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SOME REACTIONS OF 4-AMINOPYRAZOLO[3,4-d]PYRIMIDINES

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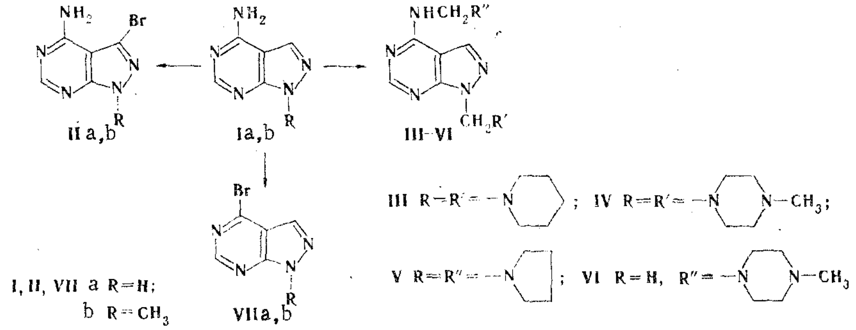
New 3-bromo and 1,4-diaminomethyl derivatives of 4-aminopyrazolo[3,4-d]pyrimidine were obtained by bromination and aminomethylation, respectively. 4-Bromopyrazolo[3,4-d]pyrimidines were synthesized for the first time by diazotization of 4-aminopyrazolo[3,4-d]pyrimidines.

We have previously studied the electrophilic substitution reactions of 4-hydroxypyrazolo[3,4-d]pyrimidines [1, 2]. It seemed of interest to extend them to 4-aminopyrazolo[3,4-d]pyrimidine (I) and substituted I. We found that the bromination of Ia, b also proceeds readily. 3-Bromo-substituted IIa, b were obtained in 50% yields when pyrazolopyrimidines Ia, b were heated with bromine in water on a water bath. The structures of these compounds were confirmed by the PMR spectra, in which, as compared with the starting substances, the signal of the proton attached to C_3 vanishes.



Under conditions similar to those in the aminomethylation of 4-hydroxypyrazolo[3,4-d]pyrimidine [2], Ia formed a Mannich base upon reaction with formalin and a secondary amine. Piperidine, methylpiperazine, and pyrrolidine were introduced into the reaction. On the basis of the results of elementary analysis and the PMR spectra it was concluded that bis(aminomethyl) derivatives III-V are obtained in this reaction. Mannich monobase VI was synthesized by the action of N-methylpiperazine on pyrazolopyrimidine Ib.

In contrast to 4-hydroxypyrazolo[3,4-d]pyrimidines, in the case of the 4-amino analogs one of the reaction centers is not the N_5 atom but rather the exocyclic amino group; this was demonstrated by means of the PMR spectra. The spectra of III and IV contain two signals of methylene protons: a singlet at 5.19 ppm and a doublet at stronger field (4.32 ppm). Splitting of the signal of the methylene protons by the proton attached to the exocyclic amino group is observed (Fig. 1). The assignment of the second reaction center to the N_1 atom was made on the basis of a comparison of the UV spectra of aminomethyl-substituted VI, i.e., with

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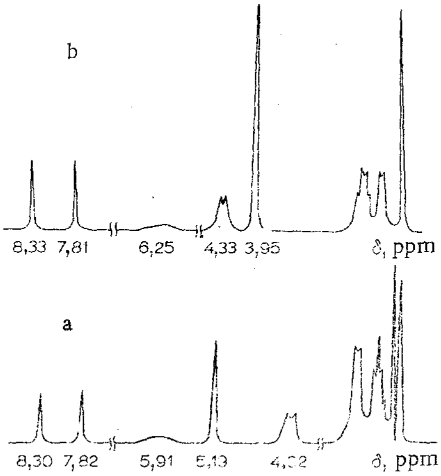

Fig. 1. PMR spectra of Mannich bases IV (a) and VI (b) in $CDCl_3$.

a compound with a known position of the substituent, and Mannich base IV. The spectra of these compounds differ only with respect to their extinctions, while substituted N_2 pyrazolopyrimidines differ from the N_1 analogs with respect to a 15-25 nm bathochromic shift of the long-wave absorption maximum [3].

It is known that the amino group in the adenine molecule can be converted only to a hydroxy group under diazotization conditions [4]. It has also been shown that 4-aminopyrazolo[3,4-d]pyrimidine derivatives can be converted to their hydroxy analogs [5].

We were able to replace the amino group in Ia, b by bromine. The presence of signals of protons attached to the C_3 and C_6 atoms in the PMR spectrum confirmed that the bromine atom in the molecule is in the 4 position. The spectrum of VIIb contains a singlet from the methyl protons at 3.97 ppm and a singlet from two ring proton at 8.28 ppm.

EXPERIMENTAL

The UV spectra of solutions with $c = 1 \cdot 10^{-4}$ mole/liter were obtained with a Shimadzu MRS-50L spectrophotometer. The PMR spectra of solutions in $CdCl_3$ were recorded with a Varian HA-100 spectrometer relative to hexamethyldisiloxane.

