Competitive *ipso*-Attack at C-3 and *N*-Substitution in the Trifluoroacetylation of 2,3-Dimethylindole

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Summary ^{1}H N.m.r. evidence is given for the formation of an indoleninium ion pair intermediate and for the direct *N*-attack in the trifluoroacetylation of the title and related compounds.

PREVIOUS reports on the mechanism of electrophilic substitution of indoles suggested that the initial attack occurs predominantly at the 3- or *N*-position, depending upon the substrate structure and experimental conditions. In particular Jackson and his co-workers[1] showed that preliminary attack at C-3 is favoured even in 3-substituted indoles, followed by rearrangement of the electrophile at the 2-position. Kinetic results of the Vilsmeier–Haack acetylation of a number of indoles giving *N*-substituted products were interpreted in terms of direct attack at the nitrogen atom.[2]

Trifluoroacetylation of unsubstituted indole was shown to give 3- and/or *N*-substituted products, depending on the relative concentration of reactants and on the solvent, as well as some 2-indol-3-yl-*N*-trifluoroacetylindoline.[3] Further support for the competition between 3- and *N*-substitution is given by quantitative measurements of relative reactivities in the Vilsmeier–Haack acetylation[2] and acid-catalysed hydrogen exchange in aqueous acetonitrile.[4] In both cases the reactivity at the nitrogen atom is larger (40 to 80 fold) than that at C-3.

N-Substituted indole and 3-substituted-3*H*-indole were detected or suggested as intermediates in the chlorination of indole[5] and 2,3-dimethylindole,[6] as well as in the base-catalysed hydrogen exchange[7] and diazo-coupling[8] of a number of indole derivatives, under conditions in which the actual substrate is probably the conjugate base.

In order to clarify the relative importance of *ipso*-attack at C-3, *N*-substitution, and rearrangements, we report experimental evidence for the reaction products and the intermediates formed in the trifluoroacetylation of 2,3-dimethylindole and other alkylindoles by trifluoroacetic anhydride in 1,2-dichloroethane or CCl_4 at 0 °C.

2,3-Dimethylindole (**1**), treated with anhydride (*ca.* 1 M; 1 : 1) in either solvent, gave, after 30 min, two main products. The v.p.c. analysis showed, besides a large amount of unreacted substrate (50%), only 25% of the expected 2,3-dimethyl-*N*-trifluoroacetylindole (**2**) [^{1}H n.m.r. (CCl_4) δ 2·12 (3H, s, 3-Me), 2·42 (3H, s, 2-Me), 6·95—7·35 (3H, m, Ar-H), and 7·71 (1H, m, 7-H)] and *ca.* 10% of a disubstituted compound (g.c–m.s. m/e^+ 337) whose ^{1}H n.m.r. spectrum [δ (CCl_4 1·70 (3H, s, 3-Me), 4·85 (1H, d, 2-CH_2), 5·75 (1H, d, 2-CH_2), 6·95—7·45 (3H, m, Ar-H) and 7·78 (1H, d, 7-H)] shows the presence of an upfield shifted methyl-group and a methylene-group linked by a double bond to the ring. The i.r. spectrum exhibits two carbonyl bands indicating a ketone (ν 1750 cm^{-1}) and an amidic (ν 1700 cm^{-1}) C=O. On the basis of this spectral evidence we suggest that this compound has the structure of 3-methyl-2-methylene-1,3-bis(trifluoroacetyl)indoline (**3**).

The reaction mixture, before the usual work-up with $NaHCO_3$, contains, however, a much lower amount of substrate and a more volatile (on a 10% column packed with LAC 728 at 140 °C) product (20%, m/e 241) which could not be isolated under the preparative conditions. The for-

mation of (**3**) and the observation that (**2**) does not react further with the anhydride to yield (**3**) suggested to us that this product derives from a preliminary attack at C-3.

