mole) of thiourea in 30 ml. of water and the mixture heated at reflux 6 hr. at which time one layer formed. Aqueous sodium hydroxide was added and heated at reflux an additional 6 hr. under nitrogen. Acidification and separation of the oily layer and distillation afforded 20.8 g. (79.5%) of a colorless liquid, b.p. 120° (26 mm.), $n^{25}D$ 1.4978.

Anal. Calcd. for $C_7H_{16}S_2$: C, 51.16; H, 9.82; S, 39.03. Found: C, 51.26; H, 10.10; S, 38.70.

Acknowledgment.—We wish to acknowledge gratefully the partial support of this work by the Public Health Service Grant No. 5-1425 (G7).

The Preparation and Properties of 6-Halomethylpurines[1]

SASSON COHEN,[2] EDNA THOM, AND AARON BENDICH

Division of Nucleoprotein Chemistry, Sloan-Kettering Institute for Cancer Research, and Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York 21, New York

Received April 16, 1962

6-Methylpurine (I) was converted by sulfuryl chloride or N-chlorosuccinimide into 6-trichloromethylpurine in trifluoroacetic acid solution. Stepwise or partial chlorination of the methyl group was not achieved. N-Bromosuccinimide converted I into the 6-dibromo- and, by further substitution, 6-tribromomethylpurine. Stepwise catalytic reduction of the trihalomethylpurines afforded dihalo- and monohalomethylpurines. The chemical and physical properties of the new compounds are described.

6-Methylpurine (I), an analog of adenine, is highly toxic to mammals and human tumor cells.[3,4] This outstanding biological potency made I an attractive model for the synthesis of potential anticancer agents through minor alterations in its structure.[5-9] Accordingly, studies of the preparation and properties of compounds derived from I by direct halogenation of the methyl group were undertaken.

A number of examples of the exhaustive halogenation of methyl groups in heterocyclic compounds have been published.[10-12] These procedures require the use of elemental chlorine or bromine in the presence of sodium acetate and may involve a polar reaction mechanism. In the present investigation, we have used sulfuryl chloride, N-chloro-, and N-bromosuccinimide in trifluoroacetic acid solution. The action of these agents on organic compounds is known to be more selective than that of elemental halogen.[13]

When an equimolar mixture of I and sulfuryl chloride was refluxed in trifluoroacetic acid, hydrogen chloride was evolved, but the only products isolated were the trifluoroacetic acid salt (Ia) of I and its hydrochloride (Ib). The same reaction in cold acetic acid gave Ib which could be readily converted into Ia by evaporating its solution in trifluoroacetic acid to dryness. It was assumed, therefore, that the chlorinating agent had been consumed although the expected halogenated product could not be isolated. Indeed, the use of two moles of sulfuryl chloride per mole of I afforded 6-trichloromethylpurine (II), in low yield. Subsequently, II was prepared in 70–80% yield by use of excess sulfuryl chloride in trifluoroacetic acid. The reaction was exothermic and proceeded to completion within a short time.

The use of N-chlorosuccinimide in the same solvent did not prove more advantageous for the purpose of controlling the extent of chlorination. When used in equimolar ratio, this reagent afforded the trichloro product (II) only. Under similar conditions, an equimolar mixture of N-bromosuccinimide and I gave 6-dibromomethylpurine (VII), but use of excess brominating agent resulted in an excellent yield of 6-tribromomethylpurine (VI). Under the mild conditions used, the failure to achieve stepwise halogenation is unusual. At a carbon atom bearing a halogen, the tendency for further halogenation is in harmony with the known effect of halogen atoms in decreasing the carbon–hydrogen bond dissociation energy. But this tendency is usually diminished by the electron-withdrawing inductive effect of the same halogen.

A few correlations of reactions in related systems are informative: Toluene or nuclear-substituted toluenes and sulfuryl chloride yield benzyl chlorides.[14] With N-bromosuccinimide, nuclear bromination of methylpyridines takes precedence over

(1) This investigation was supported by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-3190), the Atomic Energy Commission (Contract No. AT [30-1], 910), and the American Cancer Society (Grant No. T-128B).

