THE SYNTHESIS OF 8-PURINYLAZOMETHINES AND/OR ESTERS OF 8-PURINYL-(TOLYLAMINO)METHYL PHOSPHINIC ACIDS

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 5, pp. 900–903, 1969

UDC 547.857'574.4.07+546.183

The syntheses of some new 8-purinylazomethines and esters of 8-purinyl(o-, m-, and p-tolylamino)methyl phosphinic acids are described.

In developing the syntheses of dialkyl esters of 8-phosphopurine alkaloids [1, 3], the addition of dialkyl phosphites to the azomethine grouping [4, 5] of 8-purinylazomethines was investigated. For this purpose, some new 8-purinylazomethines were prepared, in addition to known 8-purinylideneanilines [6–9].

Condensation of caffeine-8-aldehyde and isocaffeine-8-aldehyde with aromatic amines by heating in ethanolic solution affords the 8-caffeinylazomethines I–VII, and the 8-isocaffeinylazomethines VIII–XIV, in good yield. Since theobromine-8-aldehyde is only sparingly soluble in alcohol, the 8-theobrominylazomethines XV–XXI were obtained by heating the reactants in ethanol-acetic acid solution. The 8-purinylazomethines I–XXI (Tables 1–3) are colorless or yellow crystalline compounds, stable on keeping, soluble in glacial acetic acid and chloroform, sparingly soluble in ethanol and benzene, and insoluble in ether and water.

Condensation of 8-purinylidene-o-, m-, and p-toluidines with dialkyl phosphites in presence of sodium methoxide as catalyst gave poor yields of dimethyl 8-caffeinyl-(o-tolylamino)- and -(m-tolylamino)methyl phosphinates (XXII and XXIII), dimethyl and diethyl 8-caffeinyl-(p-tolylamino)- (XXIV and XXV) and 8-isocaffeinyl-(p-tolylamino)methyl phosphinates (XXVI and XXVII), dimethyl 8-theobrominyl-(m-tolylamino)-methyl phosphinate (XXVIII), and dimethyl and diethyl 8-theobrominyl-(p-tolylamino)methyl phosphinates (XXIX and XXX). The properties and conditions for the synthesis of esters XXII–XXX are given in Table 4. They are crystalline solids, soluble in ethanol, glacial acetic acid, and benzene, but insoluble in ether and only very sparingly soluble in hot water.

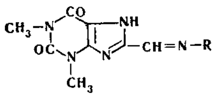
The reaction of 8-purinylidene-anilines, -β-naphthylamines, and -p-anisidines with dimethyl phosphite was effected under similar conditions, but the expected dimethyl 8-purinyl(arylamino)methyl phosphinates were not obtained.

The synthetic difficulties were apparently related to the complexity of the heterocyclic system in the 8-purinylazomethines as compared with the simpler structure of the 2-pyridylazomethines [10] and the 6-quinolinylazomethines [11].

The IR spectra of the azomethines III, X, and XVIII show strong absorption bands at 1700–1715 and 1665–1670 cm^{-1}, and bands of medium intensity at 1632 cm^{-1}. In the esters XXIV, XXVI, and XXIX, the bands at 1700–1715 and 1665–1670 cm^{-1} are preserved, while the bands at 1632 cm^{-1} have disappeared, and strong bands at $\nu_{P=O}$ 1240–1268 cm^{-1} have appeared. The

Table 1

8-Caffeinylazomethines



Compound	Name	Quantity of compound reacted, g*		Mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
		caffeine-8-aldehyde	amine			C	H	N	C	H	N	
I	8-Caffeinylidene-o-toluidine	1.0	0.49	244—245	$C_{16}H_{17}N_5O_2$	61.58	5.33	22.75	61.70	5.50	22.50	95.7
II	8-Caffeinylidene-m-toluidine	1.0	0.49	201—202	$C_{16}H_{17}N_5O_2$	61.82	5.72	22.42	61.70	5.50	22.50	94.3
III	8-Caffeinylidene-p-toluidine	1.0	0.49	203—204	$C_{16}H_{17}N_5O_2$	61.65	5.24	22.13	61.70	5.50	22.50	93.0
IV	8-Caffeinylidene-α-naphthylamine	1.0	0.65	261—262	$C_{19}H_{17}N_5O_2$	65.32	5.22	22.44	65.67	4.93	20.17	96.2
V	8-Caffeinylidene-β-naphthylamine	1.0	0.65	272—273	$C_{19}H_{17}N_5O_2$	65.41	4.63	20.29	65.67	4.93	20.17	97.0
VI	8-Caffeinylidene-p-anisidine	1.0	0.56	226—227	$C_{16}H_{17}N_5O_3$	58.42	5.62	21.17	58.68	5.23	21.40	95.4
VII	8-Caffeinylidene-p-phenetidine	1.0	0.62	235—236	$C_{17}H_{19}N_5O_3$	60.02	5.55	20.18	59.79	5.61	20.52	96.1

