SYNTHESES IN THE FIELD OF PURINE DERIVATIVES

XXXII. SOME REACTIONS OF 2-R-1,9-DIMETHYLHYPOXANTHINES

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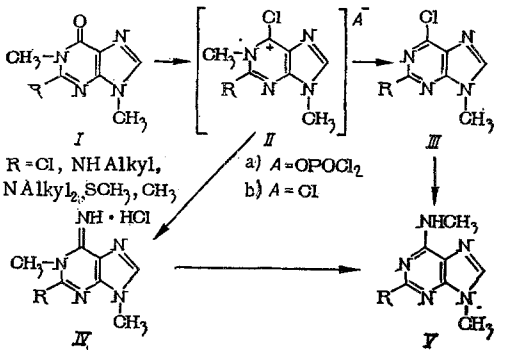
The reaction of phosphorus oxychloride with 2-R-derivatives of 1,9-dimethylhypoxanthine (I) was studied [1] with the objective of synthesizing 2-R-6-chloro-9-methylpurines, which are starting materials intended for the preparation of biologically active substances. It had previously been shown [2] that 2-R-3,7-dimethylhypoxanthines react very easily with phosphorus oxychloride (the reaction takes place with heat evolution, regardless of what R is) and that the primary reaction products are largely so-called adducts or amidochlorides.

The derivatives of I proves less reactive – the formation of adducts (IIa) or amidochlorides (IIb) from them requires heating. Moreover, they differ from the isomeric compounds of the 3,7-dimethylhypoxanthine series in the effect of the nature of R on the course of the process. Thus, if, in I, R=SCH_3, then heating it with phosphorus oxychloride leads to obtaining a IIa adduct, and not the amidochloride, IIb, as might have been expected by analogy with 2-methylmercapto-3,7-dimethylhypoxanthine [2]. And, conversely, when R=NHAlkyl, type IIb amidochlorides are formed instead of the expected IIa adducts. When R=CH_3 or $NAlkyl_2$, the reaction product is a mixture of the IIa adduct and the IIb amidochloride.



On more prolonged heating with phosphorus oxychloride, the derivatives of I can be converted into the corresponding 2-R-6-chloro-9-methylpurines (III). In this reaction also, a difference is displayed between the isomeric 2-R-3,7- and 2-R-1,9-dimethylhypoxanthines. While in the 3,7-dimethylhypoxanthine series only the compound with a chlorine in the 2-position is capable of being converted to 2,6-dichloro-7-methylpurine, the derivatives of 1,9-dimethylhypoxanthine are converted to the corresponding 2-R-6-chloropurines (III) somewhat more easily. Of these, the 2-dialkylamino-1,9-dimethylhypoxanthine (I, R=$NAlkyl_2$) reacts

TABLE 1. NMR Spectra (δ)

Compound	Solvent	Chemical shifts (in ppm)				
		2-CH_3	1-CH_3	9-CH_3	N-CH_3	8-H
IV, R=CH_3	Dimethyl sulfoxide	2,39	3,43	3,56		7,65
V, R=CH_3	»	2,39		3,64	2,96	7,85
V, R=OH	»			3,50	2,82	7,52
	NaOD			3,51	2,86	7,48

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TABLE 2. Adducts and Amidochlorides of 2-R-1,9-Dimethylhypoxanthines (IIa and IIb)

Compound	R	Found (%)					Empirical formula	Calculated (%)				
		C	H	N	Cl	P		C	H	N	Cl	P
IIb	$NHCH_3$	39,06	4,61	29,08	25,72	—	$C_8H_{11}Cl_2N_5$	38,71	4,44	28,21	28,61	—
IIb	NHC_2H_5	40,56	5,31	25,66	24,90	—	$C_9H_{13}Cl_2N_5$	41,20	4,95	26,75	27,10	—
IIb	$NHCH(CH_3)CH_2C_6H_5$	54,01	5,75	18,67	17,33	—	$C_{16}H_{18}Cl_2N_5$	54,54	5,40	19,89	20,17	—
IIa	SCH_3	26,13	2,93	15,19	27,04	8,15	$C_8H_{10}Cl_2N_4O_2PS$	26,41	2,75	15,41	29,30	8,53

especially easily — one hour of boiling with phosphorous oxychloride is enough for it to enter completely into reaction. 2-Methylmercapto-1,9-dimethylhypoxanthine (I, R=SCH_3) is comparatively rapidly converted into III (R=SCH_3), although the yield in this reaction does not exceed 35%. However, if the substituent in the 2-position is a methyl group, then the yield of III (R=CH_3) drops to 5-10%; and with a 2-alkylamino-1,9-dimethylhypoxanthine (I, R=NHAlkyl) the reaction does not take place at all and the starting hypoxanthine I (R=NHAlkyl) can be recovered quantitatively from the reaction. From the foregoing, it follows that not only the position of the N-methyl group in the dimethylhypoxanthine molecule, but also the character of the substituent in the 2-position exerts a considerable effect on its conversion to a 6-chloropurine.

