PYRIMIDINES

XL.* REACTION OF BISUREAS WITH ISOMERIC HYDROXYAMINOPYRAZOLES

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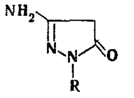
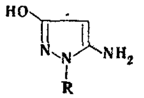
It is shown that the reaction of benzalbisurea with 3-amino-5-hydroxy-1-R-pyrazoles gives 1-R-dipyrazolo[3,4-b:4',3'-e]pyridine (R = CH_3) or a spiro(pyrazole-4,5'-pyrimidine) derivative (R = C_6H_5). Similar reactions of benzalbisurea with 3-hydroxy-5-amino-1-methylpyrazole give 2-methyldipyrazole[3,4-b:4',3'-e]pyridine or substituted tetrahydropyrazolo[3,4-d]pyrimidine. Only the corresponding dipyrazolo[3,4-b:4',3'-e]pyridines are formed in the reaction of 1-methylhydroxyaminopyrazoles with methylenebisurea.

It has been shown that pyrazoles containing hydroxyl or amino groups in the 3 or 5 position condense with arylidenebisureas to give, depending on the structure of the starting pyrazole, spiropyrazolepyrimidines [2], pyrazolooxazines [3], pyrazolopyrimidines [4], or products with more complex structures [5]. In the present research we have investigated the behavior of pyrazoles simultaneously containing hydroxyl and amino groups in the 3 and 5 positions of the pyrazole ring in similar condensations. Two isomers – I and II – are possible for 3,5-disubstituted pyrazoles when there is a substituent in the 1 position.



I



II

On the basis of the results obtained in [2], it was natural to assume that one should most likely expect the formation of a spiro(pyrazole-4,5'-pyrimidine) derivative in the reaction of isomer I, which is a compound of the pyrazolone class [6], on reaction with arylidenebisureas. In fact, III, to which the 3-amino-1,4',6'-triphenylspiro(pyrazole-4,5'-hexahydropyrimidine)-2,5'-dione structure (III) was assigned on the basis of the results of elementary analysis and the spectral characteristics, was isolated in the condensation of 1-phenyl-3-amino-5-pyrazolone (Ia) with benzalbisurea (the reagent molar ratio was 1:2).

However, the chief product of the reaction was IVa, which presumably had empirical formula $C_{39}H_{30}N_6O_2$ on the basis of the analytical data and the experimentally determined molecular weight. This made it possible to suppose that IVa is formed from two molecules of pyrazole Ia ($C_{18}H_{18}N_6O_2$) and three molecules of benzaldehyde ($C_{21}H_{18}O_3$) with splitting out of three molecules of water. The formation of IVa in the reaction of Ia with benzaldehyde confirmed this assumption. Considering the IR spectroscopic data – the presence of absorption bands at 1720 cm^{-1} (C=O in 4,4-disubstituted 5-pyrazolones [7]) and at 3380 cm^{-1} (NH) – the formula of one of the three structural isomers in Scheme 1 could be proposed for IVa.

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*See [1] for communication XXXIX.

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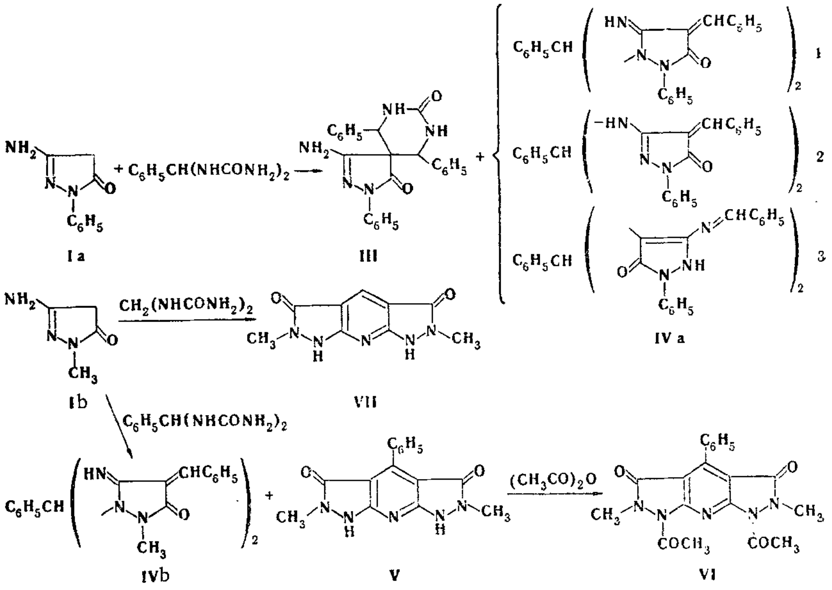
Scheme 1



