1. **Nitration.**[10]—From a mixture of X (1.48 g., 0.01 mole), in acetic anhydride (125 ml.), and nitrating solution (1.3 ml., 0.013 mole) there was obtained: (a) an amorphous brown solid (0.30 g.), insoluble in ether, acetone, ethyl acetate, chloroform and acetic acid. After alcohol extraction (26% loss of weight) the material had the composition: C, 22.9; H, 1.99; N, 3.13; ash, 4.7; (b) a chloroform-soluble oil (1.12 g.) which gave, upon oxidation with hydrogen peroxide in acetic acid, only the disulfone of X.

2. **Chlorination.**[3]—From X (3.2 g., 0.22 mole) in carbon tetrachloride (25 ml.) and chlorine (1.6 g., 0.22 mole) at 0° there was obtained: (a) a chloroform-insoluble black tar, and (b) a chloroform-soluble oil, which, after distillation (b. p. 70(2.2) 86° (0.2 mm.)) rapidly decomposed to black tar and hydrogen chloride.

3. **Bromination.**[11]—From X (1.40 g., 0.01 mole) in acetic anhydride (130 ml.), and bromine (1.6 g., 0.01 mole) there was obtained: (a) A brown amorphous solid (0.36 g., m.p. 40–70°) which was partially soluble in hot acetone and chloroform and insoluble in hot ethanol. *Anal.* Calcd. for $(C_6H_3S_2Br)_x$: C, 32.29; H, 3.16. Found: C, 43.72; H, 4.13. The solid contained bromine but decomposed upon attempted recrystallization. (b) An unidentified ether-soluble oil (0.95 g.) which gave no solid on oxidation with hydrogen peroxide in acetic acid at 70°.

4. **Acylation.**[12]—From X (1.5 g., 0.011 mole), acetic anhydride (1.4 g., 0.014 mole) and 85% phosphoric acid (two drops) at 100°, there was obtained: (a) unchanged X (0.6 g., 40%), (b) an orange oil (0.22 g., $n^{25}D$ 1.5850) which distilled at 0.35 mm. This oil showed carbonyl absorption in the infrared spectrum, although reaction of this product with 2,4-dinitrophenylhydrazine gave a black precipitate; attempts to purify this material by recrystallization were unsuccessful.

5. **Mercuration.**[13]—From X (1.00 g., 0.070 mole) and a solution prepared from mercuric chloride (58 g., 0.015 mole), 33% sodium acetate solution (12 g.), and 95% alcohol (54 g.) there was obtained 1.35 g. of solid, m.p. 100–130°, which was insoluble in hot benzene, ether, petroleum ether and nitromethane. A sample was digested with hot ethanol and filtered while hot. The solid (m.p. 85–100°) that crystallized from the ethanol had the composition: C, 13.15; H, 2.06; Cl, 10.95; S, 11.33.

Different products were obtained when the reaction was carried out in the absence of sodium acetate; however, the resulting amorphous solids were not obtained pure. The percentage composition of two products (m.p. >285° and 100–200° dec., respectively) were: C, 7.71; H, 1.09; Cl, 11.09; S, 8.47; and C, 20.89; H, 2.51; Cl, 8.41; S, 16.93.

(10) W. E. Parham and V. J. Traynelis, THIS JOURNAL, **77**, 68 (1955).

(11) W. E. Parham, I. Nicholson and V. J. Traynelis, *ibid.*, **78**, 850 (1956).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XX. The Preparation and Reactions of Some Methylthiopurines[1]

BY C. WAYNE NOELL AND ROLAND K. ROBINS

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A study has been made of the reaction of chlorine and various methylthiopurines in absolute and aqueous methanol. In aqueous methanol the alkyl sulfone was isolated. In absolute methanol, replacement of the methylthio group by chlorine was observed in positions 6 and 8 of the purine nucleus. Under these conditions the methylthio group in position 2 was converted to the expected methyl sulfone. A possible general mechanism for these reactions is discussed. A preliminary study of the nucleophilic displacement of the methylsulfonyl group in the purine series has been made, and a new synthesis for 2,6,8-purinetrithiol is reported.

The anti-tumor activity reported for 6-methylthiopurine[2] stimulated our interest in the preparation of additional methylthiopurine derivatives. The preparation of 8-methylthiopurine[3] and 2-methylthiopurine[4] have previously been reported. The syntheses of 2,6-bis-methylthiopurine[5] and 6,8-bis-methylthiopurine[6] have also recently been described. The remaining compounds, 2,8-bis-methylthiopurine (II) and 2,6,8-tris-methylthiopurine (VII), were prepared for this study.

When 4,5-diamino-2-pyrimidinethiol[7] was treated with carbon disulfide in pyridine, a good yield of 2,8-purinedithiol (I) was obtained. This preparation proved superior to the cyclization of 4,5-diamino-2-pyrimidinethiol by thiourea fusion. Treatment of 2,8-purinedithiol (I) with 2 moles of methyl iodide in the presence of aqueous potassium hydroxide readily provided the desired 2,8-bis-methylthiopurine, (II). The preparation of 2,6,8-tris-methylthiopurine (VII) was accomplished by methylation of 2-methylthio-6,8-purinedithiol[8] and also by reaction of 6-chloro-2,8-bis-methylthiopurine (VI) with methanethiol in basic solution.

The compound 6-chloro-2,8-bis-methylthiopurine (VI) was prepared readily by chlorination of 6-hydroxy-2,8-bis-methylthiopurine (V) with phosphorus oxychloride. Compound V was obtained from methylation of 6-hydroxy-2,8-purinedithiol (III)[9] which was conveniently obtained by thiourea fusion of 4,5-diamino-6-hydroxy-2-pyrimidinethiol.[10]

The need for large quantities of 2,6,8-tris-methylthiopurine (VII) for this study led to the investigation of a more convenient method of synthesis from 2,6,8-purinetrithiol (IV). Fischer[11] records the preparation of IV from 2,6,8-trichloropurine

(1) Supported by Research Contract SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Institutes of Health, U. S. Public Health Service.

(2) G. S. Tarnowsky and C. C. Stock, *Proc. Am. Soc. Cancer Res.*, **51** (1955).

(3) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).

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(5) K. L. Dille and B. E. Christensen, THIS JOURNAL, **76**, 5087 (1954).

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(10) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

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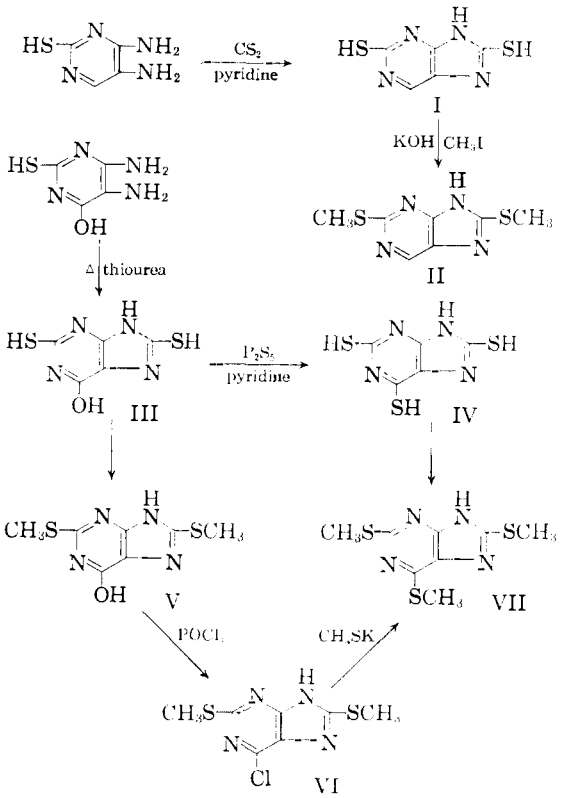


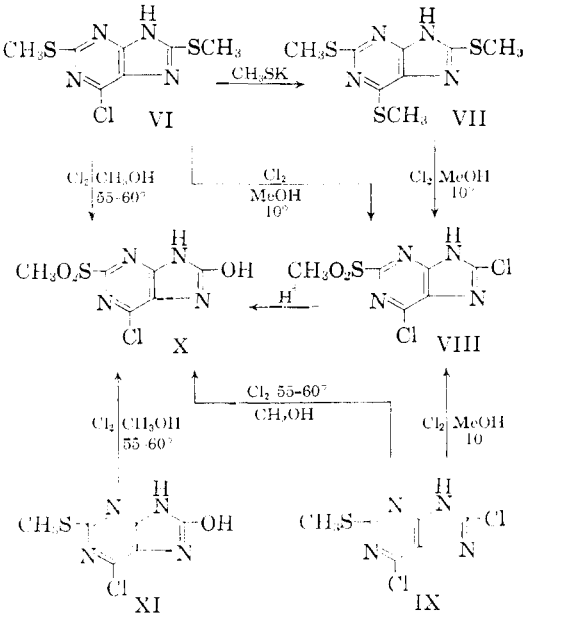
REACTION SCHEME I

and potassium hydrosulfide. A much more convenient synthesis of 2,6,8-purinetrithiol (IV) was accomplished on a large scale and in good yield by treatment of 6-hydroxy-2,8-purinedithiol (III) with phosphorus pentasulfide in pyridine. The preparation of 2,6,8-tris-methylthiopurine (VII) then was accomplished by methylation of 2,6,8-purinetrithiol (IV) with methyl iodide in the presence of aqueous potassium hydroxide.

