AZAINDOLE DERIVATIVES.

62.* SYNTHESIS AND TRANSFORMATIONS OF CONDENSED THREE-RING SYSTEMS THAT INCLUDE A 5-AZAINDOLINE FRAGMENT

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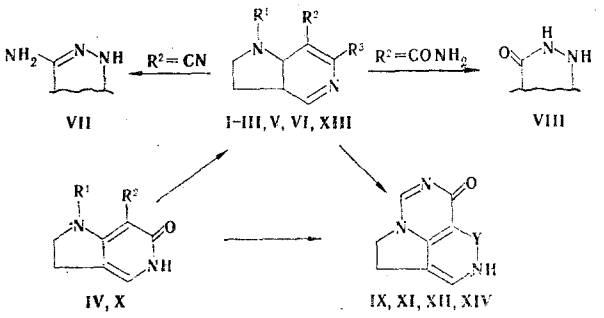
The reaction of 7-carbamoyl- and 7-cyano-6-chloro-5-azaindolines with hydrazine leads to the formation of pyrrolo[2,3-d]pyrazolo[5,4-b]pyridine, whereas the reaction of 7-carbamoyl-5-azaindolines with dimethylformamide diethylacetal gives pyrrolo[1,2-c]pyrido]4,3-d]pyrimidines — two new heterocyclic systems. The chemical properties of the synthesized compounds, including cleavage of the pyrimidine ring under the influence of nucleophilic agents, were studied.

Our previously developed [1-3] methods for the preparation of diverse polyfunctional 5-azaindoline derivatives have opened up possibilities for research on the synthesis of new condensed heterocyclic systems that include a 5-azaindoline fragment.

As the starting compounds for conducting these studies we used the previously described 7-substituted 1-benzyl-6-chloro-5-azaindolines (I, II) [2, 3] and the previously unknown 7-carbamoyl-5-azaindolines (III-VI).



I $R=CH_2Ph$, $R^2=CN$, $R^3=Cl$; II $R^1=CH_2Ph$, $R^2=CONH_2$, $R^3=Cl$, III $R^1=R^3=H$, $R^2=CONH_2$, IV $R^1=H$, $R^2=CONH_2$, V $R^1=H$, $R^2=CONH_2$, $R^3=Cl$, VI $R^1=H$, $R^2=CONH_2$, $R^3=N(CH_3)_2$, IX Y=CH, X $R^1=CH_2Ph$, $R^2=CN$, XI Y=CO, XII Y=CCl, XIII $R^1=H$, $R^2=CONH_2$, $R^3=$ piperidino, XIV $Y=CN(CH_3)_2$

In the reaction of I and II with hydrazine hydrate we obtained, respectively, 1-amino-6,7-dihydro- (VII) and 1-oxo-6,7-dihydro-2H-pyrrolo[2,3-d]pyrazolo[4,5-b]-pyridine (VIII) in high yields. Nucleophilic substitution of the chlorine atom in the 6 position of the starting azaindoline derivatives I and II by a hydrazine residue evidently occurs initially in both cases, after which cyclization takes place. Absorption bands at 3020, 3120, 3180, 3310, and 3395 cm^{-1}, which are characteristic for the stretching vibrations of NH and NH_2 groups, are observed in the IR spectrum of VII, and this constitutes evidence in favor of an amino rather than an imino structure, whereas bands at 3100 (NH) and 1640 cm^{-1} (CO), which constitute evidence for a lactam structure, are observed in the spectrum of VIII. A shift of the lactam—lactim and amino—imino tautomeric equilibria virtually completely to favor the lactam and amino forms is also confirmed by the UV spectroscopic data. Both VII and VIII are characterized by high stability, and they remain unchanged when they are refluxed in aqueous solutions of mineral acids and alkalis.

*See [1] for communication 61.

