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AZAINDOLE DERIVATIVES.

63.* EFFECT OF THE SOLVATING CAPACITIES OF SOLVENTS ON THE PATHWAYS OF REACTIONS UNDER THE CONDITIONS OF THE HOFMANN REARRANGEMENT

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It is shown that 1-benzyl-6-chloro-7-carbamoyl-5-azaindoline undergoes primarily normal skeletal rearrangement to give 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline under the conditions of the Hofmann reaction in the presence of pyridine, whereas the primary process in aqueous methanol is splitting out of an isocyanate anion to give 1-benzyl-6-chloro-7-bromo-5-azaindoline. Under the same conditions 1-benzyl-6-chloro-7-carbamoyl-5-azaindole is converted to a mixture of 1-benzyl-6-chloro-7-methoxycarbonylamine-5-azaindole and products of electrophilic substitution of the hydrogen in the 3 position of the starting compound and the final reaction products by bromine, whereas 1-benzyl-7-carbamoyl-5-azaindoline forms 1-benzyl-7-methoxy-carbonylamino-5-azaindoline in ∿50% yield.

In a continuation of our earlier research [1] on the synthesis and biological activity of 6,7-disubstituted 5-azaindolines we studied the Hofmann reaction for 1-benzyl-6-chloro-7-carbamoyl-5-azaindoline (I) [2]. As a consequence of the low solubility of amide I in water, the process was carried out under anhydrous conditions with bromine and sodium methoxide. However, when refluxing methanol was used as the solvent, considerable amounts of starting I were recovered unchanged. The addition of pyridine made it possible to raise the boiling point of the mixture and led to the production of the normal rearrangement product, viz., 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline (II).

*See [1] for communication 62.

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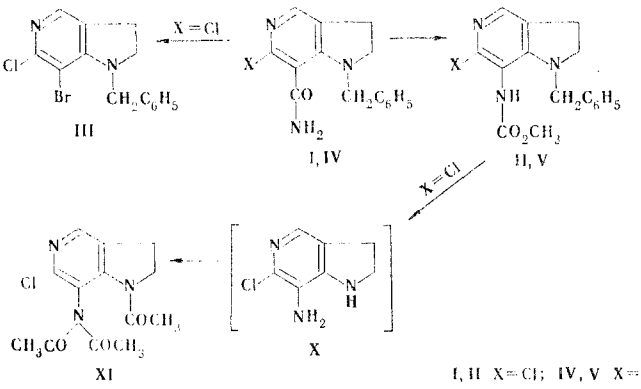


Absorption bands of the stretching vibrations of a methoxycarbonylamino group at 1730 (C=O) and 3400 cm^{-1} (NH) are present in the IR spectrum of II. The mass spectrum contains a molecular-ion peak at 317* and peaks of fragment ions at 258 (M–$COOCH_3$) and 243 (M–$NHCOOCH_3$).

In connection with the relatively low yield (46%) of urethane II, the remaining reaction mixture was subjected to a more detailed study, and a second reaction product, viz., 1-benzyl-6-chloro-7-bromo-5-azaindoline (III), was isolated from it in ∿1.5% yield by chromatography with a column filled with silica gel. The IR spectrum of III does not contain absorption bands at 1620-1800 and 3000-3400 cm^{-1}; a molecular-ion peak at 322 and peaks of fragments at 245 (M–C_6H_5) and 231 (M–$CH_2C_6H_5$) are observed in the mass spectrum.

Replacement of the carbamoyl residue by a bromine atom under the conditions of the Hofmann reaction has been previously described in the case of heptafluoropropionamide [3], which reacts with sodium hypobromite to give the $[C_3F_7CONBr]Na$ salt, which upon pyrolysis gives isocyanate C_3F_7NCO and upon decomposition in aqueous sodium hydroxide solution gives heptafluoropropyl bromide.

