SYNTHESIS OF 3-SUBSTITUTED 4-METHYLMERCAPTO- AND 4-AMINOPYRAZOLO-[3,4-d]PYRIMIDINES AND THEIR RIBOSIDES

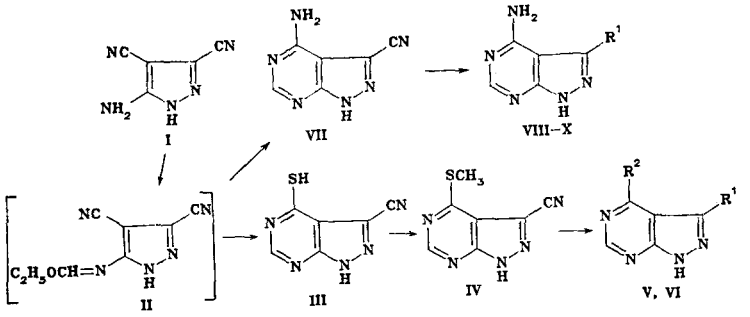
Yu. N. Bulychev, I. A. Korbukh, and M. N. Preobrazhenskaya

UDC 547.859.963.32:543.422.25

3-Cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine, fusion of which with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose gave its per-O-acetylated 1-β-D-ribofuranoside in 61% yield, was synthesized from 3,4-dicyano-5-aminopyrazole. O-Deacetylation of the per-O-acetylated 1-β-D-ribofuranoside was carried out by the action of 1% HCl in methanol. New pyrazolo[3,4-d]pyrimidines were obtained by the reaction of 3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine and its 1-riboside, as well as 3-cyano-4-aminopyrazolo[3,4-d]pyrimidine, with a number of nucleophilic reagents. The cytotoxic activities of the compounds obtained were studied.

The high cytotoxic activities of 4-aminopyrazolo[3,4-d]pyrimidine and its 1-β-D-ribofuranoside are known [1]. 1-β-D-Ribofuranosides of 3-substituted 4-aminopyrazolo[3,4-d]-pyrimidines also have pronounced cytotoxic activity [2]. Nucleosides of 3,4-disubstituted pyrazolo[3,4-d]pyrimidines with substituents other than an amino group in the 4 position have not been described. The preparation of 3-substituted pyrazolo[3,4-d]pyrimidines and the corresponding nucleosides with a methylmercapto group in the 4 position, which is capable of imitating an amino group in several enzymatic processes, seems of interest.

We accomplished the synthesis of 3-substituted 4-methylmercaptopyrazolo[3,4-d]pyrimidines from 3,4-dicyano-5-aminopyrazole (I), which was obtained from malononitrile by a known four-step synthesis [3]. 3-Cyano-4-mercaptopyrazolo[3,4-d]pyrimidine (III) was obtained in 78% yield on the basis of starting pyrazole I when I was heated in excess ethyl orthoformate [4], without isolation and purification of the intermediate 3,4-dicyano-5-ethoxymethyleneaminopyrazole (II), with subsequent condensation with sodium hydrosulfide in absolute methanol [5] and treatment of the reaction product with alkali. Methylation of pyrazolopyrimidine III with methyl iodide in NaOH gave 3-cyano 4-methylmercaptopyrazolo[3,4-d]pyrimidine (IV) in 89% yield; the latter was subsequently used in reactions with nucleophilic reagents and to obtain nucleosides.



V, VIII $R^1=CSNH_2$; VI, X $R^1=C(=NH)NHNH_2$; IX $R^1=C(=NOH)NH_2$; V $R^2=SCH_3$; VI $R^2=NHNH_2$

3-Thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (V) was obtained in 50% yield when dry hydrogen sulfide was passed through a solution of IV in absolute ethanol containing triethylamine. The reaction of IV with hydrazine hydrate in ethanol led to 4-hydrazinopyrazolo[3,4-d]pyrimidine-3-carboxylic acid iminohydrazide (VI) in 60% yield.

