Advances in HETEROCYCLIC CHEMISTRY

Edited by

A. R. KATRITZKY

A. J. BOULTON

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Preface

The present volume encompasses a wide range of heterocyclic chemistry. Syntheses of heterocycles from thioureas are reviewed by T. S. Griffin, T. S. Woods, and D. L. Klayman, while S. W. Schneller describes the chemistry of benzothiins and their derivatives (thiochromans, thiochromones, and thiochromanones). Developments in chrom-3-ene chemistry are reviewed by L. Merlini. F. D. Popp contributes a chapter on the isatins. A discussion of theoretical aspects of the tautomerism of pyrimidines, by J. S. Kwiatkowski and B. Pullman, follows up a corresponding earlier contribution (Vol. 13) on tautomeric purines. In the final chapter P. and D. Cagniant describe the natural occurrence and synthesis of the benzofurans.

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A. J. Boulton

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Contents

The Chemistry of Isatin

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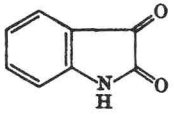
I. Introduction

Isatin (1) was the subject of a comprehensive review, containing 416 references, by Sumpter in 1944.[1] Since that time an even larger number



(1)

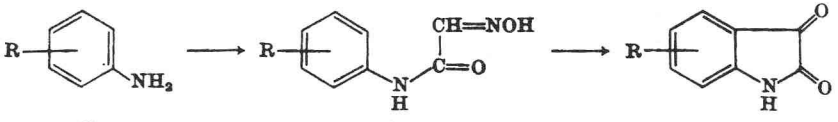
of papers have appeared concerning the preparation, properties, and reactions of isatin. Although isatin has been included as a small subtopic in several reviews concerned with indoles, no comprehensive review devoted to isatin has appeared since 1944.

It is the purpose of this review to cover the literature of isatin from the previous review[1] to late 1974. As far as possible it will adopt the same format as the earlier review, and materials that only updates subjects covered in depth in that review[1] will be listed, without extended comment.

II. Synthesis of Isatins

A. Ring Closure

The most frequently used synthesis of isatins is the Sandmeyer procedure, which involves the formation of an isonitrosoacetanilide (3) from an aniline (2), chloral hydrate, and hydroxylamine. The isonitroso-



(2) (3) (4)

acetanilide (3) is converted into the isatin (4) on treatment with sulfuric acid,[1] or less frequently polyphosphoric acid.[2–5] Using the Sandmeyer

[1] W. C. Sumpter, *Chem. Rev.* **34**, 407 (1944).

[2] J. Gripenberg, E. Honkanen, and O. Patoharju, *Acta. Chem. Scand.* **11**, 1485 (1957).

[3] F. Piozzi, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat. Rend.* **22**, 629 (1957).

[4] F. Piozzi and G. Favini, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat. Rend.* **18**, 647 (1955).

[5] D. Răileanu and C. D. Nenitzescu, *Acad. Repub. Pop. Rom. Stud. Cercet. Chim.* **11**, 19 (1963).

reaction, *o*-substituted anilines have been converted into 7-alkyl,[4,6–11] 7-methoxy,[2,4] 7-nitro,[12] 7-amino,[13] 7-carboxy,[14] 7-trifluoromethyl,[15] and 7-halo[4,16–20] isatins. Similarly *p*-substituted anilines have been used to prepare 5-alkyl,[4,6,8,9,21–23] 5-methoxy,[4,24–28] 5-hydroxy,[13] 5-trifluoromethyl,[15] 5-carboxy,[14] 5-carboxymethyl,[29] 5-amino,[27] 5-acetamido,[30] and 5-halo[4,27,31,32] isatins.

Although *o*-bromo,[4] *o*-chloro,[4,16,17,20] and *o*-iodo[17] anilines give 7-haloisatins, *o*-fluoroaniline has been reported[32] not to give an isatin. 2,4-Difluoroaniline also fails to give an isatin[32] although cyclization

