[CONTRIBUTION NO. 235 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

DERIVATIVES OF 1,3-DIMETHYL-2-AZAFLUORENE (1,3-DIMETHYL-9-INDENO[2,1-*c*]PYRIDINE)

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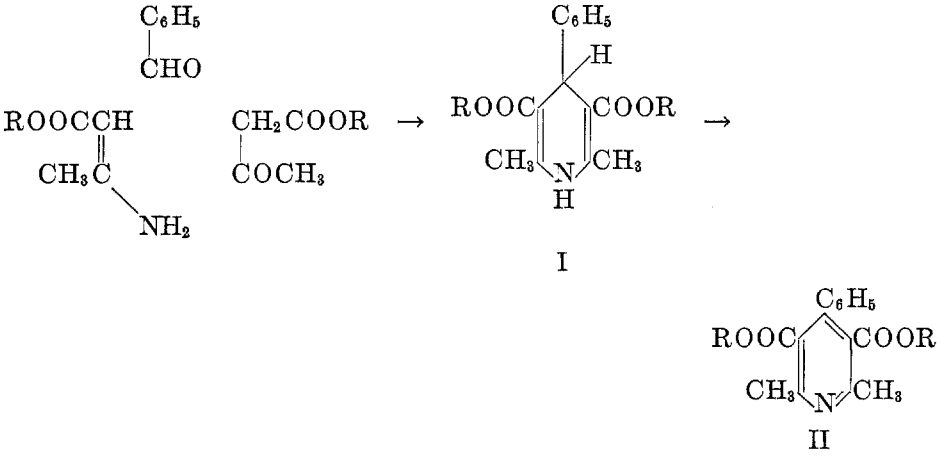
The chemistry of indeno[2,1-*c*]pyridine[1] or, as it has been previously called, pyridofluorene, azafluorene, or pyridindene had its inception in the work of Mills, Palmer, and Tomkinson (1) who first synthesized 2-azafluorene and some of its derivatives in an effort to throw some light on the isomerism occurring among certain 9-substituted derivatives of fluorene. Though they failed in their immediate objective, they did open a new field which was subsequently expanded by Borsche and Hahn (2) and more lately by work in these laboratories (3) which resulted in the discovery of potent antihistaminics. Borsche and Hahn, incidentally, made no mention of the English workers who preceded them by about 14 years.

The present study may be conveniently divided into two parts. Part A concerns 1,3-dimethyl-4-carboxy-9-oxo-2-azafluorene and its esters, and Part B concerns 1,3-dimethyl-9-oxo-2-azafluorene and the compounds derived from it. The starting compounds for both series were prepared by reacting benzaldehyde, acetoacetic ester, and β-aminocrotonic ester according to the procedure developed by Schiff and Puliti (4), Hantzsch (5), and Kirchner (6). The resulting 3,5-dicarbethoxy-4-phenyldihydrolutidine (I) was oxidized with nitric acid (7) to give 3,5-dicarbethoxy-4-phenyllutidine (II). At this point the procedures were



I

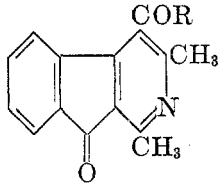
II

varied, depending upon which series was to be synthesized.

[1] Though the name indeno[2,1-*c*]pyridine is the official designation, for the sake of simplicity in nomenclature the term azafluorene is used throughout this paper.

PART A

For the preparation of the 4-substituted derivatives of Part A, compound II was saponified to 3,5-dicarboxy-4-phenyllutidine (III), and the latter was cyclodehydrated to 1,3-dimethyl-4-carboxy-9-oxo-2-azafluorene (IV) (1).

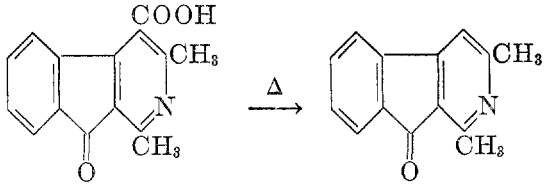


IV R = OH VI R = OC_2H_5
V R = Cl VII R = $OCH_2CH_2N(CH_3)_2$

Treatment of compound IV with thionyl chloride gave the corresponding acid chloride (V) which, *without purification*, was reacted with ethanol and with β-dimethylaminoethanol to give 1,3-dimethyl-4-carbethoxy-9-oxo-2-azafluorene (VI) and 1,3-dimethyl-4-(β-dimethylaminoethyl)carboxy-9-oxo-2-azafluorene (VII) respectively.

PART B

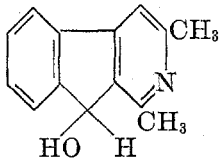
The compounds of Part B were derived from 1,3-dimethyl-9-oxo-2-azafluorene (VIII). This parent structure was first synthesized by Mills, Palmer, and Tomkinson (1) who obtained it in poor yield by the destructive distillation of 2-g. batches of the 4-carboxy derivative (IV). Their method was unsuited to the preparation of large quantities of the material, so recourse was taken to the more involved procedure used by Petrow (8). Subsequently, however, it was discovered that the decarboxylation of compound IV could be readily effected in good yield without limiting the size of the batch. This improved procedure for the preparation of compound VIII is described in the experimental part.



