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# INDOLOPYRIDINES WITH A BRIDGING HETEROATOM.

# 9*. SYNTHESIS, STRUCTURE, AND THERMOLYSIS OF 5-HYDROXY-5-(2-PYRIDYL)-FLUORENE AND -4-AZAFLUORENE

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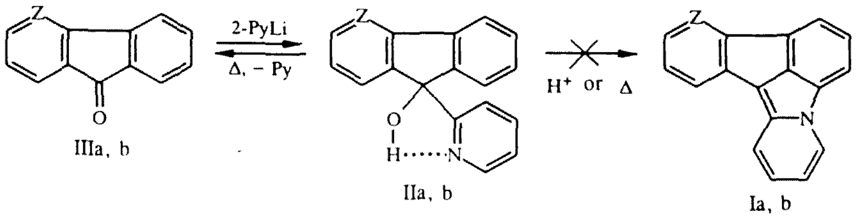
*Treatment of fluorenone or 4-azafluoren-9-one with 2-pyridyllithium gives 5-hydroxy-5-(2-pyridyl)fluorene and its aza analog. The structure of the former has been studied by x-ray crystallography. It was found that, in contrast to the non-condensed diaryl-2-pyridylcarbinols, these alcohols do not undergo acid catalyzed dehydration and heterocyclization. Under pyrolytic conditions, 5-pyridylfluorenol undergoes fission to form fluorenone.*

Under acid catalyzed dehydration conditions, diaryl-2-pyridyl- and 1-isoquinolyl carbinols are converted in good yields to indolopyridines with a bridging heteroatom [2, 3]. In this study of the possible synthesis of indolopyridines of type I through treatment of fluorenone (IIIa) or 4-azafluorenone (IIIb) with 2-pyridyllithium we obtained 5-hydroxyl-5-(2-pyridyl)fluorene (IIa) and its 4-azafluorene analog (IIb) in 73 and 24% yields respectively.



IIIa, b IIa, b Ia, b

I-III a Z = CH, b Z = N

The molecular structure of IIa was determined by x-ray analysis. The overall view is given in Fig. 1. Atomic coordinates, bond lengths, and valence angles are given in Tables 1-4. The fluorene system is planar to within 0.009 Å. The configuration at $C_5$ is tetrahedral but the intracyclic angle $C_{4a}-C_5-C_{5a}$ is decreased by 8° to 101.9(1)°. The remaining angles at this atom are in the range 109.7-111.9(1)°. The bond length $C_{1A}-C_{9A}$ is 1.465(2) Å (1.475 Å in unsubstituted fluorene [4]). The pyridine ring in IIa is virtually perpendicular to the mean plane of the fluorene system (at an angle of 88.8(1)°). There is present an intramolecular $O_1-H-N_1$ hydrogen bond with parameters $O_1$-$N_1$ 2.577 Å, $N_1$-H 1.92 Å, and $O_1-H-N_1$ angle 125°. The five membered, hydrogen-bonded ring, linked to the pyridine ring, is planar to within 0.035 Å. Torsional angle $O_1-C_5-C_{10}-N_1$ is 6.5° and the twist angle around $C_{10}-N_1$ between the mean planes of these two rings is only 1.4°.

In this study of the possible synthesis of Ia, b, the alcohols IIa b were heated in formic or polyphosphoric acids using known methods [2, 3]. However, the carbinols did not undergo any kind of reaction under these conditions. This stability towards acid catalyzed dehydration and subsequent cyclization can evidently be related to the existence of an intramolecular hydrogen bond as strongly supported by the x-ray structure (see above) and by PMR (hydroxyl proton resonance at 6.5-6.6

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*For Communication, 8 see [1].

