

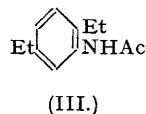
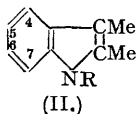
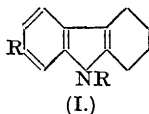
325. *The Friedel-Crafts Reaction with 1-Acyl-2 : 3-dimethylindoles.*

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Substances derived from 1-acetyl- and 1-benzoyl-2 : 3-dimethylindole by the Friedel-Crafts reaction have been hydrolysed to a compound which has been proved to be 6-acetyl-2 : 3-dimethylindole. 2 : 3-Dimethyl-6-ethylindole has been obtained from it by reduction and subsequent dehydrogenation, as well as from 2-acetamido-1 : 4-diethylbenzene by the action of potassium *tert.*-butoxide. The results are analogous to those previously observed in the carbazole group. Certain reactions of 1 : 6-diacetyl-2 : 3-dimethylindole have been studied.

EARLIER work has shown that while disubstitution at the 3- and 6-positions readily takes place when acid chlorides and anhydrides act under the conditions of a Friedel-Crafts reaction on carbazole and its 9-alkyl derivatives, similar treatment of the 9-acylcarbazoles leads to monosubstitution at the 2-position (see, *e.g.*, Plant, Rogers, and Williams, *J.*, 1935, 741;

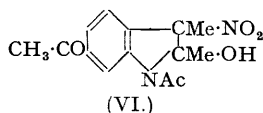
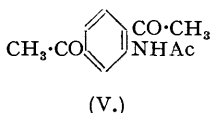
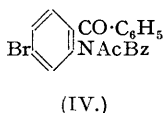
Mitchell and Plant, *J.*, 1936, 1295). Plant and Rogers (*J.*, 1936, 40) found that 9-acetyl- and 9-benzoyl-tetrahydrocarbazole gave their 7-acetyl and 7-benzoyl derivatives (I; R = Ac or Bz) under similar conditions, and it seemed probable that the 6-position would be that normally



taken by the substituent in Friedel-Crafts reactions with simple indoles such as the 1-acyl-2 : 3-dimethylindoles (II; R = Acyl). In order to investigate this, 1-acetyl-2 : 3-dimethylindole was treated with acetyl bromide (or chloride) and aluminium chloride, and a diacetyl-2 : 3-dimethylindole, m. p. 116°, was obtained. A small quantity of a *triacetyl-2 : 3-dimethylindole* was formed at the same time, and this was also prepared by a further application of the Friedel-Crafts reaction to the diacetyl compound, m. p. 116°. 1-Benzoyl-2 : 3-dimethylindole was converted under similar conditions into an *acetyl* derivative, which, on hydrolysis, gave an acetyl-2 : 3-dimethylindole, m. p. 154°, identical with that obtained by the hydrolysis of the diacetyl compound. That the substance, m. p. 154°, was not 5-acetyl-2 : 3-dimethylindole was proved by reducing it by the Clemmensen method. The resulting 2 : 3-*dimethylethylindoline*, which formed a characteristic *phenylcarbonyl* derivative, gave, on dehydrogenation, a 2 : 3-*dimethylethylindole*, m. p. 74°, different from 2 : 3-*dimethyl-5-ethylindole* synthesised from *p*-ethylphenylhydrazine and methyl ethyl ketone. Further investigations into the structure of these products had to be discontinued early in 1940 for the duration of the war. In the meantime Borsche and Groth (*Annalen*, 1941, 549, 238) have treated 1-acetyl-2 : 3-dimethylindole with acetyl chloride and aluminium chloride and obtained a compound, m. p. 115–116°, which they called 1 : 6-diacetyl-2 : 3-dimethylindole. It was hydrolysed to a substance, m. p. 153°, stated to be 6-acetyl-2 : 3-dimethylindole. No experimental evidence was adduced for the structures, which were assigned on the basis of the work of Plant and others referred to above.

