The Relationship of the Structure of Mercury Derivatives of Purines to Their Reaction with Acylglycosyl Halides[1]

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The ultraviolet, infrared, and pmr spectra of a number of mercury or chloromercury purines has been compared with those of the corresponding sodium salts and N-7 and N-9 alkylpurines. These data indicate that the mercury derivatives are covalent and that the chloromercury group is attached to N-7 of 3-benzylhypoxanthine and the mercury group is attached to N-7 of theophylline. The chloromercury group is attached to N-9 of 1-benzylhypoxanthine, 1-benzylpurine-6(1H)-thione, and 6-dimethylaminopurine. The nucleosides obtained from these mercury or chloromercury derivatives show that acylglycosyl halides attack the nitrogen bearing the mercury group.

Three mechanisms for the N-substitution of conjugated heterocyclic compounds containing an imino group have been proposed[2]—an SE2, an SE2cB, and an SE2′—using the terminology of Ingold.[3] A study of the methylation of 4(5)-nitroimidazole showed that in alkaline media the reaction proceeded by the SE2cB mechanism, whereas in neutral media it proceeded by the SE2′ mechanism. That is, in the latter case, attack occurs at the tertiary nitrogen atom of the ring followed by proton loss from the imino group.[4]

This SE2′ mechanism has been proposed, but not substantiated, for the reaction of mercury derivatives of purines with acylglycosyl halides to form purine nucleosides.[5] If this proposed mechanism is correct, then the mercury or chloromercury group of most purine derivatives of this type must be attached to N-7, since the nucleosides formed in most cases are 9-nucleosides. However, theophylline (1,3-dimethylxanthine, XII)[6] and, more recently, other purines substituted at N-3 have been found to form 7-nucleosides exclusively,[7] which, if formed by the SE2′ mechanism, must have resulted from attack at N-7 of a mercury derivative in which the mercury or chloromercury group is attached to N-9.

It would appear that a more logical explanation of nucleoside formation from mercury derivatives of purines is that of displacement of the mercury or chloromercury group from the nitrogen to which it is attached. The formation of the mercury derivative (and attack by the acylglycosyl halide) is, in the case of 3-substituted purines, probably controlled sterically by the 3-substituent. In other purines other factors such as the relative electron density at N-7 and N-9 and the solubility of the particular mercury derivative may determine which mercury derivative is isolated, which in turn controls the position of attachment of the sugar.

Obviously, a better understanding of the mercury coupling reaction can be obtained from a precise knowledge of the structure of these mercury derivatives of purines. An examination of the reactions and spectra of the chloromercury derivatives (III and X) of 1-benzylhypoxanthine and 3-benzylhypoxanthine[7] has now provided the basis for a decision about the reaction of these chloromercury purines with acylglycosyl halides.

The infrared, pmr, and ultraviolet spectra of the chloromercury derivatives (III and X) of 1-benzylhypoxanthine and 3-benzylhypoxanthine were determined. Although the infrared and pmr spectra could not easily be correlated with the position of attachment of the chloromercury group, the pmr spectra, when compared with the spectra of the parent purines (I and VIII) (Scheme I) and N-benzyl derivatives (II and IX) and sodium salts of these purines (See Table I),

