Acylations of Purine-6-thione and Related Compounds. A Reinvestigation of the Site of Acylation[1]

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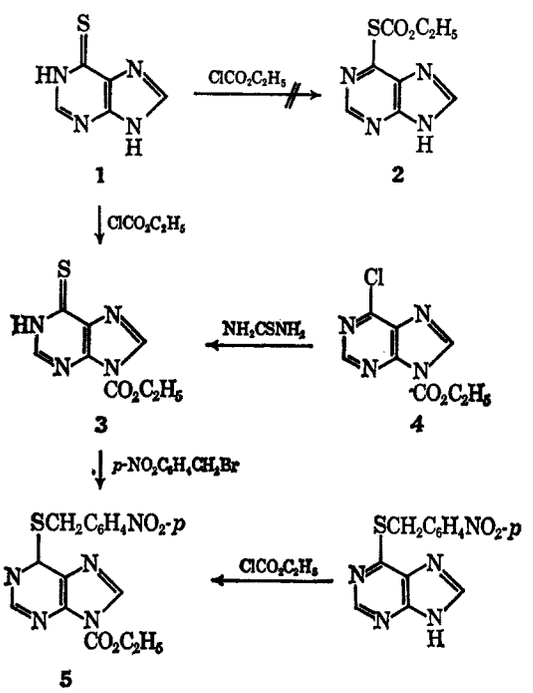
Purine-6-thione (1) is acylated on nitrogen, not on sulfur as was previously reported. Thus reaction of **1** with acetic anhydride and with ethyl chloroformate yields, respectively, 9-acetylpurine-6-thione (6) and ethyl purine-6-thione-9-carboxylate (**3**), as shown by independent syntheses and spectra. 9-Alkylpurine-6-thiones do react with ethyl chloroformate and benzoyl chloride to yield the corresponding S-acyl derivatives. 2-Aminopurine-6-thione yields ethyl 2-amino-9-carbethoxypurine 6-thiolcarbonate (**14**). The reaction of 6-chloropurine with ethyl chloroformate, aliphatic acid anhydrides, and benzyl chloroformate gives the corresponding 9-substitution products. 6-Dimethylaminopurine forms a 9-carbethoxy derivative (**15**). The dipole moments of the 9-benzyl, 7-benzyl, 9-*p*-nitrobenzyl, and 9-carbethoxy derivatives of 6-chloropurine in dioxane at 20° are 4.91, 5.03, 4.57, and 4.23 D, respectively.

The product of the reaction of purine-6-thione (**1**) with excess ethyl chloroformate was shown to be a monoacyl derivative by Dyer and Bender[2] and the acyl group was assigned to the sulfur atom on the basis of an independent synthesis involving the conversion of a thiocyanate to a thiolcarbonate. However, in the current work the observation was made that the ultraviolet spectrum of the acyl derivative failed to exhibit the pronounced hypsochromic shift expected of an S-substituted derivative of purine-6-thione,[3] and the infrared carbonyl absorption occurred at 1770 cm^{-1}, which is high for a thiolcarbonate.[4] These two facts generated doubt concerning the accuracy of the structural assignment.

The reaction of thiourea with ethyl 6-chloropurine-9-carboxylate (**4**) (the structure of which will be discussed later) in absolute ethanol gave ethyl purine-6-thione 9-carboxylate (**3**) by an unambiguous route (Scheme I). This compound proved to be identical with the compound obtained by direct acylation[2] of purine-6-thione (**1**) as shown by mixture melting point and spectral data. Hence the structure of the acylated compound is **3**, not **2**. Moreover, alkylation of **3** in dimethylformamide with triethylamine as acid acceptor yielded the same product as did the acylation of a known S-alkyl purine, thus confirming that acylation occurred on nitrogen, not sulfur (Scheme I). Thus the observed pattern of acylation is in contrast to that of alkylation, since the latter results in S substitution[3] with the single exception of Bryant and Harmon's reactions[5] of Mannich type on purine-6-thione.