(2) Visiting Research Fellow, on leave from the Israel Institute for Biological Research, Ness-Ziona, Israel.

(3) F. S. Philips, *et al.*, *Ann. N. Y. Acad. Sci.*, **60**, 283 (1954).

(4) J. J. Biesele, *Proc. Nat. Cancer Conf. 3rd*, 1957, p. 405.

(5) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, **80**, 3932 (1958).

(6) A. Giner-Sorolla and A. Bendich, *ibid.*, **80**, 5744 (1958).

(7) A. Giner-Sorolla, I. Zimmerman, and A. Bendich, *ibid.*, **81**, 2515 (1959).

(8) R. N. Prasad, C. W. Noell, and R. K. Robins, *ibid.*, **81**, 193 (1959).

(9) H. Lettré and C. Woenckhaus, *Liebigs Ann. Chem.*, **649**, 131 (1961).

(10) B. R. Brown, D. L. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, 1145 (1951).

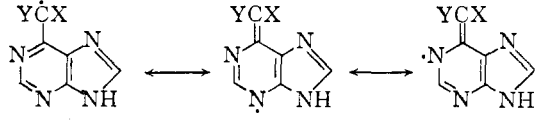
(11) R. R. Hunt, J. F. W. McOmie, and E. R. Sayer, *ibid.*, 525 (1959).

(12) H. Bredereck, W. Jentzsch, and G. Morlock, *Chem. Ber.*, **93**, 2405 (1960).

(13) For a review, see C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, 1957.

side chain bromination.[15] The methyl group in 6-methyl-2,4,5-trichloropyrimidine is less reactive towards N-bromosuccinimide than that in 5-methyl-2,4,6-trichloropyrimidine, but the monobromomethyl derivative is the end product with each.[16] Indeed, in almost all 6-methylpyrimidine derivatives studied, it is the lack of reactivity towards free radical halogenation that characterizes the methyl group. 6-Methyluracil and sulfuryl chloride in acetic acid[17] or in trifluoroacetic acid yield the 5-chloro derivative only. West and Barrett[18] have reported the formation of 6-chloromethyl-2-methylthiouracil from N-chlorosuccinimide and 6-methyl-2-methylthiouracil. However, Carbon[19] has since indicated that the only product of this reaction is 6-methyl-5-chloro-2-methylthiouracil. We have now synthesized, by condensation of S-methylpseudothiourea and ethyl γ-chloroacetoacetate, authentic 6-chloromethyl-2-methylthiouracil which displays properties different from those reported by West and Barrett.

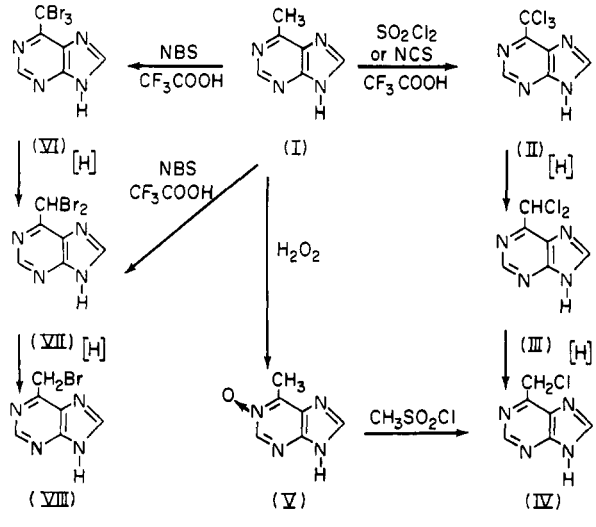
In a consideration of the mechanism of the halogenation, it could be argued that the strongly acidic conditions of the reaction would not favor nucleophilic attack by "positive" halogen on the alkyl carbon in I. A free radical mechanism would obviate this difficulty. The observed reactivity of the methyl group in I may be due to the intermediate formation of resonance stabilized radicals involving structures such as



in which X and Y may both be hydrogen, hydrogen and halogen, or both halogen. The last case would then represent the most stable radical. The nature of the initiation of these reactions, which proceeded without added peroxide, is not clear.

