Experimental

D-Xylosides.—Methyl D-xylopyranosides were made by standard methods[10] and methyl α-D-xylothiapyranoside was prepared as previously described.[11]

2,3,4-Tri-*O*-acetyl-α-D-xylothiapyranosyl Bromide.—1,2,3,4-Tetra-*O*-acetyl-D-xylothiapyranose[12] (5.0 g.) was dissolved at 0° in 50 ml. of a 30% solution of hydrobromic acid in glacial acetic acid. After warming to room temperature the mixture darkened slightly in 1 hr. At this point 50 ml. of ethanol-free chloroform was added and the reaction was poured into a mixture of ice and water. The chloroform layer was separated and the aqueous phase washed twice with fresh 25-ml. portions of chloroform. The combined chloroform extracts were washed rapidly with sodium bicarbonate solution and dried over calcium chloride and a small amount of anhydrous sodium bicarbonate. The solution was removed and evaporated to a sirup which was taken up in petroleum ether (b.p. 66–68°). Crystals formed on cooling, m.p. 115°; $[\alpha]^{25}D$ +245 (*c* 1.75 in methanol); yield, 4.5 g. (85%).

Anal. Calcd. for $C_{11}H_{15}BrO_6S$: S, 9.02. Found: S, 8.92.

Methyl 2,3,4-Tri-*O*-acetyl-β-D-xylothiapyranoside.—Five grams of the previous bromide was stirred with 100 ml. of anhydrous methanol and 25 g. of silver carbonate for 48 hr. The reaction mixture was filtered through Celite and concentrated to a sirup which crystallized upon addition of petroleum ether; yield, 3.0 g. (70%). Recrystallization from ethyl acetate–petroleum ether gave 2.0 g. of crystals, m.p. 122°; $[\alpha]^{25}D$ −70.6 (*c* 0.99 in methanol).

Anal. Calcd. for $C_{12}H_{18}O_7S$: S, 10.46; OCH_3, 10.12. Found: S, 10.41; OCH_3, 10.11.

Methyl β-D-Xylothiapyranoside.—The prior acetate (3.0 g.) was dissolved in 20 ml. of anhydrous methanol, and 1.0 ml. of 2 *N* sodium methoxide in methanol was added. After 16 hr. the solution was treated with 1 g. of cation-exchange resin Amberlite 120 (H), filtered, and concentrated. The residue crystallized from ethyl acetate, m.p. 162°; $[\alpha]^{25}D$ −66.3 (*c* 1.03 in water); yield, 1.3 g. (74%).

Anal. Calcd. for $C_6H_{12}O_4S$: S, 17.77; OCH_3, 17.22. Found: S, 17.51; OCH_3, 17.08.

Methyl 1-thio-β-D-xylopyranoside and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide were made by the method of Zinner, Koine, and Nimz.[13]

Solvolysis.—Rates of acid-catalyzed hydrolysis of methyl D-xylopyranosides and the sulfur analogs were determined by the method of Isbell and Frush.[14] Hydrolyses were conducted in 0.50 *N* hydrochloric acid solution at 75° and were followed polarimetrically (Table I).

Methanolysis of 0.05 *M* solutions of the acetobromosugars were conducted at 0.05 *M* sugar concentrations and followed polarimetrically at 23°. The rate for 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide was 178 sec.$^{-1}$ × 10^{-5} and that for 2,3,4-tri-*O*-acetyl-α-D-xylothiapyranosyl bromide was 4.36 sec.$^{-1}$ × 10^{-5}.

Acknowledgment.—This work was supported in part by the Department of Health, Education, and Welfare.

(10) G. N. Bollinback in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, Inc., New York, N. Y., 1963, p. 326–328.

(11) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962).

(12) J. C. P. Schwarz and K. C. Yule, *Proc. Chem. Soc.*, 417 (1961).

(13) H. Zinner, A. Koine, and H. Nimz, *Ber.*, **93**, 2705 (1960).

(14) H. S. Isbell and H. L. Frush, *J. Res. Natl. Bur. Std.*, **24**, 125 (1940).

Directive Influences in the Preparation of Purine Nucleosides[1]

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A study of some of the directive influences in the preparation of purine nucleosides by the conventional coupling reaction of acyl glycosyl halides with the chloromercuri salts of purines has led to the successful preparation of some new 7-D-pentofuranosylpurines.

The classical method for the synthesis of a glycosyl derivative of a purine or pyrimidine is the coupling of a poly-*O*-acyl glycosyl halide with the heavy metal salt of the purine or pyrimidine. This reaction leads to nucleosides "with a *C*-1–*C*-2-*trans* configuration in the sugar moiety regardless of the original configuration of *C*-1–*C*-2."[2] Applied to the reaction of heavy metal salss of purines with tri-*O*-acyl-D-ribofuranosyl halides, this rule predicts that the resulting purine ribonucleosides will have the β-configuration at the glycosyl center. Although the chemical basis for this stereochemical control of the formation of the glycosyl center was not understood at the time, Todd and co-workers fortuitously applied this reaction to the synthesis of adenosine (9-β-D-ribofuranosyladenine).[3] It was equally fortuitous that the condensation of tri-*O*-acetyl-D-ribofuranosyl chloride with 2,8-dichloroadenine led to the formation of the 9- rather than the 7-isomer.[4] Otherwise, the synthesis of the purine nucleosides that occur in the nucleic acids might have been delayed by the difficulties that have so far prevented the synthesis of the nucleoside known to occur in pseudo vitamin B_{12}. Although final proof is still lacking, this nucleoside is almost surely 7-α-D-ribofuranosyladenine.[6] At least one unsuccessful attempt to synthesize this nucleoside has been recorded.[7] Two problems must be solved for this synthesis to be accomplished. First, a method for producing the α-ribonucleoside must be devised and, second, a method for directing the entering sugar to *N*-7 rather than *N*-9 must be developed.

Since methods that can probably be applied to the production of the α-configuration of D-ribofuranose at *N*-7 have been described,[8,9] an investigation of the effect of certain substituents in the pyrimidine moiety of the purine ring on the position (*N*-7 or *N*-9) of alkylation or sugar coupling in the imidazole ring was undertaken.[10] The point of attack by various sugars

(1) This work is supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, contract no. SA-43-ph-1740, and was presented in part at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November, 1962.

(2) B. R. Baker, Ciba Foundation Symposium, *Chem. Biol. of Purines*, 120 (1957).

(3) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(4) B. R. Baker and co-workers were less fortunate in their initial studies leading to the synthesis of the "aminonucleoside" of puromycin.[5]

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

(6) W. Friedrich and K. Bernhauer, *Angew. Chem.*, **68**, 580 (1956); *Chem. Ber.*, **89**, 250g (1958).

(7) G. M. Blackburn and A. W. Johnson, *J. Chem. Soc.*, 4347 (1960).