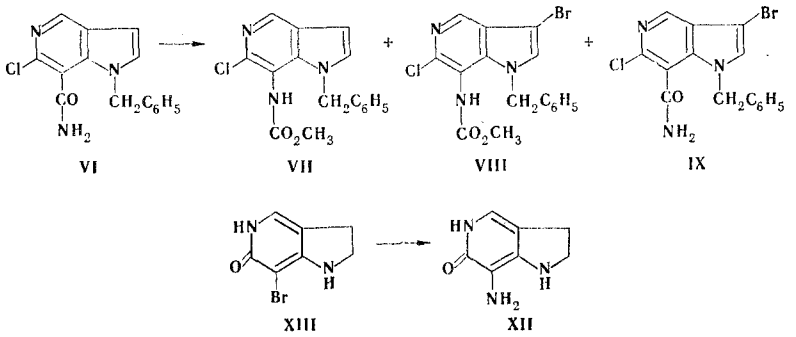
When the Hofmann reaction of amide I with sodium hypobromite was carried out in aqueous methanol solution, bromo derivative III was isolated in 50% yield, and the urethane was obtained in only 6% yield, i.e., in this case the primary reaction was not the normal sextet rearrangement that is characteristic for the Hofmann reaction but rather the previously indicated (in the case of heptafluoropropionamide) splitting out of a cyanate anion to give the corresponding bromo derivative. Barr and Haszeldine [3] explain this anomalous reaction pathway by means of the difficulty involved in the migration of the electronegative C_3F_7 residue to the electron-surplus nitrogen atom and by means of the relative separate character of the bromine and sodium atoms in solution, which hinders the splitting out of bromine from the $[C_3F_7CONBr]Na$ salt. Since in the reactions that we carried out the migrating heterocyclic residues are identical and the temperature (70°C) at which the process is carried out is the same in both cases, the different reaction pathways in an aqueous alcohol medium (preponderant formation of bromide III) and in the presence of pyridine (preponderant formation of urethane II) are evidently associated precisely with the character of the solvents, which differ substantially with respect to their solvation properties.

The migration of the hydrophobic azaindoline residue is evidently hindered in the methanol–water mixture, and the reaction is directed primarily to favor ejection of a cyanate anion and the formation of bromo derivative III. In pyridine–methanol the high solvation capacity of pyridine with respect to azaindoline derivatives facilitates the normal sextet rearrangement, and the chief reaction product becomes urethane II.

The establishment of the role of the solvents in the investigated reaction enabled us to realize the conversion of 1-benzyl-7-carbamoyl-5-azaindoline (IV) [4] to urethane V in 50% yield when we carried out the normal Hofmann reaction in a mixture of methanol with pyridine. Under the same conditions 1-benzyl-6-chloro-7-carbamoyl-5-azaindole (VI) is converted to 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindole (VII). However, in this case the process is complicated by facile electrophilic substitution reactions involving replacement of the hydrogen in the 3 position of the azaindole molecule by bromine. In addition to urethane VII (in 26% yield), 1-benzyl-3-bromo-6-chloro-7-methoxycarbonylamino- (VIII) and 1-benzyl-3-bromo-

*Here and subsequently, the mass numbers (m/z) of the ions that contain the lightest isotopes of the halogens are presented.

6-chloro-7-carbamoyl-5-azaindole (IX), the presence of which was established on the basis of data from the IR and mass spectra, and therefore also are formed in this reaction. We did



not detect even traces of bromo derivatives of the III type in either case, evidently in connection with the high capacities of IV and VI to undergo solvation.

Saponification and N-debenzylation occurred simultaneously when urethane II was refluxed with concentrated hydrochloric acid. The resulting 6-chloro-7-amino-5-azaindoline (X) is extremely unstable, and, after treatment with acetic anhydride, it was therefore isolated in the form of triacetyl derivative XI, the mass spectrum of which contains a molecular-ion peak at 295 and peaks of fragments at 253 ($M-COCH_2$) and 211 ($M-2COCH_2$); the IR spectrum contains bands of stretching vibrations of $NCOCH_3$ (1695 cm^{-1}) and $N(COCH_3)_2$ (1730 cm^{-1}) groups. 6-Hydroxy-7-amino-5-azaindoline (XII), which, just like 6-oxo-7-bromo-5-azaindoline (XIII) [5], from which it was obtained in 59% yield as a result of the reaction with hydrazine hydrate, exists primarily in the oxo form according to the IR spectral data, proved to be more stable than amine X. It is interesting to note that a reductive process takes place during this reaction, and only 6-hydroxy-7-amino-5-azaindoline (XII) is formed instead of the 7-hydrazino derivative.

