AZAINDOLE DERIVATIVES.

56.* SYNTHESIS OF 4-BROMO-6-AZAINDOLE

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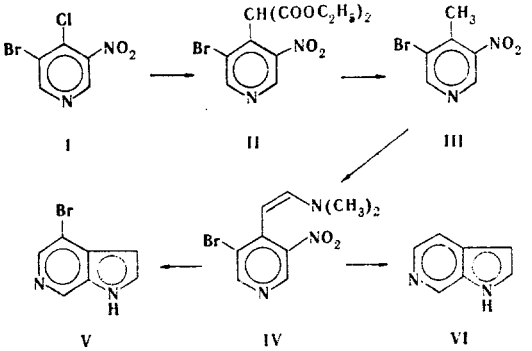
3-Bromo-5-nitro-4-(β-dimethylaminovinyl)pyridine, the reduction of which with iron filings in acetic acid led to 4-bromo-6-azaindole, was obtained from 3-bromo-4-chloro-5-nitropyridine via (3-bromo-5-nitro-4-pyridyl)malonic ester and 3-bromo-5-nitro-4-methylpyridine.

We have previously described methods for the preparation of 6-azaindole and its derivatives with various substituents in the pyrrole portion of the molecule (e.g., see [1]). The present communication is devoted to the synthesis of 4-bromo-6-azaindole, i.e., a compound with a substituent in the pyridine ring. Up until now, 6-azaindole derivatives of this type were difficult to obtain, since they could not be obtained by direct introduction of substituents in the aromatic ring of azaindole. Up until the present research, 4-substituted 6-azaindoles were completely unknown, whereas 6-azaindoles with functional substituents in the 4 position are of considerable interest from the point of view of conversion to aza analogs of known psychotropic agents of the psilocin and psilocybin type.

We used the accessible 3-bromo-4-chloro-5-nitropyridine (I) as the starting compound; condensation of I with malonic ester in the presence of sodium hydride in dimethylformamide (DMF) gives (3-bromo-5-nitro-4-pyridyl)malonic ester (II) in virtually quantitative yield. The latter, in contrast to the previously described [2] products of the condensation of 3-nitro-4-chloropyridine with β-dicarbonyl compounds, exists in dimethyl sulfoxide (DMSO) in the form of a diethoxycarbonyl derivative rather than in a cis-enol form, as evidenced by the presence in the PMR spectrum of the signal of a 4α proton at 5.50 ppm and the absence of the signal of protons of a cis-enolized structure.

The introduction of a bromine atom in the β position of the pyridine ring also affects the ease of saponification of diester II and the subsequent decarboxylation. Whereas (3-nitro-4-pyridyl)malonic ester is converted rather completely to 3-nitro-4-methylpyridine after 3 h when it is heated to 100°C with 18% hydrochloric acid [3], the analogous bromo nitro diester II, according to the results of gas–liquid chromatography (GLC) and preparative isolation of the products, remains unchanged to a significant extent; after 6 h, the formation of III is 50% complete, and the reaction is virtually complete only after heating for 10 h.



*See [1] for communication 55.

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The condensation of methylpyridine III with dimethylformamide diethylacetal at 85-90° takes less than 2 h, and this constitutes evidence for a smaller degree of steric shielding of the methyl group in 3-bromo-5-nitro-4-methylpyridine (III) as compared with the methylene group in (3-nitro-4-pyridyl)acetic ester, for which the analogous reaction is complete only after 11 h [1]. The reductive cyclization of nitro bromo enamine IV can be successfully accomplished with retention of the bromine atom in V by the action of iron in acetic acid. Hydrogenation over a palladium catalyst even at 0°C and in the case of absorption of the theoretical amount of hydrogen leads to a considerable amount of debromination and to the formation of a mixture of starting nitro bromo enamine IV, 4-bromo-6-azaindole (V), and the dehalogenation product 6-azaindole (VI).