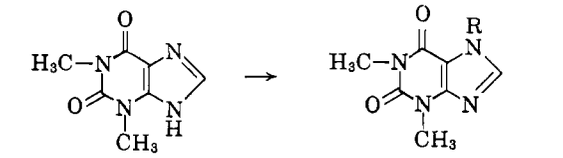
(8) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 2004 (1958).

(9) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **24**, 1618 (1959).

(10) A procedure for the preparation of 7-alkylpurines has been described but is not applicable to the preparation of 7-glycosylpurines.[11]

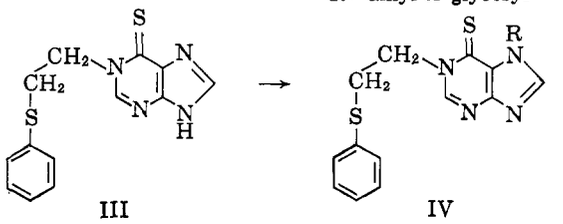
(11) J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **26**, 4469 (1961).

on the heavy metal salts of a number of purines has been discussed.[12] It was known at the time this work was initiated that in all cases theophylline (I)[13] directed alkyl groups or sugar moieties to *N*-7 (II).[14] It also was known that a 1-substituted derivative of purine-6(1*H*)-thione (III) directed alkylation at *N*-7 (IV).[15] It appeared then that the portion of these two purines involving the 6- and 1-substituents (V) was important for 7-substitution (VI). These facts led us to investigate the alkylation and coupling reactions of 1-benzylhypoxanthine (VII)[16] and 1-benzylpurine-6(1*H*)thione (XI).



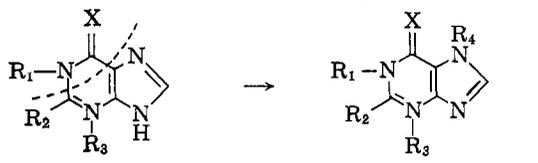
I II

R = alkyl or glycosyl



III IV

R = $C_6H_5CH_2$-, CH_3-



V VI

Despite the foregoing precedents, the chloromercuri derivative of 1-benzylhypoxanthine (VII), prepared in good yield by the method of Fox,[17] reacted with tri-*O*-benzoyl-D-ribofuranosyl chloride[18] in the usual manner[19] to give 2′,3′,5′-tri-*O*-benzoyl-1-benzylinosine (VIIIa) from which the benzoyl groups were removed by treatment with methanolic sodium methoxide. The 1-benzylinosine (IX) thus prepared was identified by a comparison of its ultraviolet and infrared spectra and chromatographic behavior with those of 1-benzylinosine (IX) prepared by the method of Shaw.[16] Catalytic debenzylation of 1-benzylinosine (IX) was slow and incomplete but did give a low yield of inosine (XII). Although this reaction sequence did not result in the preparation of the desired 7-ribonucleoside, it does constitute a novel synthesis of inosine, which will undoubtedly prove useful in the synthesis of other nucleosides of hypoxanthine and related purines.

Since the sugar coupling reaction of 1-benzylhypoxanthine (VII) was found to take place at *N*-9, the alkylation of VII with benzyl chloride in *N*,*N*-dimethylformamide in the presence of potassium carbonate[20] was investigated and found to give 1,9-dibenzylhypoxanthine (X). The identity of X was established by the fact that benzylation of 9-benzylhypoxanthine (XIII)[23] gave the same product.

Thiation of the blocked nucleosides, 2′,3′,5′-tri-*O*-benzoyl-1-benzylinosine (VIIIa) and 2′,3′,5′-tri-*O*-acetyl-1-benzylinosine (VIIIb) could not be effected with phosphorus pentasulfide in pyridine[24]; this failure may be due to the fact that enolization of the ring carbonyl cannot take place.[25] 1-Benzylhypoxanthine (VII) was successfully thiated by means of phosphorus pentasulfide in tetralin[27] to give 1-benzylpurine-6(1*H*)-thione (XI), although the yield was low and a large amount of purine-6(1*H*)-thione also was obtained, indicating that debenzylation occurs under these conditions. The thiation takes place more readily in pyridine and no debenzylation occurs.

The chloromercuri derivative of 1-benzylpurine-6(1*H*)-thione, prepared in the manner described before, was coupled with both the benzoyl and acetyl ribofuranosyl chlorides; the acetyl sugar gave superior results. Removal of the acetyl groups from the coupling product 9-(tri-*O*-acetyl-β-D-ribofuranosyl)-1-benzylpurine-6(1*H*)-thione gave 1-benzyl-9-β-D-ribofuranosylpurine-6-(1*H*)-thione (XV), whose identity was established by treatment with alcoholic ammonia. The N^6-benzyladenosine (XIX) obtained results from ring opening and reclosure.[29] This material was identical with authentic N^6-benzyladenosine[30] prepared from 6-chloro-9-β-D-ribofuranosylpurine (XVIII). Reaction of XV with dilute sodium hydroxide[16] instead of ammonia gave 5-amino-1-β-D-ribofuranosylimidazole-4-(*N*-benzylthiocarboxamide) (XX).

Since the alkylation of 1-substituted-purine-6(1*H*)-thiones was known to take place at *N*-7, the fact that the coupling reaction took place at *N*-9 is somewhat surprising. It can only be concluded that the mechanism of these two reactions is quite different. This conclusion is not unreasonable since the coupling reaction is carried out with the neutral chloromercuripurine in the nonpolar solvent xylene, whereas the

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

(13) Reference has already been made to the observations of Baker[4] on the coupling reactions of N^6,N^6-dimethyladenine and N^6,N^6-dimethyl-2,8-di(methylthio)adenine. An approach to 7-nucleosides based on these observations has been described.[7]

(14) For references see the sources cited in ref. 12 and 13.

(15)(a) J. A. Montgomery, R. W. Balsiger, A. L. Fikes, and T. P. Johnston, *J. Org. Chem.*, **27**, 195 (1962); (b) see also L. B. Townsend and R. K. Robins, *ibid.*, **27**, 990 (1962).

(16) E. Shaw, *J. Am. Chem. Soc.*, **80**, 3899 (1958).

(17) J. J. Fox, N. Yung, I. Wempen, and I. L. Doerr, *ibid.*, **79**, 5060 (1957).

(18) Since the use of the benzoyl sugar made it impossible to examine the ultraviolet spectrum of crude products, we later changed to tri-*O*-acetyl-D-ribofuranosyl chloride. This change permitted us to examine the ultraviolet spectrum of the crude blocked nucleosides, but did not affect the orientation of the entering sugar. See H. M. Kissman, C. Pidacks, and B. R. Baker, *ibid.*, **79**, 5060 (1957).

(19) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, *J. Org. Chem.*, **22**, 954 (1957).

