec. 353–356° (uncor.); infrared maxima: 3.00, 6.00, 6.30 μ. It is not soluble in concentrated hydrochloric acid.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44. Found: C, 72.42; H, 6.75.

3-Hydroxy-Δ^6-dehydro-16-oxoisomorphinan (XVIII).—The phenolic ketolactam XIV (296 mg.) was heated with a solution of 0.35 g. of potassium hydroxide and 5 cc. of 100% hydrazine hydrate in 6 cc. of diethylene glycol for one hour at 160–170°, then for four hours at 210–215°. The reaction mixture was cooled, diluted with water and carbonated to excess. After standing for 24 hours, the pale yellow solid which separated was collected, dried and recrystallized from alcohol. A first crop of 84 mg., m.p. 266–268° (uncor.), and a second crop of 41 mg., m.p. 262–265°, was obtained, yield 45%. A small sample, recrystallized several times from alcohol for analysis, gave colorless fine prisms of m.p. 266–268° (uncor.); infrared maxima: 3.07, 6.25 μ.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 75.57; H, 6.91.

3-Hydroxy-6,7-dimethyl-Δ^6-dehydro-16-oxoisomorphinan (XX).—The phenolic dimethylketolactam XVI (200 mg.) was similarly reduced to give 155 mg. of fine prisms, dec. 240–250°. One recrystallization from benzene–alcohol gave 83 mg. (45%) of pale tan, almost colorless fine prisms, dec. 251–254°. A small sample, recrystallized several times from alcohol, gave colorless fine prisms which decompose at 245–247.5° with sintering at 235°; infrared maxima: 3.05, 6.16, 6.25 μ. It does not dissolve in concentrated hydrochloric acid.

Anal. Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47. Found: C, 76.07; H, 7.57.

6-Methoxy-2-naphthol.—A mixture of 10.0 g. of 6-bromo-2-methoxynaphthalene,[7] 0.5 g. of copper bronze, 8.5 g. of sodium hydroxide and 175 cc. of water was shaken in an autoclave at 200° for 75 minutes. The cooled and diluted reaction mixture was filtered from copper and acidified with concentrated hydrochloric acid. The crude product was collected, washed with water and dried in air. It weighed 6.8 g. and melted at 140–146°. Distillation *in vacuo* and recrystallization from dilute alcohol gave 5.1 g. (70%) of flat, colorless lustrous plates, m.p. 150–152°, reported[7] 150–151°.

6-Methoxy-1-nitroso-2-naphthol.—A fine suspension of 8.0 g. of 6-methoxy-2-naphthol in dilute acetic acid (prepared by the addition of 75 g. of ice to its warm solution in 38 cc. of acetic acid) was treated all at once with vigorous stirring with 3.17 g. of solid sodium nitrite. The mixture was stirred at −5° for 20 minutes, an additional 0.35 g. of sodium nitrite was added, and stirring was continued for 15 minutes. The yellow-brown solid was collected, washed thoroughly with water, then with methanol and dried, 8.4 g. (90%), m.p. 146–149° (uncor.) with profound decomposition. For analysis, a small sample was slurried several times with methanol, in which it is sparingly soluble, and air-dried. This material cannot be recrystallized without decomposition. It dissolves in dilute aqueous alkalies with the formation of yellow-brown solutions.

Anal. Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.46. Found: C, 64.73; H, 4.78.

6-Methoxy-1,2-naphthoquinone (IV).—Twenty grams of 6-methoxy-1-nitroso-2-naphthol was hydrogenated over 10% palladium-on-carbon in 1 l. of 24% aqueous acetic acid acidified with sulfuric acid at atmospheric pressure and room temperature. The uptake of hydrogen required from one to four hours depending upon the quality of the nitroso compound. When reduction was complete (92% of theory based on 2 moles), the hydrogenation flask was flushed with nitrogen and filtered rapidly into a nitrogen-flushed receiver. The flask and catalyst were washed several times with small portions of dilute acetic acid (24%), and the filtrate, light yellow to pale green in color, was oxidized immediately by addition of a solution of 56 g. of ferric chloride hexahydrate in 500 cc. of water and 30 cc. of concentrated hydrochloric acid. The quinone separated as a light yellow-brown solid which was collected, washed thoroughly with water and air-dried, weight 16.2 g. (87%), m.p. 141–144° with decomposition. The reported melting point is 135–140°.[7]

Its azine, prepared by refluxing a mixture of 33 mg. of the quinone, 22 mg. of *o*-phenylenediamine and 2 cc. of glacial acetic acid for several minutes, melted at 165.8–167°, reported[7] 160–161°, after sublimation and crystallization from alcohol.

The Ethyl (6-Methoxy-1,2-naphthoquinonyl-6)-cyanoacetate (VII).—To a solution of 500 cc. of alcohol and 14 cc. of ethyl cyanoacetate was added 21.7 g. of 6-methoxy-1,2-naphthoquinone (IV) followed by 32 cc. of triethylamine. A deep purple color developed immediately, and the mixture was swirled for four minutes during which the quinone dissolved completely. A solution containing 75.9 g. of potassium ferricyanide in 320 cc. of water was then added. A thick dark complex separated immediately. It completely redissolved upon addition of a solution of 24 g. of sodium carbonate in 1600 cc. of water. After brief swirling, the mixture was filtered through diatomaceous filter aid and acidified with 100 cc. of 6 *M* sulfuric acid. The product separated as an orange-red powder and was collected and oven-dried at 70°, 34.8 g., m.p. 101–113°. Recrystallization from ethyl acetate gave a first crop of 19.3 g. of large ruby-red prisms, m.p. 157–158.5°. A second crop of 2.8 g., m.p. 155.2–157.3°, was obtained from the concentrated filtrate, total yield 22.1 g. (64%). A small sample, recrystallized several times from ethyl acetate, gave large red prisms of m.p. 160–162°. It dissolves readily in dilute alkalies and carbonates with the formation of deep purple solutions. On a smaller scale, yields as high as 95% were obtained.

