646. *New Syntheses of Heterocyclic Compounds. Part XVII.* Diethylaminoethyl 1 : 3-Dimethyl-2-aza-9-fluorylideneacetate.*

By B. N. Feitelson and V. Petrow.

Two routes to 1 : 3-dimethyl-2-aza-9-fluorylideneacetic acid (IV; R = H) have been investigated. (i) Reaction of 1 : 3-dimethyl-2-azafluorenone (I) with acetylene gave 9-ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H), which is partially reduced to 1 : 3-dimethyl-9-vinyl-2-azafluorenol (III), from which 1 : 3-dimethyl-2-aza-9-fluorylidene-ethanol (V; R = H) was obtained by anionotropic rearrangement. Its oxidation to (IV; R = H) could not, however, be effected. (ii) Condensation of (I) with ethoxyacetylene gave 9-ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = OEt), from which the desired acid (IV; R = H) was obtained by anionotropic rearrangement.

The acid (IV; R = H) was converted into the diethylaminoethyl ester, which was required for biological study.

Attempts to prepare 1 : 3-dimethyl-2-azafluorene-9-carboxylic acid for conversion into the diethylaminoethyl ester, reported in Part XIV (Feitelson and Petrow, *J.*, 1952, 228), proved unsuccessful owing to the inherent instability of the acid (cf. also Fox, Lewis, and Wenner, *J. Org. Chem.*, 1951, **16**, 1259). We therefore turned our attention to the synthesis of the corresponding analogue (IV; R = H), hoping thereby to obtain a substance less liable to undergo decarboxylation.

First, 1 : 3-dimethyl-2-azafluorenone (I) was condensed with acetylene in the presence of potassium *tert.*-butoxide (cf. Nef, *Annalen*, 1899, **308**, 264) to give 9-ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H) in excellent yield. The structure assigned to this compound was confirmed by (i) oxidation to 1 : 3-dimethyl-2-azafluorenone (I) (see below), (ii) formation of an unstable silver salt which deflagrated violently when heated, (iii) formation of a blue colour with concentrated sulphuric acid, and (iv) hydrogenation in presence of palladium–calcium carbonate to 1 : 3-dimethyl-9-vinyl-2-azafluorenol (III) and 9-ethyl-1 : 3-dimethyl-2-azafluorenol.

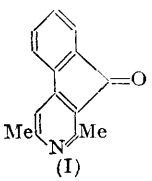
Anionotropic rearrangement of (III) into the alcohol (V; R = H) could not be effected by means of trichloroacetic acid (Dimroth, *Ber.*, 1938, **71**, 1336). The change proceeded smoothly, however, when (III) was treated with phosphorus tribromide in chloroform (Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, **14**, 78; Ruzicka and Müller, *ibid.*, 1939, **22**, 416). Reaction of the bromo-compound so formed with anhydrous potassium acetate in acetic acid led to 1 : 3-dimethyl-2-aza-9-fluorylidene-ethyl acetate (V; R = Ac), from which 1 : 3-dimethyl-2-aza-9-fluorylidene-ethanol (V; R = H) was obtained by hydrolysis. Attempts to convert this compound into the desired acid (IV; R = H) by oxidation, however, proved uniformly unsuccessful, 1 : 3-dimethyl-2-azafluorenone (I) being invariably obtained.

Inter alia, we examined the conversion of (II; R = H) into the acetylenic carboxylic acid (II; R = CO_2H) employing the procedure of Theobald and Adams (*J. Amer. Chem.*

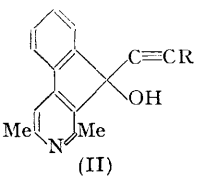
* Part XVI, *J.*, 1952, 784.

Soc., 1943, **65**, 2208; see also Haynes and Jones, *J.*, 1946, 503, 954) whereby carboxylation of the corresponding Grignard reagent is effected under pressure. An unexpected difficulty was here encountered in that, although (II; R = H) passed smoothly into the Grignard reagent, the latter proved to be completely insoluble in benzene, which is the solvent of choice in this instance. Attempts to carboxylate the reaction mixture by contact with solid carbon dioxide in an autoclave for 24 hours thus proved unsuccessful, the bulk of the starting material being recovered unchanged after hydrolysis. Similar results have been reported by Haynes and Jones (*loc. cit.*).