(20) The position of alkylation depends on the solvent used[15b] and on whether base is employed (*i.e.*, whether the anion or the neutral molecule undergoes alkylation). For example, adenine undergoes alkylation at the 3-nitrogen in the absence of base,[21] but undergoes alkylation at *N*-9 in the presence of base.[22]

(21)(a) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962); (b) J. W. Jones and R. K. Robins, *ibid.*, **84**, 1914 (1962).

(22) J. A. Montgomery and H. J. Thomas, unpublished results.

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

(24) J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *ibid.*, **80**, 1669 (1958).

(25) In a related case in the pteridine series, thiation was successful.[26]

(26) W. R. Boon and G. Bratt, *J. Chem. Soc.*, 412 (1957).

(27) Previously the use of tetralin as solvent was successful for the thiation of hypoxanthine[28a] but not for guanine, because of the insolubility of the latter compound in tetralin.[28b] Solubility was no problem here.

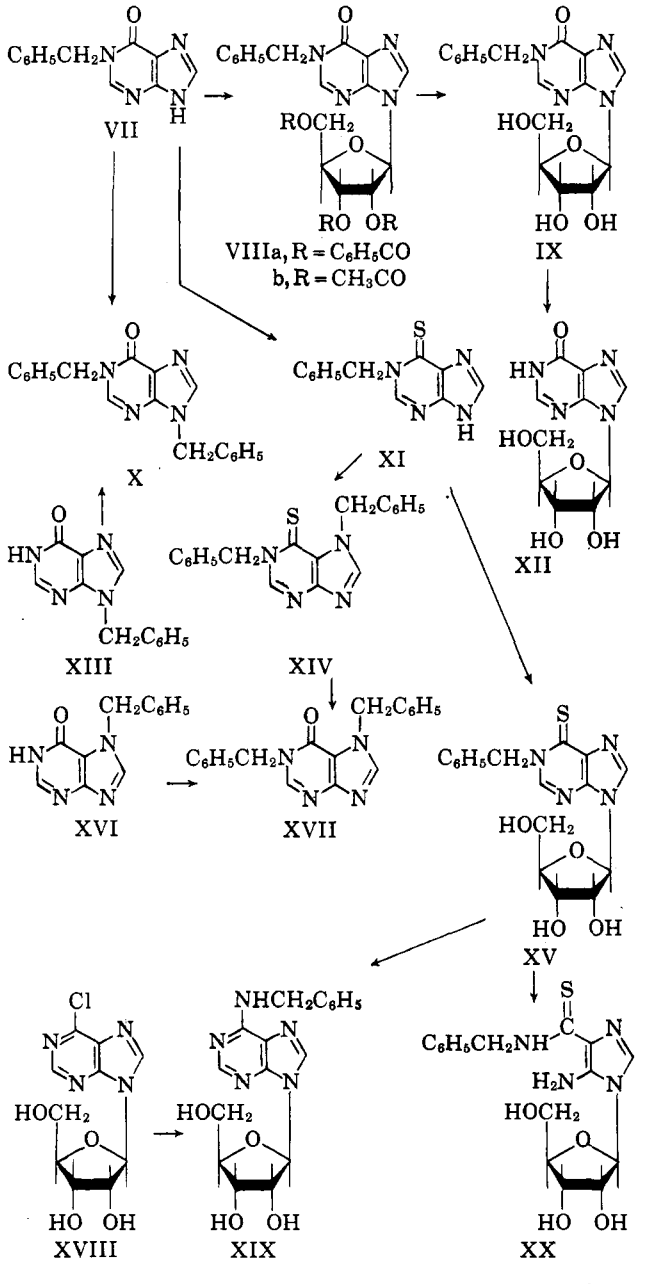
(28) (a) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952); (b) **77**, 1676 (1955).

(29) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).

(30) H. M. Kissman and M. J. Weiss, *ibid.*, **21**, 1053 (1956).

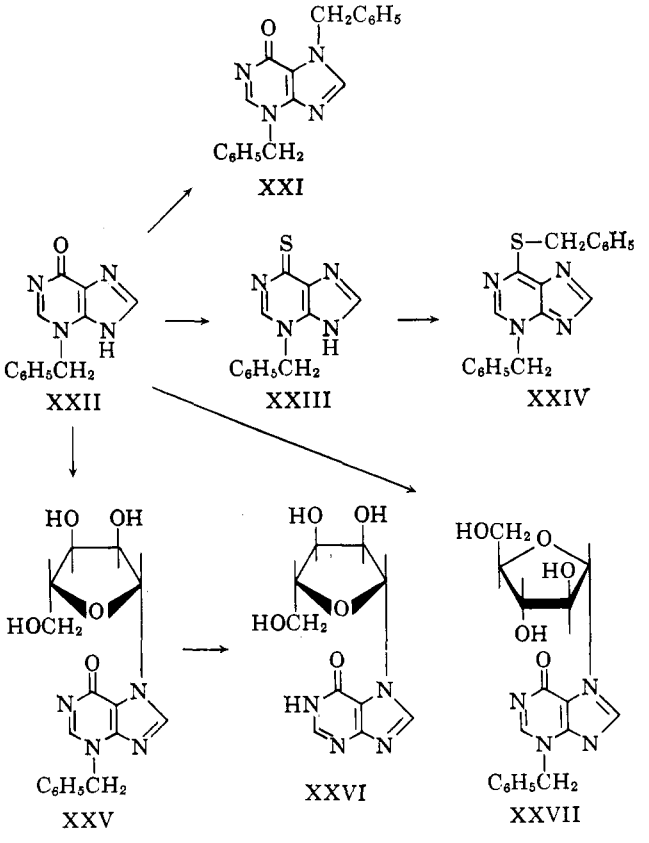
alkylation is carried out in the dipolar aprotic solvent *N*,*N*-dimethylformamide under basic conditions. As a further check on this observation 1-benzylpurine-6(1*H*)-thione was benzylated in the latter manner. The product of this benzylation was found to be 1,7-dibenzylpurine-6(1*H*)-thione by its conversion[15b] to 1,7-dibenzylhypoxanthine, which was also prepared by the benzylation of 7-benzylhypoxanthine.[23]

The results obtained with the conventional chloromercuri coupling reaction of 1-benzylhypoxanthine (VII) and 1-benzylpurine-6(1*H*)-thione (XI) caused us to investigate the recently described acidic fusion reaction of purines with tetra-*O*-acyl ribofuranosides.[31] This procedure gave a low yield of ribonucleoside from VII and an excellent yield from XI using *p*-toluenesulfonic acid as catalyst in both cases; however, only the 9-isomers (IX and XV) were formed.



After all efforts to obtain 7-nucleosides from the 1-benzyl derivatives of hypoxanthine and purine-6(1*H*)-thione resulted in the production of the 9-ribonucleosides only, we turned our attention to the preparation and reactions of 3-benzylhypoxanthine (XXII) and 3-benzylpurine-6(3*H*)-thione (XXIII). The reaction sequence described by Bergmann, *et al.*,[32] for the synthesis of 3-methylhypoxanthine was used for the preparation of 3-benzylhypoxanthine, although it was necessary to modify each reaction because of the low water solubility of the benzyl compounds. These modifications gave excellent yields of the intermediate compounds. Thiation of 3-benzylhypoxanthine (XXII) gave 3-benzylpurine-6(3*H*)-thione in good yield.

