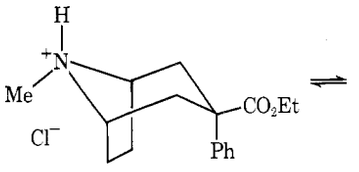
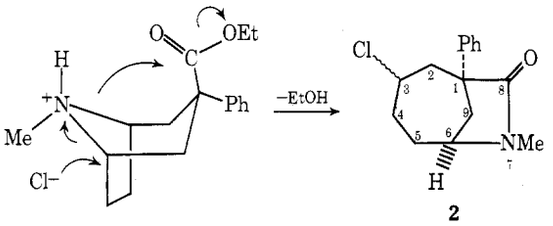
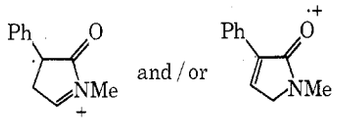
relative abundance ratio of 3:1 characteristic of chlorine-containing derivatives—probable assignments to the base (*m/e* 42) and second most abundant peak (*m/e* 173, 78%) are $H_2C{=}N^+{=}CH_2$ and (3), respectively; (iii) its ir spectrum (Nujol mull) displayed amide carbonyl bands (1670, 1678 cm^{-1}); and (iv) its 100-MHz ^1H nmr spectrum in $CDCl_3$ (TMS reference) showed 1-proton multiplets assigned to methine hydrogens at C-3 and C-6, and an *N*-methyl resonance (s, δ 2.88) typical of an *N*-methyl cyclic amide (*cf.* δ_{NMe} 2.82 for 1-methyl-2-pyrrolidone).[4] The stereochemistry at C-3 is unestablished. Pyrolysis of the amino acid hydrochloride corresponding to 1 gave the same bicyclononane.



1



2



3

The reaction 1 to 2 represents the interconversion of 8-azabicyclo[3.2.1]octane and 7-azabicyclo[4.2.1]nonane derivatives through nucleophilic attack by chloride, and the gas observed when (1) melts must therefore be ethanol vapor.[5]

Experimental Section

Pyrolysis of 3-β-Carbethoxy-3-α-phenyltropane Hydrochloride. The hydrochloride 1 (0.96 g) was heated for 15 min in an oil bath kept at 190–200°. The thermolysate in chloroform was washed with water, and the organic phase dried (Na_2SO_4) and evaporated to leave 7-aza-3-chloro-7-methyl-1-phenyl-8-oxobicyclo[4.2.1]nonane (0.59 g): mp 132–137° (142–144° from benzene–hexane); ^1H nmr δ ($CDCl_3$) 7.46 and 7.22 (2 m, 2 H, 3 H, aryl protons), 4.00 (m, 1 H, $W_{1/2}$ = 22 Hz, 3 CH or 8 CH), 3.70 (m, 1 H, $W_{1/2}$ = 8 Hz, 3 CH or 8 CH), 2.88 (s, 3 H, NMe); 2.86–1.64 (m, 8 H, 2, 4, 5 and 9 CH_2).

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; Cl, 13.44; N, 5.31. Found: C, 68.39; H, 7.01, Cl, 13.44; N, 5.09.

Similar treatment of the amino acid hydrochloride corresponding with 1 gave a comparable yield of 2.

Acknowledgment. We thank the Medical Research Council for Canada for financial support.

Registry No.—1, 52123-58-7; 2, 52123-59-8.

References and Notes

(1) A. F. Casy and J. E. Coates, *Org. Magn. Resonance*, in press.
(2) A. F. Casy and K. M. J. McErlane, *J. Chem. Soc., Perkin Trans. 1*, 726 (1972); M. A. Iorio, G. Damia, and A. F. Casy, *J. Med. Chem.*, **16**, 592 (1973).
(3) M. R. Bell and S. Archer, *J. Amer. Chem. Soc.*, **82**, 4638 (1960).
(4) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).
(5) The bicyclic parent of 2 is listed in the "Chemical Abstract Ring Indexes" (1970–1972), but we have traced no specific example.

