SYNTHESES IN THE PURINE SERIES

XX. THE ACTION OF PHOSPHORUS CHLORIDES ON 8-METHYLTHEOBROMINE

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It was found earlier that the reaction of theobromine with phosphorus oxychloride could be used as a basis in the synthesis of the so-called 2- and 6-substituted theobromines [1-4], more exactly, in the synthesis of derivatives of 6-oxo-3,6-dihydro-, and 2-oxo-2,3-dihydro-3,7-dimethylpurines substituted in positions 2 and 6. Further, a method was recently found involving almost quantitative transformation of theobromine in its reaction with phosphorus oxychloride and phosphorus pentachloride to yield 2,6-dichloro-7-methylpurine [5, 6].

The problem was to apply these reactions to the synthesis of purine derivatives substituted at C_8 by the C–C bond from various groups with the object of finding biologically active compounds to be used as a source for the synthesis of new drugs.

Boiling 8-methyltheobromine (I) [7] (easily accessible 8-substituted theobromine derivatives [8, 9]) with phosphorus oxychloride for 4-6 h, concentrating in vacuo the solution formed,* and treating the residue with ice in the presence of an excess of sodium bicarbonate yielded a substance of brutto-formula $C_8H_8ClN_4O$ corresponding to the composition of monochloro-monoxo-dihydro-3,7,8-trimethylpurine. Chromatography in a thin layer of aluminum oxide has shown that this substance is a mixture of two isomeric compounds with very close R*f* values; owing to the different solubility of the compounds in water, it was possible to separate them. One of them (chloride A, mp 241, decomp.) was obtained in a yield of 43%, the other (chloride B, mp 241-242, decomp.) in a yield of 9%. A hydrolysis of both chlorides gave readily the initial I;† consequently, they are isomeric 2-chloro-3,7,8-trimethyl-6-oxo-3,6-dihydropurines, i.e., 2-chloro-8-methyltheobromine (IIIa), and 6-chloro-3,7,8-trimethyl-2-oxo-2,3-dihydropurine, i.e., 6-chloro-8-methyltheobromine (IVa).

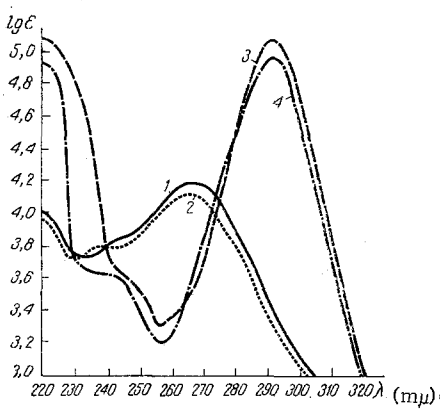

Fig. 1. UV spectra (in alcohol). 1) 2-Ethoxy-8-methyltheobromine; 2) ethoxytheobromine; 3) 6-ethoxy-8-methyltheobromine; 4) 6-ethoxy-theobromine.

Substitution of the chlorine atom in chlorides A and B by the action of sodium ethylate, ammonia, amines, thiourea, and also by condensation with sodium malonate and by subsequent hydrolytic cleavage and decarboxylation of the condensation product gave the corresponding C_2- and C_6-ethoxy-, amino-, dimethylamino-, mercapto-, and methyl-monoxodihydro-3,7,8-trimethylpurines (IIIb-IIIk and IVb-IVi):

*In the synthesis of 2,6-dichlor-7,8-dimethylpurine (II), the solution was boiled with 2 moles of phosphorus pentachloride; dichloride II could be isolated; however, its yield did not exceed 25% (compare with [6]). Admixture II (about 3%) was also found found among the products obtained in the reaction of I with phosphorus oxychloride in the absence of phorphorus pentachloride.

†A comparison of the relative reactivity of chlorides A and B in nucleophilic substitution reactions, for example, in their reaction with sodium malonate and alcoholic ammonia solution,has disclosed a high mobility of the chlorine atom in chloride B.