TABLE I
PMR SPECTRA

	Compd	τ, ppm: Purine ring protons		Phenyl protons	CH_2
	Hypoxanthine	1.88	2.03	...	...
I	1-Benzylhypoxanthine	1.49	1.81	2.69	4.73
	9-Benzylhypoxanthine	1.79	1.95	2.68	4.61
II	1,9-Dibenzylhypoxanthine	1.43	1.77	2.71	4.62, 4.77
III	1-Benzylhypoxanthine chloromercury	1.53	1.72	2.71	4.77
	1-Benzylhypoxanthine sodium salt	1.95	2.47	2.74	4.82
VI	1,7-Dibenzylhypoxanthine	1.49	1.57	2.70	4.40, 4.77
	7-Benzylhypoxanthine	1.59	1.98	2.65	4.39
VIII	3-Benzylhypoxanthine	1.40	1.79	2.62	4.53
	3-Benzylhypoxanthine sodium salt	1.81	2.55	2.67	4.63
X	3-Benzylhypoxanthine chloromercury	1.37	2.05	2.69	4.52
IX	3,7-Dibenzylhypoxanthine	1.45	1.63	2.58	4.38, 4.59
IV	1,9-Dibenzylpurine-6(1H)-thione	1.10	1.57	2.67	4.10, 4.57
V	1-Benzylpurine-6(1H)-thione chloromercury	0.93	1.67	2.67	4.19
VII	1,7-Dibenzylpurine-6(1H)-thione	1.08	1.37	2.69	3.85, 4.14
XIV	Bis(theophylline)mercury	...	2.26	...	6.52, 6.77[a]
XVIII	6-Dimethylaminopurine chloromercury	1.69	2.17	...	6.48[a]

[a] Methyl absorption.

indicate that the nitrogen–mercury bond is largely covalent[8] and that one isomer predominates. In the case of each chloromercury derivative, only two lines assignable to the 2- and 8-purine ring protons were observed. These lines occur at τ values different from both the parent purines and their sodium salts. As would be predicted, a significantly greater shielding effect on the ring protons is observed in the ionic sodium salts than in the parent purine, the dibenzylhypoxan-

(1) This work was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51.

(2) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1352 (1960).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953.

(4) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1357 (1960).

(5) G. M. Blackburn and A. W. Johnson, *ibid.*, 4347 (1960).

(6) J. A. Montgomery and H. J. Thomas, *Advan. Carbohydrate Chem.*, **17**, 301 (1962).

(7) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **28**, 2304 (1963).

(8) See also L. Pauling, "College Chemistry," 3rd ed, W. H. Freeman and Co., San Francisco and London, 1964, p 677.

