Anal. Calcd. for $C_{18}H_{21}IN_2$: C, 55.11; H, 5.39. Found: C, 54.87; H, 5.60.

5,5-Dimethyl-4-phenyl-2-(3-pyridyl)-Δ^1-pyrroline (II) did not react with phenyl isothiocyanate.

When II was heated with phthalic anhydride at 210° for 15 min., 91% of unchanged pyrroline was recovered as the dipicrate.

A mixture of 1 g. of II, 1 g. of benzoyl chloride and 10 ml. of 10% aqueous sodium hydroxide was shaken until all benzoyl chloride was decomposed. An ether extract of the reaction mixture yielded 88% of unchanged pyrroline as the dipicrate.

A solution of 856 mg. of pyrroline II in 1 ml. of acetic anhydride was heated to 100° under a nitrogen atmosphere for 7.5 hours. Water (5 ml.) was then added, heating was continued for 5 min. with vigorous stirring, and the reaction mixture was neutralized with 2.8 g. of potassium carbonate. An ether extract of this mixture yielded 70% of unchanged pyrroline in the form of its dipicrate.

The Secondary Amine (III or IV).—Decomposition of the dipicrate of III or IV with 20% aqueous lithium hydroxide and subsequent distillation of the product under reduced pressure gave the pure amine as a colorless oil, b.p. 160° at 2 mm. An infrared absorption spectrum[28] of this substance showed maxima at 2.98(m), 3.38(s), 6.12(s), 6.25(m), 6.70(m), 6.89(s), 7.34(m), 7.60(m), 8.44(m), 11.62(m), 12.92(s) and 14.20(s) μ.

A Zerewitinoff determination on this substance in *n*-butyl ether at 25° resulted in liberation of 0.99 mole of methane and decomposition of 0.04 mole of additional Grignard reagent. At 100° the quantity of methane liberated was 1.01 moles and no additional methylmagnesium iodide was consumed.

Heat was liberated when equimolecular quantities of this amine and phenyl isothiocyanate were mixed. Crystallization of the resulting phenylthiourea from ethanol afforded colorless needles, m.p. 185–186°.

Anal. Calcd. for $C_{24}H_{29}N_3S$: C, 73.61; H, 7.46. Found: C, 73.48; H, 7.52.

(28) Kindly determined by R. Bruce Scott, Parke, Davis and Co., Detroit, Mich., with a liquid film of the amine, employing a Beckman IR-2T spectrophotometer equipped with a sodium chloride prism.

LOS ANGELES, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

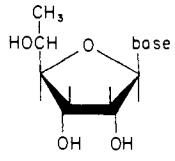
Potential Anticancer Agents.[1] VIII. Synthesis of Nucleosides Derived from L-Talofuranose

BY ELMER J. REIST, LEON GOODMAN AND B. R. BAKER

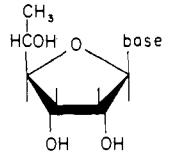
RECEIVED APRIL 24, 1958

The L-talose derivative methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VI) has been synthesized by SN2 displacement of the tosylate III of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside, epimerization at C_5 having taken place. Further conversion to 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) followed by nucleoside formation gave 9-(6′-deoxy-α-L-talofuranosyl)-adenine (XIII) and 2,6-diamino-9-(6′-deoxy-α-L-talofuranosyl)-purine (XVI).

In a preceding paper[2] of this series, a biological rationale for the synthesis of 5′-C-methyl-D-ribonucleosides was discussed. There are two stereoisomeric 5′-C-methyl-D-ribonucleosides: namely, the 6′-deoxy-D-allofuranosides (I) and the 6′-deoxy-L-talofuranosides (II). The earlier paper[2]



I



II

described the synthesis of the allose nucleosides (I) and this paper describes the synthesis of 9-(6′-deoxy-α-L-talofuranosyl)-adenine (XIII) and 2,6-diamino-9-(6′-deoxy-α-L-talofuranosyl)-purine (XVI).

6-Deoxy-L-talose (epifucose) has been synthesized[3] by the epimerization of 6-deoxy-L-galactonolactone (fucose lactone) at C_2 in boiling pyridine followed by reduction with sodium amalgam. The epifucose was obtained as an oil and characterized by its phenylosazone and *p*-bromophenylosazone.