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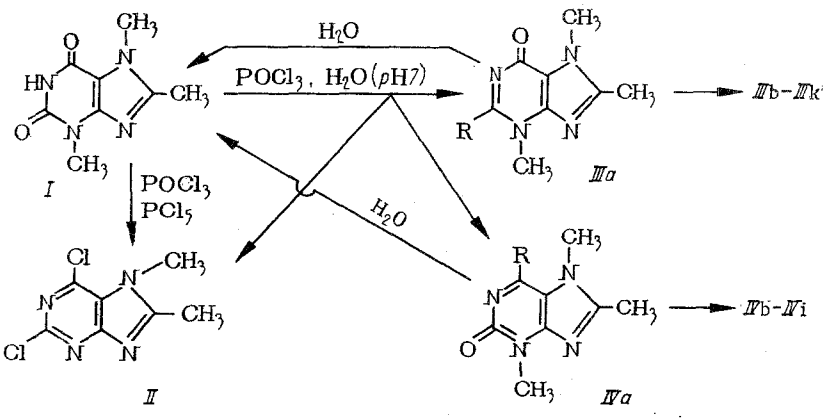
TABLE 1. UV Spectra (in Alcohol) of 2- and 6-R-8-Methyl- and Unsubstituted at C_8 Theobromines

2-R-8-Methyltheobromine (IIIf)		2-R-Theobromine [3]		6-R-8-Methyltheobromine (IV)		6-R-Theobromine [3]	
R	λ_{max} (in mμ)	lg E	λ_{max} (in mμ)	lg E	λ_{max} (in mμ)	lg E	λ_{max} (in mμ)	lg E
Cl	222, 270	4,07, 4,09	222, 268	4,00, 4,05	259, 330	3,72, 4,03	—	—
OC_2H_5	267	4,19	267	4,12	294	4,10	292	3,96
CH_3	268	4,10	269	4,05	255, 321	3,69, 4,06	254, 319	3,67, 3,98
NH_2	238, 270	3,95, 4,09	241, 269	3,95, 4,02	247, 290	3,96, 4,07	248, 289	3,98, 4,02
SH	237, 290	4,19, 4,35	236, 286	4,12, 4,32	220, 342, 348	4,13, 4,42, 4,45	219, 340, 348	4,11, 4,42, 4,36
SCH_3	240, 278	4,35, 4,18	239, 276	4,32, 4,11	270, 323	4,03, 4,19	271, 320	4,03, 4,12



R = a: Cl, b: OC_2H_5, c: NH_2, d: $N(CH_3)_2$, e: SH, f: SCH_3, g: $CH(COOC_2H_5)_2$, h: CH_3, i: $CCl(COOC_2H_5)_2$, j: $NHCH_3$, k: CN.

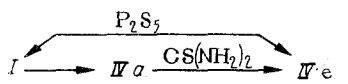
The selection between two possible structures for each of the chlorides A and B was based on the comparison of UV spectra of a number of compounds obtained by substituting various groups for chlorine atoms.

The closeness of the absorption maxima as well as the character of UV spectra of compounds obtained from chloride A showed good agreement with the data on the appropriate 2-chlorotheobromine derivatives.

The compounds prepared from chloride B were almost like the corresponding 6-substituted compound of theobromine (Figs. 1 and 2, Table 1). This suggests that chlorides A and B have the structures of IIIa and IVa, respectively.

Such a concept of the structure of chlorides A and B was confirmed by the following two reactions:

1. Thiol IVe (from IVa and thiourea) was found to be identical to mercapto-8-methyltheobromine, obtained as a result of heating I with phosphorus pentasulfite, i.e., under conditions used for the transformation of theobromine to 6-mercaptotheobromine [10]:



2. Distilling off phosphorus oxychloride from the solution obtained in boiling I in $POCl_3$, treatment of the residue with absolute alcohol and, only at this stage, treatment with sodium bicarbonate solution yielded a substance identical to IVb (from IVa and sodium ethylate):

$$I \xrightarrow{POCl_3,\ C_2H_5OH,\ NaHCO_3} IVb \xleftarrow{C_2H_5ONa} IVa.$$

This reaction clearly demonstrates the close analogy with the reactions of I and of theobromine (compare [3, 4]).

The above implies that theobromine derivatives, substituted at C_8, in reactions with phosphorus chlorides are almost similar to theobromine itself. It should be emphasized, nevertheless, that some differences between them and theobromine do exist in these reactions.

