PYRIMIDINES

XXXV.* 6-HYDROXYPYRAZOLO[3,4-d]PYRIMIDINES

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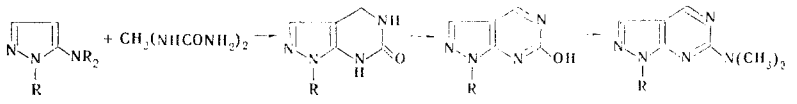
The reaction of methylenebisurea with 5-amino-1-R-pyrazoles and 3-ureido-1-phenylpyrazole gives 1- and 2-R-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidines, respectively. The 1-R-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidines are readily dehydrogenated to 1-R-6-hydroxypyrazolo[3,4-d]pyrimidines. The 2-R-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidines could not be dehydrogenated.

We have previously obtained pyrazolo[3,4-d]pyrimidine derivatives [2] containing an aryl group in the 4 position, which appreciably lowers the solubility of the compounds, by reaction of 5-aminopyrazoles with arylidenebisureas. We assumed that it would be possible to obtain pyrazolo[3,4-d]pyrimidines without substituents in the 4 position by reaction of aminopyrazoles with methylenebisurea [3] using the method described in [2].

The synthesis of the pyrimidine derivatives with participation of methylenebisurea [4] (or formaldehyde and urea separately [5]) was accomplished only in the case of the reaction with acetoacetic ester.

The condensation of 1-phenyl- and 1-benzyl-5-aminopyrazoles with methylenebisurea under the conditions in [2] gave 1-R-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidines (I) in 5-10% yields. By carrying out the reaction with greater dilution of the reaction mass with acetic acid, we were able to increase the yield of I to 30-35%. The structures of the compounds obtained were proved by the analytical and spectral data. Since neither pyrazolo[3,4-d]pyrimidines containing alkyl and aryl substituents in the 1 position and an oxo group in the 6 position nor their hydrogenated derivatives have been described in the literature, it seemed of interest to study their properties, particularly as compared with those of 4-aryl analogs.



I II III

I–III a C_6H_5; b $CH_2C_6H_5$

In contrast to 4-arylpyrazolo[3,4-d]pyrimidines [2], the dehydrogenation of I by the bromination-dehydrobromination method in acetic acid leads to their decomposition; however, the reaction does proceed smoothly in chloroform. The yield of pyrazolopyrimidine is low in the dehydrogenation of I with chloranil.

Like their 4-aryl derivatives, pyrazolopyrimidines II smoothly form the corresponding 6-dimethylaminopyrazolopyrimidines (III) on reaction with hexamethylphosphoric triamide (to accomplish the reaction under milder conditions, it was carried out in the presence of a catalyst [6]).

Compound IIb was recovered unchanged in an attempt to obtain the O-acetyl derivative by refluxing with acetic anhydride, and the compound decomposed completely when it was refluxed with added pyridine;

*See [1] for communication XXXIV.

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TABLE 1. Substituted Pyrazolo[3,4-d]pyrimidines and Tetrahydropyrazolo[3,4-d]pyrimidines

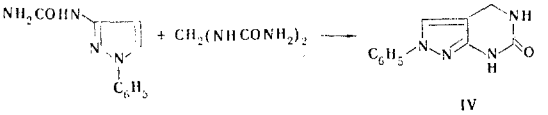
Comp.	Mp, °C	Empirical formula	Mol. wt.[b]	Found, %		
				C	H	N
Ia	245—250	$C_{11}H_{10}N_4O$	214	61,8	4,84	26,3
Ib	203—205	$C_{12}H_{12}N_4O \cdot C_2H_5OH$	228	60,6	6,45	20,6
IIa	277—280 dec.	$C_{11}H_8N_4O$	212	62,6	3,90	26,4
IIb	299—302	$C_{12}H_{10}N_4O$	226	64,1	4,56	24,8
IIIa	141—141,5	$C_{13}H_{13}N_5$	239	64,8	5,60	29,4
IIIb	55—60	$C_{14}H_{15}N_5$	253	—	—	—
Picrate, IIIb	172—174	$C_{14}H_{15}N_5 \cdot C_6H_3N_3O_7$		49,2	3,81	23,3
IV	293—294 a	$C_{11}H_{10}N_4O$	214	61,4	4,62	26,3

Comp.	Calc., %			λ_{max}, nm (log ε)	ν, cm^{-1}	Yield, %
	C	H	N			
Ia	61,7	4,67	26,2	242 (4,15)	1700 (CO), 3444 (NH)[c]	42
Ib	61,1	6,57	20,4	245 (3,90)	1690 (CO), 3450 (NH)[c]	29
IIa	62,5	3,78	26,4	256 (4,42) 290 (3,60) 331 (3,20)	1630, 1660 (CO)[d]	79
IIb	63,7	4,42	24,8	226 (4,42) 278 (3,66) 332 (3,41)	1650, 1670 (CO)[d]	81
IIIa	65,3	5,44	29,3	262 (4,43) 328 (3,82)	—	66
IIIb				244 (4,26) 330 (3,64)	—	40
Picrate, IIIb	49,5	3,74	23,2	—	—	
IV	61,7	4,68	26,2	294 (in KBr)	1640 1690 (shoulder), 1710 (CO)[d]	52

[a] From dimethylformamide; the remaining compounds were crystallized from alcohol. [b] The molecular weights were determined by mass spectrometry. [c] In chloroform. [d] In KBr pellets.

