

Synthesis of 3-Substituted Indoles Starting from Isatin

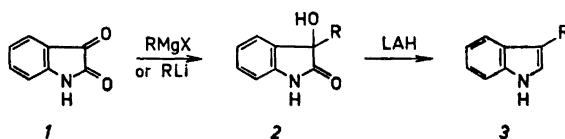
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Some indoles have been prepared in one step by adding suitable organometallic reagents, followed by LiAlH_4 , to a refluxing mixture of isatin in ether. The reactions involved are shown in Scheme 1. The transformation $2 \rightarrow 3$ also provides a convenient synthesis of α -alkyltryptophols.

Attempts to prepare the acetylenic indole 19 unexpectedly gave *trans*-3-styrylindole (20).

The possibility of converting isatin (1), via 3-hydroxyoxindole (2), into a 3-substituted indole (3) has been seldom used.¹⁻³



Scheme 1

The main reason for this is undoubtedly the time-consuming procedure and the unsatisfactory overall yields. These disadvantages can, however, be partly eliminated by integrating the steps. Table 1 shows some compounds prepared by this improved method.

Some of the compounds, e.g. 3-(2-thienyl)indole (6), are very difficult to prepare by other methods, but most of the compounds in Table 1 are more satisfactorily produced by applying other techniques. One example is 3-(diphenylmethyl)indole (8), an excellent yield of which is obtained by simply refluxing diphenyl carbinol and indole in acetic acid. Another example is a recent synthesis of 3-(4-pyridyl)indole.⁴

The method in Scheme 1 is not suitable for the synthesis of 3-(2-pyrrolyl)indole or 3,3'-biindolyl (17). The latter compound can, however, be prepared by lithium aluminium hydride reduction of 3-(3-indolyl)3-hydroxyoxindole (18). Compound 18 was readily obtained by a diethylamine-catalyzed conden-

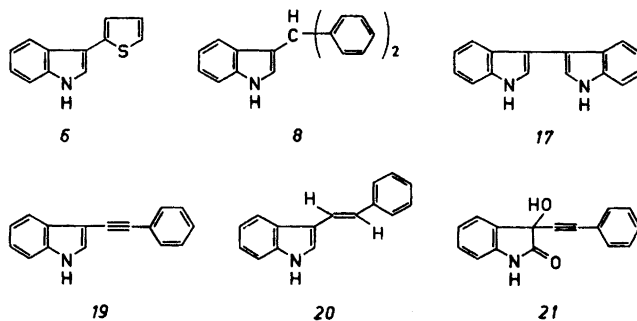
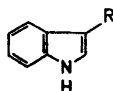


Table 1.



No.	R	Mp C°	(Lit.)	Yield %	Recryst. solvent ^a
4	Phenyl	86–87	(87–88 ^b , 85 ^c)	52	
5	Benzyl	109–110	(110 ^d)	58	
6	2-Thienyl	97–98 ^e		55	
7	2-Benzothienyl	146–148 ^f		48	Benzene
8	Diphenylmethyl	126–127	(126–127, 5 ^g)	22	Methanol
9	4-Methoxyphenyl	131–133	(134 ^c)		
10	2-Pyridyl	150–153	(150–154 ^h)	14	Benzene
11	4-Pyridyl	218–219	(218–219 ⁱ)	10	Ethanol
12	2-Pyridylmethyl	101–103	(98–101 ^j , 104 ^k)	27	
13	Methyl	94–95		37	
14	Ethyl	33–35	(33–35 ^l)	30	
15	Butyl	102–103 ^m	(102–103 ⁿ)	32	
16	<i>t</i> -Butyl	67–68	(67–68 ^o)	35	

^a Where no solvent is mentioned implies light petroleum (80–120°) as solvent.

^b Fischer, E. and Schmidt, T. *Ber.* **21** (1888) 1811.

^c Bruce, J. M. *J. Chem. Soc.* **1959** 2366.

^d Biswas, K. M. and Jackson, A. H. *Tetrahedron* **25** (1969) 227.

^e Found: C 72.1; H 4.8; N 7.1. Calc. for C₁₂H₉NS: C 72.4; H 4.6; N 7.0.

^f Found: C 77.0; H 4.5; N 5.6. Calc. for C₁₆H₁₁NS: C 77.2; H 4.5; N 5.6.

^g See Ref. 11.

^h Powers, J. C. *J. Org. Chem.* **30** (1965) 2534.

ⁱ Brodka, S. *Diss.* München 1967.

^j DeGraw, J. I., Kennedy, J. G. and Skinner, W. A. *J. Heterocyclic Chem.* **3** (1966) 67.

^k Clemo, G. and Seaton, R. *J. Chem. Soc.* **1954** 2582.

^l Weinmann, J. M., *Diss.* Minneapolis 1964.

^m Picrate.

ⁿ Bergman, J. *Acta Chem. Scand.* **22** (1968) 1063.

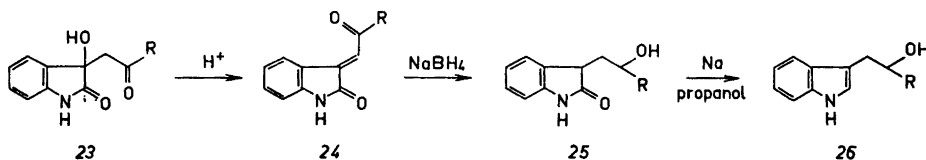
^o Smith, G. F. and Walters, A. E. *J. Chem. Soc.* **1961** 940.

sation of indole and isatin. This route to 3,3'-biindolyl is more convenient than earlier methods.^{5,6}

Attempts to prepare 3-indolylphenylacetylene (19) according to Scheme 1 unexpectedly resulted in *trans*-3-styrylindole (20), which has recently been prepared by Suvorov *et al.*⁷ starting from indole-3-carboxaldehyde and the appropriate Wittig reagent. Lithium aluminium hydride reduction of the known⁸ compound 21 also gave *trans*-3-styrylindole (20).