[6] F. Buscarons and J. M. Espinos, *Chim. Anal.* (*Paris*) **48**, 336 (1966).
[7] N. P. Buu-Hoi and P. Jacquignon, *J. Chem. Soc.*, 3095 (1959).
[8] H. Cassebaum, *J. Prakt. Chem.* **23**, 301 (1964).
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[17] M. B. Chaundhari and K. S. Nargund, *J. Univ. Bombay 19, Sect. A. Pt. 3, Sci. No. 28*, 65 (1950); *Chem. Abstr.* **47**, 1652 (1953).
[18] M. C. Chiang, C. Li, and J. L. Li, *Hua Hsueh Hsueh Pao* **22**, 235 (1956); *Chem. Abstr.* **52**, 10080 (1958).
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[30] A. Ermili and R. Giuliano, *Gazz. Chim. Ital.* **89**, 517 (1959).
[31] R. N. Castle, K. Adachi, and W. D. Guither, *J. Heterocyl. Chem.* **2**, 459 (1965).
[32] V. Q. Yen, N. P. Buu-Hoi, and N. D. Xuong, *J. Org. Chem.* **23**, 1858 (1958).

does occur when *p*-fluoroaniline[31,32] and 3,4-difluoroaniline[32] are used.

Generally meta-substituted anilines give rise to a mixture of 4- and 6-substituted isatins[9,13,19,33–37] although 4-trifluoromethyl,[15,33,35,38] 4-nitro,[13] 4-amino,[13] 4-hydroxy,[13] 4-carboxy,[13] 6-methoxy,[35] and 6-bromo[4] isatins have been reported without the other isomer.

The Sandmeyer method has been used with di- and trisubstituted anilines to prepare di-[4,6,13,14,19,32,38–55] and tri-[5,13,19,30,56] substituted isatins. Although *p*-acetamidoaniline and 5-acetamido-2-aminotoluene gave 5-acetamido- and 5-acetamido-7-methylisatin, respectively,[30] the use of 4-acetamido-2-aminotoluene and 5-acetamido-2,4-dimethylaniline gave the appropriate aminoisatins.[30,52] Other examples of hydrolysis during this cyclization are in the conversion of diethyl 5-aminoisophthalate to isatin-4,6-dicarboxylic acid[53] and 2-methyl-5-

[33] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 164 (1952).
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[40] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 149 (1952).
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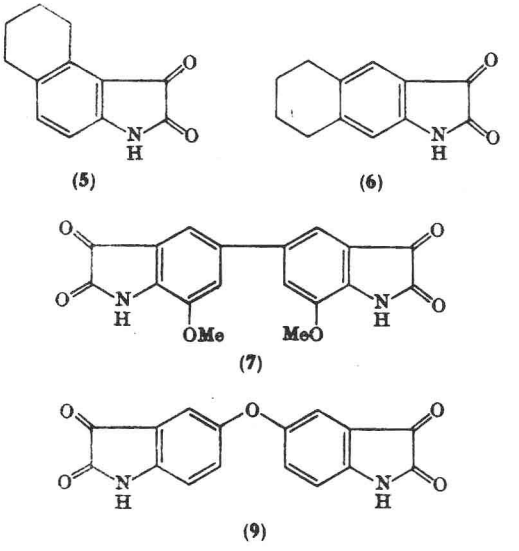
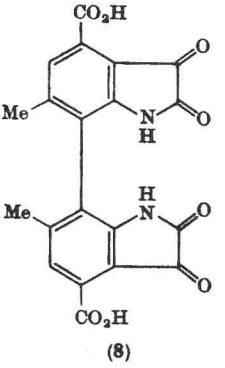
[56] R. Hodges and A. Taylor, *J. Chem. Soc.*, 4310 (1964).

cyanoaniline to 7-methylisatin-4-carboxamide.[52] An *N*-methyl analog of **3** has been converted into an *N*-methylisatin.[57,58]

Use of the appropriate tetrahydronaphthylamine has led to fused isatins such as **5** and **6**,[40] while diaminobiphenyls have given rise to





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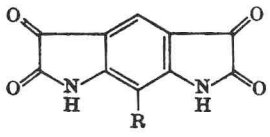
compounds of the type **7**[14] and **8**.[51] 4,4′-Diaminodiphenylether led to the isatin **9**.[59] A number of *m*-phenylenediamines have been subjected to this sequence. Thus while *m*-phenylenediamine and 2,6-diaminotoluene gave **10** and **11** respectively,[60] 2,4-diaminochlorobenzene gives **12**.[61] Finally, 2,4-diaminotoluene gives rise to **13** which has been postulated to arise in the alkali workup of **14**.[61]

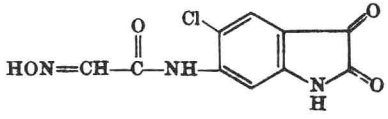
ω-Nitroacetanilide and sulfuric acid or hydrofluoric acid gave a good yield of isatin-3-oxime.[62] It is assumed that the cyclization took place via PhNHCOC(OH)=NOH.