Synthesis of 1-(6-Aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-DL-ribitol, a New "Reversed" Amino Nucleoside[1]

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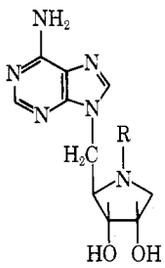
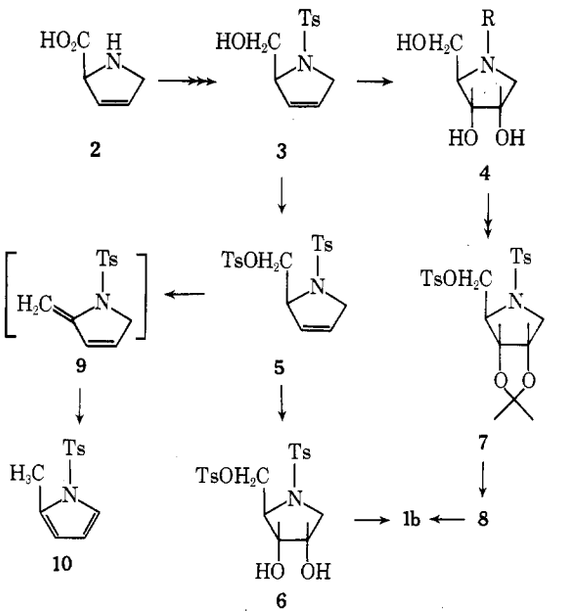
Many nucleosides which are effective agents in inhibiting the growth of malignant cells become ineffective *in vivo* because they are rapidly destroyed by enzymatic cleavage into a purine or pyrimidine and a carbohydrate moiety.[2,3] A reversed nucleoside, however, does not possess the normal linkage between the nitrogen of the base and the anomeric carbon of the sugar, and is more stable with respect to hydrolytic cleavage. A number of reversed nucleosides have already been synthesized.[4–9] Some have elicited interest in connection with cytokinin activity.[10,11] Recently, two patents have been filed which list several reversed nucleosides as antiviral and anticancer drugs.[12,13]

Our research interests in the area of amino and aminoacyl nucleosides prompted the synthesis of 1, the first example of a reversed amino nucleoside. Central to any of the several possible chemical strategies for obtaining 1 is the synthesis of the pyrrolidine sugar 4. The biologically active and synthetic imino acid dehydroproline can be modified by reduction and hydroxylation to give 4 in high yields.[14] Conversion of the amino sugar 4 to 7, subsequent coupling with the sodium salt of adenine, and removal of the isopropylidene group with formic acid gave **1b** as a stable, white, crystalline compound, mp 212–213°. The detosylated com-