3-Bromo-4-aminopyrazolo[3,4-d]pyrimidine (IIa). A 1.2-g (9 mmole) sample of Ia was suspended in 25 ml of water, and 1.5 g (18 mmole) of bromine was added. The mixture was stirred at 20°C for 1 h, after which it was heated on a boiling-water bath for 1 h. The solution was evaporated to dryness, and the residue was dissolved in water and neutralized to pH 7 with sodium hydroxide solution, during which IIa precipitated. Workup gave a product with mp 350°C (from water) in 50% yield. Found: C 28.4; H 1.9; Br 37.3; N 32.3%. $C_5H_5BrN_5$. Calculated: C 28.1; H 1.9; Br 37.3; N 32.7%.

3-Bromo-1-methyl-4-aminopyrazolo[3,4-d]pyrimidine (IIb). This compound, with mp 221-223°C (from alcohol), was similarly obtained in 55% yield. Found: C 31.8; H 2.7; Br 34.9; N 30.7%. $C_6H_6BrN_5$. Calculated: C 31.6; H 2.6; Br 35.0; N 30.7%.

1-Piperidinomethyl-4-piperidinomethylaminopyrazolo[3,4-d]pyrimidine (III). A 0.8-g sample of 36% formalin was added dropwise to a suspension of 0.5 g (3.7 mmole) of I in 4 ml of alcohol and 1.7 ml (0.02 mole) of piperidine, and the mixture was heated on a boiling-water bath for 30 min. It was then cooled and evaporated to dryness, 50 ml of ether was added to the oily residue, and the mixture was filtered to give 0.33 g (30%) of IV with mp 146-147°C (from petroleum ether). Found: C 62.3; H 7.9; N 29.9%. $C_{17}H_{29}N_7$. Calculated: C 62.3; H 7.7; N 29.9%.

1-(N-Methylpiperazinomethyl)-4-(N-methylpiperazinomethyl)aminopyrazolo[3,4-d]pyrimidine (IV). This compound, with mp 142-143°C (from ethyl acetate), was obtained in 60% yield by a method similar to that used to prepare III. Found: C 56.8; H 8.3; N 34.9%. $C_{17}H_{29}N_9$. Calculated: C 56.8; H 8.1; N 35.1%. UV spectrum, λ_{max} (ε), pH 10.9: 265 nm (7560).

1-Pyrrolidinomethyl-4-pyrrolidinomethylaminopyrazolo[3,4-d]pyrimidine (V). This compound, with mp 105-106°C (from petroleum ether), was obtained in 40% yield by a method similar to that used to prepare III. Found: C 59.7; H 7.7; N 32.5%. $C_{15}H_{23}N_7$. Calculated: C 59.8; H 7.7; N 32.5%.

1-Methyl-4-(N-methylpiperazinomethyl)aminopyrazolo[3,4-d]pyrimidine (VI). This compound, with mp 205-206°C (reprecipitation from ethyl acetate by the addition of hexane), was obtained in 60% yield by a method similar to that used to prepare III. Found: C 58.6; H 7.5; N 33.9%. $C_{12}H_{19}N_7$. Calculated: C 58.5; H 7.3; N 34.1%. UV spectrum, λ_{max} (ε), pH 10.9; 265 nm (11,600).

4-Bromopyrazolo[3,4-d]pyrimidine (VIIa). A suspension of 0.3 g (2.2 mmole) of 4-hydroxypyrazolo[3,4-d]pyrimidine in 8 ml of hydrobromic acid (sp. gr. 1.5) was cooled to 0-5°C, and 0.8 g (5 mmole) of bromine and 0.4 ml of a 10% solution of sodium nitrite were added. The mixture was stirred at 0°C for 2 h and allowed to stand in a refrigerator overnight. Workup gave 0.3 g (40%) of VII with mp 280-281°C (dec., from benzene). PMR spectrum: 8.26 (3H, s) and 8.29 ppm (6H, s). Found: Br 39.8; N 28.0%. $C_5H_3BrN_4$. Calculated: Br. 40.1; N 28.1%.

4-Bromo-1-methylpyrazolo[3,4-d]pyrimidine (VIIb). This compound, with mp 253-254°C (from benzene), was obtained in 40% yield by a method similar to that used to prepare VIIa. PMR spectrum (in $CDCl_3$): 3.97 (1CH_3, s) and 8.28 ppm (3, 6H, s).

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MOLECULAR-CRYSTAL STRUCTURE OF 5-METHYL-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-2-ONE

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5-Methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one, which is an antagonist of 5-aryl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones, was subjected to a complete x-ray diffraction study. The crystals have monoclinic syngony with a = 11.456(5), b = 8.195(3), c = 9.257(4) Å, γ = 93.10(3)°, and space group $P2_1/b$. The nonplanar molecules (with a boat conformation) form cyclic dimers by means of NH...O hydrogen bonds (2.937 Å) in the vicinity of the center of symmetry (0, 0, 1/2). Replacement of the phenyl ring in the 5 position by a less bulky methyl group does not lead to appreciable changes in the geometry and conformation of the heteroring. It is assumed that the substituent in the 5 position plays a role in determining the character of the pharmacological action of 1,4-benzodiazepines.

A study of the dependence of the IR spectra of solutions of 1-unsubstituted 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones in carbon tetrachloride on the temperature showed that the molecules of these compounds in a nonpolar solvent are associated due to hydrogen bonds between the amide groups, thereby forming, depending on the concentration, linear intermolecular associates Ia or cyclic dimers Ib [1].

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