A new synthesis of 2,6-bis-methylthiopurine[5] has been accomplished from 6-chloro-2-methylthiopurine[8] and methanethiol in the presence of sodium hydroxide. 2,6-Bis-methylthiopurine (XII) was also prepared readily by methylation of 2,6-purinedithiol.[12]

Although purine derivatives containing a methylsulfonyl group in positions 2 and 8 already have been described,[13,14] no purine derivative with a methylsulfonyl group in position 6 has previously been reported. It seemed of interest to prepare 6-methylsulfonylpurine (XXX) since it is conceivable that the anti-tumor activity of 6-methylthiopurine might be due to some metabolic oxidation product. The preparation of 6-methylsulfonylpurine has now been accomplished successfully by treatment of 6-methylthiopurine[15] with chlorine in an aqueous methanol solution. A most interesting observation in the oxidation studies of 6-methylthiopurine was that 6-methylthiopurine in anhydrous methanol, treated with chlorine, with careful cooling yielded 6-chloropurine in good yield. The replacement of the methylthio group by a chlorine atom has not been reported previously in the purine series. It therefore seemed of some interest to study the possibility of utilizing this method for the preparation of important new chloropurine derivatives.

When 2,6,8-tris-methylthiopurine (VII) was treated with chlorine in commercial anhydrous methanol, and the temperature of the reaction mixture was maintained between 5 and 10°, the product isolated was 6,8-dichloro-2-methylsulfonylpurine (VIII) (see reaction scheme II). The structure of



REACTION SCHEME II

this compound was established by conversion of 6,8-dichloro-2-methylthiopurine (IX)[8] under similar reaction conditions to 6,8-dichloro-2-methylsulfonylpurine (VIII) which was identical to that prepared from 2,6,8-tris-methylthiopurine (VII). In a similar manner 6-chloro-2,8-bis-methylthiopurine (VI) and 8-chloro-2,6-bis-methylthiopurine (XVIII) with chlorine in methanol at 10° provided the same product, VIII (see reaction scheme III). The ready availability of 6,8-dichloro-2-methylsulfonylpurine (VIII) in good yield makes this compound a desirable starting point for the preparation of new purine derivatives. Since the methylsulfonyl group is known to be susceptible to nucleophilic attack, this compound might well rival the less readily available 2,6,8-trichloropurine[16,17] as a synthetic intermediate.

When 6-chloro-2,8-bis-methylthiopurine (VI) was treated with chlorine in methanol without cooling, the reaction temperature rose to 55–60°, and the product isolated was 6-chloro-8-hydroxy-2-methylsulfonylpurine (X) (reaction scheme II). The structure of X was established since 6-chloro-8-hydroxy-2-methylthiopurine (XI),[8] when treated with chlorine in methanol under similar conditions, yielded 6-chloro-8-hydroxy-2-methylsulfonylpurine (X). In addition, acid hydrolysis of 6,8-dichloro-

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(13) K. M. J. Andrews, N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2495 (1949).

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(15) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 411 (1952).

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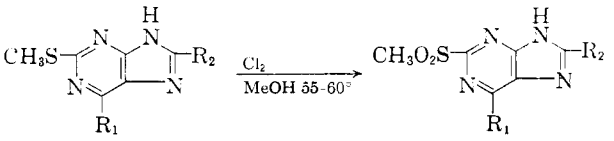
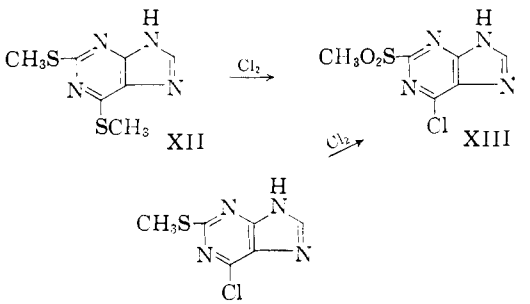
TABLE I



Formula	Product R1	Product R2	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Meth. of prepn.	Yield, %	Purine reactant R1	Purine reactant R2	Formula
	H	H	226	36.4	36.7	3.0	2.8	28.3	28.7	1	88	H	H	
XIII	Cl	H	260	31.0	30.9	2.2	2.3	24.2	24.0	1	89	Cl	H	
XIII	Cl	H	260							1	82	SCH_3	H	XII
	OH	H	>300	33.7	33.9	2.8	2.5	26.3	26.3	1	51	OH	H	
	H	OH	240–300 d.	33.7	33.6	2.8	3.0	26.2	26.6	1	75	H	OH	
	H	OH	240–300 d.							1	77	H	Cl	
X	Cl	OH	308	28.9	28.9	2.0	2.2	22.5	22.3	1	73	Cl	Cl	IX
X	Cl	OH	308							1	20	Cl	SCH_3	VI
X	Cl	OH	308							1		Cl	OH	XI
XV	SO_2CH_3	OH	>300	28.7	28.3	2.7	2.8	19.2	18.7	1	77	SCH_3	OH	XVI
XV	SO_2CH_3	OH	>300							1	47	SCH_3	SCH_3	VII

2-methylsulfonylpurine (VIII) gave X (reaction scheme II). It has been shown[6,8,16] previously that acid hydrolysis of a 6,8-dichloropurine results in preferential hydrolysis of the 8-chloro group. It would thus appear that in the preparation of 6-chloro-8-hydroxy-2-methylsulfonylpurine (X) from 6-chloro-2,8-bis-methylthiopurine (VI) the 6,8-dichloro-2-methylsulfonylpurine (VIII) is a probable intermediate which is hydrolyzed in the acidic media at the higher temperature. Additional evidence for this assumption is the fact that VIII treated in methanol with chlorine at 55° gave a good yield of X.

Treatment of 6,8-bis-methylthiopurine[6] with chlorine in methanol at 55–60° gave 6-chloro-8-hydroxypurine[6] as the only isolated product. Under similar reaction conditions 2,6-bis-methylthiopurine (XII) gave 6-chloro-2-methylsulfonylpurine (XIII).



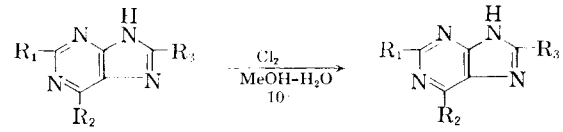
The structure assigned XIII was established by the fact that 6-chloro-2-methylthiopurine[8] under the same reaction conditions provided the same product. It would thus appear that the oxidation reaction carried out at 55–60° in general results in the oxidation of the methylthio group in position 2 to give a methylsulfonyl group; the replacement of the methylthio group in position 6 by a chlorine atom; and the conversion of the methylthio group 8 to give a hydroxyl group. To confirm these preliminary observations 2-methylthiopurine[4] was treated under these reaction conditions to give 2-methylsulfonylpurine. 6-Hydroxy-2-methylthiopurine[8] was similarly converted to 6-hydroxy-2-methylsulfonylpurine. 8-Chloro-2-methylthiopurine[8] and chlorine in methanol at 55° gave 8-hydroxy-2-methylsulfonylpurine which was prepared under similar conditions from 8-hydroxy-2-methylthiopurine.[8] However, when 2,6,8-tris-methylthiopurine (VII) was treated with chlorine gas at 55–60° in methanol, 8-hydroxy-2,6-bis-methylsulfonylpurine (XV) was isolated (reaction scheme IV). If the initial temperature was maintained below 10° and then finally raised to 55° toward the end of the reaction, the expected product, 6-chloro-8-hydroxy-2-methylsulfonylpurine (X), was isolated in good yield. The structure of 8-hydroxy-2,6-bis-methylsulfonylpurine (XV) was confirmed by the synthesis of XV from 8-hydroxy-2,6-bis-methylthiopurine (XVI) (see reaction scheme III). The reaction of 6,8-dihydroxy-2-purinethiol (XIV)[8] and phosphorus pentasulfide in pyridine gave a good yield of 8-hydroxy-2,6-purinedithiol (XVII). Methylation of XVII gave 8-hydroxy-2,6-bis-methylthiopurine (XVI); XVI was also prepared from 6-chloro-8-hydroxy-2-methylthiopurine[8] (XI) and methanethiol. Reaction of 8-hydroxy-2,6-bis-methylthiopurine (XVI) with chlorine gas in methanol at 55° gave 8-hydroxy-2,6-bis-methylsulfonylpurine (XV).