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In the reduction of 5-azaindoline II with sodium in liquid ammonia, in contrast to the analogous reactions with 1-benzyl-6-chloro-7-azaindolines [4], we observed only debenzylation and dehalogenation and no conversion of the azaindoline compound to an azaindole derivative; this is evidently associated with the previously noted [5] higher oxidation potentials of 5-azaindolines as compared with 7-azaindolines. When the resulting 7-carbamoyl-5-azaindoline (III) was refluxed with excess dimethylformamide (DMF) diethylacetal, it was converted in high yield to the 3-oxo derivative of the previously undescribed pyrrolo[1,2-c]pyrido[4,3-d]-pyrimidine system (IX). 6-Substituted 7-carbamoyl-5-azaindolines IV-VI were synthesized from azaindolines II [3] and X [2].* Brief refluxing of azaindoline X with concentrated hydrobromic acid made it possible to stop the process, which subsequently terminates with the elimination of the cyano group [2], at the step involving the formation of a mixture of equimolar amounts of indoline IV and 6-hydroxy-5-azaindoline. The isolation of amide IV from this mixture proved to be a difficult task, and the mixture of the substances was used for the synthesis of pyrrolopyridopyrimidine XI without isolation. As in the case of III, the reaction with DMF diethylacetal gave the product in high yield. The PMR spectrum (CF_3COOH) contains signals at 3.37 (2H, t, 7-H), 4.71 (2H, t, 8-H), 7.64 (1H, s, 6-H), and 8.8 ppm (1H, s, 1-H).

Refluxing azaindoline II with hydrobromic acid proceeded more unambiguously and made it possible to obtain the corresponding dibenzylated product, viz., azaindoline V.

It is interesting to note that, in contrast to N-benzyl derivative II, in which the chlorine atom in the 6 position undergoes nucleophilic substitution by an amino group with extreme difficulty (it does not react with sodium amide in refluxing xylene, with ammonia under pressure at 220°C for 6 h, with excess potassium phthalimide in refluxing DMF for 20 h, etc.), dibenzylated product V reacts with dimethylamine to give 6-dimethylaminoazaindoline VI.

Reactions involving nucleophilic substitution of the chlorine atom by amine residues are realized under more severe conditions in the case of 3-chloropyrrolopyridopyrimidine XII, which was obtained by cyclization of chloro amide V with DMF diethylacetal; in this case, in addition to nucleophilic substitution of the chlorine atom, the pyrimidine ring is opened,† and the final products of the reaction of chlorine-substituted three-ring system XII with amines are azaindolines XIII and VI.

In this connection, in order to obtain 3-dimethylaminopyrrolopyridopyrimidine XIV it was necessary to use cyclization of 6-dimethylaminoazaindoline VI with DMF diethylacetal via the method described above rather than substitution of the chlorine atom by the dimethylamino group in chlorine-substituted three-ring product XII.

The possibility of substitution of the chlorine atom in XII by residues of various amines to give 6-amino-substituted 7-carbamoyl-5-azaindolines of the VI and XIII type and subsequent production, via ring closure of them, of 3-amino derivatives of pyrrolo[1,2-c]pyrido[4,3-d]-pyrimidine by means of DMF diethylacetal opens up wide-ranging prospects for the production of diverse amino-substituted three-ring compounds of the XIV type.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The UV spectra of solutions in ethanol were recorded with a Perkin-Elmer 402 spectrometer. The PMR spectra were obtained with a JNH-4H-100 spectrometer with tetramethylsilane as the internal standard.

The mass spectra were recorded with an MAT-112 mass spectrometer by direct introduction of the samples at 70 eV.‡

*Here and subsequently, it is demonstrated by IR spectroscopy that the 6-hydroxy-5-azaindolines IV and X described in the paper actually exist primarily in the oxo form, as represented in their structural formulas.

†Cleavage of the pyrmidine ring in two-ring systems that contain a pyrimidine fragment under the influence of amines and other nucleophilic agents has been previously noted [6, 7].

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

7-Carbamoyl-5-azaindoline (III). A 300-ml sample of anhydrous liquid ammonia was added to 2.67 g (9.3 mmole) of azaindoline II, after which 3 g (130 mmole) of sodium was added to the mixture. The ammonia was allowed to evaporate freely with cooling, 100 ml of methanol was added, the mixture was evaporated to dryness *in vacuo*, and 50 ml of water was added. The mixture was extracted with chloroform (ten 50-ml portions), and the combined chloroform extracts were dried and evaporated to give 0.95 g (63%) of amide III with mp 256-257°C (from isopropyl alcohol). The product was quite soluble in DMF, less soluble in chloroform and alcohols, and only slightly soluble in benzene, heptane, and water. IR spectrum: 1677 (CO); 3140, 3270 cm^{-1} (NH_2). Found: C 58.8; H 5.5; N 25.9; M^+ 163. $C_8H_9N_3O$. Calculated: C 58.9; H 5.5; N 25.8%; M 163.