The availability of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside (IV) in three steps from L-rhammose[2,4] made this an attractive starting material for the synthesis of 6-deoxy-L-talose derivatives (such as VI) if the 5-*O*-tosylate III could be inverted in configuration by SN2 displacement. Secondly, the 6-deoxy-L-talose would thus be obtained in the furanose form necessary for conversion to the nuceosides; this is a distinct advantage over the method starting with the sequence L-fucose → 6-deoxy-L-talose[3] which, although requiring only three steps, would then require a number of steps to obtain the requisite furanose form by some, as yet, unknown and not easily predictable sequence.

Little work has been reported on the displacement of secondary tosylates of sugars beyond stating that they are more difficult to displace than primary tosylates.[5,6] In a simpler system, Phillips[7] reported that the tosylate of α-methylphenethyl alcohol could be displaced by potassium acetate in alcohol to give the corresponding carbinyl acetate with Walden inversion. Since the 5-benzoate VI of methyl 2,3-*O*-isopropylidene-α-L-talofuranoside would be more useful for further transformations to the blocked sugar XI suitable for nucleoside coupling, and since sugar benzoates frequently give higher yields in nucleoside coupling reactions than sugar acetates,[8,9] the direct displacement of the

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper in this series *cf.* C. D. Anderson, L. Goodman and B. R. Baker, THIS JOURNAL, **80**, 5247 (1958).

(2) E. J. Reist, L. Goodman, R. R. Spencer and B. R. Baker, *ibid.*, **80**, 3962 (1958).

(3) E. Votocek and J. Cervany, *Ber.*, **48**, 658 (1915).

(4) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936).

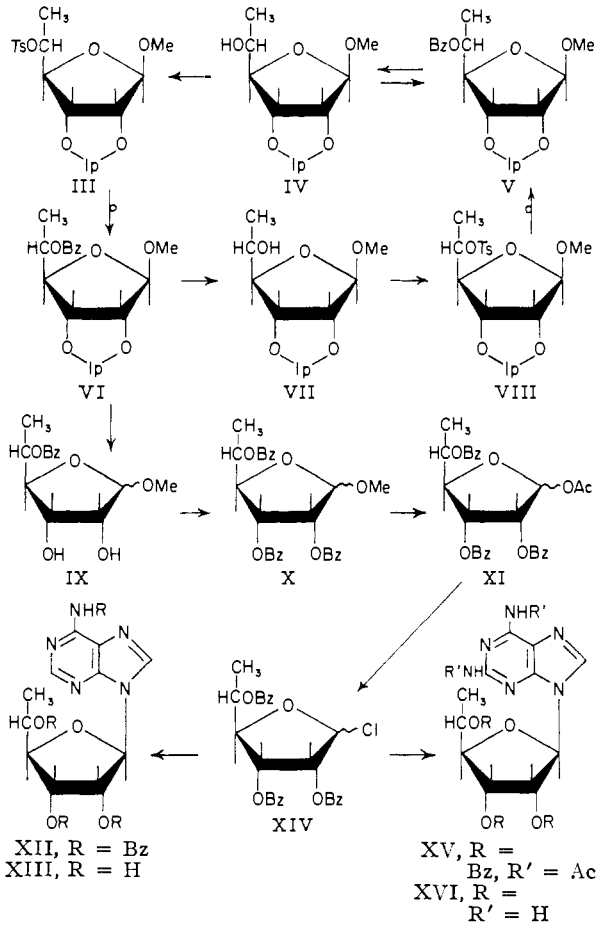
(5) R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 167 (1953).

(6) J. M. Sugihara, *ibid.*, **8**, 26 (1953).

(7) H. Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

(8) H. M. Kissman, C. Pidacks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

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



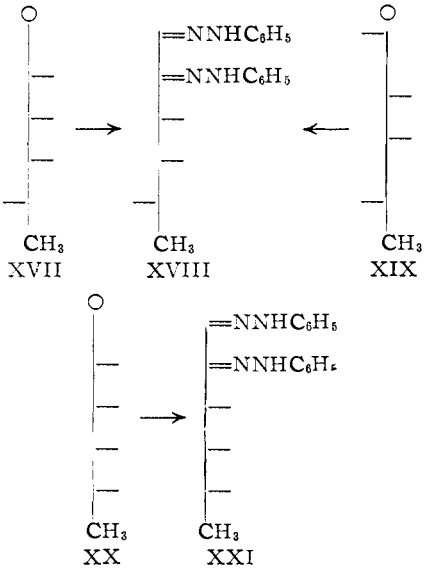
secondary tosylate of II to give the L-taloside 5-benzoate (VI) would be desirable. However, no example of the displacement of a tosylate by benzoate ion could be found in the literature.