The choice made between them was made on the basis of the PMR spectral data. The PMR spectrum of IVa contains signals at 4.30 δ (s,* —CH<), 4.95 δ (s, C=CH–), and 7.26 δ (m, H_{arom}) with an intensity ratio of 1:2:25. Inasmuch as the signal of a proton of the $-N=CHC_6H_5$ group (8–8.5 δ [8]) is absent in the spectrum, one can reject structure 3. The proton signal of the >CH— group appears as a rather narrow singlet, while splitting (or at least broadening) of the signal due to coupling of the protons in the –NH–CH–NH– grouping should have occurred for structure 2; on the basis of this, we propose structure 1 as most probable for IVa.

Condensation of Ia with an equimolecular amount of benzalbisurea gives only IVa. A compound of a similar structure (IVb) was obtained by reaction of 1-methyl-3-amino-5-pyrazolone (Ib) with a twofold amount of benzalbisurea, but spiro(pyrazole-4,5'-pyrimidine) was not detected in the reaction mixture in this case.

A bright-yellow high-melting product that was practically insoluble in the usual organic solvents was isolated in the condensation of equimolecular amounts of Ib and benzalbisurea. The determination of the molecular weight and the IR spectral data (broad band of the absorption of a C=O group at 1640 cm^{-1}) enabled us to propose a substituted dipyrazolo[3,4-b:4',3'-e]pyridine structure (V) for it. The formation of condensed pyridines of this kind is known for the reaction of aldehydes with both aromatic amines and aminopyrazoles [9, 10]. An additional proof of the structure of V was the formation of diacetyl derivative VI by refluxing dipyrazolopyridine V with acetic anhydride; this was evidenced by the appearance of new bands in the IR spectrum of VI in the region of absorption of the C=O group and also by the disappearance of the bands of the NH stretching vibration, as compared with the IR spectrum of starting V.

Condensation of pyrazolone Ib with methylenebisurea [11] gave dipyrazolopyridine VII, the structure of which was established as described above on the basis of analytical and spectral data.

The reaction of hydroxyaminopyrazole II (an isomer of the compound under consideration) with bisurea most likely should have given condensation systems containing either an oxazine [3] or a pyrimidine [4] ring.

A multicomponent mixture with predominance of two compounds, for the first of which, with empirical formula $C_{18}H_{14}N_2O$, the structure was not unambiguously established, was obtained when isomer II was condensed with benzalbisurea (in a ratio of 1:2). The IR spectrum of the second compound contained absorp-

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*Here and subsequently, s is singlet and m is multiplet.

