

A Simple Synthesis of 2-Acyl Indoles from Isatins

By DAVID ST C BLACK* and LAURENCE C H WONG

(Department of Chemistry, Monash University, Clayton, Victoria, 3168, Australia)

Summary *N*-Phenacyl- and *N*-acetyl-isatins can be prepared and converted by treatment with sodium hydroxide into 2-acyl indoles and/or 2-acyl indole-3-carboxylic acids

In connection with ligand synthesis, we required some 2-acyl indoles and considered that they should be obtainable from *N*-phenacyl- and *N*-acetyl-isatins (4) by hydrolytic

ring-opening and base-catalysed cyclization. However, such isatin derivatives have not been described. Ainley and Robinson¹ have reported that the reaction of sodium isatin and phenacyl bromide gives a product for which they suggested the structure (2a) rather than *N*-phenacyl-isatin (4a). We have confirmed the validity of this structure (2a) and have found that it is formed under a wide range of basic conditions.

Nevertheless, we now report the preparation of compounds (4) by combination of the *o*-aminoglyoxylic acid salts (3) [obtained by alkaline hydrolysis of the isatins (1)] with α -halogeno-ketones in dimethylformamide (DMF). The orange or red *N*-alkyl-isatins (4) can be isolated in moderate to high yields (35–90%). Hydrolysis of compounds (4) for 12 h with 20% aqueous sodium hydroxide affords easily separable mixtures of the 2-acyl indoles (5) and the corresponding carboxylic acids (6) in uniformly good yields (75–85%). The proportion of compounds (5) to (6) depends on the ease of decarboxylation, which is affected by substituent electronic effects (see Table). Our conditions have been designed to encourage decarboxylation.

TABLE Relative percentages of compounds (5) and (6) after 12h reflux of compounds (4) with 20% NaOH

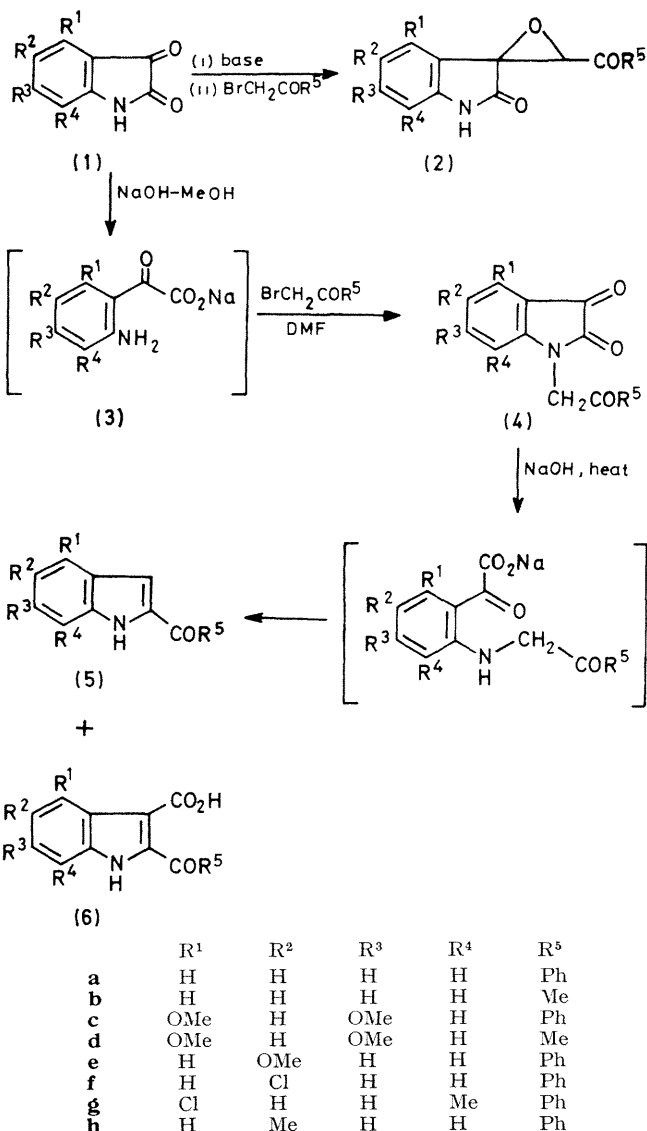
Compound	a	b	c	d	e	f	g	h
(5)	90	100	100	100	60	40	30	65
(6)	10	0	0	0	40	60	70	35

The versatility of this indole synthesis is demonstrated by the fact that only the indoles (5a,b) have been described previously^{2,3}. The remaining indoles (5c–h) have now been fully characterised. Some 2-acyl indoles have been formed⁴ using the Fischer synthesis, but this method is severely restricted by the available range of aryl hydrazines and α -diketones. Our synthetic route is related to the formation of indoles from *o*-aminoaryl ketones and α -halogeno-ketones,² but has the considerable advantage of providing indoles unsubstituted in the 3-position. Furthermore, substituted isatins are far more readily available than substituted *o*-aminoaryl ketones.

It is surprising that such a conceptually simple indole synthesis has not been reported previously, but its discovery seems to have been thwarted not only by the observation of Ainley and Robinson¹ but also by their assertion that *N*-phenacylisatin would be convertible by basic treatment into a 2,4-dihydroxyquinoline.

We thank the Wool Research Trust Fund for financial support.

(Received, 28th November 1979, Com 1238)



¹ A D Ainley and R Robinson *J Chem Soc*, 1934 1508

² C D Jones and T Suarez *J Org Chem* 1972, **37** 3622

³ K S Bhandari and V Snieckus, *Canad J Chem* 1971 **49** 2354

⁴ V I Shvedov, V V Alekseev, and A N Grinev, *Khim Farm Zhur*, 1968, **2**, 8, (*Chem Abs*, 1969 **70**, 11,469f)