Treatment of the allose tosylate (III) with sodium benzoate in boiling alcohol resulted in quantitative recovery of III. However, with sodium benzoate in boiling dimethylformamide, a smooth displacement of tosylate took place with formation of a crystalline benzoate in 77-79% yield, presumably methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VI). Since the 5-benzoate V of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside (IV) is an oil and since the two compounds have differences in the fingerprint region of the infrared, it is clear that these compounds are isomeric. In order to demonstrate that only a change in configuration at C_5 took place during the reaction of benzoate ion with III to give VI, the taloside VI was converted back to the alloside IV in the following manner.

Methanolysis of methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VI) removed the benzoate to form VII, a distillable oil, isomeric with the alloside IV. The corresponding 5-tosylate (VIII), although it could not be crystallized, underwent smooth SN2 displacement with sodium benzoate in boiling dimethylformamide to give the oily 5-*O*-benzoyl-D-alloside V, which gave an infrared spectrum identical with that of an earlier sample[2] prepared from methyl 6-deoxy-2,3-*O* - isopropylidene - β - D - allofuranoside (IV). When the inversion product V (prepared from VIII) was debenzoylated to IV and IV was then tosylated, crystalline methyl 6-deoxy-2,3-*O*-isopropylidene-5-tosyl-β-D-allofuranoside (III) was obtained that was identical in all respects with the starting tosylate for this Walden sequence. Thus, both inversion reactions, III → VI and VIII → V, took place only at C_5 and involved no other asymmetric center or any change in ring size.

Treatment of methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VI) with methanolic hydrochloric acid gave methyl 5-*O*-benzoyl-L-talofuranoside (IX) in 83% yield as an an oil which was free of isopropylidene group in the infrared, but which could be a mixture of anomers. Benzoylation of IX in pyridine with benzoyl chloride afforded the tribenzoate X in 84% yield as an oil that was free of hydroxyl in the infrared. Acetolysis of the methyl glycosidic group of X with acetic acid–acetic anhydride–sulfuric acid[2,10] gave 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) in 88% yield as an anomeric mixture. In contrast to the crystalline, epimeric alloside,[2] XI was obtained as an oil, but was suitable for nucleoside formation.

That the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) had configurations at C_3, C_4 and C_5 as assigned in structure XI was demonstrated unambiguously in the following manner. Deacylation of XI with cold methanolic sodium methoxide to 6-deoxy-L-talose (XVII)[3] and then reaction with phenylhydrazine gave an osazone (XVIII) identical with that prepared from L-



fucose (XIX),[3] thus proving that epimerization at C_5 had taken place during the conversion of III to VI. Secondly, deacylation of crystalline 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-D-allofuranose[2] to 6-deoxy-D-allose (XX) followed by reaction with phenylhydrazine afforded 6-deoxy-D-allose osazone (XXI)[4] that was clearly different from the isomeric XVIII as shown by mixed melting points and dif-

(10) B. R. Baker, J. P. Joseph and R. E. Schaub, THIS JOURNAL, **77**, 5905 (1955).

ferences in their infrared spectra in the 9- to 10-μ region.

Reaction of the acylated talofuranose XI with ethereal hydrogen chloride[11] at 0° in the presence of acetyl chloride[12] afforded the blocked talofuranosyl chloride XIV as an oil, which was condensed with chloromercuri-6-benzamidopurine[13] to give the crude blocked nucleoside XII. Debenzoylation with methanolic sodium methoxide required a longer reaction time and a higher ratio of sodium methoxide than usually required[8,14] in order to remove the *O*-blocking groups completely. Partition between water and chloroform gave an aqueous solution which contained adenine and the desired nucleoside XIII as major components along with two minor components, as was determined by paper chromatography. Isolation of the methanol-insoluble picrates and regeneration of the bases from the picrate with Dowex 2 (CO_3)[14] gave a mixture free of sugar impurities. A paper chromatogram with solvent A[15] showed thep resence of three spots, adenine with R_{ad} 1.00 ,the major spot of the desired nucleoside with R_{ad} 1.64 and a minor spot with R_{ad} 1.29. Similarly, solvent B showed a minor spot of adenine (R_{ad} 0.98), a major spot of the desired nucleoside (R_{ad} 1.12) and a minor component with R_{ad} 1.42. Determination of the relative quantities in each spot by ultraviolet analysis indicated a ratio of 8% adenine, 20% of the minor impurity and 70% of the major spot.

