The Synthesis and Properties of Substituted 6-Hydroxylaminopurines*

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ABSTRACT: The 2-amino-, 2-amino-9-β-D-ribofuranosyl-, 2-hydroxy-, 9-methyl-, 9-methoxymethyl-, and 8-aza-6-hydroxylaminopurines have been synthesized. The first two possessed an outstanding inhibitory activity against several mouse leukemias. The syntheses were accomplished by the interaction of 2-substituted 6-halogeno-, methylmercapto-, or benzylmercaptopurines with hydroxylamine under the catalytic influence of chloride ion, although catalyst was not required for the last three mentioned compounds above. Whereas 6-hydroxylaminopurine was toxic by virtue of its conversion to 2,8-dihydroxyadenine, its ribosyl derivative was not toxic. It is presumed that these agents exert their biological effects by interference with purine metabolism.

The antileukemic and antitumor activities of 6-hydroxylaminopurine (6-HAP)[1] and 9-β-D-ribofuranosyl-6-hydroxylaminopurine (Giner-Sorolla *et al.*, 1965, 1966; A. Giner-Sorolla, J. H. Burchenal, and A. Bendich, 1966, unpublished data) prompted a study of related derivatives. 6-Hydroxylaminopurine (Giner-Sorolla and Bendich, 1958; Giner-Sorolla, 1958) was found to be toxic to cells of mouse sarcoma 180 in tissue culture as seen in the inhibition of mitosis and induction of nuclear degeneration when compared with normal embryo skin fibroblasts (Biesele, 1957). The effect of sarcoma 180 *in vivo* was slight as was observed with other types of hydroxylamines such as 6-hydroxyamidinopurine (Giner-Sorolla and Bendich, 1958; Giner-Sorolla, 1958) and purine-6-carboxamic acid (A. Giner-Sorolla, 1966, unpublished data).

Administration of 6-HAP increased the survival time of mice bearing sarcoma 180 ascites cells and inhibited the growth of Ehrlich ascites carcinoma (Sartorelli *et al.*, 1964). These authors concluded that 6-HAP may function as an antagonist of adenine and hypoxanthine metabolism in the mammalian cell, and attributed the inhibition of cell growth to its interference with the biosynthesis of purine nucleotides. Similar conclusions have been drawn regarding the growth inhibitory activity of 9-β-D-ribofuranosyl-6-hydroxylaminopurine, 2-amino-6-hydroxylaminopurine (IV), and 2-amino-9-β-D-ribofuranosyl-6-hydroxylaminopurine (VI) (J. H. Burchenal, 1966, unpublished data; H. S. Rosenkranz, 1966, personal communication).

Results

Although the free hydroxylaminopurines showed a growth inhibition of several types of mouse leukemias, the compounds were quite toxic. On the other hand, the ribosyl derivatives of 6-HAP and IV, which possessed a marked antileukemic activity, were much less toxic (*cf.* Giner-Sorolla, 1958).

In the present series of hydroxylaminopurines, we have found crystal inclusions in the kidneys of mice only when 2-hydroxy-6-hydroxylaminopurine (VIII) was administered; these crystals have not yet been identified. The absence of acute toxicity after administration of the two ribosyl derivatives (of 6-HAP and IV) in mice might be due to the greater solubility of their metabolic products.

We have observed that hydroxylaminopurines with no substituents in the 9 position are easily transformed to 6,6′-azoxypurines by treatment with alkali (pH 8–10) in the presence of air. Such a conversion does not occur in the case of any of the 9-substituted hydroxylaminopurines in the pH range 8–10; at higher pH values, however, 6,6′-azoxypurine derivatives are formed. The formation of azoxy derivatives from the hydroxylamino compounds could contribute to their toxicity as we have found that 6,6′-azoxypurine (Bendich *et al.*, 1957; A. Giner-Sorolla, 1966, unpublished data) is toxic in mice (lethal dose *ca.* 50 mg/kg).