Previously [3] the preparation of 2-R-1,9-dimethyl-6-iminopurine hydrochlorides (IV) by treatment of IIa or IIb with ammonia, plus isolation of the bases from the hydrochlorides by the action of alkali at room temperature, had been described. It was observed that when the iminopurines (IV) are boiled with alkali, they undergo various transformations which also depend on the nature of R. When R=CH_3, a Dimroth rearrangement takes place to form a 2,9-dimethyl-6-methylaminopurine (V, R=CH_3), which was found to be identical with the compound obtained by heating 2,9-dimethyl-6-chloropurine (III, R=CH_3) with methylamine solution. If R=$NHCH_3$ or NHC_2H_5, a hydrolytic cleavage of the 6-imino group partially occurs, and the reaction product is a mixture of the starting iminopurine, IV (R=NHAlkyl), and the 2-monoalkylamino-1,9-dimethylhypoxanthine I (R=NHAlkyl). When alkali acts on 2-dimethylamino-6-imino-1,9-dimethylpurine [IV, R=$N(CH_3)_2$], a new compound is formed which is able to dissolve in either acid or alkali, having the empirical formula $C_7H_9N_5O$. On the basis of the analysis, one could think that the rearrangement of the dimethyl compound in this case was accompanied by the splitting off of a dimethylamino group from the 2-position, that is, by the formation of 2-oxo-2,3-dihydro-6-methylamino-9-methylpurine (V, R=OH). This supposition was confirmed by the NMR spectrum. For convenience in assigning chemical shifts, the NMR spectra of the two isomeric compounds IV and V, which are substituted by a methyl group in the 2-position, were also taken (Table 1).

It may be supposed that the cleavage of the dimethylamino group takes place at the moment of rearrangement or before it is accomplished. This is indicated by the fact that 2-dimethylamino-6-methylamino-9-methylpurine [V, R=$N(CH_3)_2$], synthesized from III [R=$N(CH_3)_2$], is not hydrolyzed either in acid or in alkaline medium.

EXPERIMENTAL

Reaction of 2-Chloro-3,7-dimethylhypoxanthine with Phosphorus Oxychloride. 2-Chloro-3,7-dimethylhypoxanthine [4] (0.85 g) was boiled with 15 ml of phosphorus oxychloride for 6 h, the mixture was evaporated to dryness, the residue was dissolved in ice water, and the solution so formed was neutralized to pH 2.0-3.0 with sodium bicarbonate. The precipitate of 2,6-dichloro-7-methylpurine which separated was removed, washed with water, and dried. A yield of 0.42 g (48.2%) was obtained, mp 186-189°. A mixed mp with a sample of 2,6-dichloro-7-methylpurine previously prepared [5] showed no depression. When the aqueous filtrate was allowed to stand, 0.33 g of theobromine was isolated.

If the reaction is conducted for 12 h, 0.47 g (54%) of 2,6-dichloro-7-methylpurine can be isolated from the reaction mixture.

TABLE 3. 2-Substituted Derivatives of 1,9-Dimethylhypoxanthine (I), 6-Imino-1,9-dimethylpurine (IV), and 9-Methylpurine (III, V)