Since neither the nucleoside XIII nor its salts could be obtained crystalline, the ion exchange method of Cohn[17] was investigated to separate adenine from the nucleoside. The crude mixture was dissolved in ammonium formate solution adjusted to *p*H 10 with ammonia water and loaded on a column of Dowex 2 (formate). The nucleoside (s) were eluted with 0.01 *N* ammonium formate until no more material was removed as evidenced by lack of ultraviolet absorption in the eluate. The adenine was then eluted with 0.1 *N* formic acid. Paper chromatography[15] in solvents A and B showed that the ammonium formate had eluted only the desired nucleoside and the formic acid had eluted only adenine. Apparently, the second minor component was held by the resin. The adenine amounted to 10% of the total bases put on the column. Evaporation of the ammonium formate solution gave the desired nucleoside XIII as 70% of the total bases put on the column. Not only was this material free of impurities by paper chromatography[15] in solvents A, B and C, but Celite partition chromatography[8] in a butanol–water system also showed only one component. The free base, though pure, could not be crystallized. Analysis of the free base showed that there was still solvent present. A crystalline hydrochloride of XIII was not obtained from alcoholic solution containing an equivalent of hydrogen chloride; instead, slow alcoholysis to adenine hydrochloride, which crystallized from solution, occurred. In a larger run, it was observed that most of the 6-benzamidopurine could be removed by recrystallization of the crude blocked nucleoside from benzene. Debenzoylation of the purified blocked nucleoside followed by purification of the crude nucleoside XIII *via* its picrate as described above gave a non-crystalline nucleoside which contained less than 5% impurity as shown by paper chromatography.

The over-all yield of nucleoside XIII based on 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) was 19%. This talose nucleoside XIII was assigned the α-configuration in agreement with the postulated rule[18] that nucleosides with a C_1–C_2-*trans*-configuration would be obtained under these conditions.

Condensation of 2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranosyl chloride (XIV) with chloromercuri-2,6-diacetamidopurine[13] gave a crude blocked nucleoside XV that was deacylated with excess methanolic sodium methoxide.[13,14] After isolation of the picrate and regeneration of the bases with Dowex 2 (CO_3),[13] the diaminopurine taloside XVI was obtained in 29% yield (based on XI) and gave a paper chromatogram with solvent A that showed a trace spot of 2,6-diaminopurine (R_{ad} 0.48) and a major spot with R_{ad} 0.97. Solvent B failed to separate the bases. An alcoholic solution of the 2,6-diamino-9-(6′-deoxy-α-L-talofuranosyl)-purine (XVI) when treated with hydrochloric acid gave a crystalline hydrochloride which still contained a trace of 2,6-diaminopurine. This nucleoside is again assumed to have an α-configuration following the prediction from the C_1–C_2-*trans* rule.[18]

Experimental[15,19]

Methyl 5-*O*-Benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VI).—A mixture of 2.00 g. (5.4 mmoles) of methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-allofuranoside (III),[3,4] 4.0 g. (27.8 mmoles) of sodium benzoate and 50 ml. of dimethylformamide was refluxed for 6 hours. The mixture, diluted with 50 ml. of water, was extracted with two 50-ml. portions of ether. The combined ether extracts, washed with aqueous sodium bicarbonate and then with water, were dried with magnesium sulfate. Evaporation to dryness *in vacuo*, finally at 100° (1 mm.), gave 1.37 g. (79%) of a yellow oil which crystallized on standing and was suitable for further transformations; λ_{max}^{film} 5.84 μ (benzoate C=O), 7.85, 8.96 μ (benzoate C–O–C), 14.08 μ (monosubstituted phenyl); no tosylate bands at 7.30 or 8.50 μ. Recrystallization from methanol afforded white crystals, m.p. 93.5–95°, $[\alpha]^{27}D$ −38° (2.86% in MeOH). In a larger run the yield was 77 g. (77%).

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.3; H, 6.88. Found: C, 63.1; H, 6.91.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VII).—A solution of 3.28 g. (10 mmoles) of VI in 140 ml. of

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

(12) B. R. Baker and R. E. Schaub, THIS JOURNAL, **77**, 5900 (1955).

(13) J. Davoll and B. A. Lowy, *ibid.*, **73**, 1650 (1951).

