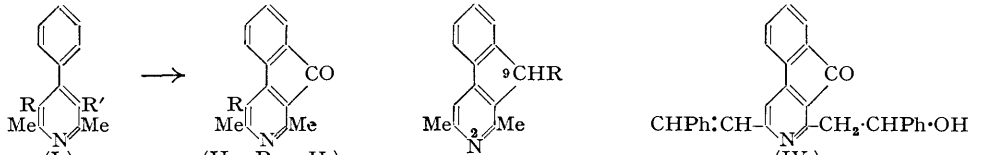
## 452. *Some Derivatives of* 1 : 3-*Dimethyl-2-azafluorenone.*

By H. J. Kahn, V. Petrow, E. L. Rewald, and B. Sturgeon.

Methods for the ready synthesis of 1 : 3-dimethyl-2-azafluorenone (II) and certain of its functional derivatives, required for biological study, have been developed. The chemistry of the group has been extended and compounds such as 9-*amino*-1 : 3-*dimethyl*-2-*azafluorenone* (III; R = $NH_2$) have been prepared.

1 : 3-Dimethyl-2-azafluorenone (II), required for collateral studies (Petrow, *J.*, 1946, 200, 888), was kindly examined at our request by Dr. R. H. Thorp (Wellcome Physiological Research Laboratories, on behalf of The Therapeutic Research Corporation of Great Britain Ltd.) and found to be a better spasmolytic agent than papaverine. We therefore prepared further compounds of this group for biological study, the results of which will be reported elsewhere.

Mills, Palmer, and Tomkinson (*J.*, 1924, 2365) prepared 1 : 3-dimethyl-2-azafluorenone (II) by decarboxylation of its 4-carboxylic acid (II*a*) in 500-mg. quantities. Borsche and Hahn (*Annalen*, 1939, **537**, 219), on the other hand, employed a Friedel–Crafts ring closure on 4-phenyllutidine-3-carboxyl chloride (I; R′ = COCl, R = H), preparing the required acid by an unwieldy process involving regeneration from its copper salt with hydrogen sulphide. These methods proved unsatisfactory for the preparation of 1 : 3-dimethyl-2-azafluorenone (II) in quantity, the compound being ultimately prepared as follows. Method (i) : 1 : 3-dimethyl-2-azafluorenone-4-carboxylic acid (II*a*) was prepared essentially as described by Mills *et al.*




(*loc. cit.*) but was decarboxylated by heating in a neutral solvent such as liquid paraffin; large quantities of (II) were thus readily obtained for the first time. Method (ii) : ethyl 4-phenyl-

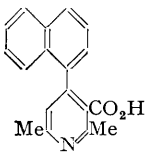
lutidine-3 : 5-dicarboxylate (I; R = R′ = $CO_2Et$) was converted into the acid ester (I; R′ = $CO_2Et$, R = $CO_2H$) by partial hydrolysis (cf. Hantzsch, *Ber.*, 1884, **17**, 2910), thence into ethyl 4-phenyl-lutidine-3-carboxylate (I; R′ = $CO_2Et$, R = H) by decarboxylation, and into the corresponding potassium salt by hydrolysis (see Experimental). Treatment of this salt with dilute sulphuric acid gave 4-*phenyl-lutidine*-3-*carboxylic acid sulphate*, from which (II) was obtained in *ca.* 90% yield by ring closure with sulphuric acid or in somewhat lower yield by the Friedel–Crafts route.

Reduction of (II) with zinc dust in aqueous alcoholic ammonia gave 1 : 3-*dimethyl*-2-*azafluorenol* (III; R = OH), characterised as the *picrate*. Further reduction with sodium in alcohol led, rather surprisingly, to the loss of the 9-hydroxyl group and the formation of 1 : 3-*dimethyl*-2-*azahexahydrofluorene* together with some 1 : 3-dimethyl-2-azafluorene. Condensation of (II) with benzaldehyde in the presence of zinc chloride gave 1-(2′-*hydroxy*-2′-*phenylethyl*)-3-*styryl*-2-*azafluorenone* (IV), but this compound proved too insoluble for biological study. Further experiments in this direction were therefore discontinued.

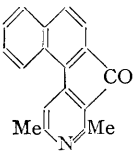
Reduction of 1 : 3-dimethyl-2-azafluorenone oxime with zinc dust and acetic acid gave 9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene* (III; R = NHAc) (20%) together with appreciable quantities of 1 : 3-dimethyl-2-azafluorene (20%). Reduction with zinc dust and acetic anhydride, however, was more satisfactory (III; R = NHAc) being obtained in nearly quantitative yield. 9-Acetamido-1 : 3-dimethyl-2-azafluorene proved remarkably resistant to hydrolysis, being recovered unchanged after prolonged heating with concentrated hydrochloric acid or with 30% sulphuric acid (see Bennett, Jewsbury, and Dupuis, *J. Amer. Chem. Soc.*, 1946, **68**, 2489). However, syrupy phosphoric acid at 200° gave smoothly 9-*amino*-1 : 3-*dimethyl*-2-*azafluorene* (III; R = $NH_2$), a strong base which rapidly absorbed carbon dioxide on exposure to air. Its structure followed from conversion into the *benzylidene*- and the *benzoyl* derivative. Nitration of (III; R = NHAc) gave a *nitro*-derivative in very high yield, to which the constitution 7-*nitro*-9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene* has been provisionally assigned (cf. Bennett *et al.*, *loc. cit.*); reduction with zinc dust and acetic anhydride gave 7(?) : 9-*diacetamido*-1 : 3-*dimethyl*-2-*azafluorene*, which could not be hydrolysed.

