[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WHEATON COLLEGE]

The Synthesis of 4-Nitro-, 5-Nitro-, 6-Nitro- and 7-Nitroindole[1]

BY STANLEY M. PARMERTER,[2] A. GILBERT COOK AND WILLIAM B. DIXON

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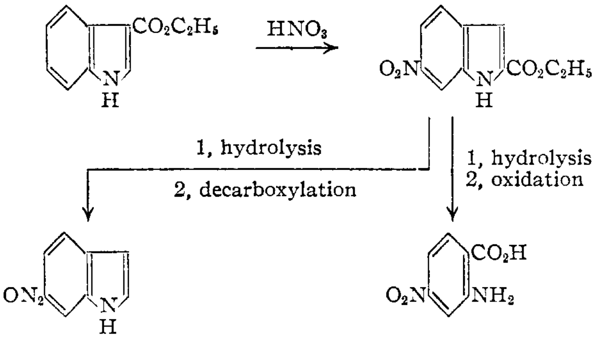
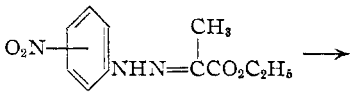
The *o*-nitro- and *p*-nitrophenylhydrazones of ethyl pyruvate undergo the Fischer rearrangement in polyphosphoric acid to form ethyl 7-nitroindole-2-carboxylate and ethyl 5-nitroindole-2-carboxylate, respectively. Ethyl pyruvate *m*-nitrophenylhydrazone gives a mixture of ethyl 4-nitroindole-2-carboxylate and ethyl 6-nitroindole-2-carboxylate under the same conditions. Hydrolysis of these esters yields the corresponding nitroindole-2-carboxylic acids, which upon decarboxylation give 4-nitro-, 5-nitro-, 6-nitro- and 7-nitroindole.

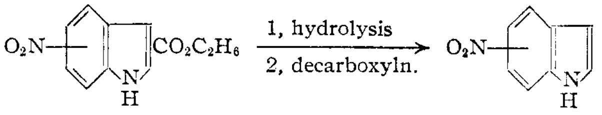
Little information has been published about the simple nitroindoles. In 1930, Majima and Kotake obtained 6-nitroindole by the nitration of ethyl indole-3-carboxylate with subsequent hydrolysis and decarboxylation.[3] The position of the nitro group was established by oxidation of the nitroindole-2-carboxylic acid to the known 4-nitro-anthranilic acid.



A synthesis of 7-nitroindole (IIId) employing the Fischer cyclization of ethyl pyruvate *o*-nitrophenylhydrazone (Ia) and then hydrolysis and decarboxylation has been reported.[4] The key step in this preparation was the cyclization using concentrated hydrochloric acid. When Rydon and Siddappa[5] attempted to repeat this synthesis, they were unable to effect the ring closure with either hydrochloric acid or other acidic catalysts. They concluded that 7-nitroindole had not been prepared, and reported a communication from the earlier workers concurring in this conclusion.



Ia, *o*-nitro
b, *m*-nitro
c, *p*-nitro



IIa, 4-nitro	IIIa, 4-nitro
b, 5-nitro	b, 5-nitro
c, 6-nitro	c, 6-nitro
d, 7-nitro	d, 7-nitro

In a reinvestigation of this method of synthesis it has been found that polyphosphoric acid[6] is a good catalyst for the Fischer cyclization of the nitrophenylhydrazones of ethyl pyruvate. When the *o*-nitrophenylhydrazone of ethyl pyruvate was warmed with this catalyst, a 66% yield of ethyl 7-nitroindole-2-carboxylate was obtained. Hydrolysis followed by decarboxylation yielded 7-nitroindole. After this work had been completed a note was published describing the synthesis of 7-nitroindole by the same synthetic route.[7] Since the present experimental method gives considerably higher yields, its description is included in the Experimental section.

Rydon and Siddappa[5] were unsuccessful in their attempts to carry out the Fischer synthesis with the *m*-nitro- and *p*-nitrophenylhydrazones of ethyl pyruvate. The use of polyphosphoric acid now has made possible these cyclizations as well. The *p*-nitrophenylhydrazone (Ic) was converted into ethyl 5-nitroindole-2-carboxylate (IIb). This ester was hydrolyzed and the resulting acid was decarboxylated to give the previously unknown 5-nitroindole (IIIb).