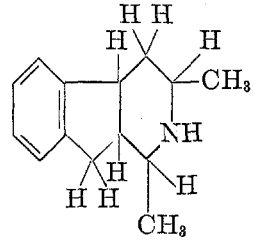
IV VIII

Catalytic reduction of VIII resulted in five different compounds, depending upon the catalyst used and the conditions under which the reduction was carried out. When an ethanolic solution of the azafluorenone was reduced with platinum catalyst at room temperature and about 50 p.s.i. of hydrogen, the keto group was reduced to a hydroxyl group and 1,3-dimethyl-9-hydroxy-2-azafluorene (XIV) was obtained. Upon increasing the temperature to 100° and the pressure to 250 p.s.i., using the same catalyst and solvent, the pyridine ring was also reduced to give 1,3-dimethyl-9-hydroxy-1,2,3,4,4a,9a-hexahydro-2-azafluorene

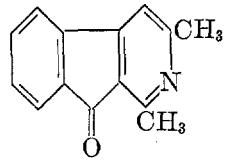
(XV). Under essentially the same conditions but with the solvent changed to dilute hydrochloric acid, even the hydroxyl group was reduced, yielding 1,3-dimethyl-1,2,3,4,4a,9a-hexahydro-2-azafluorene (XVI). It is interesting to note that the hydrochloride of XVI may be recrystallized from benzene. With Raney nickel as the catalyst and ethanol as solvent the keto group was completely reduced to give 1,3-dimethyl-2-azafluorene (XVII) (1, 2) even at room temperature and 50 p.s.i. When, however, the temperature was raised to about 90° and the pressure to 350 p.s.i., the reduction tended to continue and hydrogen was introduced into the pyridine ring. At any rate, under these latter conditions, a compound was isolated whose analysis corresponded to 1,3-dimethyl-(1,2,3,4?)-tetrahydro-2-azafluorene (XVIII).



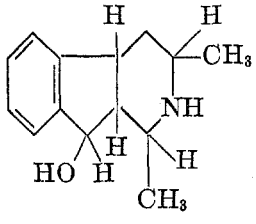
XIV



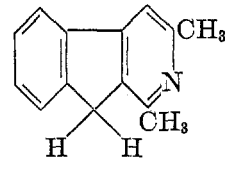
XVI



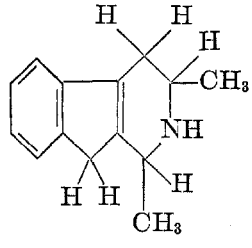
VIII



XV

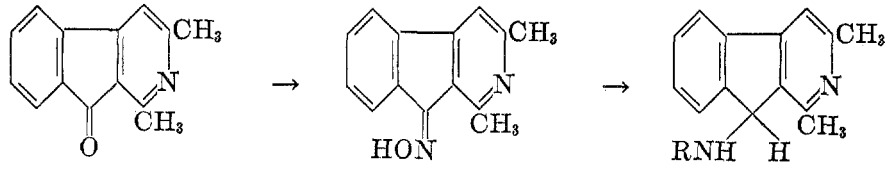


XVII



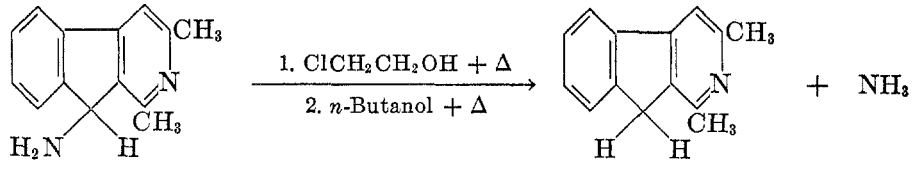
XVIII

Compound VIII on treatment with hydroxylamine readily gave the oxime (XIX) (2) which was catalytically reduced to 1,3-dimethyl-9-amino-2-azafluorene (XX).

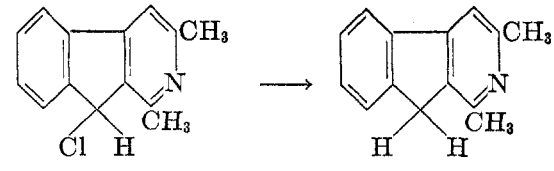


VIII XIX XX R = H; XXI R = $CONH_2$; XXII R = $COOC_2H_5$

With potassium cyanate and ethyl chloroformate the 9-amino derivative (XX) was easily converted to 1,3-dimethyl-9-ureido-2-azafluorene (XXI) and 1,3-dimethyl-9-carbethoxyamino-2-azafluorene (XXII) respectively. When, however, compound XX was treated with β-dimethylaminoethyl chloride, the desired ethylene diamine was not obtained. Accordingly, the amine (XX) was refluxed with ethylene chlorohydrin. Instead of the anticipated 9-(β-hydroxyethylamino) derivative, a compound was obtained which was shown to be 1,3-dimethyl-2-azafluorene (XVII). This unexpected result proved to be due to the extreme lability of the amino group in position 9, since it was subsequently shown that NH_3 was liberated during the reaction and that the same result could be obtained by refluxing the amine (XX) with a higher-boiling alcohol, such as *n*-butanol.