Treatment of anilines with oxalyl chloride followed by cyclization of the intermediate **15** is a useful isatin synthesis. Generally a Lewis acid

[57] F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.* **23**, 19 (1958).
[58] J. M. Z. Gladych and J. H. Hunt, S. African Patent 68 04,428 (1968); *Chem. Abstr.* **71**, 81436 (1969).
[59] I. Shopov, *Dokl. Bolg. Akad. Nauk* **21**, 241 (1968); *Chem. Abstr.* **69**, 3207 (1968).
[60] Z. J. Allan, *Chem. Listy* **46**, 228 (1952).
[61] Z. J. Allan, *Chem. Listy* **46**, 224 (1952).
[62] K. Wiechert, H. H. Heilmann, and W. Jacob, *Z. Chem.* **1**, 191 (1961).



(10) R = H
(11) R = Me



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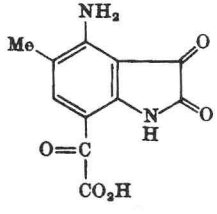

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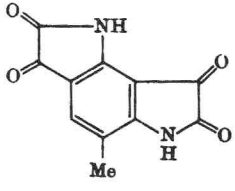
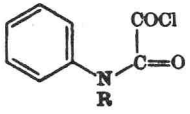


(14)

is used for the cyclization,[58,63–74] but in some cases, for example 3,5-dimethoxyaniline,[75] no Lewis acid is needed. With 2,3-dichlorodiphenylamine, cyclization takes place onto the unsubstituted ring to give *N*-(2,3-dichlorophenyl)isatin.[74] This method has also been applied to the synthesis of tetrahydroisatins.[76,77] Thus **16** and oxalyl chloride gave



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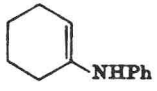

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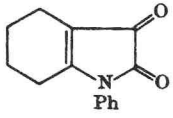

(17)

[63] H. E. Baumgarten and J. L. Furnas, *J. Org. Chem.* **26**, 1536 (1961).
[64] J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 3904 (1952).
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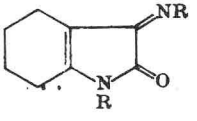
[77] E. Ziegler, F. Hradetzky, and M. Eder, *Monatsh. Chem.* **97**, 1391 (1966).

what was reported as **17**.[77] Reaction of cyclohexanone and dimethyloxalate gives a substituted glyoxylic ester which reacts with amines to form anils (**18**) which on acid hydrolysis give rise to similar compounds.[78–80] Use of guanidine or urea as the amine with 2-oxocyclohexylglyoxylic acid gave quinazoline derivatives rather than **19**.[81] Infrared[79,80]



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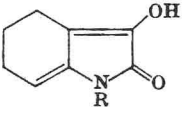

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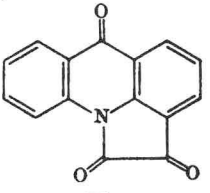

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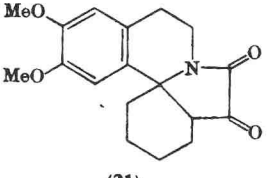

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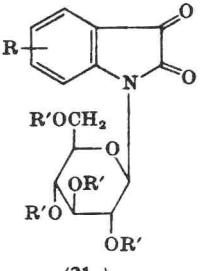

(21a)

and NMR[81] studies support the tautomeric structure **19** for these so-called tetrahydroisatins. The isatin derivative **20** was obtained from acridone by oxalate cyclization.[67] The half ester-half acid chloride of oxalic acid has also been used in this synthesis.[82] The ester of 2-oxocyclohexylglyoxylic acid and 3,4-dimethoxyphenethylamine gave **18** (R = 3,4-dimethoxyphenylethyl)[83–86] which on treatment with phosphoric acid gave the hexahydroisatin derivative **21**. 3-Acetoxy-2,4,5,6-tetrahydro-2-oxobenzofuran and ammonia, ethylamine, or aniline gave **19** (R = H, Et, or Ph, respectively).[87] 1-β-*D*-Glucopyranosides of isatins (**21a**) were