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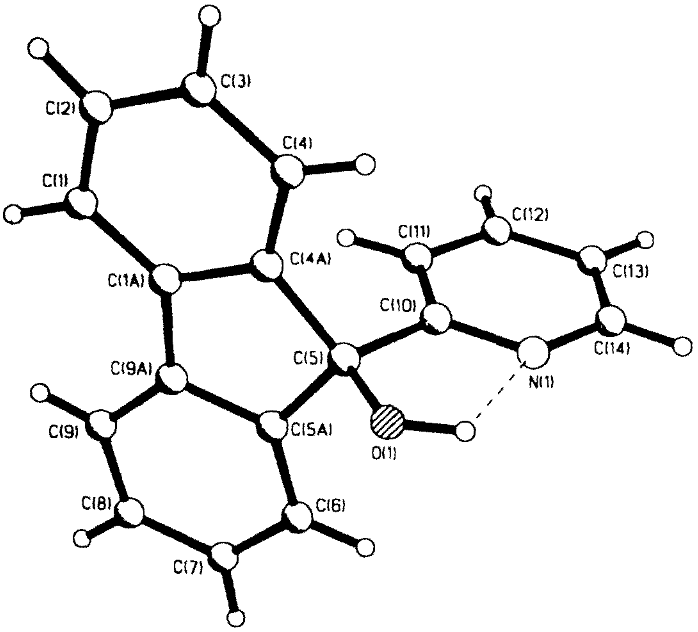

Fig. 1. Overall view and numbering of atoms in IIa.

ppm). In addition, the absence of free rotation of all structural elements in carbinols IIa,b produces additional steric hindrance for protonation of a hydroxyl group. With these considerations in mind we have used more forcing conditions for the dehydration (heating in the presence of aluminium oxide at 230°C). However, the starting carbinols are almos unchanged under these conditions. Heating alcohol IIa with aluminium oxide gives just 12% of the fluorenone fission product IIIa. Because of such a high stability for alcohols IIa, b we studied the behavior of one of them (IIa) under vapor phase conditions over mixed K-16 and No. 380 type oxide catalysts which had been used successfully before for the heterocyclization of $\alpha$-benzyl pyridines to the corresponding indolopyridine (structural analogs of I [5]). It was found that IIa at 600-650°C undergoes predominantly thermolysis to give fluorenone IIIa in yields from 38 to 80%, depending on the catalyst used.

These results show that the unsuccessful heterocyclization of 5-hydroxy-5-(2-pyridyl)fluorenes and their aza analogs is apparently associated with an energetically unfavored formation of the pentacyclic structure I which would need too severe a distortion of the geometry of the structural elements (valence angles and bond lengths) in their azapentalene fragments.

## EXPERIMENTAL

Monitoring of compound formation and purity was carried out by TLC using Silufol UV-254 plates, ether–hexane eluent (1:1), and iodine vapor visualization. Mass spectra were measured on an MX-1303 spectrometer with an electron ionization energy of 70 eV. PMR spectra were recorded on a Bruker WP-80 (80 MHz) instrument with $CDCl_3$ solvent and TMS internal standard.

**X-Ray Structural Analysis of IIa.** Crystals of IIa are monoclinic, space group $P2_1/c$, at 20°C $a = 11.532(2)$, $b = 10.851(2)$, $c = 11.419(2)$ Å, $\beta = 108.25(3)°$, $V = 1357.0(5)$ Å$^3$, $Z = 4$, $d_{calc} = 1.269$ g/cm$^3$. Unit cell parameters and intensities of 4324 reflections were measured on an Enraf-Nonius CAD4 automatic four-circle diffractometer (T = 293°K, $\lambda$Mo$\alpha$, graphite monochromator, $\theta/2\theta$ scanning to $\theta_{max}$ 27°). The structure was solved by a direct method and refined by a full matrix least squares analysis in the anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were located directly in difference Fourier synthesis and refined in the isotropic approximation. Final difference factors were $R_1 = 0.047$ for 3932 independent reflections with $I > 2\sigma(I)$ and $R_2 = 0.155$ for all 3948 independent reflections. All calculations were carried out on an IBM PC/AT-486 computer using the programs SHELXTL PLUS[1] and SHELXL-93 [6].

