# 685. *The Reaction between Indole and Acetic Anhydride.*

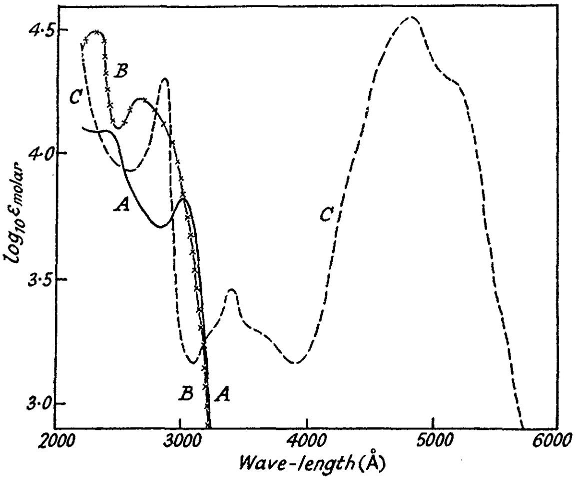
By J. E. Saxton.

The action of acetic anhydride and acetic acid on indole at the boiling point of the mixture affords 1 : 3-diacetylindole and a by-product, not previously observed, considered to be 1 : 1-di-(1-acetyl-3-indolyl)ethylene.

In connection with synthetical studies in the strychnine series, considerable quantities of 3-acetylindole were required. The principal methods which have been used for the preparation of this compound are the reaction of indole with acetic anhydride at 180—200° (Baeyer, *Ber.*, 1879, **12**, 1314; Ciamician and Zatti, *Ber.*, 1889, **22**, 1977; Zatti and Ferratini, *Ber.*, 1890, **23**, 1360) and of indolylmagnesium halides with acetyl chloride (Oddo and Sessa, *Gazzetta*, 1911, **41**, I, 234; Majima, *Ber.*, 1922, **55**, 3871; Baker, *J.*, 1946, 462).

They give varying yields of a mixture of mono- and di-acetylindoles. For example, while Majima claims a 93% yield of 3-acetylindole, Oddo and Sessa, and also Baker, make no such claims, and repetition of their experiments shows that the yield is very unsatisfactory.

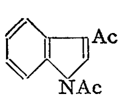
For this reason, the reaction of indole with acetic anhydride was preferred as a preparative method, but it cannot easily be adapted to a large-scale preparation owing to the conditions used (180—200° in sealed tubes). In addition the dark product had to be crystallised several times in order to obtain pure diacetylindole (I). Accordingly, the reaction was carried out at 147° for periods of 24—48 hours. Pure acetic anhydride gave an oil, which on crystallisation gave a low yield of diacetylindole, but the addition of 10% of acetic acid to the reaction mixture gave after 24 hours a product which crystallised readily during the removal of the solvent *in vacuo* and on further crystallisation gave 55—60% yields of clean diacetylindole. The *N*-acetyl group of this compound was removed quantitatively at the room temperature by aqueous-alcoholic sodium hydroxide.

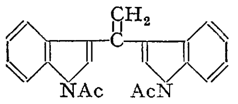


*A*, 1 : 1-*Di*-(1-*acetyl*-3-*indolyl*)*ethylene* (II) *in methanol.*
*B*, 1-3′-*Indolyl*-1-3″-*indolylidene-ethane* (III) *in methanol.*
*C*, 1-3′-*Indolyl*-1-3″-*indolylidene-ethane in methanolic* HCl.

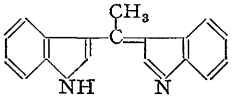
The crude diacetylindole was contaminated by 5—10% of a by-product, $C_{22}H_{18}O_2N_2$, for which structure (II) is proposed. The *N*-acyl groups are readily removed, to give a compound $C_{18}H_{14}N_2$, which must be (III*a* or *b*). This substance is a very weak base, which gives rise to deeply coloured salts of a type previously reported by Borsche and Groth (*Annalen*, 1941, **549**, 238). It is very readily reduced to a dihydro-derivative, $C_{18}H_{16}N_2$, m. p. 162°, which has all the characteristics of a β-substituted indole and must be (IV). The preparation of this (IV) from indolylmagnesium bromide and acetaldehyde has previously been reported by Oddo and Toffoli (*Gazzetta*, 1934, **64**, 359) who gave m. p. *ca.* 160° (not sharp). An independent synthesis of this compound from indole, paraldehyde, and zinc chloride has confirmed the structure (IV) for the reduction product, and hence (II) for the original by-product.

(I)

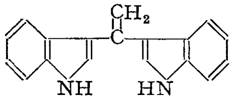




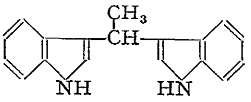
(II)



(III*a*)



(III*b*)



(IV)

The structure of the de-acetylated product has not been determined, but the available evidence supports (III*a*) rather than (III*b*). Thus, the presence of formaldehyde among the ozonolysis products of (III) could not be demonstrated. Further, in the infra-red region the substance does not exhibit the absorption bands characteristic of a methylene group, and in this respect resembles (IV). In contrast, the spectrum of (II) has pronounced maxima at 9·98, 10·68, and 11·15 μ, showing unequivocally the presence of a methylene group.