The synthesis of substituted 6-hydroxylaminopurines was carried out from the corresponding halogeno or S-substituted derivatives. In contrast to the ease with which 6-chloropurine and its 9-β-D-ribosyl derivative were converted into the corresponding hydroxylamines

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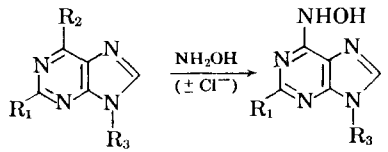
[1] Abbreviations used: 6-HAP, 6-hydroxylaminopurine; 2,8-DHA, 2,8-dihydroxyadenine; TFA, trifluoroacetic acid.

TABLE I: Reactions of Substituted 6-Hydroxylaminopurines.



Starting Material			Amt	For-	Re-	Mole Ratio NH_2OH: Purine	Re-action Time	Yield	Mp	Reaction Product			Calcd			Found		
R_1	R_2	R_3	(g)	mula	agent	(M)	(hr)	(%)	(°C)	R_1	R_3	Formula	C	H	N	C	H	N
NH_2	SCH_3	H	4	I[a]	A[b]	20	18	97										
NH_2	$SCH_2C_6H_5$	H	2.5	II[c]	A	20	18	76	310[d]	NH_2	H	IV, $C_5H_6N_6O\cdot H_2O$	32.60	4.38	45.64	32.94	3.87	45.65
NH_2	Cl	H	2	III[e]	A	50	48	60										
NH_2	SCH_3	β-D-Ribo-furan-osyl	2.5	V[f]	A	20	6	94	232[g]	NH_2	β-D-ribo-furan-osyl	VI, $C_{10}H_{14}N_6O_5\cdot H_2O$	37.97	5.09	26.57	37.78	4.91	26.92
OH	SCH_3	H	3	VII[h]	A	100[i]	1	85	355[d]	OH	H	VIII, $C_5H_5N_5O_2$	35.93	3.01	41.91	36.22	3.21	41.75
H	Cl	CH_3	4	IX[j]	B	20	6	73	244[g]	H	CH_3	X, $C_6H_7N_5O$	43.63	4.27	42.41	43.32	4.70	42.28
H	Cl	CH_2OCH_3	3	XI[k]	B	20	6	91	185[g]	H	CH_2OCH_3	XII, $C_7H_9N_5O_2$	43.07	4.65	35.88	43.03	4.97	35.69
H	Cl	H (8-aza)	5	XIII[l]	B	20	8	93	305[d]	H	H (8-aza)	XIV, $C_4H_4N_6O$	31.58	2.65	55.25	31.53	2.92	55.48

[a] Prepared according to Daves *et al.* (1960). [b] Reagent A indicates 1 M ethanolic hydroxylamine solution with 1% hydroxylamine hydrochloride; reagent B, 1 M ethanolic hydroxylamine solution only. [c] Leonard *et al.* (1959); kindly supplied by Dr. E. Falco. [d] Preheated, explodes. [e] Hitchings and Elion (1957); *cf.* also footnote *a*; supplied by Aldrich Chemical Co., Milwaukee, Wis. [f] Prepared according to Fox *et al.* (1958). [g] Preheated, effervescence. [h] Synthesized from 6-thioxanthine (Beaman, 1954) with methyl iodide and dilute NaOH. [i] Due to the low solubility of VII, a large volume of ethanolic hydroxylamine was required. [j] Prepared according to Robins and Lin (1957). [k] Supplied by Aldrich Chemical Co., Milwaukee, Wis. [l] 8-Aza-6-chloropurine (XIII) was obtained according to Ballweg (1962).

TABLE II: Ultraviolet Spectral Properties of 6-Substituted Hydroxylaminopurines.

Compound	λ_{max} mμ (ε × 10^{-3})			λ_{min} mμ (ε × 10^{-3})		
	HCl (N)	pH 6.7[a]	NaOH (N)	HCl (N)	pH 6.7[a]	NaOH (N)
6-Hydroxylaminopurine	271 (13.30)[b]	268 (11.80)	*c*	234 (2.38)[b]	232 (2.02)	*c*
9-β-D-Ribofuranosyl-6-hydroxylamino-purine[d]	265 (17.70)[e]	265 (14.30)	252[c,f]	232 (3.31)[e]	230 (4.65)	230[c,f]
2-Amino-6-hydroxylaminopurine hydrate (IV)	254 (11.50) 283 (9.72) 310 (5.15) (sh)	253 (8.37) 282 (10.88)	*c*	238 (9.76) 270 (9.29)	239 (7.69) 259 (8.14)	*c*

