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REACTION OF 3,4-DICYANO-5-AMINOPYRAZOLE WITH ETHYL ORTHOFORMATE

Yu. N. Bulychev, I. A. Korbukh, and M. N. Preobrazhenskaya

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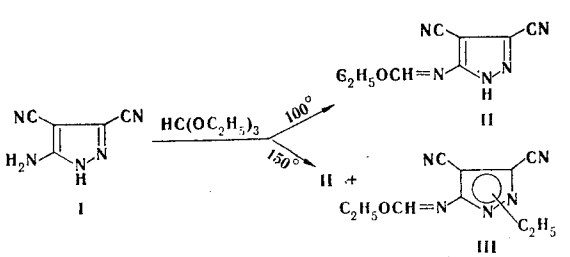
The condensation of 3,4-dicyano-5-aminopyrazole with ethyl orthoformate was studied. Under severe conditions (150°C) the principal reaction product is N-ethyl-3,4-dicyano-5-ethoxymethylaminopyrazole. Alkylation of the pyrazole ring does not occur at 100°C, but 3,4-dicyano-5-ethoxymethyleneaminopyrazole is formed. Isomeric 1- and 2-ethyl-4-aminopyrazolo[2,4-d]pyrimidine-3-carboxylic acid methyl imino esters were obtained by the action of a methanol solution of ammonia on the principal reaction product. This constitutes evidence that N-ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazole is a mixture of 1- and 2-ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazoles.

The reaction of aminoimidazoles or aminopyrazoles that contain a nitrile group in the ortho position with carboxylic acid ortho esters with subsequent cyclization under the influence of various agents is a widely used method for the synthesis of purines or pyrazolo[3,4-d]pyrimidines [1]. It is customary to assume that ethoxymethyleneamino derivatives of the corresponding azoles are formed in the reaction with ethyl orthoformate. However, neither the structure of the intermediate ethoxymethyleneamino derivatives nor the reaction itself have been studied. The aim of the present research was to study the reaction of 3,4-dicyano-5-aminopyrazole (I) with ethyl orthoformate, to identify the products of this reaction, and to synthesize substitued pyrazolo[3,4-d]pyrimidines from them.

The preparation of 5-ethoxymethyleneamino derivatives by refluxing 3,4-dicyano-5-aminopyrazole (I) and its 1- or 2-methyl derivative in ethyl orthoformate has been previously described [2-5]; the products were subsequently converted to the corresponding pyrazolo[3,4-d]-pyrimidines by the action of a methanol solution of ammonia.

We have established that not only the formation of an ethoxymethyleneamino group but also alkylation of the pyrazole ring occur when 3,4-dicyano-5-aminopyrazole (I) is refluxed in ethyl orthoformate at 150-160°C. In contrast to other authors, we isolated N-ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazole (III) as the principal products in 68% yield under these conditions and 3,4-dicyano-5-ethoxymethyleneaminopyrazole (II) in only 16% yield.

The formation of alkyl derivatives in the reaction of substituted pyrazoles with ethyl orthoformate has not been heretofore described, although there have been reports of the alkylation of some secondary amines by carboxylic acid ortho esters (for example, see [6]).



The formation of N-alkyl derivative III can be avoided by condensation of pyrazole I with ethyl orthoformate under mild conditions. 3,4-Dicyano-5-ethoxymethyleneaminopyrazole (II) was obtained in 80% yield by heating I with this ester at 100-110°C for 3 h. According

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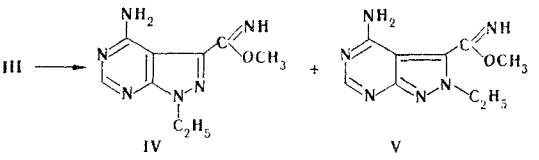
to data from thin-layer chromatography (TLC), alkylation product III is formed in the case of further refluxing of II in ethyl orthoformate at 150-160°C. This provides a basis for the assumption that all of the earlier reports regarding this reaction actually pertain precisely to these milder conditions, under which the refluxing of the alcohol liberated in the reaction simulates the refluxing of the ethyl orthoformate.

