SYNTHESES IN THE PURINE SERIES. XXI.* PREPARATION OF C_2- AND C_6-IMINOPURINES

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UDC 547.857.7:542.9

In 1962 we first put forward a proposal concerning the formation of cyclic amide chlorides [1] or adducts of the amide chloride type, i.e., the primary products of the addition of phosphorus oxychloride to carbonyl oxygen as a result of the action of phosphorus oxychloride on N-methyl-α-oxopurines, which we regarded in this reaction as cyclic N-substituted amides.

$$-CO-N\lessgtr \xrightarrow{POCl_3} \left[-\overset{+}{C}X-N\lessgtr\right]Y^-$$

Amide chloride $X = Y = Cl$

Adducts X and Y = Cl and $OPOCl_2$

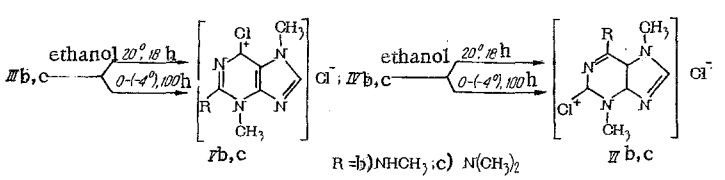
The properties of the amide chlorides and adducts formed by the action of phosphorus oxychloride on N,N-disubstituted amides have been studied in comparative detail only in the last decade [2]. The initial object of these investigations was dimethylformamide and amides of other fatty acids [3, 4], and then also cyclic N-substituted lactams, including 1-methylpyridone, 1-methylquinolone, etc. [5]. In 1966, the description of an adduct obtained from 1,3-dimethyl-4-dimethylaminouracil also appeared [6].

The object of the present work was to obtain adducts and amide chlorides from two isomeric series of 3,7-dimethylmonooxopurines and their investigation, in particular a study of the possibility of their conversion into C-iminopurines [7]. The starting materials were compounds of the general structure I and II [8, 9], i.e., 3,7-dimethyl-6-oxo-3,6-dihydro and 3,7-dimethyl-2-oxo-2,3-dihydropurines substituted by SCH_3, $NHCH_3$, and $N(CH_3)_2$ groups on C_2 in the first case and on C_6 in the second case.

It appeared likely that if these compounds could be converted, respectively, into the C_6- and C_2-imino derivatives of 3,7-dimethylpurine substituted by residues R at the 2nd ring carbon of the pyrimidine part of the molecule, the latter might prove to be a new source for the search for biologically active compounds. The possibility of varying the nature of R and the systematic comparison of the two isomeric series of iminopurines, and also the identity of the distribution of the N-methyl groups with that of theobromine, in association with the high water-solubility characteristic of imine hydrochlorides gave a basis for hoping for promising results from such searches. At this stage, the problem consisted of synthesizing the two groups of isomeric C-imines of 3,7-dimethylpurines for biological investigation.

The reaction of compounds of series I with phosphorus oxychloride at 20°C was accompanied by the evolution of heat, while for the successful performance of the same reaction with compounds of series II it was necessary to heat the reaction mixture to 50-60°C. Almost all the substances isolated from the reactions, as shown by analysis, consisted of the adducts (III and IV) and only one of them, obtained from If, proved to be the true amide chloride (Va) (see scheme A).

The adducts III and IV react with ethanol without heating. Under these conditions, they are gradually, over 18-20 h, converted into the corresponding amide chlorides Vb, c, or into the carbamide chlorides VIb, c. On being cooled (from 0 to −4°C), the adducts of series IV do not react with ethanol, while the more reactive adducts of series III form amide chlorides with satisfactory yields under these conditions.



