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FUNCTIONALLY SUBSTITUTED AZINES. 1. SYNTHESIS AND REACTIONS OF 2-(N-CYANO-N-CARBETHOXYMETHYLAMINO)-4,6-DIMETHYLPYRIMIDINE

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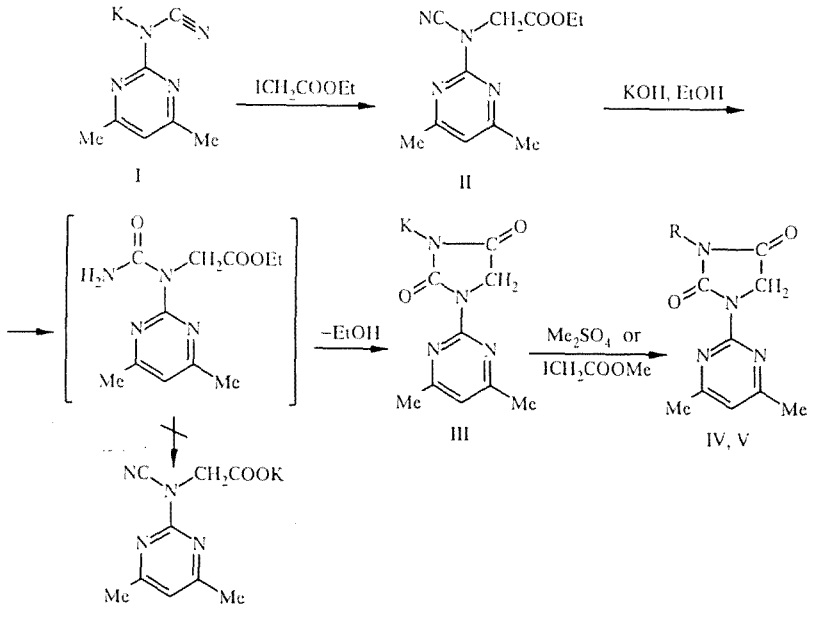
Treatment of 2-(N-potassium-N-cyanamino)-4,6-dimethylpyrimidine with ethyliodoacetate produces 2-(N-cyano-N-carbethoxymethylamino)-4,6-dimethylpyrimidine. Alkaline hydrolysis of the last gives 2-(3-potassium-2,4-dioxoimidazolidinyl-1)-4,6-dimethylpyrimidine. Ammonolysis and hydrazinolysis give imino- or amino-imidazolidinylpyrimidine, respectively.

Of all possible isomeric cyanaminopyrimidines, only the 2-cyanamino-substituted derivatives are known. These are prepared by the reaction of cyanoguanidine with malonic and acetic esters and β-diketones [1, 2]. The chemistry of the cyanaminopyrimidines is very poorly studied. Thus, only their N-methylation has been described [2]. Moreover, conversions in this series of compounds at the reactive cyanamino group, considering the broad synthetic capabilities of the related cyanamino-1,3,5-triazines [3-8], are promising both in searching for physiologically active compounds and in developing new synthetic approaches for functionally substituted pyrimidines.

Introduction into the cyanamine fragment of these compounds of a carboxyalkyl substituent seemed very interesting. This would open a new synthetic pathway for derivatives of pyrimidinylalkanecarboxylic acids. The only convenient method for preparing these is based on the reaction of amino acid derivatives with chloropyrimidines [9]. Therefore, the available 2-N-potassiumcyanamino-4,6-dimethylpyrimidine (I) was carbethoxyalkylated by ethyliodoacetate in DMF at 70-80 °C in 78% yield to give 2-(N-cyan-N-carbethoxymethylamino)-4,6-dimethylpyrimidine (II). Hydrolysis of II by KOH in alcohol at 20 °C was attempted in order to convert it to the free acid. However, 2-(3-potassium-2,4-dioxoimidazolidinyl-1)-4,6-dimethyl-pyrimidine (III) was obtained instead of the expected potassium salt of the N-pyrimidinylglycine derivative.



