A Simple Synthesis of 2-Acyl Indoles from Isatins

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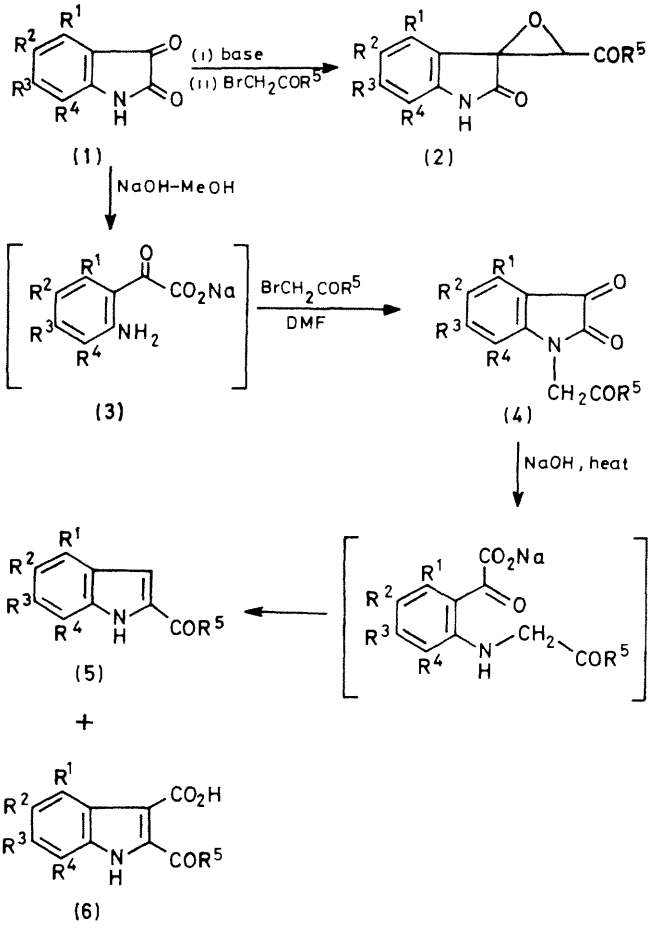
Summary *N*-Phenacyl- and *N*-acetonyl-isatins can be prepared and converted by treatment with sodium hydroxide into 2-acyl indoles and/or 2-acyl indole-3-carboxylic acids

IN connection with ligand synthesis, we required some 2-acyl indoles and considered that they should be obtainable from *N*-phenacyl- and *N*-acetonyl-isatins (**4**) by hydrolytic ring-opening and base-catalysed cyclization However, such isatin derivatives have not been described Ainley and Robinson[1] have reported that the reaction of sodio-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



(1) (2) (3) (4) (5) (6)

	R¹	R²	R³	R⁴	R⁵
a	H	H	H	H	Ph
b	H	H	H	H	Me
c	OMe	H	OMe	H	Ph
d	OMe	H	OMe	H	Me
e	H	OMe	H	H	Ph
f	H	Cl	H	H	Ph
g	Cl	H	H	Me	Ph
h	H	Me	H	H	Ph

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 formed[4] 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 Robinson[1] but also by their assertion that *N*-phenacylisatin would be convertible by basic treatment into a 2,4-dihyroxyquinoline

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

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