PYRIMIDINES

XLIV.* SYNTHESIS OF PYRAZOLO[3,4-d]PYRIMIDINES

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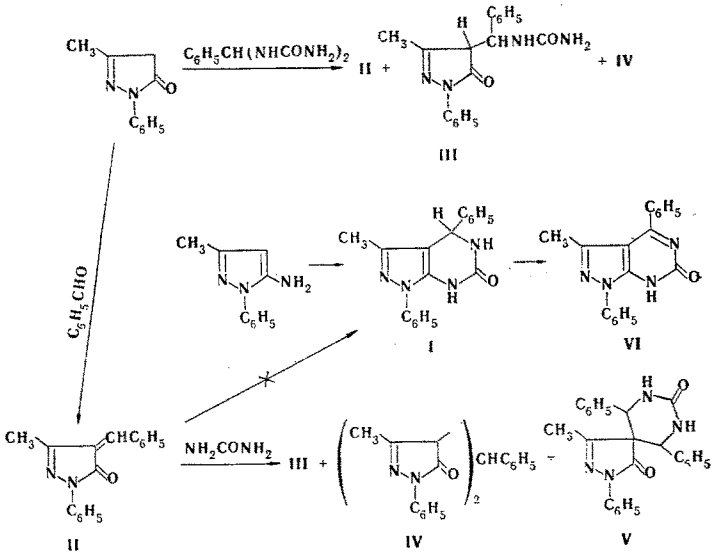
The reaction of 1-phenyl-3-methyl-4-benzal-5-pyrazolone with urea does not lead to closing of a pyrazolo[3,4-d]pyrimidine ring because of the reduced tendency of the carbonyl group of the pyrazolone to participate in cyclization reactions. The expected 1,4-diphenyl-3-methyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine was obtained by condensation of 1-phenyl-3-methyl-5-aminopyrazole with benzalbisurea and was dehydrogenated to the dihydro derivative.

A communication published in 1970 [2] regarding the synthesis of substituted pyrazolo[3,4-d]pyrimidine I by reaction of benzalpyrazolone II with urea contradicted our data on the inability of ureidobenzylpyrazolone III to undergo cyclization due to interaction of the urea fragment with the carbonyl group of pyrazolone. From our point of view, this is explained by the reduced reactivity of the C=O group of 5-pyrazolones due to its amide character [3].



A thorough investigation of the reaction mixture by the method in [2] showed that the reaction of pyrazolone II with urea does not give pyrazolo[3,4-d]pyrimidine I but rather spiro[pyrazole-4,5'-pyrimidine] V [3], benzalbispyrazolone IV, which were identified from their IR spectra and melting points, and ureidobenzyl derivative III, which, according to its IR spectrum, is identical to the product formed in the

*See [1] for communication XLIII.

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ureidobenzylation of 1-phenyl-3-methyl-5-pyrazolone with benzalbisurea. The experimental section in [2] is extremely brief, and it is therefore difficult to suppose precisely which compound was obtained by Sammour and co-workers.

We obtained 1,4-diphenyl-3-methyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine I by a previously developed method [4] from 1-phenyl-3-methyl-5-aminopyrazole and benzalbisurea. The melting point of the compound that we obtained differed by ~30° from the melting point of the product described in [2]. Dihydropyrazolo[3,4-d]pyrimidine VI was obtained by dehydrogenation of tetrahydro derivative I by the bromination-dehydrobromination method. The structures of pyrazolopyrimidines I and VI were proved, in analogy with [4], by means of their IR and UV spectra.

EXPERIMENTAL

The IR spectra of KBr pellets and 5% solutions in $CHCl_3$ were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions were recorded with a Specord spectrophotometer. The molecular weights were determined with an MS-902 mass spectrometer.

1-Phenyl-3-methyl-4-(α-ureidobenzyl)-5-pyrazolone (III). A 1.74-g (0.01 mole) sample of 1-phenyl-3-methyl-5-pyrazolone was dissolved in 20 ml of absolute n-butanol and 10 ml of glacial acetic acid, after which 2.08 g (0.01 mole) of benzalbisurea was added, and the mixture was heated at 100° for 15 min. The red solution was concentrated in vacuo, and the precipitated II (1.3 g) was separated. The filtrate was treated with water, and the resulting precipitate was removed by filtration and washed with water. The 1.32 g of a mixture of II, III, and IV thus obtained was dissolved in acetone, and the acetone solution was applied to a layer of activity III Al_2O_3 and dried. The layer of Al_2O_3 containing the substance was then placed in a column containing Al_2O_3 and chromatographed by elution with benzene. After all of the impurities had been eluted, the starting portion of the Al_2O_3 was separated and eluted with alcohol. The alcohol eluate was evaporated to dryness to give 0.6 g of III with mp 165°. The product gave a qualitative reaction for an NH_2 group with p-dimethylaminobenzaldehyde and a qualitative reaction for the enol form of a pyrazolone with $FeCl_3$. The product had R_f 0.90 [ascending chromatography on Leningrad B paper with an n-butanol–acetic acid–water system (12:3:5)]. IR spectrum ($CHCl_3$), ν, cm^{-1}: 1680 (C=O), 3340, 3430, and 3520 (NH, NH_2).