The chloromercuri derivative of 3-benzylhypoxanthine (XXII) was prepared in the usual manner,[17] but this method failed with 3-benzylpurine-6(3*H*)-thione (XXIII). It was found, however, that if, instead of adding sodium hydroxide solution to remove the hydrogen chloride formed in the reaction, the ethanol solution of the purine and mercuric chloride was simply boiled to expel the hydrogen chloride gas an excellent yield of analytically pure chloromercuri-3-benzylpurine-6(3*H*)-thione was obtained. This novel method for the preparation of chloromercuri salts of purines was found to be applicable to the preparation of chloromercuripurine and chloromercuri-N^6-benzoyladenine. It is suggested that this modification may be useful in the preparation of the chloromercuri derivatives of other purines and of pyrimidines.



Unfortunately, 3-benzylpurine-6(3*H*)-thione (XXIII) in the fusion reaction with tetra-*O*-acetyl-D-ribofuranoside and its chloromercuri derivative in its reaction with tri-*O*-acetyl-D-ribofuranosyl chloride proved to be too unstable to permit the formation of a ribonucleoside. The fact that benzylation of 3-benzylpurine-

(31) Y. Ishido and T. Sato, *Bull. Chem. Soc. Japan*, **34**, 347 (1961).

(32) F. Bergmann, G. Levin, A. Kalmus, and H. Kwietny-Govrin, *J. Org. Chem.*, **26**, 1504 (1961).

TABLE I

ULTRAVIOLET SPECTRA

No.	Compound	pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 7 λ_{max}	pH 7 $\epsilon \times 10^{-3}$	pH 13 λ_{max}	pH 13 $\epsilon \times 10^{-3}$
	Inosine	249	11.6	248	12.1	253	13.0
	7-β-D-Ribofuranosylhypoxanthine[a]	251	...	...	...	263	...
XXVI	7-β-D-Ribofuranosylhypoxanthine	251	...	257	...	263	...
XXV	3-Benzyl-7-β-D-ribofuranosylhypoxanthine	255	7.1	266	12.1	266	11.4
XXVII	7-α-D-Arabinofuranosyl-3-benzylhypoxanthine	255	10.8	266	13.2	266	13.0
XXI	3,7-Dibenzylhypoxanthine	256	10.1	266	11.8	267	11.7

[a] Data from ref. 35.

6(3*H*)-thione gave 3-benzyl-6-(benzylthio)purine (XXIV)[33] indicates that the reaction of tri-*O*-acetyl-D-ribofuranosyl chloride with the chloromercuri derivative of XXIII also may take place on S^6, rather than on a ring nitrogen, giving rise to an *S*-ribofuranoside that is not stable under the conditions of the reaction.[36]

Work with the chloromercuri derivative of 3-benzylhypoxanthine (XXII) was more successful and a moderate yield of a nucleoside from XXII and tri-*O*-acetyl-D-ribofuranosyl chloride was obtained. This nucleoside was debenzylated in low yield to 7-β-D-ribofuranosylhypoxanthine (XXVI) identified by a comparison of its ultraviolet spectrum and chromatographic behavior with those of XXVI prepared in another way[37] (see Table I). The identity of XXVI establishes that coupling of the chloromercuri derivative of XXII took place at *N*-7 to give 3-benzyl-7-β-D-ribofuranosylhypoxanthine (XXV). In the same manner 7-α-D-arabinofuranosyl-3-benzylhypoxanthine (XXVII) was prepared in good yield and further benzylation of 3-benzylhypoxanthine gave 3,7-dibenzylhypoxanthine (XXI). That XXI and XXVII are actually 7-substituted hypoxanthine derivatives is clearly shown by a comparison of their ultraviolet spectra with that of XXV (see Table I). The assignment of the β-configuration to XXVI and the α-configuration to XXVII is based on the *trans* rule[2] already discussed.

The work described here, which has led to the preparation of 7-glycosylhypoxanthines, is being extended to other purines and other sugars.

Experimental

The melting points reported were determined on a Kofler-Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 or a Beckman DK-2 (optical densities at the maxima with a Beckman DU). The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 221 spectrophotometer. The R_f values were determined by the descending chromatographic technique on Whatman no. 2 paper in water-saturated butyl alcohol.

Chloromercuri-1-benzylhypoxanthine.—To a solution of 1.20 g. (4.42 mmoles) of mercuric chloride and 1.20 g. (4.42 mmoles) of 1-benzylhypoxanthine (VII)[16] in 200 ml. of 50% aqueous ethanol was added 2.00 g. of Celite. To the resulting suspension was added dropwise with vigorous stirring 41.8 ml. of 0.1058 *N* sodium hydroxide (4.42 mmoles). The white suspension that was obtained was stirred at room temperature for 45 min. and then chilled. The white precipitate was collected, washed with water until free of chloride ions, then with ethanol, and finally with ether. It was dried for 24 hr. at 110° (0.07 mm.) over phosphorus pentoxide; yield, 3.98 g. (98%). This yield includes the 2.00 g. of Celite; therefore, the yield of pure product was 1.98 g.

In a small run the addition of Celite was omitted and an analytical sample of the chloromercuri salt obtained.

Anal. Calcd. for $C_{12}H_9ClHgN_4O \cdot 1^1/_2H_2O$: C, 30.64; H, 2.14; N, 11.94. Found: C, 30.61; H, 2.14; N, 11.84.

Chloromercuri-3-benzylhypoxanthine.—To a suspension of 8.8 g. (38.9 mmoles) of 3-benzylhypoxanthine (XXII) and 10.6 g. (38.9 mmoles) of mercuric chloride in 1600 ml. of absolute ethanol was added slowly a solution of 1.6 g. (38.9 mmoles) of sodium hydroxide in 40 ml. of water. The resulting yellow suspension became white after 40 min. of refluxing with stirring. It was diluted with 1 l. of distilled water and chilled before the precipitate was collected, washed with water until free of chloride ions, then with ethanol, and finally with ether. It was dried for 30 hr. at 78° (0.07 mm.) over phosphorus pentoxide; yield, 16.7 g. (93%).

Chloromercuri-1-benzylpurine-6(1*H*)-thione.—In the manner described for the preparation of the chloromercuri-3-benzylhypoxanthine, 3.14 g. (including 1.60 g. of Celite) (98%) of chloromercuri-1-benzylpurine-6(1*H*)-thione was obtained from 774 mg. (3.20 mmoles) of 1-benzylpurine-6(1*H*)-thione (XI) and 869 mg. (3.2 mmoles) of mercuric chloride suspended in 250 ml. of absolute ethanol.