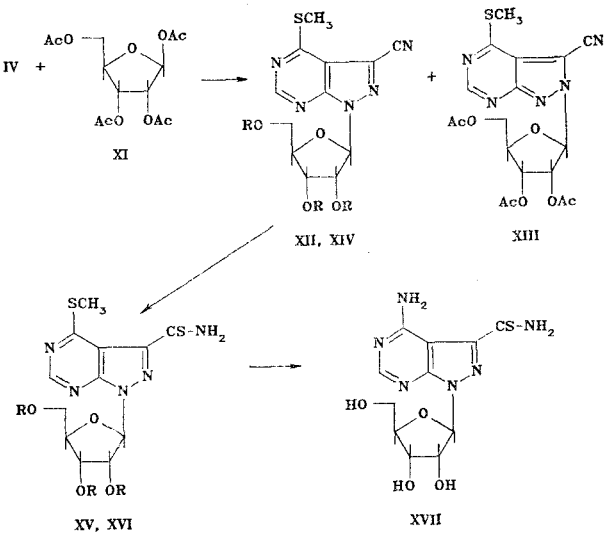
All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow 115478. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 253-258, February, 1984. Original article submitted June 17, 1983.

 0009-3122/84/2002-0210$08.50

The previously undescribed 3-thiocarbamoyl-4-aminopyrazolo[3,4-d]pyrimidine (VIII) and 4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid amidoxime or iminohydrazide (IX or X) — aglycones of the corresponding 1-ribosides, which have pronounced anticancer activity [2] — were synthesized in 50-70% yields as a result of nucleophilic addition of hydrogen sulfide, hydroxylamine, or hydrazine hydrate to the nitrile group of 3-cyano-4-aminopyrazolo[3,4-d]pyrimidine (III), which we obtained from pyrazole I by the method in [6]. For the glycosylation of 3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine IV we selected the method of fusion in the presence of iodine, by which 1-ribosides of 3-cyano- and 3-cyano-methyl-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidines were previously obtained [7, 8].

1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-cyano-4-methylmercaptopyrazolo[3,4-d]-pyrimidine (XII) was obtained in 61% yield by fusing IV with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (XI) in vacuo in the presence of 12% iodine at 165°C. In addition, 2-β isomer XIII was isolated in very low yield (∿3%).

The O-deacetylation of XII by the action of a 1% solution of hydrogen chloride in absolute methanol [9] led to 1-(β-D-ribofuranosyl)-3-cyano-4-methylmercaptopyrazolo[3,4-d]-pyrimidine (XIV) in 62% yield. We were unable to remove the O-acetyl groups by such widely used (in the chemistry of nucleosides) methods as the action of a methanol solution of ammonia or sodium methoxide in methanol without involvement of the nitrile group.



XII, XV R=Ac; XIV, XVI R=H, Ac=$COCH_3$

The structures of nucleosides XII and XIV were confirmed by conversion of riboside XII to a nucleoside with known structure XVII. 1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XV) was formed in 53% yield when hydrogen sulfide was passed through a solution of riboside XII in ethanol in the presence of triethylamine. 1-(β-D-Ribofuranosyl)-3-thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]-pyrimidine (XVI) was obtained in 75% yield when XV was deacetylated with sodium methoxide in absolute methanol. Ammonolysis of riboside XV with a saturated methanol solution of ammonia in an ampul at 100°C led to 1-(β-D-ribofuranosyl)-3-thiocarbamoyl-4-aminopyrazolo-[3,4-d]pyrimidine (XVII), which, according to the UV spectral data and the specific optical rotation, was identical to the previously described compound [10, 11].

The structure of 2-riboside XIII was confirmed by UV spectral data. Heterocycle IV and 1-nucleosides XII and XIV have similar UV spectra (Fig. 1). The UV spectrum of riboside XIII differs substantially from them; this constitutes evidence for a different type of substitution of the heterocyclic ring and makes it possible to assign the 2-isomer structure to riboside XIII.

The assumption that riboside XIII is the 5 or 7 isomer seems unlikely to us, since the formation of only 1- and 2-ribosides was previously observed in the glycosylation of 4-methylmercapto- and 4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidines by the fusion method [12, 13].