TABLE 1. Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Parameters (Å$^2$ $\times$ $10^3$) for Non-Hydrogen Atoms in IIa

| Atom | x | y | z | $u_{eq}$ |
|---|---|---|---|---|
| $O_{(1)}$ | 2424(1) | 2486(1) | 1419(1) | 59(1) |
| $N_{(1)}$ | 4530(1) | 2227(1) | 3061(1) | 66(1) |
| $C_{(1)}$ | 1489(2) | -1340(2) | -428(2) | 79(1) |
| $C_{(1A)}$ | 1744(1) | -499(1) | 541(2) | 56(1) |
| $C_{(2)}$ | 2088(2) | -1229(2) | -1287(2) | 93(1) |
| $C_{(3)}$ | 2923(2) | -300(2) | -1208(2) | 88(1) |
| $C_{(4)}$ | 3186(2) | 550(2) | -247(2) | 67(1) |
| $C_{(4A)}$ | 2585(1) | 441(1) | 618(1) | 51(1) |
| $C_{(5)}$ | 2719(1) | 1232(1) | 1749(1) | 45(1) |
| $C_{(5A)}$ | 1807(1) | 640(1) | 2288(1) | 51(1) |
| $C_{(6)}$ | 1516(2) | 994(2) | 3326(2) | 66(1) |
| $C_{(7)}$ | 658(2) | 301(2) | 3653(2) | 88(1) |
| $C_{(8)}$ | 115(2) | -711(3) | 2972(3) | 97(1) |
| $C_{(9)}$ | 405(2) | -1062(2) | 1933(3) | 81(1) |
| $C_{(9A)}$ | 1262(1) | -377(1) | 1580(2) | 57(1) |
| $C_{(10)}$ | 4009(1) | 1150(1) | 2668(1) | 43(1) |
| $C_{(11)}$ | 4573(1) | 41(1) | 3078(1) | 54(1) |
| $C_{(12)}$ | 5729(1) | 44(2) | 3924(2) | 61(1) |
| $C_{(13)}$ | 6280(1) | 1151(2) | 4332(2) | 68(1) |
| $C_{(14)}$ | 5657(2) | 2209(2) | 3889(2) | 80(1) |

TABLE 2. Coordinates ($\times 10^4$) and Isotropic Temperature Parameters (Å$^2$ $\times$ $10^3$) for Hydrogen Atoms in IIa

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| $H_{(10)}$ | 3051(26) | 2934(25) | 1995(24) | 131(9) |
| $H_{(1)}$ | 895(19) | -1974(21) | -498(19) | 98(7) |
| $H_{(2)}$ | 1964(25) | -1822(25) | -1918(25) | 127(9) |
| $H_{(3)}$ | 3324(23) | -231(22) | -1821(26) | 114(8) |
| $H_{(4)}$ | 3766(18) | 1222(18) | -140(17) | 76(6) |
| $H_{(6)}$ | 1912(19) | 1687(20) | 3818(19) | 93(7) |
| $H_{(7)}$ | 383(21) | 531(21) | 4369(24) | 107(7) |
| $H_{(8)}$ | -472(22) | -1186(21) | 3172(21) | 107(7) |
| $H_{(9)}$ | 87(19) | -1742(21) | 1487(18) | 86(6) |
| $H_{(11)}$ | 4132(16) | -749(17) | 2763(16) | 71(5) |
| $H_{(12)}$ | 6130(17) | -743(18) | 4237(17) | 76(5) |
| $H_{(13)}$ | 7114(19) | 1154(17) | 4913(17) | 80(5) |
| $H_{(14)}$ | 6033(20) | 3003(22) | 4191(21) | 103(7) |

**5-Hydroxy-5-(2-pyridyl)fluorene (IIa).** $\alpha$-Bromopyridine (6.4 g, 0.04 mole) was added at −35 to −40°C to a solution of phenyllithium which had been prepared from bromobenzene (6.4 g, 0.04 mole) and lithium (0.6 g, 0.08 g, atom) in dry ether (50 ml). Powdered fluorenone Ia (3.6 g, 0.02 mole) was added portionwise. The mixture was stirred while it did not reach room temperature and then treated with saturated ammonium chloride solution to pH 7 and extracted with ether. The extract was dried over sodium sulfate to give the alcohol IIa (3.8 g, 73%) as colorless crystals with mp 127-128°C-H and $R_f$ 0.49. Found, %: C 76.1, H 4.7, N 5.7. $M^+$ 259. $C_{18}H_{13}NO$. Calculated, %: C 75.7, H 5.0, N 5.4. M 259. PMR spectrum: 6.52 (1H, s, OH), 6.6 (1H, ddd, J = 7.6 and 1.1 Hz, 5'-H), 7.1-7.52 (8H, m, 3'-H and 7-$H_{arom}$), 7.62-7.76 (2H, m, 1- and 4'-H), 8.6 ppm (1H, br d, J = 4.8 Hz, 6'-H). Mass spectrum, m/z (%): $M^+$ 259 (100), 258 (14), $[M\text{-}OH]^{+\cdot}$ 242 (7), 241 (6), $[M\text{-}CHO]^{+\cdot}$ 230 (90), 181 (52), 180 (23), 165 (6), 152 (49), 151 (17), 130 (11).