It would thus appear that the presence of the 8-hydroxy group increased the electron density at position 6 so that the usual replacement of the 6-methylthio group by chlorine does not occur. These and additional reactions of the various methylthiopurines with chlorine in methanol at 55–60° are summarized in Table I.

A further study of the reaction of methylthiopurines treated with chlorine in aqueous methanol solution cooled below 10° revealed that in every case studied the methylthio group was smoothly converted to the corresponding sulfone. Thus, 2,6,8-tris-methylsulfonylpurine (XIX) was prepared from 2,6,8-tris-methylthiopurine (VII). 2,6-Bis-methylsulfonylpurine (XXIII) was prepared similarly from 2,6-bis-methylthiopurine (XII), and 8-chloro-2,6-bis-methylsulfonylpurine (XXVIII) was readily prepared from 8-chloro-2,6-bis-methylthiopurine (XVIII). Other methylsulfonylpurines prepared by this procedure are listed in Table II.

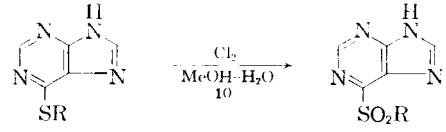
Reaction of a number of 6-alkylthiopurines with chlorine in aqueous methanol similarly was ex-

TABLE II



Formula	Product R1	Product R2	Product R3	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Meth. of prepn.	Recrystn. solvent	Yield, %	Purine reactant R1	Purine reactant R2	Purine reactant R3	Formula
XXIII	SO_2CH_3	SO_2CH_3	II	258	30.4	30.4	2.9	3.5	20.3	20.2	3	Water	97	SCH_3	SCH_3	H	XII
	H	Cl	SO_2CH_3	180–230 d.	31.0	30.6	2.2	2.1	24.2	24.6	4	Benzene–methanol	86	H	Cl	SCH_3	
	SO_2CH_3	OH	SO_2CH_3	288–290 d.	28.7	29.0	2.7	2.8	19.2		4	Water	53	SCH_3	OH	SCH_3	V
XXI	SO_2CH_3	Cl	SO_2CH_3	230	27.0	27.2	2.3	2.7	18.1	18.4	4	Benzene–methanol	88	SCH_3	Cl	SCH_3	VI
XIX	SO_2CH_3	SO_2CH_3	SO_2CH_3	153					15.9	15.6	4	Benzene–methanol	51	SCH_3	SCH_3	SCH_3	VII
XXVIII	SO_2CH_3	SO_2CH_3	Cl	240	27.0	27.4	2.3	2.4	18.1	17.9	4	Methanol	93	SCH_3	SCH_3	Cl	XVIII

TABLE III



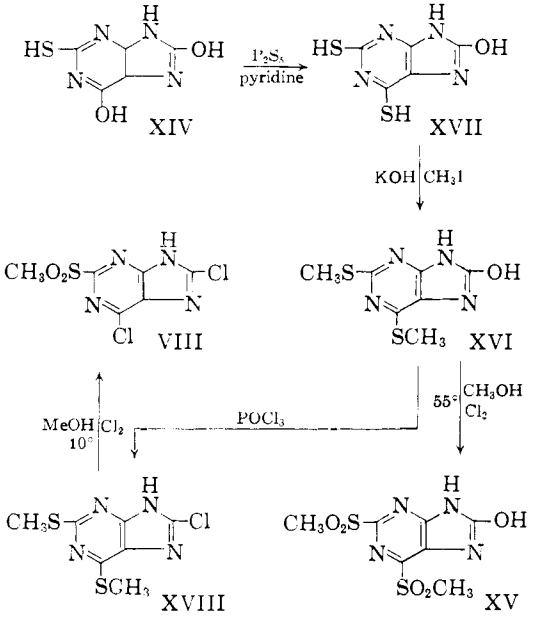
Sulfone R	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Meth. of prepn.	Recrystn. solvent	Yield, %
CH_3	208	36.4	36.3	3.0	3.1	28.3	28.6	3	Methanol	60
C_2H_5	186	39.7	40.2	3.8	4.0	26.4	26.2	3	Methanol	68
$(CH_2)_2CH_3$	175	42.5	42.8	4.4	4.3	24.8		3	Methanol	58
$(CH_2)_3CH_3$	159	45.1	45.5	5.0	4.9	23.3	23.0	3	Benzene–methanol	75

TABLE IV

Formula	Product R1	Product R2	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Meth. of prepn.	Recrystn. solvent	Yield, %	Purine reactant R1	Purine reactant R2	Formula
VIII	Cl	Cl	210	26.9	27.2	1.5	1.8	21.0	20.9	2	Benzene–methanol	70	Cl	Cl	IX
VIII	Cl	Cl	210							2		53	Cl	SCH_3	VI
VIII	Cl	Cl	210							2		41	SCH_3	SCH_3	VII

tended to yield a number of 6-alkylsulfones which are listed in Table III. The preparation of the requisite 6-alkylthiopurines[18] previously has been described.

2,6,8-Tris-methylsulfonylpurine (XIX) is a rather unstable compound which showed evidence of decomposition within 24 hr. after its preparation. A limited investigation of the ease of replacement of the methylsulfonyl group by nucleophilic reagents

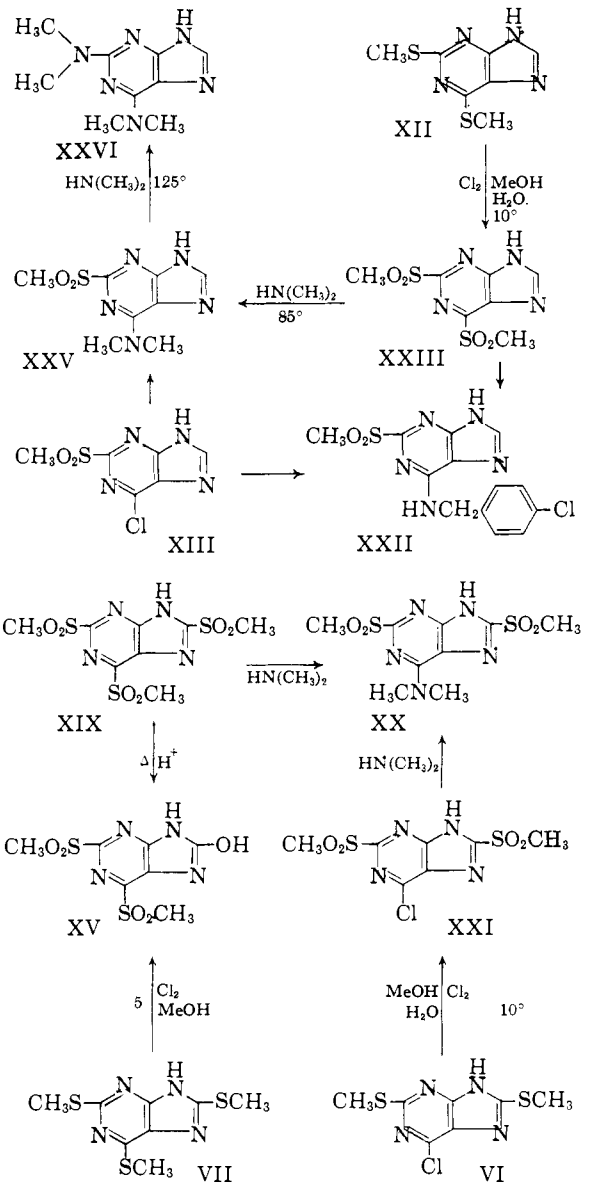


REACTION SCHEME III

was undertaken. When 2,6-bis-methylsulfonylpurine (XXIII) was treated with aqueous dimethylamine on the steam-bath, 6-dimethylamino-2-methylsulfonylpurine (XXV) resulted. The structure of XXV was established since the same compound was obtained from 6-chloro-2-methylsulfonylpurine (XIII) under similar conditions. A higher reaction temperature converted XXIII to 2,6-bis-dimethylaminopurine (XXVI) previously synthesized by Robins[19] and Christensen.

