AZAINDOLE DERIVATIVES

XXX. A New Synthetic Route to 5-Azaindole and Its Derivatives*

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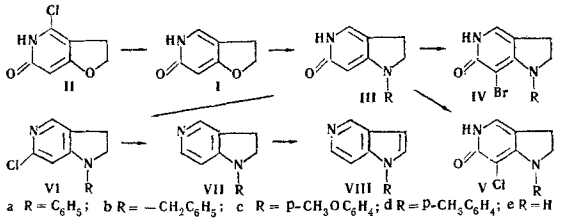
A new synthesis of 5-azaindole and its derivatives has been developed, which consists in the reaction of 6-oxo-2, 3-dihydro-5-azabenzofuran with primary amines, followed by elimination of the substituent in the 6-position and dehydrogenation of the resulting 5-azaindolines with a palladium catalyst. Electrophilic substitution reactions in the 6-oxo-5-azaindoles are investigated.

5-Azaindole and its derivatives are of great interest both from the point of view of the investigation of the chemical properties of a system consisting of condensed π-electron-deficient and π-electron-rich rings, and also for the examination of the effect on biological activity of the introduction of the aza group into various positions of heteroaromatic molecules.

Previous communications in this series [2, 3] have described the general method of closure of the pyrrole ring by reaction of 3-(β-chloroethyl)-4-chloropyridines with amines or ammonia giving, via the 2, 3-dihydro-derivatives, various derivatives of 5-azaindole, which until now have been virtually inaccessible.

In continuation of this work, we have developed a new synthetic route to 5-azaindole and its derivatives based on the reaction of 5-azabenzofurans with amines [4]. One of the starting materials for this synthesis, 6-oxo-2, 3-dihydro-5-azabenzofuran (I), is readily obtained from butyrolactone and malonyl chloride, which is converted by a previously-described method into 4-chloro-6-oxo-2, 3-dihydro-5-azabenzofuran (II) [5], which is further dehalogenated with a palladium catalyst.

Investigation of the reaction of I with various primary amines showed that the ease of replacement of the oxygen in the dihydrofuran ring by nitrogen was strongly dependent on the nature of the amine involved. For example, with aniline, other conditions remaining constant, heating at 190° C afforded 43% of 1-phenyl-6-oxo-5-azaindoline (IIIa), while raising the temperature to 250° C increased the yield of IIIa to 78.8%. Use of such amines as p-anisidine and p-toluidine, whose nucleophilic properties are enhanced by electron-donor groups in the p-position, results in high yields of the corresponding 5-azaindoline derivatives IIIc and IIId (71.5–83.2%) at temperatures as low as 190° C. The reaction of I with benzylamine at 190° C goes equally smoothly (72% yield), but in this case an increase in temperature to 250° C results in a drop in yield to 57.6% as a result of the thermal instability of IIIb. On the other hand, I fails to react with aliphatic amines even under vigorous conditions. For example, heating I with a large excess of butylamine in a sealed tube for 17 hr at 250° C led only to the recovery of starting material I.



a R = C_6H_5; b R = $-CH_2C_6H_5$; c R = p-$CH_3OC_6H_4$; d R = p-$CH_3C_6H_4$; e R = H

In a similar way to the analogous 6-oxo-2,3-dihydro-5-azabenzofurans [6], the 6-oxo-5-azaindolines have increased electron density in the 7-position, resulting in the occurrence of electrophilic substitution reactions. An example is the bromination of IIIb, which proceeds in chloroform at room temperature to give a 55.7% yield of 1-benzyl-6-oxo-7-bromo-5-azaindoline (IVb). The position of the bromine atom in this compound was established by NMR spectroscopy.

*For part XXIX, see [1]

The NMR spectrum of IIIb showed two triplets due to the $-CH_2-CH_2$ grouping of the pyrroline ring (2.44 and 3.17 ppm, separation ~8 Hz), a singlet at 4.15 ppm due to the CH_2, a series of signals from 6.85 to 7.42 ppm due to the aromatic benzene ring of the benzyl group, and also two singlets with chemical shifts of 5.71 and 6.75 ppm which apparently correspond to the protons in positions 7 and 4 of the 1-benzyl-6-oxo-5-azaindoline molecule. Conversion to the corresponding bromo derivative IVb caused a shift of the pyrrole $-CH_2-CH_2$ signals (triplets at 2.67 and 3.50 ppm, separation ~8 Hz), the benzyl CH_2 (singlet at 4.77 ppm), and the 4-proton to lower field, appearing with the multiplet due to the phenyl protons at 6.70–7.05 ppm. No signal is observed in the spectrum of IVb from 4.77 to 6.70 ppm, which could be due to the absence of the proton at C_7 of the 6-oxo-5-azaindoline system.

