AMINOETHYL DERIVATIVES OF 4-SUBSTITUTED PYRAZOLO[3,4-d]PYRIMIDINES

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New 3-aminoethyl derivatives of pyrazolo[3,4-d]pyrimidine were synthesized by reduction of 3-cyanomethylpyrazolo[3,4-d]pyrimidines with hydrazine hydrate in the presence of Raney nickel in alcohol.

The preparation of 4-amino-3-(2'-aminoethyl)-1-methylpyrazolo[3,4-d]pyrimidine (IIa) by catalytic hydrogenation of the corresponding 3-cyanomethyl derivative (Ia) was described in [1]. The entire route to the synthesis of compounds of the II type from 1-substituted 5-amino-3-cyanomethyl-4-cyanopyrazole (III) is quite convenient except for the step involving the catalytic hydrogenation of the nitrile at high pressures and temperatures and the necessity for isolating the final product by high-vacuum sublimation. This apparently could serve as an obstacle to the preparation of analogs of IIa, particularly 1-phenyl derivative IIb.

In the present research, we have studied the conditions for the reduction of 3-cyanomethylpyrazolo-[3,4-d]pyrimidines with hydrazine hydrate in the presence of Raney nickel in alcohol. This method was used to obtain 4-amino-3-(2'-aminoethyl)-1-phenylpyrazolo[3,4-d]pyrimidine (IIb), which was isolated as the maleic acid salt.

To obtain Ic, we started from the corresponding pyrazole (IIIc), which was condensed with ethyl orthoformate. The ethoxymethylene derivative could not be isolated in pure form, since the ethoxymethylene group is hydrolyzed to a formyl group during recrystallization, as indicated by the appearance of an intense band at 1720 cm^{-1} in the IR spectrum. The reaction mass, without isolation of IV, was treated with alcoholic ammonia solution to give high yields of 4-amino-3-cyanomethylpyrazolo[3,4-d]pyrimidine (Ic). Reduction of Ic with hydrazine hydrate in the presence of Raney nickel gave 3-(2'-aminoethyl) derivative IIc, which was also isolated as the maleate. To obtain its hydroxy analog (V), which is a derivative of 4-hydroxypyrazolo[3,4-d]pyrimidine, a known medicinal preparation (allopurinol), the starting pyrazole should contain an amide group rather than a nitrile group in the 4 position. Selective saponification of the aromatic CN group in dinitrile III cannot be accomplished [2], and the conditions for the replacement of the amino group in nitrile Ic by a hydroxyl group via the method described in [3] were therefore studied. We were able to convert Ic to 4-hydroxy derivative VIc in rather high yield by diazotization and subsequent heating with sodium nitrite. Its structure was confirmed by the IR spectrum, in which bands are observed at 1710 (CO) [4], 1690 (C=N), and 2270 (C≡N) cm^{-1}. The band at 1710 cm^{-1} is absent in the IR spectrum of the starting Ic.

4-Hydroxy-3-(2'-aminoethyl)pyrazolo[3,4-d]pyrimidine (V), which was isolated as the maleate, was obtained by the reduction of VI with hydrazine hydrate in the presence of Raney nickel.

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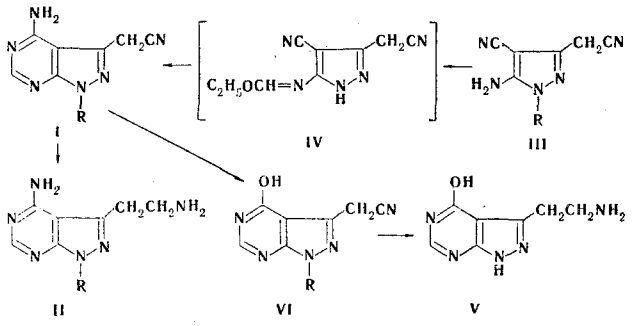

a R=CH_3; b R=C_6H_5; c R=H

EXPERIMENTAL

The UV spectra of solutions (c $1 \cdot 10^{-4}$) of the compounds were recorded with an MRS-50 spectrometer (Shimadzu) in a 1-cm-thick cuvette.

The IR spectra of thin layers of mineral-oil suspensions of the compounds were recorded with a UR-10 spectrophotometer. The PMR spectra in CF_3COOH were recorded with a Varian HA-100 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard.