The reaction of purine-6-thione (**1**) with acetic anhydride gave a monoacetyl derivative only. Substitution was believed to have occurred on sulfur because the same compound was obtained from the action of potassium thiolacetate on 6-chloropurine in dimethylformamide. However, the absence of a hypsochromic shift in the ultraviolet spectrum, even in solvents such as ethyl acetate and chloroform which would preclude solvolysis, suggested that acylation had occurred on nitrogen, not sulfur.

SCHEME I



Evidence that the compound had the N-acyl structure **6** was provided by its alkylation, which gave compound **7**, identical with that obtained from the action of acetic anhydride on a known S-alkylpurine[3] (Scheme II). An independent synthesis from 6-chloro-9-acetylpurine[6] and thiourea was not feasible because of solvolysis of the very labile N-acetyl group.[6]

The fact that thiolacetic acid can serve as an acetylating agent for nitrogen of the imidazole ring of a purine was shown by Giner-Sorolla, *et al.*,[7] who used the reaction of purine-6-carboxaldehyde oxime with thiolacetic acid to give the thioaldehyde as an N-acetyl derivative.

(1) (a) This investigation was supported by the Public Health Service Research Grant No. CA-03477 from the National Cancer Institute. (b) Abstracted in part from the Ph.D. theses of R. E. F. (1964) and C. E. M. (1968), University of Delaware.

(2) E. Dyer and H. Bender, *J. Med. Chem.*, **7**, 10 (1964).

(3) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Amer. Chem. Soc.*, **80**, 6265 (1958).

(4) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 60.

(5) C. D. Bryant and R. E. Harmon, *J. Med. Chem.*, **10**, 104 (1967).

(6) J. A. Montgomery, *J. Amer. Chem. Soc.*, **78**, 1928 (1956).

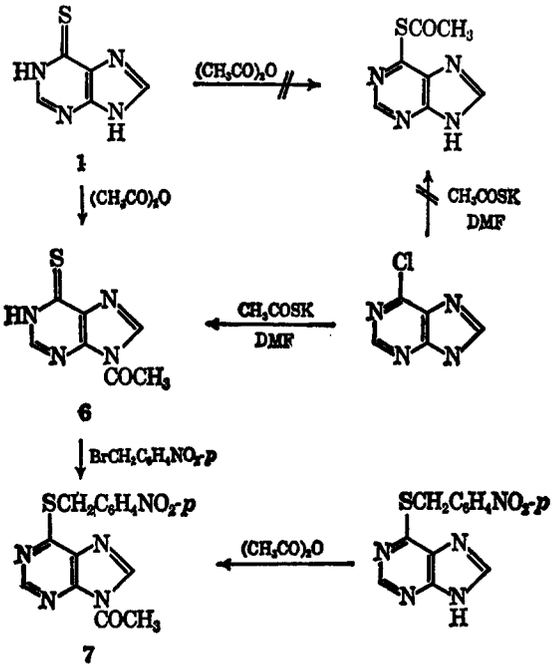
(7) A. Giner-Sorolla, E. Thom, and A. Bendich, *J. Org. Chem.*, **29**, 3209 (1964).