Some derivatives of (II) were prepared by method (ii) (above).

1-Naphthaldehyde gave 4-1′-*naphthyl-lutidine*-3-*carboxylic acid* (V), the acid chloride of which passed smoothly into a homogeneous *product*, $C_{18}H_{13}ON$, to which the constitution

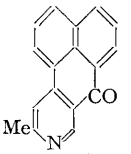


(V.)

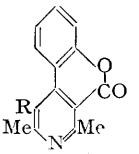


(VI.)

or



(VI*a*.)



(VII.)

1 : 3-*dimethyl*-2-*aza*-5 : 6-*benzfluorenone* (VI) has been assigned. Its alternative formulation as an azabenzanthrone (VI*a*) seems unlikely, as ring closure of aryl analogues of (V) which are substituted by a negative grouping in the position occupied by the ring nitrogen of (V) give benzfluorenones exclusively on cyclisation (Baddar and Gindy, *J.*, 1944, 450).

4-o-*Methoxyphenyl-lutidine*-3-*carboxylic acid sulphate*, prepared from *o*-anisaldehyde, gave 10-*keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene* (VII; R = H) on ring-closure of the acid chloride. The constitution assigned to this compound followed from its synthesis through 4-*o*-hydroxyphenyl-lutidine-3 : 5-dicarboxylic acid. 4-m-*Methoxyphenyl-lutidine*-3-*carboxylic acid* and 4-p-*methoxyphenyl-lutidine*-3-*carboxylic acid sulphate* behaved normally giving 8(6)-*methoxy*- and 7-*methoxy*-1 : 3-*dimethyl*-2-*azafluorenone*, respectively, which were converted into the corresponding *hydroxy*-derivatives by hydrobromic acid. Attempts to prepare 8(6)-hydroxy-1 : 3-dimethyl-2-azafluorenone directly from *m*-hydroxybenzaldehyde were unsuccessful (see Experimental).

*m*- and *p*-Nitrobenzaldehyde gave 4-m- and 4-p-*nitrophenyl-lutidine*-3-*carboxylic acid*, but all attempts at the ring closure of these compounds proved unsuccessful. 4-*p*-Benzamidophenyl-lutidine-3-carboxylic acid, isolated as the *acetate*, likewise failed to give an azafluorenone under a variety of experimental conditions. Attempts to prove the structure of the nitro-derivative of (II) described in an earlier publication (Petrow, *J.*, 1946, 888) were thus unsuccessful.

Abandonment of the work in August 1948 left certain syntheses half completed. These are recorded in the Experimental section.

## Experimental.

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

1 : 3-*Dimethyl*-2-*azafluorenone*.—(i) Finely powdered 1 : 3-dimethyl-2-azafluorenone-5-carboxylic acid (Mills, Palmer, and Tomkinson, *loc. cit.*) was rapidly added to 10 parts of well-stirred liquid paraffin maintained at 300—320°. Decarboxylation was complete in *ca.* 20 minutes. After being set aside overnight at room temperature the crystalline product was collected, washed with small quantities of ice-cold light petroleum, and recrystallised from ethanol, giving 1 : 3-dimethyl-2-azafluorenone, m. p. 159—160°, not depressed in admixture with an authentic specimen.

(ii) Ethyl 4-phenyl-lutidine-3-carboxylate (10 g.; Petrow, *loc. cit.*), potassium hydroxide (7·5 g.), and ethanol (25 ml.) were heated under reflux on the water-bath for 4 hours. After being kept at 0° for 24 hours the potassium salt was collected and dissolved in a small amount of water, and the solution made acid to Congo-red with concentrated sulphuric acid. The precipitate was collected and recrystallised from 2N-sulphuric acid. 4-*Phenyl-lutidine*-3-*carboxylic acid sulphate* formed felted needles, m. p. 256—257° (decomp.) (7·8 g., 73%) (Found : S, 6·3. $C_{14}H_{13}O_2N,\frac{1}{2}H_2SO_4$ requires S, 5·8%).

The sulphate (10 g.) and concentrated sulphuric acid (40 ml.) were heated on the water-bath for 2 hours, whereafter the solution was poured into water and made alkaline with sodium hydroxide. The precipitate was collected and recrystallised from alcohol, yielding glistening needles of 1 : 3-dimethyl-2-azafluorenone, m. p. 159—160° (Found : C, 80·3; H, 5·2. Calc. for $C_{14}H_{11}ON$ : C, 80·4; H, 5·3%), in nearly quantitative yield. The compound gave no depression in m. p. on admixture with an authentic specimen (Mills *et al.*, *loc. cit.*).

The *isethionate* separated in colourless prisms, m. p. 162·5—163° (Found : S, 9·7. $C_{14}H_{11}ON,C_2H_6O_4S$ requires S, 9·5%), from ice-cold methanol.