2-Amino-9-β-D-ribofuranosyl-6-hydroxyl-aminopurine hydrate (VI)	258 (7.70) 298 (8.04)	262 (7.73) (sh) 280 (9.75)	256 (7.88) 267 (7.65) (sh) 292–307 (2.36)	231 (0.12) 275 (4.94)	243 (5.05)	233 (5.42)
2-Hydroxy-6-hydroxylaminopurine (VIII)	294 (12.16)	272 (13.08)	275 (10.10)	249 (5.44)	234 (6.51)	244 (7.66)
6-Hydroxylamino-9-methylpurine (X)	268 (15.20)	268 (13.30)	253 (8.89) 289–302 (3.09)	234 (3.42)	234 (3.94)	230 (7.20) 258 (1.52)
6-Hydroxylamino-9-methoxymethyl-purine (XII)	265 (16.0)	266 (13.20)	252 (10.20) 290–300 (2.92)	229 (2.99)	230 (4.70)	229 (7.14) 360 (1.25)
8-Aza-6-hydroxylaminopurine (XIV)	273 (12.20)	279 (13.10)	275 (9.21) 286 (8.55) (sh) 316 (9.95)	238 (4.79)	240 (3.89)	249 (7.04) 293 (8.08)

[a] 0.1 M phosphate buffer. [b] pH 1.2 (HCl) (Giner-Sorolla and Bendich, 1958). [c] Unstable in alkaline pH. [d] Giner-Sorolla *et al.*, 1966. [e] pH 1.4 (HCl). [f] pH 12.2 (NaOH); sh indicates shoulder.

(Giner-Sorolla and Bendich, 1958; Giner-Sorolla, 1958; Giner-Sorolla *et al.*, 1965, 1966), the chlorine atom in the C-6 position of purines, substituted by OH or NH_2 at C_2, was difficult to replace by hydroxylamine in ethanol solution. The addition, however, of a small proportion of hydroxylamine hydrochloride to the reaction mixture generally enhanced the transformation of 2-substituted 6-chloropurines into the corresponding hydroxylamino compounds.[2] When 2-substituted 6-methylmercaptopurines were used instead of the 6-chloro derivatives, in the presence of a catalytic amount of hydroxylamine hydrochloride, an almost quantitative yield of hydroxylamino derivatives was obtained; 6-benzylmercapto-2-aminopurine reacted similarly. 2-Substituted 6-methyl- and 6-benzylmercaptopurines (I, II, and VII) and 2-amino-9-β-D-ribofuranosyl-6-mercaptomethylpurine (V) were not appreciably transformed into the corresponding hydroxylaminopurine derivatives IV, VIII, and VI, respectively, in the experimental conditions used when chloride ion was omitted from the ethanolic solution of hydroxylamine. Addition of sulfate or acetate ion had no catalytic effect.

The behavior of these mercapto derivatives toward ethanol hydroxylamine solutions differs from that previously reported (Giner-Sorolla *et al.*, 1966) for 6-mercapto-, 6-methylmercaptopurine, or its 9-ribosyl derivative, as hypoxanthine or inosine were formed instead of the hydroxylamino derivative. Occasionally, when the hydrochloride was added to the hydroxylamine solution, some 9-β-D-ribofuranosyl-6-hydroxylaminopurine resulted from the corresponding 6-mercaptomethyl, although the major product was inosine.

The 6-hydroxylamino function was replaced by a hydroxyl group upon reaction with dilute hydrogen peroxide in trifluoroacetic acid. In this manner, 2-amino-6-hydroxylaminopurine (IV) and 2-hydroxy-6-hydroxylaminopurine (VIII) were transformed into guanine and xanthine in 68 and 91% yield, respectively. When the hydroxylamine reaction was applied to halogenomethyl- or mercaptomethylpurines or pyrimidines, the corresponding oximes were obtained instead of the desired hydroxylamino compounds (Giner-Sorolla *et al.*, 1965).

Attempts were made to prepare 6-hydroxylaminopurine derivatives from 2-substituted 6-iodopurines or 6-thiosemicarbazino- or hydrazinopurines by reaction with hydroxylamine solutions (with or without hydroxylamine hydrochloride), with poor or negative results. Data on the effects of these new compounds on several types of mouse leukemia and experimental tumors will be presented elsewhere.

