[CONTRIBUTION FROM DYSON-PERRINS LABORATORY, OXFORD UNIVERSITY]

A SYNTHESIS OF SUBSTITUTION DERIVATIVES OF INDIGO I. ORTHO-NITROBENZOYLACETIC ACID AND RELATED COMPOUNDS[1]

BY CALVIN J. OVERMYER

RECEIVED SEPTEMBER 18, 1925 PUBLISHED FEBRUARY 5, 1926

A few years ago Perkin and his colleagues[2] reported a synthesis of indigo from *o*-nitrobenzoylacetic acid, using *o*-nitrobenzoyl chloride as a starting point. It was suggested that the synthesis probably proceeded in the following stages.

$$NO_2\cdot C_6H_4\cdot CO\cdot CH_2\cdot CO_2H \longrightarrow NHOH\cdot C_6H_4\cdot CO\cdot CH_2\cdot CO_2H \longrightarrow$$

$$C_6H_4\begin{cases}CO\\NH\end{cases}CH\cdot CO_2H \longrightarrow C_6H_4\begin{cases}CO\\NH\end{cases}CH_2 \longrightarrow \text{Indigo}$$

Since this synthesis had been used but once[3] for the formation of a substituted indigo it was deemed best to repeat the work already reported before inquiring into the application of this synthesis to the formation of various substituted indigos and their derivatives. A report by McCluskey[4] on the reduction of ethyl *o*-nitrobenzoylaceto-acetate appeared while this investigation was being carried out. The present work was, therefore, modified and extended in such a way as to include a study of the results obtained by this investigator.

A method was employed which produced *o*-nitrobenzoylchloride in a pure crystalline state, a method offering many advantages over that employed by Cohen and Armes,[5] Auwers and Düesberg[6] and others. The method of Gabriel and Gerhard[7] for the conversion of ethyl *o*-nitrobenzoylaceto-acetate to ethyl *o*-nitrobenzoylacetate was employed. The aqueous solution of the potassium compound of the latter substance, on being treated with carbon dioxide, was converted into a crystalline product melting at 35–36°, whereas Needham and Perkin[2a] obtained ethyl *o*-nitrobenzoylacetate as an oil which did not crystallize. By making use of Knorr's observation[8] that pyrazolone formation is a characteristic reaction of ketonic esters of the general type $R\cdot CO\cdot CH_2\cdot CO_2C_2H_5$ with phenylhydrazine it became apparent that little or no hydrolysis had taken

[1] This paper is constructed from a portion of a dissertation presented by Calvin J. Overmyer to the Committee for Advanced Studies of Oxford University in candidacy for the degree of Doctor of Philosophy, 1923.

[2] Perkin and others, (a) *Trans. Chem. Soc.*, **85**, 151 (1904); (b) **105**, 2182, (c) 2379 (1914). Eng. pat. 16,181 (1906); Ger. pat. 201,108 (1908).

[3] Duff, *Trans. Chem. Soc.*, **105**, 2182 (1914).

[4] McCluskey, THIS JOURNAL, **44**, 1573 (1922).

[5] Cohen and Armes, *Trans. Chem. Soc.*, **87**, 1190 (1905).

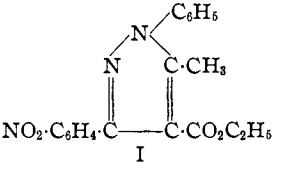
[6] Auwers and Düesberg, *Ber.*, **53**, 1207 (1920).

[7] Gabriel and Gerhard, *Ber.*, **54**, 1069 (1921).

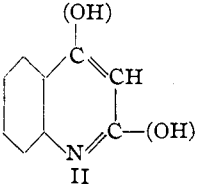
[8] Knorr, *Ber.*, **20**, 2546 (1887).

place in the method used by Needham and Perkin, 5-methyl-1-phenyl-3-*o*-nitrophenyl-4-carbethoxypyrazole I being formed rather than the expected pyrazolone, 1-phenyl-3-*o*-nitrophenyl-5-pyrazolone. On treating either the crystalline ethyl *o*-nitrobenzoylacetate or the oily product, probably impure ethyl *o*-nitrobenzoylaceto-acetate, with sulfuric acid it was possible to obtain the free *o*-nitrobenzoylacetic acid, indicating that this hydrolyzing agent can and does act in two ways, that is, by bringing about the hydrolysis of both the acetyl and the ester groups.

