PYRIMIDINES

# XXIX.* 4-ARYL-6-HYDROXYPYRAZOLO[3,4-d]PYRIMIDINES

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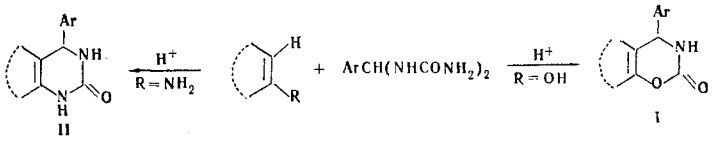
A new method was developed for the synthesis of substituted pyrazolo[3,4-d]pyrimidines by the condensation of 1-alkyl(aryl)-3- and 5-aminopyrazoles with arylidenebisureas.

A condensed 1,3-oxazine system (I) was obtained by the condensation of arylidenebisureas with compounds of phenolic character [2, 3]. An o-hydroxy-($\alpha$-ureidobenzyl) derivative is formed as the intermediate as a result of electrophilic substitution [2].

We assumed that aromatic (heterocyclic) amines in which the activity of the ortho position to electrophilic substitution reactions is retained could enter into similar condensations with the formation of condensed pyrimidines (II):




The basicity of the primary amino group apparently should not be very high in order to avoid side reactions.

We felt that 1-substituted 3- and 5-aminopyrazoles would be convenient models for carrying out this sort of condensation. These are rather weakly basic amines [4] with an active ring 4-position [5] at which electrophilic attack by the carbonium ion formed from an arylidenebisurea under the reaction conditions should primarily occur. These properties of aminopyrazoles provided a basis for assuming that their reaction with arylidenebisureas would result in the formation of pyrazolo[3,4-d]pyrimidines, which are of interest because of their structural similarity to purines [7].

We selected the readily accessible 1-phenyl-, 1-benzyl-, and 1-methyl-5-aminopyrazoles as the primary objects of the investigation.

A precipitate which was fractionally recrystallized into two compounds was isolated from the reaction mixture from the condensation of 1-phenyl-5-aminopyrazole with benzalbisurea in acetic acid. One of them had absorption bands at 1700 $cm^{-1}$ (C=O) and 3430 $cm^{-1}$ (N–H) in its IR spectrum. Its UV spectrum was close to the UV spectrum of the starting pyrazole (Table 2), which indicated the similarity of their chromophoric systems. The determination of the molecular weight and the analytical data (Table 1) enabled us to assign the 1,4-diphenyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine structure (IIIa) to this compound. The second compound, which is present in the mixture in smaller amounts, had a broad absorption band at 1630-1650 $cm^{-1}$ in its IR spectrum, and a long-wave maximum was present in its UV spectrum (Fig. 1, curves 1 and 3). Changes of this sort in the spectral characteristics are observed on passing from tetrahydro- to dihydro derivatives of 2-oxopyrimidines [8]. In fact, the mass spectrometric determination of the molecular weight made it possible to assign a dehydrogenated pyrazolopyrimidine structure (IVa) to this compound.

*See [1] for communication XXVIII.

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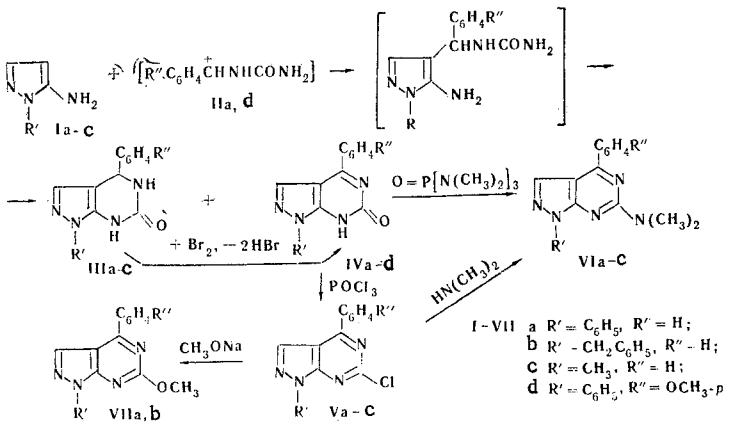
TABLE 1. 1,6-Disubstituted 4-Arylpyrazolo[3,4-d]pyrimidines