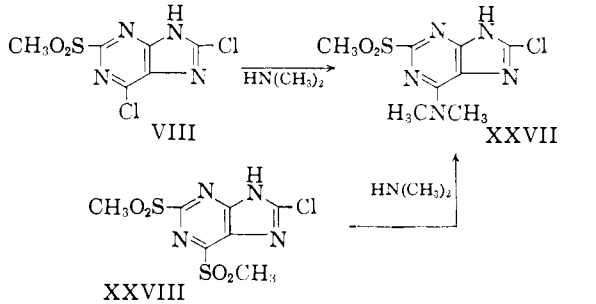
2,6,8-Tris-methylsulfonylpurine (XIX), when treated with aqueous dimethylamine on the steam-bath, gave 6-dimethylamino-2,8-bis-methylsulfonylpurine (XX) in good yield. The structure of XX was established since the same compound was prepared from 6-chloro-2,8-bis-methylsulfonylpurine (XXI) under similar conditions. Treatment of 2,6,8-tris-methylsulfonylpurine (XIX) with 1 *N* hydrochloric acid gave 8-hydroxy-2,6-bis-methylsulfonylpurine (XV) (reaction scheme IV). It was established that hydrolysis had taken place at position 8 since XV had been prepared previously from 8-hydroxy-2,6-bis-methylthiopurine (XVI) (see reaction scheme III).

Similarly, 6,8-dichloro-2-methylsulfonylpurine (VIII) and 8-chloro-2,6-bis-methylsulfonylpurine (XXVIII), when treated individually with aqueous dimethylamine on the steam-bath, gave the same



REACTION SCHEME IV

product, 8-chloro-6-dimethylamino-2-methylsulfonylpurine (XXVII). It would thus appear that a methylsulfonyl group in the purine series can be



as readily replaced as a chlorine atom by the usual nucleophilic reagents. Indeed, from preliminary reactions it would appear that the ease of replacement and order of replacement is the same as for the similarly substituted chloropurines.

(18) H. C. Koppel, D. E. O'Brien and R. K. Robins, *J. Org. Chem.*, **24**, 259 (1959).

(19) R. K. Robins and B. E. Christensen, THIS JOURNAL, **74**, 3624 (1952).

TABLE V

Formula	Product R1	Product R2	Product R5	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Meth. of prepn.	Recrystn. solvent	Yield, %	Purine reactant R1	Purine reactant R2	Purine reactant R5	Formula
XXV	SO_2CH_3	$N(CH_3)_2$	H	>300	39.8	40.1	4.6	4.3	29.1	29.2	A	D.M.F.	52	SO_2CH_3	Cl	H	XIII
XXV	SO_2CH_3	$N(CH_3)_2$	H	>300							A	D.M.F.	90	SO_2CH_3	SO_2CH_3	H	XXIII
XXII	SO_2CH_3	$NHCH_2C_6H_4Cl$	H	292	46.2	46.3	3.6	3.3	20.7	20.5	A	D.M.F. + methanol	88	SO_2CH_3	SO_2CH_3	H	XXIII
	SO_2CH_3	$N(CH_3)_2$	OH						27.3	27.3	A	Ethanol	79	SO_2CH_3	Cl	OH	X
	SO_2CH_3	$N(CH_3)_2$	OH								A	Ethanol	82	SO_2CH_3	SO_2CH_3	OH	XV
XXVII	SO_2CH_3	$N(CH_3)_2$	Cl	254	34.8		3.6	3.6	25.3	25.8	B	Ethanol	84	SO_2CH_3	Cl	Cl	VIII
XXVII	SO_2CH_3	$N(CH_3)_2$	Cl	254							B	Ethanol	87	SO_2CH_3	SO_2CH_3	Cl	XXVIII
XX	SO_2CH_3	$N(CH_3)_2$	SO_2CH_3	253	33.8	34.1	4.1	4.0	21.9	21.7	B	D.M.F. + ethanol		SO_2CH_3	Cl	SO_2CH_3	XXI
XX	SO_2CH_3	$N(CH_3)_2$	SO_2CH_3	253							B	D.M.F. + ethanol		SO_2CH_3	SO_2CH_3	SO_2CH_3	XIX
XXVI	$N(CH_3)_2$	$N(CH_3)_2$	H	256	52.5	52.2	6.8	6.8	40.7	40.8	C	D.M.F. + water	19.5	SO_2CH_3	$N(CH_3)_2$	H	XXV

TABLE VI

Formula	Product R1	Yield, %	Purine reactant R1	Purine reactant R2	Formula
X	Cl	52	Cl	Cl	VIII
	$N(CH_3)_2$	60	$N(CH_3)_2$	Cl	XXVII
XV	SO_2CH_3	72	SO_2CH_3	SO_2CH_3	XIX
	OH	63	OH	SO_2CH_3	

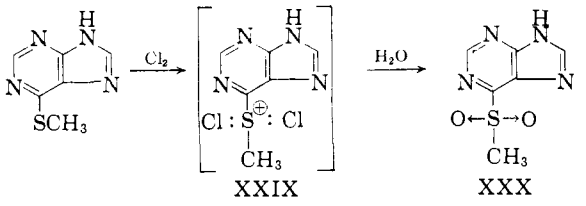
With regard to acid hydrolysis the methylsulfonyl group in position 8 is the most readily replaced. This, once again, is in accord with the expected behavior from a comparison with 2,6,8-trichloropurine under similar conditions.[16] The ready availability of the various methylsulfonylpurines described makes these compounds useful intermediates for the preparation of new purine derivatives.

In the study of the reactions of the methylthiopurines with chlorine, several interesting observations were made which shed some light on a possible mechanism for the general reactions. The replacement of the methylthio group to give a chloropurine could conceivably proceed *via* the methylsulfonylpurine. To test this hypothesis 6-methylsulfonylpurine (XXX) was treated with chlorine in anhydrous methanol under the conditions known to produce 6-chloropurine. No 6-chloropurine was isolated, and the starting material was recovered unchanged.

The reaction of 2,6,8-tris-methylthiopurine (VII) with chlorine in methanol at 5–10° gave an intermediate, polyhalogenated, low melting, unstable solid which released chlorine readily. When this product was isolated and boiled in benzene in the presence of a small amount of methanol, it was converted smoothly to 6,8-dichloro-2-methylsulfonylpurine (VIII) which crystallized from the benzene solution. When this intermediate was not isolated, and the solution finally was warmed on the steam-bath, 6-chloro-8-hydroxy-2-methylsulfonylpurine (X) was obtained in good yield. If the reaction of 2,6,8-tris-methylthiopurine (VII) and chlorine was carried out in methanol at 55–60°, initially 8-hydroxy-2,6-bis-methylsulfonylpurine (XV) was the isolated product. Thus, it is quite evident that XV cannot be an intermediate in the preparation of X. Similarly, 2,6-bis-methylsulfonylpurine was shown not to be an intermediate in the preparation of 6-chloro-2-methylsulfonylpurine (XIII) from chlorine and 2,6-bis-methylthiopurine (XII).

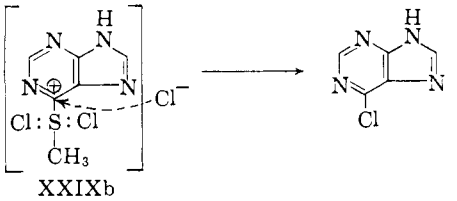
It would appear that these reactions could best be explained by assuming the existence of some intermediate which either could be replaced by a halide ion or changed to a sulfone. Such an intermediate is postulated by formula XXIX which is formed by nucleophilic attack of two positive halogen ions on the sulfur atom. Such an intermediate places a definite positive charge on the sulfur atom. In the presence of water the hydroxyl ion could replace the chlorine to give the sulfone XXX.

In considering formula XXIX the positively charged sulfur atom would also leave the adjacent



XXIX XXX

carbon at position 6 somewhat electron deficient as shown in XXIXb. In the absence of water the



XXIXb

predominant reaction is an attack by a chloride ion at position 6 to give rise to 6-chloropurine.

This postulation gains considerable support by the fact that under the conditions studied replacement of the methylthio group by chlorine takes place most readily at position 8 followed by position 6. At position 2 the predominant reaction is sulfone formation. This is exactly as would be predicted by nucleophilic displacement by a halide ion in the acidic[6,20] reaction mixture of methanol and chlorine. It is interesting to note that in one reaction, where an attempt was made to prepare a rather large quantity of 6-chloropurine from 6-methylthiopurine by this method, an extended reaction period was employed, and a substantial amount of 6-methoxypurine was isolated.