Anal. Calcd. for $C_{16}H_{13}O_5N$: C, 64.21; H, 4.38. Found: C, 64.25; H, 4.62.

6-Methoxy-1-amino-2-naphthol-4-sulfonic Acid.—Five grams of 6-methoxy-1-nitroso-2-naphthol was added to a solution of 7.07 g. of sodium bisulfite, 2 cc. of 10% sodium hydroxide and 23 cc. of water. The mixture was stirred vigorously for ten minutes during which the nitroso compound dissolved very slowly and incompletely. The unreacted starting material was removed by filtration, 3.08 g., m.p. 141–144° dec. (uncor.). It did not depress the melting point of starting material.

The orange-yellow alkaline filtrate was acidified with 5 cc. of concentrated sulfuric acid poured carefully down the side of the flask. After standing overnight in the dark, the precipitated aminonaphtholsulfonic acid was collected, washed, and air-dried, 1.89 g., lustrous pale pink plates (75% based on nitroso compound consumed). For analysis, a small amount was recrystallized from water containing a trace of stannous chloride to give slightly gray lustrous plates, which darken and char indefinitely at 250–255° (uncor.).

Anal. Calcd. for $C_{11}H_{11}O_5NS$: C, 49.06; H, 4.12. Found: C, 49.52; H, 4.18.

Preparation of VII from 6-Methoxy-1-amino-2-naphthol-4-sulfonic Acid.—The sulfonic acid (1.29 g.) was added in portions with stirring to an ice-cold solution of 2 cc. of concentrated nitric acid and 10 cc. of water, an additional 1 cc. of concentrated nitric acid being added at the end of one minute in order to start the reaction. When all of the sulfonic acid had been added and oxidation was complete, the resulting orange-red paste was mixed with 20 cc. of alcohol, 1 cc. of ethyl cyanoacetate and 15 cc. of 10% sodium hydroxide. A deep purple color was produced immediately upon addition of the base. The mixture was swirled briefly, filtered through diatomaceous filter aid and acidified with 6 *M* sulfuric acid. The crude product was recrystallized from ethyl acetate to give a total of 1.08 g. (75% based on sulfonic acid or 56% based on nitroso compound consumed), m.p. 157–159°.

6-Methoxy-4-cyanomethyl-1,2-naphthoquinone (IX).—Ten grams of VII in 50 cc. of alcohol was treated with 50 cc. of 10% sodium hydroxide and 50 cc. of water. On swirling the solution for 25 minutes, the deep purple color gradually changed to deep crimson red. The solution was filtered through diatomaceous filter aid and acidified with 6 *N* hydrochloric acid. The yellow-brown solid which separated was collected and air-dried to give 7.2 g. (95% crude), dec. 189–193° with darkening around 165°. This material is pure enough for further use but may be recrystallized from acetone. The above sample on recrystallization from acetone gave a total of 5.75 g. (76%) of golden yellow needles, m.p. 195–199° dec. A small sample, recrystallized several times from acetone, gave golden yellow needles, m.p. 196.4–199° dec.

Anal. Calcd. for $C_{13}H_9O_3N$: C, 68.72; H, 3.99. Found: C, 68.38; H, 4.02.

3-Methoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (XI).—6-Methoxy-4-cyanomethyl-1,2-naphthoquinone (1.96 g.) was suspended in 45 cc. of absolute dioxane and 25 cc. of butadiene in a glass liner of an autoclave, and the sealed bomb was heated with a steam jacket for 47 hours. The cooled reaction mixture was concentrated and the residue was crystallized from benzene to give a total, in two crops, of 1.45 g. (60%), m.p. 211–213°. A small amount, recrystallized several times from methanol, gave colorless prisms of m.p. 211–212.6° with a little sintering at 195°. It dissolves in dilute alkali to give a yellow solution.

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37. Found: C, 72.51; H, 5.49.

3-Methoxy-6,7-dimethyl-9,10-dioxo-13-cyanomethyl-5,9,-8,10,13,14-hexahydrophenanthrene (XIII).—A suspension of 2.0 g. of 6-methoxy-4-cyanomethyl-1,2-naphthoquinone in 40 cc. of absolute dioxane and 3.6 g. of 2,3-dimethylbutadiene-1,3 was heated in a pressure bottle on a steam-bath for 47 hours. Processed as above, the mixture yielded 1.93 g. (71%) of nearly colorless blades, m.p. 211–213°. A small amount, recrystallized several times from methanol for analysis, gave pale yellow blades of m.p. 212.2–214°.

Anal. Calcd. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19. Found: C, 73.59; H, 6.25.

3-Methoxy-Δ^6-dehydro-10,16-dioxoisomorphinan (XV).—One gram of XI and 200 mg. of copper chromite were suspended in 30 cc. of absolute alcohol in an autoclave and reduced with shaking at 143–150° and 25 atm. hydrogen pressure (cold) for four hours. The cooled reaction mixture was decolorized with Norit, filtered and concentrated. Pale yellow prismatic needles separated, 585 mg. (59%), m.p. 263–265.5° (uncor.). A small sample, recrystallized several times from methanol, gave colorless prismatic needles of m.p. 266–267.5° (uncor.); infrared maxima; 3.14, 5.94, 6.00, 6.25 μ.

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05. Found: C, 71.89; H, 6.14.

The ketolactam dissolves readily in concentrated hydrochloric acid and is reprecipitated unchanged (m.p. 259.6–262.3°) when the acid solution is diluted with water.