The structures of II and III are confirmed by the data from the IR, PMR, and mass spectra and by the results of elementary analysis. The IR spectra of II and III contain absorption bands of cyano groups; the group of bands at 3000-3300 cm^{-1} that is characteristic for the NH group is absent in the spectrum of III. In the PMR spectrum of alkylation product III the signal of the proton of the CH=N group is located at 8.47 ppm. In addition, there are quartets at 4.48 and 4.20 ppm ($2CH_2$) and triplets at 1.43 and 1.40 ppm ($2CH_3$) of two ethyl groups. The signals of the weaker-field quartet at 4.48 ppm are doubled, evidently as a consequence of overlapping of the quartets of two CH_2 groups related to different N_1- and N_2-ethyl groups. No doubling of any of the signals is observed in the PMR spectrum of II. Thus it may be assumed that reaction product III is a mixture of N_1-ethyl and N_2-ethyl isomers. The broadening of the signal of the proton of the CH=N group in III also constitutes evidence in favor of this assumption. Doubling of the signals of the protons of the O-ethyl group does not occur, evidently as a consequence of the closeness of their chemical shifts. However, attempts to separate mixture III into individual N_1 and N_2 isomers by means of thin-layer chromatography (TLC) or high-performance liquid choromatography (HPLC) were unsuccessful.

The mass spectrum of III contains a molecular-ion peak with m/z 217, as well as peaks of fragments corresponding to the successive splitting out of two ethyl groups and ethoxy and ethoxymethylene groups.

When we treated III with a saturated methanol solution of ammonia at room temperature we were able to isolate, by successive crystallization, isomeric imido esters of the pyrazolo-[3,4-d]pyrimidine series (IV, V) in a ratio of ∿2:1 in an overall yield of 93%.



The IR spectra of IV and V do not contain absorption bands of cyano groups. Their PMR spectra contain singlets of protons of OCH_3 groups at, respectively, 3.83 and 3.91 ppm, which confirms the presence of imido ester groupings in them.

The UV spectra of imido esters IV and V and of the known 1- and 2-substituted pyrazolo-[3,4-d]pyrimidines with similar structures (VI and VII) are presented in Table 1. The spectrum of the less soluble V is similar to the spectrum of 2-methyl-4-aminopyrazolo[3,4-d]-pyrimidine-3-carboxylic acid methyl imido ester (VII). The spectra of IV, which has higher solubility in methanol, and of the known 1-(β-D-ribofuranosyl)-4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid methyl imido ester (VI) are also extremely similar and differ substantially from the spectra of V and VII. These data make it possible to assign 1- and 2-ethyl-4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid methyl imido ester structures, respectively, to VI and V. The formation of isomeric IV and V confirm the assumption that III is a mixture of isomeric N_1- and N_2-ethyl derivatives with extremely similar properties, spectral characteristics, and chromatographic mobilities.

EXPERIMENTAL

The PMR spectra were recorded with a JNM-MH-100 spectrometer with tetramethylsilane as the internal standard. The UV spectra of solutions of the compounds in ethanol (II and III) or in methanol (IV and V) were recorded with a Unicam SP-800 spectrophotometer. The IR spectra of KBr pellets of the compounds were obtained with a Perkin-Elmer 283 spectrometer. The mass spectra were recorded with a Varian MAT-311A mass spectrometer. Analytical TLC was carried out on Silufol UV-254 in a chloroform–methanol system (9:1). Preparative chromatography was accomplished on plates (20 by 20 cm) with a loose layer of LSL 5/40 silica gel (layer thickness 1.5 mm) in the same solvent system. High-resolution liquid chromatography (HRLC) was carried out with a Hewlett-Packard 1084 V chromatograph (USA) with a Whatman col-