TABLE I

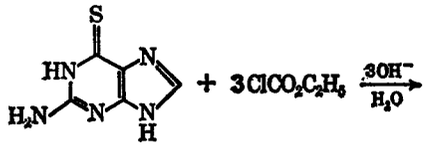
Compd no.	Solvent	λ_{max}	$\epsilon_{max} \times 10^{-3}$	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3	MeOH	322	18.9	$C_8H_8N_4O_2S$	42.85	3.59	24.99	43.35	3.70	25.01
4	Cyclohexane	248	8.3	$C_8H_7N_4O_2Cl$	42.38	3.09	24.68	42.41	3.27	24.54
5	MeOH	289	30.2	$C_{15}H_{13}N_5O_4S$	50.13	3.64	19.49	50.19	4.00	19.31
6	CH_3Cl	322[a]		$C_7H_6N_4OS$	43.29	3.11	28.85	43.53	3.12	28.87
7	CH_3CN	286	31.2	$C_{14}H_{11}N_5O_3S$	51.04	3.37	21.27	51.37	3.52	21.11
8	MeOH	277	9.7	$C_{15}H_{13}N_5O_4S$	50.12	3.64	19.48	50.19	3.96	19.60
9	CH_3CN	275	24.5	$C_{19}H_{13}N_5O_3S$	58.30	3.34	17.89	58.06	3.44	17.84
10	MeOH	354	16.0	$C_8H_8N_4O_2Se$	35.43	2.97	20.66	35.31	3.11	20.55
11	CH_3CN	245	7.15	$C_{13}H_9ClN_4O_2$	54.07	3.12	19.41	53.90	3.31	19.24
12	CH_3CN	245	45.5	$C_{10}H_{13}N_5O_3S$	58.37	3.35	17.91	58.11	3.42	16.88
		285	61.7							
13	MeOH	299	19.5	$C_{15}H_{13}N_5O_4Se$	44.34	3.22	17.24	44.53	2.91	17.41
14	0.1 *N* HCl	323[b]	4.28	$C_{11}H_{13}N_5O_4S$	42.44	4.21	22.50	42.40	4.41	22.58
	MeOH	336	7.40							
15	MeOH	272	18.3	$C_{10}H_{13}N_5O_2$	51.05	5.56	29.77	51.20	5.61	29.65
16	0.1 *N* HCl	263[c]		$C_8H_7N_4OCl$	45.62	3.35	26.60	46.02	3.40	26.95
17	0.1 *N* HCl	263[c]		$C_9H_9N_4OCl$	48.11	4.04	24.94	48.29	4.20	24.84
18	0.1 *N* HCl	325[c]		$C_8H_8N_4OS$	46.14	3.87	26.91	46.33	3.99	27.12
19	0.1 *N* HCl	325[c]		$C_9H_{10}N_4OS$	48.63	4.54	25.21	48.83	4.60	25.11
20	0.1 *N* HCl	295[c]		$C_8H_8N_4OS$	46.14	3.87	26.91	46.23	3.67	26.75

[a] Solubility insufficient for measurement of ϵ_{max}. [b] Unstable. [c] Value for parent compound formed on hydrolysis.

SCHEME II



In contrast to purine-6-thione (**1**) its 2-amino analog gave a diacyl derivative in 65% yield when allowed to react with 3 equiv of ethyl chloroformate in aqueous base. The product was assigned the S-acyl structure



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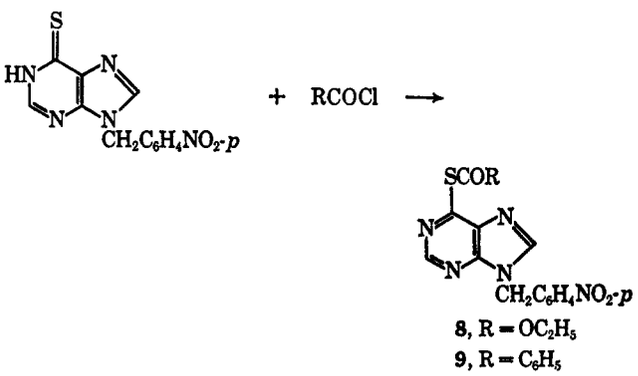
14 on the basis of spectral data. Its ultraviolet spectrum showed the hypsochromic shift expected of an S-substituted purine (Table I) and exhibited two carbonyl absorptions at 1770 and 1720 cm^{-1}, the latter being assigned to the thiolcarbonate group.[4]

Although purine-6-thione (**1**) was not acylated on sulfur, its 9-alkyl derivatives do yield S-acyl derivatives. Dyer and Bender[2] obtained ethyl 9-methylpurine-6-thiolcarbonate from the reaction of 9-methylpurine-6-thione and ethyl chloroformate in a sodium hydride–benzene system. This compound showed the hypsochromic shift expected of an S-substituted purinethione and had a carbonyl absorption at 1724 cm^{-1}. In the current work, the reaction of 9-*p*-nitrobenzylpurine-6-thione with ethyl chloroformate in either sodium hydride–benzene or aqueous sodium hydroxide yielded ethyl 9-*p*-nitrobenzylpurine-6-thiolcarbonate (**8**). Its structure was assigned on the basis of the expected hypsochromic shift. The S-benzoyl analog **9** was obtained in like manner. Thus, S acylation occurred in the absence of the imidazole –NH.