Methylation of XIV.—The phenolic ketolactam XIV (200 mg.) on methylation in the cold with an excess of dimethyl sulfate and methanolic potassium hydroxide yielded 144 mg. of crude XV, m.p. 260–268°, which on crystallization (Norit) from alcohol gave 129 mg. (62%) of XV, m.p. 260–263.5°, undepressed on admixture of a sample prepared by cyclization of XI.

If this methylation is carried out at 50°, **3-methoxy-Δ^6-dehydro-10,16-dioxo-N-methylisomorphinan** is produced. Thus, 930 mg. of XIV yielded under these conditions (with a gross excess of dimethyl sulfate) 838 mg. (82%) of lustrous plates from dilute alcohol, m.p. 167–170°. It dissolves readily in 12 *N* hydrochloric acid and is precipitated unchanged on dilution with water, and shows no absorption in the 3 μ region.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44. Found: C, 72.92; H, 6.49.

3-Methoxy-6,7-dimethyl-Δ^6-dehydro-10,16-dioxoisomorphinan (XVII).—The dimethylbutadiene adduct XIII (500 mg.) was hydrogenated in 25 cc. of absolute ethanol over 100 mg. of copper chromite at 143–150° and 41 atm. pressure (cold) for three hours with shaking. The cooled reaction mixture was filtered (Norit) and concentrated. Fine slightly pink needles deposited, 232 mg. (46%), m.p. 274–276° (uncor.). A small sample was recrystallized several times from alcohol to give long pale yellow flat blades of m.p. 274–276.5° (uncor.); infrared maxima: 3.18, 3.31, 5.96, 6.00, 6.28 μ.

Anal. Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80. Found: C, 73.26; H, 6.89.

Methylation of XVI.—The phenolic ketolactam XVI (200 mg.) was methylated as described above for XIV and yielded 123 mg. (60%) of fine prisms of XVII, m.p. 273–276° (uncor.), undepressed on admixture of a sample obtained by cyclization of XIII.

As with XIV, if this methylation is carried out at 50° with a gross excess of dimethyl sulfate, **3-methoxy-6,7-dimethyl-Δ^6-dehydro-10,16-dioxo-N-methylisomorphinan** is obtained. When crystallized from alcohol, this substance has m.p. 179.4–181.8°, large colorless prisms. It is readily soluble in concentrated hydrochloric acid and precipitates unchanged on dilution.

Anal. Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12. Found: C, 73.88; H, 6.92.

3-Methoxy-Δ^6-dehydro-16-oxoisomorphinan (XIX).—A solution of 2.88 g. of XV and 9 g. of potassium hydroxide in 15 cc. of 100% hydrazine hydrate and 35 cc. of diethylene glycol was heated to 150–155° for 1 hour. The yellow azine which separated on addition of the ketone dissolved in about five minutes. The cooled reaction mixture was diluted with water and the precipitated solid was collected, washed with water and dried to yield 2.49 g. (91%) of fine white needles, m.p. 194.5–197.5°. A small sample, recrystallized several times from benzene, gave colorless fine prisms of m.p. 196.3–197.3°; infrared maxima: 3.10, 3.25, 6.08, 6.22 μ. It dissolves readily in concentrated hydrochloric acid, and is reprecipitated unchanged (m.p. 197–199°) on dilution.

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.78; H, 7.13.

3-Methoxy-6,7-dimethyl-Δ^6-dehydro-16-oxoisomorphinan (XXI).—A similar reduction of XVII (500 mg.) yielded 440 mg. (89%) of the half-hydrate of XXI which melts very slowly and indefinitely at 215–219° with strong sintering at 192–194°. A small amount was recrystallized several times from alcohol for analysis to give fine colorless needles of m.p. 223–227°, sint. 192–194°; infrared maxima: 2.85, 3.20, 6.06, 6.35 μ.

Anal. Calcd. for $C_{19}H_{23}O_2N \cdot 1/2H_2O$: C, 74.48; H, 7.90; H_2O, 2.94. Found: C, 74.72; H, 7.86; H_2O, 2.73.

Sublimation of the half-hydrate at 10^{-4} mm. and 190–195° (bath) gave the water-free lactam of m.p. 215–219°, without prior sintering.

Anal. Calcd. for $C_{19}H_{23}O_2N$: C, 76.73; H, 7.80. Found: C, 76.45; H, 8.02.

Racemic 3-Methoxy-Δ^6-dehydro-N-methylisomorphinan (XXV).—One gram of the lactam XIX in 175 cc. of toluene was concentrated to a volume of 125 cc. by boiling. To the solution was added 96 mg. of sodium hydride, and the mixture was heated under reflux with exclusion of moisture for one hour. After cooling, 5.3 g. of methyl iodide was added, and refluxing was continued for two hours. The mixture was then concentrated to about 20 cc., cooled, taken into 100 cc. of absolute ether, treated with 5 cc. of a 1 *M* ethereal solution of lithium aluminum hydride, and heated under reflux for 48 hours. Excess hydride was destroyed by the addition of ethyl acetate followed by 30 cc. of 2 *N* hydrochloric acid. The acid layer was separated and the organic layer was extracted three times with small portions of 6 *N* hydrochloric acid. The combined acid extracts were then added slowly with vigorous stirring to an excess of a solution of potassium hydroxide and potassium sodium tartrate. The free base, which separated as a yellow-brown oil, was extracted from the alkaline mixture with six small portions of peroxide-free ether, and the ether extracts were washed, dried over sodium sulfate and taken to dryness to give 950 mg. of a yellow viscous oil. It was converted to its picrate by treating it, in boiling alcohol, with a hot solution of 920 mg. of picric acid in alcohol. **The picrate** was collected and dried to yield 1.58 g., m.p. 216–219° dec. (86%). After several recrystallizations from alcohol for analysis, it gave material of m.p. 224.5–225.5° dec.