1 : 3-*Dimethyl*-2-*azafluoren*-9-*ol*.—1 : 3-Dimethyl-2-azafluorenone (20 g.), aqueous ammonia (500 ml.; *d* 0·88), zinc dust (150 g.), and alcohol (100 ml.) were heated under reflux for 2—3 hours. The hot mixture was filtered, the residues were washed with boiling alcohol, and the bulked filtrates were concentrated until crystallisation commenced. 1 : 3-*Dimethyl*-2-*azafluoren*-9-*ol* was collected and recrystallised from benzene; m. p. 172—173° (Found : C, 74·9; H, 6·0. $C_{14}H_{13}ON$ requires C, 74·6; H, 6·2%); yield, 14 g. (70%). The *picrate* formed yellow needles, m. p. 248—249° (Found : N, 12·7. $C_{14}H_{13}ON,C_6H_3O_7N_3$ requires N, 13·0%), from alcohol.

1 : 3-*Dimethyl*-2-*azahexahydrofluorene*.—1 : 3-Dimethyl-2-azafluorenol (20 g.) in ethanol (450 ml.) was treated with sodium (60 g.) during 1 hour under reflux. Water (500 ml.) was added and the alcohol removed on the water-bath. The oil was extracted with chloroform, and the evaporated extract taken up in alcohol and treated with picric acid (20 g.). The product which separated was identified as 1 : 3-*dimethyl*-2-*azafluorene picrate*, yellow needles from alcohol, m. p. 250° (decomp.) (Found : N, 13·1. $C_{14}H_{13}N,C_6H_3O_7N_3$ requires N, 13·2%), not depressed on admixture with an authentic specimen (see below). The picrate mother-liquors, made alkaline with sodium hydroxide solution and extracted with chloroform, gave 1 : 3-*dimethyl*-2-*azahexahydrofluorene* as a pale yellow oil (5 g., 25%), b. p. 155—160°/20 mm. (Found : C, 83·5; H, 9·4; N, 6·4. $C_{14}H_{19}N$ requires C, 83·7; H, 9·4; N, 6·9%).

1-(2′-*Hydroxy*-2′-*phenylethyl*)-3-*styryl*-2-*azafluorenone*.—1 : 3-Dimethyl-2-azafluorenone (10 g.) and benzaldehyde (12·5 ml.) were warmed on the water-bath for several hours in the presence of a little anhydrous zinc chloride, and the solid product was extracted with boiling acetone. 1-(2′-*Hydroxy*-2′-*phenylethyl*)-3-*styryl*-2-*azafluorenone* formed golden-yellow needles (4·2 g., 22%), m. p. 169—170°, from aqueous acetone (Found : C, 83·7; H, 5·0; N, 3·7. $C_{28}H_{21}O_2N$ requires C, 83·4; H, 5·2; N, 3·5%).

*Reduction of* 1 : 3-*Dimethyl*-2-*azafluorenone Oxime*.—(i) To a boiling solution of 1 : 3-dimethyl-2-azafluorenone oxime (10 g.) (Borsche and Hahn, *loc. cit.*) in glacial acetic acid (70 ml.) under reflux was added in portions zinc dust (18 g.), heating being continued for a further hour. The mixture was added to water (200 ml.), and the filtered solution treated with excess of aqueous ammonia. The precipitated solids were collected, dried, and extracted with benzene–methanol. The more sparingly soluble fraction (m. p. 260—270°) was recrystallised from alcohol, giving needles of 9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene*, m. p. 274—275° (Found : C, 76·4; H, 6·3; N, 11·2. $C_{16}H_{16}ON_2$ requires C, 76·5; H, 6·3; N, 11·1%). The benzene–methanol mother-liquors were saturated with hydrogen chloride, yielding 1 : 3-dimethyl-2-azafluorene hydrochloride, m. p. 300° after crystallisation from ethanol (Found : Cl, 15·1. Calc. for $C_{14}H_{13}N,HCl$ : Cl, 15·3%). The free base formed needles (from light petroleum), m. p. 97—98° (Found : N, 7·4. Calc. for $C_{14}H_{13}N$ : N, 7·2%), not depressed on admixture with an authentic specimen. The *picrate* formed yellow needles, m. p. 250° (decomp.) (Found : N, 13·6. $C_{14}H_{13}N,C_6H_3O_7N_3$ requires N, 13·2%), from alcohol.

(ii) A warm solution of 1 : 3-dimethyl-2-azafluorenone oxime (4·5 g.; Borsche and Hahn, *loc. cit.*) and anhydrous sodium acetate (4·5 g.) in acetic anhydride (45 g.) was treated with zinc dust (9 g.) added in portions, the reaction being allowed to moderate after each addition. The mixture was finally heated under reflux for 1 hour and then filtered hot, and the filtrate poured into ice–water (200 ml.). The solution was made alkaline with aqueous sodium hydroxide, and the bulky precipitate collected and recrystallised from aqueous alcohol. 9-Acetamido-1 : 3-dimethyl-2-azafluorene separated in long needles, m. p. 274—275° (3·6 g., 74%) (Found : C, 76·4; H, 6·5; N, 11·2. Calc. for $C_{16}H_{16}ON_2$ : C, 76·5; H, 6·3; N, 11·1%).