8, R = OC_2H_5
9, R = C_6H_5

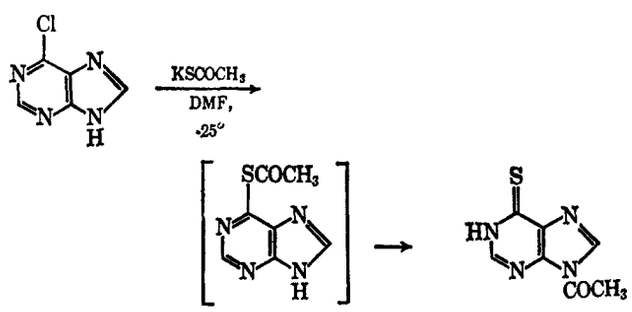
Sulfur to Nitrogen Transacylation. A Possible Mechanism.—The thiol ester group is known to effect transacylation from sulfur to other elements. Lynen[8]

(8) F. Lynen, *J. Cell. Comp. Physiol., Suppl. 1*, **54**, 33 (1959).

has proposed that the high reactivity of thiol esters is due to a unique polarization of the carbonyl carbon, and that factors activating the latter to nucleophilic attack will consequently enhance its transacylating capacity.

Miller and Lykos[9,10] calculated that the 6 position on the purine ring has the lowest charge density and their calculations have been supported by the experimental assignment of the proton magnetic resonance spectrum of purine.[11] Chemical evidence supporting a low charge density on the 6 position is the relative ease of nucleophilic substitution on 6-halopurine.[12] Moreover, the Dakin–West reaction[13] has been observed to occur on 2-(purin-6-ylthio)propionic acid, indicating a strong $-I$ inductive effect at the 6 position. All of the above observations indicate an enhancement of the transacylating ability of a thioacyl group on the 6 position.

The isolation of monoacyl derivatives from the reaction of purine-6-thione (**1**) with acetic anhydride and with ethyl chloroformate can be ascribed to a transacylation from sulfur to nitrogen as can the isolation of 9-acetylpurine-6-thione (**6**) from the reaction of 6-chloropurine with potassium thiolacetate.



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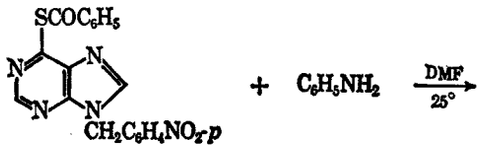
The formation of S-acyl derivatives from the reaction of 9-alkylpurine-6-thiones could be explained on this basis, too, since the absence of an NH group prevents any transacylation from occurring. The formation of an S-acyl derivative from the reaction of 2-aminopurine-6-thione can be ascribed to the decrease of the polarization of the thioacyl carbonyl carbon by the $+R$ effect of the 2-amino group.

Evidence for a sulfur to nitrogen transacylation was obtained from the reaction of 6-S-benzoylthio-9-*p*-nitrobenzylpurine (**9**) and aniline, which yielded benzanilide in 59% yield. However, further studies with purines would be necessary to show whether or not the mechanism is operative in the transfer of an acyl group from one purine to another.

Acylation of 6-Chloropurine.—Ethyl chloroformate yielded the previously mentioned ethyl 6-chloropurine-9-carboxylate (**4**), which gave ethyl purine-6-thione 9-carboxylate (**3**) and ethyl purine-6-seleno-9-carboxylate (**10**) on reaction with thiourea and selenourea,



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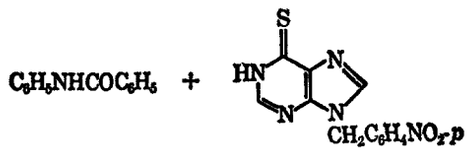


respectively. Aliphatic acid anhydrides yielded the corresponding 9-acyl derivatives including the known 9-acetyl compound.[6] Benzyl chloroformate gave benzyl 6-chloropurine-9-carboxylate (**11**) in the presence of sodium ethoxide.