EXPERIMENTAL

The IR spectra of mineral oil suspensions (if not specially stipulated in the text) were recorded with a Perkin–Elmer 457 spectrophotometer. The UV spectra of solutions in ethanol were recorded with a Perkin–Elmer 402 spectrophotometer. The PMR spectra of solutions in $CDCl_3$ (if not specially stipulated in the text) were recorded with a JNH-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with an MAT-112 mass spectrometer (direct introduction) at 70 eV. The chromatographic mass spectra were recorded with a Varian MAT-112 spectrometer at 70 eV with helium as the carrier gas.*

1-Benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline (II). A solution of 0.2 ml (4 mmole) of bromine in 4 ml of pyridine was added to a mixture of 1.27 g (4 mmole) of 1-benzyl-6-chloro-7-carbamoyl-5-azaindoline (I) in 10 ml of pyridine and sodium methoxide, prepared from 10 ml of methanol and 0.18 g (8 mmole) of sodium, after which the mixture was heated at 70°C for 1 h. It was then evaporated *in vacuo*, and the pyridine residues were removed by distillation with toluene. Water (20 ml) was added to the residue, and the aqueous mixture was extracted with chloroform (three 40-ml portions). The extract was dried with magnesium sulfate, the chloroform was removed *in vacuo* until the volume of the solution was ~10 ml, and the concentrate was applied to a chromatographic column filled with silica gel (100/160 μ, *l*/h = 9) and eluted with chloroform. Fraction (1) yielded 0.02 g (1%) of 1-benzyl-6-chloro-7-bromo-5-azaindoline (III) (identified by comparison with a genuine sample). Fraction (3) yielded 0.23 g of a mixture [according to the results of thin layer chromatography (TLC) [ethyl acetate–benzene (1:1)]] of three compounds; the principal spot was 1-benzyl-6-chloro-7-bromo-5-azaindoline (III). Fraction (3) yielded 0.64 g (46%) of yellow crystals of 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline (II) with mp 161-162°C. The product was quite soluble in dimethylformamide (DMF), alcohols, chloroform, and ethyl acetate, only slightly soluble in benzene and ether, and insoluble in hexane and water. IR spectrum (in $CHCl_3$):

*The spectral studies were made by K. F. Turchin, O. S. Anisimova, E. M. Peresleni, and coworkers in the laboratory of physical-chemical methods of investigation of the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry (under the supervision of Professor Yu. N. Sheinker).

1730 (C=O) and 3400 cm^{-1} (NH). PMR spectrum: 3.0 (2H, t, 3-H), 3.6 (2H, t, 2-H), 3.65 (3H, s, CH_3O), 4.62 (2H, s, $CH_2C_6H_5$), 4.88 (1H, broad signal, NH), 7.30 (5H, m, aromatic), and 7.7 ppm (1H, s, 4-H). Mass spectrum,* m/z values: 317 (100) [$(M^{+\cdot})$], 258 (17.9) $[M-OCOCH_3]^+$, 243 (57.2), $[M-HCO_2CH_3]^+$, 240 (78.6) $[M-C_6H_5]^+$. Found, %: C 60.9; H 5.2; Cl 10.9; N 13.2. $C_{16}H_{16}ClN_3O_2$. Calculated, %: C 60.5; H 5.1; Cl 11.2; N 13.2.

1-Benzyl-6-chloro-7-bromo-5-azaindoline (III). A solution of 0.56 g (14 mmole) of sodium hydroxide in 10 ml of water and 0.36 ml (7 mmole) of bromine were added at 10°C to a solution of 2 g (7 mmole) of azaindoline I in 100 ml of methanol, and the mixture was heated at 70°C for 4 h. It was then evaporated, and the residue was treated with chloroform (two 50-ml portions). The combined chloroform extracts were evaporated to a volume of 10 ml, and the concentrate was chromatographed with a column filled with silica gel (100/160 μ, 100 g, $l/h = 9$) by elution with chloroform. Fraction (1) yielded 1.12 g (50%) of cream-colored crystals of 1-benzyl-6-chloro-7-bromo-5-azaindoline (III) with mp 95-97°C. The product was quite soluble in DMF, alcohols, chloroform, and acetone, only slightly soluble in ether and hexane, and insoluble in water. Found, %: C 51.8; H 3.8; N 8.7; M^+ 322. $C_{14}H_{12}BrClN_2$. Calculated, %: C 52.0; H 3.7; N 8.7; M 322. Fraction (2) yielded 0.13 g (6%) of 1-benzyl-6-chloro-7-methoxycarbonylamino-5-azaindoline (II) (established by comparison with a genuine sample).