This lability was not, however, limited to the amino group. The chloro group in 1,3-dimethyl-9-chloro-2-azafluorene (XXIII), prepared from the 9-hydroxy derivative (XIV) by means of thionyl chloride, could be removed in a similar manner.

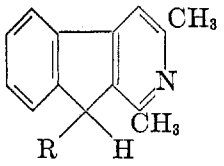


XXIII XVII

Moreover, when the 9-chloro compound (XXIII) was heated in a melting point apparatus at the usual rate, only partial melting took place at 113–115°, whereas on very rapid heating a clear melt was first obtained which partially solidified on further heating. It is highly probable that the incomplete melt is due to the partial conversion of the 9-chloro compound to the hydrochloride of 1,3-

dimethyl-2-azafluorene (XVII). It is also probably significant that this last conversion can be readily effected at room temperature with Raney nickel and hydrogen at 30 p.s.i.

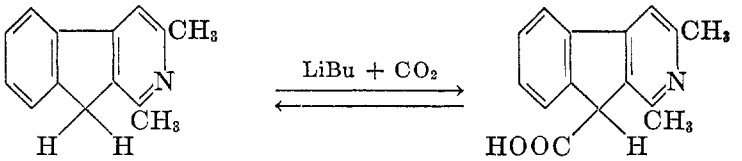
The preparation of 1,3-dimethyl-9-(β-hydroxyethylamino)-2-azafluorene (XXIV) was finally achieved in two ways, namely, by condensing the amine (XX) with ethylene chlorohydrin in dilute isopropanol in the presence of magnesium oxide and by condensing the chloro compound (XXIII) with ethanolamine. Compound XXIV was then converted to 1,3-dimethyl-9-(β-chloroethylamino)-2-azafluorene (XXV) which on treatment with dimethylamine and diethylamine gave 1,3-dimethyl-9-(β-dimethylaminoethylamino)-2-azafluorene (XXVI) and 1,3-dimethyl-9-(β-diethylaminoethylamino)-2-azafluorene (XXVII) respectively.



XX R = NH_2 XXV R = $NHCH_2CH_2Cl$
XXIII R = Cl XXVI R = $NHCH_2CH_2N(CH_3)_2$
XXIV R = $NHCH_2CH_2OH$ XXVII R = $NHCH_2CH_2N(C_2H_5)_2$
XXVIII R = $OOCCH_2Cl$

In an effort to obtain a dialkylaminoalkyl ester of 1,3-dimethyl-9-hydroxy-2-azafluorene (XIV), the latter was treated with chloroacetyl chloride to give 1,3-dimethyl-9-β-chloroacetoxy-2-azafluorene (XXVIII). However, treatment of the chloroacetoxy derivative with dimethylamine did not give the desired compound. Instead, saponification took place and the 9-hydroxy compound (XIV) was regenerated.

Several attempts were also made to prepare 1,3-dimethyl-9-carboxy-2-azafluorene (XXIX) by the action of butyllithium and CO_2 on 1,3-dimethyl-2-azafluorene (XVII). A compound was obtained which possessed the anticipated properties of the carboxy derivative. Upon standing at room temperature for several hours, however, the compound could no longer be dissolved in alkali, and on qualitative analysis, it was shown to contain 1,3-dimethyl-2-azafluorene (XVII). It was apparent, therefore, that the carboxy group in position 9 was extremely labile and that the compound decomposed spontaneously to give CO_2 and the reduced azafluorene (XVII). This behavior was completely in keeping with the prior observations on the 9-amino and 9-chloro derivatives. Because of its instability, the compound believed to be the 9-carboxy derivative could not be purified for analyses.



XXIX

Acknowledgment. The authors wish to acknowledge their indebtedness to Dr. A. Steyermark and his staff for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

I. *3,5-Dicarbethoxy-4-phenyldihydrolutidine.* Benzaldehyde (590 g.), acetoacetic ester (737 g.), and β-aminocrotonic ester (737 g.) were reacted according to the procedure developed by Schiff and Puliti (4), Hantzsch (5), and Kirchner (6). Yield of the crude product after one recrystallization from methanol was 1440 g.; m.p. *ca.* 153° [m.p. 156–157° (4)]. The compound was used in experiment II without further purification.

II. *3,5-Dicarbethoxy-4-phenyllutidine.* Compound I was oxidized by a modification of the method described in *Organic Syntheses*, Collective Volume II, 214. Since use of the method described there would be dangerous, the modified procedure is given here in detail.

To a mixture of 1429 g. of water, 378 g. of concentrated nitric acid (*d.* 1.42), and 422 g. of concentrated sulfuric acid (*d.* 1.84) in a 12-liter flask was added portionwise with stirring and shaking 1371 g. of 3,5-dicarbethoxy-4-phenyldihydrolutidine. The reaction mixture frothed vigorously and heated spontaneously. When the addition was complete, the mixture was heated on the steam-bath for a short while to complete solution and was then cooled. To the cooled solution was added 5260 g. of ice and finally sufficient concentrated ammonium hydroxide to make the mixture strongly alkaline. A gummy precipitate appeared which rapidly crystallized. The 3,5-dicarbethoxy-4-phenyllutidine on recrystallization from dilute methanol melted at 60–61° [m.p. 66–67° (4)]. Yield, 1110 g.

