Trifluoroacetylation of Trialkylindoles

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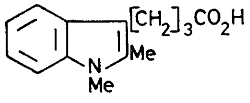
Summary The trifluoroacetylation of 1,2,3-trialkylindoles occurs by attack at C(3) followed by substitution of the 2-methyleneindoline so formed.

We have recently reported[1] that treatment of compound (**1**) with trifluoroacetic anhydride (TFAA) affords the spiran (**2**) and not the expected product (**3**). It was therefore decided to examine the reactions of some simple trialkylindoles with TFAA since the 'normal' Friedel–Crafts reactions of 1,2,3-trisubstituted indoles result in substitution in the benzene ring.[2]



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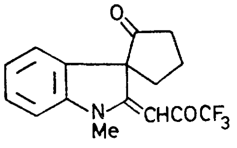

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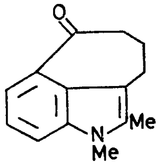

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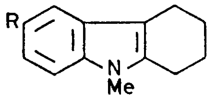

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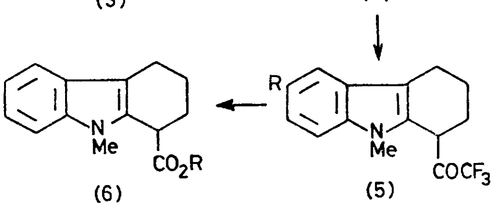

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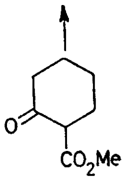

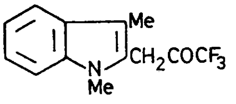

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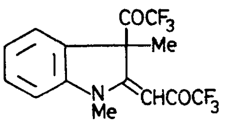

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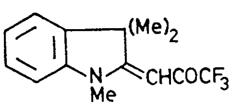

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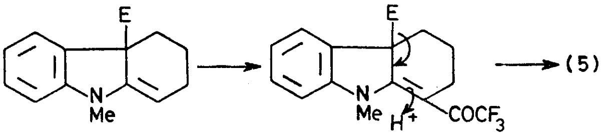


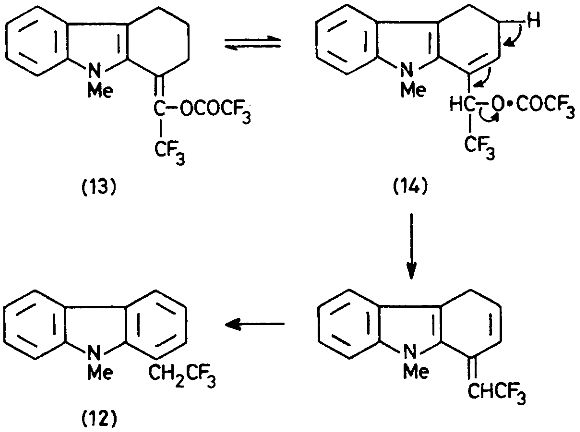
(10) (11)

Treatment of 9-methyltetrahydrocarbazole (**4**; R = H), with TFAA in pyridine afforded not the expected[2] 7-substituted compound but a ketone (80% yield) whose physical properties suggested structure (**5**; R = H). This structure was confirmed by alkaline hydrolysis of (**5**; R = H) to the known[3] acid (**6**; R = H) identical with synthetic material obtained *via* (**6**; R = Me). Similar compounds have been obtained from (**4**; R = Me) and from *N*-methylcyclohept[*b*]indole.

Treatment of 1,2,3-trimethylindole with TFAA in benzene afforded two products, the trifluoroacetylindole (**7**; yield 55%) and, with an excess of TFAA, an unstable 2:1 product (29% yield) to which we assign structure (**8**) having physical properties (u.v., n.m.r.) very similar to those of compound (**9**) obtained[1] by reaction of the Fischer base with TFAA. Compound (**8**) is also obtained by treating trimethylindole with TFAA at 0 °C in pyridine solution; it reacts with water losing CF_3CO_2H to form compound (**7**).

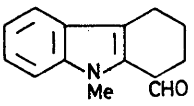
We suggest that the formation of (**5**) and of (**8**) occur by addition of an electrophile (E = either CF_3CO^+ or H^+) to C(3) of the indole nucleus followed by loss of a proton to give a methyleneindoline which is then attacked by the TFAA [*cf.* the formation of (**9**)] giving (**8**) and (**11**). Loss of E^+ from (**11**) gives (**5**), and loss from (**8**) affords (**7**).

The reaction of (**5**; R = H) with TFAA under more vigorous conditions (boiling benzene) was then examined in an attempt to acylate the benzene ring of (**5**). However, the product was 9-methyl-1-$\beta\beta\beta$-trifluoroethylcarbazole (**12**) (u.v., i.r., n.m.r.) formed by the loss of a molecule of water from (**5**). Compound (**12**) is probably formed *via* the enol-trifluoroacetate (**13**) followed by isomerisation to (**14**) and loss of CF_3CO_2H. The aromatisation of cyclohexenones by treatment with pyridine hydrochloride has been described.[4]



(13) (14)

(12)



(15)

It has been reported[5] that formylation (Vilsmeier–Haack) of 9-methyltetrahydrocarbazole gave 3-formyl-1,9-dimethylcarbazole and it was suggested that production of the 1-methyl group involved attack at the 1-methylene group of the tetrahydrocarbazole followed by dehydrogenation. We consider that the 1-formyl compound (**15**) arose by formylation of structure (**10**) and the production of the 1,9-dimethylcarbazole involved dehydration of (**15**) and not dehydrogenation.

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[5] P. Bruck, *Chem. Comm.*, 1970, 1690.