(14) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(15) Paper chromatography was run on Whatman No. 1 paper by the descending technique and spots were located by visual examination under ultraviolet light. Adenine was used as a standard and spots are assigned R_{ad} values where adenine has R_{ad} 1.00. These solvent systems were used: A, 5% aqueous disodium phosphate; B, 1-butanol–acetic acid–water (5:2:3)[16]; C, saturated ammonium sulfate–isopropyl alcohol–water (2:28:70).

(16) D. M. Brown, A. Todd and S. Varadarjan, *J. Chem. Soc.*, 2388 (1956).

(17) W. E. Cohn, THIS JOURNAL, **72**, 1471 (1950).

(18) B. R. Baker, J. P. Joseph, R. E. Schaub and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954); B. R. Baker, Ciba Foundation Symposium on the "Chemistry and Biology of Purines," J. and A. Churchill, Ltd., London, 1957, pp. 120–130.

(19) Melting points were taken on a Fisher–Johns apparatus and are uncorrected. Rotations were taken with a Standard polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.

methanol and 4.2 ml. of 1 *N* methanolic sodium methoxide was refluxed for 1 hour, then acidified with acetic acid and evaporated to dryness *in vacuo*. The residue was dissolved in ether, filtered with sodium salts, and again evaporated *in vacuo*. Evaporative distillation at 90–95° (1 mm.) gave 1.14 g. (52%) of colorless oil, $[\alpha]^{27}D$ −54° (1.58% in MeOH). In the infrared this compound, as a film, showed hydroxyl absorption at 2.94 μ, and ether C–O–C absorption at 9.17 (broad), 9.46 and 9.74 μ. Only a trace of benzoate absorption was present at 5.83 μ.

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.0; H, 8.31. Found: C, 55.3; H, 8.34.

Reconversion of Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (VII) to Methyl 6-Deoxy-2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-allofuranoside (III).—Treatment of 2.00 g. (9.2 mmoles) of VII in 10 ml. of pyridine with 3.0 g. (16 mmoles) of tosyl chloride in 5 ml. of chloroform as described[2] for the corresponding alloside IV gave 73% of the tosylate VIII as a pale yellow oil; λ_{max}^{film} 7.32 μ (–OSO_2–, CH_3), 8.43, 8.52 μ (–OSO_2–); no OH near 2.9 μ.

Reaction of 2.38 g. (6.4 mmoles) of VIII with 4.76 g. of sodium benzoate in 50 ml. of boiling dimethylformamide as described for III → VI gave an 82% yield of methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside (V) as an oil; λ_{max}^{film} identical with *V* prepared from IV.

Debenzoylation of V with methanolic sodium methoxide as described for VI → VII gave, after evaporative distillation at 65° (0.1 mm.), 68% of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside (IV) as a colorless oil with an infrared spectrum identical with authentic IV.[2]

Tosylation of 0.50 g. of this IV as previously described[2] gave 0.59 g. (70%) of crystalline III, m.p. 91.5–92°. A mixture with an authentic sample of III[2] gave no depression in m.p. and their infrared spectra were identical.

Methyl 5-*O*-Benzoyl-6-deoxy-L-talofuranoside (IX).—A solution of 1.37 g. (4.2 mmoles) of VI in 15 ml. of methanol containing 0.33 ml. of 12 *N* hydrochloric acid was refluxed for 90 minutes, then evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of chloroform and the solution was washed twice with saturated aqueous sodium bicarbonate; the washings were back extracted with 10 ml. of chloroform. Dried over magnesium sulfate, the combined organic solutions were evaporated to dryness *in vacuo*, leaving 0.90 g. (75%) of a yellow oil; λ_{max}^{film} 2.90 μ (OH); 5.80 μ (benzoate C=O). In a larger run the yield was 51.7 g. (83.5%).

Methyl 2,3,5-Tri-*O*-benzoyl-6-deoxy-L-talofuranoside (X).—To a solution of 0.90 g. (3.2 mmoles) of IX in 13 ml. of dry pyridine cooled in an ice-bath was added 1.05 ml. (9 mmoles) of benzoyl chloride dropwise with stirring. After 24 hours at 0° in a stoppered flask, the mixture was slowly added to ice and an excess of saturated sodium bicarbonate solution. The aqueous mixture was extracted with two 25-ml. portions of ether. The combined extracts, washed with water and dried with magnesium sulfate, were evaporated to dryness *in vacuo*; the last traces of pyridine were removed by addition and removal *in vacuo* of three 5-ml. portions of toluene; yield 1.25 g. (80%) of a yellow oil which was slightly contaminated with benzoic anhydride since in the infrared (film) the oil showed weak absorption at 5.58 μ along with strong benzoate C=O at 5.78 μ. No appreciable hydroxyl absorption was present near 2.90 μ. In a larger run the yield was 75 g. (84%).