The absorption of (III) in the ultra-violet region is shown in the Figure, and a noteworthy feature is the striking change that occurs on salt formation.

## EXPERIMENTAL

*Reaction between Indole and Acetic Anhydride.*—Indole (25 g.), acetic acid (25 c.c.), and acetic anhydride (225 c.c.) were refluxed for 24 hours. The solvent was removed *in vacuo*, and the residue, which was crystalline at 100°, recrystallised from ethanol. 1 : 3-Diacetylindole (16—18 g.; pure material from 24—26 g. of crude material) was obtained as colourless needles, m. p. 150—151° (Found: N, 7·0. Calc for $C_{12}H_{11}O_2N$: N, 7·0%). Zatti (*Ber.*, 1889, **22**, 1978) reports m. p. 151°; the substance also crystallised from benzene.

1 : 3-Diacetylindole (20 g.) was suspended in ethanol (100 c.c.), and sodium hydroxide (50 c.c. of 2N) added. The mixture was stirred and warmed if necessary until the diacetylindole had dissolved. The product was then precipitated by dilution with water, collected, and crystallised from ethanol. 3-Acetylindole was obtained as long, colourless prisms, m. p. 191° (Found: C, 75·9; H, 5·8; N, 8·8. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·7; N, 8·8%), in almost quantitative yield; Zatti (*loc. cit.*) reports m. p. 190—191°.

The small amount of insoluble residue after the first crystallisation of the crude diacetylindole was collected and crystallised from acetone or dioxan. 1 : 1-*Di*-(1-*acetyl*-3-*indolyl*)*ethylene* (II) was obtained as long, colourless rods or needles, m. p. 220—221° (Found: C, 77·1, 77·1; H, 5·3, 5·5; N, 8·1, 7·9. $C_{22}H_{18}O_2N_2$ requires C, 77·2; H, 5·3; N, 8·2%). This gave an orange colour when heated with Ehrlich's reagent; its deep red solution in concentrated sulphuric acid became dark greenish-brown on the addition of potassium dichromate.

Complete separation of the diacetylindole from the by-product by fractional crystallisation resulted in substantial losses of material. In order to ensure the optimum yield of 3-acetylindole, the by-product was removed in the hydrolysis stage, by the following procedure:

A mixture of crude diacetylindole (30 g.) with ethanol (225 c.c.) and sodium hydroxide solution (75 c.c. of 2N) was stirred until solution of the diacetylindole was complete. The by-product remained as an insoluble crystalline powder (3 g.) and was collected and washed with a little warm ethanol. 3-Acetylindole was precipitated from the combined filtrates on dilution with water. It separated from ethanol as long, colourless prisms, m. p. 191° (18 g.).

Crystallisation of 1 : 1-di-(1-acetyl-3-indolyl)ethylene from aqueous pyridine, or treatment with hot aqueous-alcoholic alkali, followed by crystallisation from dioxan, gave 1-3′-*indolyl*-1-3″-*indolylidene-ethane* (or its tautomeride) (III*a* or *b*) as colourless rhombs, m. p. 232—234° (decomp.) (Found: C, 83·5, 83·9; H, 5·3, 5·4; N, 11·2, 11·3; *C*-Me, 5·7%; *M*, 234, 273. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·4; N, 10·9; *C*-Me, 5·8%; *M*, 258). In hot dilute hydrochloric acid this gave an orange-red solution from which long, orange-red needles of the *hydrochloride* separated on cooling. After drying at 100° for 8 hours, it was obtained as greenish-black plates with a metallic lustre, decomp. > 155° (Found: C, 73·0; H, 5·5. $C_{18}H_{14}N_2$,HCl requires C, 73·4; H, 5·1%).

1 : 1-*Di*-3′-*indolylethane* (IV).—(*a*) 1-3′-Indolyl-1-3″-indolylidene-ethane (1·0 g.) was hydrogenated in dioxan–ethanol at room temperature and pressure with a palladised strontium carbonate catalyst. 1 Mol. of hydrogen was rapidly absorbed and hydrogenation then ceased. The filtered solution was evaporated *in vacuo*, and the residue crystallised from ethanol. 1 : 1-*Di*-3′-*indolylethane* (0·8 g.) was obtained as colourless prisms, m. p. 162° (Found: C, 83·5; H, 6·2; N, 10·7. $C_{18}H_{16}N_2$ requires C, 83·1; H, 6·2; N, 10·8%). This substance gave a magenta colour with Ehrlich's reagent which gradually became blue.

(*b*) Indole (2 g.), paraldehyde (0·4 g.), and zinc chloride (0·5 g.) were heated on the steam-bath for 5 hours and then extracted with light petroleum (b. p. 40—60°), and the residue was crystallised from ethanol. 1 : 1-Di-3′-indolylethane (0·5 g.) was obtained as colourless prisms, m. p. and mixed m. p. with the previous sample 162° (Found: C, 83·4; H, 6·3; N, 10·8%).

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