1a, R = H
b, R = tosyl



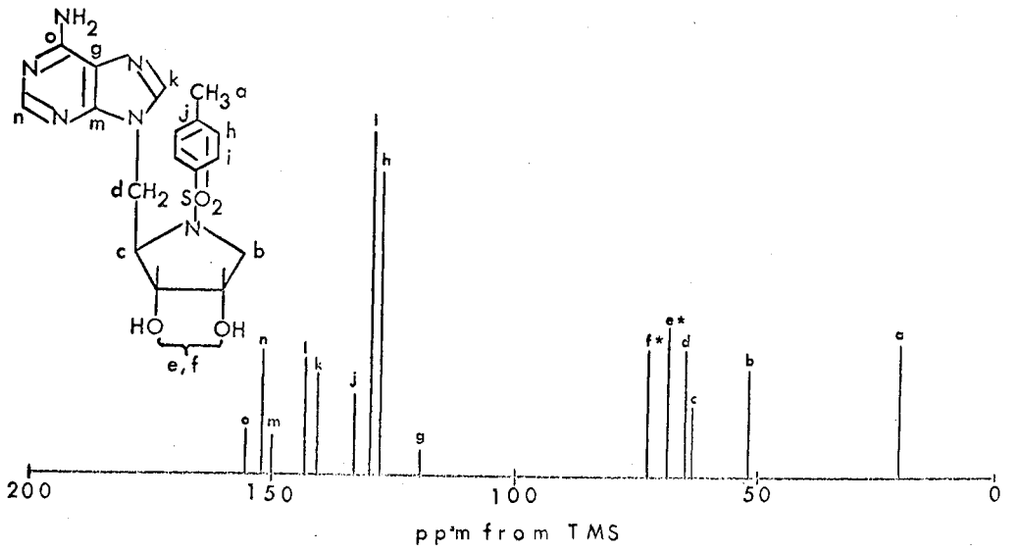


Figure 1. ^{13}C nmr spectrum of 1-(6-aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-2-(*p*-toluenesulfonamido)-DL-ribitol.

pound **1a** was found to be extremely unstable and difficult to handle. A superior route to the reversed nucleoside is direct coupling of **6** with the sodium salt of adenine, which gives **1b** in 73% yield. Confirmation of the structure of **1b** was provided by its pulsed Fourier transform (PFT) ^{13}C nmr (Figure 1).

Nucleosides containing unsaturation in the sugar moiety have aroused biochemical interest in recent years.[15] Because of this we attempted the displacement of the *p*-toluenesulfonyloxy group of **5** with the sodium salt of adenine. The product of this reaction was *N*-*p*-toluenesulfonyl-2-methylpyrrole (**10**), presumably arising from a base-induced elimination to **9** followed by a facile 1,5-sigmatropic hydrogen shift.

Experimental Section

***N*-Tosyl-3,4-dehydro-DL-prolinol (3)**[14] was prepared as a clear yellow oil from dehydro-DL-proline[17] by tosylation,[18] methylation with diazomethane,[18] and reduction of the *N*-tosyl-3,4-dehydro-DL-proline methyl ester with lithium borohydride.[14]

2,5-Anhydro-2-deoxy-3,4-isopropylidene-2-(*p*-toluenesulfonamido)-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol (7). The dehydroprolinol **3** can be hydroxylated[19] in almost quantitative yield with osmium tetroxide to give **4** as white crystals, mp 139°. The triol **4** can be converted to **7** (mp 143°) by reaction with 2,2-dimethoxypropane and subsequent tosylation with tosyl chloride and pyridine.[14]

1-(6-Aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-3,4-isopropylidene-2-(*p*-toluenesulfonamido)-DL-ribitol (8). Adenine (233 mg, 1.5 mmol) was dissolved in 10 ml of dry DMF. Sodium hydride (50% in mineral oil, 70 mg, 1.65 mmol) was added to the solution and it was stirred for 0.5 hr. The suspension was then placed in an oil bath at 60° for an additional 0.5 hr to ensure completion of the reaction. After cooling to room temperature 241 mg (0.5 mmol) of 2,5-anhydro-2-deoxy-3,4-isopropylidene-2-(*p*-toluenesulfonamido)-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol in 8 ml of DMF was added to the white suspension of the sodium salt of adenine. This mixture was then stirred at 60° for 12 hr. The DMF was then stripped off to give a light-brown residue that was extracted with methylene chloride. After filtering off the insoluble portion that remained, the methylene chloride was evaporated *in vacuo* to give a yellow oil that was chromatographed on preparative layer silica gel plates to give 104 mg (47%) of product as white crystals: mp 232–233°; nmr spectrum δ_{TMS} ($CDCl_3$) 0.80 (s, 3 H), 1.08 (s, 3 H), 2.41 (s, 3 H), 3.22–3.68 (m, 2 H), 4.02–5.03 (m, 5 H), 6.17–6.38 (br s, 2 H), 7.20–7.90 (m, 4 H), 8.05 (s, 1 H), 8.36 (s, 1 H); mass spectrum (70 eV, direct inlet 200°) *m/e* 444 (M^+).