Attempts were made to confirm the location of the acyl group in the acetyl derivatives of 6-chloropurine and of 6-methylthiopurine by hydrogenation in tetrahydrofuran solution with lithium aluminum hydride in the presence of aluminum chloride (reported to eliminate hydrogenolysis in the case of N-acetylpyrrole[14]). The products were 6-chloropurine (95%) and 6-methylthiopurine (78%).

Evidence for Acylation at the 9 Position.—Neiman and Bergmann[15] showed that the spectra of derivatives of purine-6-thione (**1**) substituted in the 3 or 7 position exhibited a bathochromic shift when compared to **1**, whereas the 9-substituted derivatives did not exhibit such a shift. Comparison of the ultraviolet spectra of ethyl purine-6-thione 9-carboxylate (**3**) and ethyl 6-methylthiopurine-9-carboxylate with the spectra of the known alkyl derivatives strongly indicated 9 substitution (Table II). The spectra of ethyl 2-amino-9-carbethoxypurine-6-thiolcarbonate (**14**) agreed closely with the spectra of the known 2-amino-9-methyl-6-methylthiopurine,[16] indicating 9 substitution here also.

Further evidence against the 3 and 7 positions can be obtained from the known preference of 6-chloropurine for alkylation on the 9 position. For example,

TABLE II

ULTRAVIOLET SPECTRA[a] OF PURINE-6-THIONE DERIVATIVES

	λ_{max}
Purine-6-thione	322[b]
3-Methyl-	338[b]
7-Methyl-	328[b]
9-Methyl-	321[b]
Ethyl purine-6-thione 9-carboxylate (**3**)	322
6-Methylthiopurine	291[b]
3-Methyl-	312[b]
7-Methyl-	293[b]
9-Methyl-	288[b]
Ethyl 6-methylthiopurine-9-carboxylate	288[c]
2-Amino-6-methylthio-9-methylpurine	322[d]
Ethyl 2-amino-9-carbethoxy-purine-6-thiolcarbonate (**14**)	322

[a] At pH 7 except for the last two compounds at pH 1. [b] Reference 15. [c] Reference 2. [d] C. W. Noell and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 558 (1962).

(9) R. L. Miller, P. G. Lykos, and H. N. Schmeising, *J. Amer. Chem. Soc.*, **84**, 4623 (1962).

(10) R. L. Miller and P. G. Lykos, *Tetrahedron Lett.*, **11**, 493 (1962).

(11) M. P. Schweizer, S. J. Chan, G. K. Helmkamp, and P. O. P. T'so, *J. Amer. Chem. Soc.* **86**, 696 (1964).

(12) R. K. Robins in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 291 ff.

(13) E. Dyer and C. E. Minnier, *J. Org. Chem.*, **33**, 880 (1968).

(14) R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

(15) Z. Neiman and F. Bergmann, *Israel J. Chem.*, **3**, 161 (1965).

(16) See Table II, footnote *d*.

the reaction of 6-chloropurine and ethyl iodide yields the 9-ethyl derivative in 50% yield, but the 7-ethyl derivative in only 5% yield.[17] Since ethyl purine-6-thione 9-carboxylate (3) and its alkyl derivatives were synthesized from 6-chloropurine in good yields, it would seem unlikely that substitution occurred on the 7 or 3 position. Finally, Reddy, Goldstein, and Mandell[18] have shown that acetylation of purine is sensitive to the steric hindrance caused by substitution in the 6 position; acetylation of purine itself gave an almost equal mixture of 7- and 9-acetylpurine, while acetylation of 6-methylpurine gave exclusively 9-acetylation.