| Comp. | Mp., °C | M[a] | Empirical formula | Found, % | | | | Calc., % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | | C | H | N | | |
| IIIa | 204—205 | 290 | $C_{17}H_{14}N_4O$ | 70,4 | 4,6 | 19,3 | — | 70,4 | 4,8 | 19,3 | — | 34 |
| b | 199—202 | 304 | $C_{18}H_{16}N_4O$ | 71,2 | 5,2 | 18,3 | — | 71,0 | 5,2 | 18,4 | — | 30 |
| c | 257—260 | 228 | $C_{12}H_{12}N_4O$ | 63,1 | 5,3 | 24,4 | — | 63,2 | 5,3 | 24,5 | — | 37 |
| IVa | 310—313 (sublim.) | 288 | $C_{17}H_{12}N_4O$ | 71,1 | 4,2 | 19,4 | — | 71,0 | 4,2 | 19,4 | — | 91[b] |
| b | 266—269 (sublim.) | 302 | $C_{18}H_{14}N_4O$ | — | — | 18,5 | — | — | — | 18,5 | — | 86[b] |
| c | 293—295 (sublim.) | 226 | $C_{12}H_{10}N_4O$ | — | — | 24,5 | — | — | — | 24,7 | — | 46[b] |
| d | 320—324c (sublim.) | 318 | $C_{18}H_{14}N_4O$ | 67,7 | 4,6 | 17,4 | 10,0[d] | 68,0 | 4,4 | 17,6 | 9,8[d] | 18 |
| Va | 181—182 | 306 | $C_{17}H_{11}ClN_4$ | — | — | 18,1 | 11,4[e] | — | — | 18,3 | 11,6[e] | 51 |
| b | 108—109 | — | $C_{18}H_{13}ClN_4$ | — | — | 17,4 | 11,2[e] | — | — | 17,5 | 10,9[e] | 26 |
| c | 151 | 244 | $C_{12}H_9ClN_4$ | — | — | 22,5 | — | — | — | 22,9 | — | 65 |
| VIa | 140—142 | — | $C_{19}H_{17}N_5$ | 72,1 | 5,5 | 22,1 | — | 72,4 | 5,4 | 22,2 | — | 56 |
| b | 127—129 | — | $C_{20}H_{19}N_5$ | 72,9 | 6,1 | 21,3 | — | 72,9 | 5,8 | 21,3 | — | 73 |
| c | 110—111 | 253 | $C_{14}H_{15}N_5$ | 66,6 | 5,7 | — | — | 66,4 | 5,9 | — | — | 71 |
| VIIa | 125—126 | — | $C_{18}H_{14}N_4O$ | — | — | 18,5 | 10,3[d] | — | — | 18,5 | 10,3[d] | 82 |
| b | 80—82 | — | $C_{19}H_{16}N_4O$ | — | — | 17,7 | 9,9[d] | — | — | 17,7 | 9,8[d] | 94 |

[a]The molecular weights were determined by mass spectrometry.
[b]The yield is given with respect to the dehydrogenation.
[c]From dioxane; the remaining compounds were recrystallized from alcohol.
[d]p-$OCH_3$.
[e]Cl.

TABLE 2. UV Spectra of 1,6-Disubstituted 4-Arylpyrazolo[3,4-d]-pyrimidines

| Comp. | $\lambda_{max}$, nm(lg ε) | Comp. | $\lambda_{max}$, nm(lgε) |
|---|---|---|---|
| Ia | 202(4.33),243(4,01) | Va | 205(4,30),266(4,22) |
| b | 210(3,90),228(3,68) | b | 220(4,50),266(4,05), 291(4,20) |
| c | 202(3,57),228(3,78) | c | 204(4,72),218(4,78), 289(3,30) |
| IIIa | 203(4,57),243(4,11) | VIa | 206(4,57),260(4,56), 355(3,70) |
| b | 204(4.43),247(3,72) | b | 208(4,47),252(4,49), 351(3,69) |
| c | 206(4,24),244(3,76) | c | 205(4,55),250(4,71), 353(3,83) |
| IVa | 205(4,53),263(4,51), 308(3,87),358(3,45) | VIIa | 206(4,82),259(4,83), 295(4,30) |
| b | 204(4,48),254(4,00), 286(3,81),333(3,62) | b | 207(4,24),216(4,24), 259(3,78),282(3,73) |
| c | 204(4,36),229(4,23), 333(3,60) | | |
| d | 207(4,09),254(4,18), 325(3,87) | | |