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with a Hitachi EPS-3 spectrophotometer. The course of the reactions and the purity of the substances were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in chloroform or ethanol (with detection from the luminescence in UV light) and by GLC with a Pye–Unicam 104 chromatograph with a catharometer. The column (2.1 m by 4 mm) was filled with 10% SE-30 silicone elastomer on silanized diatomaceous earth (100-120 mesh), and the helium flow rate was 30 ml/min. The retention times were as follows: II (140°C) 3.9 min, III (140°C) 17 min, and IV (250°C) 6.6 min. The mass spectrum was recorded with a Varian MAT-112 chromatographic mass spectrometer at an ionizing-electron energy of 50 eV and an emission current of 1.5 μA; the chromatographic conditions are indicated above.

Diethyl (3-Bromo-5-nitro-4-pyridyl)malonate (II). An 8-ml (52.7 mmole) sample of malonic ester was added gradually in a stream of argon with vigorous stirring to a suspension of 1.26 g (52.5 mmole) of sodium hydride in 15 ml of DMF while maintaining the temperature at no higher than 50°C. When hydrogen evolution was complete, the mixture was allowed to stand for 20 min. It was then treated portionwise with 5.2 g (21.9 mmole) of 3-bromo-4-chloro-5-nitropyridine (I) [4] while maintaining the temperature of the reaction mixture at 30–40°C, after which it was stirred at room temperature for 7 h. At the end of the reaction, 50 ml of water was added, and the aqueous mixture was acidified with acetic acid and extracted with ether. The ether extract was dried with magnesium sulfate and vacuum evaporated to give 7.65 g (97%) of II. The compound was purified for analysis by column chromatography (on L 40/100μ silica gel for chromatography) with elution with chloroform–petroleum ether (1:1) to give a light-yellow substance with n_D^{20} 1.5331 that darkened on standing and was quite soluble in ordinary organic solvents but only slightly soluble in water. IR spectrum: 1750 ($COOC_2H_5$); 1580 and 1532 cm^{-1} (C=C, C=N, and NO_2). PMR spectrum (d_6-DMSO): 9.17 (1H, s, 2-H), 9.02 (1H, s, 6-H), 5.50 (1H, s, 4α), 4.26 (4H, q, CH_2), and 1.27 ppm (6H, t, Me). Found: C 40.2; H 3.8; Br 22.2; N 8.1%. $C_{12}H_{13}BrN_2O_6$. Calculated: C 39.9; H 3.6; Br 22.1; N 7.8%.

3-Bromo-5-nitro-4-methylpyridine (III). A mixture of 7.6 g of ester II and 80 ml of 18% hydrochloric acid solution was heated on a boiling-water bath for 10 h, after which it was cooled to room temperature and extracted with ether. The ether solution was dried with magnesium sulfate and vacuum evaporated to give 3.2 g (70%) of III as colorless crystals with mp 57–58°C (from heptane). The product was quite soluble in ether, benzene, acetone, ethyl acetate, alcohols, and chloroform but only slightly soluble in water and heptane. IR spectrum: 1580 and 1510 cm^{-1} (C=C, C=N, and NO_2). UV spectrum, λ_{max} (log ε): 220 (4.1) and 284 nm (3.1). PMR spectrum ($CDCl_3$): 8.93 (1H, s) and 8.86 (1H, s) (2-H and 6-H); 2.66 ppm (3H, s, Me). Mass spectrum: M* 215 (^{79}Br) and 217 (^{81}Br). Found: C 33.3; H 2.4; Br 36.9; N 13.0%. $C_6H_5BrN_2O_2$. Calculated: C 33.2; H 2.3; Br 36.9; N 12.9%.