9-*Amino*-1 : 3-*dimethyl*-2-*azafluorene*.—9-Acetamido-1 : 3-dimethyl-2-azafluorene (15 g.) was dissolved in syrupy phosphoric acid (75 ml.) and heated in an oil-bath at 180—200° for 1 hour. The cooled solution was diluted with water and made alkaline with aqueous ammonia. The oily precipitate, which solidified when kept, was collected, washed with water, and dried *in vacuo* over phosphoric oxide. The dried material was extracted with benzene, and the benzene extract recrystallised from light petroleum at room temperature under reduced pressure. 9-*Amino*-1 : 3-*dimethyl*-2-*azafluorene* formed long white needles (11·7 g., 94%), m. p. 89°, which absorbed carbon dioxide on

exposure to the air (Found : C, 80·0; H, 6·7; N, 13·4. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7; N, 13·4%). The *dihydrochloride* formed white platelets, m. p. 260° (decomp.) (Found : Cl, 24·0. $C_{14}H_{14}N_2,2HCl$ requires Cl, 25·0%), from alcohol. The *monobenzoyl* derivative formed feathery white needles, m. p. 283° (Found : C, 80·2; H, 5·8; N, 9·2. $C_{21}H_{18}ON_2$ requires C, 80·3; H, 5·7; N, 8·9%), from alcohol. The *benzylidene* derivative formed platelets, m. p. 188° (Found : C, 84·4; H, 6·0; N, 9·7. $C_{21}H_{18}N_2$ requires C, 84·6; H, 6·0; N, 9·4%), from aqueous alcohol.

7(?)-*Nitro*-9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene*.—9-Acetamido-1 : 3-dimethyl-2-azafluorene (5 g.) dissolved in concentrated sulphuric acid (20 ml.) was treated with finely powdered potassium nitrate (2 g.) during 3 hours, the mixture being stirred mechanically at room temperature. The mixture was poured on crushed ice and made alkaline with aqueous ammonia. The precipitate was collected and extracted with a little boiling alcohol. The residue, on crystallisation from a large volume of alcohol, gave felted needles of 7-*nitro*-9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene*, m. p. 300° (decomp.) (Found : C, 64·5; H, 5·2; N, 13·6. $C_{16}H_{15}O_3N_3$ requires C, 64·8; H, 5·1; N, 14·1%), in nearly quantitative yield.

7(?) : 9-*Diacetamido*-1 : 3-*dimethyl*-2-*azafluorene*.—7(?)-Nitro-9-acetamido-1 : 3-dimethyl-2-azafluorene (2 g.), suspended in boiling acetic anhydride (80 ml.), was treated with zinc dust (4 g.) added in portions. The mixture was filtered hot and the solids were washed with acetic anhydride. The combined filtrates were decomposed with water and made alkaline with sodium hydroxide solution. The precipitated solids were collected and purified from aqueous alcohol, giving 7 : 9-*diacetamido*-1 : 3-*dimethyl*-2-*azafluorene*, ivory-coloured needles, m. p. >300° (Found : C, 69·8; H, 6·4; N, 13·6. $C_{18}H_{19}O_2N_3$ requires C, 69·9; H, 6·2; N, 13·6%).

*Ethyl* 4-1′-*Naphthyldihydrolutidine*-3 : 5-*dicarboxylate*.—1-Naphthaldehyde (13 g.), ethyl 2-aminocrotonate (11 g.), and ethyl acetoacetate (11 g.) were heated on the water-bath for 8 hours. The semi-solid mixture was triturated with hot methanol, and the crystalline residue heated under reflux with acetic anhydride (10 volumes). The solution was poured into water and made alkaline with aqueous ammonia, the precipitate being collected and recrystallised from aqueous alcohol. *Ethyl* 4-1′-*naphthyldihydrolutidine*-3 : 5-*dicarboxylate* formed cream-coloured plates, m. p. 197·5—198° (Found : C, 72·8; H, 6·8; N, 3·5. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6; N, 3·7%).

*Ethyl* 4-1′-*Naphthyl-lutidine*-3 : 5-*dicarboxylate*.—The foregoing dihydro-ester (2·5 g.) in glacial acetic acid (20 ml.) was treated at 100° with chromium trioxide (500 mg.) dissolved in a little water. After being heated for 10 minutes on the water-bath the mixture was made alkaline with aqueous ammonia, and the product extracted with chloroform and recrystallised from light petroleum (b. p. 40—60°). *Ethyl* 4-1′-*naphthyl-lutidine*-3 : 5-*dicarboxylate* formed rhombic crystals (2·1 g., 85%), m. p. 58°, b. p. 272°/20 mm. (Found : C, 73·0; H, 6·1. $C_{23}H_{23}O_4N$ requires C, 73·2; H, 6·1%).

3-*Carbethoxy*-4-1′-*naphthyl-lutidine*-5-*carboxylic Acid*.—The foregoing ester (87·5 g.) and potassium hydroxide (14 g.) were heated under reflux in ethanol (140 ml.) for 100 hours, whereafter the alcohol was removed on the water-bath, and the residual liquid diluted with water. Unchanged material separated and was removed. The filtrate was then neutralised with dilute sulphuric acid, and the precipitate collected and recrystallised from alcohol. 3-*Carbethoxy*-4-1′-*naphthyl-lutidine*-5-*carboxylic acid* formed colourless platelets (46 g., 70%), m. p. 238—239° (Found : C, 72·7; H 5·5; N, 4·5. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·4; N, 4·0%), from ethanol–light petroleum.