Anal. Calcd for $C_{20}H_{24}N_6O_4S \cdot 1H_2O$: C, 51.95; H, 5.19; N, 18.18. Found: C, 51.79; H, 5.29; N, 17.98.

2,5-Anhydro-2-deoxy-2-(*p*-toluenesulfonamido-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol (6) was prepared by tosylation of **3** followed by hydroxylation.[14]

1-(6-Aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-2-(*p*-toluenesulfonamido)-DL-ribitol (1b). Adenine (127 mg, 0.941 mmol) and sodium hydride (50% in mineral oil, 50 mg, 1.035 mmol) were dissolved in 10 ml of dry DMF and stirred for 1.5 hr to form a white suspension of the sodium salt of adenine. To this was added 415 mg (0.941 mmol) of 2,5-anhydro-2-deoxy-2-(*p*-toluenesulfonamido)-1-*O*-(*p*-toluenesulfonyl)-DL-ribitol in 18 ml of DMF. The above mixture was then heated in an oil bath at 60° for 21 hr. The DMF was then stripped off *in vacuo* and further pumped down on a vacuum pump. Addition of a small amount of CH_2Cl_2 resulted in a beige-colored precipitate which was filtered and recrystallized twice from hot methanol to give a 73% yield (279 mg) of the stable, white, crystalline adduct (**1b**): mp 212–213°; uv spectrum λ_{max} (pH 7) 233 nm (ϵ 13,925), 266 (10,735); ^1H nmr spectrum δ_{TMS} (DMSO-d_6) 2.38 (s, 3 H), 3.21–4.63 (m, 9 H), 7.24 (s, 2 H), 7.30–7.95 (m, 4 H), 8.10 (s, 1 H), 8.22 (s, 1 H); ^{13}C nmr spectrum δ_{TMS} (DMSO-d_6) 20.97, 51.78, 63.52, 64.79, 68.47, 72.75, 119.30, 127.79, 129.44, 132.90, 140.90, 143.20, 150.1, 152.4, 155.8; mass spectrum (70 eV, direct inlet 175°) *m/e* 404 (M^+).

Anal. Calcd for $C_{17}H_{20}N_6O_4S$: C, 50.49; H, 4.98; N, 20.86. Found: C, 50.38; H, 5.23; N, 20.95.

***N*-Tosyl-2-methylpyrrole (10).** *N,O*-Ditosyl-3,4-dehydro-DL-prolinol (194 mg, 0.476 mmol) in 3 ml of DMF was added to a suspension of the sodium salt of adenine formed by treating 64 mg (0.476 mmol) of adenine with 71 mg (0.704 mmol) of sodium hydride (50% in mineral oil) in 2 ml DMF for 2.5 hr. After 6 hr of stirred heating at 50°, and an additional 12 hr of reaction time at room temperature, the DMF was removed *in vacuo*. The brown residue remaining was extracted with chloroform (3 × 20 ml) and filtered. After washing the chloroform extracts with water and drying (Na_2SO_4), the solvent was removed to give 99 mg of brown product. This product was purified by preparative layer chromatography on silica gel plates to give 55 mg (49% yield) of the *N*-tosyl-2-methylpyrrole: mp 87.5–89° (lit. mp 93–94°);[16] nmr spectrum δ_{TMS} ($CDCl_3$) 2.29 (s, 3 H), 2.42 (s, 3 H), 5.85–6.03 (m, 1 H), 6.17 (t, 1 H), 7.28 (m, 1 H), 7.20–7.82 (m, 4 H); mass spectrum (70 eV) *m/e* 235 (M^+).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.55; H, 5.57; N, 5.80.

Acknowledgments. We thank the National Science Foundation for funds toward the purchase of the PFT nmr spectrometer. One of us (R. H. W.) thanks the 3M Co. for a 3M Research Fellowship.