It is interesting that the rule which we discovered previously [6], according to which the separation of ~8 Hz which is characteristic for the triplets of the cyclic 2,3-dihydro-5-azabenzofurans holds also in the 5-azaindoles (as distinct from the triplets of 3-(β-substituted ethyl)pyridines, where the $-CH_2-CH_2$ grouping is not part of a ring, when the separation is only about 6 Hz). This rule may be used to assign the compounds under investigation either to the mono- or to the bicyclic series of pyridine derivatives, on the basis of their NMR spectra.

1-Benzyl-6-oxo-7-chloro-5-azaindoline (Vb), which was examined as for the above-mentioned bromo derivative (IVb), was obtained by heating IIIb with a mixture of phosphorus pentachloride and phosphoryl chloride at 120° C.

If the reaction of III with phosphoryl chloride is carried out at higher temperatures (140–150° C), conversion to 6-chloro-5-azaindole (VI) occurs. Subsequent reduction of VIa in the presence of a palladium catalyst gave 1-phenyl-5-azaindoline (VIIa), and VIb gave 5-azaindoline, identical with those synthesized previously [3].

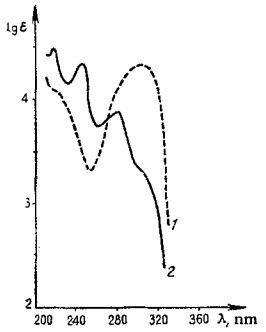


Fig. 1. UV Spectra: 1) 1-phenyl-5-azainodline; 2) 1-phenyl-5-azaindole.

Dehydrogenation of the 5-azaindoline derivatives occurred with somewhat greater difficulty than in the case of the 7-isomers, and the most convenient method for the conversion of 1-substituted 5-azaindolines into the corresponding 5-azaindoles is by heating with palladized charcoal at 255–265° C, as in the case of the 5,7-diazaindolines [7].

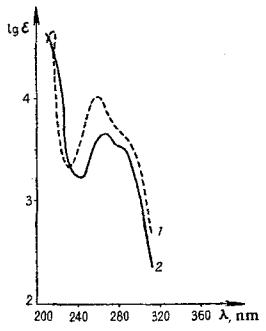


Fig. 2. UV Spectra: 1) 5-azaindoline; 2) 5-azaindole.

It is interesting that the hypsochromic shift of the long-wavelength maximum and the simultaneous increase in intensity (Fig. 1) which is observed in passing from 1-phenyl-5-azaindoline (VIIa) to 1-phenyl-5-azaindole (which is also characteristic of other azaindoline and indoline compounds [2, 7, 8, 9, 10]), is reversed in passing from the 1-

unsubstituted-5-azaindoline (VIIe) to 5-azaindole (VIIIe). In this case, the corresponding maximum in VIIIe is shifted by 6 nm towards the long-wavelength region and the value of lg ε falls from 4.01 to 3.65 (Fig. 2). Similar behavior has been noted previously [11] for 5-isothiocyanatoindoline and 5-isothiocyanatoindole.

EXPERIMENTAL

All the NMR spectra given in this paper were measured on a JNM-4H-100 (100MHz) spectrometer using TMS as internal standard. The solvents used were trifluoroacetic acid and deuteropyridine. The IR spectra were recorded on a UR-10 recording spectrometer, as pastes in vaseline oil, and the UV spectra were taken on an EPS-3 recording spectrophotometer using ethanol as solvent. We thank Yu. N. Sheinker, E. M. Peresleni, L. M. Alekseeva, N. P. Zosimova and Yu. I. Pomerantseva for their help in carrying out the spectral investigations.

6-Oxo-2,3-dihydro-5-azabenzofuran (I). 30.72 g (0.18 mole) of II [5] was dissolved in 300 ml of ethanol and hydrogenated at room temperature under a pressure of 20–30 cm of water, in the presence of a catalyst prepared from 3 g of palladium chloride. The catalyst was filtered off and the solvent removed in vacuo to give 30.8 g (92.6%) of I hydrochloride as colorless crystals, mp 205–206° C (from alcohol). The compound was insoluble in ether and benzene, sparingly soluble in alcohol, and soluble in water. Found, %: Cl 20.84; N 8.36. Calculated for $C_7H_7NO_2 \cdot HCl$, %: Cl 20.42; N 8.08.

Free base. Colorless crystals, mp 212–213° C (from propan-2-ol). Found, %: C 61.40; H 5.05; N 9.84. Calculated for $C_7H_7NO_2$, %: C 61.30; H 5.14; N 10.21.