*Ethyl* 4-1′-*Naphthyl-lutidine*-3-*carboxylate*.—The foregoing acid ester (20 g.) was heated at 260—270° in a metal-bath for 30 minutes, and the residue distilled under reduced pressure. *Ethyl* 4-1′-*naphthyl-lutidine*-3-*carboxylate* formed a pale yellow viscous oil (14·5 g., 85%), b. p. 264—266°/20 mm. (Found : C, 78·4; H, 6·4; N, 4·9. $C_{20}H_{19}O_2N$ requires C, 78·7; H, 6·2; N, 4·6%).

4-1′-*Naphthyl-lutidine*-3-*carboxylic Acid*.—Ethyl 4-1′-naphthyl-lutidine-3-carboxylate (37·1 g.), potassium hydroxide (8 g.), and alcohol (80 ml.) were heated under reflux for 45 hours. Alcohol was removed on the water-bath, the residue dissolved in water and extracted with ether to remove unchanged material, and the aqueous solution treated with sulphuric acid (3·8 ml.). The precipitate was collected and recrystallised from alcohol–light petroleum. 4-1′-*Naphthyl-lutidine*-3-*carboxylic acid* formed colourless prismatic needles, m. p. 265° (Found : C, 77·9; H, 5·5; N, 5·1. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%). Yield, 22·6 g. (68%).

1 : 3-*Dimethyl*-2-*aza*-5 : 6-*benzfluorenone*.—The foregoing acid (2 g.) was treated with thionyl chloride (20 ml.) under reflux for 30 minutes. The excess of thionyl chloride was removed under reduced pressure, and the residue taken up in nitrobenzene (20 ml.). The mixture was treated with aluminium chloride (4 g.) and kept at 60° for 3 hours. The nitrobenzene was removed in steam, and the aqueous solution saturated with sodium acetate. The precipitate was collected and recrystallised from aqueous alcohol containing a pellet of potassium hydroxide. 1 : 3-*Dimethyl*-2-*aza*-5 : 6-*benzfluorenone* separated from benzene–ligroin in very small golden needles (1·1 g., 59%), m. p. 212—213·5° (Found : C, 83·4; H, 5·0; N, 5·4. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0; N, 5·4%). The *isethionate* formed mustard-coloured prisms, m. p. 234·5—235·5° (Found : S, 8·4. $C_{18}H_{13}ON,C_2H_6O_4S$ requires S, 8·3%), from alcohol–acetone.

4-*o*-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylic Acid*.—Ethyl 4-*o*-methoxyphenyl-lutidine-3 : 5-dicarboxylate (85 g.; Hinkel and Madel, *J.*, 1929, 752), potassium hydroxide (130 g.), and ethanol (450 ml.) were heated under reflux on the water-bath for 4 hours. After being kept at 0° for 24 hours the potassium salt was collected and dissolved in water (250 ml.), and the solution made acid to Congo-red with dilute sulphuric acid. The precipitate was collected and repeatedly crystallised from glacial acetic acid. 4-*o*-Methoxyphenyl-lutidine-3 : 5-dicarboxylic acid formed fine white crystals, m. p. 314° (decomp.), which could not be obtained analytically pure (Found : C, 61·8; H, 5·0; N, 4·5. Calc. for $C_{16}H_{15}O_5N$ : C, 63·8; H, 5·0; N, 4·7%). Yield, 53 g. (74%).

10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*-4-*carboxylic Acid*.—The foregoing acid (10 g.) was heated under reflux for 1 hour with hydrobromic acid (100 ml.; constant-boiling). The thin yellow crystals of the resulting hydrobromide were collected, suspended in water (150 ml.), and made alkaline with potassium hydroxide (4·0 g.). The mixture was filtered, the filtrate made acid

to Congo-red with dilute sulphuric acid, and the precipitate collected and recrystallised from aqueous alcohol. 10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*-4-*carboxylic acid* formed white needles, m. p. 257·5° (decomp.) (Found : C, 66·9; H, 3·7; N, 5·3. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1; N, 5·3%).

Unless otherwise stated the procedure described in detail for the 1-naphthyl series was employed in the preparation of the compounds listed below.

5-*Carbethoxy*-4-o-*methoxyphenyl-lutidine*-3-*carboxylic acid*, white crystals from dilute alcohol, m. p. 195—196° (Found : C, 65·7; H, 5·8; N, 4·6. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·3%); yield, 60%.

*Ethyl* 4-o-*methoxyphenyl-lutidine*-3-*carboxylate*, a faintly yellow viscous oil, b. p. 238°/30 mm. (Found : N, 5·4. $C_{17}H_{19}O_3N$ requires N, 4·9%); yield, 75%.

4-*o*-Methoxyphenyl-lutidine-3-carboxylic acid *sulphate*, white crystals (from alcohol–light petroleum), m. p. 170° (Found : S, 5·0. $C_{15}H_{15}O_3N,\frac{1}{2}H_2SO_4$ requires S, 5·2%); yield, 56%.

10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*.—(i) 10-Keto-1 : 3-dimethyl-9-*oxa*-2-*aza*-9 : 10-dihydrophenanthrene-5-carboxylic acid (10 g.) was heated above its m. p. for 5 minutes, and the residue crystallised from dilute acetic acid. 10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene* formed squat angular rods (5·9 g., 70%), m. p. 203—204° (Found : C, 74·5; H, 5·0; N, 6·3. $C_{14}H_{11}O_2N$ requires C, 74·7; H, 4·9; N, 6·2%).