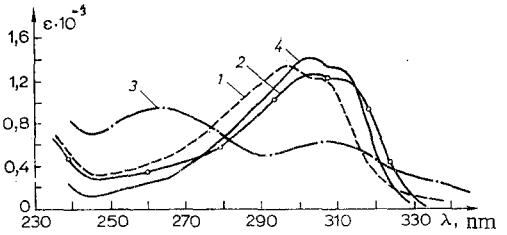


Fig. 1. UV spectra: 1) heterocycle IV; 2) 1-riboside XII; 3) 2-riboside XIII; 4) 1-riboside XIV.

TABLE 1. PMR Spectra of Ribosides of 3-Substituted 4-Methylmercaptopyrazolo[3,4-d]pyrimidines (XII-XVI)

Compound	6-H	Chemical shift, δ, ppm (SSCC)						
		1′-H (J_{12})	2′-H (J_{23})	3′-H (J_{34})	4′-H, 5′-H	SCH_3	$COCH_3$	solvent
XII	8,79	6,66 (4,0)	6,01 (5,4)	5,74 (5,4)	4,44—4,15	2,76	2,13; 2,13; 2,09	$CDCl_3$
XIII	7,94	6,38 (3,6)	5,82 (5,4)	5,64 (5,6)	4,37—4,16	2,60	2,07; 2,07; 2,05	$CDCl_3$
XIV	8,79	6,43 (4,0)	4,78 (5,4)	4,49 (5,0)	4,14—3,74	2,75	—	CD_3OD
XV*	8,67	6,66 (4,4)	5,92 (5,0)	5,67 (4,9)	4,48—4,26	2,55	2,07; 2,01; 1,97	$CDCl_3$
XVI	8,95	6,33 (4,6)	4,80	4,22	3,68—3,24	2,75	—	d_6-DMSO

*The signals of the protons of the $C(=S)NH_2$ group are located at 8.22 and 7.67 ppm.

It may be concluded that riboside XIII has a β configuration on the basis of the $J_{1'2'}$ spin—spin coupling constants (SSCC) of riboside XIII (3.6 Hz) and riboside XII (4.0 Hz) (Table 1), the anomeric configuration of which was established above. In addition, in the PMR spectra of nucleosides XII and XIII the signals of all three O-acetyl groups are extremely close and are located in the weaker-field region below 2.05 ppm. A shift of the signal of the 2′-O-acetyl group to the region below 1.96 ppm is characteristic for per-O-acetylated α-nucleosides [14].

The cytotoxic activities in vitro of the new III-VI, VIII-X, XIV, and XVI were investigated with respect to retardation of the incorporation of [^{3}H]thymidine in the DNA of cells of the CaOv strain of human ovary carcinoma in the laboratory of cell pharmacology of the All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR by the method in [15]. Thioamides V and VIII displayed pronounced cytotoxic activity (CE_{50} $8.90 \cdot 10^{-6}$ and $5.15 \cdot 10^{-5}$ mole/liter, respectively). Mercapto derivative III stimulated the incorporation of [^{3}H]thymidine in DNA. The remaining compounds were less active (CE_{50} from $1.46 \cdot 10^{-4}$ to $4.83 \cdot 10^{-4}$ mole/liter). The extremely low solubilities of these compounds in water hinders further study of their anticancer activity.*

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM-MH-100 spectrometer with tetramethylsilane as the internal standard. The UV spectra were obtained with a Unicam SP-800 recording spectrophotometer. The IR spectra of KBr pellets of the compounds were recorded with a Perkin-Elmer 283 spectrometer. The specific rotation was determined by means of a Perkin-Elmer 241 polarimeter. Analytical thin-layer chromatography (TLC) was carried out on Silufol UV-254 silica gel in chloroform—methanol systems: 95:5 (A), 9:1 (B), and 4:1 (C). Preparative chromatography was accomplished on plates (20 × 20 cm) with a loose layer of LSL 5/40 silica gel (Czechoslovakian SSR) in the same systems.

*The authors thank Ya. V. Dobrynin and T. A. Ivanova for studying the cytotoxic activities of the compounds obtained.