Anal. Calcd. for $C_{24}H_{26}O_8N_4$: C, 57.82; H, 5.26. Found: C, 57.55; H, 5.57.

The free base was regenerated by partition between chloroform and 1% aqueous lithium hydroxide. The washed and dried chloroform solution was taken to dryness, and the resulting pale yellow oil was distilled at 135° and 10^{-4} mm. to give an almost colorless viscous oil.

Anal. Calcd. for $C_{18}H_{23}ON$: C, 80.25; H, 8.61. Found: 80.48; H, 8.39.

Its methiodide, prepared in ethyl acetate and recrystallized several times from alcohol–ethyl acetate, melted at 198.2–200.5° dec.

Anal. Calcd. for $C_{19}H_{26}ONI$: C, 55.48; H, 6.37. Found: C, 55.42; H, 6.40.

Racemic 3-Methoxy-6,7-dimethyl-Δ^6-dehydro-N-methylisomorphinan (XXVII).—A similar alkylation and reduction of the lactam XXI (500 mg., half-hydrate) gave 771 mg. (85%) of **picrate**, m.p. 219.5–221.5° dec. For analysis, a small sample was recrystallized several times from alcohol and from benzene to give material of m.p. 222.6–224.6° dec.

Anal. Calcd. for $C_{26}H_{30}O_8N_4$: C, 59.31; H, 5.74. Found: C, 59.23; H, 5.93.

The base, regenerated from its picrate as above and distilled at 125–130° and 10^{-4} mm., is a very viscous colorless oil.

Anal. Calcd. for $C_{20}H_{27}ON$: C, 80.76; H, 9.15. Found: C, 80.73; H, 9.26.

Racemic 3-Hydroxy-Δ^6-dehydro-N-methylisomorphinan (XXIV).—The methyl ether XXV, regenerated from 205 mg. of its picrate by partition between chloroform and dilute lithium hydroxide, was heated for three hours under nitrogen at 225° with a solution of seven pellets of potassium hydroxide, 4 drops of hydrazine hydrate and 6 cc. of diethylene glycol. (The mixture was blown gently with nitrogen during the first seven minutes). The cooled straw-yellow reaction mixture was diluted with water containing a small amount of sodium hydrosulfite and carbonated to excess. The precipitated solid was taken into chloroform (six extractions) and the extracts were washed with water, dried over sodium sulfate, and concentrated. The residual pale yellow glass crystallized spontaneously on moistening with ethyl acetate, m.p. 198–213° with strong sintering at 188°. Two recrystallizations from ethyl acetate and one from alcohol gave 53 mg. (51%) of colorless prismatic needles, m.p. 221–223°. Recrystallization from alcohol several times for analysis gave material of m.p. 221–223°.

Anal. Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29. Found: C, 79.96; H, 8.36.

Its methiodide, prepared in ethyl acetate and crystallized several times from alcohol–ethyl acetate, melted at 220.6–222° with gas evolution.

Anal. Calcd. for $C_{18}H_{24}ONI$: C, 54.41; H, 6.09. Found: C, 54.54; H, 6.20.

Remethylation of a small amount of the free base with an excess of diazomethane in ether–methanol gave, after processing and conversion to the picrate, material of m.p. 220–221.5° dec., undepressed by admixture of the picrate of XXV.

Racemic 3-Hydroxy-6,7-dimethyl-Δ^6-dehydro-N-methylisomorphinan (XXVI).—A similar cleavage of the methyl ether XXVII (from 221 mg. of its picrate) gave, after chromatography on alumina, a small amount of starting material (37 mg. as picrate, m.p. 220–222.6°) and 68 mg. of a glass which crystallized readily from hot benzene to yield 62 mg. of large slightly pink prisms, m.p. 176–181°. When allowed to crystallize very slowly from hot concentrated benzene solution, this material gave 51 mg. (52%) of large colorless prisms, m.p. 184.6–186.8°. It is dimorphic and gives fine colorless needles of m.p. 164.4–166.2° when allowed to crystallize rapidly from benzene. The forms are interconvertible. It was recrystallized several times from benzene for analysis to give colorless fine needles of m.p. 164.4–166.2°.

Anal. Calcd. for $C_{19}H_{25}ON$: C, 80.52; H, 8.89. Found: C, 80.96; H, 8.96.

Its methiodide, prepared in ethyl acetate and recrystallized several times from alcohol–ethyl acetate, melted at 217.4–219° with gas evolution.

Anal. Calcd. for $C_{20}H_{28}ONI$: C, 56.47; H, 6.63. Found: C, 56.57; H, 6.64.

Racemic 3-Hydroxy-N-methylisomorphinan (II).–Twenty-four milligrams of XXIV was hydrogenated over 5 mg. of Adams catalyst in 15 cc. of alcohol. Uptake of hydrogen (91%) was complete in 35 minutes. The solution was filtered, concentrated and the residue crystallized from benzene to to give 24 mg. of colorless fine prisms of m.p. 206–209°, turning pink at 190°. Several further crystallizations from benzene and from ethyl acetate gave material of m.p. 217–218.5°. It is soluble in 5% potassium hydroxide and is reprecipitated on carbonation; infrared maxima: 2.99, 6.21, 6.37, 12.50, 13.69, 14.00, 14.30 μ.

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01. Found: C, 79.58; H, 8.68.

Its methiodide, prepared in ethyl acetate and recrystallized from alcohol–ethyl acetate, melted at 224–225.8° with gas evolution. Its mixed melting point with a sample of the methiodide of XXIV (m.p. 220.6–222°) was 210–218°.