(ii) 4-*o*-Methoxyphenyl-lutidine-3-carboxylic acid sulphate (10 g.) and thionyl chloride (50 ml.) were heated under reflux for 10 minutes. Excess of thionyl chloride was removed under reduced pressure, and the residue dissolved in nitrobenzene (80 ml.). The solution was treated with aluminium chloride (9 g.) and warmed for 2 hours at 50°. The nitrobenzene was removed in steam, and the aqueous residues saturated with sodium acetate. The precipitate was collected and recrystallised from aqueous alcohol, giving 10-*keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*, white crystals, m. p. 203—204° (Found : C, 74·3; H, 5·0; N, 6·4. Calc. for $C_{14}H_{11}O_2N$ : C, 74·7; H, 4·9; N, 6·2%). The compound gave no depression of melting point on admixture with a specimen prepared by method (i).

*Ethyl* 4-m-*Acetoxyphenyldihydrolutidine*-3 : 5-*dicarboxylate*.—Ethyl 4-*m*-hydroxyphenyldihydrolutidine-3 : 5-dicarboxylate (100 g.) (Hinkel and Madel, *loc. cit.*) was heated under reflux with acetic anhydride (250 ml.) for 30 minutes, and the cooled mixture decomposed with water. The oily precipitate solidified when kept and was recrystallised from aqueous alcohol. *Ethyl* 4-m-*acetoxyphenyl-dihydrolutidine*-3 : 5-*dicarboxylate* (105 g., 96%) had m. p. 125—126° (Found : C, 64·6; H, 6·5; $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5%).

*Ethyl* 4-m-*Acetoxyphenyl-lutidine*-3 : 5-*dicarboxylate*.—The foregoing ester (10·5 g.) in glacial acetic acid (25 ml.) was treated with chromium trioxide (2·1 g.) in water (5 ml.) and glacial acetic acid (5 ml.). The mixture was warmed on the water-bath for 10 minutes and made alkaline with aqueous ammonia. The oily precipitate was recrystallised from aqueous methanol, giving *ethyl* 4-m-*acetoxyphenyl-lutidine*-3 : 5-*dicarboxylate*, m. p. 98° (Found : C, 65·4; H, 6·2; N, 3·8. $C_{21}H_{23}O_6N$ requires C, 65·5; H, 6·0; N, 3·6%); yield, 9·5 g. (90%).

*Ethyl* 4-m-*Hydroxyphenyl-lutidine*-3 : 5-*dicarboxylate*.—The foregoing ester (30 g.) and potassium hydroxide (7·5 g.) were heated under reflux in alcohol (250 ml.) for 3 hours. The solvent was removed on the water-bath, and the residue taken up in water and filtered. The clear filtrate was acidified with acetic acid, and the precipitate collected and recrystallised from aqueous alcohol. *Ethyl* 4-m-*hydroxyphenyl-lutidine*-3 : 5-*dicarboxylate* had m. p. 180—181° (Found : C, 66·6; H, 6·3; N, 4·3. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2; N, 4·1%); yield, 23 g. (88%).

5-*Carbethoxy*-4-m-*hydroxyphenyl-lutidine*-3-*carboxylic acid*, m. p. 279° (from alcohol) (Found : C, 64·9; H, 5·5; N, 4·6. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4; N, 4·5%) (yield, 70%), and *ethyl* 4-m-*hydroxyphenyl-lutidine*-3-*carboxylate*, m. p. 164—165° (from acetone–light petroleum) (Found : C, 70·9; H, 6·4; N, 5·2. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·4; N, 5·2%) (yield, 47%), were also prepared.

*Ethyl* 4-m-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylate*.—Ethyl 4-*m*-hydroxyphenyl-lutidine-3 : 5-dicarboxylate (50 g.) was dissolved in a solution of potassium hydroxide (15 g.) in water (500 ml.). The filtered solution was treated with methyl sulphate (25 ml.), added in portions with shaking during 40 minutes. After the mixture had been kept overnight at room temperature the precipitate was collected and crystallised from aqueous alcohol. *Ethyl* 4-m-*methoxyphenyl-lutidine*-3 : 5-*dicarboxylate* melted at 70° (Found : C, 67·0; H, 6·3; N, 4·0. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4; N, 3·9%) (yield, 50 g.; 94%).

The following were also obtained. 5-*Carbethoxy*-4-m-*methoxyphenyl-lutidine*-3-*carboxylic acid* platelets (from aqueous alcohol), m. p. 195° (Found : C, 65·4; H, 5·9; N, 4·7. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·3%) (yield, 61%); *ethyl* 4-m-*methoxyphenyl-lutidine*-3-*carboxylate*, a nearly colourless viscous oil, b. p. 245°/40 mm. (Found : N, 5·2. $C_{17}H_{19}O_3N$ requires N, 4·9%) (yield, 77%); 4-m-*methoxyphenyl-lutidine*-3-*carboxylic acid*, m. p. 261° (decomp.) (from aqueous spirit) (Found : C, 69·6; H, 6·0; N, 5·6. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8; N, 5·5%) (yield, 42%); 6(8)-*methoxy*-1 : 3-*dimethyl*-2-*azafluorenone*, faintly yellow crystals [from light petroleum (b. p. 80/100°)], m. p. 141° (Found : C, 75·3; H, 5·4; N, 5·8. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%) (yield, 65%).