The reaction of 6-dimethylaminopurine and ethyl chloroformate in aqueous sodium hydroxide as well as in refluxing benzene with 1 equiv of the purine as acid acceptor gave ethyl 6-dimethylaminopurine-9-carboxylate (15) in good yield (94%). The carbethoxy group was assigned to the 9 position from nmr data; the small (8 cps) difference in the shift of the 2- and 8-proton signal is expected for substitution of the imidazole ring according to the $\Delta\delta$ rule.[19]

A study of the dipole moments of some isomeric purine derivatives was initiated in the hopes of obtaining supporting data on the position of substitution. Very little work has been done in determining the dipole moments of purines, probably because of solubility difficulties.[20,21]

Symmetry considerations would lead one to predict that 6-chloropurine substituted in the 7 position with a $-I$ polar group would have a greater moment than would a 9-substituted derivative. For example, 1,8-dichloronaphthalene (2.82 D) has a greater moment than 1,5-dichloronaphthalene (0.00 D).[22] The dipole moments of the 9- and 7-benzyl,[17] the 9-nitrobenzyl,[23] and the 9-carbethoxy (4) derivatives of 6-chloropurine were determined by the method of Hedestrand[24] in dioxane at 20° to be 4.91, 5.03, 4.57, and 4.25, respectively. The 7-*p*-nitrobenzyl derivative[23] interacted with the dioxane to give an insoluble precipitate. This behavior precluded the measurement of its dipole moment. Lack of other suitable derivatives necessary to establish a correlation of substitution with dipole moment rendered this method of approach of little value.

Reinvestigation of the site of acylation of purine-8-thione is now in progress; the results indicate that acylation occurs at N-9 or N-7, not sulfur as previously reported.[2]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Ultraviolet spectra were obtained on a Perkin-Elmer 202 spectrophotometer. Infrared spectra (in potassium bromide) were obtained on a Perkin-Elmer 337 or 137 spectrophotometer. The nmr spectra (in DMSO-d_6) were obtained on a Varian A-60A spectrometer using tetramethylsilane as internal standard. Diple moements were determined on a Kahlsico dipolmeter.

Preparation of Purines.—The procedures cited by letters in Table III are illustrated for typical compounds.

Procedure A. Ethyl *p*-Nitrobenzylthiopurine-9-carboxylate (5).—Ethyl chloroformate (0.183 g, 1.69 mol) was added to a stirred solution of 6-*p*-nitrobenzylthiopurine[3] (0.5 g, 1.69 mol) and triethylamine (0.239 ml, 1.69 mol) in 10 ml of anhydrous dimethylformamide. The suspension was stirred for 3 hr, poured into 20 ml of ice–water and the pH adjusted to 5 with glacial acetic acid. The precipitate was filtered and dried *in vacuo* to yield the crude product.

Procedure B. Ethyl Purine-6-thione 9-Carboxylate (3).—To a refluxing solution of ethyl 6-chloropurine-9-carboxylate (4) (1.0 g, 4.4 mmol) in 20 ml of absolute ethanol, thiourea (0.35 g, 4.6 mmol) was added and the mixture was refluxed for 1 hr during which a precipitate formed. The suspension was cooled to room temperature, filtered, washed with 5 ml of warm ethanol and dried *in vacuo* to give the product.

Procedure C. 6-*p*-Nitrobenzylthio-9-acetylpurine (7).—A solution of 6-*p*-nitrobenzylthiopurine[3] (0.5 g, 1.74 mmol) and acetic anhydride (6 ml) in 12 ml of dry benzene was refluxed for 2.5 hr, cooled and the resulting precipitate filtered and dried *in vacuo* over potassium hydroxide to yield the product. In the case of compounds 6, 18, and 19 the appropriate anhydride (*ca.* 30 ml/g of purine) was used without benzene.

Procedure D. 6-S-Benzoylthio-9-*p*-nitrobenzylpurine (9).—A suspension of 9-*p*-nitrobenzylpurine-6-thione[23] (0.2 g, 0.7 mmol) and sodium hydride (0.0356 g of a 50% mineral oil suspension, 0.74 mmol) in 60 ml of dry benzene was refluxed for 2 hr. To this gray-green suspension was added benzoyl chloride (0.104 g, 0.74 mmol) and the mixture was refluxed for an additional 6 hr, filtered hot and evaporated to dryness on a flash evaporator. The residue was triturated with *n*-hexane, yielding the product.