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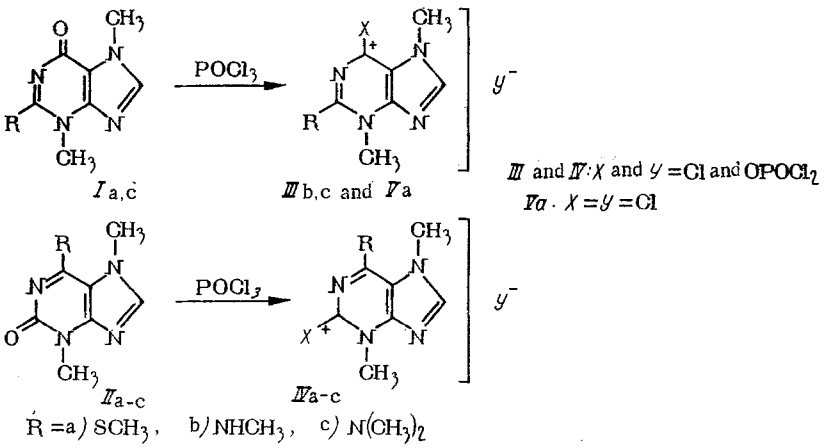
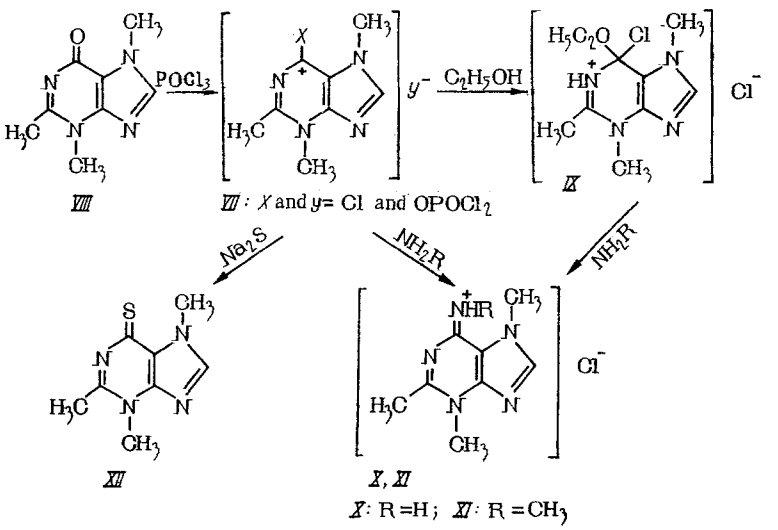
Scheme A



The adducts and amide chlorides obtained are crystalline substances slowly decomposing in the air but relatively stable in the absence of moisture, which are insoluble in nonpolar organic solvents.

It must be mentioned that none of the adducts, amide chlorides, and, particularly, carbamide chlorides mentioned are capable of adding a molecule of ethanol with formation of aminochloro ether hydrochlorides as has been reported previously for the amide chlorides [2]. Only the adduct VII obtained from 2-methyltheobromine VIII showed this property. *

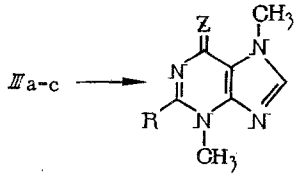
In contrast to the adducts III and IV, it reacts with ethanol, to form not the amide chloride but the hydrochloride of 6-chloro-6-ethoxy-2,3,7-trimethyl-3,6-dihydropurine (IX). The formation of the latter was shown by the characteristic reactions for aminochloro ethers [2], in particular those that we have described previously for the hydrochloride of an aminochloro ether substituted with chlorine at $C_{(2)}$ [9]. Thus, it decomposes with the evolution of C_2H_5Cl on boiling in toluene or on heating to 150-160°C, being converted into the hydrochloride of the initial 2-methyltheobromine – VIII · HCl – and on treatment with a solution of ammonia it forms the hydrochloride of 6-imino-2,3,7-trimethylpurine (X), identical with the compound obtained under the same conditions from the adducts VII:



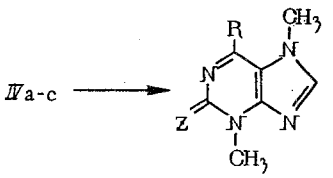
In reactions with such nucleophilic reagents as sodium sulfide, ammonia, and primary amines, which take place at high rates and are accompanied by the spontaneous emission of heat, it is impossible to observe differences in the reactivities of the two isomeric series of adducts and of the amide and carbamide chlorides. The final products of these reactions were 2-R-6-thio- and 6-R-2-thio-3,7-dimethyldihydropurines (XI, XIIIa-XIIIc, XIVa, b), and also the hydrochlorides of 2-R-6-imino- and 6-R-2-imino-3,7-

*See following communication.

dimethyldihydropurines (X, XV-XVc, XVIa-XVIc) and of 2-R-6-methylimino- and 6-R-2-methylimino-3,7-dimethyldihydropurines (XII, XVIIa-XVIIc, XVIIIa,c).