Stepwise catalytic reduction of II proceeded smoothly to yield, first, 6-dichloromethylpurine (III). However, further reduction resulted in a troublesome mixture of III, 6-chloromethyl- (IV) and 6-methylpurine (I). The use of strongly acidic conditions failed to inhibit the concomitant reduction of IV. When the reduction was carried out in presence of excess sodium acetate in aqueous solution, IV could be isolated in 45% yield. This compound was also prepared in 30% yield by the reaction of 6-methylpurine 1-N-oxide (V)[20] with methanesulfonyl chloride. Analogous reactions in pyridine[21] and pyrimidine series[11] have been reported.

Stepwise catalytic reduction of 6-tribromomethylpurine (VI) in the presence of excess sodium acetate, afforded successively 6-dibromomethyl- (VII) and 6-bromomethylpurine (VIII) (Scheme I). The latter is highly irritating to the skin.



Scheme I

The conversion of 6-trichloromethylpurine (II) into 6-carboxypurine (IX) proceeded smoothly in aqueous solutions of sodium acetate or sodium bicarbonate at room temperature. The use of stronger base induced the formation of a substantial amount of a dark brown amorphous material of uncertain constitution. This side reaction did not proceed appreciably in solvents other than water. Thus, refluxing methanolic potassium hydroxide converted II into the ortho ester, 6-(trimethoxymethyl)purine (X), which, in turn, gave 6-(carbomethoxy)purine (XI) upon treatment with acid. Aqueous ammonia, buffered with ammonium bicarbonate, transformed II into the known 6-purinecarboxamide (XII) (Scheme II). The reaction with amines will be presented in a separate report.

The spectral properties of the new compounds are shown in Table I. The uncharged compounds display a bathochromic shift of 5 to 6 mμ in the position of the maximum for every additional halogen atom introduced.

The anionic dissociation constants in 50% methanol were determined for the more stable com-

(14) R. van Helden and E. C. Kooyman, *Rec. trav. chim.*, **73**, 269 (1954).

(15) E. Tenenbaum in "Pyridine and its Derivatives," E. Klingsberg, ed., Interscience Publishers, Inc., New York, 1961.

(16) H. Gershon, K. Dittmer, and R. Braun, *J. Org. Chem.*, **26**, 1874 (1961).

(17) H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).

(18) R. A. West and H. W. Barrett, *ibid.*, **76**, 3146 (1954).

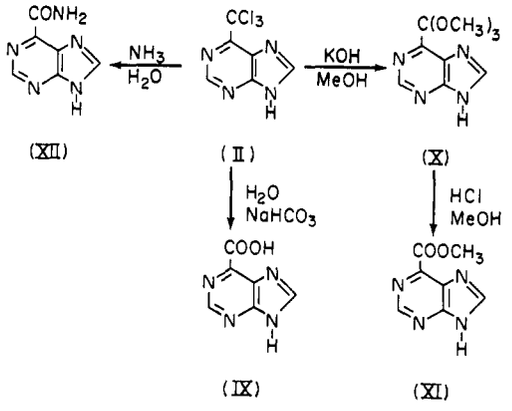
(19) J. A. Carbon, *J. Org. Chem.*, **25**, 1731 (1960).

(20) M. Stevens, A. Giner-Sorolla, H. W. Smith, and G. B. Brown, *ibid.*, **27**, 567 (1962).

(21) For a review, see E. N. Shaw in E. Klingsberg "Pyridine and its Derivatives," ref. 13.

(22) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

pounds by potentiometric titration.[22] The results are shown in Table II. It can be seen that the



Scheme II

pK_a of 6-methylpurine is higher than that of 6-chloromethylpurine which, in turn, is higher than that of 6-dichloromethylpurine. So far, this trend is in strict analogy with that observed in the well studied series of chlorinated acetic acids.[23] However, the analogy is no longer valid with 6-trichloromethylpurine. The pK_a found for this compound is higher than that of the dichloro derivative. A similar situation is encountered in the bromine derivatives. Unfortunately, 6-bromomethylpurine was not sufficiently stable under the conditions of the titration. If increase of acid constant is due to inductive electron withdrawal by halogen, then a decrease would be due to electron release by resonance.[24] In the 6-trihalomethylpurines, the latter effect may be important enough to compensate partly for electron withdrawal from the imidazole nitrogens.