IIb was also decomposed when it was refluxed with $POCl_3$ in the presence of dimethylaniline. The corresponding 4-aryl-substituted pyrimidines smoothly form O-acetyl [7] or 6-chloro derivatives [2] in these reactions.

Compounds I, II, and IIIa dissolve much more satisfactorily in alcohol than the corresponding 4-arylpyrazolopyrimidines and are quite soluble in chloroform, while IIIb is quite soluble in petroleum ether and other organic solvents.



As previously demonstrated, 3-amino-1-phenylpyrazole does not undergo condensation with arylidenebisureas to give pyrazolopyrimidines; the pyrazolopyrimidine could be obtained only when 3-ureido-1-phenylpyrazole [2] was used. This ureidopyrazole was therefore also used in the condensation with methylenebisurea. 2-Phenyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (IV) was obtained in good yield when the ureidopyrazole was fused with methylenebisurea. We were unable to dehydrogenate this compound. The various methods (chloranil, 10% Pd/C, bromination-dehydrobromination, PdO_2 [8], sulfur, and diphenyl disulfide) used for dehydrogenation did not give positive results.

It is interesting to note that while tetrahydropyrazolopyrimidines [2] and their dehydrogenated derivatives are formed simultaneously in the condensation of aminopyrazoles with benzylidenebisurea, dihydro derivatives II are absent in the reaction mixture when the condensation is carried out with methylenebisurea. This is probably explained both by the lower tendency of I to undergo dehydrogenation because of

the absence of a ring aryl substituent and by the lower (or completely absent) dehydrogenating capacity of methylenebisurea as compared with benzylidenebisurea [9].

EXPERIMENTAL*

The IR spectra were recorded with a UR-10 spectrophotometer. The UV spectra of alcohol solutions were recorded with a Unicam-SP700C spectrophotometer. The yields, melting points, and results of analysis of the compounds are presented in Table 1.

1-Phenyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (Ia). A 3-g (19 mmole) sample of 1-phenyl-5-aminopyrazole was refluxed for 5 h with 4.98 g (38 mmole) of methylenebisurea in 100 ml of glacial acetic acid. The mixture was cooled and poured into 1 liter of water, and the aqueous mixture was filtered. The filtrate was neutralized with $NaHCO_3$, and 0.7 g of Ia was removed by filtration. The filtrate yielded an additional 1 g of Ia on extraction with chloroform.

A similar procedure was used to obtain 1-benzyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (Ib).

1-Phenyl-6-oxopyrazolo[3,4-d]pyrimidine (IIa). A. A solution of 1.35 g (8.3 mmole) of Br_2 in 10 ml of $CHCl_3$ was added dropwise with stirring to a suspension of 1.78 g (8.3 mmole) of Ia in 15 ml of $CHCl_3$, and the mixture was stirred at room temperature for 30 min. The chloroform was then removed by vacuum distillation, and 10 ml of ethanol and 1 ml of pyridine were added to the residue. The mixture was triturated, heated for 1-2 min on a hot water bath, and stored for 2 h in a refrigerator. The resulting IIa was removed by filtration and washed with a small amount of alcohol and ether.

B. A mixture of 0.42 g (2 mmole) of Ia and 0.59 g (2.4 mmole) of chloranil was refluxed in 8 ml of absolute xylene for 40 min, after which it was allowed to stand overnight. The resulting precipitate was removed by filtration and washed thoroughly with methanol and ether.

A similar procedure was used to obtain 1-benzyl-6-hydroxypyrazolo[3,4-d]pyrimidine (IIb).

1-Phenyl-6-dimethylaminopyrazolo[3,4-d]pyrimidine (IIIa). A mixture of 1.2 g (5.65 mmole) of IIa and 1 g (5.65 mmole) of hexamethylphosphoric triamide was heated in the presence of 0.04 g of dimethylamine hydrochloride at 220-260° for 15 min. The melt was cooled and triturated with 3% NaOH solution. The precipitate was removed by filtration and washed thoroughly with water and once with a small amount of alcohol.

1-Benzyl-6-dimethylaminopyrazolo[3,4-d]pyrimidine (IIIb). A mixture of 0.9 g (3.98 mmole) of IIb and 4 ml of hexamethylphosphoric triamide was heated with shaking in the presence of 0.03 g of dimethylamine hydrochloride at 220° for 15 min. The resulting solution was cooled and poured into 30 ml of water, and the aqeuous mixture was extracted with three 20-ml portions of ether. The ether extract was shaken with activated charcoal, washed with 3% NaOH solution and water, and dried with $MgSO_4$. The ether was removed by distillation to dryness, and the residual dark oil was extracted with hot petroleum ether (70-100°). The petroleum ether was removed by distillation to give 0.4 g of yellowish crystals with IIIb.

2-Phenyl-6-oxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine (IV). A mixture of 0.9 g (4.46 mmole) of 1-phenyl-3-ureidopyrazole [2] and 0.59 g (4.46 mmole) of methylenebisurea was heated at 220° for 30 min. The solidified melt was cooled and triturated with alcohol, and the solid was removed by filtration and washed thoroughly with hot alcohol and hot dioxane until an almost colorless filtrate was obtained.

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