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INVESTIGATION OF THE ELECTROPHILIC REACTIONS OF 5-HYDROXYPYRIMIDINE

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The possibility of the electrophilic substitution of various positions of the 5-hydroxypyrimidine ring in a weakly basic medium is demonstrated in the case of aminomethylation and diazo coupling. It was found that the ortho positions of 5-hydroxypyrimidine are more reactive than the para position with respect to the hydroxy group.

Electrophilic substitution reactions have not yet been described for 5-hydroxypyrimidine. In addition, it has been reported that 5-hydroxypyrimidine cannot undergo electrophilic substitution because of its low stability in acidic media.

We have previously demonstrated the possibility of electrophilic substitution of the 5-hydroxypyrimidine ring in the case of the aminomethylation and diazo coupling of 4,6-dimethyl-5-hydroxypyrimidine, which were carried out in alkaline media [1].

In this connection, it seemed of interest to extend the indicated reactions to unsubstituted 5-hydroxypyrimidine and in this way to ascertain the relative reactivities of the various positions of the hydroxypyrimidine ring.

It is known that the aminomethylation of phenol takes place initially in the ortho positions and subsequently in the para position [2]. In addition, an aza analog of phenol — 3-hydroxypyridine — is aminomethylated in only one ortho position and subsequently in the para position, and this made it possible to conclude that the ortho positions in the hydroxypyridine ring are not equivalent [3].

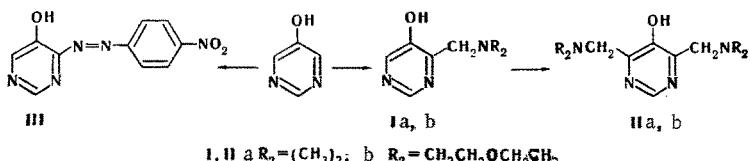
In the case of 5-hydroxypyrimidine, the structure of which, in contrast to 3-hydroxypyridine, is distinguished by its symmetry, one might have expected an orientation in aminomethylation similar to that in phenol.

We confirmed this assumption during an experimental study of the aminomethylation of 5-hydroxypyrimidine, which was carried out with N,N,N',N'-tetramethylmethylenediamine as the aminomethylating agent. When it was heated with 5-hydroxypyrimidine, the starting compound gradually passed into solution, which, depending on the treatment time, contained a mixture of mono- and bis(dimethylaminomethyl) derivatives in various ratios. The individual Mannich bases were isolated by chromatography. Since they were uncyclizable liquids, they were identified and analyzed in the form of the hydrochlorides, which proved to be rather hygroscopic.

Morpholinomethyl derivatives of 5-hydroxypyrimidine were obtained by the method in [4] by refluxing with the calculated amounts of morpholine and paraformaldehyde in chlorobenzene in the presence of triethylamine.

The PMR spectrum of the starting 5-hydroxypyrimidine consists of two singlets belonging to the protons in the 2 and 4(6) positions of the pyrimidine ring with an integral intensity ratio of 1:2. In the spectrum of monoaminomethyl derivative I, however, the intensity of the 4-H signal is half the intensity of the signal observed for the starting compound, and the appearance of a signal of a CH₂ group and signals of the aliphatic part of the amine in the form of a singlet (dimethylamine) or two multiplets (morpholine) is observed.

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The PMR spectrum of bis(aminomethyl) derivative II retains one signal at weak field but also contains signals of a methylene group and the aliphatic part of the amine that are doubled in intensity. The fact that the remaining signal at weak field pertains to the 2 rather than the 4 position of the pyrimidine ring was elucidated from a comparative examination of the PMR spectra of samples of 5-hydroxypyrimidine and its aminomethyl derivatives prepared at identical concentrations and the same pD values (3.67 ± 0.03) in D_2O . It follows from an examination of the spectra that the chemical shift of the 2-H proton of the starting compound (8.93 ppm) changes only slightly (9.05 ppm) for I and even less for II as compared with the shift of the proton of I but is also in the weak-field region; this makes it possible to sufficiently validly assign the proposed structure to bis(aminomethyl) derivative II.