Experimental

Melting points were determined with a Thomas-Hoover apparatus.

The R_f values are for ascending chromatograms on Whatman No. 1 paper, using *n*-butyl alcohol (77%), formic acid (10%), water (13%) (v./v.).

The spectrophotometric measurements were made with a Cary Model 11 recording spectrophotometer.

Reaction of 6-Methylpurine (I) with Sulfuryl Chloride.—(a). 6-Methylpurine (Cyclo Chemical Corp.) (2.7 g.) in trifluoroacetic acid (20 ml.) was treated for 48 hr. at room temperature with sulfuryl chloride (2.7 g.) and benzoyl peroxide (0.1 g.). The solvent was evaporated under reduced pressure and the residue was freed from adhering acid by repeated addition of methanol and evaporation. Finally, the residue was taken up in ethyl acetate and filtered to remove the hydrochloride of I, 0.5 g. (15%). Concentration of the filtrate gave the trifluoroacetic acid salt of I, 2 g. (40%), m.p. 126–128°, λ_{max} 261 mμ (in water), chromatographically identical with I, R_f 0.54.

Anal. Calcd. for $C_8H_7O_2N_4F_3$: C, 38.7; H, 2.8; N, 22.6; F, 23.0. Found: C, 39.0; H, 2.2; N, 22.9; F, 23.1.

(b). A solution of I (2.7 g.) in glacial acetic acid (20 ml.) was treated at room temperature with sulfuryl chloride (3

TABLE I

ULTRAVIOLET SPECTRAL PROPERTIES OF 6-SUBSTITUTED PURINES

Substituent	λ_{max} mμ ($A_M \times 10^{-3}$) 0.1 *N* HCl	pH 6.55[a]	0.1 *N* NaOH	λ_{min} mμ ($A_M \times 10^{-3}$) 0.1 *N* HCl	pH 6.55[a]	0.1 *N* NaOH
—CH_3[b]	265 (7.59)	261 (8.32)	271 (8.51)			
—CH_2Cl	266 (7.82)	269 (8.04)	278 (8.16)	228 (2.31)	226 (1.64)	238 (0.86)
—$CHCl_2$	272 (8.47)	274 (8.73)	282 (8.05)	230 (1.62)	224 (1.49)	240 (0.79)
		274 (8.89)[c]			245 (3.41)[c]	
—CCl_3	277 (7.65)	279 (8.53)	282[d] (7.11)	226 (1.31)	233 (1.31)	242[d] (1.09)
—CH_2Br	272 (8.15)	274 (8.77)	282[d] (8.28)	229 (2.48)	228 (2.11)	242[d] (1.24)
—$CHBr_2$	277 (8.64)	279 (9.59)	288 (8.35)	231 (2.64)	234 (2.19)	245 (1.38)
—CBr_3	282 (8.37)	285 (8.40)	280[e] (7.10)	237 (3.46)	236 (2.89)	242[e] (1.73)
—$COOCH_3$	285 (7.98)	292 (8.70)	279[e] (7.48)	230 (1.52)	235 (0.94)	241[e] (1.38)
—$C(OCH_3)_3$	268[d] (10.75)	271 (14.09)	276 (11.60)	230[d] (3.30)	229 (2.83)	239 (1.27)
—COOH[f]	280 (7.72)	279[g] (7.72)				
—$CONH_2$	241 (4.12)	289 (8.29)	297 (5.90)	250 (3.46)	224 (2.01)	240 (2.83)
	280 (7.65)					
—$CONH_2$[f]	240 (4.52)[h]	292[g] (6.68)				
	279 (7.91)					

[a] 0.1 *M* phosphate buffer. [b] Data from S. F. Mason, *J. Chem. Soc.*, 2072 (1954). [c] 0.1 *M* formate buffer, pH 4.6. [d] Unstable reading made immediately after dilution. [e] Highly unstable, reading made at end of change. [f] Data from L. B. McKay and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3511 (1956). [g] At pH 11. [h] At pH 1.