III. *3,5-Dicarboxy-4-phenyllutidine.* The diester II (282 g.) was saponified according to the method of Mills, Palmer, and Tomkinson (1) to yield 208 g. of the diacid which melted with decomposition at 287–288° [m.p. 296° (1)].

IV. *1,3-Dimethyl-4-carboxy-9-oxo-2-azafluorene.* This compound was obtained in the form of its sulfate salt by a slight modification of the Mills, Palmer, and Tomkinson method (1). A mixture of 86 g. of the diacid (II) and 160 cc. of concentrated sulfuric acid was heated at 130° for 10 hours. The mixture was cooled and then diluted with 160 g. of ice. On further cooling and scratching, 84 g. of the sulfate salt of 1,3-dimethyl-4-carboxy-9-oxo-2-azafluorene precipitated out; m.p. 263° [m.p. 275–276° (1)]. It was noted that the sulfate salt readily dissolved in hot water and that the resulting solution on cooling yielded a precipitate which no longer dissolved in hot water and which decomposed at 272–273°. On analysis, the hot-water-insoluble material proved to be the free base [m.p. 280.5° (1)]. It is evident, therefore, that the sulfate salt readily hydrolyzes in hot water.

Anal. Calc'd for $C_{15}H_{11}NO_3$: C, 71.1; H, 4.4.

Found: C, 71.0; H, 4.8.

The *free base* was most conveniently prepared by dissolving the sulfate salt in dilute sodium hydroxide and precipitating the base with glacial acetic acid.

V. *1,3-Dimethyl-4-chloroformyl-9-oxo-2-azafluorene.* A mixture of 5 g. of the acid IV and 20 cc. of thionyl chloride was refluxed for about 3 hours. The thionyl chloride was then recovered under a vacuum to leave a solid residue of crude acid chloride which was used as such without further purification.

VI. *1,3-Dimethyl-4-carbethoxy-9-oxo-2-azafluorene.* About 5 g. of crude acid chloride V was refluxed with an excess of ethanol for several hours (until solution took place). The ethanol solution was decolorized with Nuchar and then diluted with water to yield yellow needles of 1,3-dimethyl-4-carbethoxy-9-oxo-2-azafluorene which melted at 112–113°.

Anal. Calc'd for $C_{17}H_{15}NO_3$: C, 72.6; H, 5.3.

Found: C, 72.5; H, 5.4.

VII. *1,3-Dimethyl-4-(β-dimethylaminoethyl)carboxy-9-oxo-2-azafluorene.* To 20 cc. of dimethylaminoethanol was added portionwise about 10 g. of crude acid chloride V. The mixture was then heated at 110–120° for one hour, at the end of which time the excess of dimethylaminoethanol was removed by distillation under a vacuum. The crystalline residue was dissolved in cold, dilute hydrochloric acid, and the ester was precipitated with a slight

excess of cold, dilute sodium hydroxide. Recrystallization from dilute 2-propanol and then from dilute methanol gave golden flakes of 1,3-dimethyl-4-(β-dimethylaminoethyl)carboxy-9-oxo-2-azafluorene which melted at 125–126°.

Anal. Calc'd for $C_{19}H_{20}N_2O_3$: C, 70.4; H, 6.2; N, 8.6.

Found: C, 70.2; H, 6.0; N, 8.2.

VIII. *1,3-Dimethyl-9-oxo-2-azafluorene.* (A) This compound was most conveniently prepared from 1,3-dimethyl-4-carboxy-9-oxo-2-azafluorene (IV) by the following improved procedure. The free base of compound IV (77 g.) was heated at 280–290° until all the CO_2 had come off. The hot residue was then distilled under a water-pump vacuum using a short, wide air condenser to prevent clogging, since the yellow distillate tended to solidify in the condenser. Yield, 43 g. of 1,3-dimethyl-9-oxo-2-azafluorene, m.p. 155–156° [m.p. 158° (1) and 154–155° (2)].

(B) Before the development of the above improved method, compound VIII was prepared from 3-chloroformyl-4-phenyllutidine (XIII) according to a modification of the Borsche and Hahn procedure (2). The crude chloroformyl derivative, prepared in experiment XIII, was dissolved in 1600 cc. of dry nitrobenzene. The solution was cooled to 10°, and 132 g. of anhydrous aluminum chloride was added in portions, keeping the temperature between 20–25° during the addition. The mixture was then warmed to 45° and kept at that temperature for about 12 hours. At the end of that time the mixture was extracted six times with a total of 3 liters of water. The aqueous extract was washed with ether and treated with an excess of sodium acetate to yield 45 g. of a white, crystalline product, m.p. 155°.