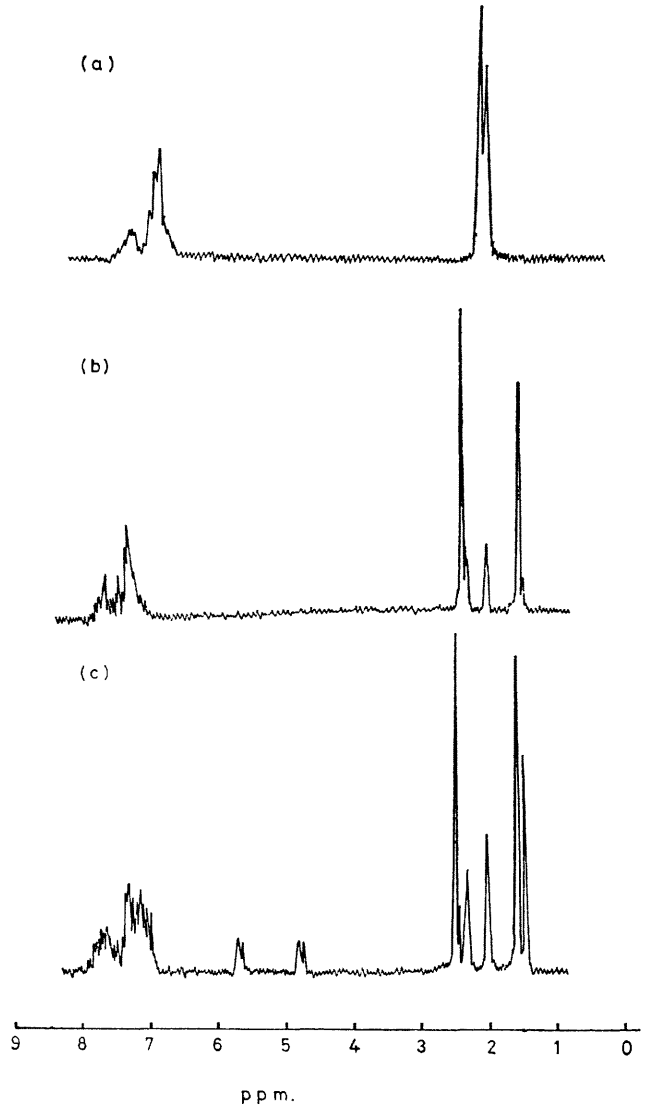
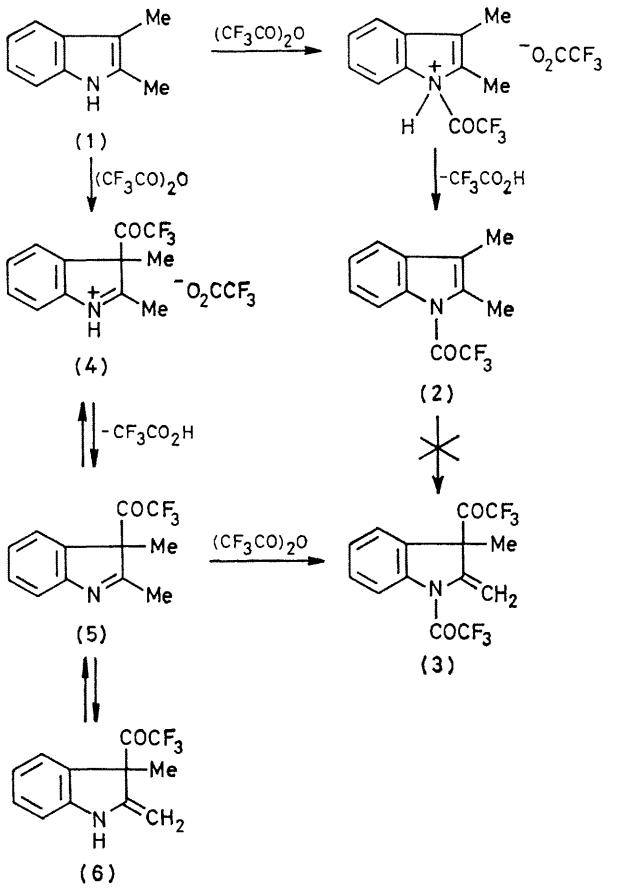


FIGURE. ^{1}H N.m.r. spectra of the reaction mixture of 2,3-dimethylindole in CCl_4 at 0 °C: (a) substrate, (b) immediately after addition of trifluoroacetic anhydride, (c) after 15 min at 0 °C.

The ^{1}H n.m.r. study of the reacting mixture at 0 °C in CCl_4, on adding the indole to the anhydride, showed no trace of the starting material (**1**) or of the substituted product (**3**). The spectrum, taken immediately after the addition (Figure 1), is interpreted as a 1 : 3 mixture of (**2**) (25%) and a compound exhibiting a structure with two methyl-groups and five protons. The upfield shifted methyl-group peak shows the same chemical shift as the 3-methyl-group of (**3**) (which cannot be present as the methylene peaks do not appear), whereas the other methyl-group signal (2-Me) is shifted downfield if compared with the substrate. This spectrum constitutes compelling evidence that the main, stable product first formed in solution is the ion pair (**4**), *i.e.* 2,3-dimethyl-3-trifluoroacetylindoleninium trifluoroacetate. On standing at 0 °C for some minutes the peaks characteristic of (**3**) increase, whilst the amount of (**4**) decreases slightly. Apparently, (**4**) loses trifluoroacetic acid giving the indolenine (**5**) [which should be more stable than the enaminic form (**6**)],[9] which rapidly reacts to yield (**3**).

The whole framework of the reaction can be described as in the Scheme. Nitrogen and C-3 compete for the attack by trifluoroacetic anhydride, thus confirming that both mechanistic hypotheses previously suggested by Jackson and ourselves are correct. Although attack at C-3 is favoured, as shown by the n.m.r. ratio, proton loss from (**4**) should be relatively slow which would explain the product distribution. The gas chromatography results are in agreement with the n.m.r. data, provided, as seems likely, the ion pair (**4**) readily reverts to the substrate in the presence of water and loses a proton under v.p.c. conditions, to give (**5**) and/or (**6**).



SCHEME.

Preliminary n.m.r. data on trifluoroacetylation of 3-methyl-, 1,3-dimethyl-, and 1,2,3-trimethyl-indole are in agreement with the general mechanism depicted in the Scheme, as *ipso*-attack at C-3 and direct *N*-substitution compete very closely. *N*-substitution prevails when the nitrogen atom bears no substituent. In the other cases

attack at the 3-carbon prevails and the subsequent step of the reaction strongly depends upon the presence of a methyl-group at the 2-position. When the 2-position is unsubstituted, rearrangement of the electrophile from C-3 to C-2 becomes a relevant process.

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