Registry No.—**1b**, 51932-88-8; **3**, 51932-89-9; **4**, 52019-89-3; **5**, 51932-90-2; **6**, 51932-91-3; **7**, 51932-92-4; **8**, 51932-93-5; **10**, 17900-53-7; adenine, 73-24-5.

References and Notes

(1) Abstracted from the Ph.D. Thesis of R. H. W., University of Iowa, 1974. Presented at the 8th Midwest Regional Meeting of the American Chemical Society, Columbia, Mo., Nov 8–10, 1972.
(2) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.
(3) J. A. Montgomery, *Progr. Med. Chem.*, 7 (1970).
(4) J. Defaye and T. Reyners, *Bull. Soc. Chim. Biol.*, **50**, 1625 (1968).
(5) J. Defaye and M. Naumburg, Abstracts of Papers, Chemistry of Nucleic Acid Components N-32, The XXI International Congress of IUPAC, Prague, 1967.
(6) N. J. Leonard, F. C. Sciavolino, and V. Nair, *J. Org. Chem.*, **33**, 3169 (1968).
(7) M. Kawazu, T. Kanno, S. Yamamura, T. Mizoguchi, and S. Saito, *J. Org. Chem.*, **38**, 2887 (1973).
(8) N. Takamura, N. Taga, T. Kanno, and M. Kawazu, *J. Org. Chem.*, **38**, 2891 (1973).
(9) S. Fukatsu, Y. Takeda, and S. Umezawa, *Bull. Chem. Soc. Jap.*, **46**, 3165 (1973).
(10) J. Cleophax, J. Defaye, and S. D. Gero, *Bull. Soc. Chim. Fr.*, 104 (1967).
(11) J. Hildesheim, J. Cleophax, S. D. Gero, and R. D. Guthrie, *Tetrahedron Lett.*, 5013 (1967).
(12) M. Kawazu and T. Kanno, Japanese Patent 72 20, 194 (Sept 27, 1972); *Chem. Abstr.*, **78**, 4486w (1973).
(13) M. Kawazu and T. Kanno, Japanese Patent 72 20, 195 (Sept 27, 1972); *Chem. Abstr.*, **78**, 30158k (1973).
(14) V. Nair and R. H. Walsh, *Carbohyd. Res.*, in press.
(15) J. Žemlička, J. V. Freisler, R. Gasser, and J. P. Horwitz, *J. Org. Chem.*, **38**, 990 (1973), and references cited therein.
(16) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).
(17) A. Corbella, P. Gariboldi, G. Jommi, and F. Mauri, *Chem. Ind. (London)*, 583 (1969).
(18) N. Izumiya, J. E. Francis, A. V. Robertson, and B. Witkop, *J. Amer. Chem. Soc.*, **84**, 1702 (1962).
(19) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

Bromination of Methyl 3-Oxo-5β-cholanate at C-2

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Molecular bromine is usually used to prepare α-bromo ketones and α-bromo aldehydes. On the other hand, iodine monobromide has been used for this purpose only in a few cases.[1,2]

In the present study **1** was subjected to the action of 2 equiv of iodine monobromide. Two definite stages could be distinguished (Scheme I) by using the nmr technique.

The compound obtained in the first stage, which terminated after about 2 hr, was characterized by its singlet at δ 1.09 and somewhat broad doublet centered at δ 4.98. From the melting point and other physical data this compound proved to be identical with 4β-bromo ketone[3] obtained by the usual bromination of **1** with 1 equiv of bromine.