[78] L. Horwitz, *J. Amer. Chem. Soc.* **75**, 4060 (1953).
[79] D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 876 (1959).
[80] R. J. S. Beer and J. Hollowood, *J. Chem. Soc.*, 991 (1964).
[81] W. L. F. Armarego and B. A. Milloy, *J. Chem. Soc., Perkin Trans. 1*, 2814 (1973).
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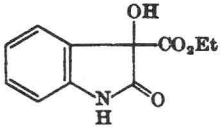
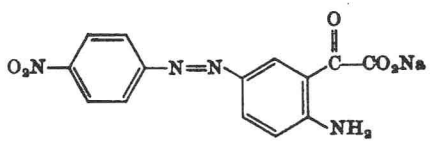
prepared by condensation of the appropriate glucopyranosyl aniline derivatives with oxalyl chloride.[87a]

The Martinet reaction is a somewhat similar method that makes use of the reaction of an aniline and oxomalonic ester to give 22, which on



(22)

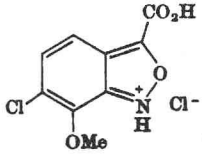


(23)

treatment with alkali in the presence of oxygen gives an isatin via a dioxindole.[88–97]

Treatment of potassium isatinate with sodium formate in acetic-formic anhydride gave 1-formylisatin,[98] while the sodium isatinate 23 was cyclized by treatment with acid to the expected 5-substituted isatin.[99]

o-Nitrobenzoyldiazomethanes have been cyclized by acid to *N*-hydroxyisatins.[100,101] Use of a ^{14}C label in the diazo carbon led to an isatin with all of the ^{14}C in the 2-position; the mechanism of this



(24)

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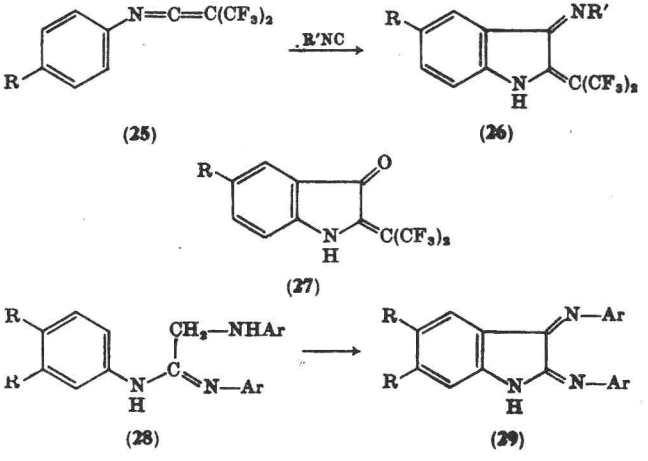
conversion has been discussed.[101] Treatment of **24** with ammonium hydroxide followed by ferrous sulfate gave 6-chloro-7-methoxyisatin.[102]

A number of ring closures have been reported that lead to 2- or 3-substituted isatins. Thus, treatment of nitromalonbis-*N*-methylanilide with acid gives *N*-methylisatin-3-oxime.[103] Reaction of **25** with cyclohexyl or *t*-butylisocyanide gives **26**, which was hydrolyzed by acid to **27**.[104] Heating of **28** gives, with oxidation, the isatin-2,3-dianil **29**.[105]



B. Ring Contractions

A number of so-called 2,4-dihydroxyquinolines, after the introduction of a 3-hydroxyimino,[106] 3-nitroso,[107,108] 3-hydroxy-3-amino,[109] or more frequently 3,3-dihalo groups,[110–114] give isatins with sulfuric acid or sodium hydroxide. Treatment with sodium hydroxide of 3,3-

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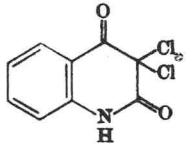
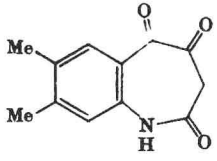
dichloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (30) labeled at carbon 3 with ^{14}C resulted in 100% loss of the activity as $^{14}CO_2$ and gave isatin which contained no ^{14}C.[115]



(30)

7-Methoxy-2-methyl-1,4-dihydro-4-oxoquinoline was converted into 6-methoxyisatin by an oxidative ring opening followed by ring closure.[115a] Oxidation of 4-methyl-*N*-(2,3-dimethylphenyl)-carbostyril with alkaline permanganate gave *N*-(2,3-dimethylphenyl)isatin.[74]



(31)

Treatment of **31** with alkali gave 5,6-dimethylisatin in addition to a quinoline derivative.[116]

C. From Indole Derivatives

Chromic acid oxidation of a variety of indoles has been used as a synthetic route to isatins.[117–124] A variety of other oxidative methods

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