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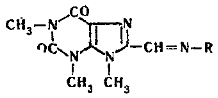
*Heated for 15 min in 30 ml of ethanol.

Table 2

8-Isocaffeinylazomethines



Compound	Name	Quantity of compound reacted, g*		Mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
		isocaffeine-8-aldehyde	amine			C	H	N	C	H	N	
VIII	8-Isocaffeinylidene-o-toluidine	0.5	0.25	282—283	$C_{16}H_{17}N_5O_2$	61.46	5.23	22.35	61.70	5.50	22.50	83.0
IX	8-Isocaffeinylidene-m-toluidine	0.5	0.25	273—274	$C_{16}H_{17}N_5O_2$	61.52	5.76	22.87	61.70	5.50	22.50	91.0
X	8-Isocaffeinylidene-p-toluidine	0.5	0.25	309—310	$C_{16}H_{17}N_5O_2$	61.81	5.68	22.42	61.70	5.50	22.50	93.0
XI	9-Isocaffeinylidene-α-naphthylamine	0.5	0.33	286—287	$C_{19}H_{17}N_5O_2$	65.42	5.42	20.39	65.67	4.93	20.17	80.0
XII	8-Isocaffeinylidene-β-naphthylamine	0.5	0.33	322—323	$C_{19}H_{17}N_5O_2$	65.77	5.10	20.10	65.67	4.93	20.17	89.7
XIII	8-Isocaffeinylidene-p-anisidine	0.5	0.28	309—310	$C_{16}H_{17}N_5O_3$	58.71	5.30	21.72	58.68	5.23	21.40	90.5
XIV	8-Isocaffeinylidene-p-phenetidine	0.5	0.31	260—261	$C_{17}H_{19}N_5O_3$	59.62	5.93	20.36	59.79	5.61	20.52	91.0

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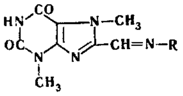
*Heated in 15 ml of ethanol for 15 min.

Table 3

8-Theobrominylazomethines



Compound	Name	Quantity of compound reacted*		Mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
		theobromine-8-aldehyde	amine			C	H	N	C	H	N	
XV	8-Theobrominylidene-o-toluidine	0.5	0.26	309—310	$C_{15}H_{15}N_5O_2$	60.52	5.47	23.83	60.57	5.08	23.57	62.5
XVI	8-Theobrominylidene-m-toluidine	0.5	0.26	294—295	$C_{15}H_{15}N_5O_2$	60.24	5.36	23.61	60.57	5.08	23.57	51.4
XVII	8-Theobrominylidene-p-toluidine	0.5	0.26	306—307	$C_{15}H_{15}N_5O_2$	60.32	5.41	23.80	60.57	5.08	23.57	83.3
XVIII	8-Theobrominylidene-α-naphthylamine	0.5	0.35	300—301	$C_{18}H_{15}N_5O_2$	65.03	4.83	21.48	64.83	4.53	21.02	45.1
XIX	8-Theobrominylidene-β-naphthylamine	0.5	0.35	311—312	$C_{18}H_{15}N_5O_2$	65.38	4.90	21.16	64.83	4.53	21.02	76.8
XX	8-Theobrominylidene-p-anisidine	0.5	0.30	304—305	$C_{15}H_{15}N_5O_3$	57.71	5.30	22.02	57.47	4.82	22.36	60.0
XXI	8-Theobrominylidene-p-phenetidine	0.5	0.33	284—285	$C_{16}H_{17}N_5O_3$	58.46	5.47	21.12	58.68	5.23	21.40	72.3

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*Heated in 15 ml of ethanol–glacial acetic acid (1 : 1) for 3 min.