First, the action of boiling phosphorus oxychloride on I gave rise to a red coloration (which was completely lacking in a similar reaction with theobromine); with 8-benzyl-(V) [11] and 8-diethylaminomethyl- [12, 13] theobromine derivatives, the reaction mixture was tarred to such an extent

TABLE 2. Properties and Analysis of 2-R-8-Methyltheobromines (III) and 6-R-8-Methyltheobromines (IV)

Compound	Found (%)			Brutto-formula	Calculated (%)			Melting point, °, solvent for crystallization	Yield (%)
	C	H	N		C	H	N		
II	33,07*	—	25,41	$C_7H_6Cl_2N_4$	32,72*	—	25,81	150, Water	24
IIIa	17,00*	—	26,04	$C_8H_9ClN_4O$	16,70*	—	26,35	241 (Decomp.), dry benzene	43
IIIb	54,26	6,21	24,90	$C_{10}H_{14}N_4O_2$	54,08	6,31	25,23	176, Benzene	43
IIIc	49,96	5,89	35,66	$C_8H_{11}N_5O$	49,74	5,70	36,27	338—340(Decomp.) water	63
IIId	54,27	6,97	31,61	$C_{10}H_{15}N_5O$	54,30	6,79	31,67	169—70, Benzene	79
IIIe	45,78	4,86	14,92 †	$C_8H_{10}N_4OS$	45,71	4,76	15,24†	280—1, Alcohol	95
IIIf	48,03	5,25	13,82 †	$C_9H_{12}N_4OS$	48,21	5,36	14,29†	226—7, Benzene	74
IIIg	53,45	5,87	16,64	$C_{15}H_{20}N_4O_5$	53,57	5,95	16,67	160—1, Alcohol	73
IIIh	56,43	6,36	29,02	$C_9H_{12}N_4O$	56,25	6,25	29,17	213—4, Acetone	93
IIIi	9,66*	—	15,34	$C_{15}H_{19}ClN_4O_5$	9,58*	—	15,11	139—40, CCl_4	90,6
IIIj	52,50	6,18	33,58	$C_9H_{13}N_5O$	52,17	6,28	33,82	359—60 (Decomp.), alcohol	—
IIIk	52,91	4,50	33,63	$C_9H_9N_5O$	53,20	4,43	34,55	194—5 (Decomp.), toluene	74
IVa	16,78*	—	25,83	$C_8H_9ClN_4O$	16,70*	—	26,35	241—2 (Decomp.), dry benzene	9
IVb	53,91	6,02	24,78	$C_{10}H_{14}N_4O_2$	54,08	6,31	25,23	270—1, Alcohol	~45‡
IVc	49,66	5,61	35,74	$C_8H_{11}N_5O$	49,74	5,70	36,27	311—2 (Decomp.), water	82,6
IVd	54,37	6,80	31,36	$C_{10}H_{15}N_5O$	54,30	6,79	31,67	205—6, Benzene	72
IVe	45,87	4,61	15,66 †	$C_8H_{10}N_4OS$	45,71	4,76	15,24 †	315—7 (Decomp.), DMPA, butanol	99‡
IVf	48,00	5,08	14,04 †	$C_9H_{12}N_4OS$	48,21	5,36	14,29 †	252—3, Alcohol	~100
IVg	53,22	5,92	16,72	$C_{15}H_{20}N_4O_5$	53,57	5,95	16,67	211—2, »	95 ‡
IVh	56,41	6,09	29,13	$C_9H_{12}N_4O$	56,25	6,25	29,17	259—61 **	95
IVi	9,60*	—	15,33	$C_{15}H_{19}ClN_4O_5$	9,58*	—	15,11	176—7 **	95
VII	25,96	1,12	55,17*	$C_7H_3Cl_5N_4$	26,21	0,94	55,38*	207—8, CCl_4	60
VIII	58,26	5,58	19,44	$C_{14}H_{16}N_4O_3$	58,33	5,56	19,41	292—3, Water	76

*Cl %.

†S %.

‡ From No. IVa.