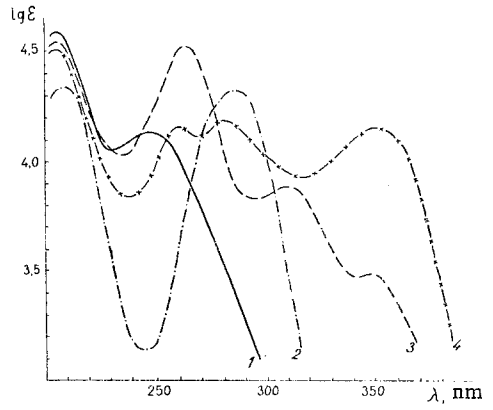



Fig. 1. UV spectra (alcohol): 1) IIIa; 2) IX; 3) IVa; 4) X.

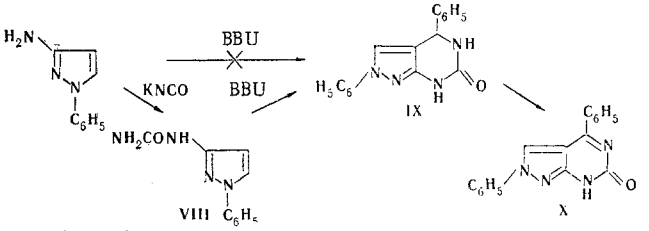
The condensation of 1-benzyl- and 1-methyl-5-aminopyrazoles with benzalbisurea proceeded similarly. The corresponding tetrahydro (Table 1) and dihydro derivatives were isolated from the reaction mixture in all cases. The yields of the dihydro derivatives were 5-10%. The tetrahydropyrazolopyrimidines (III) are readily dehydrogenated by the bromination-dehydrobromination method to the corresponding IV.

The formation of IV in the condensation attests to the occurrence of oxidative-reductive processes in the reaction medium. The ratio of the III and IV formed should probably depend on the arylidenebisurea used in the reaction since, for example, the formation of dibenzylurea [9] indicates its participation in oxidative-reductive processes during similar condensations. Thus the predominant formation of dehydrogenated pyrimidines was noted in [10] when anisalbisurea was used in place of benzalbisurea in similar condensation. A similar result was obtained in the condensation of Ia with anisalbisurea. Compound IVd was isolated from the reaction mixture. The corresponding tetrahydro derivative is formed only in traces.

The synthesized pyrazolo[3,4-d]pyrimidines were characterized by the preparation of a number of derivatives. The 6-chloro derivatives (V), from which the 6-methoxy derivatives (VII) were obtained by reaction with sodium methoxide, were obtained by refluxing IV with phosphorus oxychloride in the presence of dimethylaniline. The 6-dimethylamino derivatives (VI) were isolated in good yields by the reaction of IV with hexamethylphosphoric triamide by the method proposed in [11]. The VIa synthesized by this method was identical to the compound obtained from Va and dimethylamine.

3-Aminopyrazoles, which are isomers of 5-aminopyrazoles, could give 2-substituted 6-hydroxypyrazolo[3,4-d]pyrimidines (IX) if the reaction proceeded similarly.

However, despite variation of the conditions (changing the reagent ratio, reaction time, temperature, and solvent), we could not obtain the pyrimidine derivative directly from the 3-aminopyrazole.




BBU = benzalbisurea

Considering the greater difficulty involved in the formation of cyclic pyrazole derivatives at the 3-4 bond as compared with the 4-5 bond [12, 13], we attempted to synthesize IX through the 3-ureido derivative (VIII), which is readily obtained from 3-aminopyrazole by reaction with potassium cyanate. Compound VIII was recovered unchanged from the reaction mixture on attempts to cyclize it by reaction with benzaldehyde or acetaldehyde. Compound VIII is readily formed from 3-aminopyrazole by reaction with urea under the conditions of the reaction with benzalbisurea. In view of the inability of VIII to cyclize with aldehydes or benzalbisurea (under the same conditions), the facile transformation of 3-aminopyrazole to VIII probably prevents the formation of IX during the condensation of 3-aminopyrazole with benzalbisurea.