Table 4

Esters of 8-Purinyl-(o-, m-, and p-tolylamino)methyl Phosphinic Acids

Compound	Quantity of compound reacted, g		Mp, °C	Molecular formula	Found, %		Calculated, %		Yield, %
	azomethine	dialkyl phosphite			N	P	N	P	
XXII	0.9	0.94	189—190	$C_{18}H_{24}N_5O_5P$	16.33	7.72	16.62	7.36	20.0
XXIII	1.0	1.05	160—161	$C_{18}H_{24}N_5O_5P$	16.56	7.52	16.62	7.36	24.0
XXIV	1.0	1.05	200—201	$C_{18}H_{24}N_5O_5P$	16.42	6.98	16.62	7.36	39.0
XXV	1.0	1.3	168—169	$C_{20}H_{28}N_5O_5P$	15.83	7.22	15.59	6.90	28.0
XXVI	0.8	0.84	201—202	$C_{18}H_{24}N_5O_5P$	16.84	7.66	16.62	7.36	37.0
XXVII	0.9	1.2	194—195	$C_{20}H_{28}N_5O_5P$	15.46	7.22	15.59	6.90	23.0
XXVIII	1.0	1.1	159—160	$C_{17}H_{22}N_5O_5P$	17.36	7.89	17.19	7.61	10.0
XXIX	1.0	1.1	220—221	$C_{17}H_{22}N_5O_5P$	17.42	7.96	17.19	7.61	30.0
XXX	1.0	1.38	207—208	$C_{19}H_{26}N_5O_5P$	16.41	7.47	16.09	7.12	12.0

disappearance of the bands at 1632 cm^{-1} permits their assignment as due to stretching of the azomethine group.

EXPERIMENTAL

8-Purinylazomethines (I-XXI). The purine-8-aldehyde (caffeine-8-aldehyde, mp 166° C; isocaffeine-8-aldehyde, mp 204-205° C; theobromine-8-aldehyde, mp 286-287° C) and the aromatic amine (an equimolar amount) were heated briefly in solution in ethanol or a mixture of ethanol and glacial acetic acid (1 : 1). A voluminous precipitate soon separated, and this was filtered off after cooling, and washed with ethanol. The azomethines **I-XIV** were recrystallized from a mixture of ethanol and glacial acetic acid (1 : 1), and **XV-XXI** from glacial acetic acid. Yields and constants are given in Tables 1-3.

8-Caffeinylidene-, 8-isocaffeinylidene-, and 8-theobrominylideneanilines were synthesized under the same conditions as **I**, **VIII**, and **XV**, with similar results [6-8]; the yield of 8-theobrominylidene was 40-45%.

All the 8-purinylazomethines, as a result of the presence of the azomethine group, gave a coloration with conc H_2SO_4 which disappeared on dilution with water. The sulfuric acid solutions of the azomethines **I-III**, **IX**, **X**, **XV-XVII**, and of the anilines, were of a golden-yellow color; those of **IV**, **V**, **XI**, **XII**, **XVIII**, and **XIX** were dark blue; and those of **VI**, **VII**, **XIII**, **XIV**, **XX**, and **XXI** were cherry-colored.

Esters of 8-purinyl-(o-, m-, and p-tolylamino)methyl phosphinic acids (XXII-XXX). To a stirred mixture of the azomethine and the dialkyl phosphite (A threefold excess, enough to wet the azomethine completely. When a smaller excess of the acid was used, stirring was difficult) was added 0.3 ml of a saturated solution of sodium methoxide in methanol (use of piperidine or triethylamine as catalyst resulted in recovery of the azomethines **III**, **X**, and **XVII**). The reaction was carried out with thorough stirring, heat being evolved (the temperature rising to 20-35° C), and heating was continued at 85-90° C for 2-3 min. The reaction product was washed twice with dry ether, and heated with ethanol (96%; 3-4 ml). Unreacted azomethine was filtered off after cooling, and the ester separated from the filtrate on standing as colorless crystals which were recrystallized from 1-1.5 ml of ethanol (Table 4). Esters **XXII-XXX** gave no color with conc H_2SO_4.

The IR spectra were recorded in vaseline oil suspension on a UR-10 spectrometer. I wish to thank V. S. Vinogradov, of the Butlerov Kazan Chemical Institute, for the IR spectra.

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5 May 1967

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