TABLE II

DISSOCIATION CONSTANTS[a] OF 6-SUBSTITUTED PURINES IN 50% AQUEOUS METHANOL AT 15°

Substituent	pK_{a_1}	pK_{a_2}
—CH_3[b]	2.6	9.02
—CH_2Cl	*ca.* 1.7	8.62
—$CHCl_2$	[c]	7.79
—CCl_3	[c]	7.93
—$CHBr_2$	[c]	8.00
—CBr_3	[c]	8.27[d]
—CF_3		7.35[e]

[a] Determined by potentiometric titration according to T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954). [b] Data from A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954). [c] No evidence of protonation at pH 1.4. [d] Hydrolysis is noticeable at pH 8.7. [e] Data from A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, **80**, 5744 (1958).

(23) G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1183 (1934).

(24) See, for a discussion of this effect, L. Pauling, "Nature of the Chemical Bond," 3rd ed., Cornell University Press, Ithaca, 1960, p. 314.

g.) and benzoyl peroxide (0.1 g.). A solid product formed gradually which finally disappeared again in the dark brown reaction mixture. This was processed as under (a) to yield the hydrochloride of I, 2 g. (59%), m.p. 238–240° dec. λ_{max} 261 mμ (in water), R_f value 0.54.

Anal. Calcd. for $C_6H_7N_4Cl$: C, 42.2; H, 4.1; N, 32.9; Cl, 20.1. Found: C, 42.6; H, 3.1; N, 33.2; Cl, 21.4.

(c). Sulfuryl chloride (50 ml.) was added slowly to a solution of I (13 g.) in trifluoroacetic acid (50 ml.). When the exothermic reaction had subsided, the solution was refluxed for 1–2 hr., a period of time which may have been unnecessarily long. The solution was brought to a sirupy consistency by evaporation under reduced pressure and the clear residue freed from acid by addition of methanol and evaporation. The product was taken up in water (100 ml.) and shaken vigorously to ensure thorough mixing. 6-Trichloromethylpurine (II), 17 g. (73%) was obtained as a white crystalline material of acceptable purity for further reactions. An analytical sample was recrystallized from chloroform, m.p. 204–206° dec., R_f 0.92.

Anal. Calcd. for $C_6H_3N_4Cl_3$: C, 30.3; H, 1.3; N, 23.6; Cl, 44.8. Found: C, 29.8; H, 1.4; N, 23.7; Cl, 44.9.

Reaction of 6-Methylpurine with N-Chloro- and N-Bromosuccinimide.—(a). A solution of I (1.3 g.) and N-chlorosuccinimide (1.4 g.) in trifluoroacetic acid (10 ml.) was refluxed for 2 hr. The solvent was evaporated under reduced pressure and the residue diluted with methanol and dried again. The product was dissolved in water (20 ml.) and the pH of the solution adjusted to 4–5 with solid sodium acetate. After some time, crystals of II formed, 0.3 g. (36% with respect to NCS), identical to the product described above.

(b). A solution of I (1.3 g.) in trifluoroacetic acid (10 ml.), treated with N-bromosuccinimide (1.8 g.) as described above, gave 6-dibromomethylpurine (VII), 1.1 g. (38%), m.p. 165–166° dec. (from methanol), R_f 0.85.

Anal. Calcd. for $C_6H_4N_4Br_2$: C, 24.7; H, 1.4; N, 19.2; Br, 54.8. Found: C, 24.5; H, 1.5; N, 19.0; Br, 53.4.

(c). A solution of I (1.3 g.) in trifluoroacetic acid (20 ml.), treated as above with N-bromosuccinimide (5.4 g.), gave 6-tribromomethylpurine (VI), 3.4 g. (91%), m.p. 194–195° dec. (from ethyl acetate); R_f 0.87.

