SYNTHESIS OF PYRROLO[1,2-a]PYRIMIDINE DERIVATIVES

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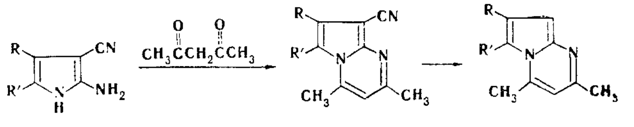
8-Cyanopyrrolo[1,2-a]pyrimidines, the cyano group of which is eliminated when they are heated with phosphoric acid, were obtained by reaction of 2-amino-3-cyanopyrroles with acetylacetone.

Continuing our studies [1, 2] of the condensation of acetylacetone with 2-amino-3-cyanopyrroles (Ia-h),* we have found that the yields of pyrrolo[1,2-a]pyrimidines are substantially affected not only by the nature of the solvents but also by the temperature conditions of the reaction. Thus if the reaction is carried out at 100-120°C in dioxane, pyridine, or acetic acid, 2,4,6,7-tetramethyl-8-cyanopyrrolo[1,2-a]pyrimidine (IIc) is formed in 20, 50, or 80% yield, respectively. Particularly high yields of pyrrolopyrimidines IIa-h (up to 94%) are obtained when the aminopyrroles are heated in excess acetylacetone at 140°.

We have observed that heating IIa, c, g with 100% phosphoric acid leads to elimination of the cyano group to give the corresponding pyrrolo[1,2-a]pyrimidines (IIIa, c, g) with a free 8 position, which up until now were unknown, in 80-90% yields. The only representative of this series – 2,4-dimethyl-7-phenylpyrrolo[1,2-a]pyrimidine – could previously be isolated only in the form of the picrate [4].



I a-h   II a-h   III a, c, g

I–III a R, R′=$(CH_2)_4$; I, II b R, R′=$(CH_2)_5$; I–III c R=R′=CH_3; I, II d R=CH_3, R′=C_2H_5; e R=CH_3, R′=C_3H_7; f R=C_2H_5, R′=CH_3; I–III g R=C_6H_5, R′=H; I, II h R=CH_3, R′=$COOC_2H_5$

As compared with the starting compounds, pyrrolo[1,2-a]pyrimidines IIIa, c, g have lower melting points, are more soluble in organic solvents, and do not fluoresce during irradiation with UV light with λ_{max} 254 nm. A strong absorption band corresponding to a conjugated C ≡ N group is observed in the IR spectra of IIIa-h at 2200-2220 cm^{-1}. This band is absent in the spectra of IIIa, c, g. The stretching vibrations of the C = O group in IIh appear at 1700 cm^{-1}. A strong absorption band of ring C = N bonds is observed at 1620-1630 cm^{-1}. The UV spectra of pyrrolo[1,2-a]pyrimidines II and III contain an intense absorption maximum at 260 nm and low-intensity absorption maxima at 310 and 380 nm; this constitutes evidence for the heteroaromatic condensed nature of these compounds. The introduction of electron-acceptor substituents (CN, $COOC_2H_5$) and groups of atoms that participate in conjugation with the pyrrolopyrimidine system gives rise to corresponding changes in the character of the absorption curve (see Fig. 1). Thus the presence of a phenyl substituent in the pyrrole portion of the molecule leads to a bathochromic shift of the absorption maxima at 260 and 310 nm of 7-17 nm, respectively, and to a substantial increase in the extinction. The presence of a cyano group (IIa-f) leads to splitting of these absorption maxima in the same regions, and the spectrum acquires a fine structure, which is smoothed out when an electron-acceptor substituent ($COOC_2H_5$, C_6H_5) is present.

Distinct molecular ion peaks, the m/e values of which correspond to the empirical formulas of the proposed structures, are observed in the mass spectra of II and III. The principal pathways of fragmentation

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*Compounds Ia, c-g were described earlier in [3], while Ib, h are described in the present work.