Procedure E. Ethyl 2-Amino-9-carbethoxypurine-6-thiolcarbonate (14).—A solution of 2-aminopurine-6-thione[25] (1.67 g, 10 mmol) and sodium hydroxide (1.2 g, 30 mmol) in 75 ml of water was added dropwise over a period of 0.5 hr to a stirred mixture of ethyl chloroformate (3.24 g, 30 mmol) and 5 ml of water at room temperature. The mixture was stirred for 1 hr longer while a precipitate formed. The pH was adjusted to 5 with glacial acetic acid and the precipitate was filtered, washed with water and dried to yield 3.1 g. This was extracted with hot toluene, and the extract evaporated to give 2.0 g (65%) of product, mp 158–161° dec. Recrystallization from toluene gave a white solid: mp 158–161° dec; nmr δ 1.32 (two t, 6), 4.42 (two q, 4), 8.47 (s, 1).

Procedure F. Ethyl 6-Dimethylaminopurine-9-carboxylate (15).—A solution of 6-dimethylaminopurine (1.0 g, 6.14 mmol) and sodium hydroxide (0.252 g, 6.3 mmol) in 20 ml of water was added over a period of 15 min to a stirred mixture of ethyl chloroformate (0.682 g, 6.3 mmol) and 10 ml of water at 0°. The solution was then stirred for an additional 15–20 min, the pH adjusted to 5 with glacial acetic acid, the solution extracted with five 20-ml portions of chloroform, and the dried extract evaporated to give 1.35 g (94%) of product, mp 91–92°. Recrystallization from petroleum ether (bp 30–60°) gave colorless needles: mp 91–92°; nmr δ 1.42 (t, 3), 3.43 (s, 6), 4.53 (q, 2), 8.32 (s, 1), 8.46 (s, 1). This compound was also prepared in 94% yield by a modification of procedure D using 2 equiv of purine to 1 equiv of ethyl chloroformate.

Procedure G. Benzyl 6-Chloropurine-9-carboxylate (11).—Benzyl chloroformate (0.7 g, 4 mmol) was added dropwise to a stirred ice-cooled solution of 6-chloropurine[26] (0.309 g, 2 mmol) and sodium ethoxide (4 mmol) in 25 ml of ethanol. After 5 min a precipitate appeared and the mixture was stirred for 1 hr at 0°. The white solid was filtered, washed with water, and dried to yield the crude product. Recrystallization from 200 ml of ethyl ether–petroleum ether (1:1) gave 0.38 g (66%) of needles: mp 102° dec; nmr δ 5.62 (s, 2), 7.56 (m, 5), 8.97 (s, 1), 9.07 (s, 1).

Procedure H. Ethyl 6-Chloropurine-9-carboxylate (4).—Ethyl chloroformate (4.03 g, 34 mmol) was added to an ice-cooled

(17) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **83**, 630 (1961).

(18) G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963).

(19) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, **86**, 5320 (1964).

(20) H. deVoe and I. Tinico, Jr., *J. Mol. Biol.*, **4**, 500 (1962).

(21) A Veillard and B. Pullman, *J. Theoret. Biol.*, **4**, 37 (1963).

(22) C. P. Smith, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p 339.

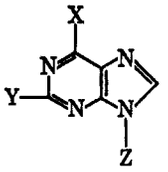
(23) H. J. Schaeffer and E. Odin, *J. Med. Chem.*, **9**, 576 (1966).

(24) G. Hedestrand, *Z. Phys. Chem.*, **2**, 428 (1929).

(25) G. D. Daves, Jr., C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, *J. Amer. Chem. Soc.*, **82**, 2638 (1960).

(26) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *ibid.*, **76**, 6073 (1954).

