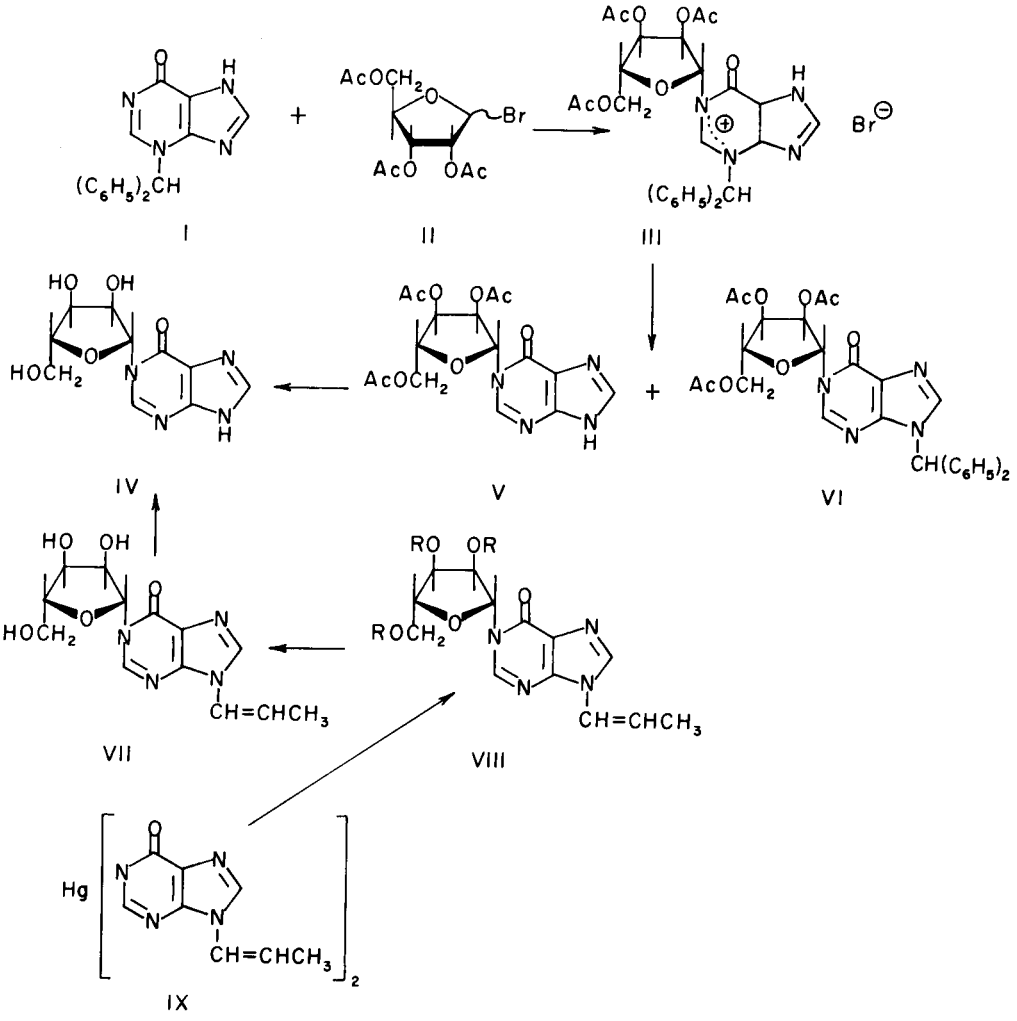
The Synthesis of 1-β-D-Ribofuranosylhypoxanthine (I)

John A. Montgomery and H. Jeanette Thomas

Kettering-Meyer Laboratory, Southern Research Institute

Sir:

The synthesis of only one 1-ribofuranosylpurine — by ring closure of 5-aminocytidine with diethoxymethyl acetate (2) — has been described in the literature, although many papers describing the synthesis of 3- and 7-glycosylpurines (in addition to the classical work on 9-glycosylpurines) have appeared. Previous work from this laboratory has resulted in preparation of 7-glycosylhypoxanthines by two different methods (3-5). One of these methods involves the reaction of tri-*O*-benzoylribofuranosyl bromide with 9-propenylhypoxanthine followed by oxidative removal of the propenyl group (5). Since we have shown that the reaction of alkyl halides with 3-substituted hypoxanthines takes place at *N*-1 of the purine ring (6), it appeared that the reaction of an acylglycosyl halide with a 3-substituted



TABLE

Ultraviolet Spectral Data

Compound	0.1 *N* HCl		*p*H 7 Buffer		0.1 *N* NaOH	
	λ max (ϵ x 10^{-3})	λ min (ϵ x 10^{-3})	λ max (ϵ x 10^{-3})	λ min (ϵ x 10^{-3})	λ max (ϵ x 10^{-3})	λ min (ϵ x 10^{-3})
1,3-Dibenzylhypoxanthinium bromide (a)	254 (10.2) 280 sh	236 (7.1)	245 sh 290-300 (0.55)		unstable	
3-Benzhydryl-1-(tri-*O*-acetyl-β-D-ribofuranosyl)hypoxanthine bromide (III)	253 (9.78) 280 sh	238 (7.98)	255 sh 290-310 (3.13)		unstable	
3,7-Dibenzylhypoxanthine (b)	255.5 (10.1)	237 (7.06)	266 (11.8)	238.5 (5.8)	266 (11.7)	238 (5.5)
1-Benzylhypoxanthine (b)	249 (9.58)	228 (5.60)	251 (9.15)	230 (4.8)	261 (9.75)	239 (4.67)
1-Methylhypoxanthine (c)	249 (9.40)	219 (2.22)	250 (9.00)	224 (2.70)	260 (9.60)	236 (3.36)
1-β-D-Ribofuranosylhypoxanthine (IV)	249 (9.58)	223 (3.76)	251 (8.55)	228 (3.91)	261 (8.53)	238 (3.32)
1,9-Dibenzylhypoxanthine (b)	253 (10.6)	232 (6.2)	253 (10.4)	232.5 (5.5)	252 (10.4)	232.5 (5.7)
9-Benzhydryl-1-β-D-ribofuranosylhypoxanthine (VI)	253 (9.50)	238 (7.93)	253 (9.10)	238 (7.38)	254 (8.96)	240 (7.65)
1-Methyl-9-propenylhypoxanthine (c)	220 (18.4) 253 sh		225 (24.2) 254 sh 270 sh		225 (25.0) 254 sh 270 sh	
9-Propenyl-1-β-D-ribofuranosylhypoxanthine (VII)	223 (21.4) 253 sh		226 (26.3) 270 sh		226 (25.8) 270 sh	