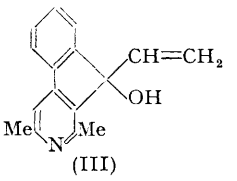
Attempts to convert 9-ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H) into the corresponding hydroxy-acid by oxidation likewise proved discouraging. Ozone, which is claimed to be satisfactory for this purpose (Hurd and Christ, *J. Org. Chem.*, 1936, **1**, 141) failed to give the hydroxy-acid when passed through a solution of the acetylenic alcohol in acetic acid, the bulk of the starting product being recovered unchanged. Neutral



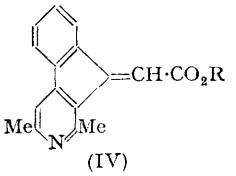
(I)



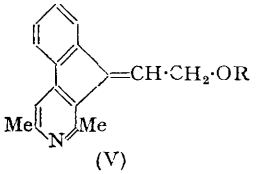
(II)



(III)



(IV)



(V)

potassium permanganate in acetone (Nazarov and Kuznetsova, *Chem. Abs.*, 1942, **36**, 1296) gave 1 : 3-dimethyl-2-azafluorenone, presumably by way of the required acid, which thus resembles 1 : 3-dimethyl-2-azafluorenone-9-carboxylic acid in the facility with which it undergoes decarboxylation.

9-Ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = OEt) was readily obtained in excellent yield from 1 : 3-dimethyl-2-azafluorenone (I) and ethoxyethynylmagnesium bromide (Arens and van Dorp, *Nature*, 1947, **160**, 189) and was smoothly rearranged by dilute sulphuric acid in a few minutes at 100° (cf. Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823); ethyl 1 : 3-dimethyl-2-aza-9-fluorylideneacetate (IV; R = Et) was thus obtained in 45% yield. Hydrolysis with aqueous-ethanolic potassium carbonate furnished the corresponding acid (IV; R = H), from which the diethylaminoethyl ester (IV; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$), the required analogue of the antispasmodic drug Trasentin, was obtained *via* the acid chloride.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

9-Ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H).—Potassium (18 g.) was dissolved in *tert.*-amyl alcohol (350 ml.) in a current of dry nitrogen. The solution was diluted with dry ether (350 ml.) and saturated with acetylene which had been passed through concentrated sulphuric acid. 1 : 3-Dimethyl-2-azafluorenone (10·45 g.) in warm benzene (150 ml.) was then added fairly rapidly with stirring, passage of acetylene being maintained for a further 4 hours. After decomposition with saturated aqueous ammonium chloride, the ethereal layer was removed and shaken repeatedly with ammonium chloride solution, then with water, after which it was extracted with dilute hydrochloric acid. The resulting hydrochloride formed a sludge which was collected and cautiously decomposed with potassium hydroxide solution, to give *9-ethynyl-1 : 3-dimethyl-2-azafluorenol* (96%) in small needles, m. p. 210—211° (Found: C, 81·2; H, 5·5; N, 6·0. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%) after crystallisation from benzene.

9-Ethyl-1 : 3-dimethyl-2-azafluorenol.—The foregoing alcohol (2·35 g.) in absolute ethanol

(50 ml.) was shaken with hydrogen in the presence of 2% palladium–calcium carbonate (1 g.) until absorption was complete. Crystallisation of the product from benzene gave *9-ethyl-1 : 3-dimethyl-2-azafluorenol* (85%), glistening flakes, m. p. 169—170° (Found : C, 80·1; H, 7·1; N, 6·1. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). The *picrate*, after crystallisation from ethanol, formed yellow needles, m. p. 204—205° (Found : C, 56·3; H, 4·2; H, 12·0. $C_{16}H_{17}ON,C_6H_3O_7N_3$ requires C, 56·4; H, 4·3; N, 12·0%).

1 : 3-Dimethyl-9-vinyl-2-azafluorenol (III).—9-Ethynyl-1 : 3-dimethyl-2-azafluorenol (2·35 g.) in absolute ethanol (50 ml.) was shaken with hydrogen in the presence of palladium–calcium carbonate (0·25 g.; 2%) until 1 mol. of hydrogen had been absorbed. The product, after crystallisation from benzene–light petroleum, yielded *1 : 3-dimethyl-9-vinyl-2-azafluorenol*, fluffy needles, m. p. 165° (Found : C, 80·6; H, 6·4; N, 6·0. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%). The *picrate* separated in fine yellow needles, m. p. 199—200° (Found : C, 56·1; H, 3·9; N, 11·8. $C_{16}H_{15}ON,C_6H_3O_7N_3$ requires C, 56·7; H, 3·9; N, 12·0%), from ethanol.