It would seem that in the absence of an excess of chloride ion (the chlorine was added to the reaction mixture at the same rate for a large run as for a small one) the methoxide ion effected nucleophilic displacement instead to yield 6-methoxypurine.

Table VII lists the ultraviolet absorption data for some of the methylthiopurines and the corresponding alkylsulfonylpurines. Inspection of this table reveals that in general the oxidation of a methylthio group to a methyl sulfone involves a hypsochromic shift of from 10 to 40 mμ depending on the number of methylthio groups involved. This hypsochromic shift usually is accompanied by a definite hypochromic effect.

Experimental[21]

Preparation of 2,6-Bis-methylthiopurine (XII).[5] Method A.—Eighteen grams of 6-chloro-2-methylthiopurine[8] was dissolved in 250 ml. of cold dilute potassium hydroxide solution. To this solution was added 40 g. of methanethiol and approximately 50 g. of chopped ice. This mixture was allowed to stand at room temperature and then placed on the steam-bath for a period of 2 hr., treated with Norit, and filtered. The filtrate was acidified while hot with glacial acetic acid. The precipitate that formed was filtered from the hot solution, washed with water, and dried at 100° to yield 11.5 g. of a colorless product. Crystallization from absolute methanol yielded an analytical sample, m.p. 261°. The previously recorded melting point is 253–254°.

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.6; H, 3.7; N, 26.4. Found: C, 39.4; H, 3.5; N, 26.4.

Method B.—Twenty grams of 2,6-purinedithiol[12] was placed in 500 ml. of warm water, and just enough solid potassium hydroxide was added to dissolve all solid material. The solution was then cooled to 25°, and 26.9 g. of methyl iodide was added. The mixture was stirred vigorously for 1 hr. at room temperature. The temperature of the solution then was raised to 70°, and the solution was treated with Norit and filtered. The filtrate was acidified with glacial acetic acid, and the precipitate was filtered from the warm solution and washed with water. It was then recrystallized from methanol to give 11 g. of product, m.p. 258–260°. The ultraviolet absorption spectrum agreed with that of the product obtained by method A. A mixed melting point with the product from method A showed no depression.

2,8-Purinedithiol (I).—Forty grams of 4,5-diamino-2-pyrimidinethiol[4] was covered with 500 ml. of pyridine and 60 ml. of carbon disulfide. Five grams of solid sodium hydroxide then was added. This mixture was refluxed for 5 hr., allowed to cool, and then diluted with 500 ml. of 2 *N* hydrochloric acid solution. The precipitate that appeared was filtered and thoroughly washed with water. The yellow needles then were dissolved in 500 ml. of dilute ammonium hydroxide, and the solution was treated with Norit, filtered, and finally acidified with concentrated hydrochloric acid. The product was filtered from the hot solution and dried at 120° to yield 35 g. of pure product.

Anal. Calcd. for $C_5H_4N_4S_2$: C, 32.6; H, 2.2; N, 30.4. Found: C, 32.7; H, 2.1; N, 30.2.

2,8-Bis-methylthiopurine (II).—Twenty grams of 2,8-purinedithiol (I) was placed in 300 ml. of water, and just enough potassium hydroxide was added to dissolve all solid material. The solution was then cooled to 20°. Twenty-eight grams of methyl iodide was added, and the mixture then was stirred vigorously for 1 hr. at room temperature. The solution was acidified with glacial acetic acid, and the precipitate which formed was filtered while hot, washed with water, and once more reprecipitated to yield 12 g. of pale-yellow product. An analytical sample was obtained by recrystallization from a methanol–water mixture. The product gradually began decomposing near 225°, with final decomposition at > 300°. The sample was dried at 130° for 10 hr.

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.6; H, 3.8; N, 26.4. Found: C, 39.0; H, 3.4; N, 26.4.

6-Hydroxy-2,8-purinedithiol (III).—4,5-Diamino-6-hydroxy-2-pyrimidinethiol[10] (200 g.) was powdered and thoroughly mixed with 400 g. of thiourea. This mixture was heated directly in a stainless steel beaker on a hot-plate. At first the melt was rather lumpy and difficult to stir, but upon further heating the mixture became liquid, and the evolution of ammonia was evident. The melt was heated at 180–200° for approximately 30 min. at which time the mixture became quite viscous and difficult to stir. Three liters of boiling water was added directly to the cooled solid mass. Potassium hydroxide was added to the hot solution to dissolve all solid material. The solution was treated with Norit and filtered. The hot filtrate was acidified with concentrated hydrochloric acid. One more reprecipitation from dilute base with concentrated hydrochloric acid yielded 205 g. of product, m.p. > 300°.

Anal. Calcd. for $C_5H_4N_4OS_2$: C, 27.4; H, 2.3; N, 25.6. Found: C, 27.2; H, 2.7; N, 26.0.

6-Hydroxy-2,8-bis-methylthiopurine (V).—6-Hydroxy-2,8-purinedithiol (III) (200 g.) was placed in 2800 ml. of warm water, and potassium hydroxide was added to effect solution. The solution was cooled to 20° and mechanically stirred. Methyl iodide (284 g.) was added. Vigorous stirring of the solution was continued for 1 hr. and followed by acidification with glacial acetic acid. The precipitate was filtered, washed with water, and reprecipitated from a hot basic solution. It was again filtered, thoroughly washed with water, and dried at 110° to yield 160 g. A sample was obtained for analysis by a similar reprecipitation to yield a product, m.p. 301°.

Anal. Calcd. for $C_7H_8N_4OS_2$: C, 36.8; H, 3.5; N, 23.5. Found: C, 36.5; H, 3.8; N, 23.8.

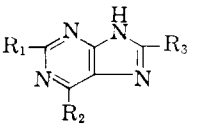
6-Chloro-2,8-bis-methylthiopurine (VI).—Eighty grams of 6-hydroxy-2,8-bis-methylthiopurine (V) was covered with 1 l. of phosphorus oxychloride. This mixture was refluxed for 4 hr. until all the solid had gone into solution. The excess phosphorus oxychloride was removed by vacuum distillation on a steam-bath. The residue then was poured over chopped ice, with manual stirring. The aqueous mixture

(20) E. Fischer, *Ber.*, **30**, 2220 (1897).

(21) All melting points are uncorrected and were taken on a Fisher–Johns melting point apparatus, unless otherwise stated.

TABLE VII

ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN ALKYLSULFONYLPURINES



R_1	R_2	R_3	pH 1 λmax, mμ	pH 1 ε	pH 11 λmax, mμ	pH 11 ε	Formula
SCH_3	H	SCH_3	223	13,100	232	18,000	II
			275	17,400	252	16,300	
			336	19,100	333	23,100	
SO_2CH_3	H	OH	281	15,800	293	14,300	
SO_2CH_3	Cl	OH	284	14,200	231	20,700	X
					302	12,900	
SO_2CH_3	Cl	Cl	276	12,300	299	18,700	VIII
					285	10,400	
SCH_3	SCH_3	SCH_3	260	23,200	252	31,000	VII
			333	19,900	330	21,400	
SCH_3	SCH_3	Cl	226	16,800	244	24,700	XVIII
			260	21,900	315	14,300	
			315	14,300			
SCH_3	SCH_3	OH	225	15,000	241	21,700	XVI
			256	16,400	317	14,800	
			315	12,300			
SO_2CH_3	SO_2CH_3	OH	299	16,000	233	19,800	XV
					320	16,000	
SO_2CH_3	$N(CH_3)_2$	OH	231	18,000	236	19,000	
			285	15,400	293	14,100	
SO_2CH_3	Cl	*H*	270	10,200	228	23,300	
					279	8,100	XIII
SCH_3	SCH_3	H	262	17,600	245	22,900	XII
			316	9,500	312	11,000	
SO_2CH_3	OH	H	254	8,600	223	10,700	
					265	7,900	
SO_2CH_3	SO_2CH_3	H	282	9,100	231	25,400	XXIII
					287	7,500	
SO_2CH_3	$N(CH_3)_2$	H	279	12,800	232	15,200	XXV
					282	12,000	
SO_2CH_3	$N(CH_3)_2$	Cl	224	26,000	233	20,700	XXVII
			279	17,600	284	16,800	
SH	OH	SH	245	10,000	267	16,400	III
			317	27,600	295	20,000	
SCH_3	OH	SCH_3	282	22,800	230	22,300	V
					291	18,200	
SH	SH	SH	264	19,900	278	30,200	IV
			309	32,600	376	17,900	
			386	26,400			
SCH_3	Cl	SCH_3	231	17,000	252	22,700	VI
			253	15,800	322	17,000	
			322	16,300			
SCH_3	SH	SCH_3	265	22,000	224	16,600	
			358	22,700	263	23,200	
					338	23,200	
SCH_3	$N(CH_3)_2$	SCH_3	259	21,700	242	30,900	
			311	27,500	306	22,700	
SCH_3	$HNCH_2C_6H_4Cl$-*p*	SCH_3	256	22,400	233	30,600	
			314	30,200	304	24,300	
SH	SH	OH	300	22,400	243	28,400	XVII
			359	3,000	275	16,400	
SO_2CH_3	OH	SO_2CH_3	268	20,700	231	14,900	
					292	12,800	
SO_2CH_3	Cl	SO_2CH_3	278	9,300	284	11,500	XXI
SO_2CH_3	SO_2CH_3	Cl	288	13,200	286	11,500	XXVIII
H	SO_2CH_3	OH	265	17,800	275	16,000	
H	SO_2CH_3	H	280	7,900	285	7,700	XXX