The validity of these assumptions has now been established by the synthesis of 2 : 3-dimethyl-6-ethylindole from 2-*acetamido-1 : 4-diethylbenzene* (III), m. p. 154°, by heating it with potassium *tert.*-butoxide under conditions similar to those used by Marion and Ashford (*Canadian J. Res.*, 1945, 23B, 26; see also Tyson, *J. Amer. Chem. Soc.*, 1941, 63, 2024) for the preparation of 2 : 3-dimethylindole from *o*-acetamidoethylbenzene. The product proved to be identical with the substance, m. p. 74°, obtained by the reactions already mentioned. Voswinkel (*Ber.*, 1889, 22, 315) claims to have prepared 2-*acetamido-1 : 4-diethylbenzene* from the corresponding amine, obtained from 2-nitro-1 : 4-diethylbenzene, but the m. p. is given as 99° and the substance was not analysed. The conditions described in the experimental section for the nitration of *p*-diethylbenzene were found to be more satisfactory than those mentioned by Voswinkel, which led to a considerable quantity of a dinitro-compound, as was evident from the fact that a *bisacetamido-1 : 4-diethylbenzene* could be prepared from the basic material obtained by reduction of the product.

Koelsch (*J. Amer. Chem. Soc.*, 1944, 66, 1983) has found that 6-bromo-1-acetyl-2 : 3-dimethylindole can be oxidised to 5-bromo-2-benzoyl-*N*-acetylbenzanilide (IV) by chromic acid in acetic acid solution. When 1 : 6-diacetyl-2 : 3-dimethylindole was treated in this way,



2 : 5-*diacetyllacetanilide* (V) was isolated, evidently after removal of one of the *N*-acetyl groups from the analogous primary oxidation product. It was also found that *o*-acetamidoacetophenone could be similarly obtained from 1-acetyl-2 : 3-dimethylindole. Nitration of 1 : 6-diacetyl-2 : 3-dimethylindole has given a *nitro*-derivative together with 3-*nitro-2-hydroxy-1 : 6-diacetyl-2 : 3-dimethylindoline* (VI). The latter, which was colourless, soluble in alkali, and melted with evolution of oxides of nitrogen, had the behaviour characteristic of this type of compound, the formation of which is a well-established feature of the 1-acyl-2 : 3-dialkylindoles (see, *e.g.*, *J.*, 1933, 955; 1940, 283).

3-Acetylcarbazole can be readily prepared by heating 9-acetylcarbazole with aluminium chloride in nitrobenzene (Plant, Rogers, and Williams, *loc. cit.*). Attempts to obtain 5-acetyl-2 : 3-dimethylindole similarly from the 1-acetyl compound have given an unsatisfactory

product, from which a little 6-acetyl-2:3-dimethylindole was the only pure material isolated. This behaviour is reminiscent of that observed with 9-acetyltetrahydrocarbazole (Plant and Rogers, *loc. cit.*).

EXPERIMENTAL.

1:6-Diacetyl-2:3-dimethylindole.—Aluminium chloride (25 g.) was added to 1-acetyl-2:3-dimethylindole (9.4 g.) and acetyl bromide (17 g.) in carbon disulphide (120 c.c.), the whole refluxed for 2½ hours, the solvent distilled off, and the residue added to ice-dilute hydrochloric acid. When the product was crystallised from alcohol, 1:6-diacetyl-2:3-dimethylindole (8.5 g.) was obtained in colourless prisms, m. p. 116° (Found: C, 73.2; H, 6.5. Calc. for $C_{14}H_{15}O_2N$: C, 73.4; H, 6.5%). The same substance resulted from the use of a restricted amount (6.4 g.) of acetyl chloride instead of acetyl bromide. When the material obtained by concentrating the alcoholic mother liquors was recrystallised from light petroleum, a triacetyl-2:3-dimethylindole separated in colourless needles, m. p. 117° (Found: C, 70.8; H, 6.3. $C_{16}H_{17}O_3N$ requires C, 70.8; H, 6.3%).

The same triacetyl compound (mixed m. p.) was obtained in good yield when a mixture of 1:6-diacetyl-2:3-dimethylindole (1.15 g.), acetyl chloride (0.5 g.), aluminium chloride (2.5 g.), and carbon disulphide (15 c.c.) was refluxed for 2 hours, and the product crystallised from alcohol.