IX. *3-Carboxy-4-phenyl-5-carbethoxylutidine.* A mixture of 1110 g. of compound II, 224 g. of KOH, and 5 liters of 95% ethanol was reacted according to the method of Hantzsch (5) to yield 762 g. of the desired monoester which melted at 177–179° without purification [m.p. 179–180° (5)]. About 173 g. of unreacted diester II was recovered for reprocessing.

X. *4-Phenyllutidine.*

XI. *3-Carbethoxy-4-phenyllutidine.* Compound IX (669 g.) was thermally decomposed according to the method of Hantzsch (5) to yield 361 g. of crude distillate. Upon redistillation at atmospheric pressure, two fractions were obtained. The first of these came over at 281–283° as a pale yellow oil which solidified to a white solid, m.p. 59–60°; yield 144 g. The compound could not be saponified and gave a picrate which melted at 230–232°. It was, therefore, 4-phenyllutidine (X); m.p. 54.5–55° (9); m.p. 58–59° (10); b.p.$_{731}$ 287° (9). *Picrate:* m.p. 230° (9, 10).

The second fraction came over at 310–320° and consisted of 3-carbethoxy-4-phenyllutidine (XI). The yield was approximately 200 g.; b.p. 316–320° (5).

In general practice, the original crude distillate was not fractionated but was used as such in experiment XII.

XII. *3-Carboxy-4-phenyllutidine hydrochloride.* The crude distillate, obtained from the thermal decomposition of 882 g. of compound IX, (525 g.) was refluxed for about 12 hours with 1900 cc. of 95% ethanol containing 172 g. of potassium hydroxide. The alcohol was then removed, and the residue was treated with water to yield an aqueous and an oily phase. The oil which consisted of 4-phenyllutidine (X) was removed by extraction with ether, and the aqueous layer was then strongly acidified with concentrated hyrochloric acid and finally evaporated to dryness. The dry crystalline residue was purified by solution in 2-propanol and reprecipitation with ethyl acetate. The desired 3-carboxy-4-phenyllutidine hydrochloride was obtained in the form of colorless prisms and plates which decomposed at 236–241°.

XIII. *3-Chloroformyl-4-phenyllutidine.* A mixture of 105 g. of 3-carboxy-4-phenyllutidine hydrochloride (XII) and 500 cc. of thionyl chloride was heated to solution. The thionyl chloride was then removed to leave the crude chloroformyl derivative as a dark colored residue. The crude product was used as such in experiment VIII B.

XIV. *1,3-Dimethyl-9-hydroxy-2-azafluorene.* To a suspension of 14.6 g. of the keto compound VIII in 130 cc. of ethanol was added 200 mg. of platinum oxide, and the whole was shaken at room temperature with hydrogen at 50 p.s.i. The ketone went into solution as the reduction proceeded. When no further hydrogen was taken up, the reaction mixture

was filtered, concentrated to about ½ volume, and treated with an excess of water. The precipitated 1,3-dimethyl-9-hydroxy-2-azafluorene was recrystallized from dilute methanol to yield 12 g. of white needles which melted over a wide range. The variation in different samples covered the range from about 140–160° due no doubt to the presence of optical isomers since carbon 9 is asymmetric.

Anal. Calc'd for $C_{14}H_{13}NO$: C, 79.6; H, 6.2.

Found: C, 79.6; H, 6.0.

Oxalate: dec. 154–163°. *Hydrochloride:* dec. 216–220°. *Picrate:* m.p. 217–222°.

XV. *1,3-Dimethyl-9-hydroxy-1,2,3,4,4a,9a-hexahydro-2-azafluorene.* To 4.18 g. of the ketone VIII in 50 cc. of ethanol was added 250 mg. of platinum oxide, and the mixture was reduced in a shaking autoclave at 100° and about 250 p.s.i. of hydrogen. When the hydrogen uptake ceased, the mixture was filtered and evaporated to dryness. The residual oil solidified on scratching and was recrystallized from dilute ethanol to yield long, fine, colorless needles of the hexahydro derivative; m.p. 157–158°.

Anal. Calc'd for $C_{14}H_{19}NO$: C, 77.4; H, 8.8.

Found: C, 77.2; H, 8.6.

XVI. *1,3-Dimethyl-1,2,3,4a,9a-hexahydro-2-azafluorene.* A solution of 6.27 g. of ketone VIII in 100 cc. of dilute hydrochloric acid was reduced with hydrogen and a platinum catalyst in a shaking autoclave at 100° and 300 p.s.i. When the hydrogen uptake ceased, the mixture was filtered, and the filtrate was made alkaline with an excess of sodium hydroxide solution. The alkaline mixture was extracted with ether, the ether extracts were dried, and the ether was removed to leave an oil. The residual oil solidified on scratching to give white needles of the free base which melted at 62–64° on purification. The compound was best purified, however, by converting it to the hydrochloride and recrystallizing the latter from butyl acetate and then from benzene in which it is surprisingly soluble. The hydrochloride of 1,3-dimethyl-1,2,3,4,4a,9a-hexahydro-2-azafluorene was obtained in the form of colorless needles which decomposed at 189–191°.

Anal. Calc'd for $C_{14}H_{19}N \cdot HCl$: C, 70.7; H, 8.4.