In an experiment on the exhaustive aminomethylation of 5-hydroxypyrimidine we isolated a compound in the form of a hydrochloride, the PMR spectrum of which contains only signals from morpholinomethyl groups with no signals at weak field; the compound gives a characteristic (for 5-pyrimidinols) dark-red coloration with FeCl_3 . This makes it possible to assume the production of 2,4,6-tris(morpholinomethyl)-5-hydroxypyrimidine. However, we were unable to fully characterize this compound in view of its high hygroscopicity.

We also demonstrated the possibility of electrophilic substitution of the hydroxypyrimidine ring in another case, viz., diazo coupling of 5-hydroxypyrimidine.

In contrast to aminomethylation, the diazo coupling of phenol, as well as 3-hydroxypyridine, is directed primarily to the para position relative to the OH group [5].

The diazo coupling of 5-hydroxypyrimidine with p-nitrobenzenediazonium chloride in a weakly alkaline medium led to the production of 4-(p-nitrophenylazo)-5-hydroxypyrimidine (III), which, as in the case of aminomethylation, confirms the higher reactivity of the ortho position of the 5-hydroxypyrimidine ring. Two equally intense signals of 2-H and 6-H protons at weak field and signals of a phenyl ring are seen in the PMR spectrum of the azo compound.

Thus in the case of aminomethylation and diazo coupling we have demonstrated the possibility of electrophilic substitution of various positions of the 5-hydroxypyrimidine ring in weakly basic media and have found that the ortho positions of 5-hydroxypyrimidine are more reactive than the para position. These results constitute evidence that the orientation of substitution in aminomethylation is similar to that in phenol by virtue of the symmetrical character of the 5-hydroxypyrimidine structure, whereas diazo coupling proceeds via a different pathway than in the case of phenol and 3-hydroxypyridine.

EXPERIMENTAL

The PMR spectra of 8-10% solutions of the compounds in D_2O ($\text{pD } 3.67 \pm 0.03$) and $(\text{CD}_3)_2\text{SO}$ were recorded with an HA-100 spectrometer with hexamethyldisiloxane as the external standard. Column chromatography was carried out on 40/100 μ silica gel (Czechoslovakian SSR), while thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates.

The samples of 5-hydroxypyrimidine were obtained by the method in [5], were purified by sublimation in vacuo at 150-155°C, and were ground with a mortar and pestle.

4-Dimethylaminomethyl-5-hydroxypyrimidine (Ia). A suspension of 0.1 g (1 mmole) of 5-hydroxypyrimidine in 0.8 ml of $\text{N},\text{N},\text{N}',\text{N}'\text{-tetramethylenediamine}$ [7] was refluxed with stirring until the solid material dissolved completely, after which it was stirred for another 30 min until the starting compound was almost completely absent in the reaction mixture (according to chromatographic monitoring). At the end of the reaction the volatile components were evaporated in vacuo at 100°C (30 mm), and the residue was dissolved in acetone and separated with a column by elution with acetone. The R_f value was 0.53 [methanol-acetone (3:1)]. All of the compounds obtained were developed satisfactorily by spraying with an aqueous alcohol solution of FeCl_3 . The fraction containing Ia was evaporated to dryness in vacuo, and the residue was triturated with 0.5 ml of absolute alcohol saturated with hydrogen chloride with external cooling with ice. The precipitate was removed by filtration and washed with 0.2 ml of cold absolute alcohol. The hydrochloride was sublimed in vacuo at 150-160 g (26%) of Ia with mp 199-201°C (from isopropyl alcohol). PMR spectrum: 9.05 (s, 1H, 2-H), 8.76 (s, 1H, 6-H),

4.88 (s, 2H, CH_2), 3.31 (s, 6H, $\text{CH}_3-\text{N}-\text{CH}_3$). Found: C 36.7; H 6.1%. $\text{C}_7\text{H}_{11}\text{N}_3\text{O} \cdot 2\text{HCl}$. Calculated: C 37.2, H 5.8%.