Anal. Calcd. for $C_6H_3N_4Br_3$: C, 19.4; H, 0.8; N, 15.1; Br, 64.8. Found: C, 19.3; H, 1.0; N, 15.5; Br, 63.3.

Catalytic Reduction of 6-Trichloromethylpurine.—(a). A solution of II (2.4 g.) in ethanol (100 ml.) containing suspended 5% platinum on charcoal (100 mg.) was shaken with hydrogen gas at atmospheric pressure. When about 255 ml. of hydrogen were absorbed the reduction was discontinued and the catalyst filtered off and washed with ethanol. The combined filtrate and washings were evaporated to dryness under reduced pressure, the solid residue dissolved in water (50 ml.), and the solution neutralized with solid ammonium acetate; 6-dichloromethylpurine (III) crystallized spontaneously, 1.5 g. (75%), m.p. 176–177° dec. (from cold methanol); R_f 0.86.

Anal. Calcd. for $C_6H_4N_4Cl_2$: C, 35.5; H, 2.0; N, 27.6; Cl, 35.0. Found: C, 35.9; H, 2.2; N, 27.6; Cl, 34.9.

(b). 6-Trichloromethylpurine (II) (2.4 g.) was reduced as above, but 480 ml. of hydrogen were used. The product consisted mainly of I and III, as revealed by paper chromatography.

(c). A solution of II (4.8 g.) in methanol (50 cc.) and 5% platinum on charcoal (480 mg.) were added to a solution of sodium acetate trihydrate (20 g.) in water (200 ml.). Reduction with 900 ml. of hydrogen was carried out as described above. The solution was filtered from the catalyst. The filtrate was concentrated under reduced pressure to *ca.* 50 ml., and the white crystals of 6-chloromethylpurine (IV) that had formed were collected and washed with a little cold water. The wet product was dissolved in tetrahydrofuran (100 ml.), treated with anhydrous sodium sulfate, and filtered. The filtrate was brought to dryness under reduced pressure, the solid residue was redissolved in hot methanol (50 ml.), and the resulting solution filtered and chilled at −10° for 24 hr. to yield 1 g. of chromatographically pure IV. The methanolic mother liquor was brought to dryness and the residue recrystallized from boiling ethyl acetate to yield a second crop of 0.5 g. The total yield is 45%; m.p. 165–166° dec.; R_f 0.75.

Anal. Calcd. for $C_6H_5N_4Cl$: C, 42.7; H, 3.0; N, 33.5; Cl, 21.2. Found: C, 42.8; H, 3.1; N, 33.3; Cl, 21.1.

Reaction of 6-Methylpurine-1 N-Oxide with Mesyl Chloride.—6-Methylpurine 1-N-oxide[20] (1.4 g.) was stirred with methanesulfonyl chloride (20 ml.) at room temperature until an almost clear solution was obtained (*ca.* 2 hr.). The mixture was diluted with methylene chloride (50 ml.) and extracted twice with water (50 ml.); the combined water extracts were neutralized with solid sodium acetate, treated with charcoal, and filtered. The filtrate was brought to dryness under reduced pressure and the semisolid residue extracted with boiling acetone. Evaporation of this solvent gave crude IV, 0.5 g. (30%) which was further purified by recrystallization from methanol. The product was identical in all regards to the one described in the preceding paragraph.

Reduction of 6-Tribromomethylpurine (VI).—(a). A solution of VI (3.7 g.) in ethanol (50 ml.) was added to sodium acetate (5 g.) in water (250 ml.), and hydrogenated in presence of 5% platinum on carbon until about 250 ml. of hydrogen was absorbed. After filtration, the solution was brought to dryness under reduced pressure, the solid residue was taken up in water (25 ml.), filtered, and recrystallized from boiling ethyl acetate to yield VII, 1.7 g. (58%), identical to the product described above.