SO_2CH_3	H	H	267	8,700	226	29,300	
					275	8,100	
H	Cl	SO_2CH_3	273	15,600	280	19,800	
SO_2CH_3	$N(CH_3)_2$	SO_2CH_3	228	28,400	229	21,400	XX
			311	13,000	309	15,300	
$N(CH_3)_2$	$N(CH_3)_2$	H	241	15,500	244	24,700	XXVI
			263	20,600	294	10,100	
SO_2CH_3	$HNCH_2C_6H_5Cl$-*p*	H	272	16,300	275	12,200	XXII
H	$SO_2C_4H_5$	H	280	8,300	283	7,200	
H	$SO_2CH_2CH(CH_3)_2$	H	285	9,400	291	9,400	
H	$SO_2(CH_2)_2CH_3$	H	285	8,800	285	7,900	
H	$SO_2(CH_2)_3CH_3$	H	281	9,600	283	8,200	
SH	H	SH	299	12,500	235	4,300	
			362	1,800	268	5,500	
					342	4,300	I

was made strongly basic with a concentrated potassium hydroxide solution and was kept cold by additional ice. The basic solution was adjusted to *p*H 5 with glacial acetic acid and allowed to stand 20 min. The precipitate was filtered and washed with water. It was dissolved in 2 l. of boiling dilute ammonium hydroxide, treated with Norit, and filtered. The hot solution was adjusted to *p*H 7 with dilute acetic acid. The precipitate that formed was filtered, washed with water, and dried at 110° to yield 84 g. of product, m.p. 253–256°. Recrystallization from ethanol raised the melting point to 258°.

Anal. Calcd. for $C_7H_7N_4ClS_2$: C, 34.1; H, 2.8; N, 22.7. Found: C, 34.3; H, 3.3; N, 22.8.

2,6,8-Tris-methylthiopurine (VII). Method A.—2-Methylthio-6,8-purinedithiol[8] (13.2 g.) was dissolved in 300 ml. of water containing 20 g. of potassium hydroxide. Then 16.4 g. of methyl iodide was added, and the mixture was vigorously stirred for 1 hr. at room temperature. The solution then was acidified with glacial acetic acid, and the precipitate that formed was filtered and washed with water. The white mass was dissolved in 200 ml. of boiling dilute potassium hydroxide solution, treated with Norit, and filtered. The filtrate was acidified with glacial acetic acid. The white precipitate was filtered, washed with water, and dried to yield 11.5 g. of product. Recrystallization from methanol yielded an analytically pure sample, m.p. 284°.

Anal. Calcd. for $C_8H_{10}N_4S_3$: C, 37.2; H, 3.9; N, 21.7. Found: C, 37.2; H, 3.8; N, 21.4.

Method B.—Twenty grams of 6-chloro-2,8-bis-methylthiopurine (VI) was treated with methanethiol in the presence of potassium hydroxide in a manner similar to that for the preparation of 2,6-bis-methylthiopurine[8] from method A to yield 19.5 g. of product. Recrystallization of the crude product from methanol gave a melting point of 284° which exhibited no depression when mixed with the same product prepared by method A.

Method C.—Ten grams of 2,6,8-purinetrithiol (IV) was placed in 100 ml. of a 2 *N* sodium hydroxide solution, and then 20 g. of methyl iodide was added. This mixture was vigorously stirred at 20° for 1 hr. and then acidified with glacial acetic acid. The precipitate was filtered, washed with water, and dried to yield 11.2 g. of colorless product. The ultraviolet absorption spectrum and melting point agree with those of the same product obtained by methods A and B.

2,6,8-Purinetrithiol (IV).—6-Hydroxy-2,8-purinedithiol (III)[8] (170 g.) and 340 g. of phosphorus pentasulfide were intimately mixed and covered with 3 l. of pyridine. This mixture then was refluxed for 6 hr. The excess pyridine was removed by vacuum distillation with a steam-bath as the source of heat. The residue was covered with 3 l. of water and allowed to stand overnight. The mixture then was heated on the steam-bath for 6 hr.; 200 ml. of ammonium hydroxide was added, and the solution was boiled with Norit and filtered. The hot filtrate was acidified with concentrated hydrochloric acid. The yellow precipitate was filtered from the hot solution and thoroughly washed with water. It was purified by precipitation from boiling dilute ammonium hydroxide with hydrochloric acid. The precipitate then was washed thoroughly with water, then acetone, and dried at 140° to yield 110 g. of pure product.

Anal. Calcd. for $C_5H_4N_4S_3$: C, 27.8; H, 1.9; N, 25.8. Found: C, 27.9; H, 2.3; N, 26.1.

8-Hydroxy-2,6-purinedithiol (XVII).—Twenty grams of 6,8-dihydroxy-2-purinethiol (XIV)[8] and 60 g. of phosphorus pentasulfide were covered with 500 ml. of pyridine, and this mixture was refluxed for 3 hr. The excess pyridine was removed *in vacuo* with a steam-bath as the source of heat. The residue was covered with 500 ml. of ice-water and allowed to stand for 2 hr. Then it was placed on the steam-bath for approximately 2.5 hr. The hot mixture was treated with Norit and filtered. The filtrate was acidified with concentrated hydrochloric acid. The product was washed with water and dried to yield 12 g. of crude material. Two more reprecipitations from hot dilute ammonium hydroxide yielded a product which was washed with water and dried at 150° to yield an analytically pure product.

Anal. Calcd. for $C_5H_4N_4OS_2$: C, 30.0; H, 2.0; N, 28.0. Found: C, 30.1; H, 2.5; N, 28.2.

8-Hydroxy-2,6-bis-methylthiopurine (XVI). Method A.—Four grams of sodium hydroxide was dissolved in 50 ml. of water. To this solution were added approximately 30 g. of ice and 10 g. of methanethiol followed by 4 g. of 6-chloro-8-hydroxy-2-methylthiopurine.[8] The mixture was placed on the steam-bath for 1.5 hr. The solution then was treated with Norit and filtered. The filtrate was acidified with glacial acetic acid, and the precipitate was filtered from the warm solution. One more reprecipitation from dilute sodium hydroxide solution with glacial acetic acid yielded 3.8 g. of analytical product which decomposed near 300°.

Anal. Calcd. for $C_7H_8N_4OS_2$: C, 36.7; H, 3.5; N, 24.6. Found: C, 36.3; H, 3.7; N, 24.6.

Method B.—Ten grams of 8-hydroxy-2,6-purinedithiol (XVII) was placed in 500 ml. of water, and just enough potassium hydroxide was added to dissolve all solid material. Then 14.3 g. of methyl iodide was added (temperature of solution 25°), and the solution was stirred vigorously for 1 hr. It then was acidified with glacial acetic acid, and the product was purified as before to yield 6 g. The ultraviolet absorption spectrum coincided with that of the product obtained by method A.

8-Chloro-2,6-bis-methylthiopurine (XVIII). Method A.—Fifteen grams of 6,8-dichloro-2-methylthiopurine (IX)[8] was treated in a manner similar to that employed in the preparation of 2,6-bis-methylthiopurine (XII) (method A) using methanethiol and potassium hydroxide to give 13 g. of crude product, m.p. 239–240°. Recrystallization from methanol yielded a product of melting point 244°.