**9-Hydroxy-9-(2-pyridyl)-4-azafluorene (IIb).** Obtained similarly from 4-azafluorenone (0.02 mole) in 24.1% yield as white crystals with mp 199-200°C and $R_f$ 0.3. Found, %: C 78.3, H 4.8, N 10.5. $M^+$ 260. $C_{17}H_{12}N_2O$. Calculated, %:

TABLE 3. Bond Lengths (Å) in IIa

| Bond | Length, Å | Bond | Length, Å |
|---|---|---|---|
| $O_{(1)}—C_{(5)}$ | 1,424(2) | $C_{(5)}—C_{(10)}$ | 1,531(2) |
| $N_{(1)}—C_{(10)}$ | 1,326(2) | $C_{(5A)}—C_{(6)}$ | 1,383(2) |
| $N_{(1)}—C_{(14)}$ | 1,347(2) | $C_{(5A)}—C_{(9A)}$ | 1,396(2) |
| $C_{(1)}—C_{(2)}$ | 1,371(4) | $C_{(6)}—C_{(7)}$ | 1,385(3) |
| $C_{(1)}—C_{(1A)}$ | 1,392(2) | $C_{(7)}—C_{(8)}$ | 1,377(4) |
| $C_{(1A)}—C_{(4A)}$ | 1,391(2) | $C_{(8)}—C_{(9)}$ | 1,383(4) |
| $C_{(1A)}—C_{(9A)}$ | 1,465(2) | $C_{(9)}—C_{(9A)}$ | 1,394(2) |
| $C_{(2)}—C_{(3)}$ | 1,378(3) | $C_{(10)}—C_{(11)}$ | 1,378(2) |
| $C_{(3)}—C_{(4)}$ | 1,392(3) | $C_{(11)}—C_{(12)}$ | 1,380(2) |
| $C_{(4)}—C_{(4A)}$ | 1,379(2) | $C_{(12)}—C_{(13)}$ | 1,371(2) |
| $C_{(4A)}—C_{(5)}$ | 1,517(2) | $C_{(13)}—C_{(14)}$ | 1,365(3) |
| $C_{(5)}—C_{(5A)}$ | 1,518(2) | | |

