less variable and dimensionless parameters. Uni-bi-, bi-uni- and bi-bi-molecular reactions are the cases considered.

2. Experimental evaluation of the rate constants is discussed. A separate determination of the rate of decay of the initial substance is desirable for the interpretation of the mechanism and the evaluation of rate constants.

3. Practical applications of the results are limited only by the possible reversibility of the reaction steps involved.

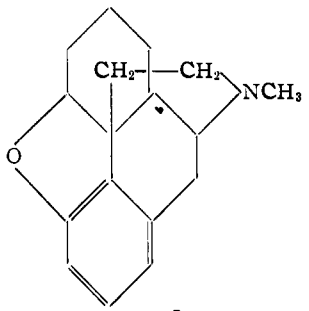
IOWA CITY, IOWA RECEIVED DECEMBER 9, 1947

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

The Synthesis of Ring Systems Related to Morphine. I. 9,10-Dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene

BY MARSHALL GATES AND WILLIAM F. NEWHALL

A synthesis of the ring system (I) present in morphine and its close relatives has not yet been achieved although a number of interesting at-

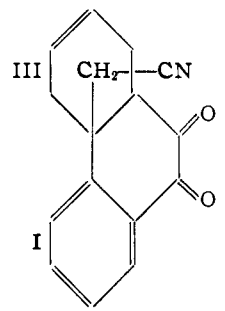


I

tempts have been reported.[1] We have been engaged for some time in an attempt to synthesize derivatives of such a ring system which might be compared with certain degradation products of the morphine alkaloids. Such a synthesis would offer a rigorous solution to the question of the point of attachment of the ethanamine side chain of morphine. The appearance in recent months of several publications[1a,c,d] bearing on this general problem has prompted us to offer our results for publication.

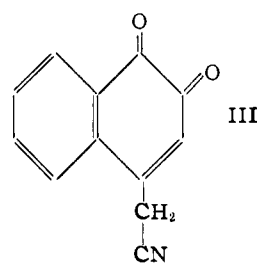
We have developed a convenient synthesis for 9,10 - dioxo - 13 - cyanomethyl - 5,8,9,10,13,14-hexahydrophenanthrene (II) which appears to be flexible enough to allow the introduction of substituents into rings I and III by suitable choice of starting materials.

The starting point for the preparation of this substance is the 4-(carbethoxycyanomethyl)-1,2-naphthoquinone of Sachs and Craveri,[2] which is available from ammonium 1,2-naphthoquinone-4-sulfonate by an improved procedure in 91% yield. This material is reduced, hydrolyzed and decarboxylated in one step giving 4-cyanomethyl-1,2-



II

naphthohydroquinone in 91% yield. Dichromate oxidation of this hydroquinone in glacial acetic acid affords 4-cyanomethyl-1,2-naphthoquinone (III)[3] in 83% yield.



The quinone III condenses readily with butadiene in acetic acid to give the diketone II. Excellent quality adduct is readily obtained in 56% yield.[4] Its formulation as II appears to be required by the fact that its azine IV, easily prepared by condensation with *o*-phenylenediamine, yields 1,2,3,4-dibenzophenazine (9,10-phenanthrenequinone azine) (V) on distillation with zinc dust.

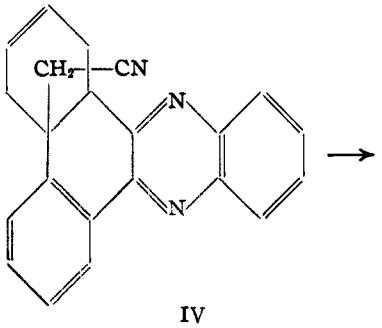
Experiments are in progress on the reduction of II by a variety of methods. We hope to effect a

(1) See, for example, (a) Holmes' recent [THIS JOURNAL, **69**, 2000 (1947)] extension of (b) Fieser and Holmes' [*ibid.*, **60**, 2548 (1938)] work; also the recent papers of (c) Horning, *ibid.*, **69**, 2929 (1947); (d) Newman, *ibid.*, **69**, 942 (1947), (e) Grewe, *Ber.*, **76**, 1072, 1076 (1943); (f) Ghosh and Robinson, *J. Chem. Soc.*, 506 (1944); (g) Ganguly, *Science and Culture*, **7**, 319 (1941); (h) Koelsch, THIS JOURNAL, **67**, 569 (1945), and others.