Compound	R	Yield (%)	Mp (deg); crystallization solvent	Found (%)					Empirical formula	Calculated (%)				
				C	H	Cl	N	S		C	H	Cl	N	S
I	$NHCH_2$	96,7	240—3(water)	49,60	5,44	—	36,55	—	$C_8H_{11}N_5O$	49,74	5,70	—	36,27	—
I	$NHCH(CH_3)CH_2C_6H_5$	77,5	173—5 (ethyl acetate)	64,30	6,29	—	23,26	—	$C_{16}H_{19}N_5O$	64,64	6,40	—	23,57	—
I	SC_4H_9	80	149—51 (ethyl acetate)	—	—		22,12	12,92	$C_{11}H_{16}N_4OS$	—	—		22,22	12,70
III	SCH_3	—	142—4 (water+alcohol)	—	—	14,47	23,39	13,31	$C_7H_7ClN_4 \cdot 0{,}5C_2H_5OH$	—	—	14,95	23,58	13,47
III	CH_3	—	167—9 (ethyl acetate)	46,24	3,90	19,67	30,30	—	$C_7H_7ClN_4$	46,00	3,84	19,47	30,68	—
IV	SC_4H_9	54,8	239—40,5 (alcohol + ethyl acetate)	—	—	12,75	23,89	10,93	$C_{11}H_{17}N_5S \cdot HCl$	—	—	12,35	24,35	11,12
IV	$NHCH_3$	61,2	328—30 (water + alcohol) 1 : 1)	—	—	15,83	36,62	—	$C_8H_{12}N_6 \cdot HCl$	—	—	15,54	36,76	—
IV	NHC_2H_5	66,9	318—9(water)	44,82	6,34	14,46	34,53	—	$C_9H_{14}N_6 \cdot HCl$	44,51	6,18	14,65	34,61	—
IV	$NHCH(CH_3)CH_2C_6H_5$	70	278—9(alcohol)	58,05	6,37	10,71	25,13	—	$C_{16}H_{20}N_6 \cdot HCl$	57,73	6,32	10,68	25,26	—
IV	CH_3	—	330,5—2,5 (dec., alcohol)	—	—	17,10	32,68	—	$C_8H_{11}N_5 \cdot HCl$	—	—	16,63	32,79	—
IV	$(CH_3)_2$	38,5	246—7 (dec., alcohol)	—	—	14,48	34,07	—	$C_9H_{14}N_6 \cdot HCl$	—	—	14,60	34,60	—
IV	SCH_3	—	271—3 (dec., water)	—	—	14,17	28,48	13,25	$C_8H_{11}N_5S \cdot HCl$	—	—	14,46	28,51	13,31
V	$(CH_3)_2$	74	226—8(alcohol)	52,08	7,05	—	40,70	—	$C_9H_{14}N_6$	52,43	6,80	—	40,78	—
V	CH_3	85,5	210—12 (alcohol)	54,33	6,20	—	40,15	—	$C_8H_{11}N_5$	54,24	6,24	—	39,55	—

2-Monoalkylamino-1,9-dimethylhypoxanthines [I, R=$NHCH_3$ or $NHCH(CH_3)CH_2C_6H_5$]. These were prepared by boiling 2-chloro-1,9-dimethylhypoxanthine (I, R=Cl) [1] with an aqueous solution of the monoalkylamine by the previously described method [1] (Table 2).

General Method of Preparing Hydrochlorides of 2-R-6-Imino-1,9-dimethylpurines [IV, R=$NHCH_3$, NHC_2H_5, $NHCH(CH_3)CH_2C_6H_5$, SC_4H_9, $N(CH_3)_2$, or CH_3]. The appropriate type I compound [R=$NHCH_3$, NHC_2H_5, $NHCH(CH_3)CH_2C_6H_5$, SC_4H_9, $N(CH_3)_2$*, or CH_3] was boiled with a 5 to 8-fold amount of $POCl_3$ for 5-10 min, the crystalline precipitate of II (see Table 2) was separated or the mixture was evaporated to dryness, and the residue was treated with a 25% aqueous ammonia solution, with cooling. The precipitate of IV which formed was separated and recrystallized.

In the case where R=CH_3, a mixture of IV and the iminopurine base was formed. Therefore 2 ml of 40% sodium hydroxide was added to the mixture formed and the type IV compound (R=CH_3) was separated in the form of the base. After crystallization from ethyl acetate, it had a mp of 149-151°. A yield of 9.9 g (62.4%) was obtained. Found, %: C 54.28; H 6.61; N 39.83. $C_8H_{11}N_5$. Calculated, %: C 54.24; H 6.24; N 39.55. The imine hydrochloride (IV, R=CH_3) was prepared by adding an alcoholic hydrogen chloride solution to a hot alcoholic solution of the base (Table 3).

2-Butymercapto-1,9-dimethylhypoxanthine (I, R=SC_4H_9). Compound I (R=SH) (31.6 g) [3] was boiled with 19 ml of butyl bromide in a mixture of 100 ml of alcohol and 486 ml of 0.33 N sodium hydroxide solution for 2.5 h. The hot solution was treated with charcoal, filtered, and cooled. The oil which separated crystallized; the crystals were separated out and washed with water.