6(8)-*Hydroxy*-1 : 3-*dimethyl*-2-*azafluorenone*.—The foregoing compound (2 g.) was heated under reflux with 50% hydrogen bromide (50 ml.) for 1 hour. The yellow hydrobromide was collected and dissolved in sodium hydroxide solution, and the mixture saturated with carbon dioxide. The precipitate was collected and crystallised from alcohol, giving 6(8)-*hydroxy*-1 : 3-*dimethyl*-2-*azafluorenone*, yellow needles, m. p. >300° (Found : C, 75·0; H, 5·1. $C_{14}H_{11}O_2N$ requires C, 74·7; H, 4·9%), in nearly quantitative yield.

4-p-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylic Acid*.—Ethyl 4-*p*-methoxyphenyl-lutidine-3 : 5-dicarboxylate (55 g.; Hinkel and Madel, *loc. cit.*) was heated under reflux with potassium hydroxide (75 g.) and ethanol (250 ml.) for 3 hours. After the mixture had been set aside at 0° the potassium

salt was collected, dissolved in water, and acidified with 2N-sulphuric acid (70 ml.). The precipitate was collected and recrystallised from dilute acetic acid. 4-p-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylic acid* formed prismatic needles, m. p. 295—296° (decomp.) (Found : C, 63·8; H, 4·9. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0%).

Also prepared were 5-*carbethoxy*-4-p-*methoxyphenyl-lutidine*-3-*carboxylic acid* octahedra (from aqueous alcohol), m. p. 189·5—191·5° (Found : C, 65·7; H, 5·8. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8%), ethyl 4-*p*-methoxyphenyl-lutidine-3-carboxylate, a faintly yellow viscous oil, b. p. 218—219°/20 mm. (Found : N, 5·2. Calc. for $C_{17}H_{19}O_3N$ : N, 4·9%) (cf. Borsche and Hahn, *loc. cit.*), 4-*p*-methoxyphenyl-lutidine-3-carboxylic acid, isolated as the *sulphate*, m. p. 161—162° (from alcohol) (Found : S, 9·8. $C_{15}H_{15}O_3N,H_2SO_4$ requires S, 9·0%) (yield, 51%), 7-methoxy-1 : 3-dimethyl-2-azafluorenone, yellow needles, m. p. 137—138° (from alcohol) (Found : N, 6·2. Calc. for $C_{15}H_{15}O_2N$ : N, 5·9%) (Borsche and Hahn, *loc. cit.* give m. p. 131°) (yield, 75%), 7-*hydroxy*-1 : 3-*dimethyl*-2-*azafluorenone*, yellow crystals, m. p. > 300° (from alcohol) (Found : C, 74·5; H, 5·1; N, 6·4. $C_{14}H_{11}O_2N$ requires C, 74·7; H, 4·9; N, 6·2%) (yield, nearly quantitative), 5-*carbethoxy*-4-m-*nitrophenyl-lutidine*-3-*carboxylic acid* (prepared from the di-ester; Hinkel, Ayling, and Morgan, *J.*, 1931, 1840), m. p. 220·5° (from aqueous alcohol) (Found : C, 59·3; H, 4·8; N, 8·3. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·1%) (yield, 55%), *ethyl* 4-m-*nitrophenyl-lutidine*-3-*carboxylate picrate*, deep-yellow prisms (from methanol), m. p. 160° (Found : N, 13·4. $C_{16}H_{16}O_4N_2,C_6H_3O_7N_3$ requires N, 13·2%) (the base crystallised after many months, forming white needles, m. p. 57°), 4-m-*nitrophenyl-lutidine*-3-*carboxylic acid*, nearly white crystals (from aqueous alcohol), m. p. 263° (decomp.) (Found : N, 10·5. $C_{14}H_{12}O_4N_2$ requires N, 10·3%) (yield, 96%), 5-*carbethoxy*-4-p-*nitrophenyl-lutidine*-3-*carboxylic acid* (prepared from the di-ester; Hinkel, Ayling, and Morgan, *loc. cit.*), yellow needles (from methanol), m. p. 232° (Found : C, 59·3; H, 4·8; N, 8·4. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·2%) (yield, 69%), *ethyl* 4-p-*nitrophenyl-lutidine*-3-*carboxylate picrate*, stout yellow needles (from aqueous spirit), m. p. 201—203° (Found : N, 13·5. $C_{16}H_{16}O_4N_2,C_6H_3O_7N_3$ requires N, 13·2%) (yield, 72%), and 4-p-*nitrophenyl-lutidine*-3-*carboxylic acid*, yellow crystals, m. p. 274·5° (from alcohol) (Found : N, 10·5. $C_{14}H_{12}O_4N_2$ requires N, 10·3%) (yield, 95%).

*Ethyl* 4-p-*Benzamidophenyl-lutidine*-3-*carboxylate.*—Ethyl 4-*p*-nitrophenyl-lutidine-3-carboxylate (5 g.), reduced iron (10 g.), and 70% ethanol (80 ml.) were heated under reflux for 1 hour. The mixture was filtered hot and the filtrate evaporated to dryness on the water-bath under reduced pressure. The glassy residue was dissolved in pyridine (20 ml.) and treated with benzoyl chloride (2·4 g.). After being heated for 1 hour on the water-bath the mixture was diluted with water, and the precipitate collected and crystallised from light petroleum (b. p. 80—100°). *Ethyl* 4-p-*benzamidophenyl-lutidine*-3-*carboxylate* formed platelets, m. p. 144—145° (Found : C, 73·4; H, 5·9; N, 7·6. $C_{23}H_{22}O_3N_2$ requires C, 73·8; H, 5·9; N, 7·5%) (yield, 5 g., 80%).