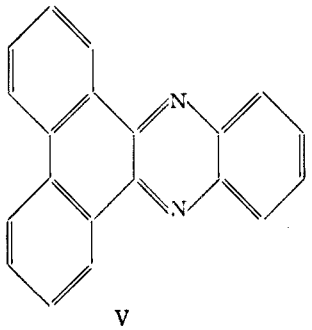
(2) Sachs and Craveri, *Ber.*, **38**, 3685 (1905).

(3) The position of the cyanomethyl group in this substance has been conclusively demonstrated by Miss Elizabeth R. Carmichael, working in this laboratory on another problem, by hydrolyzing and decarboxylating the azine of this substance to 4-methyl-1,2-naphthophenazine [Fieser and Bradsher, THIS JOURNAL, **61**, 417 (1939)] which was compared with an authentic sample kindly furnished us by Professor Louis F. Fieser of Harvard University.

(4) Compare the work of Fieser and Bradsher, THIS JOURNAL, **61**, 417 (1939), in which 2,3-dimethylbutadiene was shown to add slowly to 4-benzyl- and 4-dicarbethoxymethyl-1,2-naphthoquinones.



IV



V

ring closure to the 9 position through the nitrogen atom.

We are also investigating the condensation of III with other dienes, such as chloroprene, 2-ethoxybutadiene, piperylene, isoprene and others, and are in process of preparing derivatives of II and III carrying hydroxyl and alkoxyl groups in the 3 and 4 positions of II (5 and 6 positions of III).

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 expenses of this work have been defrayed.

Experimental Part[5]

4-Carbethoxycyanomethyl-1,2-naphthoquinone was prepared from ammonium 1,2-naphthoquinone-4-sulfonate[5] by a modification of the method of Sachs and Craveri.[6] A solution of 20 g. of ethyl cyanoacetate in 300 cc. of methanol was added with vigorous stirring to a solution of 30 g. of ammonium 1,2-naphthoquinone-4-sulfonate in 500 cc. of water. Thirty cc. of 25% sodium hydroxide was then added, and the resulting deep purple solution, on acidification to congo red with 12 *N* hydrochloric acid, yielded 28.8 g. (91%) of bright yellow material, m. p. 129.9–130.4°.

4-Cyanomethyl-1,2-naphthohydroquinone.—A solution of 20 g. of 4-carbethoxycyanomethyl-1,2-naphthoquinone in the minimum quantity of methanol was reduced by excess sodium hydrosulfite solution. After the color had been completely discharged, 30 cc. of 25% sodium hydroxide solution was added, and the mixture was refluxed until a test portion turned clear red with no purple on exposure to air. This required about seventy minutes. While still warm the mixture was acidified to congo red, and on cooling 13.4 g. (91%) of 4-cyanomethyl-1,2-naphthohydroquinone crystallized as colorless or pink needles, m. p. 220–227° with much decomposition. For analysis, a small sample was crystallized several times from dilute alcohol containing stannous chloride and a little hydrochloric acid and dried at 110° and 10^{-4} mm. Its melting point is not a reliable criterion of purity.

(5) All melting points are corrected.

(6) "Organic Syntheses," **21**, 91 (1941).

Anal. Calcd. for $C_{13}H_9O_2N$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.36; H, 4.64; N, 6.63.

The hydroquinone is easily soluble in methanol, moderately soluble in cold acetic acid, and sparingly soluble in cold benzene. It dissolves in concentrated sulfuric acid with the production of a deep blue color changing to blue-green, then to amber-green, finally to a clear amber-yellow.

4-Cyanomethyl-1,2-naphthoquinone (III) was prepared by oxidation of the above hydroquinone as follows: A warm suspension of 13.4 g. of 4-cyanomethyl-1,2-naphthohydroquinone in 200 cc. of glacial acetic acid was treated with a solution of 6 g. of sodium dichromate in aqueous acetic acid. On cooling, the quinone separated as yellow needles (10.9 g., 83%), m. p. 190–194°, with decomposition. A small sample was recrystallized several times from alcohol and dried at 110° and 10^{-4} mm. for analysis, m. p. 191–194° with decomposition.

