PYRIMIDINES.

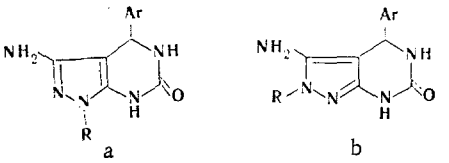
XLIII.* 3,5-DIAMINOPYRAZOLE IN THE SYNTHESIS OF PYRAZOLO[3,4-d]PYRIMIDINES

M. A. Mikhaleva, L. N. Il'chenko, and V. P. Mamaev

UDC 547.779.1'859.2:542.953

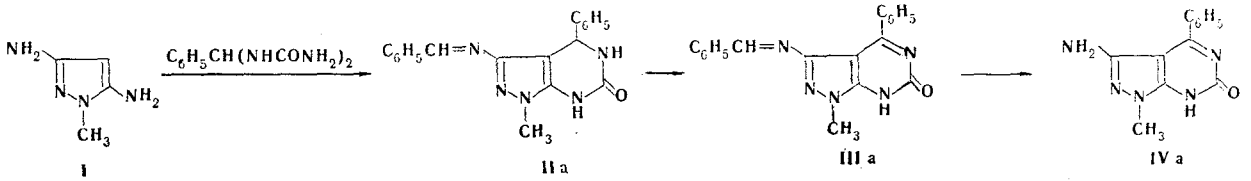
In the condensation of benzalbisurea with 1-methyl-3,5-diaminopyrazole the pyrimidine ring closes through the amino group of pyrazole in the 5 position to give 1-methyl-4-phenyl-3-benzalamino-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine. The latter is converted to 1-methyl-4-phenyl-3-amino-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine by dehydrogenation and subsequent hydrolysis of the benzylidene group.

It has been shown that pyrazolo[3,4-d]pyrimidines can be obtained by condensation of 1-R-5-aminopyrazoles with arylidenebisureas [2], while 3-aminopyrazoles reacted under these same conditions to give completely different compounds [2, 3]. Proceeding from this, we assumed that in the preparation of pyrazolo[3,4-d]pyrimidines from 1-substituted 3,5-diaminopyrazole and bisureas the pyrimidine ring would close through the amino group in the 5 position of pyrazole to give a 1-R-pyrazolo[3,4-d]pyrimidine derivative (a) rather than the isomeric 2-R-pyrazolo[3,4-d]pyrimidine (b).



a b

Compound II, in which an NH_2 group was absent, was obtained by condensation of 1-methyl-3,5-diaminopyrazole (I) [4] with benzalbisurea. Absorption bands at 1690 cm^{-1} (urea ring C=O) and 3440 cm^{-1} (ν_{NH}) were present in the IR spectrum of this compound.



I IIa IIIa IVa

*See [1] for communication XLII.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1422-1424, October, 1974. Original article submitted July 19, 1973.

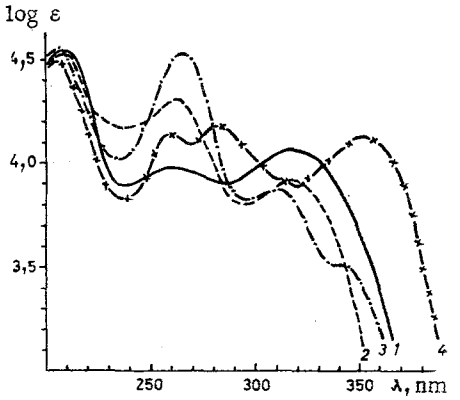


Fig. 1. UV spectra of alcohol solutions (c $1 \cdot 10^{-4}$ M): 1) 1-methyl-4-phenyl-3-amino-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (IVa); 2) 1-methyl-4-phenyl-3-hydroxy-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine [6]; 3) 1,4-diphenyl-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine [2]; 4) 2,4-diphenyl-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine [2].

The IR spectral data, the results of elementary analysis, and the molecular weight determination by mass spectrometry provided a basis to assume that II is the N-benzylidene derivative of the expected 3-amino-6-oxo-4,5,6,7-tetrahydropyrazolopyrimidine (IIa or IIb).

Compound II could not be dehydrogenated by bromination—dehydrobromination, in contrast to the 3-unsubstituted pyrazolo[3,4-d]pyrimidines [2]. The dihydro derivative (III) was obtained by refluxing II with chloranil in absolute xylene. As one should have expected [2], the absorption band of the C=O group (1640 cm^{-1}; 1670 cm^{-1}, shoulder) in the IR spectrum of III is shifted as compared with its position in the IR spectrum of II. It is interesting to note that the absorption maxima in the UV spectrum of III are not shifted to the long-wave region as compared with the UV spectrum of II, as was previously observed on passing from the tetrahydro to the dihydro derivatives [2, 5, 6]. Signals of protons of an NCH_3 group (singlet, 3.82 ppm), of a —CH=N proton (singlet, 7.80 ppm), and of aromatic protons (7.25 and 7.50 ppm) with an intensity ratio of 3:1:5:5 are present in the PMR spectrum of III; this corresponds to the dehydrogenated pyrazolopyrimidine structure.

In order to obtain an aminopyrazolopyrimidine we hydrolyzed the Schiff base (III) by refluxing in aqueous alcoholic HCl. The absorption band of a C=O group at 1640 cm^{-1} (1670 cm^{-1}, shoulder) is retained in the IR spectrum of the hydrolysis product (IV); absorption bands at 3360 and 3430 cm^{-1} are present in the region of NH stretching vibrations.

