The Acylation of 3-Alkyl-indoles

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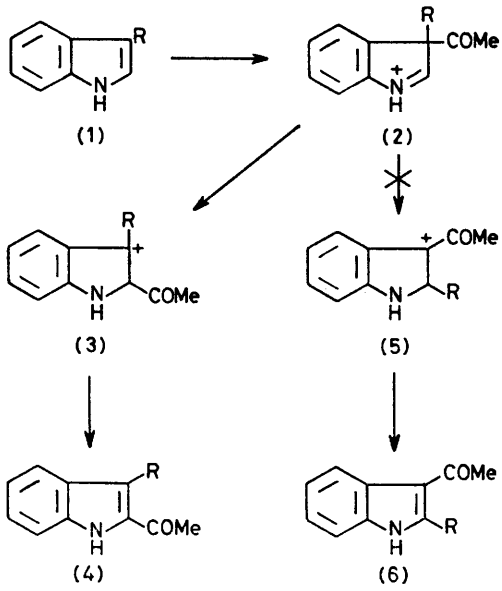
Summary Evidence is presented that the acylation of 3-alkyl-indoles to form 2-acyl-3-alkyl-indoles proceeds by initial attack at the 3-position of the indole nucleus, followed by migration of the acyl group.

IT has been established previously that alkylation of 3-alkyl-indoles generally occurs *via* initial attack at the 3-position followed by migration of the incoming substituent (or that already present) to the neighbouring 2-position[1] (although electron releasing substituents in the 4- and 6-positions of the indole nucleus may also activate the 2-position to direct attack[1d]). Many other electrophilic substitution reactions of 3-alkyl-indoles[2] also occur by initial attack at the 3-position, *e.g.* sulphenylation,[3] chlorination,[4] peroxidation,[5] diazo-coupling,[6] and cyclisation reactions of tryptamines with aldehydes.[7,8]

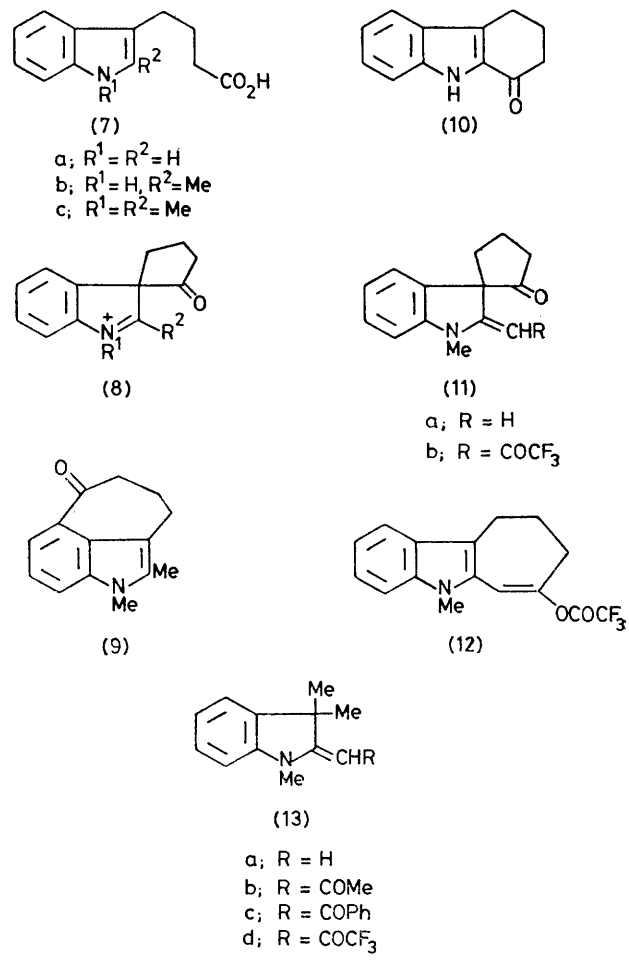
The mechanism of acylation of 3-alkylindoles (**1**) has not, however, been determined hitherto, and indeed relatively few examples of acylation at C-2 have been described.[9] The Vilsmeier–Haack procedure, now widely used for acylations at C–3 in 3-unsubstituted indoles, is not generally applicable.[9,10] However we now find that 3-methylindole gives 2-acetyl-3-methylindole (**4a**) in virtually quantitative yield by brief treatment with acetic anhydride, acetic acid, and boron trifluoride–ether at 20 °C; 3-benzylindole affords a good yield of 2-acetyl-3-benzylindole

(**4b**) under similar conditions. 3-Alkylindole Grignard derivatives give both 1- and 2-acyl derivatives depending on the conditions and substituents.[9,11] 4-Indol-3-ylbutyric acid (**7a**) can also be cyclised to 1-oxotetrahydrocarbazole (**10**) in excellent yield by use of the boron trifluoride–acetic anhydride reagent; this has proved to be a general procedure for the synthesis of a range of methoxy-substituted 1-oxotetrahydrocarbazoles (*cf.* refs. 1e and f) and the mild conditions employed (*e.g.* 15 min at 20 °C) represent a considerable improvement over similar cyclisations described previously.[9]