On the reduction of *o*-nitrobenzoylacetic acid in alkaline solution by means of dextrose or zinc dust about an 80% yield of indigo was obtained. When it was reduced with ferrous sulfate and ammonia, however, 2,4-dihydroxyquinoline II was formed, a product previously described by Gabriel and Gerhard.[7]



I

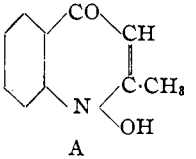


II

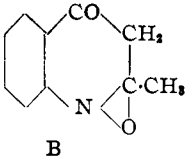
The constitution of the series of quinoline oxide derivatives obtained in the reduction of ethyl *o*-nitrobenzoylaceto-acetate was further established when 2-methyl-4-hydroxyquinoline-3-carboxylic acid oxide IV was reduced by means of zinc dust and hydrochloric acid to 2-methyl-4-hydroxyquinoline-3-carboxylic acid VII, a quinoline derivative previously described by Conrad and Limpach.[9] When heated, this acid lost carbon dioxide to form 2-methyl-4-hydroxyquinoline VI, the same substance that was obtained by the reduction of 2-methyl-4-hydroxyquinoline oxide V.

All attempts to prepare a dimethoxy derivative similar to the dibenzoyl derivative of 2-methyl-4-hydroxyquinoline oxide V as described by McCluskey were unsuccessful, although a product with but one methoxy group, 2-methyl-4-methoxyquinoline-3-carboxylic acid oxide VIII, was obtained when the corresponding hydroxy acid IV was treated with dimethyl sulfate and sodium methoxide.

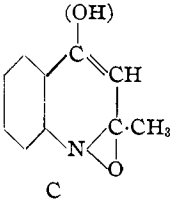
Gabriel and Gerhard[10] first reported these quinoline oxide derivatives and suggested the following as four possible formulas for the new product, 2-methyl-4-hydroxyquinoline oxide.



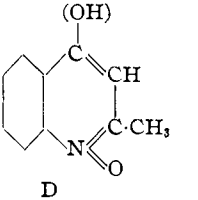
A



B



C

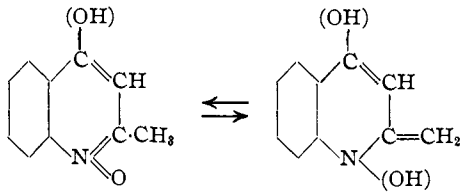


D

[9] Conrad and Limpach, *Ber.*, **21**, 1975 (1888).

[10] Cef. 7, pp. 1067, 1615.

They preferred either C or D, while McCluskey suggested that the compound existed as a tautomeric mixture between D and a form which contains two hydroxy groups, as indicated by the dibenzoyl derivative IX.



That Formula C was not applicable became apparent in the course of this investigation when an attempt was made to add hydrogen to the trivalent nitrogen, a procedure which took place very readily when a compound containing a similar trivalent nitrogen, ethyl isatogenate, was reduced[11] by Baeyer to form indoxylic ester. This quinoline oxide derivative merely lost oxygen on reduction and did not take on hydrogen.

The pentavalent nitrogen in Formula D suggested an amine oxide, a class of compounds which readily loose oxygen on reduction, do not reduce Fehling's solution, form salts, such as chlorides, picrates and chloroplatinates and do not liberate iodine from potassium iodide. The quinoline oxide derivatives described in the present work fulfil all of the requirements outlined above and in addition have a further characteristic in that all of them when in alkaline solution quickly decolorize potassium permanganate, giving an emerald-green solution. This color change did not take place after the quinoline oxide derivative had been acted upon by a reducing agent. Indications are, therefore, that Formula D is probably correct for 2-methyl-4-hydroxyquinoline oxide, with possibly a tautomeric form to account for the dibenzoyl derivative.