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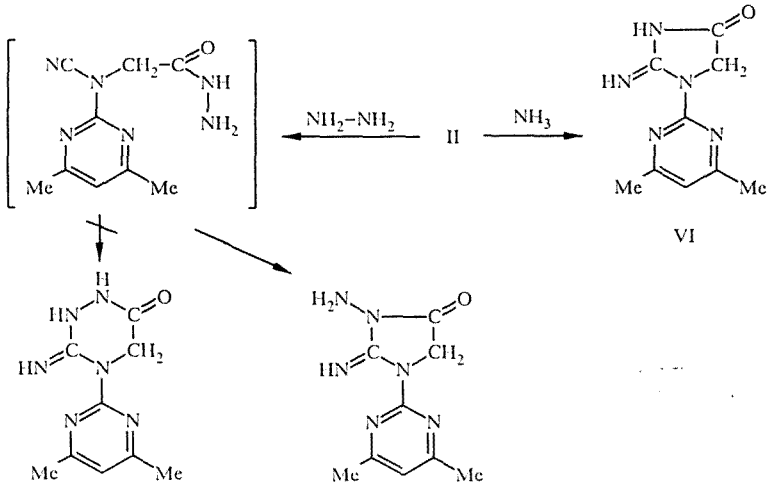

VI

VII

IV R=Me; V R=CH_2COOMe

Formation of the intermediate urea derivative probably explains this result. The intermediate eliminates ethanol and cyclizes into III. Reaction of III with dimethylsulfate or methyliodoacetate gives 3-methyl- (IV) or 3-carbmethoxymethyl-(2,4-dioxoimidazolidinyl-1)-4,6-dimethylpyrimidine (V), respectively. Ammonolysis of II over a long period in 25% NH_4OH at 20 °C converts it almost entirely to 2-(2-imino-4-oxoimidazolidinyl-1)-4,6-dimethylpyrimidine (VI). Absorption bands characteristic of the NH_2 group are absent from the IR spectrum of VI. This is consistent with a practically complete shift of the imine—amine tautomeric equilibrium toward the imine form. Under analogous conditions, II easily undergoes hydrazinolysis to form 2-(2-amino-2,4-dioxoimidazolidinyl-1)-4,6-dimethylpyrimidine (VIII).

EXPERIMENTAL

Infrared spectra were recorded on a UR-20 spectrophotometer in mineral oil or KBr pellets. A Varian T-60 (60 MHz) instrument was used to record PMR spectra (TMS internal standard). Mass spectra were obtained on a MX-1303 spectrometer by direct insertion into the source with an ionization energy of 50 eV. Silufol UV-254 plates were used for TLC.

Elemental analyses of the synthesized compounds for C, H, and N agreed with the calculated values.

2-(N-Cyano-N-carbethoxymethyl)amino-4,6-dimethylpyrimidine (II, $C_{11}H_{14}N_4O_2$). A solution of the ethyl ester of iodoacetic acid (2.14 g, 0.01 mole) in DMF (10 ml) was added dropwise with stirring to I (1.86 g, 0.01 mole) in DMF (3 ml). The mixture was kept at 70-80 °C for 6 h. The DMF was vacuum distilled at 70-80 °C (80 mm Hg). The residue was treated with H_2O (20 ml). Compound II was filtered off. Yield 1.8 g (78%), mp 107-108 °C, R_f 0.45 (heptane–acetone, 1:2). IR spectrum: 1730 (C=O), 2210 cm^{-1} (C≡N). Found: M^+ = 234.

2-(3-Potassium-2,4-dioxoimidazolidinyl-1)-4,6-dimethylpyrimidine (III, $C_9H_9KN_4O_2$). Compound II (2.34 g, 0.01 mole) was added to KOH (84%, 0.7 g, 0.01 mole) in ethanol (20 ml). The mixture was stirred at 20°C for 6 h. The precipitate of III was filtered off. Yield 1.76 g (73%), mp >270°C. PMR spectrum (D_2O): 2.42 (6H, s, $2CH_3$), 4.42 (2H, s, CH_2), 6.95 ppm (1H, s, CH).

2-(3-Methyl-2,4-dioxoimidazolidinyl-1)-4,6-dimethylpyrimidine (IV, $C_{10}H_{12}N_4O_2$). Dimethylsulfate (1 ml, 0.01 mole) was added dropwise with stirring at −5 to 0°C to a suspension of III (2.44 g, 0.01 mole) in acetone (20 ml). The mixture was kept for 3 h at 45-50°C. The acetone was distilled off. The residue was soaked in H_2O (10 ml). Compound IV was filtered off. Yield 1.2 g (59%), mp 54-55°C, R_f 0.52 (octane–acetone, 1:2.5). PMR spectrum (acetone-D_6): 2.40 (6H, s, $2CH_3$), 3.77 (3H, s, NCH_3), 4.70 (2H, s, CH_2), 6.95 ppm (1H, s, CH).