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI).—To a cooled magnetically-stirred solution of 1.25 g. (2.55 mmoles) of X in 1.1 ml. of acetic anhydride and 10 ml. of acetic acid was added dropwise 0.6 ml. of 96% sulfuric acid at such a rate that the temperature was 20–25°. After 24 hours in a stoppered flask at room temperature, the solution was poured into 85 ml. of ice-water and extracted with two 25-ml. portions of ether. The combined extracts were cautiously washed with excess aqueous sodium bicarbonate, then with water. Dried with magnesium sulfate, the organic solution was evaporated to dryness *in vacuo*, leaving 0.90 g. (68%) of a yellow oil; λ_{max}^{film} 5.78 μ (ester C=O), 7.90, 9.00 μ (benzoate C–O–C), 8.17 μ (acetate C–O–C); $[\alpha]^{27}D$ +40° (0.604% in $CHCl_3$). In a larger run the yield was 71 g. (88%).

Anal. Calcd. for $C_{29}H_{26}O_9$: C, 67.2; H, 5.05. Found: C, 66.7, 66.6; H, 5.43, 5.50.

6-Deoxy-L-talose Osazone (XVIII).—A solution of 0.9 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) in 18 ml. of methanol containing 0.6 ml. of 1 *N* methanolic sodium methoxide was kept at room temperature for 18 hours. The solution was neutralized with glacial acetic acid, then evaporated to dryness *in vacuo*. The residue was countercurrently extracted between two 6-ml. portions each of water and chloroform. The aqueous layers were combined and evaporated to dryness *in vacuo*. The resultant residue was extracted with two 2-ml. portions of hot ethanol. The ethanol extracts were evaporated to dryness *in vacuo* to yield 0.35 g. of a white foam (XVII) which gave a positive Benedict test for reducing sugar. The osazone XVIII prepared from XVII was recrystallized from 50% ethanol, m.p. 168–171°. A mixed melting point with the osazone XVIII of L-fucose (XIX) gave no depression and their infrared spectra were essentially identical.

Votocek and Cervany[3] reported m.p. 177–178° for 6-deoxy-L-talose osazone.

6-Deoxy-D-allose Osazone (XXI).—This osazone, prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-D-allofuranose[2] by the above procedure, melted at 180–182°. A mixture with 6-deoxy-L-talose osazone (XVIII) melted at 157–171°. In addition, their infrared spectra were profoundly different. Levene and Compton[4] reported m.p. 184–185° for 6-deoxy-D-allose osazone.

2,3,5-Tri-*O*-benzoyl-6-deoxy-L-talofuranosyl Chloride (XIV).—To a solution of 2.0 g. (3.86 mmoles) of XI in 60 ml. of dry ether saturated with hydrogen chloride at 0° was added 2 ml. of acetyl chloride. After 3 days at 0° in a stoppered flask, the solution was evaporated to dryness *in vacuo* (bath 30°) protected from moisture back-up. The last traces of acetic acid were removed by the addition and removal *in vacuo* of two 5-ml. portions of benzene. The resulting colorless oil was used immediately for condensation with a chloromercuripurine.

6-Benzamido-9-(2′,3′,5′-tri-*O*-benzoyl-α-L-talofuranosyl)-purin (XII).—A mixture of 1.82 g. (3.86 mmoles) of chloromercuri-6-benzamidopurine,[20] 1.80 g. of Celite and 180 ml. of xylene was distilled with stirring until traces of water were removed. After the addition of a solution of XIV, prepared from 2.0 g. (3.86 mmoles) of XI, in 50 ml. of dry xylene, the mixture was refluxed with stirring for 3 hours. The reaction mixture was processed in the usual way[2,14] to give 2.57 g. (97%) of crude blocked nucleoside as a glass.