Chloromercuri-3-benzylpurine-6(3*H*)-thione.—A solution of 2.72 g. (10.0 mmoles) of 3-benzylpurine-6(3*H*)-thione (XXIII) and 272 mg. (10.0 mmoles) of mercuric chloride in 1 l. of absolute ethanol was boiled to expel hydrogen chloride. After a few minutes a white precipitate began to form and the yellow color of the solution gradually faded. After 15-min. boiling the mixture was cooled and the solid collected by filtration, washed with ethanol, and then with ether. It was recrystallized from a mixture of *N*,*N*-dimethylformamide and ethanol; yield, 4.8 g. (100%); λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—326 (25.5), pH 7—321 (13.2), pH 13 (unstable).

Anal. Calcd. for $C_{12}H_9ClHgN_4S$: C, 29.63; H, 2.07; N, 11.52. Found: C, 29.68; H, 2.62; N, 11.30.

In the same manner **chloromercuripurine** was prepared in 90% yield and **chloromercuri N^6-benzoyladenine** was prepared in 94% yield.

1-Benzylinosine (IX).[16] **A.**—A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, prepared from 3.06 g. (6.1 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, in 50 ml. of dry xylene was added to an azeotropically dried suspension of 2.80 g. (6.1 mmoles) of chloromercuri-1-benzylhypoxanthine mixed with 3.00 g. of Celite in 200 ml. of xylene. After a 2-hr. reflux period the mixture was filtered and the filter cake washed with boiling chloroform (three 200-ml. portions). The residue

(33) Under different conditions Bergmann[32] found that 3-methylpurine-6(3*H*)-thione underwent methylation at S^6 to give 3-methyl-6-(methylthio)-purine. Robins[21b] found that under conditions very similar to those employed by us methylation of purine-6(1*H*)-thione gave 3-methyl-6-(methylthio)purine. Since we have found that, under the same conditions, 6-(methylthio)purine was benzylated with difficulty to give a mixture of 7-benzyl-6-(methylthio)purine and 9-benzyl-6-(methylthio)purine,[34] we suggest that the dimethylation of purine-6(1*H*)-thione under neutral conditions in a dipolar aprotic solvent proceeds *via* 3-methylpurine-6(3*H*)-thione. Previously we found that, under basic conditions, dibenzylation of purine-6(1*H*)-thione gave a mixture of 9-benzyl-6-(benzylthio)purine and 7-benzyl-6-(benzylthio)purine.[35] Bergmann's results in aqueous base[32] cannot safely be applied to the alkylation of purine-6(1*H*)-thione in *N*,*N*-dimethylacetamide since Robins found that, in the presence of base, 1-methylpurine-6(1*H*)-thione gave 1-methyl-6-(benzylthio)purine in water and 7-benzyl-1-methylpurine-6(1*H*)-thione in *N*,*N*-dimethylformamide.

(34) J. A. Montgomery and H. J. Thomas, unpublished data.

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

(36) The *N*-3,S^6-dialkyl derivatives of purine-6(3*H*)-thione are decomposed easily.

(37) J. Baddiley, J. G. Buchanan, F. E. Hardy, and J. Stewart, *J. Chem. Soc.*, 2893 (1959).

from evaporation of the xylene filtrate *in vacuo* was dissolved in 200 ml. of chloroform and this solution, after combination with the chloroform extracts, was washed with 30% potassium iodide (two 300-ml. portions), then water (two 300-ml. portions), dried with magnesium sulfate, and then evaporated to dryness *in vacuo*. The residue was a quantitative yield of the blocked ribonucleoside, 671 mg. of which was dissolved in 57 ml. of methanol containing 4 ml. of 0.1 *N* sodium methoxide. After a half-hour reflux period, this solution was neutralized with acetic acid and evaporated to dryness *in vacuo*. The resulting residue was dissolved in 50 ml. of water, and the aqueous solution was extracted with chloroform (two 50-ml. portions), treated with charcoal, filtered, and evaporated to dryness *in vacuo*. The residue crystallized from ethanol solution after seeding; yield, 89 mg. (25%); m.p. 226° (lit.[16] m.p. 219–222°); R_f 0.68; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—251 (10.0); pH 7—249 (9.95); pH 13—243 (sh) (9.80), 249 (9.95).

B.—A 10% yield of 1-benzylinosine was obtained by the fusion of 1-benzylhypoxanthine with tetra-*O*-acetyl-D-ribofuranose in the presence of *p*-toluenesulfonic acid.

1,9-Dibenzylhypoxanthine (X). A.—A solution of 1.00 g. (4.4 mmoles) of 1-benzylhypoxanthine (VII)[16] and 1.12 g. (8.8 mmoles) of benzyl chloride in 100 ml. of *N,N*-dimethylformamide containing a suspension of 615 mg. (4.4 mmoles) of anhydrous potassium carbonate was stirred at 95° for 2.5 hr. The insoluble solid was collected and the filtrate evaporated to dryness *in vacuo*. The residue was twice suspended in water and the suspensions evaporated *in vacuo*. The residue from this treatment crystallized upon the addition of ethanol; yield, 320 mg. One recrystallization of this material from ethanol gave the analytical sample; yield, 260 mg. (20%); m.p. 208°; R_f 0.90. λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—253 (10.6), pH 7—252 (10.4), pH 13—252 (10.4).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.11; H, 5.10; N, 17.70. Found: C, 71.84; H, 4.97; N, 17.50.

B.—In the same manner the benzylation of 200 mg. (0.88 mmole) of 9-benzylhypoxanthine[23] gave 199 mg. (72%) of 1,9-dibenzylhypoxanthine that was identical in all respects with analytical sample described.

1-Benzylpurine-6(1*H*)-thione (XI).—A mixture of 3.00 g. (13.3 mmoles) of 1-benzylhypoxanthine (VII)[16] and 10.0 g. (45.0 mmoles) of phosphorus pentasulfide in 90 ml. of pyridine refluxed with vigorous stirring for 5 hr. The dark solution was filtered to remove trace amounts of insolubles and evaporated *in vacuo* to about 30 ml. It was then poured slowly into 800 ml. of boiling water. The resulting light brown mixture was boiled with stirring for 20 min. After cooling, the mixture was filtered, and a brown powder, weighing 2.40 g., was obtained.

The crude material was recrystallized from 250 ml. of ethanol with the aid of charcoal to give a white crystalline solid; yield, 1.64 g. (51%); m.p. 269–271°.

The analytical sample was obtained from a previous run using tetralin. It was dried 16 hr. at 110° (0.07 mm.) over phosphorus pentoxide; m.p. 271°; R_{Ad} 0.90; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—324 (16.8); pH 7—238 (sh) (10.8), 325 (18.6); pH 13—240 (sh) (11.9), and 326 (23.6).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.49; H, 4.16; N, 23.12. Found: C, 59.31; H, 4.39; N, 23.11.