3-Cyano-4-mercaptopyrazolo[3,4-d]pyrimidine (III). A suspension of 3.9 g (29.3 mmole) of 3,4-dicyano-5-aminopyrazole (I) in 30 ml of freshly distilled ethyl orthoformate was heated for 3 h on an oil bath (bath temperature 100-110°C) without access to moisture, after which the turbid solution was filtered, and the filtrate was evaporated. The residue was evaporated twice with 15-ml portions of toluene to give II [R_f 0.30 (B)] in the form of a viscous oil. A solution of 1 g of Na in 300 ml of absolute methanol was added to this oil, and dry hydrogen sulfide was passed through the resulting solution at 20°C for 3 h. The solution was then refluxed for 4 h, after which it was cooled and evaporated, and the residue was dissolved in 200 ml of water. The solution was neutralized to pH 6.5-7.0 with concentrated acetic acid, and the mixture was maintained at 0°C for 12 h. The yellow precipitate was removed by filtration, washed with water, and dried in vacuo over P_2O_5 at 60°C to give 4.05 g (78%) of III. An analytically pure product was obtained by recrystallization from water. UV spectrum (in ethanol), λ_{max} (log ε): 253 (3.83) and 329 nm (3.94). IR spectrum: 2222 cm^{-1} (CN). The product melted above 350°C. Found: C 34.1; H 3.6%. $C_6H_3N_5S \cdot 2H_2O$. Calculated: C 33.8; H 3.3%.

3-Cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (IV). A 1.10-g (7.5 mmole) sample of CH_3I was added to a solution of 1.30 g (6.1 mmole) of III in 40 ml of 1 NaOH, and the mixture was stirred at 20°C for 2 h, after which it was neutralized to pH 6.5-7.0 with concentrated acetic acid. The resulting precipitate was removed by filtration, washed with water, and dried in vacuo over P_2O_5 at 60°C to give 1.04 g (89%) of product. An analytically pure product with mp 282-284°C was obtained by recrystallization from methanol. IR spectrum: 2244 cm^{-1} (CN). PMR spectrum (in C_5D_5N): 8.82 (6-H) and 2.54 ppm (SCH_3). The product had R_f 0.26 (TLC in system B). Found: C 44.5; H 3.0; N 36.5%. $C_7H_5N_5S$. Calculated: C 44.0; H 2.7; N 36.6%.

3-Thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (V). Dry hydrogen sulfide was passed into a solution of 0.20 g (1.05 mmole) of IV in 30 ml of absolute ethanol containing 0.9 ml of triethylamine at 20°C for 6 h, after which the solution was evaporated, and the residual yellow oil was crystallized from methanol to give 0.12 g (50%) of V with mp > 350°C. UV spectrum (in ethanol), λ_{max} (log ε): 330 nm (3.82). PMR spectrum (in d_6-DMSO): 10.20 and 9.84 ($CSNH_2$), 8.74 (6-H), and 2.60 ppm (SCH_3). The product had R_f 0.18 (TLC in system B). Found: C 36.1; H 3.6; N 31.1%. $C_7H_7N_5S_2 \cdot 0.25H_2O$. Calculated: C 36.6; H 3.3; H 30.6%.

4-Hydrazinopyrazolo[3,4-d]pyrimidine-3-carboxylic Acid Iminohydrazide (VI). A 0.5-ml sample of hydrazine hydrate was added to a solution of 0.20 g (1.05 mmole) of IV in 35 ml of absolute ethanol, and the solution was refluxed with stirring for 5 h, after which it was maintained at 0°C for 12 h. The precipitated crystals were removed by filtration, washed with ethanol, and dried in vacuo to give 0.13 g (60%) of VI with mp > 350°C. UV spectrum (in ethanol), λ_{max} (log ε): 300 nm (4.19). Found: C 34.9; H 4.6%. $C_6H_9N_9$. Calculated: C 34.8; H 4.4%.