The determination of the molecular weight with a high-resolution mass spectrometer and the empirical formula calculated on the basis of this constitute evidence in favor of cleavage of the benzylidene grouping and the formation of an aminopyrazolopyrimidine (IV). This is also confirmed by the data from the PMR spectrum of IV. Signals of aromatic protons (5H, multiplet, 7.52 ppm), a broadened signal of protons of an NH_2 group (5.74 ppm), and signals of an NCH_3 group (3H, singlet, 3.51 ppm) are present in the PMR spectrum of IV, while signals of an N-benzylidene group are absent. Some of the peculiarities in the behavior of IV, namely, the absence of reaction of IV with benzaldehyde and p-dimethylaminobenzaldehyde, are probably associated with the reduced basicity of the 3-NH_2 group in 6-oxopyrazolo[3,4-d]pyrimidine (see [6]).

In order to ascertain the structure of IV (IVa or IVb) we compared its UV spectrum with the spectra of the previously obtained 1- and 2-substituted pyrazolo[3,4-d]pyrimidines [2, 6]. The UV spectra of 1- and 2-substituted pyrazolo[3,4-d]pyrimidines differ with respect to the presence of a longer-wave maximum in the spectra of the 2-substituted compounds as compared with the spectra of the 1-substituted compounds. It is seen from a comparison of these spectra that the UV spectrum of IV is similar to the spectra of authentic 1-R-pyrazolo[3,4-d]pyrimidines (Fig. 1, curves 1, 2, and 3, maxima at 310-320 nm), while the UV spectrum of the authentic 2-R-isomer contains an intense maximum at 350 nm. Thus condensation of 1-methyl-3,5-diaminopyrazole with benzalbisurea gives 1-methyl-4-phenyl-3-benzalamino-6-oxo-4,5,6,7-tetrahydropyrazolopyrimidine (IIa), which, after dehydrogenation and hydrolysis, is converted to 1-methyl-4-phenyl-3-amino-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (IVa).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds (c 0.25%) were recorded with UR-10 and UR-20 spectrometers. The UV spectra of alcohol solutions were recorded with a Spe-

cord spectrophotometer. The PMR spectra of d_6-DMSO solutions were recorded with a Varian A 56/60A spectrometer with hexamethyldisiloxane as the internal standard. The molecular weights were determined with an MS-902 high-resolution mass spectrometer.

1-Methyl-4-phenyl-3-benzalamino-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (IIa). A mixture of 0.80 g (7.15 mmole) of I and 3.0 g (14.3 mmole) of benzalbisurea was refluxed for 5 h in 20 ml of glacial acetic acid. The mixture was then cooled and poured into 200 ml of water, and the resulting precipitate was removed by filtration and washed successivly with water, 10% $NaHCO_3$, and water to give 0.8 g (34%) of IIa with mp 291-293° (from isopropyl alcohol). Found: C 68.5; H 5.1; N 20.9%; M 331. $C_{19}H_{17}N_5O$. Calculated: C 68.8; H 5.1; N 21.1%; M 331.

1-Methyl-4-phenyl-3-benzalamino-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (IIIa). A mixture of 0.48 g (1.45 mmole) of IIa and 0.43 g (1.74 mmole) of chloranil was refluxed in 6 ml of absolute xylene for 40 min. The mixture was then cooled, and the resulting precipitate was removed by filtration and washed with alcohol and water to give 0.35 g (73%) of IIIa with mp 262-266° (from alcohol with decolorization by activated charcoal). Found: N 21.7%; M 329. $C_{19}H_{15}N_5O$. Calculated: N 21.3%; M 329.

1-Methyl-4-phenyl-3-amino-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (IVa). A suspension of 0.30 g (0.9 mmole) of IIIa in 8 ml of alcohol and 2 ml of concentrated HCl was refluxed for 1 h. The mixture was then cooled, and the resulting yellow precipitate was removed by filtration to give 0.18 g (70%) of the hydrochloride of IVa with mp 315-317° (from alcohol). The hydrochloride was washed with 10% $NaHCO_3$ solution and water to give IVa with mp 283-285° (decomp. from alcohol). Found: C 55.5; H 5.1; N 27.1%; M 241,0964.* $C_{12}H_{11}N_5O \cdot H_2O$. Calculated: C 55.7; H 5.0; N 27.0%.

LITERATURE CITED

1. O. P. Shkurko, S. G. Baram, and V. P. Mamaev, Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Khim., No. 14, 81 (1973).
2. V. P. Mamaev and M. A. Mikhaleva, Khim. Geterotsikl. Soedin., 535 (1971).
3. M. A. Mikhaleva, L. N. Il'chenko, and V. P. Mamaev, Khim. Geterotsikl. Soedin., 233 (1974).
4. J. A. Settepani and J. B. Stokes, J. Org. Chem., 33, 2606 (1968).
5. M. A. Mikhaleva and V. P. Mamaev, Khim. Geterotsikl. Soedin., 1696 (1972).
6. M. A. Mikhaleva, L. N. Il'ichenko, and V. P. Mamaev, Khim. Geterotsikl. Soedin., 823 (1974).

*The empirical formula $C_{12}H_{11}N_5O$ was calculated from this molecular weight.