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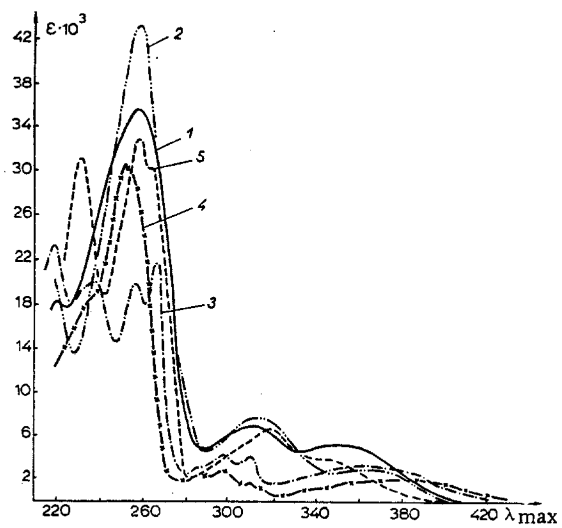
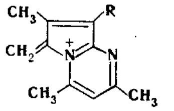


Fig. 1. UV spectra: 1) 2,4-dimethyl-7-phenyl-8-cyanopyrrolo[1,2-a]pyrimidine; 2) 2,4-dimethyl-7-phenylpyrrolo[1,2-a]pyrimidine; 3) 2,4,6,7-tetramethyl-8-cyanopyrrolo[1,2-a]pyrimidine; 4) 2,4,6,7-tetramethylpyrrolo[1,2-a]pyrimidine; 5) 2,4,7-trimethyl-6-ethoxycarbonyl-8-cyanopyrrolo[1,2-a]pyrimidine.

under the influence of electron impact are due to the formation of highly stabilized fragments A-C, which are characterized by the maximum intensities in the spectra.

The A and B fragments are formed from the molecular ions of IIc, d and IIIc by the detachment of a CH_3 group (IId) and an H atom (IIc, g). Splitting out of a C_2H_4 molecule during fragmentation of the molecular ion of IIa (ion C) is realized as a result of a retrodiene reaction. Thus, fragments that correspond to aromatic structures A-C are formed during mass spectral fragmentation of pyrrolo[1,2-a]pyrimidine molecules. The presence of rather intense ions and fragmentation directed at the substituents confirm the aromatic character of the pyrrolo[1,2-a]pyrimidines obtained (II-III).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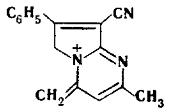
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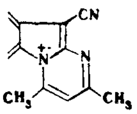
C

IId A (M—CH_3), 198*, R=CN; IIIc (M—H), 173*; IIc (M—H), 198*, R=CN; IIg B (M—H), 246*; IIa C (M—C_2H_4), 197*

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*Adduced values of m/e.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with an EPS-3T spectrophotometer. The mass spectra were obtained with an LKV-9000 chromatographic mass spectrometer (70 eV, 80°). The course of the reaction and the purity of the compounds obtained were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in acetone–heptane (1 : 1) and benzene–ethyl acetate (1 : 1) systems.

2,4,6,7-Tetramethyl-8-cyanopyrrolo[1,2-a]pyrimidine (IIc). A) A mixture of 1.35 g (0.01 mole) of 2-amino-3-cyano-4,5-dimethylpyrrole (Ic), 1 g (0.01 mole) of acetylacetone, and 5 ml of dioxane was refluxed for 2 h, after which the solvent was vacuum evaporated to give 0.4 g (20%) IIc with mp 215-216°.

B) A mixture of aminopyrrole and acetylacetone in a molar ratio of 1 : 1 was refluxed for 2 h in pyridine, after which the solvent was vacuum evaporated to give IIc, with mp 215-216°, in 48% yield.

C) A 1-g (0.01 mole) sample of acetylacetone was added to a mixture of 1.35 g (0.01 mole) of pyrrole Ic and 5 ml of glacial acetic acid, and the mixture was refluxed for 2 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with alcohol to give 1.64 g (82%) of IIc with mp 215-216°.