3-Thiocarbamoyl-4-aminopyrazolo[3,4-d]pyrimidine (VIII). Dry hydrogen sulfide was passed through a solution of 0.3 g (1.9 mmole) of VII in 100 ml of absolute ethanol containing 0.7 ml of triethylamine at 20°C for 4 h, after which the mixture was maintained at 20°C for 10 h. The resulting yellow crystals of VIII were removed by filtration to give 0.26 g (76%) of a product with R_f 0.24 (C). PMR spectrum in d_6-DMSO: 10.05 and 9.77 ($CSNH_2$) and 8.15 ppm (6-H). The product had mp 280°C (dec.). UV spectrum, λ_{max} (log ε): 234 (4.06), 258 (3.99), and 303 nm (3.97). Found: C 37.7; H 3.5; N 43.2%. $C_6H_6N_6S$. Calculated: C 37.1; H 3.1; N 43.3%.

4-Aminopyrazolo[3,4-d]pyrimidine-3-carboxylic Acid Amidoxime (IX). A 0.2-g (1.25 mmole) sample of VII was dissolved by heating in 70 ml of absolute ethanol containing 0.3 ml of triethylamine, 0.1 g (1.43 mmole) of hydroxylamine hydrochloride was added, and the mixture was refluxed for 2 h. The solution was cooled and maintained at 0°C for 12 h, and the precipitated crystals were removed by filtration and recrystallized from 50% aqueous methanol to give 0.16 g (66%) of IX with mp > 350°C and R_f 0.26 (C). UV spectrum, λ_{max} (log ε): 275 nm (3.99). Found: C 37.6; H 4.2; N 48.9%. $C_6H_7N_7O \cdot 0.25CH_3OH$. Found: C 37.3; H 4.0; N 48.8%.

4-Aminopyrazolo[3,4-d]pyrimidine-3-carboxylic Acid Iminohydrazide (X). A 1.5-ml sample of hydrazine hydrate was added to a solution of 0.2 g (1.25 mmole) of VII in 70 ml of absolute ethanol, and the solution was refluxed for 4 h. It was then concentrated in vacuo to a

volume of ≈ 30 ml and maintained at 0°C for 12 h. The precipitated crystals were removed by filtration, recrystallized from ethanol, and dried in vacuo to give 0.12 g (50%) of X with mp > 350°C and R_f 0.16 (C). UV spectrum, λ_{max} (log ε): 277 nm (3.99). Found: C 36.3; H 4.0%. $C_8H_8N_8 \cdot 0.25H_2O$. Calculated: C 36.6; H 4.2%.

1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-cyano-4-methylmercaptopyrazolo[3,4-d]-pyrimidine (XII) and 2-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-cyano-4-methylmercapto pyrazolo[3,4-d]pyrimidine (XIII). A mixture of 0.60 g (3.14 mmole) of IV, 1.19 g (3.75 mmole) of tetraacetylribofuranose XI, and 0.11 g (0.43 mmole) of iodine was fused at 150°C for 5-7 min, and the resulting homogeneous melt was stirred for 45 min in vacuo [10-15 mm (mercury column)] at 165°C. The mixture was then cooled, 5 ml of chloroform was added, and the solution was chromatographed with a column (14 × 3 cm) packed with silica gel by elution with chloroform with monitoring of the contents of the fractions by TLC to give 0.86 g (61%) of XII in the form of a light-yellow oil with R_f 0.75 (B) and 0.36 (A) and $[\alpha]_D^{25} = -16.4°$ (c 1.0; $CHCl_3$). IR spectrum: 2247 (CN) and 1756 cm^{-1} (C=O). From the fractions containing the substance with R_f 0.39 (B) we also isolated 42 mg (3%) of XIII in the form of an oil with $[\alpha]_D^{25} = -21.3°$ (c 0.3; $CHCl_3$). IR spectrum: 2247 (CN) and 1749 cm^{-1} (C=O).