9-(6′-Deoxy-α-L-talofuranosyl)-adenine (XIII). (A) Preparation.—A solution of 1.57 g. of crude blocked nucleoside in 30 ml. of methanol and 1 ml. of 1 *N* methanolic sodium methoxide was heated under reflux for 2 hours. The cooled solution was neutralized with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 30 ml. each of chloroform and water. The aqueous layer was evaporated to dryness *in vacuo* to yield 0.76 g. of a yellow-brown oil. A solution of this oil in 8 ml. of methanol was treated with 20 ml. of 10% methanolic picric acid and the mixture was cooled at 0° for several hours. The resulting picrate was recrystallized from 30 ml. of water to give 0.40 g. of crystalline picrate. To 20 ml. of water at room temperature was added portionwise, with stirring, the above picrate and 2.5 g. of Dowex 2 (carbonate form) anion exchange resin.[2,14] After the addition was complete and the picrate had gone into solution, the mixture was filtered and the filtrate was concentrated to dryness *in vacuo* to yield 175 mg. of crude nucleoside; λ_{max}^{KBr} 3.00, 3.13 μ (OH, NH), 6.18, 6.26 μ (NH_2, C=C, C=N). This crude nucleoside contained some adenine and another minor impurity as shown by paper chromatography in solvents A, B and C.[15]

(B) **Purification.**—A solution of 174 mg. of the preceding crude nucleoside in 25 ml. of 0.01 *N* ammonium formate was adjusted to *p*H 10.4 with concentrated ammonium hydroxide. The solution was transferred to the top of an 85 × 23 mm. column of Dowex 2 (formate), then the nucleoside was eluted with 0.01 *N* ammoniun formate until ultraviolet absorption in the eluate became negligible; a total of 500 ml. of eluate was required. Evaporation to dryness *in vacuo* gave a solid containing ammonium formate that was suitable for picrate formation. Paper chromatography[15] showed that the only purine present was the desired nucleoside, with R_{ad} 1.55 in solvent A, R_{ad} 1.07 in solvent B and R_{ad} 1.38 in solvent C.

The nucleoside, containing ammonium formate, was dissolved in 5 ml. of water-saturated 1-butanol. The solution was mulled with 5 g. of Celite 545,[8] then transferred to the

(20) Prepared from mercuric chloride and 6-benzamidopurine a described for the preparation of chloromercuri-2,6-diacetamidopurine.[1]

top of a Celite column (215 × 35 ml.) prepared with 40 g. of Celite 545 and 40 ml. of water-saturated butanol.[8] The column was developed with water-saturated butanol and 20-ml. fractions were collected automatically. The nucleoside appeared in fractions 8–14 and was maximal at fraction 11. No other material appeared through fraction 37. The combined fractions (8–14) were evaporated *in vacuo* to give 121 mg. (70% recovery) of pure nucleoside XIII as a colorless glass; λ_{max}^{KBr} 2.93 μ (OH, NH), 6.09, 6.15, 6.35 μ (NH_2, C=C, C=N), 8.85, 9.15 μ (C–O–C and C–O–H). The over-all yield from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) was 19%.

(C) Characterization.—A sample of the nucleoside, contaminated with ammonium formate, that was obtained from the ion exchange column was dissolved in 10% aqueous methanol and treated with an excess of 10% methanolic picric acid. The picrate was collected on a filter and recrystallized from water, then the nucleoside was regenerated with Dowex 2 (CO_3) as described previously to give a white foam, $[\alpha]^{27}D$ −35° (0.84% in H_2O). This material was chromatographically pure in solvents A, B and C,[15] but could not be completely freed of solvents without decomposition.

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 47.0; H, 5.38; N, 24.9. Found: C, 45.8; H, 5.98; N, 22.3.

2,6-Diacetamido-9-(2′,3′,5′-tri-O-benzoyl-6′-deoxy-α-L-talofuranosyl)-purine (XV).—A solution of freshly prepared XIV (from 2.00 g. (3.86 mmoles) of XI) in 50 ml. of dry xylene was added to a stirred suspension of 1.81 g. (3.86 mmoles) of chloromercuri-2,6-diacetamidopurine[14] and 2.05 g. of Celite in 130 ml. of xylene previously dried by distillation. After being refluxed with stirring for 3.5 hours, the mixture was processed in the usual way[2,14]; yield 2.47 g. (92%) of crude XV as a glass.