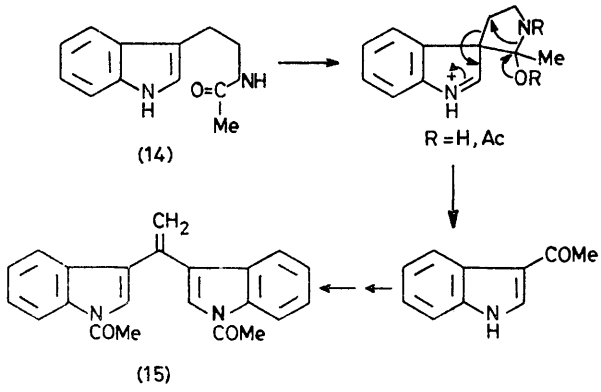
SCHEME 1
a; R = Me **b**; R = CH_2Ph

We envisage that the acylations described above proceed by the general pathway (**1**)→(**2**)→(**3**)→(**4**) shown in Scheme 1, *i.e.* by initial acylation at the 3-position followed by migration of the acyl group, as in the analogous alkylations of indoles described previously.[1] We were unable to detect the formation of any of the alternative products (**6**) which would be derived from the intermediate indolenine (**2**) by migration of the alkyl group rather than the acyl group. Attempts to cyclise the 2-methylindolylbutyric acid[1d] (**7b**) with boron trifluoride–acetic anhydride to a spirocyclic indolenine (*cf.* **8b**) [analogous to the probable intermediate (**8a**) formed in the cyclisation of indolylbutyric acid (**7a**)] were unsuccessful, and only tarry products of unknown constitution were formed. However, the corresponding 1,2-dimethylindolylbutyric acid[12] (**7c**) on treatment with trifluoroacetic anhydride [in an attempt to prepare the tricyclic ketone (**9**)] afforded a product, m.p. 179–180 °C, which was shown spectroscopically to have the structure (**11b**) ($\lambda_{max.}$ 372 nm (ϵ 20,500); $\nu_{max.}$ 1745 and 1650 cm^{-1}; τ 4·35 (CH=) and 6·65 (Me); *m/e* 309 (M^+, 31%) and 254 ($M-C_3H_2O$, 100%); M^*, 208·9. This was confirmed by the ^{13}C n.m.r. spectrum, which included signals at 20·0, 34·7, and 37·7 (3 × CH_2), 66·7 (quaternary C, C–3), 84·9 (>C=*C*H·CO), 171·1 (>*C*=CH·CO), 175·0 quartet, CO·CF_3), and 210·2 (*C*O) p.p.m. (from Me_4Si). This ruled out a possible alternative structure (**12**) formed by cyclisation on to the 2-methyl group. The spirocyclic derivative (**11b**) is probably formed by trifluoroacetylation of the initial methylene-indoline (**11a**). The acetyl (**13b**) and benzoyl (**13c**) derivatives of the Fischer base (**13a**), which



are structurally related to (**11b**), have been described previously;[13] trifluoroacetylation of the base (**13a**) gave the trifluoroacetyl derivative (**13d**), the spectral characteristics of which ($\lambda_{max.}$ 368 nm and τ 4·55 and 6·86) closely model those of (**11b**).

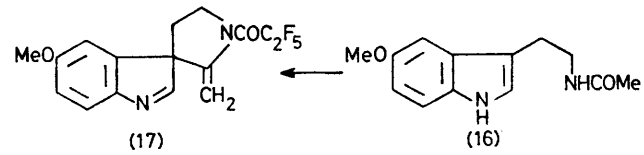
In relation to other experiments with tryptamines, which showed evidence of cyclisation to spirocyclic indole derivatives[14] (to be described later) we treated tryptamine with hot acetic anhydride, acetic acid, and pyridine. The only crystalline product isolated was the di-indolylethylene (**15**) (66%) which was identified by its spectral characteristics and comparison with authentic material prepared directly from indole.[15] We attribute this reaction to acylation at the 3-position, probably *via* internal attack of the initially formed *N*-acetyltryptamine (**14**) and expulsion of the ethylamine side-chain as shown in Scheme 2. This view is reinforced by a recent report[16] that



(14) (15)

SCHEME 2

cyclisation of melatonin (**16**) with pentafluoropropionic anhydride affords the spirocyclic indolenine (**17**), although there is no other precedent for elimination of the ethylamine side chain.



(17) (16)

These results lead to the general conclusion that in common with all the other electrophilic substitution reactions referred to above, acylation of 3-alkyl-indoles at the 2-position occurs by a two stage process involving initial attack at the 3-position followed by rearrangement. The reason for the exclusive migration of the acyl group after initial substitution at the 3-position is presumably that migration of the alkyl group is very unfavourable owing to the instability of the intermediate acyl carbonium ion [*cf.* (**5**)] which would be formed, as it has an acyl group attached to a positively charged carbon atom.

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