XIIIa-c; XIVa-c; XVIIIa-c



XIVa,c; XIIIa,c; XVIIIa,c

R = a) SCH_3 XIII and XIV: Z=S

b) $NHCH_3$ XIV and XVI: $Z=\overset{+}{N}H_2\bar{C}l$

c) $N(CH_3)_2$ XIII and XVII: $Z=\overset{+}{N}HCH_3\bar{C}l$

The comparatively simple scheme for the synthesis of derivatives of C_2- and C_6-imino-3,7-dimethylpurines that has been given ensures the availability of these new compounds for biological investigation, all the more since it permits a wide variation of the nature of the substituents R on the second carbon atom of the pyridine part of the molecule and of the substituents attached to the exocyclic nitrogen of the imino group.

EXPERIMENTAL

General Method for Obtaining Adducts from 2-R-3,7-Dimethyl-6-oxo-3,6-dihydropurines and Phosphorus Oxychloride (IIIb,c; Va; VII). Compounds Ia,b and VIII were stirred with an eightfold and compound Ic with a twofold volume of phosphorus oxychloride for 0.5 h (spontaneous heating was observed), the mixture was cooled and filtered, and the residue was washed with petroleum ether. For analysis compounds IIIa and Va were washed with ethanol and ether, and for purification compounds IIIc and VII were dissolved in ethanol and precipitated with ether (Table 1).

General Method for Obtaining Adducts from 6-R-3,7-Dimethyl-2-oxo-2,3-dihydropurines and Phosphorus Oxychloride (IVa-IVc). Compounds IIa-IIc were heated at 50-60°C with an eightfold volume of phosphorus oxychloride for 0.5 h. The mixtures were cooled and filtered and the precipitates were washed with ether. A further small amount of the products was obtained from the residues from the evaporation of the filtrate after treatment with ethanol. The precipitates were combined and purified for analysis by dissolution in absolute ethanol and precipitation with ether (see Table 1).

General Method for Obtaining Amide Chlorides of 2-R-6-Oxo- and 6-R-2-Oxy-3,7-dimethyldihydropurines (Vb,c; VIb,c). The adducts IIIb and c and IVb were treated with a 10-15-fold volume of absolute ethanol and left at room temperature for 18-20 h. An excess of ether was added to the reaction mixture and it was filtered (see Table 1).

Hydrochloride of 6-Chloro-6-ethoxy-2,3,7-trimethyl-3,6-dihydropurine (IX). A solution of 8.7 g of the adduct in 100 ml of absolute ethanol was left for a day (20-25°C) and was filtered. The precipitate consisted of 1.4 g of the hydrochloride of 2,3,7-trimethylhypoxanthine (VIII·HCl) with mp 267°C (decomp.). Found, %: C 43.00; H 5.10; Cl 15.91; N 24.89. $C_8H_{10}N_4O \cdot HCl/2H_2O$. Calculated, /: C 42.90; H 5.37; Cl 15.88; N 25.10.

From the alcoholic filtrate, ether precipitated an oil which crystallized on cooling. This gave 4.3 g of the hydrochloride of 6-chloro-6-ethoxy-2,3,7-trimethyl-3,6-dihydropurine (IX), mp 262°C (decomp.). Found, %: C 42.58; H 5.77; Cl 25.20; N 19.67. $C_{10}H_{16}Cl_2N_4$. Calculated, %: C 43.01; H 5.77; Cl 25.45; N 20.07.

Thermal Decomposition of Compound IX. A. The temperature of 0.7 g of the compound was gradually raised to 200°C. At 140-150°C, the reaction mixture became yellow and the evolution of ethyl chloride commenced. The process yielded 0.6 g of VIII·HCl, mp 267°C (decomp.). A mixture with VIII·HCl obtained from the adduct VII (see above) had mp 267°C.

B. A mixture of 0.6 g of compound IX and 10 ml of toluene was boiled for 8 h, and 0.4 g of VIII·HCl separated out with mp 267°C (decomp.). Mixtures with samples obtained by method A and from the adduct VII had mp 267°C (decomp.).