[2] Lange (I. G. Farben, Erfinder), German Patent 704,300 (1941); *Chem. Abstr.* (1942), *36*, 1191 (quoted by Spielberger, 1957), claimed that the addition of ammonium chloride in ethanolic ammonia acted as a catalyst in the conversion of halogeno compounds into the corresponding amino derivatives (*cf.* Maggiolo and Phillips, 1951; Banks, 1944).

Experimental Section

Ultraviolet absorption spectra were made with a Cary recording spectrophotometer Model 11. Melting points were determined with a Mel-Temp melting point apparatus and were corrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

The 6-hydroxylaminopurine derivatives were prepared by refluxing the corresponding chloro-, methyl-, or benzylmercapto derivatives with 1 M hydroxylamine in ethanol (according to Giner-Sorolla and Bendich, 1958). Compounds IV, VI, and VIII could only be obtained from the corresponding S-substituted (or chloro) derivatives when hydroxylamine hydrochloride was added to the hydroxylamine solutions. Compounds X, XII, and XIV were prepared from the corresponding chloro derivatives with hydroxylamine solution alone. In all cases, upon cooling, a crystalline product was isolated from the reaction mixture and in some instances an additional crop was obtained upon concentration *in vacuo*. Details on these reactions as well as the analytical data are shown in Table I.

Neutral aqueous solutions of these compounds gave a deep blue color with a solution of ferric chloride reagent, characteristic of the hydroxylamine group. They also exhibited a positive phosphomolybdate reaction. The ultraviolet spectrophotometric determinations are listed in Table II.

Aqueous solutions of these compounds were stable, with the exception of 2-amino-6-hydroxylaminopurine (IV) and its 9-ribosyl derivative VI; the former IV decomposed partially after boiling; the latter VI was destroyed after 2 weeks at 25°, or in a few minutes when boiled. 2-Amino-9-β-D-ribofuranosyl-6-hydroxylaminopurine (VI) showed an $[\alpha]_D^{26}$ −35.6° (*c* 0.5, 0.1 N HCl); its solubility in water was 1.09 g/l. at 25° (±1°).

Hydrolysis of 2-Amino-6-hydroxylaminopurine (IV). 2-Amino-6-hydroxylaminopurine (IV, 49.5 mg, 0.3 mmole) was dissolved in trifluoroacetic acid (3 ml), heated at 60° for 4 hr, but no transformation was observed; the solution was cooled to 25°, and hydrogen peroxide (30%, 0.1 ml) was added. The solution was kept at 25° for 18 hr and then evaporated to dryness *in vacuo*. The residue was washed with a little water and ethanol and dried to give 31.0 mg (68%) of a crude product, mp >350°. This substance, which no longer gave positive ferric chloride and phosphomolybdate tests, showed ultraviolet spectra at different pH and R_F values in several solvent systems indistinguishable from those of guanine (Beaven *et al.*, 1955).

Hydrolysis of 2-Hydroxy-6-hydroxylaminopurine (VIII). 2-Hydroxy-6-hydroxylaminopurine (VIII, 50.7 mg, 0.3 mmole) was treated with TFA and peroxide as above and yielded 46.4 mg (91%) of a product that had a mp >350°, and was identified as xanthine by the kind of criteria as used above.

Hydrogenation of 2-Amino-9-β-D-ribofuranosyl-6-hydroxylaminopurine (VI). 2-Amino-9-β-D-ribofuranosyl-6-hydroxylaminopurine (VI, 31.6 mg, 0.1 mmole) was dissolved in 90% aqueous ethanol; 5% platinum-on-charcoal catalyst (20 mg) was added to the solution and stirred for 5 min. The suspension was filtered through Celite, platinum-on-charcoal catalyst (20 mg) was added to the filtrate, and the suspension was hydrogenated at 1 atm at 25°. After uptake of the calculated volume of H_2, the suspension was filtered, the catalyst was washed with a little ethanol, and the combined filtrates were evaporated to dryness *in vacuo*. The residue was washed with ethanol and a crude product was obtained (12 mg). The product, which no longer gave positive $FeCl_3$ and phosphomolybdate tests, showed an ultraviolet spectrum at pH 1, 6.7, and 13 identical with that of an authentic sample of 2,6-diamino-9-β-D-ribofuranosylpurine (Davoll and Lowy, 1951); the R_F values of this substance in several solvent systems were indistinguishable from those obtained with an authentic sample of 2,6-diamino-9-β-D-ribofuranosylpurine.