(b). Reduction of VI was carried out in 50% aqueous alcohol in presence of 5% platinum on carbon (400 mg.) and sodium acetate (8.3 g.), until about 490 ml. of hydrogen were absorbed. After filtration, the solution was concentrated to 10 cc. and 6-bromomethylpurine (VIII) separated. It was filtered and recrystallized from boiling ethyl acetate to yield 0.5 g. (22%). The product turns brown at 140–150° without melting; R_f 0.76.

Anal. Calcd. for $C_6H_5N_4Br$: C, 33.8; H, 2.3; N, 26.3; Br, 37.6. Found: C, 33.6; H, 2.7; N, 26.3; Br, 37.5.

Solvolysis of 6-Trichloromethylpurine.—(a). A mixture of II (1 g.), sodium bicarbonate (2 g.) and water (50 ml.) was stirred for 2 hr. at room temperature. A further addition of sodium bicarbonate (1 g.) was made, and the mixture was stirred for 2 hr. more. The brown, clear solution was decolorized with charcoal and concentrated to a volume of 20 ml. under reduced pressure. Acidification to pH 5 with glacial acetic acid induced crystallization of the sodium salt of 6-carboxypurine (IX) m.p. above 350°. The product was dissolved in hot water (10 ml.) and the free acid (IX) precipitated by the addition of hydrochloric acid; yield 0.35 g. (50%), m.p. 200–201° with decarboxylation; λ_{max} 280 mμ (in water)[25]; R_f 0.1–0.2. The product formed after decarboxylation was found to be purine, m.p. 214–216°, λ_{max} 262 mμ (in water).[26]

When II was dissolved in 0.1 *N* sodium hydroxide, a dark brown colloidal solution was obtained from which 6-carboxypurine could not be recovered upon acidification.

(b). 6-Trichloromethylpurine (1.65 g.) was added to a cold solution of potassium hydroxide (1.5 g.) in methanol (70 ml.). The resulting solution was stirred at room temperature for 12 hr., acidified with acetic acid, and brought to a sirupy consistency under reduced pressure. The residue was extracted with an excess of hot ethyl acetate. Concentration and cooling of the extract gave 6-(trimethoxymethyl)purine (X), 0.4 g. (39%), m.p. 179–180° dec.; R_f 0.74.

Anal. Calcd. for $C_9H_{12}O_3N_4$: C, 48.2; H, 5.4; N, 25.0. Found: C, 47.7; H, 5.4; N, 25.5.

(25) L. B. McKay and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3511 (1956).

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

(c). A solution of X (1.1 g.) in methanol (20 ml.) was treated with 5 drops of concentrated hydrochloric acid and kept at room temperature for 2 hr. The solution was brought to dryness under reduced pressure and the residue, crystallized from boiling acetone, gave 6-(carbomethoxy)-purine (XI) 0.6 g. (69%), m.p. 226–227° dec.; R_f 0.57.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.2; H, 3.3; N, 31.5. Found: C, 47.5; H, 3.6; N, 31.3.

Reaction of 6-Trichloromethylpurine with Ammonia.—A solution of ammonium bicarbonate (2 g.) in water (10 ml.) was treated dropwise with concentrated aqueous ammonia until its pH was about 9. To this was added II (1 g.) and the mixture was stirred at room temperature for 3 hr., with frequent additions of ammonia to maintain a pH of 9. The resulting solution was acidified with hydrochloric acid and the gummy precipitate was separated by decantation and dissolved in boiling water to which charcoal was added. Filtration and cooling gave 6-purinecarboxamide (XII) 0.2 g. (30%), m.p. 320–325° (reported 315–320° [5,25]); R_f 0.40.

Anal. Calcd. for $C_6H_5ON_5$: C, 44.2; H, 3.1; N, 42.9. Found: C, 44.4; H, 3.1; N, 43.0.

2-Methylthio-4-hydroxy-6-chloromethylpyrimidine.—A mixture of S-methylpseudothiourea sulfate (7 g.), ethyl γ-chloroacetoacetate (8.3 g.) and methanolic 2 *M* sodium methoxide (50 ml.) was stirred at room temperature for 12 hr. The solvents were removed under reduced pressure, and the residue was dissolved in water (100 ml.). Acidification with hydrochloric acid gave the above pyrimidine, 3.5 g. (40%), m.p. 180–181°, from methanol; λ_{max} 239, 290 mμ (in water).