Found: C, 71.1; H, 8.2.

The *free base:* m.p. 62–64°.

XVIII. *1,3-Dimethyl-2-azafluorene* (1, 2). This compound was prepared in a variety of ways.

(A) *By reduction of the ketone VIII:* A mixture of 4.18 g. of VIII, 50 cc. ethanol, and 5 cc. of Raney nickel was reduced with hydrogen at 50 p.s.i. Reduction was rapid, and completeness of reduction was assured by warming the mixture to about 50°. When absorption of hydrogen ceased, the mixture was filtered, concentrated, and treated with water to yield long, colorless needles of the free base; m.p. 92–93°. On boiling the base with an excess of aqueous oxalic acid, the *oxalate* was obtained. Colorless rhomboids, m.p. 215–216°.

Anal. Calc'd for $C_{14}H_{13}N \cdot H_2C_2O_4 \cdot H_2O$: C, 63.4; H, 5.6.

Found: C, 63.6; H, 5.4.

(B) *By decomposition of the amine XX:* A mixture of 2.1 g. of amine XX and 0.8 g. of ethylene chlorohydrin was heated under reflux for 6 hours. Ammonia was liberated during the reaction. On cooling, the reaction mixture solidified. The solid was recrystallized from hot, dilute HCl, and the hydrochloride was then converted to the free base; m.p. 89–90°. The free base, so obtained, when mixed with an authentic sample of 1,3-dimethyl-2-azafluorene melted at 89–90°. The same result was obtained when *n*-butanol was substituted for ethylene chlorohydrin.

(C) *By decomposition of the 9-chloro compound XXIII:* The 9-chloro compound was refluxed for several hours with a mixture of ethanolamine and ethanol. The ethanol was then removed, and the residue was dissolved in water. The water solution was made alkaline with sodium hydroxide and an oily gum separated out which was dissolved in hot, dilute HCl. The acid solution on cooling yielded fine, white needles of a hydrochloride which gave white needles on conversion to the free base; m.p. 91–92°. A mixture with an authentic sample of 1,3-dimethyl-2-azafluorene melted at 91–92°. Sodium fusion showed no chlorine.

(D) *By reduction of the 9-chloro compound XXVIII:* A mixture of 4.6 g. of the 9-chloro compound XXVIII, 5 cc. of Raney nickel, and 150 cc. of methanol was reduced with hydrogen at 40 p.s.i. When absorption of hydrogen ceased, the mixture was filtered and evaporated to dryness to leave the *hydrochloride* of 1,3-dimethyl-2-azafluorene. Hairlike needles were obtained from dilute HCl; m.p. >300°.

Anal. Calc'd for $C_{14}H_{13}N \cdot HCl$: C, 72.6; H, 6.1.
Found: C, 72.5; H, 6.2.

XVIII. *1,3-Dimethyl-(1,2,3,4?)-tetrahydro-2-azafluorene.* A mixture of 62.7 g. of ketone VIII, 1000 cc. of ethanol, and 30 cc. of Raney nickel was reduced with hydrogen at 90° and 350 p.s.i. The residual oil, obtained by removal of the ethanol, was dissolved in dilute HCl to give 20 g. of water-insoluble 1,3-dimethyl-2-azafluorene hydrochloride (XVII) and the water-soluble hydrochloride of the tetrahydro derivative which was repeatedly recrystallized from methanol and then from dilute HCl. Small, colorless needles were obtained which decomposed at 298°. It was interesting to note that the hydrochloride of the tetrahydro compound became insoluble in cold water after it was recrystallized from methanol.

Anal. Calc'd for $C_{14}H_{17}N \cdot HCl$: C, 71.3; H, 7.6.
Found: C, 71.1; H, 7.6.

The *free base* was obtained as an oil which could not be solidified.

XIX. *1,3-Dimethyl-9-isonitroso-2-azafluorene.* To 15 g. of the ketone VIII in 200 cc. of hot ethanol was added 50 cc. water and 7 g. hydroxylamine hydrochloride. The mixture was adjusted to approximately *p*H 11 with 27 cc. of 6 *N* sodium hydroxide and was then refluxed for about ½ hour. On adjusting the reaction mixture to *p*H 7–8 with dilute acetic acid and then cooling, 17 g. of the oxime precipitated. The product was recrystallized from ethanol containing a little water and was obtained as almost colorless needles, m.p. 273.5°, with previous darkening [decomposition 280–281° (2)].

XX. *1,3-Dimethyl-9-amino-2-azafluorene.* The oxime XIX (15 g.) in ethanol was reduced at 50° and 50 p.s.i. in the presence of Raney nickel. When reduction was complete, the mixture was filtered, and dry hydrogen chloride was passed into the filtrate to yield 18.5 g. of the dihydrochloride which darkens at about 190° but has no definite melting point. The dihydrochloride was converted to the free base which was purified by recrystallization from "Skellysolve B" and then from dilute methanol to yield colorless, feathery clusters which melted with previous softening at 84–86°.

Anal. Calc'd for $C_{14}H_{14}N_2$: C, 80.0; H, 6.7.
Found: C, 80.1; H, 6.6.