Anal. Calcd. for $C_{12}H_7O_2N$: C, 73.08; H, 3.58. Found: C, 73.22; H, 3.69.

The quinone is moderately soluble in methanol, sparingly soluble even in hot benzene, and moderately soluble in glacial acetic acid. Its solution in concentrated sulfuric acid is orange-yellow.

9,10-Dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (II).—A suspension of 3.0 g. of 4-cyanomethyl-1,2-naphthoquinone in 40 cc. of glacial acetic acid and 20 cc. of butadiene was heated for twenty-two hours in a pressure bottle suspended in an oil-bath maintained at 80–85°. After cooling and opening, the excess butadiene was removed and the acetic acid decanted from the well-formed light tan prisms of adduct, m. p. 176–180°, which had separated. Crystallization from methanol with the aid of norite afforded 2.1 g. (56%) of colorless prisms, m. p. 181–182°. A small amount of additional material could be obtained from the filtrate. For analysis, a small sample was crystallized several times from methanol and dried at 110° and 10^{-4} mm., m. p. 185.6–186.6°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.47; H, 5.21. Found: C, 76.40; H, 5.22.

The diketone II dissolves in concentrated sulfuric acid to give a pale yellow solution, and is soluble in aqueous alkali with the production of a yellow color. It is sparingly soluble in cold methanol and in cold acetic acid.

The azine of 9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene was prepared by refluxing 100 mg. of the adduct described above with an equivalent amount of *o*-phenylenediamine in benzene containing a few drops of acetic acid. The solvent was removed and the residue in ether was extracted several times with dilute acid, twice with carbonate, dried and concentrated. The colorless solid residue (129 mg., m. p. 169–171.5°) was crystallized several times from methanol and dried at 110° and 10^{-4} mm. for analysis, 60 mg., m. p. 173.3–173.8°.

Anal. Calcd. for $C_{22}H_{17}N_3$: C, 81.70; H, 5.30; N, 12.99. Found: C, 81.78; H, 5.63; N, 13.09.

The azine is sparingly soluble in cold benzene, moderately soluble in methanol.

Zinc Dust Distillation of the Azine of 9,10-Dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene.—The azine of III (60 mg.), intimately mixed with zinc dust was heated at 350° (salt-bath) at atmospheric pressure for one hour in a microsublimation apparatus. During this time a sublimate of bright yellow crystals (21 mg., m. p. 193–206°) appeared on the cold finger. Several recrystallizations from alcohol yielded 4 mg. of pale yellow needles, m. p. 223.4–223.9°, whose mixed m. p. with 9,10-phenanthrenequinone azine of m. p. 223.9–224.4° was 223.4–224.9°.

Summary

A convenient preparation of 9,10-dioxo-13-

cyanomethyl - 5,8,9,10,13,14 - hexahydrophenanthrene as an intermediate and model compound for the synthesis of substances containing the morphine ring system has been developed.

BRYN MAWR, PENNSYLVANIA
RECEIVED FEBRUARY 24, 1948

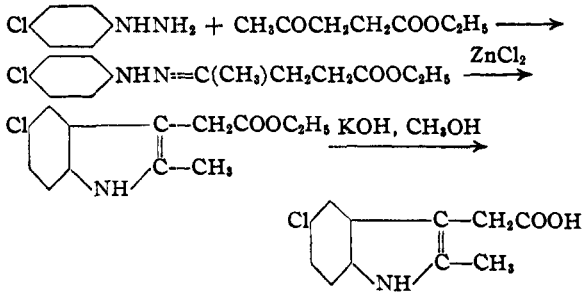
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Amino Acid Conversion Products. IV. Some Substituted 3-Indoleacetic Acids and Some Substituted Phenylhydrazones of β-Formylpropionic Acid[1]

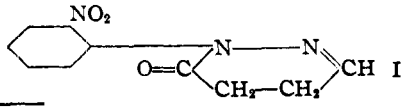
BY FRANK J. STEVENS[2] AND SIDNEY W. FOX

The natural plant growth hormone, 3-indoleacetic acid[3] (*heteroauxin*), and the substituted phenoxyacetic acids[4] have received much attention as stimulants of plant growth. A search of the literature does not reveal many syntheses of indoleacetic acid derivatives for phytological studies. The indoleacetic acid derivatives containing the types of substitution which have been useful in the phenoxyacetic acid series, are of especial interest. The present paper deals with the preparation of a number of such substances.