3-Benzylpurine-6(3*H*)-thione (XXIII).—In the manner described before for 1-benzylpurine-6(1*H*)-thione, 1.69 g. (62%) of 3-benzylpurine-6(3*H*)-thione (XXIII) was obtained from 2.52 g. (11.2 mmoles) of 3-benzylhypoxanthine (XXII) and 8.40 g. (37.8 mmoles) of phosphorus pentasulfide in 133 ml. of pyridine. The analytical sample was obtained by recrystallization of this material from a mixture of ethanol and *N,N*-dimethylformamide (3:1); R_f 0.67; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—336 (23.4), pH 7—341 (24.9), pH 13—338 (24.0).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.49; H, 4.16; N, 23.12. Found: C, 59.28; H, 4.24; N, 22.81.

1,7-Dibenzylpurine-6(1*H*)-thione (XIV).—The benzylation of 242 mg. of 1-benzylpurine-6(1*H*)-thione (XI) as described before for X gave 125 mg. (38%) of 1,7-dibenzylpurine-6(1*H*)-thione; m.p. 155°; R_f 0.92; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—245 (sh) (8.23) and 330 (15.0); pH 7—244 (10.0) and 330 (15.8); pH 13—244 (10.7) and 330 (15.8).

Anal. Calcd. for $C_{19}H_{16}N_4S$: C, 68.68; H, 4.85; N, 16.86. Found: C, 68.22; H, 5.10; N, 16.41.

1-Benzyl-9-β-D-ribofuranosylpurine-6(1*H*)-thione (XV). A.—A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride, prepared from 3.88 g. (12.2 mmoles) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribose, in 100 ml. of dry xylene was added to an azeotropically dried suspension of 5.81 g. (12.2 mmoles) of chloromercuri-1-benzylpurine-6(1*H*)-thione mixed with 6.00 g. of Celite in 400 ml. of xylene. The mixture was refluxed with stirring for 2 hr. and then filtered. The filter cake was washed with hot chloroform (three 100-ml. portions). The xylene filtrate was evaporated to dryness *in vacuo;* the residue was dissolved in 100 ml. of chloroform and the solution was combined with the chloroform washings. This solution was washed with 30% aqueous potassium iodide (two 200-ml. portions), then water (200 ml.), dried with magnesium sulfate, and evaporated to dryness *in vacuo*. The blocked ribonucleoside, a light yellow syrup that weighed 6.7 g., was refluxed for 0.5 hr. in 100 ml. of absolute methanol containing 4.88 ml. of 1 *N* sodium methoxide. This solution was then chilled in an ice bath and neutralized with dilute acetic acid. A slight amount of insoluble material was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The dark residue was recrystallized from 100 ml. of ethanol with charcoal treatment; yield, 3.15 g. (69%); m.p. 231–234° with sintering at 90–100°; R_f 0.71; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—324 (20.7); pH 7—323 (22.4); pH 13—324 (25.0).

The analytical sample was obtained by another recrystallization from ethanol. It was dried at 78° (0.07 mm.) over phosphorus pentoxide for 16 hr.

Anal. Calcd. for $C_{17}H_{18}N_4O_4S \cdot H_2O$: C, 52.01; H, 4.60; N, 14.30. Found: C, 52.04; H, 4.62; N, 14.28.

B.—A finely ground mixture of 242 mg. (1.00 mmole) of 1-benzylpurine-6(1*H*)-thione, 318 mg. (1.00 mmole) of tetra-*O*-acetyl-D-ribofuranose, and 19 mg. (0.10 mmole) of *p*-toluenesulfonic acid was heated *in vacuo* at 175–180° for 5 min. The dark residue was dissolved in 50 ml. of chloroform, and the solution was treated with charcoal, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. A solution of the residue in 12 ml. of absolute methanol containing 0.5 ml. of 1 *N* sodium methoxide was refluxed for 0.5 hr., neutralized with dilute acetic acid, and evaporated to dryness. The residue was crystallized from 7 ml. of ethanol; yield, 290 mg. (77%). This material was identical with the ribonucleoside prepared by the chloromercuri coupling.

1,7-Dibenzylhypoxanthine (XVII). A.—A solution of 400 mg. (1.77 mmoles) of 7-benzylhypoxanthine[23] and 446 mg. (3.54 mmoles) of benzyl chloride in 40 ml. of *N,N*-dimethylformamide containing 245 mg. (1.77 mmoles) of dry potassium carbonate as a suspension was heated at 105° with vigorous stirring for 16 hr. The insoluble material was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with water and again evaporated to dryness *in vacuo*. The residue was then triturated with cold 1 *N* sodium hydroxide to remove unchanged starting material. The gummy material remaining after decantation of the base was dissolved in 20 ml. of chloroform. The chloroform solution was washed with 20 ml. of cold 1 *N* sodium hydroxide, then with water, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. The residue crystallized from 3 ml. of ethanol as a white solid; yield, 100 mg. (18%); m.p. 105–106°; m.m.p. with 1,7-dibenzylhypoxanthine (from B following) 104–106°.

B.—Chlorine gas was passed into a suspension of 168 mg. (0.51 mmole) of 1,7-dibenzylpurine-6(1*H*)-thione in 50 ml. of ethanol at 15° for 2 hr., in which time complete solution was effected. The residue from evaporation of the solution to dryness *in vacuo* was recrystallized from methanol to give a 54% yield of the hydrochloride of 1,7-dibenzylhypoxanthine. The hydrochloride was dissolved in water, the solution neutralized with ammonium hydroxide, and the free base obtained as a white solid; yield, 51 mg.; m.p. 105–106°; R_f 0.88; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—255 (8.8), pH 7—256 (8.4), pH 13—256 (8.4).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.33; H, 5.19; N, 17.55.

N^6-Benzyladenosine (XIX).[30] **A.**—A solution of 287 mg. (1.00 mmole) of 6-chloro-9-β-D-ribofuranosylpurine (XVIII) in 30 ml. of absolute ethanol containing 1.07 g. (10.0 mmoles) of benzylamine was refluxed for 5 hr. The solution was evaporated to dryness *in vacuo* and the residue was crystallized from 10 ml. of ethanol to give a white solid; yield, 213 mg. (60%); m.p. 167° (lit.[30] 177–179°); R_f 0.81; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—265 (20.2), pH 7—269 (20.2), pH 13—269 (20.2). Since there was some discrepancy between the melting point of this sample and that previously reported, this sample was recrystallized from ethanol and analyzed.

Anal. Calcd. for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 57.32; H, 5.47; N, 19.58.

B.—A solution of 300 mg. (0.8 mmole) of 1-benzyl-9-β-D-ribofuranosylpurine-6(1*H*)-thione (XV) in 30 ml. of ethanolic ammonia was heated in a bomb at 160° for 24 hr. It was filtered and evaporated to dryness. The residue was recrystallized from 20 ml. of ethanol with charcoal treatment; yield, 105 mg. (37%); m.p. 165–167°; R_f 0.81; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—264 (19.7), pH 7—268 (20.0), pH 13—268 (20.2). The infrared spectrum of this product was identical to that of the sample of 6-benzylamino-9-β-D-ribofuranosylpurine prepared by method A.