The cyclization of ethyl pyruvate *m*-nitrophenylhydrazone (Ib) produced a mixture of ethyl 4-nitroindole-2-carboxylate (IIa) and ethyl 6-nitroindole-2-carboxylate (IIc) which was separated by fractional crystallization. The lower-melting isomer (m.p. 195–197°) was shown to be ethyl 6-nitroindole-2-carboxylate (IIc) when hydrolysis followed by decarboxylation gave the known 6-nitroindole (IIIc).[3] This compound was identical with a sample of 6-nitroindole prepared by the method of Majima and Kotake[3] when melting points, mixed melting points and ultraviolet spectra were compared. The higher-melting isomer (m.p. 228–230°) is then ethyl 4-nitroindole-2-carboxylate (IIa). It was converted into the new compound, 4-nitroindole (IIIa), by the procedure used for the other isomers.

Acknowledgment.—The authors are grateful to Dr. H. A. Fiess who determined the ultraviolet spectra reported in this paper. They are indebted to the Victor Chemical Works, Chicago, Ill., for generous supplies of polyphosphoric acid.

Experimental[8,9]

Ethyl 5-Nitroindole-2-carboxylate (IIb).—A mixture of 35 g. (0.14 mole) of finely-powdered ethyl pyruvate *p*-nitro-

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[2] To whom communications should be directed.

[3] R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).

[4] G. K. Hughes, F. Lions and E. Ritchie, *J. Proc. Roy. Soc. N.S. Wales*, **72**, 209 (1939); *C. A.*, **33**, 6837 (1939).

[5] H. N. Rydon and S. Siddappa, *J. Chem. Soc.*, 2462 (1951).

[6] H. M. Kissman, D. W. Farnsworth and B. Witkop, THIS JOURNAL, **74**, 3948 (1952), first reported the use of polyphosphoric acid in a Fischer cyclization.

[7] H. Singer and W. Shive, *J. Org. Chem.*, **22**, 84 (1957).

[8] Melting points were determined on a Fisher–Johns block and are uncorrected.

[9] Microanalyses by Micro-Tech Laboratories, Skokie, Ill.

phenylhydrazone[4,5] in 300 g. of polyphosphoric acid was warmed in an oil-bath with stirring. When the temperature of the mixture reached 90°, an exothermic reaction was noted. An ice-bath was used to keep the temperature below 125°. The mixture was stirred at 105–115° for 30 minutes before ice-water was added to hydrolyze the polyphosphoric acid. The solid was collected, washed thoroughly with water, and dried. Extraction with 150 ml. of ethanol removed unchanged starting material. The residue was recrystallized from ethanol to give 18.7 g. (57%) of yellow crystals, m.p. 220–223°. An analytical sample melted at 225–226°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.64; H, 4.52; N, 11.81.

Ethyl 7-Nitroindole-2-carboxylate (IId).—A mixture of 20 g. (0.080 mole) of ethyl pyruvate *o*-nitrophenylhydrazone[4,5] and 110 g. of polyphosphoric acid was treated as described for the *p*-isomer. The crude product was extracted with 3.0 l. of boiling ligroin (b.p. 60–90°). Concentration of the ligroin solution to 350 ml. and cooling gave 12.3 g. (66%) of yellow needles, m.p. 91–93°. An analytical sample recrystallized from dilute ethanol melted at 92–93°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.37; H, 4.09; N, 11.80.

Fischer Cyclization of Ethyl Pyruvate *m*-Nitrophenylhydrazone. A. Ethyl 4-Nitroindole-2-carboxylate (IIa).—A mixture of 21 g. (0.084 mole) of ethyl pyruvate *m*-nitrophenylhydrazone[4,5] and 100 g. of polyphosphoric acid was treated as described for the *p*-isomer. The crude product was crystallized from 800 ml. of benzene using charcoal. A yellow solid separated slowly at room temperature. After several days there was obtained 9.5 g. of crystalline product, m.p. 170–228°. Two recrystallizations from benzene gave 3.8 g. (19%) of yellow needles, m.p. 228–230°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.18; H, 4.48; N, 12.14.

B. Ethyl 6-Nitroindole-2-carboxylate (IIc).—The mother liquor from which crude IIa, m.p. 170–228°, was obtained was concentrated to 200 ml. and left overnight at room temperature. A crop of 3.5 g. of yellow-orange crystals, m.p. 170–192°, separated. Two recrystallizations from benzene gave 1.6 g. (8.2%) of yellow needles, m.p. 195–197°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.49; H, 4.34; N, 11.85.