XXI. *1,3-Dimethyl-9-ureido-2-azafluorene.* To 34 g. of the amine dihydrochloride (XX) in water solution was added 6 *N* sodium hydroxide to slight alkalinity. The free base precipitated at this point. The mixture was then treated with 10.2 g. of potassium cyanate dissolved in a little water. On the addition of glacial acetic acid to acidity, solution took place, followed almost immediately by precipitation of the product. Yield 27 g. The ureide on recrystallization from 90% ethanol was obtained in the form of long, fine, colorless needles which had no definite melting point.

Anal. Calc'd for $C_{15}H_{15}N_3O$: N, 16.6. Found: N, 16.3.

XXII. *1,3-Dimethyl-9-(carbethoxyamino)-2-azafluorene.* To a solution of 20 g. of the 9-amino compound XX in ether was added 5.2 cc. of ethyl chloroformate. A vigorous reaction ensued, and a solid precipitated. The mixture was refluxed for about ½ hour, then the precipitate (22 g.) was filtered off, washed with ether, and suspended in cold water. Part of the precipitate dissolved in the water and proved to be the hydrochloride of XX. The water-insoluble portion (11 g.) was the desired urethane derivative. White, silky needles were obtained from dilute ethanol; m.p. 221.5–223.5°.

Anal. Calc'd for $C_{17}H_{18}N_2O_2 \cdot H_2O$: C, 68.0; H, 6.7; N, 9.3.
Found: C, 68.0; H, 6.6; N, 9.6.

XXIII. *1,3-Dimethyl-9-chloro-2-azafluorene.* To 20 g. of the 9-hydroxy compound XIV dissolved in 500 cc. of dry benzene under reflux was added dropwise with stirring 35 cc. of

thionyl chloride. Refluxing was continued for 15 minutes after addition was complete. The solid product was then filtered off, washed with benzene, and dried. Yield, 23 g. of of 1,3-dimethyl-9-chloro-2-azafluorene hydrochloride. Long, fine, white needles were obtained from dilute hydrochloric acid; m.p. >300°.

Anal. Calc'd for $C_{14}H_{12}ClN \cdot HCl$: C, 63.2; H, 4.9.
Found: C, 63.7; H, 5.0.

The *free base* was obtained by dissolving the hydrochloride in hot water, cooling the solution, and adding dilute ammonium hydroxide to faint alkalinity. Near-white crystals from "Skellysolve B" partially melt at 113–115°.

XXIV. *1,3-Dimethyl-9-(β-hydroxyethylamino)-2-azafluorene.* This compound was prepared in two ways:

(A) A mixture of 28.3 g. (0.1 mole) of the dihydrochloride of the 9-amino compound XX, 8 g. (0.2 mole) of ethylene chlorohydrin, 8 g. (0.4 mole) of magnesium oxide, 75 cc. of water, and 50 cc. of 2-propanol was refluxed for about 72 hours. The mixture was filtered, and the filtrate was acidified with an excess of dilute HCl to precipitate the hydrochloride of 1,3-dimethyl-2-azafluorene (XVII). The latter was removed, and the acid solution was made alkaline with ammonium hydroxide to yield a viscous oil which was extracted with ether. Upon concentration and cooling of the ether extract, the desired product precipitated. Colorless needles were obtained from benzene; m.p. indefinite but below 150°.

Anal. Calc'd for $C_{16}H_{18}N_2O$: C, 75.5; H, 7.1; N, 11.0.
Found: C, 75.3; H, 7.2; N, 11.0.

(B) A mixture of 18 g. of the 9-chloro compound XXIII, 18 cc. of ethanolamine, and 10 cc. of dioxane was heated for ½ hour on the steam-bath. The mixture first formed a clear solution and then solidified. The dioxane was removed under a vacuum, and the residual mass was triturated with water, filtered, and dried. Yield, 19 g. of crude product. Colorless needles were obtained from benzene; m.p. indefinite but below 150°.

Anal. Calc'd for $C_{16}H_{18}N_2O$: C, 75.5; H, 7.1.
Found: C, 75.9; H, 7.1.

XXV. *1,3-Dimethyl-9-(β-chloroethylamino)-2-azafluorene.* To 30 cc. of cold thionyl chloride was added portionwise with stirring 7 g. of compound XXIV. The mixture was permitted to stand at room temperature for about 5 hours. The thionyl chloride was then removed under a vacuum, and cold water was added to the residue. The mixture was filtered to remove any insoluble material, and the clear solution was made mildly alkaline with dilute sodium hydroxide to give an oil which was extracted with ether. The ether extract was dried, and the ether was removed to give the desired 9-(β-chloroethylamino) derivative in the form of an oily residue which was used without further purification in experiments XXVI and XXVII.