SCHEME I

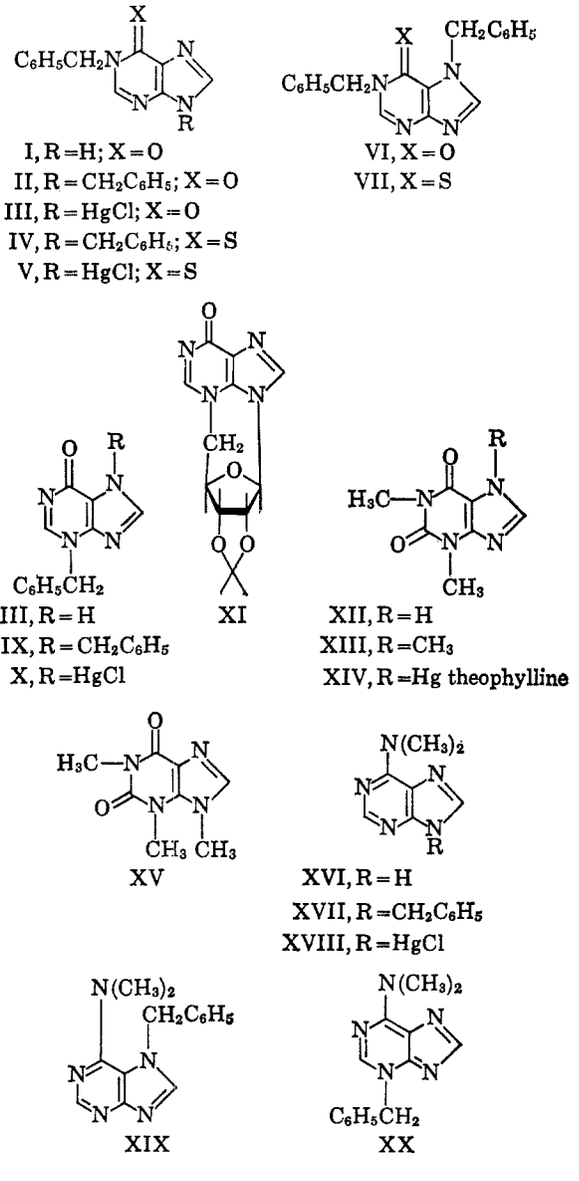

TABLE II

ULTRAVIOLET SPECTRAL DATA

	Compd	Neutral molecule, λ_{max} ($\epsilon \times 10^{-3}$)	Anion, λ_{max} ($\epsilon \times 10^{-3}$)
	Hypoxanthine	249 (10.5)	258 (11.2)
I	1-Benzylhypoxanthine	251 (9.2)	261 (9.8)
	9-Benzylhypoxanthine	251 (13.0)	255 (13.6)
II	1,9-Dibenzylhypoxanthine	253 (10.4)	...
III	1-Benzylhypoxanthine chloromercury	253.5 (9.0)	...
VI	1,7-Dibenzylhypoxanthine	257 (7.6)	...
	7-Benzylhypoxanthine	257 (9.5)	264 (10.0)
VIII	3-Benzylhypoxanthine	265 (13.8)	264 (10.5)
			275.5 (9.6)[a]
IX	3,7-Dibenzylhypoxanthine	266 (11.8)	...
X	3-Benzylhypoxanthine chloromercury	267 (11.8)	...
XI	Anhydronucleoside of 2′,3′-O-isopropylidene inosine[b]	256 (8.6)	...
IV	1,9-Dibenzylpurine-6(1H)-thione	323 (23.4)	...
V	1-Benzylpurine-6(1H)-thione chloromercury	321 (16.1)	...
VII	1,7-Dibenzylpurine-6(1H)-thione	244 (10.0) 274 (11.9)	...
XII	1,3-Dimethylxanthine (theophylline)[c]	271 (10.4) 330 (15.8)	
XIII	1,3,7-Trimethylxanthine (caffeine)[c]	273 (9.7)	...
XIV	Bis(theophylline)mercury	274 (18.2)	...
XV	1,3,9-Trimethylxanthine (isocaffeine)	239 (7.6) 267 (9.0)	...
XVI	6-Dimethylaminopurine	275 (17.3)	281 (17.6)
XVII	9-Benzyl-6-dimethylaminopurine	277 (19.7)	...
XVIII	6-Dimethylaminopurine chloromercury	277 (14.3)	...
XIX	7-Benzyl-6-dimethylaminopurine	293 (11.8)	...
XX	3-Benzyl-6-dimethylaminopurine	277 (12.5)[a] 295 (15.6)	...

[a] Shoulder. [b] Data from ref 4. [c] Data from ref 3.

thines (II and IX) or the chloromercury purines (III and X). Furthermore, a comparison of the chemical shifts of the absorption due to the ring protons of dibenzylhypoxanthines shows that the position of these lines is dependent on which ring nitrogens are substituted and, therefore, for example, one can distinguish between a mixture of 1,9- and 1,7-dibenzylhypoxanthine (II and VI) and either pure isomer.[9] Consequently, if either chloromercury purine were a mixture of isomers (both isomers being present in any significant quantity), this fact would have been evident from its pmr spectrum.

A comparison of the ultraviolet spectra of the chloromercury derivatives of these purines, 1-benzylpurine-6(1H)-thione, and 6-dimethylaminopurine[10] and of the mercury derivative of theophylline[11] with the appropriate N-alkylpurines clearly indicates the point of attachment[12] (See Table II). The spectra of the chloromercury derivatives (III and V) of 1-benzylhypoxanthine and 1-benzylpurine-6(1H)thione closely resemble the spectra of the corresponding 1,9-dibenzylpurines (II and IV) and are different from the 1,7-dibenzylpurines (VI and VII); those of the chloromercury derivative (X) of 3-benzylhypoxanthine and the mercury derivative (XIV) of theophylline resemble those of 3,7-dibenzylhypoxanthine (IX)[7] and 1,3,7-trimethylxanthine (caffeine, XIII),[13] respectively, and are different from the anhydronucleoside of 2,3-*O*-isopropylideneinosine (XI)[14] and from 1,3,9-trimethylxanthine (isocaffeine, XV).[13] The spectrum of the chloromercury derivative (XVIII) of 6-dimethylaminopurine resembles 9-benzyl-6-dimethylaminopurine (XVII) and is different from the 7 isomer (XIX).[15] Since in all cases we have compared the mercury deriva-

(9) This has, in fact, been done; it is easily possible to determine quantitatively the isomer ratio of such a mixture from its pmr spectrum.