Hydrochloride of 6-Imino-2,3,7-trimethyl-3,6-dihydropurine (X). A. From the adduct VII: 1 g of the adduct VII was slowly added to an aqueous solution of ammonia at 20°C. The precipitate was filtered off

TABLE 1. Adducts and Amide Chlorides of C_2- and C_6-Substituted Derivatives of 3,7-Dimethylmonooxodihydropurines

Compound	Yield (in %)	mp (in deg)	Found (in %)					Empirical formula	Calculated (in %)				
			C	H	Cl	N	H_2O, S or P		C	H	Cl	N	H_2O, S or P
IIIb	94	220 (decomp.)	28,0	3,23	30,99	20,0	P 8,52	$C_8H_{11}Cl_3N_5O_2P$	27,70	3,17	30,73	20,20	P 8,95
III c	74	115—7 (decomp.)	29,76	3,43	29,53	19,12	P 8,50	$C_9H_{13}Cl_3N_5O_2P$	29,96	3,60	29,54	19,42	P 8,59
IV a	76,3	156—8 (decomp.)	26,9	2,84	29,34	15,17	P 8,49	$C_8H_{10}Cl_3N_4O_2PS$	26,40	2,75	29,30	15,40	P 8,52
IV b	85,5	194—7 (decomp.)	28,13	3,13	31,0	20,38	P 8,70	$C_8H_{11}Cl_3N_5O_2P$	27,70	3,17	30,73	20,20	P 8,93
IVc	60	139—42 (decomp.)	29,84	3,36	29,85	19,83	P 8,86	$C_9H_{13}Cl_3N_5O_2P$	29,96	3,60	29,54	19,42	P 8,59
Va	91	196—9 (decomp.)	36,18	3,64	26,88	21,22	11,67	$C_8H_{10}Cl_2N_4S$	36,22	3,77	26,79	21,13	12,07
Vb	80	Above 350	39,01	4,64	28,70	27,57	—	$C_8H_{11}Cl_2N_5$	38,71	3,44	28,61	28,21	—
Vc	72,5	97—100	37,36	5,58	24,41	25,40	H_2O 9,46	$C_9H_{13}Cl_2N_5 \cdot 1,5 \cdot H_2O$	37,40	5,53	24,55	24,22	H_2O 9,35
VIb	66	235—7	—	—	26,63	26,23	H_2O 5,28	$C_8H_{11}Cl_2N_5 \cdot H_2O$	—	—	26,69	26,32	H_2O 6,76
VIc	57	173—6	38,36	5,40	25,77	24,83	H_2O 6,93	$C_9H_{13}Cl_2N_5 \cdot H_2O$	38,57	5,36	25,36	25,00	H_2O 6,43
VII	88,5	140 (decomp.)	28,42	2,80	31,92	16,85	P 9,64	$C_8H_{10}Cl_3N_4O_2P$	28,99	3,04	32,10	16,90	P 9,35

TABLE 2. Thio and Imino Derivatives of 3,7-Dimethyldihydropurine

Compound	Yield (in %)	mp (in deg) and solvent for crystallization	Found (in %)					Empirical formula	Calculation (in %)				
			C	H	Cl	N	S		C	H	Cl	N	S
XI	68,5	285.5-286, dimethylformamide	49,04	5,32	—	28,64	16,39	$C_8H_{10}N_4S$	49,46	5,19	—	28,84	16,50
XII	44	268-9(decomp.),ethanol	44,40	6,74	14,54	28,37	—	$C_9H_{14}ClN_5 \cdot H_2O$	43,99	6,56	14,43	28,50	—
XIII a	70,5	239-41, water	42,35	4,31	—	24,53	28,56	$C_8H_{10}N_4S_2$	42,47	4,42	—	24,77	28,32
XIII b	67	310-1, dimethylformamide	45,94	4,96	—	33,20	15,39	$C_8H_{11}N_5S$	45,93	5,26	—	33,49	15,31
XIII c	84	180-2, ethanol	49,06	6,32	—	31,27	14,15	$C_9H_{13}N_5S$	48,43	5,83	—	31,40	14,34
XIV a	80,5	248-9, water	43,03	4,41	—	24,76	28,77	$C_8H_{10}N_4S_2$	42,47	4,42	—	24,77	28,32
XIV b	56,4	262-3, ethanol	48,80	5,64	—	31,05	14,62	$C_9H_{13}N_5S$	48,43	5,82	—	31,39	14,35
XV a	58,7	256-8, absolute ethanol	—	—	14,70	28,03	13,09	$C_8H_{12}ClN_5S$	—	—	14,45	28,51	13,03
XV b	82	341 (decomp.0, water	42,02	5,46	15,66	36,84	—	$C_8H_{13}ClN_6$	42,01	5,68	15,53	36,85	—
XV c	58,5	276-80, ethanol	43,40	6,34	14,41	33,15	—	$C_9H_{15}ClN_6 \cdot {}^1/_2H_2O$	42,94	6,40	14,08	33,34	—
XVI a	78	248-50, absolute ethanol	—	—	14,26	27,77	13,40	$C_8H_{12}ClN_5S$	—	—	14,45	28,51	13,03
XVI b	87,9	325-7 (decomp.), absolute ethanol	41,65	5,69	15,36	36,52	—	$C_8H_{13}ClN_6$	42,01	5,68	15,54	36,76	—
XVI c	70	285-6, absolute ethanol	44,53	6,18	14,63	34,63	—	$C_9H_{15}ClN_6$	44,55	6,20	14,79	34,55	—
XVII a	77	251-3, ethanol	—	—	13,16	25,03	11,28	$C_9H_{14}ClN_5S \cdot H_2O$	—	—	12,76	25,21	11,53
XVII b	65	300-2, ethanol	44,21	6,44	14,74	34,55	—	$C_9H_{15}ClN_6$	44,51	6,18	14,65	34,60	—
XVII c	72	214-6 (decomp.), ethanol + ethyl acetate	43,71	6,67	13,13	30,86	—	$C_{10}H_{17}ClN_6 \cdot H_2O$	43,69	6,92	12,90	30,59	—
XVIII a	31,7	244-6, ethanol + ethyl acetate	—	—	12,83	24,84	11,42	$C_9H_{14}ClN_5S \cdot H_2O$	—	—	12,76	25,21	11 53
XVIII c	76,8	267-8, ethanol	46,78	6,62	13,84	32,75	—	$C_{10}H_{17}ClN_6$	46,13	6,14	13,99	32,83	—