1-Benzoyl-6-acetyl-2:3-dimethylindole.—When 1-benzoyl-2:3-dimethylindole (5 g.) was treated with acetyl chloride (2.4 g.) and aluminium chloride (8 g.) in carbon disulphide (50 c.c.) as described for the corresponding acetyl compound, and the product crystallised from alcohol, 1-benzoyl-6-acetyl-2:3-dimethylindole was obtained in colourless needles (4 g.), m. p. 117° (Found: C, 78.0; H, 5.9. $C_{19}H_{17}O_2N$ requires C, 78.3; H, 5.8%). After its solution in aqueous-alcoholic potassium hydroxide had been refluxed for 2 hours, the addition of water precipitated 6-acetyl-2:3-dimethylindole. This separated from aqueous alcohol in yellow prisms, m. p. 154° (Found: N, 7.3. Calc. for $C_{12}H_{13}ON$: N, 7.5%), identical (mixed m. p.) with the substance similarly obtained from 1:6-diacetyl-2:3-dimethylindole.

2:3-Dimethyl-5-ethylindole.—After *p*-ethylphenylhydrazine (2.89 g.) and methyl ethyl ketone (1.54 g.) had been warmed for a few minutes on the steam-bath, the resulting hydrazone was taken up in ether, the solution dried (K_2CO_3), and evaporated. The residue was heated with powdered zinc chloride (2 g.) at 180° for 5 minutes, and the product extracted with boiling light petroleum. 2:3-Dimethyl-5-ethylindole separated from the extract in colourless plates, m. p. 62° (Found: C, 82.9; H, 8.9. $C_{12}H_{15}N$ requires C, 83.2; H, 8.7%).

2:3-Dimethyl-6-ethylindole.—(a) 6-Acetyl-2:3-dimethylindole (4.7 g.) and concentrated hydrochloric acid (30 c.c.) were added to amalgamated granulated zinc (50 g.), the mixture shaken, and left overnight. After the addition of more hydrochloric acid (100 c.c. of 28%), the whole was refluxed for 12 hours, made alkaline with concentrated aqueous sodium hydroxide, and steam distilled. When the distillate was extracted with ether, and the extract dried and fractionated, 2:3-dimethyl-6-ethylindole (2.2 g.) was obtained as a colourless oil, b. p. 133°/13 mm. (Found: C, 82.7; H, 10.4. $C_{12}H_{17}N$ requires C, 82.3; H, 9.7%). The base (1 g.) was heated with palladised charcoal (0.25 g.) for 4 hours at 260° in an atmosphere of hydrogen, the product dissolved in acetone, the solution filtered and poured into dilute hydrochloric acid. The precipitated solid was crystallised from aqueous alcohol, from which 2:3-dimethyl-6-ethylindole separated in colourless plates, m. p. 74°, which soon turned brown when left in air (Found: C, 82.7; H, 8.6%).

(b) *p*-Diethylbenzene (20 g.) was gradually added to a well stirred mixture of glacial acetic acid (40 c.c.) and nitric acid (43 c.c., *d* 1.5) at 10–15°, the whole diluted with water, and the product extracted with chloroform. After the extract had been washed with aqueous sodium carbonate, dried, and the solvent removed, 2-nitro-1:4-diethylbenzene (17.4 g.) was obtained, on distillation, as a yellow oil, b. p. 137–140°/12 mm. with some decomposition. The oil (16.5 g.) was heated on the steam-bath for an hour with iron filings (65 g.) and aqueous acetic acid (70 c.c. of 5%), the mixture made alkaline with aqueous sodium carbonate, and the base removed in steam. When extracted from the distillate with ether, dried, and distilled, 2-amino-1:4-diethylbenzene (12.5 g.) was obtained as a colourless oil, b. p. 122°/13 mm. The amine was suspended in three times its volume of water, treated with a slight excess of acetic anhydride, the mixture boiled, and sufficient glacial acetic acid added to effect solution. On cooling, 2-acetamido-1:4-diethylbenzene separated in good yield in colourless needles, m. p. 154° (Found: C, 75.3; H, 8.8; N, 7.5. $C_{12}H_{17}ON$ requires C, 75.4; H, 8.9; N, 7.3%). The acetyl compound (3 g.) was added to a solution of potassium (0.91 g.) in *tert*-butyl alcohol (19 g.), the excess of the alcohol distilled off, and the residue heated at 350–360° for 20 minutes in an atmosphere of nitrogen. When cold, the mixture was treated with water, and the 2:3-dimethyl-6-ethylindole removed in steam. It then separated from aqueous alcohol in colourless plates, m. p. 74°, identical (mixed m. p.) with the substance described above.