1-(β-D-Ribofuranosyl)-3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XIV). A solution of 0.14 g (0.31 mmole) of XII in 5 ml of a 1% solution of dry hydrogen chloride in absolute methanol was maintained at 20°C in a sealed flask for 28 h, after which it was neutralized to pH 7 with Ag_2CO_3, and the AgCl was removed by filtration. Preparative chromatography of the residue on silica gel in system B gave 64 mg (62%) of riboside XIV in the form of a colorless oil that began to crystallize during storage. The product had mp 131-132°C, R_f 0.15 (B), and $[\alpha]_D^{25} = -80.0°$ (c 0.2; CH_3OH). IR spectrum: 2247 cm^{-1} (CN). Found: C 43.6; H 4.3; N 21.1%. $C_{21}H_{13}N_5O_4S \cdot 0.5H_2O$. Calculated: C 43.4; H 4.3; N 21.1%.

1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-thiocarbamoyl-4-methylmercaptopyrazolo-[3,4-d]pyrimidine (XV). Hydrogen sulfide was passed through a solution of 0.21 g (0.47 mmole) of XII in 20 ml of absolute ethanol containing 0.5 ml of triethylamine at 20°C for 1.5 h, after which the solution was evaporated, and the residue was dissolved in 2 ml of chloroform. The solution was subjected twice to preparative chromatography on silica gel in system A to give 0.12 g (53%) of XV in the form of a yellow oil with R_f 0.64 (B). IR spectrum: 1748 cm^{-1} (C=O). UV spectrum (in ethanol), λ_{max} (log ε): 292 nm (4.01).

1-(β-D-Ribofuranosyl)-3-thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XVI). A 0.2-ml sample of a 6% solution of sodium methoxide in absolute methanol was added to a solution of 120 mg (0.25 mmole) of riboside XV in 10 ml of absolute methanol, and the solution was stirred at 20°C for 40 min. It was then neutralized to pH 7 with Dowex 50 × 2 (H^+ form), and the ion-exchange resin was removed by filtration. The filtrate was concentrated in vacuo, and the concentrate was subjected to preparative chromatography on silica gel in system C to give 67 mg (75%) of nucleoside XVI in the form of a yellow oil with R_f 0.11 (B) and 0.31 (C) and $[\alpha]_D^{25} = -88.0°$ (c 0.1; CH_3OH). UV spectrum (in ethanol), λ_{max} (log ε): 292 nm (4.05). Found: C 40.1; H 4.8; N 19.0%. $C_{12}H_{15}N_5O_4S_2 \cdot 0.25H_2O$. Calculated: C 39.9; H 4.3; N 19.3%.

1-(β-D-Ribofuranosyl)-3-thiocarbamoyl-4-aminopyrazolo[3,4-d]pyrimidine (XVII). A mixture of 60 mg (0.12 mmole) of riboside XV and 10 ml of absolute methanol saturated with ammonia at 0°C was maintained at 100°C in a sealed ampul for 8 h and at 20°C for 12 h, after which it was evaporated, and the residue was subjected to threefold preparative chromatography on silica gel in system C to give 20 mg (52%) of XVII with mp 250-252°C (dec.) [mp 252-253°C (dec.) [10], 251.5-252°C (dec.) [11]] and $[\alpha]_D^{25} = -40.1°$ (c 0.3; DMF) [$[\alpha]_D^{27} = -39.2°$ (c 1.0; DMF)]. UV spectrum in water: pH 7: λ_{max} 286 (3.92), 233 nm (4.08, shoulder); λ_{min} 254 nm (3.74); pH 1: λ_{max} 268 nm (3.89); λ_{min} 259 nm (3.86); pH 11: λ_{max} 281 (3.93), 233 nm (4.08); λ_{min} 255 (3.74), 226 nm (4.07). UV spectrum (in water) [11]: pH 7: λ_{max} 293 (4.05), 234 nm (4.06); λ_{min} 253 (3.97), 224 nm (4.03); pH 2: λ_{max} 270 (4.01), 223 nm (4.23); λ_{min} 261 (4.00), 215 nm (4.22); pH 11: λ_{max} 279 (4.09), 232 nm (4.12); λ_{min} 257 (4.01), 226 nm (4.11). UV spectrum (in methanol) [10]: pH 7: λ_{max} 296 (4.18), 236 nm (4.19); λ_{min} 253 (4.07), 225 nm (4.15); pH 1: λ_{max} 275 nm (4.11); λ_{min} 261 nm (4.10); pH 11: λ_{max} 280 (4.19), 236 nm (4.19); λ_{min} 254 (4.11), 229 nm (4.14).