(a) Data from Ref. 6. (b) Data from Ref. 3. (c) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, 30, 3235 (1965).

hypoxanthine followed by removal of the 3-substituent would provide a practical route to the preparation of 1-glycosylhypoxanthines, which could be converted to other 1-glycosylpurines. The preparation of such compounds would permit a comparison of the biological activity of 1-, 3-, 7-, and 9-glycosylpurines.

We now wish to report an exceedingly facile synthesis of 1-β-D-ribofuranosylhypoxanthine (IV). Reaction of 3-benzhydrylhypoxanthine (I) (4) with tri-*O*-acetylribofuranosyl bromide (II) in *N*,*N*-dimethylacetamide at room temperature for five days gave a 39% yield of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-benzhydrylhypoxanthinium bromide (III), identified by elemental and spectral analysis (7). Heating III in ethanol effected the removal of the benzhydryl group to give 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)hypoxanthine (V), which was converted into 1-β-D-ribofuranosylhypoxanthine (8) by treatment with methanolic sodium methoxide; and a small amount of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9-benzhydrylhypoxanthine (VI), the formation of which is yet another example of group migration from *N*-3 to *N*-9 of the purine ring (9,10). The position of attachment of the ribosyl moiety of IV was firmly established by the ultraviolet spectra of it and its derivatives (III and VI) (see Table), and by its synthesis from the mercuri derivative of 9-propenylhypoxanthine (IX) (11). The β-configuration of IV was also established by the alternative synthesis (IX→VIII→VII→IV) by application of the *trans* rule (13), and by conversion of IV to its 2′,3′-*O*-isopropylidine derivative, the pmr spectrum of which showed a coupling constant of 2.2 Hz for the H_1'-H_2' coupling, which precludes the α, or *cis*, configuration (14).

It is of interest that reaction of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with 9-propenylhypoxanthine at *N*-7 gave a 1:1 mixture of α- and β-anomers, whereas in the present work reaction at *N*-1 gave no detectable amount of α-anomer. The difference in the mechanism of these two reactions is under investigation.

REFERENCES

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

(2) J. J. Fox and D. Van Praag, *J. Org. Chem.*, **26**, 526 (1961).

(3) J. A. Montgomery and H. J. Thomas, *ibid.*, **28**, 2304 (1963).

(4) H. J. Thomas and J. A. Montgomery, *ibid.*, **31**, 1413 (1966).

(5) J. A. Montgomery and H. J. Thomas, *J. Heterocyclic Chem.*, 5, 303 (1968).

(6) J. A. Montgomery, K. Hewson, S. J. Clayton, and H. J. Thomas, *J. Org. Chem.*, **31**, 2202 (1966).

(7) All new compounds were characterized by elemental analyses (C, H, and N), thin-layer chromatography, and ultraviolet, infrared, and pmr spectral data.

(8) Previously the reaction of the chloromercuri derivative of 3-benzhydrylhypoxanthine with 2,3,5-tri-*O*-acetylribofuranosyl chloride was incorrectly reported to give, after removal of the blocking groups, 7-β-D-ribofuranosylhypoxanthine (4). The identity of this compound with 1-β-D-ribofuranosylhypoxanthine described in this paper has been established by their ultraviolet, infrared, and pmr spectra. It is now apparent that under the condition employed in the coupling reaction the chloromercuri derivative of 3-benzhydrylhypoxanthine rearranged to the chloromercuri derivative of 9-benzhydrylhypoxanthine, which then reacted with the glycosyl halide. The chloromercuri derivative of 3-benzylhypoxanthine is more stable, does not rearrange, and does give authentic 7-β-D-ribofuranosylhypoxanthine (2).

(9) B. Shimizu and M. Miyaki, *Tetrahedron Letters*, 2059 (1965).

(10) J. A. Montgomery, H. J. Thomas, and K. Hewson, *Chem. Ind.* (London), 1596 (1965).

(11) The synthesis of bis(1,9-β-D-glucopyranosyl)hypoxanthine from the bromomercuri derivative of 9-β-D-glucopyranosylhypoxanthine has been reported (12).

(12) T. H. Hashizume and H. Yamazaki, *Tetrahedron Letters*, 3839 (1967).

(13) B. R. Baker, *Ciba Found. Symp. Chem. Biol. Purines*, 120 (1957).

(14) N. J. Leonard and R. A. Laursen, *J. Am. Chem. Soc.*, **85**, 2026 (1963).

Received August 9, 1968 Birmingham, Alabama 35205