TABLE 4. Valence Angles $\omega$ (deg) in IIa

| Angle | $\omega$ | Angle | $\omega$ |
|---|---|---|---|
| $C_{(10)}—N_{(1)}—C_{(14)}$ | 117,4(1) | $C_{(6)}—C_{(5A)}—C_{(9A)}$ | 122,0(1) |
| $C_{(2)}—C_{(1)}—C_{(1A)}$ | 118,9(2) | $C_{(6)}—C_{(5A)}—C_{(5)}$ | 128,0(1) |
| $C_{(1)}—C_{(1A)}—C_{(4A)}$ | 120,1(2) | $C_{(9A)}—C_{(5A)}—C_{(5)}$ | 110,0(1) |
| $C_{(1)}—C_{(1A)}—C_{(9A)}$ | 131,6(2) | $C_{(5A)}—C_{(6)}—C_{(7)}$ | 117,8(2) |
| $C_{(4A)}—C_{(1A)}—C_{(9A)}$ | 108,4(1) | $C_{(8)}—C_{(7)}—C_{(6)}$ | 121,2(2) |
| $C_{(1)}—C_{(2)}—C_{(3)}$ | 121,1(2) | $C_{(7)}—C_{(8)}—C_{(9)}$ | 121,0(2) |
| $C_{(2)}—C_{(3)}—C_{(4)}$ | 120,8(2) | $C_{(8)}—C_{(9)}—C_{(9A)}$ | 119,0(2) |
| $C_{(4A)}—C_{(4)}—C_{(3)}$ | 118,2(2) | $C_{(5A)}—C_{(9A)}—C_{(9)}$ | 119,1(2) |
| $C_{(4)}—C_{(4A)}—C_{(1A)}$ | 121,0(2) | $C_{(5A)}—C_{(9A)}—C_{(1A)}$ | 109,0(1) |
| $C_{(4)}—C_{(4A)}—C_{(5)}$ | 128,4(1) | $C_{(9)}—C_{(9A)}—C_{(1A)}$ | 132,0(2) |
| $C_{(1A)}—C_{(4A)}—C_{(5)}$ | 110,6(1) | $N_{(1)}—C_{(10)}—C_{(11)}$ | 122,6(1) |
| $O_{(1)}—C_{(5)}—C_{(5A)}$ | 111,9(1) | $N_{(1)}—C_{(10)}—C_{(5)}$ | 114,9(1) |
| $O_{(1)}—C_{(5)}—C_{(4A)}$ | 111,3(1) | $C_{(11)}—C_{(10)}—C_{(5)}$ | 122,5(1) |
| $C_{(5A)}—C_{(5)}—C_{(4A)}$ | 101,9(1) | $C_{(10)}—C_{(11)}—C_{(12)}$ | 119,0(1) |
| $O_{(1)}—C_{(5)}—C_{(10)}$ | 109,7(1) | $C_{(13)}—C_{(12)}—C_{(11)}$ | 118,9(2) |
| $C_{(5A)}—C_{(5)}—C_{(10)}$ | 110,2(1) | $C_{(14)}—C_{(13)}—C_{(12)}$ | 118,5(2) |
| $C_{(4A)}—C_{(5)}—C_{(10)}$ | 111,7(1) | $N_{(1)}—C_{(14)}—C_{(13)}$ | 123,5(2) |

C 78.4, H 4.6, N 10.8. M 280. PMR spectrum: 6.6 (1H, s, OH), 6.63 (1H, ddd, J = 7.6 and 1.1 Hz, 5'-H), 7.07 (1H, q, J = 8.0 Hz, 2-H), 7.2-7.45 (4H, m, $H_{arom}$), 7.53 (2H, m, 1- and 3'-H), 8.0 (1H, m, 4'-H), 8.6 ppm (2H, m, 3- and 6'-H).

**Attempted Cyclocondensation of Alcohols II.** A. A solution of alcohol IIa (0.12 g, 0.46 mmole) in HCOOH (10 ml) was held for 12 h at 100°C with vigorous stirring. The solvent was evaporated and the residue crystallized from hexane to give starting alcohol IIa (0.11 g, 92%).

B. A solution of alcohol IIa (0.12 g, 0.46 mmole) in polyphosphoric acid (10 g) was held for 8 h at 120°C and poured onto ice (50 g). The precipitate was separated, washed with water, and dried to give starting alcohol IIa (0.1 g, 83%).

C. A mixture of alcohol IIa (0.12 g, 0.46 mmole) and aluminium oxide (1 g) was held for 1 h at 180°C and 45 min at 230°C. After cooling, the mixture was extracted with chloroform and the extract separated on a chromatography column using silica gel to give fluorenone IIIa (10 mg, 12%) and starting alcohol IIa (82 mg, 68%).

Similar experiments with alcohol IIb returned almost quantitative yields of starting material.

**Pyrolysis of Alcohol IIa.** A solution of fluorenol IIa (1.85 g, 7.14 mmole) in benzene (50 ml) was passed for 0.5 h through a continuous flow type quartz reactor containing 10 ml of catalyst K-16 at 600°C. The catalyzate was filtered, the solvent evaporated, and the residue separated on a silica chromatography column using benzene eluent to give fluorenone IIIa (1.16 g, 90%) and unreacted alcohol IIa (0.19 g, 10%).

A solution of alcohol IIa (1.2 g, 0.46 mmole) in benzene (50 ml) was passed through the reactor with catalyst No. 380 [5]. There were separated fluorene (0.19 g, 24.7%), fluorenone IIIa (0.32 g, 38.4%), and a reddish, crystalline material (70 mg, mp 135-136°C) of unidentified structure. The PMR spectrum of the latter (broadened, unresolved multiplets in the region 6.5-7.9 ppm) pointed to a polymeric material.

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