# AMINOMETHYLATION OF 4-HYDROXYPYRAZOLO[3,4-d]-PYRIMIDINE AND ITS METHYL DERIVATIVES

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The Mannich reaction was used to synthesize a series of mono- and bisaminomethyl derivatives of 4-hydroxypyrazolo[3,4-d]pyrimidine and its methyl analogs, the structures of which were studied by PMR spectroscopy.

In a continuation of our research on the chemistry of purine analogs – pyrazolo[3,4-d]pyrimidines [1] – we have studied the aminomethylation of 4-hydroxypyrazolo[3,4-d]pyrimidine (I), a medicinal preparation known as allopurinol.

It was recently shown [2] that the corresponding bisaminomethyl derivatives at the nitrogen atoms in both rings of the purine system are formed when the Mannich reaction is carried out with hypoxanthine, the closest analog of which is allopurinol, in excess piperidine and formalin.

We subjected diethylamine, pyrrolidine, piperidine, N-methylpiperazine, and morpholine to reaction with I. The reaction was carried out in water, and fourfold molar amounts of amine and formalin with respect to I were used. The allopurinol dissolved after addition of the amine, apparently owing to salt formation.

On the basis of analytical data and the PMR spectra, it was established that the products of the reaction of I with piperidine, N-methylpiperazine, and morpholine are, as in the case of II, bisaminomethyl derivatives (III, IV, and V), while the products obtained with diethylamine and pyrrolidine contain one aminoalkyl group (VI and VII).

In the case of diethylamine, it was shown that Mannich monobase VI is also obtained when the reaction is carried out in alcohol without subsequent crystallization. However, bis(diethylaminomethyl)allo-

TABLE 1. PMR and UV Spectra of Aminomethyl and Methyl Derivatives of Allopurinol

| Comp. | Chemical shifts, ppm | | | | | | | $\lambda_{max}$, nm (lg ε) |
|---|---|---|---|---|---|---|---|---|
| | in $CDCl_3$ | | | | | in $D_2O$ | | |
| | $C_3$–H | $C_6$–H | $>N_5$–$CH_2$–N | $>N_1$–$CH_2$–N | $CH_3$ | $C_3$–H | $C_6$–H | |
| III | 7,96 | 8,00 | 4,72 | 5,11 | | | | 253 (3,74) |
| IV | 7,86 | 7,94 | 4,73 | 5,08 | | | | 253 (3,91) |
| V | 7,88 | 7,98 | 4,75 | 5,10 | | | | 253 (3,74) |
| VIII | 7,99 | 8,06 | 4,80 | 5,20 | | | | |
| VI | 7,95 | 8,08 | | 5,44 | | 8,37 | 8,49 | 253 (3,92) |
| VII | 7,96 | 8,10 | | 5,30 | | 8,40 | 8,50 | 253 (3,92) |
| XII | 7,99 | 7,99 | 4,73 | | 3,92 | | | |
| XI | 7,94 | 7,94 | 4,68 | | 4,03 | | | |
| XIII | 8,00 | | | 5,12 | 2,50 | | | |
| IX | | | | | | 8,40 | 8,47 | |
| X | | | | | | 8,64 | 8,37 | |
| XIV | 7,80 | 7,93 | | | 3,90 | | | 257 (3,79) |
| | | | | | 3,48 | 8,35 | 8,58 | 267 (3,76) |
| XV | 7,88 | 7,95 | | | 3,83 | | | 260 (3,89) |
| | | | | | 4,37 | 8,64 | 8,50 | 267 (3,89) |