1-Phenyl-6-oxo-5-azaindoline (IIIa). A mixture of 1 g (0.0073 mole) of I and 2 g (0.021 mole) of aniline was heated for 8 hr at 250° C. The excess aniline was distilled in vacuo to 150° (2mm), and the residue recrystallized from alcohol giving 1.22 g (78.8%) of IIIa as colorless crystals, mp 215–216° C. The compound was sparingly soluble in ether, benzene, ethyl acetate, and chloroform. Found, %: C 73.68; H 5.62; N 13.01. Calculated for $C_{13}H_{12}N_2O$, %: C 73.56; H 5.70; N 13.20.

Hydrochloride. Colorless crystals, mp 201–202° C (from alcohol). Found, %: Cl 14.20; N 11.25. Calculated for $C_{13}H_{12}N_2O \cdot HCl$, %: Cl 14.30; N 11.28.

1-Benzyl-6-oxo-5-azaindoline (IIIb). A mixture of 3 g (0.0219 mole) of I and 7 g (0.065 mole) of benzylamine was heated for 8 hr at 190° C. The excess benzylamine was removed in vacuo at 200° C (15 mm). The residue was recrystallized from dioxane to give 3.56 g (72%) of IIIb as colorless crystals, mp 187–188° C, insoluble in ether, light petroleum, acetone, ethyl acetate, and benzene, and sparingly soluble in chloroform, alcohols, and water, but soluble in hot dioxane. IR spectrum: 1670 cm^{-1} (—CON═). Found, %: C 73.95; H 5.99; N 12.06. Calculated for $C_{14}H_{14}N_2O$, %: C 74.30; H 6.20; N 12.40.

Hydrochloride. Colorless crystals, mp 225–226° C (from alcohol). Found, %: Cl 13.41; N 10.82. Calculated for $C_{14}H_{14}N_2O \cdot HCl$, %: Cl 13.53; N 10.68.

1-p-Methoxyphenyl-6-oxo-5-azaindoline (IIIc). One gram (0.0073 mole) of I and 1.35 g (0.011 mole) of p-anisidine were heated for 8 hr at 190° C. The excess of p-anisidine was removed by washing the reaction mixture with ether, giving 1.47 g (83.2%) of IIIc, colorless crystals, mp 241–242° C (from absolute alcohol). The compound was insoluble in ether, acetone, ethyl acetate, and benzene, and sparingly soluble in chloroform, water, and alcohols. Found, %: C 69.74; H 5.95; N 11.50. Calculated for $C_{14}H_{14}N_2O_2$, %: C 69.44; H 5.78; N 11.56.

1-p-Tolyl-6-oxo-5-azaindoline (IIId). Obtained as for IIIc from 1 g (0.0073 mole) of I and 1.17 g (0.011 mole) of p-toluidine. Yield of IIId 1.18 g (71.5%), colorless crystals, mp 230–231° C (from alcohol). Sparingly soluble in ether, benzene, ethyl acetate, and chloroform, and soluble in hot ethanol. Found, %: C 74.28; H 5.90; N 12.66. Calculated for $C_{14}H_{14}N_2O$, %: C 74.34; H 6.18; N 12.40.

1-Benzyl-6-oxo-7-bromo-5-azaindoline (IVb). To a solution of 1.07 g (0.0048 mole) of IIIb in 10 ml of chloroform was added dropwise 1.75 g (0.0096 mole) of bromine in 3 ml of chloroform. The reaction mixture was kept overnight in the refrigerator (at +3°), the precipitate filtered off, washed with chloroform, acetone and ether, and finally recrystallized from propan-2-ol, giving 0.42 g of IVb. The mother liquors were evaporated to half their original volume to yield a further 0.38 g of IVb. Total yield 0.80 g (55.7%), bright yellow crystals, mp 180–181° C. Sparingly soluble in acetone, ethyl acetate, benzene, chloroform and alcohols, and insoluble in ether, light petroleum and water.

Found; %: C 55.22; H 4.37; Br 26.27; N 9.11. Calculated for $C_{14}H_{13}BrN_2O$, %: C 55.08; H 4.26; Br 26.23; N 9.18.

1-Benzyl-6-oxo-7-chloro-5-azaindoline (Vb). 1.08 g (0.0041 mole) of IIIb hydrochloride was mixed with 1.83 g (0.0088 mole) of phosphorus pentachloride, and 1.5 ml (~0.0098 mole) of phosphoryl chloride added dropwise. The mixture was heated cautiously to 80° C (in a bath). The vigorous reaction which set in was practically complete after 10–15 min, whereupon the mixture was heated at 120° C with stirring for a further 4 hr (in a bath). The reaction mixture was poured onto ice, basified with sodium carbonate, and extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated in vacuo, and the residue was recrystallized from absolute alcohol giving 0.25 g (23.6%) of Vb as colorless crystals, mp 231–232° C. Readily soluble in chloroform, but less so in alcohols and other organic solvents, and insoluble in water. IR spectrum: 1680 cm^{-1} (CONH). Found, %: C 64.62; H 5.30; Cl 13.22; N 10.78. Calculated for $C_{14}H_{13}ClN_2O$, %: C 64.50; H 4.98; Cl 13.60; N 10.77.

