REDUCTIVE DEALKOXYLATION OF 5-AZAINDOLE DERIVATIVES

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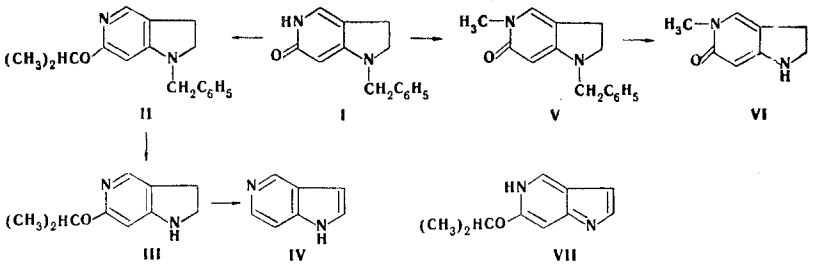
The dehydrogenation of azaindolines is a general method for the synthesis of azaindoles [1]. We have found that reductive dealkoxylation, which leads to an unsubstituted 5-azaindole (IV), proceeds along with dehydrogenation when 6-isopropoxy-5-azaindoline (III) is heated with palladium on carbon.



Compound II was obtained from 1-benzyl-6-oxo-5-azaindoline (I) [2] through its silver salt in analogy with O-alkylation of 1-substituted uracils [3] and was catalytically debenzylated to III. Dimethyl sulfate or methyl iodide gave the N-methyl derivative (V), even when the process was carried out with the silver salt of I. Compounds II, V, and VI were not dehydrogenated when they were heated with palladium on carbon, and II was not oxidized when it was refluxed with $CuCl_2$ in pyridine for 1.5 h. It can be assumed that the dehydrogenation of III proceeds through the quinoid form (VII), the aromatization of which is accompanied by cleavage of an alkoxy group with migration of a hydrogen atom.

EXPERIMENTAL

1-Benzyl-6-isopropoxy-5-azaindoline (II). A 1.23-g (7.2 mmole) sample of silver nitrate in 5 ml of water cooled to 10° was added to 1.64 g (7.2 mmole) of I in 50 ml of boiling water containing 0.3 g (7.4 mmole) of sodium hydroxide. The precipitated silver salt of I was removed by filtration, washed with water and acetone, dried over P_2O_5, and mixed with 2.49 g (14.6 mmole) of isopropyl iodide and 20 ml of anhydrous toluene. The mixture was refluxed for 9 h, the precipitate was removed by filtration, and the filtrate was vacuum-evaporated to give 1.32 g (72%) of II with mp 63-64° (petroleum ether). Found: C 75.8; H 7.2; N 10.6%. $C_{17}H_{20}N_2O$. Calculated: C 76.1; H 7.5; N 10.4%.

1-Benzyl-5-methyl-6-oxo-5-azaindoline (V). A 1.11-g (8.8 mmole) sample of dimethyl sulfate was added in portions at 50° to 0.5 g (2.2 mmole) of I in 40 ml of 20% sodium hydroxide solution. The mixture was refluxed for 1 h and cooled to 20°. Compound V was extracted with chloroform to give 0.35 g (66%) of a product with mp 107.5-108.5° (petroleum ether–benzene). IR spectrum: 1680 cm^{-1} (CON). Found: C 74.9; H 6.5; N 11.7%. $C_{15}H_{16}N_2O$. Calculated: C 75.0; H 6.7; N 11.7%.

Compound V was also obtained by refluxing 2.82 g (8.5 mmole) of the silver salt of I (prepared as described above. Found: N 8.5%. $C_{14}H_{13}AgN_2O$. Calculated: N 8.4%) with 2.45 g (17 mmole) of methyl iodide in 30 ml of anhydrous toluene for 9 h to give 0.9 g (44.2%) of product.

6-Isopropoxy-5-azaindoline (III). A 1.19-g (4.5 mmole) sample of II in 50 ml of methanol was debenzylated with a Pd catalyst (from 2.7 g of palladium chloride) at 20° and a hydrogen pressure of 20-30 cm

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(water standard). The methanol was removed by distillation, and the residue was made alkaline with 25% potassium carbonate solution. Base III was extracted with ether to give 0.7 g (88.5%) of a product with mp 78-79° (petroleum ether). Found: C 67.3; H 7.8; N 15.4%. $C_{10}H_{14}N_2O$. Calculated: C 67.4; H 7.9; N 15.7%.

5-Methyl-6-oxo-5-azaindoline (VI). This compound [0.84 g (91.5%)] was obtained in the same way as III from 1.47 g (6.3 mmole) of V and had mp 164-165° (acetone). Found: C 63.7; H 6.9; N 18.8%. $C_8H_{10}N_2O$. Calculated: C 64.0; H 6.7; N 18.7%.

Dehydrogenation of III and Formation of 5-Azaindole (IV). A mixture of 0.2 g (1 mmole) of III and 0.2 g of 9% palladium on carbon was heated under nitrogen at 207-210° for 10 min. The mixture was cooled to 20° and extracted with chloroform. The chloroform was evaporated, and the residue was chromatographed with a column (d 1 cm, h 25 cm) filled with aluminum oxide with elution by ether to give 0.5 g (37.6%) of IV with mp 109.5-110°. The product did not depress the melting point of a sample of 5-azaindole obtained by the method in [2], and the UV and IR spectra of the samples were identical.

LITERATURE CITED

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