The following scheme of the reactions involved in the present discussion may prove of value in this connection.

Experimental Part

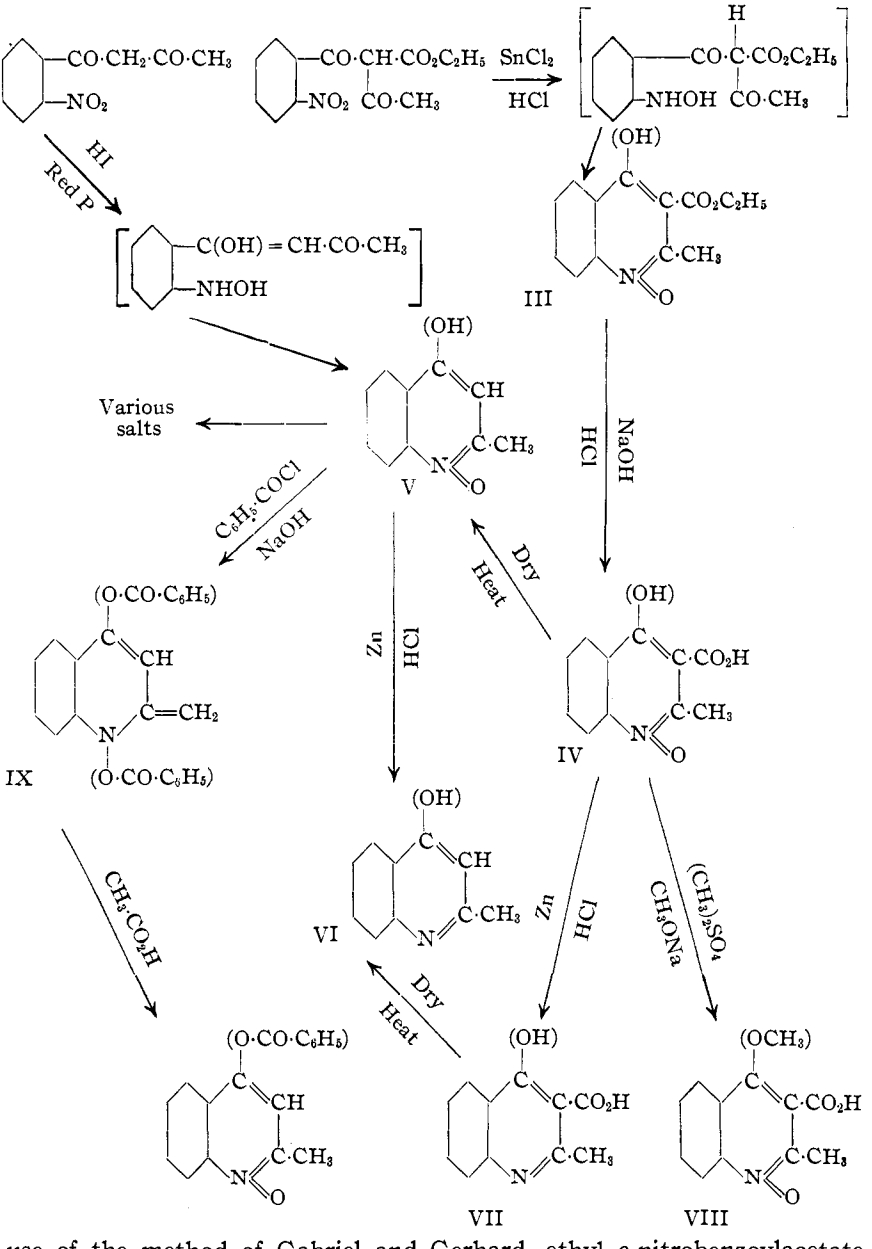
o-**Nitrobenzoyl Chloride,** $NO_2 \cdot C_6H_4 \cdot COCl$.—In the preparation of *o*-nitrobenzoyl chloride a method was used which differs but slightly from that recommended by Auwers and Düesberg[6] and which is entirely different from that used by Needham and Perkin.[2a]

Ethyl *o*-**Nitrobenzoylaceto-acetate,** $NO_2 \cdot C_6H_4 \cdot CO \cdot CH(CO \cdot CH_3) \cdot CO_2 C_2H_5$.—It was found that very good results could be obtained in the preparation of ethyl *o*-nitrobenzoylaceto-acetate by using a method recommended by Bülow and Hailer[12] for the preparation of the corresponding *m*-compound.