Anal. Calcd, for $C_{18}H_{26}ONI$: C, 54.14; H, 6.56. Found: C, 53.88; H, 6.66.

Resolution of 3-Methoxy-Δ^6-dehydro-N-methylisomorphinan.—A solution of 1.33 g. of racemic 3-methoxy-Δ^6-dehydro-N-methylisomorphinan (recovered from 2.41 g. of its picrate of m.p. 224.5–225.5°) in 2 cc. of methanol was treated with 1.80 g. of dibenzoyl-L(+)-tartaric acid in 2 cc. of methanol. After three hours, 1.31 g. of crude crystalline ***d*-3-methoxy-Δ^6-dehydro-N-methylisomorphinan dibenzoyl-L(+)-tartrate**, m.p. 165–166°, dec., $\alpha^{25}D$ −14°, was collected. Recrystallization from methanol and a little chloroform gave 1.26 g. (81%), m.p. 175–175.5°, gas evol., $\alpha^{25}D$ −8.8 ± 2°. Further recrystallization did not alter the m.p.

Anal. Calcd, for $C_{36}H_{37}O_9N$: C, 68.88; H, 5.94. Found: C, 69.20; H, 6.17.

Partition of this salt (1.21 g.) between dilute ammonia and chloroform gave, after processing and molecular distillation of the base, 503 mg. (theory 519 mg.) of colorless viscous *d*-3-methoxy-Δ^6-dehydro-N-methylisomorphinan which crystallized spontaneously, m.p. 61–62°, $\alpha^{25}D$ +33.9°.

Anal. Calcd. for $C_{18}H_{23}ON$: C, 80.25; H, 8.61. Found: C, 80.14; H, 8.64.

Its **picrate**, crystallized from chloroform–methanol, melted at 240.5–242° dec.

Anal. Calcd. for $C_{24}H_{26}O_8N_4$: C, 57.82; H, 5.26. Found: C, 57.78; H, 5.64.

The filtrates from the crystallization of the salt of the *d*-base with dibenzoyl-L(+)-tartaric acid were partitioned between dilute ammonia and chloroform, and the base recovered from the chloroform solution (786 mg.) was treated in methanol with 1.05 g. of dibenzoyl-D(−)-tartaric acid. The crude crystalline salt (1.36 g., m.p. 174–175°, gas evol.) on recrystallization from chloroform–methanol, gave 1.28 g. (82.5%) of ***l*-3-methoxy-Δ^6-dehydro-N-methylisomorphinan dibenzoyl-D(−)-tartrate**, m.p. 174–175°, gas evol., $\alpha^{25}D$ +6.5 ± 2°.

Anal. Calcd. for $C_{36}H_{37}O_9N$: C, 68.88; H, 5.94. Found: C, 68.58: H, 6.22.

Partition of this salt (1.23 g.) between dilute ammonia and chloroform gave, after processing and molecular distillation of the base, 471 mg. (theory 528 mg.) of colorless viscous ***l*-3-methoxy-Δ^6-dehydro-N-methylisomorphinan** which crystallized spontaneously, m.p. 61.5–63°, $\alpha^{25}D$ −34.3°.

Anal. Calcd. for $C_{18}H_{23}ON$: C, 80.25; H, 8.61. Found: C, 80.19; H, 8.71.

Its **picrate**, crystallized from chloroform–methanol, melted at 239–241°.

Anal. Calcd. for $C_{24}H_{26}O_8N_4$: C, 57.82; H, 5.26. Found: C, 57.85; H, 5.56.

***d*-3-Hydroxy-Δ^6-dehydro-N-methylisomorphinan** was prepared from the *d*-methoxy compound by cleavage with potassium hydroxide essentially as described above for the racemic compound, except that purification was by chromatography on alumina. From 477 mg. of methyl ether, 345 mg. (76%) of crude phenolic material, m.p. 163–166°, was obtained. Recrystallization from ethyl acetate gave material of m.p. 166–167.5°, $\alpha^{25}D$ +23.4°.

Anal. Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29. Found: C, 79.87; H, 8.39.

***l*-3-Hydroxy-Δ^6-dehydro-N-methylisomorphinan** was similarly obtained in 69% yield from the *l*-methoxy compound, and melted at 166–167.5°, $\alpha^{25}D$ −26.6°.

Anal. Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29. Found: C, 80.44; H, 8.44.

Catalytic hydrogenation of these two substances gave the enantiomorphic forms of 3-hydroxy-N-methylisomorphinan, m.p. 171.5–173.5°, identical with the samples described below.

16-Oxo-Δ^6-dehydroisomorphinan.—When treated according to the procedure of Huang-Minlon, but at 165–170° for one hour, 10,16-dioxo-Δ^6-dehydroisomorphinan[6c] (13.1 g.) yielded 12.1 g. (97%) of 16-oxo-Δ^6-dehydroisomorphinan, m.p. 236–239°. Material of this quality is sufficiently pure for use in subsequent steps. For analysis, a small sample was crystallized several times from benzene to give small colorless prismatic blades, m.p. 240–242.5°. It is readily soluble in methanol, sparing soluble in cold benzene. It dissolves readily in 12 *N* hydrochloric acid and is precipitated unchanged on dilution with water.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16. Found: C, 80.10; H, 7.11.

Hydrogenation of this substance over platinum in acetic acid gave an essentially quantitative yield of **16-oxoisomorphinan**,[6c] m.p. 208–210°.