Compound IX, which was of interest to us, could be obtained only by fusing VIII with benzalbisurea at 220-250°. As before, a small amount of dehydrogenated product (X) was isolated from the reaction mixture. It is also readily obtained by dehydrogenation of IX with chloranil by refluxing in xylene.

The isomeric 1- and 2-substituted pyrazolo[3,4-d]pyrimidines obtained, which have similar properties and IR spectra, differ appreciably with respect to their UV spectra. The spectrum of the 2-substituted derivatives is shifted to the long-wave region (Fig. 1). We also noted similar regularities in the character of the change in the UV spectra for the isomeric pyrazolooxazines [3], and the same was observed for isomeric pyrazolopyridines in [12].

## EXPERIMENTAL*

The IR spectra were recorded with a UR-10 spectrophotometer. The UV spectra in alcohol were obtained with a Unicam-SP 700C spectrometer.

1,4-Diphenyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (IIIa) and 1,4-Diphenyl-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (IVa). A mixture of 20.3 g (127 mmole) of Ia and 25 g (127 mmole) of benzalbisurea (IIa) in 200 ml of glacial acetic acid was refluxed for 5 h. The mixture was cooled, poured into water, and allowed to stand overnight. The resulting precipitate was filtered, washed with water, dried, and washed thoroughly with ether. Alcohol (150 ml) was then added to the precipitate, and the mixture was heated to the boiling point. The undissolved IVa was filtered. Very pure IIIa precipitated from the filtrate on cooling.

Compounds IIIb,c and IVb were similarly obtained. Compound IVc precipitated on neutralization of the filtrate after separation of IIIc. Compound IVd precipitated on cooling of the reaction mixture without pouring into water.

IR spectra, $\nu$, $cm^{-1}$: IIIb ($CHCl_3$) 1690 and 3445; IIIc (KBr) 1700, 1720, and 3400; IVb (KBr) 1640 broad; IVc (KBr) 1630-1650; IVd (KBr) 1630-1650.

Preparation of IV by Dehydrogenation of III. A solution of 10 mmole of bromine in 15 ml of glacial acetic acid was added dropwise with stirring to a solution of 10 mmole of III and 20 ml of glacial acetic acid at room temperature. After 30 min, the reaction mixture was poured into 150-200 ml of water, and a yellow bromo derivative was filtered after 30 min. It was suspended in 10 ml of methanol, 2 ml of pyridine was added, and the mixture was heated for 10 min on a water bath. The mixture was cooled, and IV, which was yellowish and slightly soluble in the usual organic solvents, was filtered.

1-R'-4-Phenyl-6-chloropyrazolo[3,4-d]pyrimidines (V). A mixture of 10 mmole of IV, 100 mmole of $POCl_3$, and 1 ml of dimethylaniline was refluxed for 28-30 h. The reaction mixture was then poured over ice and neutralized with $NaHCO_3$, and V was filtered and washed thoroughly with water. For purification, V was dissolved in benzene, the solution was filtered through a layer of aluminum oxide, the benzene was evaporated, and the residue was triturated with petroleum ether.

1-R'-4-Phenyl-6-dimethylaminopyrazolo[3,4-d]pyrimidines (VI). A mixture of 5 mmole of IV and 5 mmole of hexamethylphosphoric triamide was heated at 220° for 40 min. After cooling, the solid mass was treated with 3% NaOH, and VI was filtered and washed with water.

1,4-Diphenyl-6-dimethylaminopyrazolo[3,4-d]pyrimidine (VIa). A mixture of 0.03 g (0.1 mmole) of Va and 0.02 g (0.5 mmole) of dimethylamine in 2.5 ml of absolute alcohol was heated at 60° for 5 h. The alcohol was removed by distillation to dryness, and the residue was washed with small amounts of alcohol and ether to give 0.025 g (82%) of VIa with mp 142-145°.