4-Amino-3-(2'-aminoethyl)-1-phenylpyrazolo[3,4-d]pyrimidine (IIb). A 7-g sample of Raney nickel was added to a refluxing solution of 3 g (0.012 mole) of Ib [1] in 210 ml of anhydrous alcohol, and 42 ml of 99% hydrazine hydrate was then added carefully. After ammonia evolution had ceased, the filtrate was evaporated to dryness, and the residue was placed in alcohol and treated with alcoholic maleic acid solution to give 2.7 g (45%) of the maleate of IIb with mp 206-207° (from alcohol). Found: C 52.0; H 4.4; N 17.1%. $C_{13}H_{14}N_6 \cdot 2C_4H_4O_4$. Calculated: C 51.8; H 4.6; N 17.3%. UV spectrum (in water), λ_{max}, nm: 204, 240, and 288.

4-Amino-3-cyanomethylpyrazolo[3,4-d]pyrimidine (Ic). A 27-g (0.18 mole) sample of 5-amino-3-cyanomethyl-4-cyanopyrazole [2] was refluxed with 250 ml of ethyl orthoformate for 7 h. The reaction mixture was evaporated in vacuo, and the residue was taken up in 300 ml of absolute alcohol and added to 50 ml of anhydrous alcohol saturated with ammonia at 0°. The mixture was stirred at room temperature for 18 h, and the precipitate was recrystallized from acetic acid and water to give 26.2 g (83%) of Ic with mp > 350° (from water). Found: C 48.5; H 3.6; N 48.4%. $C_7H_6N_6$. Calculated: C 48.3; H 3.5; N 48.3%. UV UV spectrum, λ_{max}, nm (ε): (pH 11) 260 (6800); (pH)* 258 (9850). The PMR spectrum contains a singlet from two methylene protons of the cyanomethyl group attached to C_3 at δ 4.18 ppm and a singlet from the proton attached to C_6 at δ 8.28 ppm.

4-Amino-3-(2'-aminoethyl)pyrazolo[3,4-d]pyrimidine (IIc). This compound was obtained by the method used to synthesize IIb. The yield of the maleate of IIc with mp 157° (from alcohol) was 30%. Found: C 43.6; H 4.9; N 19.9%. $C_7H_{10}N_6 \cdot 2C_4H_4O_4$. Calculated: C 43.9; H 4.4; N 20.5%. UV spectrum (in water), λ_{max}, nm (ε): 253 (9000). The PMR spectrum contains a multiplet from the four methylene protons of the aminoethyl group attached to C_3 at 3.30-3.80 ppm, a singlet from the four methylidyne protons of maleic acid at 6.5 ppm, and a singlet from the proton attached to C_6 at 8.19 ppm.

4-Hydroxy-3-cyanomethylpyrazolo[3,4-d]pyrimidine (VIc). A solution of 30 g of sodium nitrite in 100 ml of water was added dropwise in the course of 2 h to 8 g (0.046 mole) of 4-amino-3-cyanoamethylpyrazolo[3,4-d]pyrimidine in 240 ml of 8% hydrochloric acid. Another 6 g of sodium nitrite was added, and the solution was brought to the boiling point. The mixture was then cooled to room temperature and allowed to stand at 0-5° for 20 h. The precipitate was recrystallized from water to give 6.3 g (74%) of VIc with mp 297-298°. Found: C 47.8; H 3.4; N 40;3%. $C_7H_5N_5O$. Calculated: C 48.0; H 2.9; N 40.0%. UV spectrum, λ_{max}, nm (ε): (pH 1) 254 (11,000); (pH 11) 262 (14,600). The PMR spectrum contains a singlet from the two methylene protons of the cyanomethyl group attached to C_3 at 4.05 ppm and a singlet from the proton attached to C_6 at 8.45 ppm.

4-Hydroxy-3-cyanomethyl-1-phenylpyrazolo[3,4-d]pyrimidine (VIb). This compound was obtained in 30% yield via the method used to synthesize VIc and had mp 253-254° (from water). Found: C 62.2; H 3.7; N 27.8%. $C_{13}H_9N_5O$. Calculated: C 62.1; H 3.6; N 27.9%.

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4-Hydroxy-3-(2'-aminoethyl)pyrazolo[3,4-d]pyrimidine (Vc). This compound, with mp 179-180°, was obtained in 38% yield via the method used to synthesize IIc. UV spectrum (in water), λ_{max}, nm (ε): 253 (9000). Found: C 44.7; H 4.6; N 23.5%. $C_7H_9N_5 \cdot C_4H_4O_4$. Calculated: C 44.7; H 4.4; N 23.7%.

LITERATURE CITED

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