16-Oxo-N-methylisomorphinan (XXVIII).—A solution of 13.0 g. of 16-oxoisomorphinan in 300 cc. of toluene was concentrated to four-fifths its volume by boiling, treated with 1.5 g. of sodium hydride, heated under reflux for 2 hours, cooled, and then treated with 10 cc. of methyl iodide. On slight warming, sodium iodide began to precipitate. The mixture was heated under reflux for 30 minutes, allowed to stand overnight, and then treated cautiously with water. The toluene layer was washed several times with water, dried, and concentrated to yield an oily residue, 14.2 g. (theory 13.8 g.) which crystallized on standing, m.p. 115–119°. A small sample crystallized several times from cyclohexane–methanol melted at 117.5–118.5° and showed no absorption in the 3.0 μ region in the infrared.

Anal. Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29. Found: C, 80.46; H, 8.35.

Nitration of 16-Oxo-N-methylisomorphinan.—A solution of 65 cc. of fuming nitric acid and 40 cc. of glacial acetic acid cooled to 5° was treated dropwise with a solution of 13.5 g. of 16-oxo-N-methylisomorphinan in 25 cc. of glacial acetic acid. The mixture was allowed to stand at room temperature for 20 hours, diluted with 2 liters of water, made basic with solid sodium carbonate, and extracted several times with chloroform. The washed and dried chloroform solution on concentration yielded a residue (15.9 g.) which crystallized completely, m.p. 148–212°. Little or no separation of this mixture was obtained by chromatography on alumina, but by a systematic fractional crystallization from ethyl acetate during which full advantage was taken of differences in crystalline form (mechanical separation) the mixture was separated into the following pure components: (a) **3-Nitro-16-oxo-N-methylisomorphinan (XXIX)**, 8.08 g. (50%), colorless prismatic needles, m.p. 241–242°. The substance is also sometimes obtained in a dimorphic form which when introduced into a bath at 225°, melts completely, resolidifies, and remelts at 240–242°. When heated slowly, it undergoes an easily apparent change in crystalline form in the neighborhood of 190°. The infrared spectra in chloroform of these two forms are indistinguishable. *Anal.* Calcd. for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71. Found: C, 67.70; H, 6.68.

(b) **2-Nitro-16-oxo-N-methylisomorphinan (XXX)**, 2.69 g. (16.5%), m.p. 188–189.5°. *Anal.* Calcd. for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71. Found: C, 68.31; H, 6.88.

(c) **1-Nitro-16-oxo-N-methylisomorphinan (XXXI)**, 1.65 g. (10%), m.p. 227.5–229.5°. *Anal.* Calcd. for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71. Found: C, 68.30; H, 6.74.

3-Amino-16-oxo-N-methylisomorphinan (XXXII).—A solution of 7.71 g. of the 3-nitro compound XXIX in 250 cc. of warm alcohol and 10 cc. of hydrazine hydrate was treated cautiously with a spatula full of Raney nickel. After the initial vigorous foaming had abated, the mixture was heated on the steam-bath for 30 minutes, filtered, and concentrated. The residue, 7.02 g. (6.4 g. theory), crystallized readily, m.p. 185–204°. It was impossible, even by repeated crystallization, to obtain material of sharp melting point, and since the crude product on further reduction to the diamino compound (*vide infra*) gave sharply melting material in nearly quantitative yield, we were forced to conclude that the wide melting range is the result of polymorphism. The crude material is completely soluble in 1% hydrochloric acid. On reprecipitation with base and three crystallizations from ethyl acetate, it melted at 207.5–211°.

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20. Found: C, 74.89; H, 8.54.

2-Amino-16-oxo-N-methylisomorphinan (XXXIII).—Similar treatment of 1.30 g. of XXX gave 1.22 g. (theory 1.17 g.) of crude amino compound, m.p. 186–188°. It is readily soluble in 1% hydrochloric acid and its mixed m.p. with starting material (XXXI) of m.p. 187–188.5° was 150–170°. A small sample was recrystallized from ethyl acetate and a little methanol for analysis, small colorless prisms, m.p. 188–190°.

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20. Found: C, 75.89; H, 8.51.

1-Amino-16-oxo-N-methylisomorphinan (XXXIV) was similarly prepared from 1.40 g. of XXXI and melted at 219–227° (crude), 1.26 g. Recrystallization from ethyl acetate–alcohol gave 1.02 g. (81%), m.p. 228–230.5°. A small sample recrystallized again for analysis melted at 229.5–231.5, colorless fine felty needles.

Anal. Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20. Found: C, 75.32; H, 8.15.

3-Amino-N-methylisomorphinan (XXXV).—A solution of 6.92 g. of XXXII and 7.0 g. of lithium aluminum hydride in 600 cc. of absolute ether was heated under reflux for 54 hours. The excess lithium aluminum hydride was decomposed cautiously with ethyl acetate, and the mixture was treated, cautiously at first, with an excess of dilute hydrochloric acid. The acid layer was then run slowly with cooling into an excess of strong potassium hydroxide solution containing Rochelle salt. The precipitated oil which crystallized on standing was taken into chloroform (four extractions) and the chloroform solution was washed, dried, filtered and concentrated to leave a residue, 6.50 g. (theory 6.55 g.), which crystallized readily, m.p. 117–121°. A small sample was recrystallized several times for analysis from cyclohexane, m.p. 124–124.5°.

Anal. Calcd. for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 80.07; H, 9.70; N, 10.47.

2-Amino-N-methylisomorphinan (XXXVI).—A similar reduction of 941 mg. of XXXIII gave 1.03 g. (theory 890 mg.) of residue which crystallized spontaneously, m.p. 117–125°. A small amount was recrystallized several times for analysis from ethyl acetate–cyclohexane, m.p. 125–127°.

Anal. Calcd. for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44. Found: C, 79.97; H, 9.90.