Ethyl *o*-**Nitrobenzoylacetate,** $NO_2 \cdot C_6H_4 \cdot CO \cdot CH_2 \cdot CO_2C_2H_5$.—Making

[11] Baeyer, *Ber.*, **15**, 745, 779 (1882).

[12] Bülow and Hailer, *Ber.*, **35**, 392 (1902).



use of the method of Gabriel and Gerhard, ethyl *o*-nitrobenzoylacetate was prepared as fine, white needles after crystallization from a small amount of alcohol.

In an experiment embodying an exact repetition of the method described by Needham and Perkin for the preparation of this compound it was found that an omission

as regards temperature had occurred in the printed report. The sodium compound of ethyl *o*-nitrobenzoylacetate does not dissolve in the aqueous ammonium chloride-ammonium hydroxide solution at the ordinary temperature, even after six hours of vigorous stirring. An oil was obtained, which was the ethyl *o*-nitrobenzoylacetate, when the acetyl group was hydrolyzed at 35–40° on a water-bath, the sodium compound quickly dissolving at this temperature.

In an endeavor to ascertain the extent of the hydrolysis that had taken place in the experiment described above, an attempt was made to form the corresponding pyrazolone by the action of phenylhydrazine upon the oil that had been obtained. One g. of the dark red oily product was added to the calculated quantity of phenylhydrazine contained in a test-tube and the mixture stirred with a glass rod. The solution became quite warm and turbidity ensued, due to the elimination of water. A mass of fine crystals completely filled the solution when it had cooled to the ordinary temperature. A small quantity of ether was added in order to remove any unchanged phenylhydrazine and the crystalline compound was collected. It was recrystallized as yellow plates from alcohol; m. p., 146°; yield, almost quantitative. It was insoluble in water, in dilute acids, in ligroin and in cold, dil. sodium hydroxide solution. It was soluble in chloroform and hot alcohol, and moderately soluble in ether.

Anal. Subs., 0.0967: CO_2, 0.2308; H_2O, 0.0423. Subs., 0.0990: 9.9 cc. of dry N_2 (14°, 769 mm.). Calcd. for 1-phenyl-3-*o*-nitrophenyl-5-pyrazolone, $C_{15}H_{11}O_3N_3$, C, 64.06; H, 3.92; N, 14.95. Calcd. for 5-methyl-1-phenyl-3-*o*-nitrophenyl-4-carbethoxy-pyrazole, $C_{19}H_{17}O_4N_3$: C, 64.96; H, 4.84; N, 11.96. Found: C, 65.09; H, 4.86; N, 11.78.

The analyses, melting point and properties of the compound indicated that the substance was not a pyrazolone body, but that it was 5-methyl-1-phenyl-3-*o*-nitrophenyl-4-carbethoxy-pyrazole, a substance that had previously been prepared by Knorr and Jödicke[13] by heating a glacial acetic acid solution of phenylhydrazine and ethyl *o*-nitrobenzoylaceto-acetate for several hours. The identity of the pyrazole compound was further established by means of the corresponding acid. Two g. of the ester was warmed with 20 cc. of a 10% methyl alcoholic solution of potassium hydroxide for 30 minutes, water was added and the aqueous solution partially evaporated. On cooling, and on acidifying with dil. hydrochloric acid a white crystalline compound separated. It was recrystallized from alcohol as fine, yellowish-white prisms; m. p., 225°. This substance was soluble in dil. aqueous sodium carbonate, acetic acid, benzene, alcohol and ether. It was insoluble in ligroin and water.