5-Amino-1-β-D-ribofuranosylimidazole-4-(*N*-benzylthiocarboxamide) (XX).—A solution of 400 mg. of 1-benzyl-9-β-D-ribofuranosylpurine-6(1*H*)-thione (XV) in 120 ml. of 95% ethanol and 2.8 ml. of 6 *N* sodium hydroxide was refluxed for 3 hr., cooled, and the pH adjusted to 8 with 1 *N* ethanolic hydrogen chloride. Insoluble inorganic material was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in 30 ml. of ethanol, the solution filtered, evaporated to about 10 ml., and then diluted with 10 ml. of water. A crystalline solid was obtained; yield, 228 mg. (58%); m.p. 113°.

The analytical sample was obtained by recrystallization from ethanol. It was dried for 6 hr. at 78° (0.07 mm.) over phosphorus pentoxide, R_f 0.80; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—286 (12.8) and 321 (15.4); pH 7—275 (12.5) and 327 (16.3); pH 13—274 (12.2) and 327 (16.3).

Anal. Calcd. for $C_{16}H_{20}N_4O_4S$: C, 52.75; H, 5.53; N, 15.38. Found: C, 52.45; H, 5.56; N, 15.18.

3,7-Dibenzylhypoxanthine (XXI).—A solution of 680 mg. (3.0 mmoles) of 3-benzylhypoxanthine and 759 mg. (6.0 mmoles) of benzyl chloride in 100 ml. of *N*,*N*-dimethylacetamide containing 414 mg. (3.0 mmoles) of anhydrous potassium carbonate as a suspension was stirred vigorously and heated at 105° for 16 hr.; it was then filtered and evaporated to dryness. The residue was triturated with water and the water was evaporated *in vacuo*. The residue crystallized from acetone–ethanol (5 ml. of each) as a white solid; yield, 705 mg. (74%); m.p. 181–183°; R_f 0.84; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—256 (10.1), pH 7—266 (11.8), pH 13—267 (11.7).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.27; H, 5.01; N, 17.76.

6-Amino-1-benzyl-4-hydroxypyrimidine-2(1*H*)-thione.—This compound was prepared in 64% yield by refluxing 6.73 g. (40.2 mmoles) of benzylthiourea and 4.55 g. (40.2 mmoles) of ethyl cyanoacetate in 44 ml. of absolute ethanol containing 67 mmoles of sodium ethoxide, m.p. 262°.

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.61; H, 4.75; N, 18.01. Found: C, 56.62; H, 4.82; N, 18.19.

5,6-Diamino-1-benzyl-4-hydroxypyrimidine-2(1*H*)-thione.—To a solution of 466 mg. (2.00 mmoles) of 6-amino-1-benzyl-4-hydroxypyrimidine-2(1*H*)-thione in 138 ml. of dioxane was added 0.30 ml. (2.20 mmoles) of isoamyl nitrite. The solution was stirred for 2.5 hr. and then evaporated *in vacuo* to about 35 ml. After the solution was cooled for several hours, the purple 6-amino-1-benzyl-4-hydroxy-5-nitrosopyrimidine-2(1*H*)-thione was collected by filtration and dried; yield, 100%.

The nitroso compound was added to 115 ml. of boiling water in small amounts. Each addition gave a purple color that was discharged by addition of small amounts of sodium hydrosulfite. This process was repeated until all the nitroso compound had been added. The resulting yellow solution was filtered to remove insoluble material and cooled. A crystalline solid was obtained; yield, 486 mg. (98%); m.p. 242°; R_f 0.74; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—284 (17.4); pH 7—242 (8.65) and 303 (15.1); pH 13—242 (13.7) and 264 (8.20).

The analytical sample was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.20; H, 4.87; N, 22.56. Found: C, 53.22; H, 4.83; N, 22.69.

3-Benzylhypoxanthine (XXII).—To 2.08 g. (8.40 mmoles) of 5,6-diamino-1-benzyl-4-hydroxypyrimidine-2(1*H*)-thione was added 84 ml. of diethoxymethyl acetate. Immediately upon solution, a precipitate began to form. The mixture was stirred for 1 hr., then chilled, and filtered. The 2-thio-3-benzylhypoxanthine was obtained as a yellow solid; yield, 1.77 g. (82%).

3-Benzylhypoxanthine was obtained in 50% yield by refluxing an ammonium hydroxide solution of the thio compound with Raney nickel. It was recrystallized from ethanol, m.p. 250°; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—254 (11.3); pH 7—265 (13.8); pH 13—264 (10.5) and 277 (sh) (9.24).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.77. Found: C, 63.79; H, 4.40; N, 24.48.

3-Benzyl-6-benzylthiopurine (XXIV).—A solution of 242 mg. (1.00 mmole) of 3-benzylpurine-6(3*H*)-thione (XXIII) and 253 mg. of benzyl chloride in 10 ml. of *N*,*N*-dimethylacetamide containing as a suspension 138 mg. (1.00 mmole) of dry potassium carbonate was stirred and heated at 110° for 16 hr. The solution was filtered and evaporated to dryness. The residue crystallized from ethanol–acetone as a white solid; yield, 46 mg. (14%).

The analytical sample was obtained by recrystallization from ethanol–acetone; m.p. 147–148°; R_f 0.92; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—234 (9.55), 275 (6.04), and 321 (29.2); pH 7—239 (14.7) and 316 (22.4); pH 13 (unstable).

Anal. Calcd. for $C_{19}H_{16}N_4S$: C, 68.75; H, 4.85; N, 16.86. Found: C, 69.25; H, 4.66; N, 16.91.

A second run gave 866 mg. (58%) of pure XXIV from 1.10 g. of XXIII. No other purine could be detected in the reaction mixture.

3-Benzyl-7-β-D-ribofuranosylhypoxanthine (XXV).—A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride, prepared from 2.00 g. (6.3 mmoles) of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose, in 75 ml. of dry xylene was added to an azeotropically dried suspension of 2.90 g. (6.3 mmoles) of chloromercuri-3-benzylhypoxanthine and 3.33 g. of Celite in 250 ml. of xylene. The mixture was refluxed with stirring for 50 min. and then filtered. The filter cake was washed with hot chloroform (three 75-ml. portions). The xylene filtrate was evaporated to dryness *in vacuo;* the residue was dissolved in 75 ml. of chloroform and this solution was combined with the chloroform washings. The solution was washed with 30% potassium iodide (two 150-ml. portions), then water (150 ml.), dried with magnesium sulfate, and evaporated to dryness *in vacuo*. The blocked riboside, 3.52 g. of a light orange syrup, was dissolved in 36 ml. of methanol containing 2 ml. of 1 *N* sodium methoxide, and the solution was refluxed for 0.5 hr. It was neutralized with 1 *N* acetic acid and evaporated to dryness. The residue was dissolved in ethanol, and the solution was treated with charcoal and evaporated to dryness. The residue was dissolved in 200 ml. of water and the aqueous solution washed with chloroform (two 200-ml. portions), then treated with charcoal, and evaporated to dryness. This residue was dissolved in 20 ml. of ethanol and precipitated by the addition of 20 ml. of ethyl acetate; yield, 670 mg. (33%). This material was shown to be essentially pure by its ultraviolet and infrared spectra and its chromatographic behavior in four solvent systems.