**See experimental part.

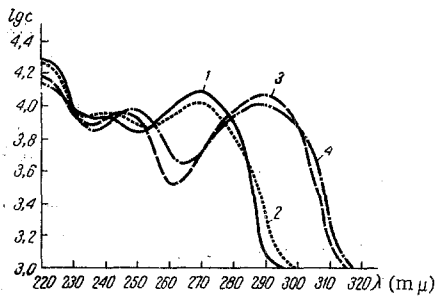


Fig. 2. UV spectra (in alcohol). 1) 2-Amino-8-methyltheobromine; 2) 2-aminotheobromine; 3) 6-amino-8-methyltheobromine; 4) 6-amino-theobromine.

that no individual products could be separated. Slightly lesser tarring was observed in the reaction of 8-trichloromethyltheobromine (VI) [14] which on boiling with phosphorus pentachloride gave 2,6-dichloro-7-methyl-8-trichloromethylpurine (VII) in a 60% yield [15].

Second, the reaction of I with phosphorus oxychloride gave two possible monochloride isomers, IIIa and IVa, whereas the reaction with unsubstituted-at-C_8 theobromine gave only 2-chlorotheobromine [1]. It is quite probable that the second isomer, 6-chlorotheobromine, was formed, but it could not be isolated because in the reaction mixture treatment it underwent hydrolytic cleavage (upon neutralization, the reaction mixture always contained a small amount of theobromine).

EXPERIMENTAL*

The purity of the products was determined by thin-layer chromatography on aluminum oxide (degree of activity, II). Solvent systems: chloroform-ethyl acetate-alcohol (5:5:1), chloroform alcohol (9:1).

2-Chloro-3,7,8-trimethylhypoxanthine (IIIa) and 6-Chloro-3,7,8-trimethyl-2-oxo-2,3-dihydropurine (IVa). Sixty grams of I in 400 ml of $POCl_3$ was boiled for 4-6 h, the solution concentrated in vacuo to a volume of 100-150 ml, the residue introduced in portions into a salt bath containing 900 g of ice and 700-800 g of $NaHCO_3$ for 30 min; the cooling was discontinued, the mixture stirred until the CO_2 evolution stopped, filtered, and the residue extracted with warm chloroform (total ~0.8 liter) to yield a dark-red precipitate (about 40-42 g), crystallized from 2.2-2.4 liters of toluene. Yield of IIIa 28-29 g, white needles, mp 235-238° (decomp.).

The aqueous filtrate was repeatedly extracted with chloroform,† which was partially distilled off to a 50 ml volume, the precipitate‡ crystallized from ~850 ml of toluene to yield ~6 g of IVa, mp 241-242° (decomp.), mp of mixture samples with IIIa, 205-210°.

2-Ethoxy-3,7,8-trimethylhypoxanthine (IIIb). To 1.8 g of IIIa in 5 ml of absolute alcohol was added dropwise a solution of sodium ethylate (from 0.2 g of Na and 10 ml of absolute alcohol); the alcohol was distilled off, the solution of the residue in water was acidified with acetic acid to pH 6.0, and 1.2 g of substance extracted with chloroform and crystallized from dry benzene to yield 0.8 g of IIIb.

6-Ethoxy-3,7,8-trimethyl-2-oxo-2,3-dihydropurine (IVb). A) A solution of sodium ethylate (from 0.05 g of Na and 5 ml of absolute alcohol) was added to 0.4 g of IVa in 3 ml of absolute alcohol, the alcohol was distilled off, the residue treated as in preparation IIIb, and crystallized from alcohol, mp 270-271°.

B) To a concentrated reaction mixture (from 10 g of I and 30 ml of $POCl_3$) cooled by ice with salt was added 150 ml of cold absolute alcohol to yield a solution at 0°; 0.2 liter of dry ether was added to the solution and refrigerated for several days. The precipitate was introduced into a NaOH solution (pH ~10.0), the precipitate filtered, crystallized from water to yield 0.3-0.35 g (2.7-3%) of II, mp 149-150°.

The alcohol-ether filtrate was neutralized with $NaHCO_3$ solution, the lower layer extracted with chloroform. The chloroform solution was concentrated to a volume of 0.1 liter and washed with two 50 ml portions of water to yield 2.85 g of a substance, mp 239-243°; recrystallization from absolute alcohol with charcoal gave 1.85 g (16%) of IVb, mp 270-271°. A sample mixed with IVb, prepared by the procedure A, had a mp 270-271°.