TABLE 1. UV Spectra of IV-VII in Methanol

Compound	Name	λ_{max}, nm (log ε)	λ_{min}, nm (log ε)
IV	1-Ethyl-4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid methyl imido ester	284 (4.08), 243 (3.99)	257 (3.82), 255 (3.82)
VI[a]	1-(β-D-Ribofuranosyl)-4-aminopyrazolo-[3,4-d]pyrimidine-3-carboxylic acid methyl imido ester	284 (4.10), 242 (4.01)	257 (3.84), 222 (3.84)
V	2-Ethyl-4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid methyl imido ester	304 (3.98), 253 (3.90)	266 (3.80), 238 (3.79)
VII[b]	2-Methyl-4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid methyl imido ester	350 (3.99), 263 (3.90)	266 (3.82), 238 (3.79)

[a]Data taken from [5]. [b]Data taken from [4].

umn (4.6 by 250 mm, ODS, 5 μm) and a forecolumn (4.6 by 50 mm, Co:PelODS); the mobile phase was acetonitrile, and the elution rate was 2 ml/min.

N-Ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazoles (III). A 1.33-g (10 mmole) sample of 3,4-dicyano-5-aminopyrazole I was refluxed in 12 ml of freshly distilled ethyl orthoformate for 4-5 h on an oil bath (the bath temperature was 150-155°C) without access to moisture. The turbid solution was filtered, the filtrate was evaporated, two 6-ml portions of toluene were added to the residual oil, and the mixture was again evaporated. Preparative chromatography of the residue on silica gel gave 1.47 g (68%) of III with R_f 0.70 in the form of a colorless oil that crystallized upon standing to give a product with mp 135-137°C. IR spectrum: 2230 cm^{-1} (CN). UV spectrum, λ_{max} (log ε): 255 nm (3.89). Mass spectrum (m/z): 217 (M^+), 188 ($M^+ - C_2H_5$), 161 ($M^+ - 2C_2H_5$), 146 ($M^+ - C_2H_5 - C_2H_5O$), 133 ($M^+ - C_2H_5 - C_2H_5OCH$); PMR spectrum in CD_3OD: 8.47 (CH=N); 4.48 (CH_2); 4.47 (CH_2); 4.20 (CH_2); 1.43 (CH_3); 1.40 (CH_3); in d_6-DMSO: 8.57 (CH=N), 4.44 (CH_2), 4.43 (CH_2), 4.14 (CH_2), 1.36 (CH_3), and 1.33 ppm (CH_3). The product has R_f 0.69 (TLC); the retention time (R_t) in HRLC was 8.71 min. Found: C 55.1; H 5.2; N 31.9%. $C_{10}H_{11}N_5O$. Calculated: C 55.3; H 5.1; N 32.2%.

Workup of the zone with R_f 0.30 gave 0.30 g (16%) of II in the form of a colorless oil. IR spectrum: 2239 (CN) and 2900-3100 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 274 nm (3.58). Mass spectrum (m/z): 189 (M^+), 161 ($M^+ - C_2H_5$), 146 ($M^+ - OC_2H_5$), 133 ($M^+ - C_2H_5OCH$); PMR spectrum in CD_3OD: 8.31 (CH=N), 4.34 (CH_2), and 1.60 (CH_3); in d_6-DMSO: 8.31 (CH=N), 4.32 (CH_2), and 1.43 ppm (CH_3). The product had R_f 0.29 (TLC). Found: C 51.1; H 3.7; N 37.0%. $C_8H_7N_5O$. Calculated: C 50.8; H 4.0; N 37.1%.

3,4-Dicyano-5-ethoxymethylmethyleneaminopyrazole (II). A suspension of 0.66 g (5 mmole) of pyrazole I in 8 ml of ethyl orthoformate was heated for 4 h on an oil bath (the bath temperature was 100-110°C) without access to moisture. The turbid solution was filtered, the filtrate was evaporated, and the residue was worked up as in the preceding method to give 0.77 g (81%) of II, which was identical to the reaction product described above.