Preparation of 2-R-6-Chloro-9-methylpurines [III, R=$N(CH_3)_2$, $N(C_2H_5)_2$, or CH_3]. Compound I [R=$N(CH_3)_2$, $N(C_2H_5)_2$, or CH_3] [6] was boiled with a 10-fold amount of phosphorus oxychloride for 1 h, the solution was evaporated to dryness, the residue was dissolved in ice water, and the solution was neutralized to pH 7.0; the precipitate formed was filtered off. The yield of III [R=$N(CH_3)_2$ or $N(C_2H_5)_2$] was 54-57%. The mixed mp of samples of these compounds with samples of the 2-dialkylamino-6-chloro-9-methylpurines previously prepared by another method showed no depression. In the case where R=CH_3, a precipitate did not separate; therefore the solution was extracted with chloroform. A mixture of I and III was extracted (R=CH_3). These substances were separated on a column containing aluminum oxide, and compound III (R=CH_3) was isolated from benzene eluates (see Table 3).

Reaction of 2-Methylmercapto-1,9-dimethylhypoxanthine (I, R=SCH_3) with Phosphorus Oxychloride. a) Compound I (R=SCH_3) (1 g) [1] was boiled with 5 ml of phosphorus oxychloride for 10 min, the mixture was cooled, the precipitate of II (R=SCH_3) (see Table 2) which was formed was separated, and it was treated with ammonia with cooling. The yield of IV (R=SCH_3) was 0.5 g (42.7%). The phosphorus oxychloride mother liquor was evaporated to dryness, the residue was dissolved in ice water, and the solution was neutralized. The yield of III (R=SCH_3) was 0.06 g (7.5%).

b) The experiment was conducted as described above. Boiling was carried out for 2.5 h. The yield of IV (R=SCH_3) was 25.7%; and that of III (R=SCH_3) was 34.7%.

Reaction of 1,2,9-Trimethyl-6-iminopurine Hydrochloride (IV, R=CH_3) with Alkali Solution. The imine hydrochloride (IV, R=CH_3) (0.5 g) was boiled with 10 ml of 0.6 N sodium hydroxide solution for 3 h; the solution was cooled, neutralized, and extracted with chloroform. There was obtained 0.4 g of V (R=CH_3), which melted at 210-212° after crystallization from alcohol; a mixed mp with 2,9-dimethyl-6-methylaminopurine gave no depression.

2,9-Dimethyl-6-methylaminopurine (V, R=CH_3). Compound III (R=CH_3) (1 g) was heated with 10 ml of 25% methylamine solution for 0.5 h. The V (R=CH_3) was extracted with chloroform and crystallized.

Reaction of 2-Methylamino-6-imino-1,9-dimethylpurine Hydrochloride (IV, R=$NHCH_3$) with Alkali Solution. The imine hydrochloride IV (R=$NHCH_3$) (0.2 g) was boiled with 4 ml of 0.5 N sodium hydroxide solution. The solution obtained was cooled and neutralized, and the precipitate formed was separated. It was crystallized from a small amount of water, and a compound of mp 230-265° was obtained. Judging from the chromatogram on aluminum oxide in the systems chloroform–ethyl acetate–methanol (1:1:1) and ethyl acetate–methanol (5:3), the precipitate was a mixture of two substances – the starting imine hydrochloride, IV (R=$NHCH_3$) and 2-methylamino-1,9-dimethylhypoxanthine (I, R=$NHCH_3$).

*The compound where R=$N(CH_3)_2$ was heated with a smaller amount of phosphorus oxychloride (1:1.5), and at a temperature of 70-80°.

Reaction of 2-Dimethylamino-6-imino-1,9-dimethylpurine Hydrochloride [IV, R=$N(CH_3)_2$] with Alkali Solution. The imine hydrochloride (IV, R=$N(CH_3)_2$) (0.35 g) was boiled with 7 ml of 0.5 N sodium hydroxide solution. The solution formed was cooled and neutralized, and the precipitate formed was separated. There was obtained 0.19 g of 2-oxo-2,3-dihydro-6-methylamino-9-methylpurine, mp > 350°. Found, %: C 47.04; H 5.16; N 39.82. $C_7H_9N_5O$. Calculated, %: C 46.95; H 5.03; N 39.12.

2-Dimethylamino-6-methylamino-9-methylpurine [V, R=$N(CH_3)_2$]. Compound III (R=$N(CH_3)_2$) (1 g) [7] was boiled with 10 ml of 25% aqueous methylamine solution plus 5 ml of alcohol for 2 h; the mixture was cooled, the precipitate was separated, and it was recrystallized.

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