(10) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954).

(11) L. Rosenthaler and A. Abelmann, *Ber. Deut. Pharm. Ges.*, **33**, 186 (1923). Although most sugar coupling reactions were actually carried out with silver theophylline [E. Fischer and B. Helferich, *Chem. Ber.*, **47**, 210 (1914)], this derivative was too insoluble to study.

(12) The pmr spectra of these mercury derivatives (V, XIV, and XVIII) also indicate that they are largely covalent and essentially one isomer in all three cases.

(13) J. M. Gulland, E. R. Holiday, and T. F. Macrae, *J. Chem. Soc.*, 1639 (1934).

(14) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28**, 3483 (1963).

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

tives with *both* the N-7 and the N-9 alkyl purines,[16] an assignment of N-7 as the predominant point of attachment of the chloromercury and mercury groups in the case of 3-benzylhypoxanthine and theophylline and of N-9 as the predominant point of attachment in the case of 1-benzylhypoxanthine, 1-benzylpurine-6(1H)-thione, and 6-dimethylaminopurine seems warranted.

Because it is known that the mercury derivatives of 3-benzylhypoxanthine and theophylline couple with acylglycosyl halides at N-7,[6,7] whereas those of 1-benzylhypoxanthine,[7] 1-benzylpurine-6(1H)-thione,[7] and 6-dimethylaminopurine[18] couple at N-9, the correlation between the structure of the mercury derivatives and the point of attack by the halides appears good, and thus supports the mechanism involving direct displacement of the mercury or chloromercury group from nitrogen by the incoming acylglycosyl halide.

(16) In the case of 6-dimethylaminopurine the chloromercury group could conceivably be attached to N-3. Fortunately the ultraviolet spectra of the 3-substituted purines resemble those of the 7-substituted purines[17] and thus attachment at N-3 can also be eliminated.

(17) N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocyclic Chem.*, **2**, 291 (1965).

(18) The reaction of the chloromercury derivative of 6-dimethylaminopurine with acylglycosyl halides is less clear cut than the other examples, since in some cases lesser amounts of the 3-glycosylpurines[19-22] are obtained and in the case of one sugar, α-bromoacetoglucose, apparently only the 3-isomer is obtained.[23] These results may be due to the unusual electron density at N-3 of this purine because of the 6-dimethylamino group. Other observations in these laboratories show that this purine has an unusual propensity for attack at N-3 by alkyl halides.[24]

(19) The compounds described in the following references[20-23] as 7-glycosylpurines have been shown to be 3-glycosylpurines [L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964)].

(20) H. M. Kissman, C. Pidacks, and B. R. Baker, *ibid.*, **77**, 18 (1955).

(21) B. R. Baker and R. E. Schaub, *ibid.*, **77**, 5900 (1955).

(22) B. R. Baker, J. P. Joseph, and R. E. Schaub, *ibid.*, **77**, 5905 (1955).

(23) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954).

(24) J. A. Montgomery and K. Hewson, unpublished observations.

Experimental Section

The ultraviolet spectra were determined with a Cary Model 14 spectrophotometer in aqueous solution at three different pH values, except for the spectra of the mercury derivatives which, because of solubility, were determined in aqueous ethanol.

The pmr spectra were determined in 10% (w/v) DMSO-d_6 solutions with a Varian A-60 spectrometer using tetramethylsilane as an internal reference.