1-R'-4-Phenyl-6-methoxypyrazolo[3,4-d]pyrimidines (VII). A solution of 1 mmole of V in 10 ml of absolute methanol was added to a solution of 4 mmole of sodium metal in 20 ml of absolute methanol, and the mixture was refluxed for 10-13 h. It was then cooled, the alcohol was removed by distillation to dryness, and the residue was washed with water to give VII.

1-Phenyl-3-ureidopyrazole (VIII). A. 1-Phenyl-3-aminopyrazole [3.18 g (0.02 mole)] was suspended in 5 ml of water, 2.5 ml of concentrated hydrochloric acid was added, and a concentrated solution of 1.6 g (0.02 mole) of KNCO in water was added to the resulting solution with cooling and stirring. The precipitated VIII was allowed to stand for 1 h, filtered, and washed with water to give 3.15 g (78%) of a product with mp 182-184° (from alcohol). Found %: C 59.2; H 4.80; N 27.6; mol. wt. 202. $C_{10}H_{10}N_4O$. Calculated %: C 59.4; H 4.95; N 27.7; mol. wt. 202. IR spectrum (KBr), $\nu$, $cm^{-1}$: 1710 (C=O), 3375 (N-H). UV spectrum, $\lambda_{max}$, nm ($\log \varepsilon$): 278 (4.37). PMR spectrum,† $\delta$, ppm, 8.95 (singlet, N-H), 8.30 (doublet, 5-H), 7.30 (multiplet, $C_6H_5$), 6.62 (doublet, 4-H), 6.37 (singlet, $NH_2$) with an intensity ratio of 1:1:5:1:2 and $J_{4H-5H}$ = 2 Hz.

*With the participation of L. N. Il'chenko.

† The PMR spectrum was obtained with a Varian A-60/56A spectrometer with tetramethylurea as the solvent; the chemical shifts are given in parts per million relative to the signal of hexamethyldisiloxane.

B. A mixture of 1.59 g (0.01 mole) of 1-phenyl-3-aminopyrazole and 1.2 g (0.02 mole) of urea was refluxed in 10 ml of glacial acetic acid for 4 h. The mixture was allowed to stand overnight, and 1 g of precipitated large crystals of VIII · $CH_3COOH$ with mp 183-185° (from acetic acid) was filtered. Found %: C 55.4; H 5.24. $C_{10}H_{10}N_4O \cdot C_2H_4O_2$. Calculated %: C 55.0; H 5.35. Compound VIII was obtained after washing the acetate with 10% $NaHCO_3$ and water.

2,4-Diphenyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (IX) and 2,4-Diphenyl-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (X). A mixture of 2.02 g (0.01 mole) of VIII and 2.08 g (0.01 mole) of benzalbisurea was fused at 220-240° for 1 h. The cooled melt was triturated with alcohol, and 1.2 g (41%) of IX with mp 258-262° (from alcohol) was filtered. Found %: C 70.3; H 4.83; N 19.0; mol. wt. 290. $C_{17}H_{14}N_4O$. Calculated %: C 70.4; H 4.83; N 19.3; mol. wt. 290. IR spectrum ($CHCl_3$), $\nu$, $cm^{-1}$: 1700 (C=O) and 3435 (N−H). UV spectrum, $\lambda_{max}$, nm (log ε): 206 (4.31) and 286 (4.29).

Bright yellow X [0.3 g (10%)] with mp 269-272° (from alcohol) precipitated from the filtrate on standing. Found %: N 19.2; mol. wt. 288. $C_{17}H_{12}N_4O$. Calculated %: N 19.4; mol. wt. 288. IR spectrum ($CHCl_3$), $\nu$, $cm^{-1}$: 1630 and 1675 (C=O); 3410 (N−H). UV spectrum, $\lambda_{max}$, nm (log ε): 204 (4.51), 255 (4.14), 279 (4.18), and 350 (4.13).

Preparation of X by Dehydrogenation of IX. A mixture of 0.2 g (0.69 mmole) of IX and 0.25 g (1 mmole) of chloranil was refluxed for 1.5 h in 20 ml of dry xylene. A precipitate began to appear on the walls of the flask 30 min after refluxing commenced. The mixture was cooled, and the precipitate was filtered and washed thoroughly with methanol and ether to give 0.13 g (65%) of X with mp 270-271°.

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