

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF THE OZARKS]

THE PREPARATION OF CERTAIN IODINATED DERIVATIVES OF PHENOLISATIN

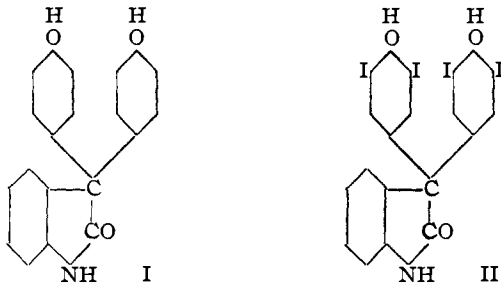
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RECEIVED MAY 31, 1932

PUBLISHED SEPTEMBER 5, 1932

Especial interest is attached to compounds of the oxindole series because of their possible use as therapeutic agents. While but little is known concerning the physiological effects of compounds of this series, such information as is available indicates that the further study of the chemical and pharmacological properties of such compounds may well lead to the discovery of valuable therapeutic agents.

Kendall has shown that certain synthetic oxindole derivatives¹ cause an increase in basal metabolism as well as in respiration rate. Oxindole and some of its derivatives² have been reported to possess antipyretic and anti-neuralgic properties. Phenolisatin (3,3-bis-(4'-hydroxyphenyl)-oxindole), I, and its diacetyl derivative³ (Isacene) are finding use as mild purgatives.



In view of the general interest attached to derivatives of oxindole, the similarity in the physiological properties of phenolisatin and phenolphthalein, and the fact that tetraiodophenolphthalein (Nosophen) possesses powerful antiseptic properties, it seemed desirable to undertake the preparation of a series of iodinated derivatives of phenolisatin.

5-Iodophenolisatin and 5,7-di-iodophenolisatin were prepared by condensing 5-iodoisatin and 5,7-di-iodoisatin with phenol. When heated with acetic anhydride for two hours at 130–135°, 5-iodophenolisatin yielded the triacetyl derivative while 5,7-di-iodophenolisatin on similar treatment gave the diacetyl derivative. This is in accord with the findings of Liebermann and Danaïla⁴ in the preparation of the acetyl derivatives of the corresponding chloro- and bromphenolisatins.

¹ Kendall, *Ind. Eng. Chem.*, **17**, 525 (1925).

² German Patent 218,477.

³ Bergell, *Z. Mediz. Chem.*, **4**, 65 (1926); *Chem. Abstracts*, **21**, 3708 (1927); Christensen, *Archiv. Pharm. Chem.*, **88**, 47–56, 69–78 (1931); *Chem. Abstracts*, **25**, 4264 (1931).

⁴ Liebermann and Danaïla, *Ber.*, **40**, 3588–3597 (1907).

Derivatives of the type of II were prepared by iodinating phenolisatin, 5-iodophenolisatin, and 5,7-di-iodophenolisatin by the method of Datta and Prosad.⁵ These highly iodinated derivatives are very insoluble in organic solvents and cannot be purified satisfactorily. Heating with acetic anhydride gave the corresponding triacetyl derivatives except in the case of the compound with iodine in position 7. In this case the diacetyl derivative was obtained.

Pharmacological tests of the compounds described in this paper are being made by Dr. T. H. Rider of the Wm. S. Merrell Co. and will be reported elsewhere by him.

Experimental

5-Iodophenolisatin (3,3-Bis-(4'-hydroxyphenyl)-5-iodo-oxindole).—Five cc. of concentrated sulfuric acid was added a drop at a time to a solution of 5 g. of 5-iodoisatin in 20 g. of molten phenol. After standing for ten minutes the reaction mixture was poured into one liter of water and the mixture stirred for one hour with a mechanical stirrer. The precipitate was filtered off and purified by crystallization from glacial acetic acid. The compound separated from this solvent in the form of colorless plates. When heated slowly from room temperature the substance seemingly undergoes a change at about 220° and melts with decomposition at 264–265°. When the melting point tube is introduced into the heating bath at 220°, the substance melts, solidifies and melts again at 264–265°. The lower melting point can be realized only by introducing the melting point tube into the heating bath at 220°. The yield was 5.7 g. or 70% of the theoretical.

Anal. Calcd. for $C_{20}H_{14}O_2NI$: N, 3.16. Found: N, 2.98, 2.98.

5,7-Di-iodophenolisatin (3,3-Bis-(4'-hydroxyphenyl)-5,7-di-iodo-oxindole).—The procedure was identical with that described above. The yield from 5 g. of 5,7-di-iodoisatin was 5.3 g. or 74% of the theoretical. The substance separated from glacial acetic acid in colorless plates; m. p. 239–240°.

Anal. Calcd. for $C_{20}H_{12}O_2NI_2$: N, 2.46. Found: N, 2.54, 2.42.