The material is quite soluble, however, and losses during crystallization were heavy, so that the bulk of the sample was purified through its **picrate**, m.p. 237–238.5°, gas evol. The picrate is too insoluble in methanol for satisfactory crystallization, and was merely boiled up in this solvent and then collected, 1.04 g. (60%).

Anal. Calcd. for $C_{23}H_{27}O_7N_5$: C, 56.90; H, 5.61. Found: C, 56.56; H, 5.75.

1-Amino-N-methylisomorphinan Picrate (XXXVII).—A similar reduction of 1.02 g. of XXXIV gave, after processing, 1.08 g. of clear pale yellow glass which was immediately converted to its picrate, 1.36 g. (74%), m.p. 197–200°. A small sample was boiled up with methanol, in which it is very insoluble, m.p. 198–199°.

Anal. Calcd. for $C_{23}H_{27}O_7N_5$: C, 56.90; H, 5.61. Found: C, 56.87; H, 6.00.

3-Hydroxy-N-methylisomorphinan (II).—A solution of 6.47 g. of XXXV in 200 cc. of 3 *N* sulfuric acid was cooled to 5° and treated portionwise with swirling over about 15 minutes with 1.80 g. of solid sodium nitrite. The mixture was allowed to stand 15 minutes, then added all at once to a solution of 150 cc. of water and 150 cc. of concentrated sulfuric acid containing a large scoop of Norit and held at 60°. After 30 minutes on the steam-bath, the mixture was filtered and made basic to excess with aqueous ammonia. The precipitated solid was taken into chloroform (four extractions) and the washed, dried and filtered chloroform extracts were concentrated. The residue, in acetone, was passed through a short column of alumina and crystallized from benzene, 5.85 g. (90%), m.p. 215–217.5°. A small sample on recrystallization from ethyl acetate melted at 217–218.5° and did not depress the m.p. of a sample of 3-hydroxy-N-methylisomorphinan prepared as described above from 6-methoxy-2-naphthol. Their infrared spectra were indistinguishable.

2-Hydroxy-N-methylisomorphinan (XXXVIII).—A similar conversion to the diazonium salt and hydrolysis of XXXVI (550 mg., recovered from the picrate) yielded a total of 309 mg. of the chloroform solvate of 2-hydroxy-N-methylisomorphinan, m.p. 181–182.5°.

Anal. Calcd. for $C_{17}H_{23}ON \cdot CHCl_3$: C, 57.38; H, 6.42. Found: C, 57.64; H, 6.43.

The substance is rather sparingly soluble in chloroform. On drying at 100° and reduced pressure, unsolvated material of the same melting point is obtained. It is soluble in dilute potassium hydroxide and is precipitated on carbonation. Infrared maxima: 3.00, 6.23, 6.35, 12.50, 13.64, 13.80, 14.08 μ.

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01. Found: C, 79.57; H, 9.10.

1-Hydroxy-N-methylisomorphinan (XXXIX).—A similar conversion to the diazonium salt and hydrolysis of 1-amino-N-methylisomorphinan (XXXVII) (686 mg., recovered from the picrate) yielded 664 mg. (97%) of crude crystalline 1-hydroxy compound, m.p. 190–198°, which after two crystallizations from benzene gave 529 mg. (77%) of colorless small prisms, m.p. 201–202°; infrared maxima: 2.96, 6.31, 12.85, 14.10 μ.

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01. Found: C, 79.32; H, 8.96.

Resolution of 3-Hydroxy-N-methylisomorphinan.—A solution of 4.79 g. of racemic II, m.p. 215–217.5°, and 7.00 g. of dibenzoyl-L(+)-tartaric acid monohydrate in 15 cc. of methanol deposited on standing 5.37 g. of crude ***d*-3-hydroxy-N-methylisomorphinan dibenzoyl-L(+)-tartrate**, m.p. 153–159°, gas evol., $\alpha^{25}\text{D}$ −48.1°, which after recrystallization from methanol gave 4.47 g., m.p. 156–158°, gas evol., $\alpha^{25}\text{D}$ −46.6°. Careful reworking of the filtrate gave an additional 0.50 g., m.p. 155–157°, gas evol., $\alpha^{25}\text{D}$ −46°, total yield 4.97 g. (89% on the basis of racemic material not recovered). A small sample was recrystallized twice more for analysis, colorless needles, m.p. 156–158°, gas evol.

Anal. Calcd. for $C_{35}H_{37}O_9N \cdot 1^1/_2H_2O$: C, 65.41; H, 6.27. Found: C, 65.48, 65.83, 65.70; H, 6.43, 6.74, 6.70.

The filtrates from the above crystallizations were partitioned between dilute ammonia and chloroform and the free base, recovered from the chloroform extracts after drying and concentration, was taken into alcohol and treated with 4.25 g. of dibenzoyl-D(−)-tartaric acid. Crude ***l*-3-hydroxy-N-methylisomorphinan dibenzoyl-D(−)-tartrate**, 5.14 g., m.p. 154–156°, gas evol., $\alpha^{25}\text{D}$ +49°, separated. Recrystallization from alcohol gave 4.89 g. (87% on the basis of racemic material not recovered), m.p. 156–158°, gas evol., $\alpha^{25}\text{D}$ +47.9°. A small sample was recrystallized for analysis, colorless needles, m.p. 156–158°, gas evol.

Anal. Calcd. for $C_{35}H_{37}O_9N \cdot 1^1/_2\ H_2O$: C, 65.41; H, 6.27. Found: C, 65.08, 65.57, 65.73; H, 6.36, 6.62, 6.40.

The filtrates were concentrated and partitioned between dilute ammonia and chloroform. The residue after removal of the chloroform gave, after three crystallizations from ethyl acetate, 0.24 g. of recovered racemic 3-hydroxy-N-methylisomorphinan, m.p. 215–217.5°.