4,6-Bis(dimethylaminomethyl)-5-hydroxypyrimidine (IIa). This compound was similarly obtained from 1.5 ml of $\text{N},\text{N},\text{N}',\text{N}'$ -tetramethylmethylenediamine; however, heating was continued until almost half of the monosubstituted Ia vanished, which took $\sim 2.5-3$ h. The product was isolated in the same way as Ia by elution with methanol (R_f 0.48). The hydrochloride was recrystallized from isopropyl alcohol with charcoal and had mp 105-107°C; the yield was 0.15 g (53%). PMR spectrum: 9.03 (s, 1H, 2-H), 4.83 (s, 4H, CH_2), and 3.37 ppm (s, 12H, $\text{CH}_3-\text{N}-\text{CH}_3$). Found: C 42.0, H 7.3%. $\text{C}_{10}\text{H}_{18}\text{N}_4\text{O} \cdot 2\text{HCl}$. Calculated: C 42.4, H 7.1%.

4-Morpholinomethyl-5-hydroxypyrimidine (Ib). A mixture of 0.1 g (1 mmole) of 5-hydroxypyrimidine, 0.1 g (1.15 mmole) of morpholine, 0.06 g (2 mmole) of previously dried paraformaldehyde, and 0.01 ml of triethylamine was refluxed with 5 ml of chlorobenzene for 5-10 min until the starting compound vanished. The R_f value was 0.42 [acetone-methanol (9:1)]. Isolation and purification of the product as in the preparation of IIa gave 0.08 g (31%) of a product with mp 188-190°C. PMR spectrum: 9.18 (s, 1H, 2-H), 8.91 (s, 1H, 6-H), 4.92 (s, 2H, CH_2), 4.38 (m, 4H, α - CH_2), and 3.96 ppm (m, 4H, β - CH_2). Found: C 40.2, H 5.7%. $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$. Calculated: C 40.3, H 5.6%.

4,6-Bis(morpholinomethyl)-5-hydroxypyrimidine (IIb). This compound was obtained in the same way as Ib with doubled amounts of morpholine and paraformaldehyde. The treatment time was 1.5-2 h. Purification and isolation of the product as in the preparation of Ib with acetone-methanol (1:1) as the eluent [R_f 0.36 [acetone-methanol (4:1)]] gave 0.28 g (76%) of a product with mp 155-157°C. PMR spectrum: 9.21 (s, 1H, 2-H), 5.00 (s, 4H, CH_2), 4.40 (m, 8H, α - CH_2), and 3.95 ppm (m, 8H, β - CH_2). Found: C 45.8; H 6.8%. $\text{C}_{14}\text{H}_{22}\text{N}_4\text{O}_3 \cdot \text{HCl}$. Calculated: C 45.8, H 7.3%.

4-(p-Nitrophenylazo)-5-hydroxypyrimidine (III). A filtered solution of p-nitrobenzenediazonium salt prepared from 0.6 g (4.2 mmole) of p-nitroaniline was added with stirring at 0-2°C to a solution of 0.2 g (2 mmole) of 5-hydroxypyrimidine in 10 ml of 1 N NaOH, after which stirring was continued for 30 min as the temperature was raised to 20° during which the solution turned red-orange. The reaction mixture was stirred at 20°C for 2 h, after which it was acidified to pH 4-5 with 5% HCl and evaporated in vacuo at 30°C. The residue was dissolved in acetonitrile, the solution was filtered, and III was isolated with a column (R_f 0.32). The fraction containing III was evaporated to 1 ml, and the concentrate was cooled in ice. The precipitated crystals were removed by filtration and dried to give 0.05 g (22%) of a substance with mp 265-266°C (from acetone). PMR spectrum: 8.98 (s, 1H, 2-H); 8.75 (s, 1H, 6-H); 8.68, 8.58 (d); 8.52, 8.42 ppm (d, 4H, Ar). Found: C 49.2; H 3.0%. $\text{C}_{10}\text{H}_7\text{N}_5\text{O}_3$. Calculated: C 49.0; H 2.9%.

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