1-Phenyl-6-chloro-5-azaindoline (VIa). 5.49 g (0.026 mole) of IIIa was heated in an autoclave for 5 hr at 150° C with 55 ml (0.61 mole) of phosphoryl chloride. The reaction mixture was evaporated in vacuo, and 25 ml of water added to the residue. The mixture was basified with a 50% solution of potassium carbonate, and VIa extracted with benzene. The benzene extract was evaporated in vacuo, and pure VIa was isolated from the crude material by solution in boiling heptane. Removal of the heptane left 2.35 g (39.5%) of VIa as colorless crystals, mp 99–100° C (from alcohol). The compound was soluble in ether, choroform, benzene and acetone, hot alcohol and pentane, and insoluble in water. Found, %: C 68.03; H 5.03; Cl 14.98; N 11.92. Calculated for $C_{13}H_{11}ClN_2$, %: C 67.68; H 4.81; Cl 15.37; N 12.14.

1-Benzyl-6-chloro-5-azaindoline (VIb). Obtained as for VIa, from 4.1 g (0.0182 mole) of IIIb and 41 ml (0.45 mole) of phosphoryl chloride. Extraction was effected with ether (~2 *l*), giving 1.67 g (37.7%) of VIb as colorless crystals, mp 75–76° C (from ethyl acetate). The compound was readily soluble in benzene, acetone, chloroform and alcohols, but less so in ether and ethyl acetate, and insoluble in water. Found, %: C 68.44; H 5.12; Cl 14.89; N 11.7. Calculated for $C_{14}H_{13}ClN_2$, %: C 68.70; H 5.32; Cl 14.54; N 11.44.

5-Azaindoline (VIIe). 5.55 g (0.0226 mole) of VIb was dissolved in 100 ml of alcohol, and hydrogenated at room temperature under a pressure of 20–30 cm of water, in the presence of a catalyst prepared from 5 g of palladium chloride. When the hydrogenation was complete, the catalyst was filtered off, the alcohol distilled off, the residue basified with 50% potassium carbonate, and VIIe extracted with ether giving 2.25 g (82.7%) of colorless crystals, mp 102–103° C. The substance did not depress the mp on admixture with a sample of VIIe obtained by the dehalogenation of 6-chloro-5-azaindoline [3].

1-Phenyl-5-azaindoline (VIIa). Obtained as for VIIe by dehalogenation of 4.5 g (0.0195 mole) of VIa in 150 ml of methanol in the presence of a palladium catalyst. The dehalogenation product, after liberation of the free base, was extracted with ether and distilled in vacuo to give 3.24 g (84.5%) of VIIa, bp 180–182° C (1.2 mm). Colorless crystals, mp 59–60° C (from light petroleum), readily soluble in benzene, acetone, choroform, and ethyl acetate, sparingly soluble in ether and water. UV spectrum: λ_{max}, nm (lg ε): 219 (4.09), 303 (4.34). Found, %: C 79.33; H 6.38; N 14.09. Calculated for $C_{13}H_{12}N_2$, %: C 79.59; H 6.13; N 14.28.

1-Phenyl-5-azaindole (VIIIa). One gram (0.0051 mole) of VIIa and 1 g of 9% palladium-charocoal were heated in a nitrogen atmosphere at 255–265° C until evolution of hydrogen ceased (15 min). The dehydrogenation product was extracted from the reaction mixture with anhydrous ether, giving 0.8 g (80.7%) of VIIIa as colorless crystals, mp 58–59° C (from light petroleum). Readily soluble in ether, benzene, acetone, ethyl acetate, alcohols, and chloroform, but less so in light petroleum, and insoluble in water. UV spectrum: λ_{max}, nm (lg ε): 217 (4.45), 246 (4.35), 280 (3.88). Found, %: C 80.51: H 5.15; N 14.80. Calculated for $C_{13}H_{10}N_2$, %: C 80.50; H 5.17; N 14.43.

5-Azaindole (VIIIa). Obtained similarly by dehydrogenation of 0.9 g (0.0075 mole) of 5-azaindoline (VIIe) by heating with 0.9 g of palladium-charcoal under nitrogen for 5 min at 215–225° C, and 10 min at 260° C. Yield 0.5 g (57.6%), mp 109.5–110° C (from water). A mixed melting point with a sample of VIIIe obtained from 6-chloro-5-azaindoline [2] gave no depression.

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