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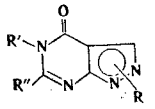
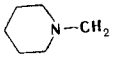
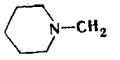
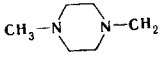
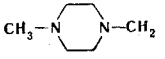
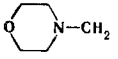
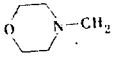
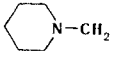
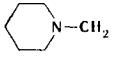
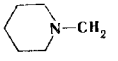
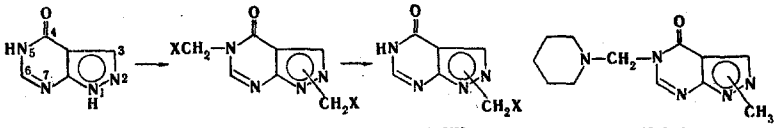
TABLE 2. Mannich Bases



| Comp. | R | R′ | R″ | mp, °C | Empirical formula | Found, % | | | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | C | H | N | |
| III |  |  | H | 212—213 | $C_{17}H_{26}N_6O$ | 61,8 | 7,9 | 25,3 | 61,8 | 7,9 | 25,4 | 90 |
| IV |  |  | H | 213—215 | $C_{17}H_{28}N_8O$ | 56,5 | 8,0 | 31,1 | 56,6 | 7,9 | 30,1 | 70 |
| V |  |  | H | 215—216 | $C_{15}H_{22}N_6O_3$ | 53,8 | 6,7 | 25,0 | 53,9 | 6,6 | 25,1 | 70 |
| VIII | $(C_2H_5)_2NCH_2$ | $(C_2H_5)_2NCH_2$ | H | 73—74 | $C_{15}H_{26}N_6O$ | 58,8 | 8,7 | 27,4 | 58,8 | 8,6 | 27,4 | 78 |
| VI | $(C_2H_5)_2NCH_2$ | H | H | 190—191 | $C_{10}H_{15}N_5O$ | 54,4 | 6,8 | 31,8 | 54,3 | 6,8 | 31,8 | 70 |
| VII |  | H | H | 200—201 | $C_{10}H_{13}N_5O$ | 54,3 | 6,0 | 31,0 | 54,2 | 6,0 | 31,6 | 70 |
| XI | 2-$CH_3$ |  | H | 189—190 | $C_{12}H_{17}N_5O$ | 57,9 | 6,7 | 27,8 | 58,3 | 6,9 | 28,3 | 40 |
| XII | 1-$CH_3$ | | | | | | | | | | | |
| | |  | H | 182—183 | $C_{12}H_{17}N_5O$ | 57,9 | 6,8 | 28,5 | 58,3 | 6,9 | 28,3 | 87 |
| XIII |  | H | $CH_3$ | 222—223 | $C_{12}H_{17}N_5O$ | 58,1 | 6,8 | 27,9 | 58,3 | 6,9 | 28,3 | 60 |



I III–V, VIII VI, VII XI, XII

III X=  ; IV X=CH$_3$–  ; V X=O  ; VI, VIII X=(C$_2$H$_5$)$_2$N; VII X=  ;

XI 2-CH$_3$; XII 1-CH$_3$

purinol (VIII) was isolated from the reaction of allopurinol with diethylamine and formalin in the absence of a solvent.

The behavior of the 1-methyl and 2-methyl derivatives of allopurinol (IX and X) in the Mannich reaction proved to be somewhat different. We were unable to obtain the product of reaction of IX with piperidine and formalin in aqueous media, while X under the same conditions reacted smoothly to give piperidylmethyl derivative XI. Its isomer (XII) was obtained by the action of piperidine and formalin on IX in the absence of water. Like the 2-methyl analog, 6-methylallopurinol reacts with piperidine in aqueous media to give a monoaminomethylation product (XIII).

Like other N-dialkylaminomethyl derivatives, the compounds that we obtained are unstable in acidic media. When base III was treated with a solution of hydrogen chloride in alcohol, allopurinol was isolated instead of the corresponding hydrochloride. A similar result was obtained in an attempt to synthesize the quaternary salts of III and VI by the action of methyl iodide.

Data from the PMR spectra of the synthesized compounds and of model methyl derivatives of allopurinol are presented in Table 1. The spectra of all of the Mannich bases contain signals of protons attached to $C_{(3)}$ and $C_{(6)}$ of the heterocyclic ring; this unambiguously attests to the location of the aminomethyl groups on the nitrogen atoms.