The analytical sample was prepared by chromatographing some of this material on a cellulose column using water-saturated butanol as the eluent; the eluate was evaporated to dryness and the residue was crystallized from ethanol; R_f 0.51; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—255 (10.8), pH 7—266 (13.2), pH 13—266 (13.0).

Anal. Calcd. for $C_{17}H_{18}N_4O_5 \cdot {}^1/_2C_2H_5OH$: C, 56.58; H, 5.55; N, 14.69; O, 23.18. Found: C, 56.48; H, 5.45; N, 14.68; O, 23.71.

7-β-D-Ribofuranosylhypoxanthine (XXVI).—A solution of 200 mg. (0.56 mmole) of 3-benzyl-7-β-D-ribofuranosylhypoxanthine in 20 ml. of ethanol was hydrogenated at atmospheric pressure with the batch-wise addition of 600 mg. of 5% palladium-on-charcoal catalyst. The catalyst was filtered off and washed with ethanol. The filtrate and washing were combined and evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of ethanol and precipitated as a solid by the addition of 5 ml. of ethyl acetate; yield, 10 mg. (6.7%); the ultraviolet spectrum and R_f values of this material were in agreement with those reported for 7-β-D-ribofuranosylhypoxanthine prepared by another method.[37] Furthermore, its infrared spectrum was different from inosine and the differences were similar to those found between the infrared spectra of 7- and 9-benzylhypoxanthine. Baddiley, *et al.*, did not report the infrared spectrum of their 7-β-D-ribofuranosylhypoxanthine.

7-α-D-Arabinofuranosyl-3-benzylhypoxanthine (XXVII).—To an azeotropically dried suspension of 4.20 g. (9.1 mmoles) of chloromercuri-3-benzylhypoxanthine and 4.20 g. of Celite in 200 ml. of xylene was added with vigorous stirring at reflux temperature a solution of 4.77 g. (9.1 mmoles) of 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide in 50 ml. of dry xylene. Refluxing and stirring were continued for 1 hr. During this time a trans-

lucent tan mixture resulted. The cooled mixture was filtered and the xylene filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in 100 ml. of chloroform. The original xylene-insoluble material was extracted with boiling chloroform (three 100-ml. portions). All the chloroform solutions were combined and washed with 30% potassium iodide (two 200-ml. portions), then water (200 ml.), dried over magnesium sulfate, and evaporated *in vacuo* to dryness.

The orange syrup thus obtained was dissolved in 60 ml. of absolute methanol and 3 ml. of 1 *N* sodium methoxide in methanol was added. The dark red solution that resulted was refluxed for 30 min., evaporated *in vacuo* to about 25 ml., and then poured quickly into 25 ml. of cold water. Amberlite IR-120 (H) ion-exchange resin was added in small batches to the stirred mixture until pH 7 was obtained. The resin was removed by filtration and washed first with water and then with methanol until the methanol removed no more color. The filtrate and washings were combined and evaporated to dryness *in vacuo*. The residue was dissolved in 30 ml. of warm water and the aqueous solution was washed with 30-ml. portions of chloroform until the chloroform layer remained colorless (four 30-ml. portions). The aqueous layer was evaporated to dryness *in vacuo*. The residue, dried thoroughly by evaporating it twice with 25 ml. of absolute ethanol, was crystallized from 15 ml. of hot ethanol with charcoal treatment; yield, 1.19 g. (37%).

The analytical sample was obtained by recrystallization from absolute ethanol. It was dried at 78° (0.07 mm.) over phosphorus pentoxide for 16 hr.; m.p. 208–210°; R_f 0.49; λ_{max} mμ ($\epsilon \times 10^{-3}$): pH 1—255 (7.05), pH 7—266 (12.1), pH 13—266 (11.4).

Anal. Calcd. for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 56.93; H, 5.12; N, 15.51.

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The Direct Conversion of Chloropurines to Fluoropurines[1]

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A general method is described for the direct conversion of various 7- or 9-alkylated 2-, 6-, and 8-chloropurines to the corresponding fluoropurines. This procedure utilizes silver fluoride in the presence of toluene or xylene. Several of the requisite methylated chloropurine intermediates have been prepared for the first time.

Although new general methods for the preparation of chloropurines[2,3] and bromopurines[4] have been described recently, only a few fluoropurines have been prepared. The conversion of 2-aminopurines to the corresponding 2-fluoropurines[5] by the modified Schieman reaction appears to be limited to the synthesis of 2-fluoropurines.[6]

The synthesis of 9-substituted 6-fluoropurines has been reported recently[7] by the ring closure of the appropriate 5-amino-4-substituted-amino-6-fluoropyrimidine. This method, however, is obviously inapplicable to the preparation of 8-fluoropurines.

The synthesis of various fluorinated nitrogen heterocyclic compounds has been reported from the corresponding chloro derivatives in the *s*-triazines,[8-11] pyrimidines,[7,12,13] and thiadiazoles.[14] In all instances reported, the halogen exchange was accomplished by repeated distillation of the chloro heterocycle over antimony trifluoride dichloride,[9,10] potassium fluorosulfinate,[8] or silver fluoride[7,11-14] to yield the final product.

This general method of synthesis of fluoro derivatives of nitrogen heterocycles, however, is limited to compounds which are relatively volatile and which do not decompose during the distillation processes. In the application of this procedure to the synthesis of more complex fluoroheterocycles, *i.e.*, those possessing a condensed ring system such as purine, considerable difficulty was encountered. In an effort to accomplish halogen exchange successfully in purine derivatives, a variety of reaction conditions were tried in the hope that the required fluoropurines would be isolated without decomposition.

Finger and Starr[15] report the use of potassium fluoride in dimethylformamide for the conversion of various chloropyridines to fluoropyridines. This method, however, when applied to 6-chloropurine, gave only decomposition and polymeric products. It has now been discovered that treatment of the appropriate 7- or 9-methylchloropurines with silver fluoride in refluxing toluene or xylene provides a facile and general route for the preparation of the corresponding methylated 2-, 6-, and 8-fluoropurines. This method has the advantage that the product need not be distilled to be recovered. The cooled reaction mixture need only to be filtered to remove the silver fluoride and silver chloride, and the solid product is recovered from the hydrocarbon filtrate. In this manner, treatment of

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