and crystallized from aqueous ethanol. The yield of the hydrochloride of 6-imino-2,3,7-trimethyl-3,6-dihydropurine (X) was 0.42 g (65%), mp 309-310°C (decomp.). Found, %: C 44.74; H 5.75; Cl 16.99; N 32.69. $C_8H_{12}ClN_5$. Calculated, %: C 44.96; H 5.62; Cl 16.64; N 32.79.

B. From compound IX: 0.5 g of compound IX was added to 2 ml of aqueous ammonia and the precipitate was dissolved in boiling aqueous ethanol; the solution was brought to pH 5.0-6.0 with hydrochloric acid and filtered. This gave the hydrochloride of 6-imino-2,3,7-trimethyl-3,6-dihydropurine with mp 309-310°C; a mixture with compound X obtained by method A had mp 309-310°C.

General Method for Obtaining 2-R-6-Thio-3,6-dihydro- and 6-R-2-Thio-2,3-dihydro-3,7-dimethylpurines (XI, XIIIa-XIIIc, XIVa, c). To a saturated aqueous solution of sodium sulfide one of the adducts IIIb, c, IVa-IVc, or VII or the amide chloride Va was added gradually at a temperature not exceeding 20°C. The mixture was stirred at 20°C for 1 h and filtered, and the precipitate was crystallized for analysis (Table 2).

General Method for Obtaining the Hydrochlorides of 2-R-2-Imino- (and -methylimino-) -3,6-dihydro- or 6-R-2-Imino- (and -methylimino-) -2,3-dihydro-3,7-dimethylpurines (XII, XVa-c, XVIa-XVIc, XVIIa-XVIIc, XVIIIa, c). One of the adducts IIIa-IIIc, IVa-IVc, and VII, or one of the amide chlorides Va-Vc, VIb, c, was gradually added to an excess of an aqueous solution of ammonia (or methylamine) at a temperature not exceeding 20°C, and the precipitate* was filtered off and crystallized (see Table 2).

CONCLUSIONS

The action of phosphorus oxychloride on 2-R-6-oxo- and 6-R-2-oxo-3,7-dimethyldihydropurines has given two isomeric series of adducts. Their properties and reactions have been studied. The majority of the adducts react with ethanol without heating to form amide chlorides or carbamide chlorides. A general method for the synthesis of the hydrochlorides of 2-R-6-imino- or (-methylimino-) and 6-R-2-imino (or -methylimino-) -3,7-dimethyldihydropurines by the action of ammonia or primary amines on the adducts and amide chlorides or carbamide chlorides has been found. The action of sodium sulfide on the adducts and amide chlorides or carbamide chlorides has given 2-R-6-thio- and 6-R-2-thio-3,7-dimethyldihydropurines.

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* Compounds XVIIc and XVIIIa were extracted from the aqueous solution with chloroform.