NOTES

One-step conversion of isatins to oxindoles and phthalonimides to homophthalimides

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The palladium-catalyzed hydrogenation of isatins and phthalonimides in acetic acid containing perchloric acid produced oxindoles and homophthalimides directly. A general, one-step synthesis of phthalonimides from isocarbostyrils is described.

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The conversion of isatin to oxindole was first effected by von Baeyer and Knop (1) in 1866 in connection with studies which culminated in the first rational synthesis (2) of the important dyestuff indigo. The transformation was achieved by the reduction of isatin (1) with sodium amalgam in water to dioxindole (2), which, without isolation, could be further reduced to oxindole (3) with the same reagent in aqueous acidic medium. Since von Baeyer's original work, numerous methods have been developed¹ for the preparation of 3 from 1, but to date, only one of these has not involved a two-step process,² i.e. in 1942 Sakurai (4) showed that electrolysis of isatin in aqueous sodium sulfate at a mercury cathode gave a mixture which was comprised of oxindole, dioxindole, and isatide (3,3'-dihydroxy-3,3'-bioxindole).



We have found that oxindole can be prepared in one step by the palladium-catalyzed hydrogenation (at 60°) of isatin in glacial acetic acid containing approximately two equivalents of perchloric acid. The reduction evidently proceeds in two stages, since the first equivalent of hydrogen is absorbed rapidly and the second slowly. The reduction is also applicable to the synthesis of *N*-methyloxindole (see Table I) and presumably could be used for the preparation of other oxindoles bearing substituents stable to the reaction conditions.

Under somewhat milder conditions (see Table I) the reaction can be utilized for the synthesis of homophthalimides (6) from the corresponding readily available (see below) phthalonimides (5),



but this method will probably not be extensively applied to simple homophthalimides inasmuch as these are easily prepared from homophthalic acid and ammonia or primary amines (for example see refs. 5 and 6). On the other hand, it should find use in the synthesis of homophthalimides substituted in the benzene ring since the requisite homophthalic acids are relatively difficult to obtain.

Phthalonimides, a long known but comparatively rare class of compounds, have heretofore been synthesized by the chromic acid oxidation of tetrahydroisoquinolines (7), the nitric acid oxidation of 4-hydroxyisocarbostyrils (8, 9), and recently, by the selenium dioxide oxidation of homophthalimides (5). We have found that phthalonimides are generally available by the oxidation of isocarbostyrils (4) with chromic acid in acetic acid at room temperature. A number of examples of this oxidation are shown in Table II.

Several synthetic consequences of the results

¹For a summary of these methods through 1952, see

ref. 3. ²Note added in proof:—After this manuscript was ac-Peckett Daisley, and Walker (12) described the palladium-catalyzed hydrogenation, at atmospheric pressure, of isatin to oxindole, and Foglia and Swern (13) showed that zinc-copper couple in refluxing acetic acid converted isatins to oxindoles.

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TABLE I

Catalytic reduction of isatins and phthalonimides

	Temperature	Time			Melting point (°C)	
Reactant	(°C)	(h)	Product	% Yield*	Observed	Literature
Isatin N-Methylisatin Phthalonimide N-Methylphthalonimide N-Ethylphthalonimide N-Benzylphthalonimide	60 60 25 25 25 25 25	16 14 8.5 5 10.5 12	Oxindole N-Methyloxindole Homophthalimide N-Methylhomophthalimide N-Ethylhomophthalimide N-Benzylhomophthalimide	63 73 40 81 76 91	124-126† 85.5-87§ 234-236 120-121 102-103 124-126#	127‡ 88‡ 230–233¶ 121–122** 106††

*Unless specified otherwise, the yields and melting points refer to crude, unrecrystallized products.
†See Experimental.
‡See ref. 10.
§After one crystallization from cyclohexane.
[After one crystallization from acetic acid.
**See ref. 11.
**See ref. 11.
†See ref. 5.
‡After one crystallization from cyclohexane followed by sublimation at 110°/0.001 mm, the m.p. was raised to 128-130°.
Anal. Calcd. for C₁₆H₁₃NO₂: C, 76.42; H, 5.22. Found: C, 76.52; H, 5.38.

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Chromic acid oxidation of isocarbostyrils to phthalonimides

			Melting point (°C)	
Reactant*	Product	% Yield†	Observed	Literature
Isocarbostyril N-Methylisocarbostyril N-Ethylisocarbostyril N-Benzylisocarbostyril	Phthalonimide N-Methylphthalonimide N-Ethylphthalonimide N-Benzylphthalonimide	45 81 67 75¶	221-223 185-186 102.5-103.5 181.5-183.5¶	224‡ 186–187§ 101∥

*The isocarbostyrils described herein are known and were synthesized according to published procedures. †Unless specified otherwise, the yields and melting points refer to crude, unrecrystallized products. ‡See ref. 8. §See ref. 7. [See ref. 5. ¶After crystallization from benzene-cyclohexane 3:1. Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18. Found: C, 72.44; H, 4.50.

described herein will be submitted for publication in due course.

Experimental

The melting points were determined in a Gallenkamp melting point apparatus and are not corrected.

Oxindole

The following method was typical for the reduction of isatins.

A mixture consisting of isatin (5.98 g, 40 mmoles), glacial acetic acid (192 ml), 60-62% perchloric acid (8 ml), and 600 mg of 10% palladium on charcoal was hydrogenated in a Parr apparatus at 60° and an initial hydrogen pressure of 60 p.s.i.g. The theoretical amount of hydrogen was absorbed in 16 h. The cooled mixture was filtered through Celite, and the filtrate was concentrated to a small volume in vacuo at 40°. The residue was diluted with 300 ml of water and then extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated in vacuo. The solid thus obtained was boiled with 200 ml of cyclohexane to

give an insoluble residue which was collected by filtration and dried. It weighed 1.669 g and had m.p. 124-126°; mixture m.p. with oxindole was undepressed. The cyclohexane solution on cooling deposited 1.681 g of a cream-colored solid, m.p. 122.5-124°; mixture m.p. with oxindole, 123-126°. The total yield of oxindole was 3.35 g or 63%.