Iodination Procedure.—Iodination of phenolisatin, 5-iodophenolisatin, and 5,7-di-iodophenolisatin. The procedure in the case of phenolisatin is typical. One gram of phenolisatin was dissolved in 150 cc. of concentrated ammonium hydroxide and 25.2 cc. of a normal iodine-potassium iodide solution (four molecular proportions) slowly added. A colorless precipitate began to separate when about two-thirds of the iodine solution had been added. The reaction mixture was poured into an excess of dilute hydrochloric acid and the precipitate filtered off. In all three iodinations the products were very insoluble in organic solvents and could be purified only superficially by washing with acetic acid and water. None of the products melted on heating to 265°. The yields averaged 80% of the theoretical. The analyses indicate that the products were not obtained in a pure state.

Anal. (3,3-Bis-(3',5'-di-iodo-4'-hydroxyphenyl)-oxindole). Calcd. for $C_{20}H_{11}O_2NI_4$: N, 1.70; I, 61.85. Found: N, 1.69, 1.45; I, 58.38.

Anal. (3,3-Bis-(3',5'-di-iodo-4'-hydroxyphenyl)-5-iodo-oxindole). Calcd. for $C_{20}H_{10}O_2NI_5$: N, 1.47; I, 67.05. Found: N, 1.54, 1.52; I, 65.49.

Anal. (3,3-Bis-(3',5'-di-iodo-4'-hydroxyphenyl)-5,7-di-iodo-oxindole). Calcd. for $C_{20}H_9O_2NI_6$: N, 1.30; I, 71.00. Found: N, 1.41, 1.42; I, 68.08.

⁵ Datta and Prosad, *THIS JOURNAL*, **39**, 441 (1917).

Acetyl Derivatives.—These derivatives were obtained by heating the appropriate phenolisatins with acetic anhydride at 130–135° for two hours.

TABLE I

Oxindole	Formula	M. p., °C.	Nitrogen, %		Iodine, %	
			Calcd.	Found	Calcd.	Found
A. 1-Acetyl-3,3-bis-(4'-acetoxyphenyl)-5-iodo-	$C_{26}H_{20}O_6NI$	169–170 ^{oa}	2.46	2.51, 2.47	22.31	22.13
B. 3,3-Bis-(4'-acetoxyphenyl)-5,7-di-iodo-	$C_{24}H_{17}O_6NI_2$	256–257 ^{ob}	2.29	2.09, 2.18	38.89	38.93
C. 1-Acetyl-3,3-bis-(3', 5'-di-iodo-4'-acetoxyphenyl)-	$C_{26}H_{17}O_6NI_4$	267–268 ^{oc}	1.47	1.31, 1.34	53.64	53.99
D. 1-Acetyl-3,3-bis-(3', 5'-di-iodo-4'-acetoxyphenyl)-5-iodo-	$C_{26}H_{16}O_6NI_5$	272–273 ^{od}	1.30	1.24, 1.19	59.17	59.07
E. 3,3-Bis-(3', 5'-di-iodo-4'-acetoxyphenyl)-5,7-di-iodo-	$C_{24}H_{13}O_6NI_6$	255–256 ^{oe}	1.21	1.11, 1.25	65.86	66.04

^a Colorless prisms from glacial acetic acid. ^b Colorless plates from glacial acetic acid. ^c Colorless prisms from acetic anhydride. ^d Colorless prisms from acetic anhydride. ^e Colorless plates from acetic anhydride.

The writer is indebted to Messrs. Lee Graves and Thell C. Woods for assistance in making the analyses reported herein, to Dr. S. H. Con'é of Wilmington, Delaware, for financial assistance and to the Dow Chemical Co. for the gift of a generous supply of indigo from which the isatin, iodoisatin, and di-iodoisatin used in this work were prepared.

Summary

Several iodinated derivatives of phenolisatin have been prepared.

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

OPTICALLY ACTIVE DIAZO COMPOUNDS. VI. DIAZOCAMPHOR

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RECEIVED JUNE 6, 1932

PUBLISHED SEPTEMBER 5, 1932

This is a continuation of a study of the question whether diazo compounds of the type, $R: \overset{\cdot}{C}: N:: N:$, may occur in optically active forms.¹

Some of the previous investigations have not been satisfactory because the instability of some of the diazo compounds has prevented their isolation in a state of sufficient purity to demonstrate conclusively that the small rotations observed were not due to optically active impurities. The fact that in many of them the diazo group was attached to a carbon atom adjacent to a carbonyl group, may also have been an important factor (see below).

¹ Fifth paper, W. A. Noyes and Ulrich Heubaum, *THIS JOURNAL*, 52, 5070 (1930). Further references will be found in that paper.