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The Synthesis of *O*-Serine Glycosides*

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ABSTRACT: A general, three-step procedure was developed for the chemical synthesis of *O*-glycosylserine glycosides, starting with the acetobromoglycoses and *N*-carbobenzoxy-L-serine benzyl ester. The acetobromo derivatives of D-glucose, D-galactose, and D-xylose were used.

The synthesis involved Koenigs–Knorr condensation of the bromo sugar with the serine derivative, hydrogenolysis to remove the benzyl and carbobenzoxy groups, and ammonolysis to remove the acetyl groups. The acetyl derivatives and the final products were obtained as crystalline solids, and the over-all yields ranged between 24 and 40%. The optical rotations of the 3-*O*-(D-glycopyranosyl)-L-serine derivatives corresponded to those expected for the β anomers.

Glycoproteins contain carbohydrate side chains linked to the polypeptide by glycosidic bonds. In some cases, as in ovalbumin and the blood glycoproteins, this bond involves the amide nitrogen atom of asparagine (Marshall and Neuberger, 1964) and the bond is stable to alkali. Another class of glycoproteins contains sugars linked to protein through alkali-sensitive bonds; this group includes the submaxillary mucins (Tanaka *et al.*, 1964), blood group substances (Schiffman *et al.*, 1964), and at least some mucopolysaccharide–protein complexes (Anderson *et al.*, 1965; Lindahl *et al.*, 1965). The sensitivity to alkali results from the fact that the sugar chains are *O*-glycosides of serine (and sometimes threonine), and are therefore susceptible to β elimination in the presence of alkali. In the case of the mucopolysaccharides, such as the chondromucoprotein from cartilage, and a heparin–protein complex, the polysaccharide chains contain equimolar quantities of sulfated hexoamine and uronic acid, and are linked to the protein through xylose, and perhaps galactose. Thus, in studies concerned with the chemistry of these macromolecules, *O*-xylosylserine, and *O*-galactosylserine are of prime interest. In addition to its presence in the complex polymers, xylosylserine has been isolated from normal human urine; 1 mg/l. was obtained (Tominaga *et al.*, 1965), and the proposed structure was 3-*O*-(β-D-xylosyl)serine.[1]

Our interest in the serine glycosides was stimulated by enzymatic studies on the biosynthesis of glycoproteins, including the mucins (Carlson *et al.*, 1964), and sphingoglycolipids such as the gangliosides and cerebrosides (Basu *et al.*, 1965). In the glycolipids, the

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[1] Unless otherwise indicated, sugars are of the D configuration, glycosides are pyranosides, and serine and its derivatives are of the L configuration. The term carbobenzoxy signifies the benzyloxycarbonyl group. Acetobromoglycose signifies a fully *O*-acetylated 1-bromoglycopyranose, *e.g.*, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide is described by its conventional name, acetobromoglucose. The *O*-glycosides of serine described in the literature are not named in a consistent manner. Some examples of these are as follows: 1-*O*-β-L-seryl-*N*-acetyl-D-glucosaminide (Jones *et al.*, 1961), *O*-β-D-(2,3,4,6-tetra-*O*-acetyl)-glucopyranoside of the methyl "ether" of *N*-carbobenzoxy-DL-serine (Derevitskaya *et al.*, 1964), *O*-β-D-xylopyranosyl-L-serine (Lindberg and Silvander, 1965), and 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-*N*-2,4-dinitrophenyl-L-serine methyl ester (Vercellotti and Luetzow, 1966). While an abbreviated nomenclature is employed in some cases in the present paper, such as "serine glycosides," these terms are meant to describe only 3-*O*-(β-D-glycopyranosyl)-L-serine and its derivatives. For future reference, we suggest that *O*-glycosides of serine be named in a manner similar to that employed for oligosaccharides, *viz.*, β-D-glycopyranosyl-(1→3)-L-serine.