Anal. Subs., 0.1027: CO_2, 0.2389; H_2O, 0.0362. Calcd. for $C_{17}H_{13}O_4N_3$: C, 63.2; H, 4.0. Found: C, 63.44; H, 3.91.

Knorr and Jödicke prepared this acid by hydrolyzing the corresponding ester with concd. sulfuric acid. These observers gave the melting point of this compound, 5-methyl-1-phenyl-3-*o*-nitrophenylpyrazole-4-carboxylic acid, as 218°.

In preparing ethyl *o*-nitrobenzoylacetate, Needham and Perkin adopted a method similar to that used by Claisen[14] in analogous cases. Claisen's process consisted in warming a mixture of the sodium compound of ethyl benzoylaceto-acetate, aqueous ammonium chloride and ammonium hydroxide on a water-bath at 35–40° for 5 to 10 minutes, during frequent shaking. Assuming that Needham and Perkin employed approximately the same method in the present case it becomes apparent from the investigations described above that little, if any, hydrolysis of the acetyl group had taken place. A similar investigation was made into the hydrolysis of the acetyl group in the case of ethyl nitro-trimethylgallylaceto-acetate and it was found that very little split-

[13] Knorr and Jödicke, *Ber.*, **18**, 2257 (1885).

[14] Claisen, *Ann.*, **291**, 70 (1896).

ting off of the acetyl group took place under these conditions, more drastic treatment being necessary to produce material free from the acetyl grouping.

An excess of concd. sulfuric acid, on remaining at the ordinary temperature for three days, completely hydrolyzed either ethyl *o*-nitrobenzoylaceto-acetate or ethyl *o*-nitrobenzoylacetate to form *o*-nitrobenzoylacetic acid. This substance may be crystallized as colorless needles from benzene in which it is sparingly soluble; m. p., 117°, with decomposition.

o-Nitrobenzoylacetic acid, on reduction with dextrose, or zinc dust in either sodium or ammonium hydroxide solutions, forms indigo. The method with dextrose is preferable, however, on account of its simplicity and the ease in obtaining the desired product.

2,4-Dihydroxyquinoline, II, prepared according to the method of Gabriel and Gerhard, is insoluble in the ordinary solvents, although it crystallizes as needles from a mixture of alcohol and hydrochloric acid. Its solution in dil. aqueous sodium hydroxide quickly decolorizes potassium permanganate, forming an emerald-green solution, this being undoubtedly due to the reducing properties of the hydroxyl groups. It colors ferric chloride solution a deep red.

Ethyl 2-Methyl-4-hydroxyquinoline-3-carboxylate Oxide, III, was prepared by the method suggested by McCluskey. It was also obtained when ethyl *o*-nitrobenzoyl-aceto-acetate was dissolved in an excess of dil. ammonium or sodium hydroxide solution and then treated with a hot saturated solution of ferrous sulfate. The iron hydroxides were removed by filtration and the filtrate, on being acidified with hydrochloric acid, yielded the quinoline oxide compound. It crystallized from absolute alcohol as a mass of very fine, white needles. A mixed melting point with the compounds obtained by the acid reduction of McCluskey with the product obtained by the alkaline reduction showed them to be identical substances.

2-Methyl-4-hydroxyquinoline-3-carboxylic Acid Oxide, IV.—For the hydrolysis of the ester described above to form the corresponding acid the method recommended by McCluskey was used. The product was crystallized from hot absolute alcohol and obtained as very fine clusters of white needles, m. p. 214°, the former investigator reporting 209° as the melting point of this substance.

Anal. Subs., 0.1051: CO_2, 0.2331; H_2O, 0.0390. Subs., 0.0811: 4.4 cc. of dry N_2 (12°, 746 mm.). Calcd. for $C_{11}H_9O_4N$: C, 60.27; H, 4.11; N, 6.39. Found: C, 60.41; H, 4.02; N, 6.32.