6-Chloro-7-carbamoyl-5-azaindoline (V). A mixture of 22.07 g (76.5 mmole) of azaindoline II and 500 ml of concentrated hydrobromic acid was refluxed for 1 h with removal of the resulting benzyl bromide with the hydrobromic acid by distillation. The residue was evaporated to dryness *in vacuo*, 100 ml of water was added with cooling, and the mixture was made alkaline with potassium carbonate and extracted with chloroform. The chloroform extract was dried and evaporated to give 7.6 g (50%) of amide V in the form of colorless crystals with mp 234-235°C (from DMF). Found: Cl 17.5; N 20.8%; M^+ 197. $C_8H_8ClN_3O$. Calculated: Cl 17.9; N 21.2%; M 197.

6-Dimethylamino-7-carbamoyl-5-azaindoline (VI). Dimethylamine was bubbled through a refluxing solution of 3.0 g (16.2 mmole) of azaindoline V in 125 ml of DMF for 5 h, after which the solvent was removed by vacuum distillation. The residue was treated with water and potassium hydroxide and extracted with chloroform. The residue was crystallized from benzene to give 1.72 g (55%) of amide VI as colorless crystals with mp 205.6-206.5°C. Found: C 58.4; H 7.1; N 27.5%; M^+ 206. $C_{10}H_{14}N_4O$. Calculated: C 58.2; H 6.8; N 27.2%; M 206.

1-Amino-8-benzyl-6,7-dihydropyrrolo[2,3-d]pyrazolo[5,4-b]pyridine (VII). A 20-ml sample of hydrazine hydrate was added to 1.42 g (5 mmole) of azaindoline I, and the mixture was refluxed for 3 h. The reaction mixture was then cooled to 20°C, and the precipitate was removed by filtration, washed with water, and dried to give 1.4 g (100%) of VII as colorless crystals with mp 252-254°C. The product was only slightly soluble in DMF and alcohols and insoluble in water, ethyl acetate, and chloroform. IR spectrum: 3020, 3120, 3180, 3310, and 3395 cm^{-1} (NH, NH_2). UV spectrum, λ_{max} (log ε): 208 (5.61); 232 (5.66); 272 (5.18); 337 nm (5.42). PMR spectrum ($CDCl_3$+CF_3COOH): 3.3 (2H, t, 6-H), 4.1 (2H, t, 7-H), 5.1 (2H, s, $CH_2C_6H_5$), 7.45 (5H, m, $CH_2C_6H_5$), and 7.75 ppm (1H, s, 5-H). Mass spectrum: 265 $[M]^+$, 188 $[M-C_6H_5]^+$, 174 $[M-CH_2C_6H_5]^+$. Found: C 68.2; H 5.6; N 26.6%; $M^{+\cdot}$ 265. $C_{15}H_{15}N_5$. Calculated: C 67.9; H 5.7; N 26.4%; M 265.

1-Oxo-8-benzyl-6,7-dihydro-2H-pyrrolo[2,3-d]pyrazolo[5,4-b]pyridine (VIII). Hydrazine hydrate (20 ml) was added to 0.58 g (17 mmole) of the hydrochloride of II, and the mixture was refluxed for 10 h, after which it was evaporated, and the residue was crystallized from ethanol to give 0.41 g (85%) of pyridine VIII as green crystals with mp > 300°C. The product was only slightly soluble in DMF, alcohols, and water. UV spectrum, λ_{max} (log ε): 210 (5.46); 232 (5.56); 297 (5.46); 375 nm (3.90). PMR spectrum (d_6-DMSO): 2.89 (2H, t, 6-H_2), 3.60 (2H, t, 7-H_2), 5.56 (2H, s, $CH_2C_6H_5$), 7.24 (5H, s, $CH_2C_6H_5$), and 7.32 ppm (1H, s, 5-H). Mass spectrum: 266 $[M]^{+\cdot}$, 189 $[M-C_6H_5]^+$, 175 $[M-CH_2C_6H_5]^+$. Found: C 67.5; H 5.4; N 21.0%; $M^{+\cdot}$ 266. $C_{15}H_{14}N_4O$. Calculated: C 67.7; H 5.3; N 21.0%; M 266.