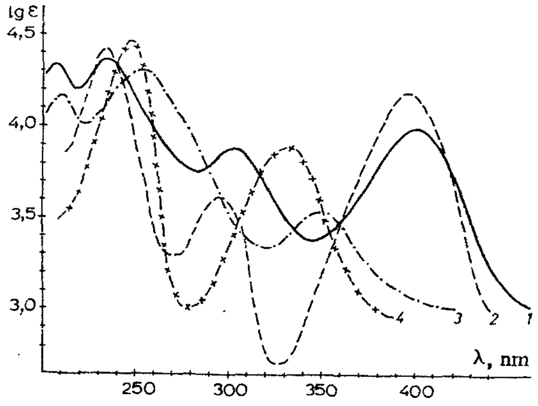
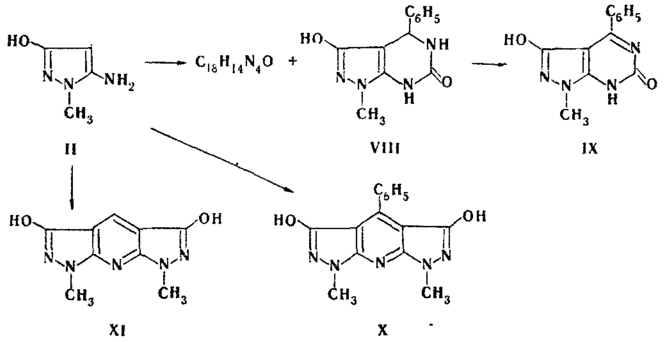


Fig. 1. UV spectra of dipyrazolopyridines: 1) V; 2) VIII; 3) X; 4) XI.

Scheme 2



tion bands at 1690 cm^{-1} (C=O) and at 3396 cm^{-1} (NH) and the compound gave a qualitative reaction for a phenolic OH group and, with respect to its molecular weight and empirical formula, correspond to the expected tetrahydropyrazolopyrimidine (VIII). We were unable to dehydrogenate it by the bromination-dehydrobromination method. The corresponding pyrazolopyrimidine (IX) was obtained by dehydrogenation of tetrahydro compound VIII with chloranil.

The condensation of equimolecular amounts of hydroxypyrazone II and benzalbisurea gave, in addition to VIII, a compound with an IR spectrum that did not contain absorption bands of C=O and NH groups; moreover, it gave a qualitative reaction for a phenolic hydroxyl group with $FeCl_3$. These data, the results of elementary analysis, and the molecular weight determination enabled us, in analogy with the preceding case, to assign the 1,7-dimethyl-4-phenyl-3,5-dihydroxydipyrazolo[3,4-b:4',3'-e]pyridine structure (X) to the isolated compound.

In the reaction of II with methylenebisurea in various molar ratios, we were able to isolate only 1,7-dimethyl-3,5-dihydroxydipyrazolo[3,4-b:4',3'-e]pyridine (XI), the structure of which was established on the basis of analytical and spectral data.

The regularity in the change in the UV spectra of condensed pyrazole systems as a function of which edge of the pyrazole ring undergoes fusion (as we noted in [3, 4]) is observed for the isomeric dipyrazolopyridines obtained by the reaction of hydroxyaminopyrazoles I and II with bisureas. In the case of V and VII, for which ring fusion occurs at the 3-4 edge of pyrazole, the UV spectra are characterized by the presence of an intense long-wave maximum, as compared with the UV spectra of X and XI, which are fused at the 4-5 edge of pyrazole (Fig. 1).

EXPERIMENTAL

The IR spectra of KBr pellets (c = 0.25%) were recorded with UR-10 and UR-20 spectrometers. The UV spectra of alcohol solutions were recorded with a Unicam SP-700C spectrophotometer. The PMR spectra of deuterodimethyl sulfoxide solutions were recorded with a Varian A56/60A spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The molecular weights were determined with an MS-902 mass spectrometer.

2,2'-Benzalbis(1-phenyl-4-benzal-3-imino-5-pyrazolone) (IVa). A mixture of 1.75 g (0.01 mole) of Ia and 2.12 g (0.02 mole) of benzaldehyde in 10 ml of glacial CH_3COOH was refluxed for 1 h, after which it was cooled and poured into 250 ml of water. The aqueous mixture was neutralized with dry $NaHCO_3$, and the resulting precipitate was removed by filtration and washed with alcohol to give 2.46 g (80%) of IVa with mp 258-260° (from alcohol). Found: C 75.1; H 5.2; N 13.2%; mol. wt. 671,659.* $C_{39}H_{30}N_6O_2 \times 0.5C_2H_5OH$. Calculated: C 75.2; H 5.2; N 13.2%; mol. wt. 637. UV spectrum, λ_{max}, nm (log ε): 207 (4.68), 259 (4.45).