D) A mixture of 1.35 g (0.01 mole) of pyrrole Ic and 5 ml of acetylacetone was heated on a water bath at 90° for 2 h, and the resulting precipitate was removed by filtration and washed with alcohol to give 1.5 g (75%) of IIc with mp 215-216°.

E) A mixture of 1.35 g (0.01 mole) of Ic and 5 ml of acetylacetone was refluxed. After 10 min, crystals began to precipitate from the refluxing solution. The mixture was refluxed for another 30 min, after which it was cooled, and the precipitate was removed by filtration and washed with alcohol to give 1.88 g (94%) of IIc with mp 216-216.5° (from methanol) (mp 210-211° [1]). UV spectrum, λ_{max}, nm (log ε): 220 (4.37), 233 (4.29), 237 (4.3), 258 (4.29), 266 (4.33), 285 shoulder (3.46), 298 (3.61), 310 (3.6), 365 (3.54).

The other pyrrolo[1,2-a]pyrimidines (IIa, b, d-g), data on which are presented in Table 1, were similarly obtained under the conditions of experiment E.

General Method for the Preparation of Pyrrolo[1,2-a]pyrimidine Derivatives (IIIa, c, g). A mixture of 1 g of the appropriate 8-cyanopyrrolo[1,2-a]pyrimidine and 10 ml of 100% phosphoric acid [5] was heated on a silicone bath at 230-250° until CO_2 evolution ceased. It was then cooled to 70° and poured over 25 g of finely crushed ice. The ice mixture was neutralized to pH 7-8 with ammonium hydroxide, and the resulting precipitate was removed by filtration and dried. It was then chromatographed with a column filled with SiO_2 (elution with ether). Data on IIIa, c, g are presented in Table 1.

2,4-Dimethyl-6,7-tetramethylenepyrrolo[1,2-a]pyrimidine Hydrochloride. A 4.2-g sample of base IIIa was dissolved in acetone, and an ether solution of hydrochloric acid was added dropwise with cooling to the resulting solution. The bright-yellow precipitate was removed by filtration and washed with ether to give 3.8g

TABLE 1. Pyrrolo[1,2-a]pyrimidine Derivatives

Compound	mp, °C*	Empirical formula	Found, %			Calc., %			UV spectra, λ_{max}, nm (log ε)	Yield, %
			C	H	N	C	H	N		
IIa	232—233	$C_{14}H_{15}N_3$	—	—	—	—	—	—	221 (4,33), 235 (4,3), 249 (4,32), 259 (4,3), 268 (4,34), 298 (3,7), 309 (3,68), 364 (3,57)	80
IIb	147—148	$C_{15}H_{17}N_3$	75,4	7,3	17,9	75,3	7,2	17,6	223 (4,35), 240 (4,3), 242 (4,3), 258 (4,28), 267 (4,31), 292 (3,58), 299 (3,67), 360 (3,57)	75
IId	152—152,5	$C_{13}H_{15}N_3$	73,3	7,1	19,6	73,2	7,1	19,7	222 (4,41), 235 sh† (4,34), 240 (4,35), 257 (4.31), 267 (4,34), 285 sh† (3,54), 297 (3,67), 308 (3,68), 364 (3,38)	92
IIe	102—103	$C_{14}H_{17}N_3$	73,8	7,7	18,4	73,9	7,5	18,5	220,5 (4,38), 235 (4,30), 241 (4,31), 253 (4,25), 265 (4,31), 297 (3,65), 310 (3,65), 364 (3,55)	70
IIf	162—163	$C_{13}H_{16}N_3$	73,2	7,1	19,7	73,2	7,1	19,7	220 (4,33), 235 (4,28), 238 (4,28), 257 (4.29), 266 (4,32), 286 sh† (3,54), 309 (3,65), 366 (3,52)	85
IIg	248—249	$C_{16}H_{13}N_3$	—	—	—	—	—	—	221 (4,26), 260 (4,55), 315 (3,84), 350 (3,72)	78
IIh	115—116	$C_{14}H_{15}N_3O_2$	65,3	5,9	16,2	65,3	5,9	16,3	231 (4,49), 257 (4,52), 265 (4,49), 318 (3,83), 345 (3,54)	73
IIIa	122—123	$C_{13}H_{16}N_2$	77,9	8,3	13,9	77,9	8,0	13,9	235 sh† (4,2), 255 (4,43), 285 sh† (3,37), 298 (3,44), 310 (3,25), 380 (3,27)	90
IIIc	95—96	$C_{11}H_{14}N_2$	75,6	8,0	16,1	75,8	8,0	16.0	236 sh† (4,27), 252 (4,48), 288 (3,39), 296 (3,45), 310 (3,24), 384 (3,33)	78
IIIg	116—117,5	$C_{15}H_{14}N_2$	81,1	6,4	12,5	81,0	6,3	12,6	259 (4,63), 315 (3,88), 360 (3,49)	90