1-Benzyl-7-carbamoyl-5-azaindoline (IV). A 3.2-g sample of 5% palladium on charcoal was added to a solution of 2.2 g (7.7 mmole) of azaindoline I in 250 ml of 95% ethanol, and the mixture was shaken with hydrogen for 12 h. The catalyst was removed by filtration and washed with ethanol, and the filtrate was evaporated. The residue was treated with a concentrated aqueous solution of potassium carbonate, and the precipitate was removed by filtration, washed with water, and dried to give 1.3 g (67%) of colorless crystals of azaindoline IV with mp 186-187°C. The product was quite soluble in DMF and alcohols, only slightly soluble in benzene and ethyl acetate, but insoluble in ether and water. IR spectrum: 1660 (C=O); 3160, 3300 cm^{-1} (NH_2). UV spectrum, λ_{max}(log ε): 208 (4.42) and 275 nm (4.41). PMR spectrum: 3.15 (2H, t, $3CH_2$), 3.65 (2H, t, 2-H), 4.65 (2H, s, $CH_2C_6H_5$), 5.60 (2H, broad signal, NH_2), 7.25 (5H, m, $CH_2C_6H_5$), 8.02 (1H, s, 4-H), and 8.22 ppm (1H, s, 6-H). Found, %: C 70.8; H 6.3; N 16.6; M^+ 253. $C_{15}H_{15}N_3O$. Calculated, %: C 71.1; H 6.0; N 16.6; M 253.

1-Benzyl-7-methoxycarbonylamino-5-azaindoline (V). A solution (25 ml) of sodium methoxide, prepared from 25 ml of methanol and 0.24 g (10 mmole) of sodium, and 0.26 ml (5 mmole) of bromine were added to a solution of 1.3 g (5 mmole) of azaindoline IV in 10 ml of pyridine, and the mixture was heated at 70°C for 15 min until the starting substance had vanished according to TLC [methanol–chloroform (1:1)]. The reaction mixture was evaporated, and the pyridine residues were removed by azeotropic distillation with toluene. Water (30 ml) was added to the residue, and the aqueous mixture was extracted with chloroform (three 50-ml portions). The combined extracts were dried with magnesium sulfate and evaporated, and the residue was crystallized from benzene to give 0.72 g (50%) of yellow crystals of azaindoline V with mp 173-175°C. The product was quite soluble in DMF, alcohol, and chloroform, only slightly soluble in benzene and ether, and insoluble in heptane and water. IR spectrum: 1680 (C=O); 3100, 3260, and 3420 cm^{-1} (NH). Found, %: C 67.4; H 6.4; N 14.6; M^+ 283. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.8; H 6.1; N 14.8; M 283.

1-Benzyl-6-chloro-7-carbamoyl-5-azaindole (VI). A 10-g sample of γ manganese dioxide was added to a solution of 0.87 g (3 mmole) of azaindoline I in 150 ml of methylene chloride, and the mixture was stirred at 20°C for 20 h. The precipitate was removed by filtration, and the solution was evaporated *in vacuo* to give 0.53 (61%) of colorless crystals of amide VI with mp 191-192°C. The product was quite soluble in DMF and ethanol, only slightly soluble in chloroform, and insoluble in ether, ethyl acetate, and water. IR spectrum: 1682 (C=O) and 3100-3250 cm^{-1} (NH_2). UV spectrum, λ (log ε): 229 (4.96) and 240 nm (4.12). PMR spectrum: 5.45 (2H, s, $CH_2C_6H_5$), 5.8 (2H, broad signal, NH_2), 6.7 (1H, d, 3-H), 7.15 (1H, d, 2-H), 7.2-7.4 (5H, m, $CH_2C_6H_5$), and 8.7 ppm (1H, s, 4-H). Found, %: C 62.5; H 4.1; Cl 12.2; N 14.5; M^+ 285. $C_{12}H_{15}ClN_3O$. Calculated, %: C 62.5; H 4.2; Cl 12.4; N 14.7; M 285.