2-(3-Carbmethoxymethyl-2,4-dioxoimidazolidinyl-1)-4,6-dimethylpyrimidine (V, $C_{12}H_{14}N_4O_4$). A mixture of methylchloroacetate (1.18 g, 0.01 mmole) and sodium iodide (1.5 g, 0.01 mole) in DMF (10 ml) was kept for 24 h at 20°C. The reaction mixture was filtered. The filtrate (solution of methyliodoacetate) was added dropwise to a suspension of III (2.44 g, 0.01 mole) in DMF (10 ml). The mixture was kept at 70-80 °C for 4 h. The DMF was distilled off (80 mm Hg). The

residue was treated with H_2O (5 ml). Compound V was filtered off. Yield 1.6 g (67%), mp 58-60°C, R_f 0.47 (heptane–ethylacetate, 4:2). IR spectrum: 1560, 1605 (C=C, C=N), 1700 (C=O ring), 1760 cm^{-1} (C=O). Found: M^+ = 248.

2-(2-Imino-4-oxoimidazolidinyl-1)-4,6-dimethylpyrimidine (VI, $C_9H_{11}N_5O$). A mixture of II (2.34 g, 0.01 mole) and NH_4OH (8-10 ml, 20%) was stirred for 24 h at 20 °C. Water (10 ml) was added. Compound VI was filtered off. Yield 2.0 g (90%), mp >270 °C. IR spectrum: 1550, 1600 (C=C, C=N), 1660 (C=NH), 1700 (C=O), 3300 cm^{-1} (NH). PMR spectrum ($CDCl_3$ + CD_3OD): 2.40 (6H, s, $2CH_3$), 4.40 (2H, s, CH_2), 6.77 ppm (1H, s, CH).

2-(3-Amino-2-imino-4-oxoimidazolidinyl-1)-4,6-dimethylpyrimidine (VII, $C_9H_{12}N_6O$). Hydrazine hydrate (3.4 ml, 55%) was added dropwise to II (2.34 g, 0.01 mole) in H_2O (151 ml). The mixture was kept for 5 h at 20°C. The precipitate of VII was filtered off. Yield 2.1 g (91%), mp >270°C, R_f 0.40 (hexane—acetone, 1:1). Found: M^+ = 220. IR spectrum: 1560, 1605 (C=C, C=N), 1690 (C=O ring), 3375 cm^{-1} (NH_2). PMR spectrum ($CDCl_3$ + CD_3OD): 2.42 (6H, s, $2CH_3$), 4.43 (2H, s, CH_2), 6.75 ppm (1H, s, CH).

REFERENCES

1. D. J. Brown, The Pyrimidines, Interscience Pubs., New York–London (1962).
2. S. Birtwell, J. Chem. Soc., 1725 (1953).
3. V. V. Dovlatyan, L. A. Khachatryan, and É. N. Ambartsumyan, Arm. Khim. Zh., No. 4, 311 (1980).
4. V. V. Dovlatyan, L. A. Khachatryan, and É. N. Ambartsumyan, Arm. Khim. Zh., No. 12, 799 (1982).
5. V. V. Dovlatyan, É. N. Ambartsumyan, and L. M. Gyul'budagyan, Arm. Khim. Zh., No. 5, 322 (1982).
6. V. V. Dovlatyan, É. N. Ambartsumyan, L. M. Gyul'budagyan, and R. G. Mirzoyan, Khim. Geterotsikl. Soedin., No. 6, 817 (1984).
7. G. S. Amazaspyan, É. N. Ambartsumyan, and V. V. Dovlatyan, Arm. Khim. Zh., No. 11, 710 (1990).
8. V. V. Dovlatyan, K. A. Éliazyan, V. V. Pivazyan, and A. M. Akopyan, Khim. Geterotsikl. Soedin., No. 6, 818 (1993).
9. V. V. Dovlatyan, É. N. Ambartsumyan, L. M. Gyul'budagyan, and G. S. Amazaspyan, Khim. Geterotsikl. Soedin., No. 8, 1114 (1993).
10. H. Ritthausen, Ber., **29**, 2108 (1896).