N-Methylhomophthalimide

The following procedure was typical for the reduction of phthalonimides.

Å mixture of N-methylphthalonimide (7.57 g, 40 mmoles), glacial acetic acid (192 ml), 60-62% perchloric acid (8 ml), and 760 mg of 10% palladium on charcoal was hydrogenated at room temperature and an initial hydrogen pressure of 60 p.s.i.g. After 5 h, the catalyst was removed by filtration through Celite, and the filtrate was evaporated to a volume of ca. 10 ml in vacuo at 40°. The solution was carefully diluted with 300 ml of water with swirling, whereupon a white, crystalline solid separated from solution. After being cooled in ice, the product was collected by filtration, washed well with ice-cold water, and dried in vacuo. The product weighed

5.68 g (81 %) and had m.p. 120–121°. A mixture melting point with an authentic specimen of N-methylhomophthalimide was undepressed.

N-Methylphthalonimide

The following procedure was typical for the oxidation of isocarbostyrils.

A magnetically stirred solution of N-methylisocarbostyril (20.0 g, 125.8 mmoles) in 200 ml of glacial acetic acid was titrated with 0.649 M sodium dichromate in 2.5 M sulfuric acid (194 ml, 377.7 m eq.) at a rate such that the reaction temperature did not exceed 30°. When the addition was completed the mixture was stirred for an additional $\frac{1}{2}$ h at room temperature, and then it was poured with stirring into ca. 1.51 of ice-cold water. The precipitated yellow solid was collected by filtration, washed well with ice-cold water, and dried in vacuo. The yellow solid obtained in this way had m.p. 185-186° (lit. (7), m.p. 186–187°), and weighed 19.2 g (81%).

1. A. VON BAEYER and C. KNOP. Ann. Chem. 140, 1 (1866).

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 - A. VON BAEYER. Chem. Ber. 11, 582 (1878).
 P. L. JULIAN, E. W. MEYER, and H. C. PRINTY. Heterocyclic compounds. Vol. III. *Edited by* R. C. Elderfield. John Wiley and Sons, Inc., New York. 1952. pp. 126–130.
 B. SAKIBAL, L. Chem. Soc. Lance. 17, 260 (1017).
 - B. SAKURAI, J. Chem. Soc. Japan, 17, 269 (1942); Chem. Abstr. 41, 4486 (1947).
 - N. P. BUU-HOI, G. SAINT-RUF, and J. C. BOURGEADE. J. Heterocyclic Chem. 5, 545 (1968). 5.
 - B. R. HARRIMAN, R. S. SHELTON, M. G. VAN CAMPEN 6. and M. R. WARREN. J. Am. Chem. Soc. 67, 1481 (1945)
 - M. FREUND and H. BECK. Chem. Ber. 37, 1942 7. (1904).
 - S. GABRIEL and J. COLEMAN. Chem. Ber. 35, 2421 8. (1902).

 - W. FINDEKLEE. Chem. Ber. 38, 3542 (1905).
 R. STOLLE, R. BERGDOLL, M. LUTHER, A. AUERHAHN, and W. WACKER. J. Prakt. Chem. 128, 1 (1930).
 J. M. MUCHOWSKI. Tetrahedron Letters, 1773 (1966).
 A. H. Beckett, R. W. Daisley, and J. Walker. Tet-rahedron 24 (1968)
 - rahedron, 24, 6093 (1968). 13. T. A. Foglia and D. Swern. J. Org. Chem. 33, 4440 (1968).

Facile preparation of thioacetals in neutral medium starting from sodium borohydride

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Sodium borohydride can be sulfurated to give NaBH₂S₃. The sulfurated hydride, when treated with a mercaptan, gives an orthothioborate: $(RS)_3B$. The orthoborates react with aldehydes and ketones to give the corresponding thioacetals with quantitative yields, in neutral medium.

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We have reported (1) the preparation of thioacetals in neutral media (benzene or petroleum ether) using alkyl orthothioborates (eq. [1]).

[1]
$$2(RS)_3B + 3R'COR'' \rightarrow C + B_2O_3$$

R'' SR

The orthothioesters can be prepared from boron sulfide (2) or boron halides (3) but in both cases, these preparations are somewhat tedious. Recently, we have reported the partial sulfuration of sodium borohydride to give a sulfurated borohydride formulated as $NaBH_2S_3$ (4).

This sulfurated borohydride reacts very easily with mercaptans to give the corresponding orthothioborates, according to eq. [2]:

$$[2] NaBH_2S_3 + RSH \rightarrow (RS)_3B + H_2 + RSSR + NaS_3H$$

The sulfuration of the borohydride is an extremely simple reaction; a mixture of $NaBH_4$ (1) mole) and sulfur (3 moles) is treated by anhydrous tetrahydrofuran and the solvent is evaporated under vacuum after a short contact. This sulfurated hydride is then treated with an excess of the selected mercaptan in petroleum ether. The use of a stoichiometric amount of mercaptan gives rather low yields of orthothioborate (10-20%) but a 100% excess of mercaptan brings the yield in the 50-60% range. In petroleum ether the sodium polysulfide is insoluble and the organic fraction can be filtered off. Due care must be exercized in the course of this filtration since orthothioborates are very hygroscopic. The orthothioborate is then separated from the disulfide by distillation and can be used for the preparation of the thioacetal.

This sequence of reactions besides giving a new