XXVI. *1,3-Dimethyl-9-(β-dimethylaminoethylamino)-2-azafluorene.* Crude 1,3-dimethyl-9-(β-chloroethylamino)-2-azafluorene, obtained as described in experiment XXV above, was heated for 3 hours in a bomb tube at 100° with an excess of methanolic dimethylamine. The excess of methanol and dimethylamine was then removed on the steam-bath to leave the free base as an oily residue which solidified on standing. To facilitate purification the free base was converted to the trihydrochloride by solution in a little hot 3 *N* HCl and reprecipitation with 2-propanol. White needles from a water-2-propanol mixture decomposed at 208–211° with previous darkening. The *trihydrochloride* was first obtained as a *monohydrate* which could be converted to the *hemihydrate* on further drying.

Anal. Calc'd for $C_{18}H_{23}N_3 \cdot 3HCl \cdot H_2O$: C, 52.8; H, 6.9.
Found: C, 52.7; H, 6.8.

Anal. Calc'd for $C_{18}H_{23}N_3 \cdot 3HCl \cdot 0.5\ H_2O$: C, 54.1; H, 6.7.
Found: C, 54.2; H, 7.2.

A portion of the trihydrochloride was converted to the *free base* by solution in water and treatment with dilute sodium hydroxide. Since the free base was more soluble in cold water than in hot water, the alkaline solution was carefully warmed, upon which the free base crystallized out. Colorless needles were obtained from dilute methanol; m.p. 109–111°.

Anal. Calc'd for $C_{18}H_{23}N_3$: C, 76.9; H, 8.2.
Found: C, 77.0; H, 7.9.

XXVII. *1,3-Dimethyl-9-(β-diethylaminoethylamino)-2-azafluorene trihydrochloride.* Crude 1,3-dimethyl-9-(β-chloroethylamino)-2-azafluorene, obtained as described in experiment XXV above, was dissolved in an excess of diethylamine. The mixture was permitted to stand at room temperature over the weekend during which time a precipitate appeared. The excess of diethylamine was evaporated off, and the residue was dissolved in 2-propanol and then treated with an excess of concentrated HCl to give a precipitate of the trihydrochloride of 1,3-dimethyl-9-(β-diethylaminoethylamino)-2-azafluorene. The product was purified by recrystallization from a mixture of dilute HCl and 2-propanol and then from a mixture of ethanol and 2-propanol. Near-white microcrystals were obtained which decomposed at 179–182° with previous darkening.

Anal. Calc'd for $C_{20}H_{27}N_3 \cdot 3HCl \cdot 2H_2O$: C, 52.8; H, 7.5.
Found: C, 52.7; H, 7.3.

XXVIII. *1,3-Dimethyl-9-β-chloroacetoxy-2-azafluorene.* The hydroxy compound XIV (3 g.), 10 cc. of glacial acetic acid, and 10 cc. of chloroacetyl chloride were mixed and refluxed for about 15 minutes. The acetic acid was removed under a vacuum, and the residue was poured into water. The water solution was filtered, cooled, and adjusted to *p*H 8 with alkali, whereupon the product precipitated. The yield of crude 1,3-dimethyl-9-β-chloroacetoxy-2-azafluorene was 3.2 g. Upon recrystallization from dilute methanol, small, flesh-tinted, feathery crystals were obtained which melted at 146.5–147.5°. The compound was soluble in alcohol, benzene, and dilute acetic acid and was insoluble in water and alkali.

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: C, 66.8; H, 4.9.
Found: C, 66.9; H, 5.2.

The *picrate* melted with previous darkening at 189–190°.

XXIX. *Attempt to prepare 1,3-dimethyl-9-carboxy-2-azafluorene.* Several attempts were made to prepare the 9-carboxy derivative by the action of butyllithium and CO_2 on 1,3-dimethyl-2-azafluorene (XVII). Typical of these attempts is the following:

To 50 cc. of ether and 1.17 g. of lithium (beaten flat for increased surface) was added portionwise 7.1 g. of *n*-butyl chloride. A vigorous reaction ensued and the ether refluxed spontaneously. The mixture was stirred and refluxed for 2 hours after complete addition of the butyl chloride, then 12 g. of 1,3-dimethyl-2-azafluorene was added portionwise and refluxing continued for one hour. The mixture was then poured on to Dry Ice, and the excess of lithium was removed. After standing overnight, most of the ether had evaporated, and the solid residue was treated with a little cold water and then filtered. The alkaline filtrate was acidified with acetic acid to give white needles of a compound which was soluble in sodium hydroxide, sodium carbonate, ammonium hydroxide, and very dilute hydrochloric acid and was insoluble in cold water, 3 *N* hydrochloric acid, dilute acetic acid, and ether. It decomposed immediately on solution in methanol or ethanol at room temperature with the liberation of CO_2. It also decomposed in warm water and on heating the dry substance to 48–49°. Upon standing at room temperature for several hours, the compound could no longer be dissolved in alkali, and on qualitative analysis, it was shown to contain 1,3-dimethyl-2-azafluorene (XVII).

SUMMARY

This report concerns the synthesis and chemical behavior of several derivatives of 1,3-dimethyl-2-azafluorene (XVII) and an improved procedure for the synthesis of 1,3-dimethyl-9-oxo-azafluorene (VIII). The latter compound on hydrogenation under a variety of conditions yielded five different products. It was also discovered that groups attached to the 9 position of the dimethyl-2-azafluorene structure tended to be labile.

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