2-Amino-3,7,8-trimethylhypoxanthine (IIIc). Compound IIIa, 0.35 g, was refluxed with 10 ml of 25% NH_4OH solution for 1.5 h, cooled, filtered, dissolved in 1 N HCl solution, and precipitated (2 N NaOH solution, pH 10.0) to yield 0.2 g of IIIc, mp 338-340°(decomp.). Solution of IIIc in alcohol precipitated the chlorohydrate.

*See Table 2.

†A precipitate of chloride IVa (1-1.5 g) was sometimes formed in the first extract.

‡The filtrate contained a colored mixture of chlorides IIIa, IVa, and II which was difficult to separate.

6-Amino-3,7,8-trimethyl-2-oxo-2,3-dihydropurine (IVc). Prepared from IVa by the same procedure given for IIIc; mp of IVc 311-312° (decomp.).

2-Dimethylamino-3,7,8-trimethylhypoxanthine (IIId). A solution of 1.7 g of IIIa in 10 ml of 30% dimethylamine solution gave in vacuo at 20° 1.4 g of crystals which were dried in vacuo, mp 168-169°.

6-Dimethylamino-3,7,8-trimethyl-2-oxo-2,3-dihydropurine (IVd). A solution of 0.4 g of IVa in 2 ml of 30% dimethylamine solution was evaporated to dryness, crystallized from benzene to yield 0.3 g of IVd, mp 196-200°.

2-Mercapto-3,7,8-trimethylhypoxanthine (IIIe). Heating to boiling 5 g of IIIa and 1.9 g of thiourea in 40 ml of absolute alcohol yielded 4.7 g of IIIe, mp 277-279°.

6-Mercapto-3,7,8-trimethyl-2-oxo-2,3-dihydropurine (IVe). A) To a suspension of 40 g of dried I in 0.4 liter of dry pyridine was added with stirring 72 g of P_2S_5 and refluxed for 7 h. After the addition of 0.6 liter of water with cooling, the mixture was refluxed for 2-3 h, and concentrated in vacuo to 0.3 liter. The precipitate was dissolved in 1 N NaOH solution, filtered through charcoal, acetic acid added to yield 37-40 g of IVe, mp 303-307° (decomp.), mp after crystallization 314-316°.

B) Heating to boiling 0.5 g of IVa and 0.2 g of thiourea in 10 ml of alcohol yielded 0.49 g of IVe, mp 314-316°; samples mixed with purified IVe, prepared by procedure A, had a mp 314-316°.

2-Methylmercapto-3,7,8-trimethylhypoxanthine (IIIf). A solution of 3 g of IIIe in 15 ml of 1 N NaOH solution with 0.9 ml of CH_3I was shaken for 30 min, extracted with chloroform, and the product crystallized from 160 ml of benzene to yield 2.35 g of IIIf, mp 223-225°.

6-Methylmercapto-3,7,8-trimethyl-2-oxo-2,3-dihydropurine (IVf). A solution of 20 g of unpurified IVe in 0.1 liter of 1 N NaOH solution with 6 ml CH_3I was shaken for 30-40 min, and the crystals filtered to yield 17 g of IVf, mp 248-250°; a chloroform extraction of the filtrate gave an additional 4.3 g of IVf, mp 241-245°.

3,7,8-Trimethylhypoxanthinyl-2-malonic Ester (IIIg). To a suspension of sodium malonate (from 2.8 g of Na and 28 ml of malonic ester) in 0.1 liter of dry toluene was added 10 g of IIIa, stirred for 1 h, water added to dissolve the precipitate,and the aqueous layer acidified with 40% H_2SO_4 solution to pH 5.0 to yield 11.7 g of IIIg, mp 156-158°.

3,7,8-Trimethyl-2-oxo-2,3-dihydropurinyl-6-malonic Ester (IVg). A) Prepared from IVa by the procedure used in the preparation of IIIg, yield 95%, mp 209-211°.

B) To a suspension of sodium malonate (from 1 g of Na and 10 ml of malonic ester) in 40 ml of dry toluene was added 4.4 g of IVf, refluxed for 6 h to yield (see IIIg) 5.5 g of IVg, and crystallized from alcohol, mp 209-211°; a mixture sample with IVg, obtained by method A, had a mp of 209-211°.