Anal. Calcd. for $C_6H_7ON_2ClS$: C, 37.8; H, 3.7; N, 14.7; Cl, 18.7. Found: C, 37.8; H, 3.9; N, 14.8; Cl, 18.9.

West and Barrett[18] reported a m.p. of 230–235° for a product which they believed to be the above compound and which was unstable and, therefore, could not be obtained analytically pure. However, no evidence of instability in presence of water could be found for the compound described above.

Acknowledgment.—The authors wish to thank Dr. G. B. Brown for his advice and interest. They are grateful to J. J. Dannenberg for assistance in the experiments.

Acyclic Sugar Nucleoside Analogs. II. Sulfur Derivatives[1,2]

M. L. WOLFROM, P. MCWAIN, AND A. THOMPSON

Department of Chemistry, The Ohio State University, Columbus 10, Ohio

Received April 19, 1962

The sulfur-containing, acyclic nucleoside analogs 1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose (and D-glucose) aldehydrol (VIII, IX) have been prepared and characterized.

In a previous communication[2] we have described a pair of acyclic sugar nucleoside analogs which could be considered as derived from the aldehydrol (hydrate) of *aldehydo*-D-galactose pentaacetate. With few exceptions, penta-*O*-acetyl-*aldehydo*-D-galactose being one of them, the aldehydrol group is so unstable that it exists only in aqueous solution. Stable derivatives may, however, be obtained in which halogens, oxyacyl, oxyalkyl and thio-oxyalkyl groups are substituted for the hydroxyl groups. A number of these derivatives have been described.[3]

Penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose aldehydrol (I) was first reported by Wolfrom and associates,[4] but is more easily prepared by the method of Gauthier[5] as adapted by Weygand and co-workers.[6] The corresponding D-glucose derivative (II) was prepared in this laboratory but failed to crystallize and was used in the synthesis described below as a sirup without further characterization.

We report herein the preparation of sulfur-containing acyclic nucleoside analogs by condensing the penta-*O*-acetyl-1-bromo-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose (D-glucose) aldehydrols (I, II) with 6-acetamido-9-chloromercuripurine (III)[7,8] by a procedure similar to that of Davoll and Lowy[7] for the synthesis of cyclic nucleosides. The products (IV, V) were purified through the crystalline picrates (VI, VII), the formation of which involves *N*-deacetylation.[9] The *O*-acetylated nucleoside analogs (X, XI) were regenerated from picrate salts (VI, VII) with an ion exchange resin. Deacetylation of X and XI with *n*-butylamine in boiling methanol solution produced 1-(9-adenyl)-1,1-dideoxy-1-ethylthio-*aldehydo*-D-galactose (and D-glucose) aldehydrols (VIII, IX). These substances were also obtained by deacetylation of the fully acetylated crude products (IV, V) with a boiling methanol solution of *n*-butylamine.

(1) Supported by Grant No. CY3232(C4) from the Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda 14, Maryland (R. F. Project 759D).

(2) Preceding paper in this series: M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3093 (1961).

(3) M. L. Wolfrom and D. I. Weisblat, *J. Am. Chem. Soc.*, **62**, 878 (1940).

(4) M. L. Wolfrom, D. I. Weisblat, and A. R. Hanze, *J. Am. Chem. Soc.*, **62**, 3246 (1940).

(5) B. Gauthier, *Ann. pharm. franc.*, **12**, 281 (1954); *Chem. Abstr.*, **48**, 13547 (1954).

(6) F. Weygand, H. Ziemann, and H. J. Bestmann, *Ber.*, **91**, 2534 (1958).

(7) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(8) J. J. Fox, N. Yung, Iris Wempen, and Iris L. Doerr, *J. Am. Chem. Soc.*, **79**, 5060 (1957).

(9) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Am. Chem. Soc.* **79**, 2778 (1957).