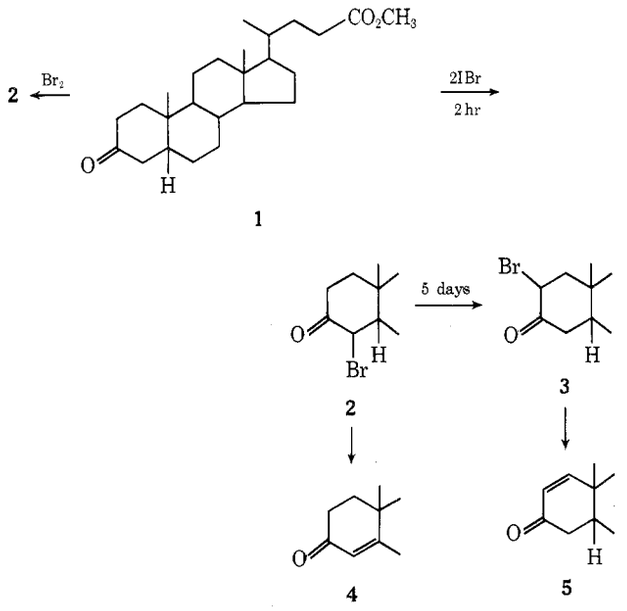
The second stage extended over a longer period of time (5 days), during which a singlet at δ 1.07 and a quartet centered at δ 4.73 gradually developed at the expense of the previous signals, which eventually completely disappeared (see Experimental Section). The characteristic quartet of the final product **3** unequivocally establishes the location and orientation of the bromine atom in this compound to be 2β (equatorial).[4] The configuration of the hitherto unknown compound **3** was also confirmed by other spectroscopic data.

The carbonyl frequency in the ir spectrum of **3** is higher than that of the parent ketone **1**. The observed shifts of 24 and 17 cm^{-1} for **3** and **2**, respectively, are to be expected for equatorial bromine substituents.[5] Additional evidence for the proposed orientation of the bromine substituent in both **2** and **3** was obtained from the location of the carbonyl absorption in the uv spectrum; the values of their λ_{max} are very close to that of the parent compound **1** (see Experimental Section).

Surprisingly, despite the distinct differences in the other physical constants, the mass spectra of the two bromo compounds **2** and **3** have much in common, indicating possible rearrangement during the fragmentation process.

Chemical evidence for the above assigned structure was provided by the conversion of **3** to the known α,β-unsaturated ketone **5**[3] (~50% yield) by the action of Li_2CO_3 in DMF.[6] The parallel reaction carried out on the isomeric 4β-bromo ketone **2** (Scheme I) proceeded smoothly to give methyl 3-oxo-4-cholenate (**4**)[3] as the major product, but the 2β-bromo isomer **3** reacted much more slowly. The elimination process involved, as expected,[7,8] a partial rearrangement yielding a mixture of methyl 3-oxo-5β-chol-1-enoate (**5**) and methyl 3-oxo-4-cholenate (**4**) in approximately 1:1 ratio. The location of the double bond in **5** was disclosed in the nmr spectrum; the two doublets centered at δ 6.8 and 5.84 are attributable to C-1 and C-2 vinylic protons, respectively. In contrast the single vinylic proton in compound **4** resonates at δ 5.71.

Scheme I



Preliminary experiments showed that complete monobromination could not be achieved with less than 2 equiv of IBr. It was assumed, therefore, that the reaction might be represented stoichiometrically as follows: 1 + 2IBr → 2 + I_2 + HBr. Accordingly, complete rearrangement of the 4β-bromo ketone **2** to 2β-bromo ketone **3** was effected by subjecting the former to the action of 1 equiv of I_2 and a catalytic amount of HBr in acetic acid. Thus, it is evident that the iodine formed during the first stage of the bromination was responsible for the rearrangement in the second stage of the reaction.

The migration of the bromine atom from C-4 to the less hindered C-2 position[9–12] was effected by iodine and hydrogen bromide taken together; in the presence of iodine alone the rearrangement was slower; hydrogen bromide in the absence of iodine proved to be entirely ineffective.

In our opinion the driving force for the migration is the ability of the iodine molecule to form a charge-transfer complex with the carbonyl group of the substrate.[13] The coordinated iodine molecule adjusts itself to the steric and stereoelectronic requirements of the rearrangement reaction. The debromination at C-4 and rebromination at C-2

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