***d*-3-Hydroxy-N-methylisomorphinan** was recovered from its dibenzoyl-L(+)-tartrate (4.81 g.) by partition between dilute ammonia and chloroform. The washed, dried, filtered and concentrated chloroform extracts yielded 2.23 g. of *d*-base, m.p. *ca.* 100°, gas evol., resolidification, remelting at 169–171°. Recrystallization from benzene–cyclohexane gave 1.85 g. of colorless fine felty needles, m.p. 171–172.5°, after melting at 90–95° and resolidification, $\alpha^{25}\text{D}$ +55.5°. It is much more soluble in benzene and in alcohol than the racemic base. From ethyl acetate it crystallizes in a form which does not exhibit the preliminary melting described above. Its infrared spectrum was indistinguishable from that of *d*-3-hydroxy-N-methylisomorphinan prepared by hydrogenation of the corresponding *d*-Δ^6-dehydro compound (*vide supra*).

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01. Found: C, 79.43; H, 9.51.

Its methiodide, prepared in ethyl acetate and crystallized from alcohol, melted at 255–258° dec.

Anal. Calcd. for $C_{18}H_{26}ONI$: C, 54.14; H, 6.56. Found: C, 54.42; H, 6.77.

Its hydriodide, crystallized from water, melted at 154–156°, colorless plates.

Anal. Calcd. for $C_{17}H_{24}ONI \cdot {}^1/_2H_2O$: C, 51.78; H, 6.39. Found: C, 51.49, 52.02; H, 6.35, 6.50.

***l*-3-Hydroxy-N-methylisomorphinan** was recovered in like manner from its dibenzoyl-D(–)-tartrate (4.74 g.). After recrystallization from benzene–cyclohexane, 1.95 g. of colorless fine felty needles, m.p. *ca.* 110°, solidification, remelting at 171–173°, $\alpha^{25}D$ –53.8°, was obtained.

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01. Found: C, 79.80; H, 9.33.

Its methiodide, prepared and crystallized as above, melted at 255–257.5° dec.

Anal. Calcd. for $C_{18}H_{26}ONI$: C, 54.14; H, 6.56. Found: C, 54.32; H, 6.75.

Its hydriodide, crystallized from water, melted at 153–156°, colorless plates.

Anal. Calcd. for $C_{17}H_{24}NI \cdot {}^1/_2H_2O$: C, 51.78; H, 6.39. Found: C, 52.10, 52.01; H, 6.45, 6.39.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

The Total Synthesis of Sphingosine[1]

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The synthesis of DL-1,3-dihydroxy-2-amino-4-octadecene (VIII) and its optical resolution is described. The key intermediate, ethyl 2,3-dioxo-4-octadecenoate-2-phenylhydrazone (III) is reductively acetylated to the amide IV. Selective reduction with sodium borohydride, followed by hydrolysis of the carbinol VI leads to the ester hydrochloride VII which is reduced to racemic sphingosine.

Sphingosine was discovered in 1882 by Thudichum who obtained it as a waxy unstable substance from hydrolysis of a lipid fraction of brain tissue. Early investigators[2–4] recognized it as dihydroxyaminoöctadecene. However, no convincing evidence for the relative position of the three functional groups was presented until 1947, when Carter and co-workers[5–6] established the correct structure of sphingosine. The D-configuration of the carbons 2 and 3 was confirmed by several investigators.[7–11] More recently, it has been shown by Mislow,[12] and Marinetti and Stotz,[13] that the double bond has the *trans* form. Taken together, these results have conclusively established the structure of sphingosine as *trans*-D-*erythro*-1,3-dihydroxy-2-amino-4-octadecene (VIII). In a recent communication[14] we announced the synthesis of the racemic base. More recently, a synthesis of sphingosine and its isomers has been described by Grob and Gadient.[21] In this paper we wish to report the total synthesis of sphingosine.

A Knoevenagel–Doebner condensation of myristaldehyde with malonic acid gave a fairly good yield of *trans*-2-hexadecenoic acid. We found this new approach to the hexadecenoic acid more satisfactory than the method of Ponzio[15] which involves dehydroiodination of α-iodopalmitic acid and gives poor yields after repeated crystallization. Ethyl 2-acetyl-3-oxo-4-octadecenoate (I) was obtained in a 75% yield by treatment of pure hexadecenoyl chloride with ethyl sodioacetoacetate. It was found, however, that slightly decomposed acid chloride gave predominantly the O-acyl isomer IX.[16]

In the past 15–20 years the Japp–Klingemann reaction[17a] has been applied to the synthesis of various amino acids. This method, which was developed by Feofilaktov,[17b] is based on the coupling of a diazonium salt with alkyl substituted acetoacetic esters. However, the formation of a phenylhydrazone of the type described in this paper is, apparently, the first example of a Japp–Klingemann reaction carried out on an α,α-diacyl ester in which one of the acyl groups is α,β-unsaturated. Thus Bülow,[18] in 1902, reported the failure to couple a diazonium salt with ethyl cinnamoylacetoacetate. After an intensive study we found that reactions of this type can be realized under a number of carefully controlled conditions, and we were able to obtain not only the phenylhydrazone

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[1] Presented in part before the XIVth International Congress of Pure and Applied Chemistry, Zürich, 1955.

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[16] (a) The C-acyl structure of (I) is supported by the absence of an absorption at about 1750–1755 cm.$^{-1}$ which would be expected of IX as an α,β-unsaturated vinyl ester (L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 155–156); (b) as the infrared spectrum of I shows no ester band, it may be formulated as X where the ester carbonyl group, chelated to the enolic hydroxyl, is characterized by a band at 1644 cm.$^{-1}$.

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