Further concentration of the mother liquor yielded 1.9 g. of product melting at 175–177°. Repeated recrystallizations failed to change the melting point of this material. It appears to be a mixture of the 4- and 6-isomers, since a mixture of equal parts of IIa and IIc melted at 175–177° and gave no melting point depression when mixed with the above material. A similar phenomenon has been observed for a mixture of the corresponding trifluoromethylindole esters.[10]

Nitroindole-2-carboxylic Acids (Table I).—To a solution of 9.7 g. (0.04 mole) of the ethyl nitroindole-2-carboxylate in 75 ml. of hot ethanol was added a solution of 7.5 g. (0.13 mole) of potassium hydroxide in 18 ml. of water. A copious precipitate of the potassium salt separated as the mixture stood for six hours at room temperature. The addition of 350 ml. of warm water gave a solution which was added slowly with stirring to excess dilute hydrochloric acid. The solid was collected, washed thoroughly with water and dried. The crude acids were decarboxylated without further purification. Analytical samples were prepared by crystallization from dilute ethanol.

TABLE I

NITROINDOLE-2-CARBOXYLIC ACIDS

	M.p., °C.	Yield, %	Analyses, % C	H	N
4-Nitro-	317–318	91	53.03	3.27	13.22
5-Nitro-	326–328	90	52.15	3.45	13.87
6-Nitro-	304–305	92	52.45	3.04	13.38
7-Nitro-	269–272	90	52.53	3.07	13.93
	Calcd. for $C_9H_6N_2O_4$:		52.44	2.93	13.59

Nitroindoles (Table II).—A mixture of 11.3 g. (0.055 mole) of the nitroindole-2-carboxylic acid, 1.1 g. of cupric oxide and 90 ml. of quinoline was refluxed for two hours. The dark mixture was stirred into 100 ml. of concentrated hydrochloric acid and 200 g. of ice. Filtration removed a dark solid. Both the solid and filtrate were extracted with ether. The combined extracts were washed with dilute sodium bicarbonate solution and water before they were dried and evaporated. The residue was recrystallized from dilute ethanol.

TABLE II

NITROINDOLES

Nitro group	M.p., °C.	Yield, %	Analyses, %[c] C	H	N	Ultraviolet spectra[a] λ_{max}, mμ ($\epsilon \times 10^{-3}$)	λ_{min}, mμ ($\epsilon \times 10^{-3}$)
4-	205–206	51	59.76	3.85	17.02	235(10.9) 380(6.4)	283(0.5)
5-	141–142	71	59.35	3.95	16.85	265(17.7) 324(8.4)	238(6.2) 290(3.3)
6-	144–145	38	59.48	3.50	16.96	250(10.1) 326(8.4) 355–360[b] (7.7)	227(6.4) 280(1.7)
7-	95–96	78	59.28	4.03	16.78	232(9.4) 250(7.8) 365(7.2)	223(8.5) 244(7.7) 285(0.4)

[a] In 95% ethanol. [b] Inflection. [c] Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28.

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[10] J. Bornstein, S. A. Leone, W. F. Sullivan and O. F. Bennett, THIS JOURNAL, **79**, 1745 (1957).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of Indoles by Catalytic Reduction of *o*-Nitrobenzyl Cyanides

BY H. R. SNYDER, E. P. MERICA, C. G. FORCE AND E. G. WHITE

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Numerous substituted indoles have been synthesized by the use of a recently developed method involving catalytic reduction of *o*-nitrobenzyl cyanides over palladium-on-carbon. By the same method indole has been prepared from the benzoate of *o*-nitromandelonitrile. Possible mechanisms are discussed. Attempts to prepare indole and simple substituted indoles by the Stephen reduction of *o*-nitrobenzyl cyanides have been unsuccessful. In some instances 2-aminoindoles were obtained instead.

In studies of the synthesis of certain 6-substituted indoles, an attempt was made to utilize the Stephen reaction[1] on the appropriate *o*-nitrobenzyl cyanides. When ethyl 2-nitro-4-carbethoxyphenylcyanoacetate (I) was treated with the Stephen reagent–an ethereal solution of anhydrous stannous chloride, saturated with dry hydrogen chloride–2-amino-3,6-dicarbethoxyindole (II) was isolated in 68% yield instead of the expected 3,6-dicarbethoxyindole

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[1] H. Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).