3-METHYL-9-ARYL(ARALKYL)-2-AZA-9-FLUORENOLS

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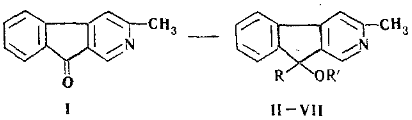
3-Methyl-9-phenyl(o-tolyl, benzyl)-2-aza-9-fluorenols were synthesized, and some of their transformations were examined.

New azafluorenols that are of interest for pharmacological testing as spasmolytics can be obtained from the previously described 3-methyl-2-azafluorenone (I) [1]. The reaction of I with phenyl- and o-tolyllithium gives 9-phenyl- and 9-(o-tolyl)-3-methyl-2-aza-9-fluorenols (II and III). 3-Methyl-9-benzyl-2-aza-9-fluorenol (IV) is obtained by means of benzylmagnesium chloride and I.



I II–VII

The corresponding esters of propionic acid (V-VII) are obtained by the acylation of II-IV with propionic anhydride in pyridine. However, these esters cannot be obtained by the reaction of II-IV with propionyl chloride in benzene; the hydrochlorides of azafluorenols II-IV are isolated in quantitative yield.

One must note the anomaly observed during the determination of the melting point of 3-methyl-9-phenyl-2-aza-9-fluorenol (II). Compound II, which is obtained by the phenyllithium synthesis, is isolated as acicular crystals with mp 144-146 deg (from benzene, IIa). Conversion of free base IIa into the hydrochloride (mp 338-340 deg) and again to the free base is not accompanied by a change in its melting point. However, II isolated by the acid or alkaline hydrolysis of the propionate (V) crystallizes from benzene to give needles with mp 164-165 deg (IIb). (The hydrochloride of IIb melts at 344-350 deg.) A mixture of IIa and IIb melts at 144-164 deg. It was established that after prolonged storage of IIa, this sample melts at 142-166 deg, and refluxing it in alcoholic potassium hydroxide does not change the indicated melting point. The IR spectra of IIa and IIb are identical. They contain a characteristic band at 3055 cm^{-1} from an associated hydroxyl group. Unfortunately, the complete absence of data on the configuration of substituted azafluorenes of the II type makes it as yet impossible to explain the facts noted above. It can only be assumed that the reason for the observed anomaly in the melting points of II rests in the stereochemical peculiarities of its molecule and in the possible (in connection with this) different character of the interaction of the hydroxyl group and the nitrogen in this system.

The dehydration of 3-methyl-9-benzyl-2-aza-9-fluorenol (IV) gave 3-methyl-9-benzylidene-2-azafluorene (VIII), which was isolated as a mixture of two isomers (VIIIa and VIIIb). These isomers are also obtained by the condensation of 3-methyl-2-azafluorene with benzaldehyde in the presence of potassium ethoxide [2].

EXPERIMENTAL

3-Methyl-9-phenyl-2-aza-9-fluorenol (IIa and IIb). An ether solution of phenyllithium [prepared from 0.56 g (0.081 g-atom) of lithium and 2.6 g (0.017 mole) of bromobenzene] that had been thoroughly filtered away from lithium was added rapidly by drops to a solution of 2 g (0.01 mole) of I in 350 ml of absolute

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TABLE 1. Characteristics of the Compounds Obtained

Compound	Mp, deg C	R_f*	Empirical formula	Found, %			Calc., %			IR spectrum cm^{-1}†	Hydrochloride mp, deg C‡	Yield, %
				C	H	N	C	H	N			
IIa	144—146	0,10	$C_{19}H_{15}NO$	83,4	5,6	5,3	83,5	5,4	5,1	3055; 1616; 765; 720; 705	338—340	65
III	225—226	0,12	$C_{20}H_{17}NO$	83,3	6,2	4,8	83,3	5,9	4,9	3065; 1616; 760; 750; 743	273—274	28
IV	192—193	0,16	$C_{20}H_{17}NO$	83,0	5,9	4,9	83,3	5,9	4,9	3290; 3082; 3060; 3025; 1622; 757; 745; 703	217—218	35
V	166—167	0,63	$C_{22}H_{19}NO_2$	80,5	5,8	4,2	80,8	5,7	4,2	3072; 1752; 1615; 770; 750; 701	189—190	32,6
VI	117—119	0,70	$C_{23}H_{21}NO_2$	80,7	6,2	4,2	80,5	6,1	4,1	3060; 1749; 1618; 772; 752	221—223	20
VII	102—103	0,52	$C_{23}H_{21}NO_2$	80,4	6,4	4,2	80,5	6,1	4,1	3085; 3060; 3030; 1750; 1616; 756; 746; 703	208—209	35,6