1-Benzyl-6-chloro-7-methoxycarbonylamino-5-azaindole (VII). A solution (20 ml) of sodium methoxide, prepared from 20 ml of methanol and 0.18 g (7.8 mmole) of sodium, and 0.2 ml (4

*Here and subsequently, the relative intensities of the ion peaks in percent relative to the maximum peak are presented in parentheses.

mmole) of bromine was added to a solution of 0.56 g (2 mmole) of azaindole VI in 10 ml of pyridine, and the mixture was heated at 70°C for 3 h. It was then evaporated, and the residue was crystallized from benzene to give 0.16 g (26%) of yellow crystals of azaindole VII with mp 193-194°C. The product was quite soluble in alcohols, chloroform, and ethyl acetate and only slightly soluble in benzene and ether. IR spectrum: 1710 (C=O), 3120, 3210 cm^{-1} (NH). Found, %: C 61.1; H 4.7; Cl 11.0; N 13.2; M^+ 315. $C_{16}H_{14}ClN_3O_2$. Calculated, %: C 60.9; H 4.6; Cl 11.2; N 13.3; M 315. According to the mass spectrum, the residue after crystallization contained 1-benzyl-3-bromo-6-chloro-7-carbamoyl-5-azaindole (M^+ 365) and 1-benzyl-3-bromo-6-chloro-7-methoxycarbonylamino-5-azaindole (M^+ 393). When the amounts of sodium and bromine per mole of starting VI were halved as compared with the ratio described above, the reaction did not go to completion under the same conditions.

1-Acetyl-6-chloro-7-diacetylamino-5-azaindoline (XI). A solution of 1 g (3 mmole) of azaindoline II in 50 ml of concentrated HCl was refluxed for 30 h, after which it was evaporated, 20 ml of concentrated NH_4OH was added to the residue, and the mixture was extracted with two 25-ml portions of chloroform. The combined chloroform extracts were dried with magnesium sulfate, the chloroform was removed *in vacuo*, 20 ml of acetic anhydride was added to the residue, and the mixture was refluxed for 4 h. The acetic anhydride residues were decomposed with ethanol, the resulting ethyl acetate was removed by distillation, and the residue was crystallized from ether to give 0.51 g (57%) of yellow crystals of azaindoline XI with mp 128-130°C. The product was quite soluble in alcohols, ethyl acetate, and chloroform, only slightly soluble in ether and benzene, and insoluble in water. IR spectrum: 1695 (1-$COCH_3$) and 1730 cm^{-1} [7-$(COCH_3)_2$]. Mass spectrum: 295 (25.0) [M^+], 253 (21.2) [$M-COCH_2$]$^+$, 211 (100) [$M-2COCH_2$]$^+$. Found, %: C 52.8; H 4.7; N 14.3; M 295. $C_{13}H_{14}ClN_3O_3$. Calculated, %: C 52.9; H 4.8; N 14.2; M 295.

6-Hydroxy-7-amino-5-azaindoline (XII). A 70-ml sample of hydrazine hydrate was added to 4.05 g (11 mole) of 6-hydroxy-7-bromo-5-azaindoline (XIII), and the mixture was refluxed for 10 h. It was then evaporated to half its original volume, the concentrate was cooled to room temperature, and the precipitate was removed by filtration, washed with water, and dried to give 1.69 g (59%) of colorless crystals of azaindoline XII (mp 265-267°C), which rapidly darkened during storage. The product was quite soluble in acids, DMF, and methanol, only slightly soluble in ethanol and water, and insoluble in ethyl acetate, chloroform, and isopropyl alcohol. IR spectrum: 1665 (C=O); 3090, 3250, and 3495 cm^{-1} (NH_2, NH). PMR spectrum (in CD_3OD): 2.9 (2H, t, 3-H), 3.6 (2H, t, 2-H), and 6.7 ppm (1H, broad signal, 4-H). Found, %: C 55.6; H 6.3; N 27.8; M^+ 151. $C_7H_9N_3O$. Calculated, %: C 55.6; H 6.0; N 27.8; M 151.

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