For the compounds reported here, the reactions involved are typified by the sequence below. In this example, the chlorophenylhydrazone of levulinic ester was converted *via* Fischer's ring closure[5] to the substituted indoleacetic acid



In attempts to cyclize β-formylpropionic acid phenylhydrazones, there was obtained in some cases an anhydride of the type reported as a by-product by Fischer in his experiments on cyclization of the phenylhydrazone of levulinic acid.[6] In the present study, ring closure of this type was obtained with the phenylhydrazone and *o*-nitrophenylhydrazone of β-formylpropionic acid. The product in the case of the nitrophenylhydrazone was 4,5-dihydro-2-(*o*-nitrophenyl)-3(2)-pyridazone, represented by I.



Of the compounds prepared in the present series, the 2-methyl-5-chloro derivative was more active in preliminary Pea Tests[7] than the 2-methyl-5-chloro and 2-methyl-7-chloro or 2-methyl-5,7-dichloro derivatives of 3-indoleacetic acid.

The indoleacetic acids reported all are substituted in the 2-position. For the corresponding unsubstituted indoleacetic acids obtained from β-formylpropionic acid, only the phenylhydrazones are recorded here. Ring closure has not been effected as readily with these latter compounds as with the derivatives of levulinic acid. The synthesis of indoleacetic acid itself, however, has been accomplished, and work is continuing on this series.

Experimental

All m.p.'s were corrected.

All nitrogen analyses were made by the micro Dumas method.

Levulinic Acid *o*-Nitrophenylhydrazone.—A hot solution of 7.65 g. (0.05 mole) of *o*-nitrophenylhydrazine[8] in 150 cc. of 20% acetic acid was added to 5.8 g. (0.05 mole) of levulinic acid (stores) in 200 cc. of hot water. The red-orange oil which precipitated crystallized upon cooling; yield 10.2 g. (81%). The solid was recrystallized from ethanol with the addition of water; m. p. 149–150°. Two more such recrystallizations raised the m. p. to 150–150.5°.

Anal. Calcd. for $C_{11}H_{13}O_4N_3$: N, 16.7. Found: N, 16.9, 16.3.

Ethyl Levulinate *o*-Nitrophenylhydrazone.—Dry hydrogen chloride was bubbled rapidly into a solution of 1.00 g. (0.0040 mole) of levulinic acid *o*-nitrophenylhydrazone in 60 cc. of absolute ethanol, and the solution was refluxed for two hours. The preparation was diluted with 200 cc. of water and extracted with four 50-cc. portions of ether. The combined ether extracts were washed with sodium bicarbonate solution and water. After drying with Drierite the ether was distilled off and the residue was recrystallized from ethanol; yield 0.88 g. (80%), m. p. 57.5–58.5°. Recrystallization from ethanol with the addition of water gave orange crystals of m. p. 58.5–59°. A mixed m. p. with the ester prepared from ethyl levulinate[9] and *o*-nitrophenylhydrazine showed no depression.

Anal. Calcd. for $C_{13}H_{17}O_4N_3$: N, 15.1. Found: N, 14.9.

2-Methyl-7-nitro-3-indoleacetic Acid.—To 20.0 cc. of a saturated solution of zinc chloride in concentrated hydrochloric acid solution, 2.0 g. (0.0071 mole) of the ester hydrazone was added and the mixture was refluxed

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(1) From the thesis submitted by Frank J. Stevens to the Graduate School of Iowa State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Department of Chemistry, Alabama Polytechnic Institute, Auburn, Ala.

(3) Thimann, *Ann. Rev. Biochem.*, **4**, 545 (1935).

(4) Zimmerman and Hitchcock, *Contrib. Boyce Thompson Inst.*, **12**, 321 (1941–1942).

(5) Fischer, *Ber.*, **19**, 1563 (1886).

(6) Fischer, *Ann.*, **236**, 147 (1886).

(7) Went and Thimann, "Phytohormones," Macmillan Company, New York, N. Y., 1937.

(8) Müller, Montigel and Reichstein, *Helv. Chim. Acta*, **20**, 1472 (1937).

(9) Grote, Kehrer and Tollens, *Ann.*, **206**, 221 (1881).