Anal. Calcd. for $C_7H_7N_4ClS_2$: C, 34.1; H, 2.8; N, 22.7. Found: C, 34.5; H, 3.2; N, 23.1.

Method B.—Ten grams of 8-hydroxy-2,6-bis-methylthiopurine (XVI) was placed in 300 ml. of phosphorus oxychloride. This mixture was refluxed for 3 hr. or until all solid material had gone into solution. The excess phosphorus oxychloride then was removed *in vacuo* with a steam-bath as the source of heat. The residue was poured over chopped ice and allowed to stand 5 min. The aqueous acid solution was made strongly basic with a concentrated potassium hydroxide solution, with occasional addition of ice to keep the solution cold. The basic solution was allowed to stand 10 min., with occasional stirring, and then adjusted to *p*H 5 with acetic acid. The precipitate that formed was filtered and washed with ice-water and then extracted with 300 ml. of absolute ethanol by soxhlet extractor for 5 hr. The hot alcoholic solution was treated with Norit, filtered, and cooled.

The precipitate which appeared was filtered. Another crop was obtained from the mother liquor to give a total yield of 5.4 g. of pure product. A mixed melting point with the product obtained by method A showed no depression, and the ultraviolet absorption spectra of the products obtained by the two methods were identical.

2,8-Bis-methylthio-6-purinethiol. Method A.—Twenty grams of 6-hydroxy-2,8-bis-methylthiopurine (V) and 60 g. of phosphorus pentasulfide were covered with 500 ml. of pyridine, and this mixture was refluxed for 2 hr. The excess pyridine was removed *in vacuo* over a steam-bath. To the residue was added 500 ml. of ice-water, and the mixture was allowed to stand for 1 hr. It then was heated on a steam-bath for approximately 2 hr. The hot mixture was filtered, and the precipitate was washed with water. The compound was precipitated from boiling dilute sodium hydroxide with acetic acid to give 12 g. of product. Recrystallization from a mixture of N,N-dimethylformamide and water gave an analytically pure sample which decomposed at 295°.

Anal. Calcd. for $C_7H_8N_4S_3$: C, 34.5; H, 3.3; N, 22.9. Found: C, 34.3; H, 3.4; N, 23.3.

Method B.—Ten grams of 6-chloro-2,8-dimethylthiopurine (VI) was covered with 100 ml. of absolute ethanol, and 20 g. of thiourea was added. This mixture was refluxed for 4 hr. and allowed to cool. The precipitate was filtered. The crystalline product was extracted with boiling methanol, and the insoluble solid was dried at 120° to yield 8.5 g. of product. The ultraviolet absorption spectrum was identical to that of the product obtained by method A.

2,8-Dimethylthio-6-substituted-aminopurines. 6-Dimethylamino-2,8-bis-methylthiopurine.—Five grams of 6-chloro-2,8-bis-methylthiopurine (VI) was covered with 120 ml. of absolute ethanol, and then 25 ml. of dimethylamine solution (25% in water) was added. This mixture was heated on the steam-bath for approximately 2 hr. The cooled solution was filtered, and the precipitate was washed with a small portion of ethanol. The dried product, 5 g., was recrystallized from N,N-dimethylformamide and melted at 272°.

Anal. Calcd. for $C_9H_{13}N_5S_2$: N, 27.5. Found: N, 27.8.

6-(*p*-Chlorobenzylamino)-2,8-bis-methylthiopurine.—Three grams of 6-chloro-2,8-bis-methylthiopurine (VI) was covered with 80 ml. of absolute ethanol, and 6 g. of *p*-chlorobenzylamine was added. This mixture was boiled on a hot-plate for 15 min. and then adjusted to *p*H 1 with concentrated hydrochloric acid. The precipitate[11] was filtered, washed with water, and dried at 120° to yield 2.7 g. of product. Recrystallization from N,N-dimethylformamide raised the melting point to 217°.

Anal. Calcd. for $C_{14}H_{14}N_5ClS_2$: C, 47.8; H, 4.0; N, 19.9. Found: C, 48.1; H, 3.9; N, 19.7.

Reactions of Methylthiopurines with Chlorine in Methanol at 55–60°. Preparation of Compounds Listed in Table I. Method 1.—Ten grams of the appropriate 2-methylthio-6,8-disubstituted purine (see Table I) was covered with approximately 150 ml. of absolute methanol. Then, as the mixture was stirred with a mechanical stirring device, chlorine was passed into the solution for a period of 1–2 hr. at such a rate that the reaction temperature was maintained at 55–60°. The mixture then was cooled, and the precipitate was filtered and washed with a small amount of cold methanol, then dried at 100°. The product was recrystallized from methanol for analysis.

Reactions of Alkylthiopurines with Chlorine in Methanol below 10°. Preparation of 6,8-Dichloro-2-methylsulfonylpurine (VIII). Method 2.—Ten grams of the appropriate 2-methylthio-6,8-disubstituted purine (see Table IV) was placed in 100 ml. of absolute methanol, and chlorine gas was then passed into the cooled mixture for approximately 1 hr., with stirring, at such a rate that the reaction temperature remained at less than 10° with external cooling using crushed ice. The solution then was evaporated in a stream of dry air to approximately 30 ml. The precipitate which had formed was collected and washed with a small portion of cold methanol (20 ml.), then benzene. The white needles were allowed to air-dry for 2 hr. The product then was suspended in 80 ml. of boiling benzene, and just enough methanol was added to dissolve all solid material. The solution was vigorously boiled for approximately 10 min., treated with Norit, and filtered. The filtrate was reduced to approximately 40-ml. volume by continued boiling. The solution then was allowed to cool, and the product was filtered and washed with small portions of cold benzene. The white crystalline mass was dried at 80° for approximately 4 hr. It was recrystallized from a benzene–methanol mixture.

Reaction of 6-Alkylthiopurines with Chlorine in Aqueous Methanol. Preparation of 6-Alkylsulfonylpurines Described in Table III. Method 3.—Ten grams of the appropriate 6-alkylthiopurine was placed in 200 ml. of a 30–70% methanol–water solution, and this mixture was cooled to 5–10°. As the mixture was being stirred mechanically, chlorine gas was passed into the solution for approximately 1 hr. during which time the temperature was maintained below 20°. The starting material gradually dissolved, and the product precipitated. The mixture now was allowed to stir for 1 hr. longer. The precipitate was filtered, washed with water, then benzene, and finally dried at 50°. The sulfone was purified by recrystallization from the solvents indicated.

Reactions of Alkylthiopurines in Methanol and Water. Method 4. (See Table II).—The alkylthiopurine was treated as in method C, except that after the crude precipitate had been filtered and washed with water, it next was suspended in 150 ml. of water, and the *p*H was adjusted to 7 with dilute ammonium hydroxide. The aqueous mixture was brought to a boil, at which time complete solution was obtained. The hot solution was carefully adjusted to *p*H 1 with dilute hydrochloric acid and allowed to stand. The precipitate was filtered, washed with water, then benzene, and dried at 50°. It was recrystallized from the indicated solvents in Table II.

Reactions of 2-Methylsulfonyl-6,8-disubstituted-purines with Amines. Preparation of Purines Listed in Table V. Method A (See Table V).—Five grams of the appropriate 2-methylsulfonyl-6,8-disubstituted-purine (see Table V) was covered with approximately 100 ml. of absolute ethanol, and then 50 ml. of dimethylamine solution (25% in water) was added. This mixture then was placed on the steam-bath for 2–3 hr., or until the final volume was approximately 40 ml. The mixture now was allowed to cool. The precipitate was filtered, washed with methanol, then dried at 110°, and recrystallized from the solvent indicated in Table V.

Method B.—Five grams of the 2-methylsulfonyl-6,8-disubstituted-purine (see Table V) was covered with 100–150 ml. of water, and then 50 ml. of dimethylamine solution (25% in water) was added. This mixture next was boiled on a hot-plate for approximately 20 min., cooled in an ice-bath, and then acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with water, and dried at 100° before recrystallization.

Method C.—Three grams of the 2-methylsulfonyl-6,8-disubstituted-purine (see Table V) was placed in 60 ml. of dimethylamine solution (25% in water). This mixture was placed in a steel bomb for 12 hr. at 125°. The cooled mixture was filtered, and the precipitate was washed with water and recrystallized from dimethylformamide and water.

Reactions of Certain 2-Methylsulfonyl-6,8-disubstituted-purines with Acid (See Table VI).—Ten grams of the 2-methylsulfonyl-6,8-disubstituted-purine (see Table VI) was refluxed in 300 ml. of 1 *N* hydrochloric acid for approximately 3 hr. The mixture then was allowed to cool, and the white precipitate was filtered, washed with water, then methanol, and dried at 100°. In each case the structure of the product was confirmed by ultraviolet absorption spectra which checked with the same compound prepared by an unambiguous method.