3-Amino-1,4',6'-triphenylspiro(pyrazole-4,5'-hexahydropyrimidine)2,5'-dione (III). A mixture of 1.75 g (0.01 mole) of Ia and 4.16 g (0.02 mole) of benzalbisurea was refluxed for 1.5 h in 10 ml of glacial CH_3COOH, after which it was cooled and poured into water. The aqueous mixture was neutralized with dry $NaHCO_3$, and the resulting precipitate was removed by filtration, dried, and washed throughouly with ether to give 1.03 g (24%) of III with mp 270-273° (from alcohol). Found: C 69.7; H 5.0; N 16.6%. $C_{24}H_{21}N_5O_2$. Calculated: C 70.2; H 5.1; N 17.0%. IR spectrum, cm^{-1}: 1680, 1700 (C=O); 3410 (N-H). UV spectrum, λ_{max}, nm (log ε): 202 (4.55), 252 (4.35).

Evaporation of the ether filtrate gave 1.85 g (60%) of IVa.

2,2'-Benzalbis(1-methyl-4-benzal-3-imino-5-pyrazolone) (IVb). A mixture of 2.0 (17.7 mmole) of Ib and 7.36 g (3.54 mmole) of benzalbisurea in 20 ml of glacial CH_3COOH was refluxed for 1.5 h, after which it was cooled and poured into 200 ml of water. The resulting precipitate was removed by filtration, washed successively with water, 10% $NaHCO_3$ solution, and water, and dried to give 8.5 g (97%) of IVb with mp 283-284° (from n-propanol). Found: C 70.9; H 5.5; N 17.3%; mol. wt. 490. $C_{29}H_{26}N_6O_2$. Calculated: C 71.0; H 5.3; N 17.1%; mol. wt. 490. IR spectrum ($CHCl_3$), cm^{-1}: 1710-1720 (C=O); 3210, 3270, and 3380 (N-H). UV spectrum, λ_{max}, nm (log ε): 208 (4.40), 294 (3.76). PMR spectrum, δ, ppm: 2.3 (s, CH_3); 3.9 (s, $-CH<$); 4.7 (s, $>CH=CH-$), and 7.4 (m, C_6H_5) with an intensity ratio of 6:1:2:15.

2,6-Dimethyl-4-phenyl-3,5-dioxodipyrazolo[3,4-b:4',3'-e]pyridine (V). A 2.0-g (17.7 mmole) sample of Ib was refluxed with 3.7 g (17.7 mmole) of benzalbisurea in 25 ml of glacial CH_3COOH for 6 h, after which the mixture was cooled, and the resulting bright-yellow precipitate was removed by filtration, washed with acetic acid, and dried over NaOH in a desiccator to give 0.27 g (10%) of V with mp > 360°. Found: C 60.8; H 4.5%; mol. wt. 295. $C_{15}H_{13}N_5O_2$. Calculated: C 61.0; H 4.4%; mol. wt. 295.

The acetic acid filtrate yielded 1.45 g (33%) of IVb.

1,7-Diacetyl-2,6-dimethyl-4-phenyl-3,5-dioxodipyrazolo[3,4-b:4',3'-e]pyridine (VI). A solution of 0.29 g (1 mmole) of V in 20 ml of acetic anhydride was refluxed for 1 h, after which the hot mixture was filtered and cooled. The precipitated crystals were removed by filtration to give 0.12 g of VI with mp 245-250° (from dioxane). Found: N 18.5; $COCH_3$ 22.7%. $C_{19}H_{17}N_5O_4$. Calculated: N 18.5; $COCH_3$ 22.7%. IR spectrum, cm^{-1}: 1700, 1720, and 1730 (C=O). UV spectrum, λ_{max}, nm (log ε): 278 (4.28).