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*The compounds were recrystallized: IIa, b, d-h from alcohol, and IIIa, c, g from aqueous alcohol.

† sh) shoulder.

(77%) of a product with mp 227-230° (dec., from acetone–methanol–ether). Found: N 11.8; Cl 14.8%. $C_{13}H_{16}N_2 \cdot HCl$. Calculated: N 11.8; Cl 14.9%.

2-Acetamidocycloheptanone. A 40-g (0.6 g-atom) sample of zinc dust was added with vigorous stirring in small portions to a heated (to 40°) suspension of 43.2 g (0.2 mole) of cycloheptane-1,2-dione [6], 20 g (0.24 mole) of fused ammonium acetate, 55 g (0.54 mole) of acetic anhydride, and 200 ml of acetic acid, after which the mixture was refluxed with stirring for 1 h. The sediment was removed by filtration and washed with hot acetic acid, and the acetic acid solution was vacuum evaporated. Water was added to the residue, and the aqueous mixture was neutralized with ammonia. The precipitated acetanilide was removed by filtration, and the aqueous solution was extracted with chloroform. The solvent was evaporated, and the residue was vacuum distilled to give 21 g (61.5%) of a product with mp 195-199° (3 mm) and mp 44°. IR spectrum, cm^{-1}: 3270 (NH); 1660, 1715 (C=O). UV spectrum, λ_{max}, nm (log ε): 242 (3.18). Found: C 64.2; H 8.7; N 8.3%. $C_9H_{15}NO_2$. Calculated: C 63.9; H 8.9; N 8.3%.

2-Amino-3-cyano-4,5-pentamethylenepyrrole (Ib). A 0.85-g (0.01 mole) sample of piperidine and 0.66 g (0.01 mole) of malononitrile in 20 ml of absolute alcohol were added at room temperature to 1.68 g (0.01 mole) of 2-acetamidocycloheptanone in 25 ml of absolute alcohol, after which the mixture was heated at 60° for 30 min. It was then cooled and poured into water, and the resulting precipitate was removed by filtration to give 0.72 g (98%) of Ib with mp 195-196° (from methanol). IR spectrum, cm^{-1}: 3460 (NH); 3370, 3315 (NH_2); 2200 ($C \equiv N$). UV spectrum, λ_{max}, nm (log ε): 270 (3.82). Found: C 68.3; H 7.5; N 24.0%. $C_{10}H_{13}N_3$. Calculated: C 68.5; H 7.5; N 24.0%.

2-Amino-3-cyano-4-methyl-5-carbethoxycarbonylpyrrole (Ih). As in the synthesis of pyrrole Ib, Ih, with mp 245-246° (from methanol), was obtained in 58% yield from acetamidoacetoacetic ester [7]. IR spectrum, cm^{-1}: 3440 (NH); 3320, 3260 (NH_2); 2200 ($C \equiv N$); 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 222 shoulder (3.93), 256 (3.89), and 302 (4.29). Found: C 55.6; H 5.7; N 21.8%. $C_9H_{11}N_3O_2$. Calculated: C 55.9; H 5.7; N 21.7%.

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