After *p*-diethylbenzene (10 g.) had been nitrated by adding it to nitric acid (20 c.c., *d* 1.5) at 0° as described by Voswinkel (*loc. cit.*), and the crude product, without distillation, reduced as described above, the 2-amino-1:4-diethylbenzene was removed in steam and the residual hot aqueous solution filtered. The solid was washed several times with hot water and the united filtrates saturated with salt and extracted with benzene. The extract was dried, acetic anhydride (10 c.c.) added, and the whole refluxed for a few minutes. When cold, the bulky precipitate was collected and recrystallised from cyclohexanone, from which a bisacetamido-1:4-diethylbenzene (2.2 g.) was obtained in pale yellow prisms, m. p. 253–256° (Found: C, 67.6; H, 7.9; N, 11.4. $C_{14}H_{20}O_2N_2$ requires C, 67.7; H, 8.1; N, 11.3%).

1-Phenylcarbonyl-2:3-dimethyl-6-ethylindole.—After a mixture of the indoline with a little less than one molecular proportion of phenyl isocyanate had been heated on the steam-bath for a few minutes, the solid was crystallised from alcohol, and 1-phenylcarbonyl-2:3-dimethyl-6-ethylindole obtained in colourless needles, m. p. 218° (Found: C, 77.1; H, 7.5; N, 9.5. $C_{19}H_{22}ON_2$ requires C, 77.5; H, 7.5; N, 9.5%).

2:5-Diacetylacetanilide.—Chromic anhydride (2.7 g.) in a little water was added to a solution of 1:6-diacetyl-2:3-dimethylindole (3.8 g.) in glacial acetic acid (80 c.c.), the whole left for 2 hours at

room temperature, and then heated for 5 minutes at 70°. After the addition of water (300 c.c.), the filtered solution was extracted with benzene, and the extract shaken with aqueous sodium carbonate, dried (MgSO₄), and evaporated under reduced pressure. When the residue was crystallised from alcohol, 2 : 5-diacetylacetanilide (1.45 g.) was obtained in yellow needles, m. p. 103° (Found : C, 65.9; H, 6.2; N, 6.4. C₁₂H₁₃O₃N requires C, 65.8; H, 5.9; N, 6.4%).

After 1-acetyl-2 : 3-dimethylindole (3.7 g.) had been similarly oxidised and the product twice crystallised from water, *o*-acetamidoacetophenone was obtained in pale yellow needles (1.25 g.), m. p. 75° (Found : C, 67.7; H, 6.1; N, 8.3. Calc. for C₁₀H₁₁O₃N : C, 67.8; H, 6.2; N, 7.9%).

Nitration of 1 : 6-Diacetyl-2 : 3-dimethylindole.—Nitric acid (0.3 c.c., *d* 1.5) was added dropwise to a solution of 1 : 6-diacetyl-2 : 3-dimethylindole (1 g.) in glacial acetic acid (3 c.c.) at 80°. On cooling, a nitro-derivative (0.2 g.) slowly separated, and, after recrystallisation from acetic acid, it was obtained in practically colourless needles, m. p. 185° (Found : C, 60.9; H, 5.0; N, 10.6. C₁₄H₁₄O₄N₂ requires C, 61.3; H, 5.1; N, 10.2%). When the mother liquor was concentrated under reduced pressure, a small amount of 3-nitro-2-hydroxy-1 : 6-diacetyl-2 : 3-dimethylindoline separated. On recrystallisation from acetic acid it was isolated in colourless prisms, m. p. 125° (decomp.) (Found : N, 9.8. C₁₄H₁₆O₅N₂ requires N, 9.6%).

Action of Aluminium Chloride on 1-Acetyl-2 : 3-dimethylindole.—After a solution of the acetyl compound (2 g.) and aluminium chloride (2 g.) in nitrobenzene (20 c.c.) had been heated at 115° for 20 minutes, water was added, and the nitrobenzene removed in steam. When the residual sticky solid was dried, distilled under reduced pressure, and twice recrystallised from alcohol, a small amount of 6-acetyl-2 : 3-dimethylindole was obtained in yellow prisms, m. p. 151–153°, and identified by mixed m. p.

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