2,3,7,8-Tetramethylhypoxanthine (IIIh). Three grams of IIIg in 15 ml of 18% HCl solution was refluxed for 30 min, evaporated in vacuo, the residue treated with 10% NaOH solution,water distilled off, and extracted with chloroform to yield 1.6 g of IIIh, mp 204-207°.

3,6,7,8-Tetramethyl-2-oxo-2,3-dihydropurine (IVh). Prepared from IVg by the procedure used for IIIh, yield 95%, mp 249-254°.

3,7,8-Trimethylhypoxanthinyl-2-chloromalonic Ester (IIIi). To a solution of 1 g of IIIg in 15 ml of dry chloroform was added a solution of 0.25 ml of SO_2Cl_2 in 1 ml of chloroform, washed with a $NaHCO_3$ solution after 12 h, chloroform distilled off,and the product crystallized from CCl_4 to yield 1 g of IIIi, mp 139-140°.

3,7,8-Trimethyl-2-oxo-2,3-dihydropurinyl-6-chloromalonic Ester (IVi). To 1 g of IVg in 25 ml of dry chloroform was added a solution of 0.25 g of SO_2Cl_2 in 1 ml of chloroform, evaporated after 12 h, the residue treated with $NaHCO_3$ solution, the precipitate dissolved in absolute alcohol, filtered, alcohol distilled off, and the residue triturated with water to yield 1.05 g of IVi, mp 176-177°.

2-Methylamino-3,7,8-trimethylhypoxanthine (IIIj). A solution of 1 g of IIIa in 3 ml of 30% dimethylamine solution was evaporated in vacuo, and the residue crystallized from alcohol to yield IIIj, mp 359-360° (decomp.).

2-Cyan-3,7,8-trimethylhypoxanthine (IIIk). A mixture of 4.4 g of IIIa with 1.35 g of KCN (or 1.9 g of Cu_2CN_2) in 45 ml of dimethylformamide was heated for 2 h (bath temperature 40-50°), filtered through charcoal, concentrated in vacuo, the residue dissolved in water, extracted with chloroform, the solution clarified with Al_2O_3, evaporated, and the residue crystallized from toluene to yield 3.1 g of IIIk, mp 194-195° (decomp.).

2,6-Dichloro-7,8-dimethylpurine (II). After refluxing 3 g of I in 15 ml of $POCl_3$, 6.45 g of PCl_5 was added and the mixture refluxed for another 4 h. The dark solution was concentrated in vacuo; the residue was introduced into a mixture of ice and $NaHCO_3$ (< 20°) and filtered. The residue and filtrate were extracted with chloroform, combined chloroform solution (~200 ml) washed twice with 100 ml portions of water, clarified with Al_2O_3; the chloroform was distilled off and the residue crystallized from water to yield 0.8 g of II, needles of mp 149-150°.

2,6-Dichloro-7-methyl-8-trichloromethylpurine (VII). After refluxing 1.5 g of VI [14] in 10 ml of $POCl_3$ for 3 h, it was cooled, 2.1 g of PCl_5 added and refluxed for another 3 h, the solution concentrated in vacuo, ice added to the residue, neutralized with concentrated NH_4OH to pH 5.0-6.0, the residue separated and dissolved in chloroform. The chloroform was distilled off, and the oil triturated with ether to yield 0.98 g of VII, mp 203-204°; 0.5 g of VII was dissolved in 8-10 ml of chloroform and decolorized by shaking with Al_2O_3. Crystallization from CCl_4 yielded 0.2 g of VII, mp 207-208°.

3-Methyl-4-amino-5-N-methyl-N-(phenylacetamide)-uracil (VIII). A mixture of 10 g of 3-methyl-4-amino-5-methylaminouracil [9, 16] and 30 g of phenylacetic acid was heated for 2 h at 120°, cooled, 50 ml of alcohol added, filtered, and the residue introduced in water at pH 8.0 to yield 13 g of VIII, mp 282-285°.

8-Benzyltheobromine (V) [11]. Five grams of VIII in 35 ml of 1 N NaOH solution, pH 6.0, was refluxed for 3 h to yield 4.2 g (90%) of V, mp 246-249°; after crystallization from alcohol, the mp was 251-252° (according to literature data [11], mp 251-252°).

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