4-p-*Benzamidophenyl-lutidine*-3-*carboxylic Acid.*—The foregoing ester (75 g.) and potassium hydroxide (12 g.) were heated under reflux in alcohol (300 ml.) for 70 hours. The alcohol was removed on the water-bath, and the residue diluted with water and filtered. The filtrate was acidified with concentrated sulphuric acid (5·7 ml.), and the precipitate collected and crystallised from glacial acetic acid. 4-*p*-Benzamidophenyl-lutidine-3-carboxylic acid separated as the *acetate*, m. p. 318° (decomp.) (Found : C, 67·0; H, 5·4; N, 6·8. $C_{21}H_{18}O_3N_2,CH_3{\cdot}CO_2H$ requires C, 68·0; H, 5·6; N, 6·9%).

*Ethyl* 4-p-*tolyl-lutidine*-3 : 5-*dicarboxylate*, a pale yellow viscous oil, b. p. 220°/20 mm. (Found : C, 70·4; H, 6·7; N, 4·3. $C_{20}H_{23}O_4N$ requires C, 70·7; H, 7·0; N, 4·3%) (yield, 72%), 5-*carbethoxy*-4-p-*tolyl-lutidine*-3-*carboxylic acid*, m. p. *ca.* 177°, decomp. 230° (from benzene–light petroleum) (Found : C, 69·0; H, 6·5; N, 4·4. $C_{18}H_{19}O_4N$ requires C, 69·1; H, 6·1; N, 4·4%), ethyl 3-acetyl-4-phenyl-lutidine-5-carboxylate [prepared in improved yield by oxidation of the dihydro-ester (Knoevenagel and Rauschhaupt, *Ber.*, 1898, **31**, 1027)], m. p. 88° (from light petroleum) (Found : C, 73·4; H, 6·6; N, 4·5. Calc. for $C_{18}H_{19}O_3N$ : C, 72·8; H, 6·4; N, 4·7%) (yield, 80%), and 3-*acetyl*-4-*phenyl-lutidine*-5-*carboxylic acid*, m. p. 264° (decomp.) (from benzene–methanol) (Found : C, 71·9; H, 5·6; N, 5·1. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6; N, 5·2%) (yield, 61%), were also synthesised.

*Ethyl* 4-(4′-*Acetoxy*-3′-*methoxyphenyl*)*dihydrolutidine*-3 : 5-*dicarboxylate.*—The corresponding 4′-hydroxy-compound (150 g.; Hinkel, Ayling, and Morgan, *J.*, 1935, 817) and acetic anhydride (500 ml.) were warmed on the water-bath for 1 hour. The mixture was poured into water, and the oily precipitate, which solidified when kept, collected and recrystallised from aqueous alcohol. *Ethyl* 4-(4′-*acetoxy*-3′-*methoxyphenyl*)*dihydrolutidine*-3 : 5-*dicarboxylate* formed crystals, m. p. 132—133° (Found : C, 63·1; H, 6·8. $C_{22}H_{27}O_7N$ requires C, 63·4; H, 6·5%); yield, 150 g. (90%).

*Ethyl* 4-(4′-*Acetoxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate.*—The foregoing dihydro-compound (87 g.) in acetic acid (200 ml.) was treated with chromium trioxide (14 g.) in acetic acid (100 ml.). The mixture was warmed on the water-bath for 30 minutes, diluted with water, and made alkaline with aqueous ammonia. The precipitate was collected, dried, and recrystallised from light petroleum–acetone. *Ethyl* 4-(4′-*acetoxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate* melted at 148° (Found : C, 63·3; H, 6·3. $C_{22}H_{25}O_7N$ requires C, 63·6; H, 6·0%); yield, 70 g. (80%).

*Ethyl* 4-(4′-*Hydroxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate.*—The foregoing compound (65 g.) in alcohol (500 ml.) was treated with potassium hydroxide (17·5 g.), and the mixture heated under reflux for 1 hour. The solvent was removed on the water-bath, and the residue diluted with water and made acid with acetic acid (17·5 ml.). The oily precipitate, which solidified when kept, was collected and crystallised from aqueous alcohol. *Ethyl* 4-(4′-*hydroxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate* melted at 160—161° (Found : C, 64·4; H, 6·3. $C_{20}H_{23}O_6N$ requires C, 64·4; H, 6·2%); yield, 58 g. (quantitative).

*Ethyl* 4-(3′ : 4′-*Dimethoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate.*—The foregoing hydroxy-compound (45 g.), water (400 ml.), and potassium hydroxide (7·5 g.), were treated with methyl sulphate (11·3 ml.) added in portions with shaking. The precipitate was collected, washed, dried, and crystallised from aqueous alcohol. *Ethyl* 4-(3′ : 4′-*dimethoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate* formed rhombic plates,

m. p. 101—102° (Found : C, 65·0; H, 6·3. $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5%); yield, 41 g. (88%).

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QUEEN MARY COLLEGE, UNIVERSITY OF LONDON, E.1. [*Received, March 26th,* 1949.]