1 : 3-Dimethyl-2-aza-9-fluorylidene-ethyl Acetate (V; R = Ac).—1 : 3-Dimethyl-9-vinyl-2-azafluorenol (3·8 g.) in dry chloroform (27 ml.) was treated with phosphorus tribromide (3·0 g.) in dry chloroform (27 ml.), after which dry pyridine (3 ml.) was added and the mixture kept for 2 hours at room temperature. The product (5·3 g.) was collected and dissolved in acetic acid (100 ml.), a solution of anhydrous sodium acetate (from 25 g. crystals) in acetic acid (100 ml.) added, and the mixture kept at room temperature for 2 days. After filtration from sodium bromide, the solution was concentrated *in vacuo*, diluted with water, and basified with aqueous ammonia. The product, isolated with ether, was purified from benzene, to give *1 : 3-dimethyl-2-aza-9-fluorylideneethyl acetate* (30%), long feathery needles, m. p. 165—166° (Found : C, 77·5; H, 5·9; N, 5·0. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

1 : 3-Dimethyl-2-aza-9-fluorylidene-ethanol (V; R = H).—The foregoing compound (1·15 g.) in alcohol (25 ml.) was treated with an aqueous solution of potassium carbonate (1·15 g.) under reflux for 1 hour. Crystallisation of the product from benzene–light petroleum, and subsequently from benzene, gave *1 : 3-dimethyl-2-aza-9-fluorylidene-ethanol* (80%), m. p. 178° (Found: C, 81·2; N, 6·1; N, 5·6. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%).

9-Ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = OEt).—Ethoxyacetylene (5 g.) (Jacob, Cramer, and Hanson, *J. Amer. Chem. Soc.*, 1942, **64**, 223; Van Dorp, Arens, and Stephenson, *Rec. Trav. chim.*, 1951, **70**, 289) in dry ether (15 ml.) was added with vigorous stirring to ethereal ethylmagnesium bromide (from 1·7 g. of magnesium) and ethyl bromide (8·0 g.) kept at 0°. The mixture was allowed to warm to room temperature and then heated under gentle reflux for 15 minutes, forming two layers. It was cooled to 0° and a solution of 1 : 3-dimethyl-2-azafluorenone (5 g.) in dry benzene (100 ml.) added fairly rapidly with vigorous stirring. After being allowed to warm to room temperature, the mixture was gently refluxed for 30 minutes, cooled, and decomposed with ice-cold saturated ammonium chloride solution. Crystallisation of the product from benzene gave *9-ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol* (64%), prisms, m. p. 125—126° (Found : C, 77·0; H, 6·0; N, 4·8. $C_{18}H_{17}O_2N$ requires C, 77·5; H, 6·1; N, 5·0%).

Ethyl 1 : 3-Dimethyl-2-aza-9-fluorylideneacetate (IV; R = Et).—The foregoing compound (2·0 g.) was added to sulphuric acid (20 ml. of 10%), and the resulting solution warmed for 5—10 minutes on the water-bath. The product, isolated with ether, was purified from ether–light petroleum, to give *ethyl 1 : 3-dimethyl-2-aza-9-fluorylideneacetate*, long needles, m. p. 90—92° (Found : C, 77·9; H, 5·8; N, 4·8. $C_{18}H_{17}O_2N$ requires C, 77·5; H, 6·1; N, 5·0%).

1 : 3-Dimethyl-2-aza-9-fluorylideneacetic Acid (IV; R = H).—The foregoing compound (1·3 g.) in methanol (10 ml.), and a solution of potassium carbonate (1·3 g.) in water (5 ml.), were heated under reflux for 30 minutes. Dilution with water led to precipitation of some (I), which was removed by filtration. After removal of methanol under reduced pressure, the aqueous alkaline liquors were neutralised with 2N-sulphuric acid, and the precipitated solids collected and crystallised from methanol. *1 : 3-Dimethyl-2-aza-9-fluorylideneacetic acid monohydrate* (36%) had m. p. 267—268° (Found : C, 71·0; H, 5·1; N 5·2. $C_{16}H_{13}O_2N,H_2O$ requires C 71·4; H 5·6; N 5·2%).

2-Diethylaminoethyl 1 : 3-Dimethyl-2-aza-9-fluorylideneacetate (IV; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—The foregoing acid (1·0 g.), benzene (10 ml.), and excess of thionyl chloride were heated on the water-bath for 45 minutes. After filtration, excess of thionyl chloride was removed under reduced pressure, and the residue heated with 2-diethylaminoethanol (2 mols.) in benzene under reflux for 2 hours. After basification, the product, in ethanol, was treated with dry hydrogen chloride, and the precipitated solids collected and crystallised from chloroform–ethanol. *2-Diethylaminoethyl 1 : 3-dimethyl-2-aza-9-fluorylideneacetate dihydrochloride sesquihydrate* (36%)

formed pale yellow prismatic needles, m. p. 215° (decomp.) (Found: C 58·5; H 6·8; N 6·7; Cl, 16·0. $C_{22}H_{26}O_2N_2,2HCl,1\frac{1}{2}H_2O$ requires C, 58·7; H, 6·9; N, 6·2; Cl, 15·8%). The *dipicrate* of the base formed large needles, m. p. 202—203° (Found: C, 50·2; H, 3·7; N, 13·8. $C_{22}H_{26}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·5; H, 4·0; N, 13·9%).

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