2,6-Dimethyl-3,5-dioxodipyrazolo[3,4-b:4',3'-e]pyridine (VII). A mixture of 1.0 g (8.85 mmole) of Ib and 1.2 g (8.85 mmole) of methylenebisurea in 20 ml of glacial CH_3COOH was refluxed for 2 h, after which it was allowed to stand overnight. The resulting yellow precipitate was then removed by filtration, washed successively with acetic acid and water, and dried thoroughly over NaOH in a desiccator to give 0.15 g (15%) of VII with mp > 360° (from acetic acid). Found: C 49.3; H 4.3; N 31.7%; mol. wt. 219. $C_9H_9N_5O_2$. Calculated: C 49.3; H 4.1; N 31.9%; mol. wt. 219. IR spectrum, cm^{-1}: 1650 broad (C=O).

1-Methyl-4-phenyl-3-hydroxy-6-oxo-4,5,6,7-tetrahydropyrazole[3,4-d]pyrimidine (VIII). A 4.0-g (35.4 mmole) sample of II was refluxed for 2 h with 14.7 g (70.8 mmole) of benzalbisurea in 70 ml of glacial CH_3COOH, after which the mixture was cooled and poured into 700 ml of water. The aqueous mixture was filtered, and the filtrate was neutralized with dry $NaHCO_3$. The resulting orange-yellow (sometimes containing resin) precipitate of A was removed by filtration, washed with ether, and recrystallized from alcohol to give 1 g of a compound with a molecular weight of 302 and mp 265-270° (decomp.).

The filtrate from the separation of precipitate A was allowed to stand for 3 days at room temperature, as a result of which a white precipitate was obtained. It was removed by filtration and washed with water to give 1.2 g (15%) of VIII with mp 290° (decomp. from alcohol). Found: C 58.9; H 5.7; N 18.4%; mol. wt. 244. $C_{12}H_{12}N_4O_2 \cdot 0.5C_2H_5OH$. Calculated: C 58.5; H 5.6; N 18.0%; mol. wt. 244. UV spectrum, λ_{max}, nm (log ε): 209 (4.14), 252 (3.80).

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*Determined by isothermal distillation.

1-Methyl-4-phenyl-3-hydroxy-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (IX). A mixture of 0.53 g (2.18 mmole) of VIII and 0.64 g (2.61 mmole) of chloranil was refluxed for 5.5 h in 9 ml of absolute xylene, after which the mixture was cooled, and the resulting precipitate was removed by filtration and washed successively with methanol and ether to give 0.38 g (89%) of IX with mp > 345° (decomp. from n-propanol). Found: C 60.0; H 4.3; N 22.5%; mol. wt. 242. $C_{12}H_{10}N_4O_2$. Calculated: C 59.5; H 4.1; N 23.1%; mol. wt. 242. IR spectrum, cm^{-1}: 1620-1640 (C =O). UV spectrum, λ_{max}, nm (log ε): 204 (4.50), 256 (4.28), 314 (3.95).

1,7-Dimethyl-4-phenyl-3,5-dihydroxydipyrazolo[3,4-b:4',3'-e]pyridine (X). The procedure used to obtain pyridine V was used to obtain this compound, with mp > 360°, in 10% yield from II and benzalbisurea. Found: C 61.4; H 4.5; N 23.4%; mol. wt. 295. $C_{15}H_{13}N_5O_2$. Calculated: C 61.0; H 4.4; N 23.7%; mol. wt. 295. IR spectrum, cm^{-1}: 1600, 1660 w.

1,7-Dimethyl-3,5-dihydroxydipyrazolo[3,4-b:4',3'-e]pyridine (XI). The procedure used to prepare pyridine X was used to obtain this compound, with mp > 340° (decomp.), in 7% yield from II and methylenebisurea. Found: C 49.3; H 4.2; N 31.8%; mol. wt. 219. $C_9H_9N_5O_2$. Calculated: C 49.3; H 4.1; N 31.9%; mol. wt. 219. IR spectrum, cm^{-1}: 1620, 1680 w.

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