Condensation of 1-Phenyl-3-methyl-4-benzal-5-pyrazolone with Urea by the Method in [2]. Seventeen drops of concentrated HCl and 5.24 g of II [5] were added to a suspension of 2 g of urea in 20 ml of alcohol, and the mixture was refluxed for 8 h. The mixture was then allowed to stand overnight, and the resulting precipitate of spiropyrazolopyrimidine V was removed by filtration to give 0.95 g of a product with mp 220-223°. A flocculent precipitate (2.12 g) of III (containing IV) precipitated from the filtrate after brief standing. The alcohol filtrate was evaporated, the residue was treated with 50 ml of 5 N NaOH, the solution was decanted, and the residual mass was treated with water. Another 0.56 g of V was obtained in the residue, and acidification of the aqueous solution to pH ~6 gave 1.5 g of benzalbispyrazolone IV. The products were identified by means of their IR spectra and the IR spectra of authentic samples obtained by the methods in [3, 5].

1,4-Diphenyl-3-methyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (I). A 3-g (17.3 mmole) sample of 1-phenyl-3-methyl-5-aminopyrazole [6] and 3.6 g (17.3 mmole) of benzalbisurea were refluxed in 30 ml of glacial acetic acid for 5 h. The resulting solution was cooled and poured into 300 ml of water. The next day, the precipitate was removed by filtration, washed with water, dried, and washed thoroughly with ether to give 2.5 g of I with mp 194-195° (methanol). Found: C 71.0; H 5.3; N 18.6%; mol. wt. 304. $C_{18}H_{16}N_4O$. Calculated: C 71.0; H 5.3; N 18.4%; mol. wt. 304. IR spectrum ($CHCl_3$), ν, cm^{-1}: 1690 (C = O), 3432 (NH). UV spectrum, λ_{max}, nm (log ε): 247 (4.25), 305 (3.11).

1,4-Diphenyl-3-methyl-6-oxo-6,7-dihydropyrazolo[3,4-d]pyrimidine (VI). A solution of 0.16 g (1 mmole) of Br_2 in 3 ml of glacial acetic acid was added dropwise with stirring to a solution of 0.3 g (1 mmole) of I in 10 ml of glacial acetic acid, and the mixture was stirred for 30 min. It was then poured into 50 ml of water, and, after ~30 min, 0.3 g of a bright-yellow precipitate of the bromo derivative was removed by filtration, washed with water, and dried. It was then suspended in 1.5 ml of methanol, 0.3 ml of pyridine was added, and the mixture was heated at 80° for 10 min. It was then cooled, and the precipitated VI was removed by filtration and washed with methanol and water to give 0.18 g (60%) of a product with mp 352-354° in a capillary (tetramethylurea). Found: C 71.6; H 4.8; N 18.5%; mol. wt. 302. $C_{18}H_{14}N_4O$. Calculated: C 71.5; H 4.6; N 18.5%; mol. wt. 302. IR spectrum (KBr), ν, cm^{-1}: 1620-1650 broad (C = O). UV spectrum, λ_{max}, nm (log ε): 260 (4.46), 302 (3.85), and 346 (3.30).

LITERATURE CITED

1. M. A. Mikhaleva, L. N. Il'chenko, and V. P. Mamaev, Khim. Geterotsikl. Soedin., 1422 (1974).
2. A. Sammour, M. J. B. Selim, M. M. Nonr El-Deen, and M. Ald-el-Halim, J. Chem. UAR, 13, 7 (1970).
3. V. P. Mamaev and M. A. Mikhaleva, Khim. Geterotsikl. Soedin., 1083 (1967).
4. V. P. Mamaev and M. A. Mikhaleva, Khim. Geterotsikl. Soedin., 535 (1971).
5. R. H. Wiley and P. Wiley, Pyrazolones, Pyrazolidones, and Derivatives New York–London–Sydney (1964).
6. E. Koike, K. Iida, M. Okawa, and A. Kashioka, J. Chem. Soc. Japan, Ind. Chem. Sect., 57, 56 (1954); Chem. Abstr., 49, 11,629 (1955).