3-Bromo-5-nitro-4-(β-dimethylaminovinyl)pyridine (IV). A 0.9-ml (5.2 mmole) sample of dimethylformamide diethylacetal was added to a solution of 0.7 g (3.2 mmole) of 4-methylpyridine III in 3 ml of anhydrous DMF, and the mixture was heated at a bath temperature of 85–90°C for 105 min; the end of the reaction was monitored by GLC from the disappearance of the peak of starting III. The reaction mixture was then vacuum evaporated to give 0.77 g (88%) of IV as bright-red crystals with mp 118–119°C (from heptane) that were quite soluble in ether, benzene, acetone, ethyl acetate, alcohols, and chloroform but only slightly soluble

in heptane and water. IR spectrum: 1620 (C=C, C=N) and 1560 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 218 (4.1), 346 (4.2), and 432 nm (3.5). PMR spectrum ($CDCl_3$): 8.53 (1H, s, 2-H), 8.50 (1H, s, 6-H), 7.19 (1H, d, 4α), 5.19 (1H, d, 4β), and 3.01 ppm (6H, s, Me). Found: C 39.7; H 3.7; Br 29.4; N 15.6%. $C_9H_{10}BrN_3O_2$. Calculated: C 39.7; H 3.7; Br 29.4; N 15.4%.

4-Bromo-6-azaindole (V). A mixture of 0.75 g (2.8 mmole) of vinylpyridine IV and 1.0 g (18 mmole) of iron filings in 6 ml (105 mmole) of glacial acetic acid was refluxed for 40 min, after which the unchanged filings were removed by filtration, and the filtrate was diluted with 20 ml of water. The resulting solution was made alkaline to pH 8-9 with potassium carbonate and extracted with chloroform. The extract was dried with magnesium sulfate and vacuum evaporated to give 0.36 g (67%) of 4-bromo-6-azaindole (V) as yellowish crystals with mp 188-189°C (from benzene). The product was insoluble in heptane and water but soluble in ether, benzene, and chloroform and very soluble in acetone, ethyl acetate, alcohols, and hot benzene. IR spectrum: 1600 and 1550 cm^{-1} (C=C and C=N). UV spectrum, λ_{max} (log ε): 375 nm (3.7). PMR spectrum [d_6-DMSO-CCl_4 (1:1)]: 11.81 (1H, s, NH), 8.67 (1H, s, 7-H), 8.12 (1H, s, 5-H), 7.55 (1H, m, 2-H), and 6.44 ppm (1H, m, 3-H). Found: C 42.8; H 2.6; Br 40.3; N 14.2%. $C_7H_5BrN_2$. Calculated: C 42.7; H 2.6; Br 40.6; N 14.2%.

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MASS-SPECTROMETRIC STUDY OF 2- AND 4-AZAFLUORENONES

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A mass-spectrometric study of 2- and 4-azafluorenones and their mono- and polymethyl derivatives showed that the presence of a methyl group in the benzene ring leads to a sharp increase in the relative intensity of the $[M - H]^+$ ion peak. In contrast to the fragmentation of 2- and 4-azafluorenes, the mass spectra of monomethyl-substituted compounds do not contain an $[M - CH_3]^+$ fragment; this is probably associated with expansion of the pyridine or benzene ring to a seven-membered ring in the step involving the formation of the molecular ion due to inclusion of the methyl group. The intensity of the $[M - CO]^+$ ion peak in the mass spectra of the 4-azafluorenones is higher by a factor of two with respect to the 2-azafluorenone isomers, and the $[M - HCN]^+$ and $[M - H, -HCN]^+$ ion peaks observed in the mass spectra of 2-azafluorenones are absent in them.

We have previously investigated the dissociative ionization of 2- and 4-azafluorenes and their derivatives [1, 2]. In the present research we examined the behavior of 2- and 4-azafluorenones under the influence of electron impact in order to ascertain the dependence of their fragmentation on the position of the nitrogen atom and on the character, position, and number of substituents in the azafluorenone ring. To solve this problem we investigated the mass spectra of compounds of this series (Table 1) (see scheme on page 81).

As in the case of 2- and 4-azafluorenes, the molecular-ion peak is the most intense peak in the mass spectra of I-XVI. The molecular ions (M^+) of unsubstituted 4- and 2-azafluorenones I and II have the highest stabilities (W_M) (Table 2). The presence of a methyl

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