2-Methyl-4-hydroxyquinoline-3-carboxylic Acid, VII.—The acid oxide from the experiment described above is added to dil. hydrochloric acid and to this small quantities of zinc dust are gradually added, the reacting mass being gently warmed to complete the reaction. When no further action takes place, sodium carbonate is added in excess, and the whole is heated to boiling and filtered hot from the unused zinc and zinc carbonate. The filtrate is cooled and then made slightly acid with dil. hydrochloric acid, whereupon a white solid separates. This substance is collected, washed with water and crystallizes as fine, white needles from dil. acetic acid.

Anal. Subs., 0.0941: CO_2, 0.2235; H_2O, 0.0410. Subs., 0.1443: 8.0 cc. of dry N_2 (10°, 770 mm.). Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.44; N, 6.89. Found: C, 64.77; H, 4.84; N, 6.73.

The composition of this acid was further controlled by titration, when it was found that 0.2779 g. required for neutralization 0.0446 g. of sodium hydroxide, whereas this amount of a monobasic acid, $C_{11}H_9O_3N$, should neutralize 0.0449 g. of the alkali.

2-Methyl-4-hydroxyquinoline-3-carboxylic acid is a white crystalline compound that melts with decomposition at 245°. It is very slightly soluble in hot water, benzene and ether and is soluble in alcohol, sodium hydroxide and sodium carbonate solu-

tions. Conrad and Limpach[9] had previously prepared this acid by the hydrolysis of its ethyl ester.

2-Methyl-4-hydroxyquinoline, VI, was prepared in two ways: by the method of Conrad and Limpach from the acid described above, and by the method of McCluskey through the reduction of 2-methyl-4-hydroxyquinoline oxide.

2-Methyl-4-methoxyquinoline-3-carboxylic Acid Oxide, VIII.—Two g. of 2-methyl, 4-hydroxyquinoline-3-carboxylic acid oxide is mixed with 3.5 g. of pure dimethyl sulfate contained in a flask, and to this is carefully added the calculated amount of sodium methoxide. After the mixture has remained overnight at the ordinary temperature, a like amount of sodium methoxide is again added, the whole thoroughly mixed and 3.5 g. of dimethyl sulfate gradually added. After 24 hours the gelatinous mass is poured into an excess of water and the aqueous mass gently warmed on the water-bath for a few minutes. The insoluble compound is collected and may be purified by crystallization as fine, white needles from methyl alcohol. For analysis it is dried in a vacuum over sulfuric acid.

Anal. Subs., 0.1299: AgI, 0.1293, equivalent to (OCH_3) 0.01743. Calcd. for $C_{11}H_8O_3N(OCH_3)$: (OCH_3), 13.30. Found: 13.41.

2-Methyl-4-methoxyquinoline-3-carboxylic acid oxide is a white, crystalline compound that melts with decomposition at 190°. It is soluble in alcohol, sodium carbonate, sodium and ammonium hydroxide, rather difficultly soluble in acetone and insoluble in ligroin and ether. It does not reduce Fehling's solution. An alkaline solution quickly decolorizes potassium permanganate, forming an emerald-green solution. Its solution in methyl alcohol gives a red color to ferric chloride.

Summary

Several improvements have been made in the synthesis of indigo from *o*-nitrobenzoylacetic acid and in addition the constitution and properties of the reduction product, together with related compounds, obtained in the reduction of ethyl *o*-nitrobenzoylaceto-acetate have been established.

BROOKLINE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL]

DERIVATIVES OF PARA-CARBOXY-PHENOXYACETIC ACID

BY WALTER G. CHRISTIANSEN

RECEIVED OCTOBER 5, 1925 PUBLISHED FEBRUARY 5, 1926

In connection with an investigation which is now in progress in this Laboratory, it became necessary to study some derivatives of *p*-carboxy-phenoxyacetic acid. The nitration of this acid was reported in a previous contribution.[1]

When methyl *p*-carbomethoxy-phenoxyacetate is treated with ammonia water under mild conditions, an amide-ester is obtained which is *p*-carbomethoxy-phenoxyacetamide I; the isomeric amide-ester II could not be isolated. By warming the reactants in a pressure bottle, the di-amide is produced. To prove that this half-amide is represented by I, *p*-hydroxy-

[1] Christiansen, THIS JOURNAL, **47**, 1158 (1925).