1-Ethyl- and 2-Ethyl-4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic Acid Methyl Imido Esters (IV, V). A 0.33-g (1.7 mmole) sample of III was maintained in 20 ml of absolute methanol saturated with ammonia (at 0°C) at 20°C for 48 h, after which the colorless crystals were removed by filtration, washed with methanol, and dried to give 0.12 g (36%) of V with mp 229-234°C (dec.). PMR spectrum (in d_6-DMSO): 9.16 (NH), 8.13 (H-6), 4.67 (CH_2), 3.91 (OCH_3), and 1.41 ppm (CH_3). The product has R_f 0.1 (TLC). Found: C 49.1; H 5.7; N 38.1%. $C_9H_{12}N_6O$. Calculated: C 49.1; H 5.5; N 38.1%. The mother liquor was evaporated, and the residue was recrystallized from methanol to give 0.19 g (57%) of IV with mp 170-171°C. PMR spectrum (in d_6-DMSO): 10.03 (NH), 8.17 (H-6), 7.93 (NH_2), 4.31 (CH_2), 3.83 (OCH_3), and 1.38 ppm (CH_3). The product had R_f 0.29 (TLC). Found: C 48.9; H 5.8; N 37.6%. $C_9H_{12}N_6O$. Calculated: C 49.1; H 5.5; N 38.1%.

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PYRIMIDINE DERIVATIVES.

57.* NEW METHOD FOR THE SYNTHESIS OF PYRROLO[2,3-d]PYRIMIDINE

R. G. Melik-Ogandzhanyan, A. S. Gapoyan, V. É. Khachatryan, and V. S. Mirzoyan

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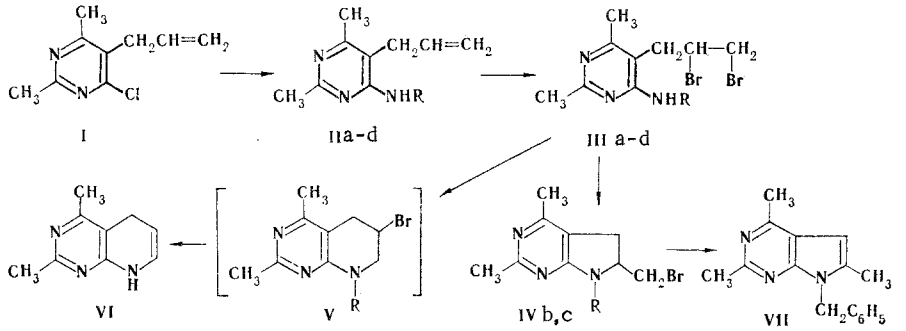
The action of bromine on 5-allyl-6-aminopyrimidines was studied. The formation of both a product of addition of bromine to the allylic bond and pyrrolo[2,3-d]-pyrimidines is possible, depending on the character of the substituent attached to the amino group. The structures of the synthesized compounds were confirmed by PMR and mass-spectrometric data.

In order to develop new methods for the synthesis of condensed pyrimidines [1-3], which are of interest as potential cancerolytics [4-6], in the present research we demonstrated the possibility of the preparation of a pyrrolo-[2,3-d]pyrimidine via the scheme



6-Aminopyrimidines (IIa-d) were obtained when 5-allyl-2,4-dimethyl-6-chloropyrimidine (I), which was synthesized by the method in [1] from the corresponding 6-hydroxypyrimidine, was heated with an alcohol solution of the amine in an autoclave at 150-200°C for 6-8 h.

The synthesis of IVb, c was carried out via a scheme similar to that which we described for furo[2,3-d]- and thieno[2,3-d]pyrimidine [1, 2]. The addition of bromine to the allyl group of IIb, c leads initially to the formation of intermediate dibromo products IIb, c, from which a molecule of hydrogen bromide is split out with the formation of a five-membered pyrrole ring.

In the case of 5-allyl-6-amino-2,4-dimethylpyrimidine (IIa) 2,4-dimethyl-5,8-dihydropyrido[2,3-d]pyrimidine (VI) is formed instead of the expected pyrrolo[2,3-d]pyrimidine (IVa). The reaction evidently proceeds through a step involving the formation of six-membered tetrahydropyrimidine V with subsequent splitting out of a molecule of hydrogen bromide to give VI.

*See [1] for Communication 56.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1686-1689, December, 1982. Original article submitted March 10, 1982.

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