3-Oxo-7,8-dihydropyrrolo[1,2-c]pyrido[4,3-d]pyrimidine (IX). A 30-ml sample of DMF diethylacetal was added to 0.87 g (5.3 mmole) of azaindoline III, and the mixture was refluxed for 3 h. It was then cooled, and the precipitate was removed by filtration and washed with isopropyl alcohol to give 0.87 g (93%) of IX in the form of light-yellow acicular crystals with mp 282-283°C (from DMSO). The product was quite soluble in ordinary organic solvents and water. Found: C 62.4; H 4.2; N 24.1%; M^+ 173. $C_9H_7N_3O$. Calculated: C 62.4; H 4.1; N 24.3%; M 173.

3,4-Dioxopyrrolo[1,2-c]pyrido[4,3-d]pyrimidine (XI). A 300-ml sample of concentrated hydrobromic acid was added to 7 g (27 mmole) of azaindoline X, and the azeotropic mixture of hydrobromic acid and benzyl bromide was removed by distillation for 2 h until benzyl bromide was absent in the distillates. The reaction mass was evaporated, 10 ml of water and 50 ml of chloroform were added to the residue, and the mixture was neutralized with 50% aqueous potassium carbonate solution and cooled to 0°C. The resulting precipitate was removed by filtration, washed with water, and dried to give 1.8 g of a mixture of 6-hydroxy-5-azaindoline and

azaindoline IV in a ratio of 1:1, according to the data from the PMR spectra. A 90-ml sample of DMF diethylacetal was added to this mixture, and the resulting mixture was refluxed for 4 h. It was then cooled to 20°C, and the precipitate was removed by filtration to give 0.74 g (49%) of XI in the form of colorless crystals with mp > 300°C. The product was quite soluble in DMF and DMSO, only slightly soluble in methanol, and insoluble in chloroform and ethyl acetate. IR spectrum: 1660-1690 (CO) and 3040-3140 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 208 (4.24); 230 (4.34); 300 nm (4.10). PMR spectrum (CD_3COOD): 3.37 (2H, t, 7-H), 4.71 (2H, t, 8-H), 7.64 (1H, s, 6-H), and 8.8 ppm (1H, s, 1-H). Found: C 57.0; H 3.7; N 22.2%; M^+· 189. $C_9H_7N_3O_2$. Calculated: C 57.1; H 3.7; N 22.2%; M 189.

3-Oxo-4-chloro-7,8-dihydropyrrolo[1,2-c]pyridino[4,3-d]pyrimidine (XII). A mixture of 3.88 g (19.7 mmole) of azaindoline V and 100 ml of DMF diethylacetal was refluxed for 4 h with removal of the resulting ethanol by distillation. The residue was cooled, and the precipitate was removed by filtration, triturated with 50 ml of isopropyl alcohol, and crystallized from DMF to give 1.61 g (39.6%) of XII in the form of colorless crystals with mp > 360°C. Found: C 52.4; H 2.8; Cl 17.6; N 20.3%; M^+ 207. $C_9H_6ClN_3O$. Calculated: C 52.1; H 2.9; Cl 17.1; N 20.2%; M 207.

6-Piperidino-7-carbamoyl-5-azindoline (XIII). A mixture of 1.0 g (4.8 mmole) of XII and 15 ml of piperidine was heated in a bomb at 180-190°C for 13 h, after which the reaction mass was diluted with water, made alkaline with potassium carbonate, and extracted with chloroform. The combined chloroform extracts were dried and evaporated, and the piperidine residues were removed *in vacuo* with xylene. The residue was crystallized from benzene–hexane to give 0.8 g (67.5% of colorless crystals of amide XIII with mp 138.5-139.5°C. Found: C 63.5; H 7.3; N 22.9%; M^+ 246. $C_{13}H_{18}N_4O$. Calculated: C 63.4; H 7.4; N 22.8%; M 246.

Compound VI was similarly obtained in 85% yield from XII and an ethanol solution of dimethylamine.

2-Dimethylamino-3-oxo-7,8-dihydropyrrolo[1,2-c]pyrido[4,3-d]pyrimidine (XIV). A 1.7-g (8.2 mmole) sample of VI was refluxed with 60 ml of DMF diethylacetal for 4 h, after which the mixture was evaporated to dryness *in vacuo*, and the residue was washed with hot benzene and crystallized from isopropyl alcohol to give 0.54 g (80%) of XIV with mp 170.5-171.5°C. Found: C 61.3; H 5.9; N 25.8%; M^+ 216. $C_{11}H_{12}N_4O$. Calculated: C 61.1; H 5.6; N 25.9%; M 216.

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