Attempts to similarly prepare the known compound⁹ 3-vinylindole (22) were unsuccessful.

Some years ago, Tacconi,¹⁰ using the method outlined in Scheme 2, reported the synthesis of some α -alkyltryptophols. The successful transformation 2 \rightarrow 3 according to Scheme 1, did suggest, however, that the direct transformation (23 $\xrightarrow{\text{LAH}}$ 26) should be possible. This was also found to be the case. The yields are usually somewhat higher than the total yields reported by Tacconi.



Scheme 2

A reductive cleavage, with the formation of 3-methylindole and a primary alcohol (RCH_2OH), was found to be a by-reaction during the transformation (23 $\xrightarrow{\text{LAH}}$ 26).

EXPERIMENTAL

3-(2-Thienyl)indole (6). Finely powdered isatin (14.7 g, 0.1 mol) was added in five portions to 2-thienyllithium (17.6 g, 0.21 mol) in ether (500 ml). After 4 h at reflux-temperature LiAlH_4 (7.6 g, 0.2 mol) was added. The mixture was then refluxed for another 4 h. After cooling, the excess LiAlH_4 was decomposed by the cautious addition of water, the mixture filtered, and the solvent removed. The residue recrystallized from light petroleum (80–120°) gave 3-(2-thienyl)indole (11.0 g, 55%), m.p. 97–98°.

3-Hydroxy-3-indolyloxindole. A mixture of indole (11.7 g), isatin (14.7 g), diethylamine (1 ml) and ethanol (150 ml) was heated to 45° for 1 h. After 20 h at 25°, water was added to the clear solution until turbidity (150–200 ml of water are required). Some minutes later, pink crystals (23.7 g) separated out. Recrystallization from methanol gave 17.7 g (74%) of 3-hydroxy-3-indolyloxindole. M.p. 122–123°. (Found: C 72.4; H 4.7; N 10.4. Calc. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$: C 72.7; H 4.6; N 10.6.)

3,3'-Biindolyl (17). 3-Hydroxy-3-indolyloxindole (13.2 g, 0.05 mol) in dioxan (200 ml) was added during a period of 30 min to a refluxing mixture of LiAlH_4 (3.8 g, 0.1 mol) and dioxan (100 ml). On completion of this step, the reflux was continued for 4 h. After cooling, water (300 ml), at first cautiously, was added and the mixture filtered. Soxhlet-extraction of the solid obtained gave 3,3'-biindolyl. Yield 6.3 g, 54%. M.p. 285–287° (lit.⁵ 285–287°).

trans-3-Styrylindole (20). *Method A*. Finely powdered isatin (14.7 g, 0.1 mol) was added in five portions to lithium phenylacetylide (0.2 mol), prepared from phenylacetylene (20.4 g, 0.2 mol) and butyllithium (0.21 mol), in ether (350 ml). This mixture was treated as described above in the synthesis of 3-(2-thienyl)indole. Yield 11.0 g, 50%. M.p. 193–194° (lit.⁷ 196–197°).

A sample (m.p. 193–194°), prepared by the Russian technique,⁷ showed no depression compared with a sample obtained when using the above procedure.

Method B. 3-Benzylidyne-3-hydroxyoxindole⁸ (0.1 mol) was employed as starting material instead of isatin and lithium phenylacetylide.

Yield 55%. M.p. 193–194°.

3-(2-Phenylethyl)indole. *trans*-3-Styrylindole (1.0 g) in ethanol (30 ml) was hydrogenated over 10% Pd/C (100 mg). The hydrogen-uptake was completed within 1 h. The reaction mixture was filtered and evaporated. The residue, crystallized from water: ethanol (1:1), gave 3-(2-phenylethyl)indole (0.7 g, 70%). M.p. 119–120° (lit.^{7,10} 122–123°, 118–119°).

3-(2-Hydroxycyclohexyl)indole. 3-(2-Oxocyclohexyl)-3-hydroxyoxindole¹⁴ (12.3 g, 0.05 mol) was added in portions to a refluxing mixture of LiAlH₄ (3.8 g, 0.1 mol) in ether (500 ml). When this step was completed, the reflux was continued for 5 h. Excess of the hydride was destroyed by the careful addition of water, while stirring. The ether phase was evaporated and the residue crystallized from cyclohexane: hexane (3:1). Yield 4.1 g, 39%. M.p. 152–155° (lit.¹³ 157°).

The following substances were similarly prepared:

3-(2-Hydroxypropyl)indole 26, R=CH₃. Yield 32%. M.p. 40–41° (lit.^{15,13} 37.5°, 44–45°).

3-(3,3'-Dimethyl-2-hydroxybutyl)indole 26, R=C(CH₃)₂. Yield 37%. M.p. 120–122° (lit.¹⁰ 119–121°).

3-(Diphenylmethyl)indole (8). Indole (11.7 g, 0.1 mol), diphenyl carbinol (18.4 g, 0.1 mol) and acetic acid (60 ml) were refluxed for 2 h. On cooling, colourless crystals were formed. Recrystallization from methanol gave 16.7 g (59%). M.p. 126–127° (lit.^{11,12} 126–127.5°, 127–128°).

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