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IODINATION OF ISATINS

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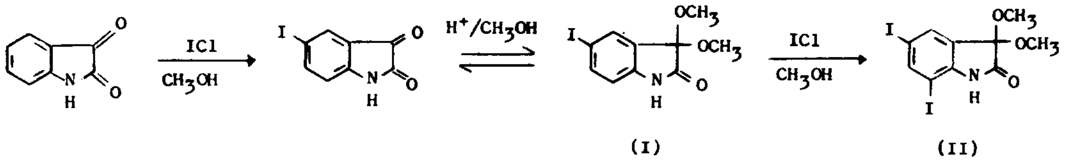
Halogenation of the isatin molecule generally follows a simple pattern. Substitution at the 5-position always occurs; with excess reagent 5,7-disubstituted products are sometimes obtained. Although, 5-chloro, 5,7-dichloro, 5-bromo and 5,7-dibromo isatins(1)(2) can be prepared by direct halogenation and 5-iodo isatin(3) may be obtained by the action of iodine monochloride in refluxing acetic acid on isatin, it has been stated many times(1-6) that a second iodine atom cannot be introduced directly. I wish to correct this view.

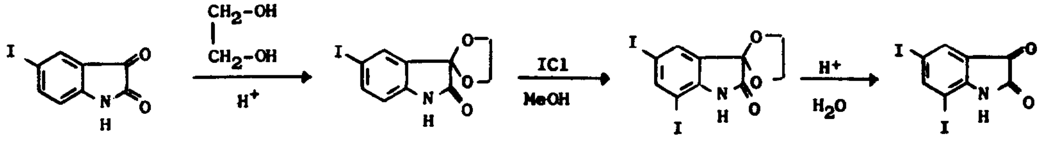
Whilst investigating the effect of different solvents on the yield of 5-iodoisatin it was found in methanol, in addition to the mono-iodo product, a small amount (3%) of an orange material was obtained which, after recrystallisation from benzene/petrol, yielded colourless needles, m.p. 198-202°, that analysed for $C_{10}H_9I_2NO_3$, ν_{max} (KBr) 3190, 1735 cm.$^{-1}$, τ (D.M.S.O.) 6.45 (6H, s, OCH_3); 2.08, 1.7 (2H, q, Ar, J=1.5 Hz)-0.91 (1H, s, NH). The presence of two aromatic protons with meta-coupling indicated that a disubstituted compound has been formed, to which the ketal structure (II) was assigned. This was confirmed by its hydrolysis to 5,7-diiodoisatin (V)(4).



(I) (II)

The initial formation of ketal (II) aids further iodination as it is considerably more soluble in methanol than 5-iodoisatin. Also, ketalization of the β-carbonyl group enhances the reactivity of the aromatic ring to electrophilic attack. The actual nature of the electrophile is uncertain, but is most probably methylhypoiodite(7).

This mechanism was supported by the synthesis of the ethylene ketal (III) which was smoothly iodinated when refluxed in methanol with iodine mono-chloride (1.1 equiv.) for 2 hr. to give (IV, 65%).



(III) (IV) (V)

When (IV) is refluxed with HCl:AcOH (3:1) for 30 min. 5,7-diiodoisatin (V) was obtained in almost quantitative yield. It is interesting to note here the more vigorous conditions required to hydrolyse (IV) compared with the mono-iodoketal (III), (2N HCl, 5 min.).

The method is a general route to 5-substituted-7-iodoisatins as shown by the synthesis of 5-bromo-7-iodoisatin m.p. 274-276° and 5-nitro-7-iodoisatin m.p. 241-243° by iodination of the ketal of the 5-substituted isatins.

The 5-nitroketal required a longer reaction time (8 hr.) with iodine monochloride, as is to be expected from the greater deactivating effect of a nitro-group towards electrophilic substitution.

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