2,6-Diamino-9-(6′-deoxy-α-L-talofuranosyl)-purine (XVI).—A solution of 2.40 g. of crude XV in 60 ml. of methanol and 5.4 ml. of 1 *N* methanolic sodium methoxide was refluxed for 3 hours. After being acidified with acetic acid, the solution was evaporated to dryness *in vacuo* and the resultant residue was partitioned between 60 ml. each of water and chloroform. The aqueous solution was evaporated to dryness *in vacuo*. The residue (1.90 g.) was converted to the picrate (0.50 g.) and regenerated with Dowex 2 (CO_3)[14] as described for the preparation of XIII; yield 0.32 g. (29% based on XI) of an amorphous glass; λ_{max}^{KBr} 2.98 μ (OH, NH), 6.10, 6.25 μ (NH_2, C=C, C=N). This was essentially pure XVI with a trace of a 2,6-diaminopurine as shown by paper chromatography.[15]

The crystalline hydrochloride was prepared by the addition of 2 drops of 2 *N* hydrochloric acid to a solution of 0.24 g. of the base in 3 ml. of alcohol. The solid which separated was recrystallized from ethanol by addition of a little ethanolic hydrogen chloride to give white crystals, m.p. 212–213° dec., $[\alpha]^{28}D$ −19° (0.25% in H_2O); λ_{max}^{KBr} 2.98 μ (OH, NH), 5.94 μ (=NH_2^+), 6.07, 6.26 μ (NH_2, C=C, C=N).

Anal. Calcd. for $C_{11}H_{16}N_6O_4 \cdot HCl$: C, 39.7; H, 5.16; N, 25.2. Found: C, 39.8; H, 5.56; N, 25.3.

Both the free base and the hydrochloride gave a major spot with R_{ad} 0.97 in solvent A and a trace spot of 2,6-diaminopurine at R_{ad} 0.48. The hydrochloride consumed 0.91 mole of periodate in 15 minutes and 1.01 moles in 24 hours, thus confirming the furanose structure.

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Potential Anticancer Agents.[1] IX. Tetrahydroquinazoline Analogs of Tetrahydrofolic Acid. I

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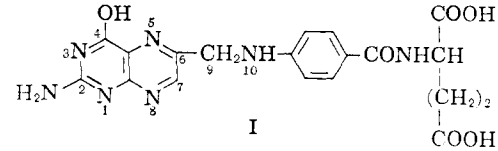
Condensation of 2,4-dicarbomethoxycyclohexanone with guanidine led to an excellent yield of 2-amino-5,6,7,8-tetrahydro-4-hydroxyquinazoline-6-carboxylic acid (VI) which, *via* its *n*-butyl ester, could be reduced in good yield to 2-amino-5,6,7,8-tetrahydro-4-hydroxy-6-hydroxymethylquinazoline (IX). Compound IX was converted to 2-amino-6-chloromethyl-5,6,7,8-tetrahydro-4-hydroxyquinazoline (X) which, in turn, was condensed with N-(*p*-aminobenzoyl)-L-glutamic acid to give the tetrahydrofolic acid analog 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (XI). The acid VI was converted to a variety of amides and esters and, *via* the acid hydrazide and acid azide, to the 6-amino compound XX. The latter compound was acylated conventionally to yield an amide and a sulfonamide.

Folic acid (I), one of the important B vitamins, serves as a precursor for the biogenetic synthesis of the cofactor, tetrahydrofolic acid conjugate. This latter, in turn, serves as both a formyl and hydroxymethyl transfer agent in a variety of biological systems. A large amount of work has been done on the synthesis of potential folic acid antagonists and a few active compounds have been found,[2] the best known of which are the clinically useful aminopterin, the 4-amino analog of folic acid (I), and amethopterin, the 4-amino-10-methyl analog of I. Both of these compounds, in microbiological systems, function by non-competitive blocking of the reduction of folic acid (I) to tetrahydrofolic acid, but their effects are competitively reversed by tetrahydrofolic acid or its formyl derivative.[3,4] Recent research has indicated that both the N_5 and N_{10} nitrogens of tetrahydrofolic acid are



I

involved in one-carbon transfer reactions. It is

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. This paper was presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 18, 1958; see Abstracts, page 84-N. For the preceding paper in this series *cf.* E. J. Reist, L. Goodman and B. R. Baker, THIS JOURNAL, **80**, 5775 (1958).

(2) A more complete discussion of folic acid antagonists is found in "The Vitamins," W. H. Sebrell, Jr., and R. S. Harris, Vol. III, Academic Press, Inc., New York, N. Y., 1954, p. 149.

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