There is no doubt that one of the alkylaminomethyl groups in III, IV, V, and VIII is located on $N_{(5)}$ in the six-member ring, while the other is attached to the $N_{(1)}$ or $N_{(2)}$ in the pyrazole ring.

It is known that methylation of allopurinol [3] leads to a separable mixture of 1,5- and 2,5-dimethyl derivatives (XIV and XV). However, it was impossible to separate the synthesized Mannich dibases preparatively or by chromatography on paper and on Silufol plates with the use of various systems. It is possible that primarily one isomer is formed in the aminomethylation.

A comparison of the PMR spectra of model 1,5- and 2,5-dimethyl derivatives of allopurinol and Mannich dibases does not make it possible to accurately establish the position of the aminomethyl substituent in the pyrazole ring of the latter, since in $CDCl_3$, a solvent in which splitting of these compounds does not occur, the chemical shifts of the protons attached to $C_6$ and, especially, $C_3$ are practically identical.

We were also unable to do this by comparison of their UV spectra (see Table 1), since they do not differ substantially.

It follows from the PMR spectra that the signals of the protons of the methylene group directly attached to one of the nitrogen atoms of the pyrazole ring are shifted to weak field as compared with the signals of similar groups attached to $N_{(5)}$. This provides a basis for asserting that the aminomethyl group in VI, VII, and XIII is in the five-membered ring.

A comparison of the chemical shifts in $D_2O$ of the proton attached to $C_{(3)}$ in 1- and 2-methyl-substituted allopurinols and monoaminomethyl derivatives VI and VII makes it possible, with a sufficient degree of probability, to conclude that the aminomethyl group in the latter is attached to $N_{(1)}$.

From the data obtained it can be assumed that in aqueous media and in the absence of a solvent all of the secondary amines that we used form a Mannich dibase with allopurinol and formalin. However, in the case of diethylamine and pyrrolidine in aqueous and alcoholic media the aminomethyl group is cleaved from the amide nitrogen atom in the 5 position; this was confirmed by quantitative isolation of monoaminomethyl derivative VI by recrystallization of VIII from alcohol.

Comparing the results of the Mannich reaction with allopurinol and its 1- and 2-methyl derivatives, it can be assumed that the observed differences are explained by the fact that the reaction with diethylamine and pyrrolidine gives 1,5-substitution products (of the XII type), which in aqueous media readily

split out an aminomethyl group from $N_{(5)}$, while 2,5-substitution occurs during reaction with six-membered bases to give products of the XI type, which are highly stable and do not undergo further transformation.

It is as yet difficult to explain these differences, but the available data do not contradict the stated concepts regarding the structure of the compounds obtained.

## EXPERIMENTAL

The UV spectra of $1 \cdot 10^{-4}$ solutions in anhydrous alcohol were recorded with an MRS-501 spectrometer (Shimadzu) in a 1-cm thick cuvette. The PMR spectra of $CDCl_3$ and $D_2O$ solutions (with an external standard) were recorded with an HA-100 spectrometer (Varian); the chemical shifts are given in parts per million relative to hexamethyldisiloxane.

Reaction of Diethylamine with Allopurinol and Formalin. A. An 0.8-ml sample of 36% formalin was added to a solution of 0.5 g (3.7 mmole) of allopurinol in 5 ml of water and 1 g (15 mmole) of diethylamine, after which the mixture was stirred at room temperature for 30 min and allowed to stand in a refrigerator overnight. The precipitate was removed by filtration to give 1.4 g of VI, which was recrystallized from a small amount of anhydrous ethanol.

Compounds III, IV, V, VII, XI, and XIII (see Table 2) were obtained under these conditions.

B. A 0.8 ml sample of formalin was added to a cooled suspension of 0.25 g (18 mmole) of allopurinol in 1 g (15 mmole) of diethylamine, and the solution was stirred for 30 min. The precipitate was removed by filtration and washed with cold ethyl acetate to give 0.44 g of VIII.

Compound XII was similarly synthesized and was purified by recrystallization from benzene.

## LITERATURE CITED

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3. P. Schmidt, K. Eichenberger, and I. Druey, Helv. Chim. Acta, 41, 1052 (1958).