Preparation of 6-Chloro-8-hydroxy-2-methylsulfonylpurine (X) from 2,6,8-Tris-methylthiopurine (VII).—Three grams of 2,6,8-tris-methylthiopurine (VII) was placed in 50 ml. of absolute methanol, and this mixture was cooled to <5° using an ice-bath. Chlorine gas then was passed slowly into the mixture for approximately 1 hr. The solution was then heated on a steam-bath for approximately 30 min. and allowed to cool. The precipitate was filtered, washed with methanol, and dried at 100° to yield 1.1 g. of the 6-chloro-8-hydroxy-2-methylsulfonylpurine. The ultraviolet absorption spectra were identical to those of the product obtained by the method shown in Table I.

Preparation of 6-Chloropurine from 6-Methylthiopurine.—Ten grams of 6-methylthiopurine[15] was placed in 50 ml. of absolute methanol which previously had been cooled to 5° in a surrounding ice-bath. Chlorine gas then was passed into the solution, with occasional shaking, for approximately 20 min. (The temperature at all times was maintained below 10°.) The precipitate was filtered and washed with a small portion of cold methanol. The crystals were dissolved

in 80 ml. of water, and the solution was adjusted to *p*H 7 with dilute ammonium hydroxide. The mixture was allowed to stand, and the precipitate was filtered, washed with water, and dried at 60° to yield 5.2 g. of colorless 6-chloropurine. The ultraviolet absorption spectra[21] were characteristic of that of 6-chloropurine.

Anal. Calcd. for $C_5H_3N_4Cl$: N, 36.2. Found: N, 36.4.

Preparation of 8-Hydroxy-6-methylsulfonylpurine from 6,8-Bis-methylthiopurine.—Three grams of 6,8-bis-methylthiopurine[6] was placed in 100 ml. of a 27:75% methanol–water solution. The solution was stirred, and chlorine gas was passed into it for approximately 1 hr. The reaction temperature was maintained <15°. The precipitate was finally filtered, and the wet crude product then was placed in approximately 60 ml. of boiling water and heated for 10 min. The solution was cooled, and the precipitate was filtered, washed with water, and dried at 110° to yield 1.5 g. of product, m.p. > 300°.

Anal. Calcd. for $C_6H_6N_4O_3S$: C, 33.7; H, 2.8; N, 26.2. Found: C, 34.2; H, 2.6; N, 26.4.

(21) A. Bendich, P. J. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954).

TEMPE, ARIZ.

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Action of Grignard Reagents. XIV.[1] Action of Organomagnesium Compounds on 1-Phenyl-3-methyl-4-arylidene-5-pyrazolones. Their Behavior toward Aromatic Secondary Amines and Aromatic Thiols

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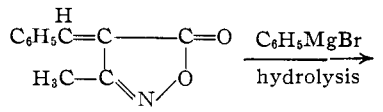
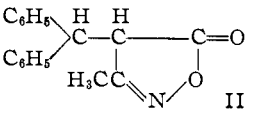
Grignard reagents add to the double bond of the lateral chain of the highly colored 1-phenyl-3-methyl-4-arylidene-5-pyrazolones (III) to give, after hydrolysis, colorless products, believed to have structure IV. Similarly, addition reaction was observed when III are allowed to react with piperidine, with morpholine or with aromatic thiols to give V and VI, respectively.

Panizzi[2] has shown that the isoxazolone ring in 3-methyl-4-benzylideneisoxazolone (I) is stable toward the action of phenylmagnesium bromide and only the double bond of the lateral chain of I enters into reaction, yielding 3-methyl-4-diphenylmethyl-5-isoxazolone (II).

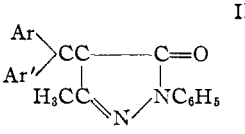




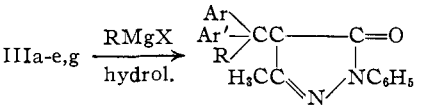
II

In extension of the work by one of us on the action of Grignard reagents on heterocyclic nitrogen compounds,[3,4] the action of these reagents on 1-phenyl-3-methyl-4-arylidene-5-pyrazolones (III-a-e) and on 1-phenyl-3-methyl-4-diphenylmethylene-5-pyrazolone (IIIg), the nitrogen analogs of I, now has been investigated. Thus, when the orange IIIa is treated with phenylmagnesium bromide, followed by hydrolysis, a colorless product believed to be 1-phenyl-3-methyl-4-diphenylmethyl-5-pyrazolone (IVa) is obtained.

The structure of IVa, which is taken as an example of compounds IVa-o, is inferred from the fact that it is colorless. Also, the finding that IVc is obtained by the action of phenylmagnesium bromide on IIIc and by the action of *p*-tolylmagnesium iodide on IIIa may be taken in favor of the assigned structure for the Grignard products (*cf.* IV).



IIIa, Ar = C_6H_5; Ar′ = H
b, Ar = $C_6H_4OCH_3$-*p*; Ar′ = H
c, Ar = $C_6H_4CH_3$-*p*; Ar′ = H
d, Ar = C_6H_4Cl-*o*; Ar′ = H
e, Ar = C_6H_3:O_2CH_2; Ar′ = H
f, Ar = $C_6H_4NO_2$-*p*; Ar′ = H
g, Ar = Ar′ = C_6H_5



IVa, Ar = C_6H_5; Ar′ = H; R = C_6H_5
b, Ar = C_6H_5; Ar′ = H; R = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_5; Ar′ = H; R = $C_6H_4CH_3$-*p*
d, Ar = C_6H_5; Ar′ = H; R = CH_3
e, Ar = $C_6H_4OCH_3$-*p*; Ar′ = H; R = $C_6H_4OCH_3$-*p*
f, Ar = $C_6H_4OCH_3$-*p*; Ar′ = H; R = $C_6H_4CH_3$-*p*
g, Ar = $C_6H_4CH_3$-*p*; Ar′ = H; R = $C_6H_4CH_3$-*p*
h, Ar = C_6H_4Cl-*o*; Ar′ = H; R = C_6H_5
i, Ar = C_6H_4Cl-*o*; Ar′ = H; R = $C_6H_4OCH_3$-*p*
j, Ar = C_6H_4Cl-*o*; Ar′ = H; R = $C_6H_4CH_3$-*p*
k, Ar = C_6H_3: O_2CH_2; Ar′ = H; R = C_6H_5
l, Ar = C_6H_3:O_2CH_2; Ar′ = H; R = CH_3
m, Ar = Ar′ = R = C_6H_5
n, Ar = Ar′ = C_6H_5; R = $C_6H_4OCH_3$-*p*
o, Ar = Ar′ = C_6H_5; R = CH_3

1-Phenyl-3-methyl-5-pyrazolone[5] proved to be stable toward the action of phenylmagnesium bromide under similar experimental conditions, thus showing the stability of the hetero-ring toward the action of Grignard reagents; IVa was identical with the product obtained by the catalytic reduction of IIIg. The activity of the vinyl group in III may be compared with the activity of the olefinic double bond in I, and the stability of the 5-membered heterocyclic ring in I and III is in contrast to the ready opening of the oxazolone ring in 2-phenyl-4-arylidene-2-oxazoline-5-ones.[4]

(1) For part XIII *cf.* W. Asker, A. Mustafa, M. K. Hilmy and M. A. Allam, *J. Org. Chem.*, **23**, 2002 (1958).

(2) L. Panizzi, *Gazz. chim. ital.*, **76**, 44 (1946).

(3) A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby and A. E. Hassan, THIS JOURNAL, **77**, 1612 (1955); A. Mustafa, W. Asker and O. H. His, *ibid.*, **77**, 5127 (1955); A. Mustafa, A. F. A. Shalaby and M. E. Sobhy, *J. Org. Chem.*, **23**, 2929 (1958).

(4) A. Mustafa and A. H. E. Harhash, *ibid.*, **21**, 575 (1956).

(5) *Cf.* its probable tautomeric structures on the basis of ultraviolet absorption spectra (D. Biquard and M. P. Grammaticakis, *Bull. soc. chim. France*, **8**, 246 (1941)); Valyashke and Bliznyukev, *J. Gen. Chem.*, (*U.S.S.R.*), *II*, 559 (1941); Westoo, *Acta Chem. Scand.*, **6**, 1499 (1952); R. C. Elderfield "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 122.