The synthesis of most of the benzylpurines and mercury derivatives whose spectra are reported here have already been described.[7,9,10,14] The sodium salts of 1- and 3-benzylhypoxanthine were prepared by dissolving the purines in a stoichiometric amount of 1 *N* sodium hydroxide and evaporating the solutions to dryness. The salts were dried for 2.5 hr at 78° (0.07 mm) over P_2O_5.

1,9-Dibenzylpurine-6(1H)-thione.—A mixture of 1.26 g (4.00 mmoles) of 1,9-dibenzylhypoxanthine and 3.02 g (13.6 mmoles) of phosphorus pentasulfide was stirred and refluxed for 5 hr. The dark solution was evaporated *in vacuo* to about 8 ml and then slowly added to 1100 ml of boiling water. The gum that resulted gradually crystallized during 30 min of boiling and stirring of the aqueous mixture. After cooling, the mixture was filtered, and a crystalline material, which was a 1:1 mixture of 1,9-dibenzylhypoxanthine and product weighing 1.13 g, was obtained. Several recrystallizations from ethanol and finally from acetonitrile were necessary to obtain pure product: yield 127 mg (9.6%); mp 163–165°; ν_{max}, cm^{-1}, 3100, 3060, 3025 (CH), 1590, 1545, 1490 (C=C, C=N), 1450 (CH_2), 1160 and 1075, 735, 710 (monosubstituted phenyl).

Anal. Calcd for $C_{19}H_{16}N_4S$: C, 68.68; H, 4.85; N, 16.86. Found: C, 68.58; H, 5.03; N, 16.99.

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7-Glycosylpurines. II. Arabinofuranosides of Hypoxanthine and Adenine[1]

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A convenient method for the preparation of 3-substituted hypoxanthines, the requisite intermediates for the preparation of 7-glycosylhypoxanthines, from the easily prepared 3-substituted adenines by treatment with nitrosyl chloride has been developed. Reaction of the mercury derivatives of the 3-substituted hypoxanthines IIIa and IIIb with tri-O-acylglycosyl halides gave 3-substituted-7-(tri-O-glycosyl)hypoxanthines, from which the blocking groups were removed by hydrogenolysis and treatment with base to give 7-α-D-arabinofuranosylhypoxanthine (IX) and 7-β-D-ribofuranosylhypoxanthine (V). 7-α-D-Arabinofuranosyladenine (XIV) was prepared from the mercury derivative of N-benzoyl-3-benzyladenine (X) by the same reaction sequence.

The classical method for the synthesis of a glycosyl derivative of a purine—the coupling of a poly-O-acylglycosyl halide with the heavy metal derivative of the purine—normally leads to 9-glycosylpurines,[2] a result probably attributable to the fact that in most cases these heavy metals are attached to N-9 of the purine, since the glycosylpurines appear to be formed by direct displacement of the heavy metal.[6]

Recently we attacked the problem of the synthesis of 7-glycosylpurines and found that substitution of a purine at N-3 by a removable blocking group allowed the preparation of this type of nucleoside,[7,8] and 7-α-D-

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(2) Some 3-glycosylpurines[3] and 7-glycosylpurines[4,5] have been obtained.

(3) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954); B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *ibid.*, **19**, 1780 (1954); H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955); B. R. Baker and R. E. Schaub, *ibid.*, **77**, 5900 (1955); B. R. Baker, J. P. Joseph, and R. E. Schaub, *ibid.*, **77**, 5905 (1955); L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *ibid.*, **86**, 5320 (1964).

(4) Z. A. Sabarova, Z. P. Polyakova, and M. A. Prokofov, *Zh. Obshch. Khim.*, **29**, 215 (1959).

(5) S. R. Jenkins, F. W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965).

(6) J. A. Montgomery and H. J. Thomas, *ibid.*, **31**, 1411 (1966).

(7) J. A. Montgomery and H. J. Thomas, *ibid.*, **28**, 2304 (1962).

(8) J. A. Montgomery and H. J. Thomas, *J. Am. Chem. Soc.*, **85**, 2672 (1963); **87**, 5442 (1965).