LITERATURE CITED

1. J. A. Montgomery, Prog. Med. Chem., 7, 69 (1970).
2. R. P. Panzica, G. A. Bhat, R.A. Earl, J.-L. Montero, L. W. Roti, and L. B. Townsend, in: Chemistry and Biology of Nucleosides and Nucleotides, R. E. Harmon, R. K. Robins, and L. B. Townsend, eds., Academic Press (1978), p. 121.
3. L. P. Dikinson, G. Willanz, and J. Kusich, J. Org. Chem., 29, 1915 (1974).
4. Yu. N. Bulychev, I. A. Korbukh, and M. N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., No. 12, 1682 (1982).
5. E. C. Taylor, S. Vromen, A. McKillop, and R. V. Ravindranathan, Angew. Chem., 78, 332 (1966).
6. E. C. Taylor and A. Abul-Husn, J. Org. Chem., 31, 342 (1966).
7. I. A. Korbukh, Yu. N. Bulychev, and M. N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., No. 12, 1687 (1979).
8. Yu. N. Bulychev, I. A. Korbukh, and M. N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., No. 4, 536 (1981).
9. A. Piskala and F. Sorm, Collect. Czech. Chem. Commun., 29, 2069 (1964).
10. R. A. Earl and L. B. Townsend, J. Heterocycl. Chem., 11, 1033 (1974).
11. S. M. Hecht, R. B. Frye, D. Werner, T. Fukui, and S. D. Hawrelak, Biochem., 15, 1005 (1976).
12. F. F. Blanko, I. A. Korbukh, and M. N. Preobrazhenskaya, Zh. Org. Khim., 12, 1132 (1976).
13. I. A. Korbukh, N. G. Yakunina, and M. N. Preobrazhenskaya, Bioorg. Khim., 6, 1632 (1976).
14. L. B. Townsend, in: Synthetic Procedures in Nucleic Acid Chemistry, Part 2, W. W. Zorbach and R. S. Tipson, eds., Wiley (1968), p. 267.
15. Ya. V. Dobrynin, T. G. Nikolaeva, V. I. Mukhanov, I. V. Yartseva, T. D. Miniker, L. V. Éktova, V. N. Tolkachev, N. D. Chkanikov, and M. N. Preobrazhenskaya, Khim.-farm. Zh., No. 5, 33 (1978).

REACTION OF 4-CYANO-5-AMINOPYRAZOLE AND 3,4-DICYANO-5-AMINOPYRAZOLE WITH DIMETHYLFORMAMIDE DIETHYLACETAL

Yu. N. Bulychev, I. A. Korbukh, M. N. Preobrazhenskaya, A. I. Chernyshov, and S. E. Esipov

UDC 547.771.1.859.07:543.422.51

The condensation of 4-cyano-5-aminopyrazole or 3,4-dicyano-5-aminopyrazole with dimethylformamide diethylacetal was studied. It was shown that, in addition to the formation of dimethylaminomethyleneamino derivatives, alkylation of the pyrazole ring occurs under severe conditions without a solvent. Only the corresponding formamidino derivatives are formed when the same reactions are carried out in methanol under milder conditions. The site of addition of an ethyl group to the pyrazole ring in the N-alkyl derivatives obtained was established by ^{13}C NMR and PMR spectroscopy. The possibility of the synthesis of 4-amino- or 4-methylmercapto-pyrazolo[3,4-d]pyrimidines by cyclization of the corresponding dimethylamino-methyleneaminopyrazoles with a cyano group in the ortho position was demonstrated for the first time.

In a previous communication we described the formation of substituted N-alkylpyrazoles in the reaction of 3,4-dicyano-5-aminopyrazole with ethyl orthoformate [1]. In the present

All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow 115478. All-Union Scientific-Research Institute of Antibiotics, Ministry of Public Health of the USSR, Moscow 113105. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 259-264, February, 1984. Original article submitted July 14, 1983.

0009-3122/84/2002-0215$08.50