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* The R_f values for activity II Al_2O_3 in ethyl acetate–hexane (1 : 2) are presented.

† The IR spectra of mineral oil pastes were recorded with a UR-20 spectrophotometer.

‡ The composition of the hydrochlorides (B·HCl) was confirmed by the determination of the percentage of N and Cl (and also C and H for IV·HCl).

ether. The mixture was stirred at 36 deg for 1 h and decomposed with water. The ether layer was dried with sodium sulfate, the ether was removed by distillation, and the crystalline residue (3.2 g), which contained I (R_f 0.51), was crystallized from benzene to give 1.82 g of colorless crystals of IIa with mp 144-146 deg and R_f 0.10. The picrate of IIa melted at 214-216 deg (from alcohol). Found: N 11.1%. $C_{19}H_{15}NO \cdot C_6H_3N_3O_7$. Calculated: N 11.1%.

A 0.2-g (6.1-mmole) sample of V was heated for 2.5 h with 10 ml of 30% alcoholic potassium hydroxide. The ethanol was removed by distillation, and the residue was extracted with ether to give 0.13 g of IIb as needles with mp 164-165 deg (from benzene). Found: C 83.5; H 5.4; N 5.4%. $C_{19}H_{15}NO$. Calculated: C 83.5; H 5.4; N 5.1%. Compound IIb was also obtained by the hydrolysis of V under the influence of concentrated HCl.

Compound III was similarly obtained (Table 1).

3-Methyl-9-benzyl-2-aza-9-fluorenol (IV). A solution of 2 g (0.01 mole) of I in 50 ml of absolute tetrahydrofuran was added by drops to benzylmagnesium chloride obtained from 1.56 g (2.4 mmole) of benzyl chloride and 0.25 g (0.01 g-atom) of magnesium in 30 ml of absolute ether. The mixture was stirred at room temperature for 2 h and decomposed with water and HCl until it gave an acid reaction to Congo. The aqueous layer was saturated with alkali, and the organic bases were extracted with ether. The extract was dried and worked up to give 0.88 g of IV with mp 192-193 deg (from benzene) and R_f 0.16.

Propionate of 3-Methyl-9-phenyl-2-aza-9-fluorenol (V). A mixture of 1 g (3.68 mmole) of IIa, 1.86 ml (14.5 mmole) of propionic anhydride, and 10 ml of pyridine was heated at 120 deg for 6 h (3 h for VII). The excess anhydride and pyridine was removed by vacuum distillation, and the dark, crystalline residue (1.29 g), which contained II, was purified with a column filled with activity II Al_2O_3 (h 6 cm, d 2.5 cm) with elution of V by hexane to give 0.4 g of colorless crystals of V with mp 166-167 deg (from ligroin). Subsequent rinsing of the column with ether gave 0.17 g of IIa.

Compounds VI and VII were similarly obtained (Table 1).

3-Methyl-9-benzylidene-2-azafluorene (VIII). A solution of 0.6 g (2.12 mmole) of IV in 3 ml of concentrated HCl was heated at 115 deg for 5 h. The reaction mass was then diluted with water, neutralized with sodium carbonate, and extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the crystalline residue (0.47 g) was dissolved in ligroin. Two forms of crystals of VIII precipitated and were separated from one another with forceps and then recrystallized from ligroin to give 0.11 g of pale-yellow crystals of VIIIa as long, fine needles with mp 119-120 deg (R_f 0.62) and 0.12 g of yellow crystals of VIIIb with mp 128.5-129.5 deg that crystallized as individual, dense colonies with short needles (R_f 0.77). The isomers of VIII did not depress the melting points of genuine samples [2].

LITERATURE CITED

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