TABLE III
6-SUBSTITUTED PURINE DERIVATIVES



Compd no.	X	Y	Z	Procedure	Time, hr	Yield, %	Recrystn[a] solvent	Mp, °C, dec
3	SH[b]	H	$CO_2C_2H_5$	B	1	71	DMF	201–202
4	Cl	H	$CO_2C_2H_5$	H	1	77	E	125–126
5	$SCH_2C_6H_4NO_2$-*p*	H	$CO_2C_2H_5$	A	3	94	E	147–148
6	SH[b]	H	$COCH_3$	C	2	56	DMF	275
7	$SCH_2C_6H_4NO_2$-*p*	H	$COCH_3$	C	2.5	82	EA	181–182
8	$SCO_2C_2H_5$	H	$CH_2C_6H_4NO_2$-*p*	D	20	40	E	126–127
9	$SCOC_6H_5$	H	$CH_2C_6H_4NO_2$-*p*	D	2	82	EA	172–174
10	SeH[b]	H	$CO_2C_2H_5$	B	1	75		189–191
11	Cl	H	$CO_2CH_2C_6H_5$	G	1	66	Et–PE	102
12	$SCH_2C_6H_4NO_2$-*p*	H	COC_6H_5	A	3	90	EA	164–165
13	$SeCH_2C_6H_4NO_2$-*p*	H	$CO_2C_2H_5$	A	4	93	E	147–150
14	$SCO_2C_2H_5$	NH_2	$CO_2C_2H_5$	E	1.5	65	Tol, E	158–161
15	$N(CH_3)_2$	H	$CO_2C_2H_5$	F	1	94	H	91–92
16	Cl	H	COC_2H_5	C	2	92	EA	139
17	Cl	H	COC_3H_7	C	2	92	EA	132
18	SH[b]	H	COC_2H_5	C	2	74	DMF	285–288
19	SH[b]	H	COC_3H_7	C	2	66	DMF	251–252
20	SCH_3	H	$COCH_3$	C	2	75	EA	151

[a] DMF, dimethylformamide; E, ethanol; EA, ethyl acetate; Et–PE, ethyl ether–petroleum ether (bp 30–60°) 1:1; Tol, toluene. [b] Drawn in thiol or selenol form for convenience.

solution of 6-chloropurine[26] (5 g, 32.3 mmol) and sodium hydroxide (1.36 g, 34 mmol) in 100 ml of water and the mixture was stirred for 1 hr at ice-bath temperature. The pH was adjusted to 5 with glacial acetic acid and the precipitate filtered to yield 5.64 g (77%) of product. Recrystallization from ethanol gave colorless plates: mp 125–126°; nmr δ 1.38 (t, 3), 4.49 (q, 2), 8.92 (s, 1), 9.00 (s, 1).

Reaction of Potassium Thiolacetate with 6-Chloropurine to Yield 6.—Potassium thiolacetate (1.26 g, 11 mmol) was added to a stirred solution of 6-chloropurine[26] (1.55 g, 10 mmol) in 30 ml of anhydrous dimethylformamide. The mixture turned reddish orange and some precipitate appeared. The mixture was stirred at room temperature for 4.5 hr. Water (30 ml) was added and the precipitate was filtered, washed with water, and dried to yield 0.9 g (46%) of product. Recrystallization from dimethylformamide gave a compound identical with **6** prepared from **1** by procedure C, as shown by spectral and analytical data and conversion to **7**.

Reaction of 6-S-Benzoylthio-9-*p*-nitrobenzylpurine (19) with Aniline.—Aniline (0.047 g, 0.5 mmol) was added to a solution of **9** (0.144 g, 0.37 mmol) in 3 ml of anhydrous dimethylformamide. The mixture was stirred for 1 hr at room temperature; a precipitate was formed. The mixture was evaporated to dryness and the solid residue extracted with 20 ml of ethyl acetate to yield 0.043 g (59%) of benzanilide, mp 163–164° (lit.[27] mp 163–164°). A mixture melting point with an authentic sample showed no depression and the infrared spectra were identical.

Registry No.—**1**, 5759-99-9; **3**, 18753-72-5; **4**, 18753-73-6; **5**, 18753-81-6; **6**, 18753-82-7; **7**, 18753-83-8; **8**, 18753-84-9; **9**, 18753-85-0; **10**, 18753-86-1; **11**, 18753-74-7; **12**, 18753-87-2; **13**, 18753-88-3; **14**, 18753-75-8; **15**, 18753-76-9; **16**, 18753-89-4; **17**, 18753-90-7; **18**, 18753-93-0; **19**, 18753-91-8; **20**, 18753-92-9.

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