m.p. 190–210°; recrystallized from ethanol, m.p. 216–218°.

Anal. Calcd. for $C_9H_9N_5O_3$; C, 46.00; H, 3.83; N, 29.80. Found: C, 46.13; H, 3.68; N, 30.02.

A mixture of VIII (15 g.) and 150 cc. concd. hydrochloric acid heated at reflux for 4 hr. gave 17.9 g. (yield 99%) of tris(2-carboxyethyl) isocyanurate (X), m.p. 226–230°; recrystallization from water, m.p. 228–229°.

Anal. Calcd. for $C_{12}H_{15}N_3O_9$; C, 41.75; H, 4.35; N, 12.17. Neut. equiv., 115.0. Found: C, 41.87; H, 4.39; N, 12.10. Neut. equiv., 115.2.

Hydrolysis of VII (7.9 g.) as described above gave 9.0 g. (yield 99%) of bis(2-carboxyethyl) isocyanurate (IX), m.p. 287–289° after recrystallization from water.

Anal. Calcd. for $C_9H_{11}N_3O_7$: C, 39.57, H, 4.03; N, 15.38. Neut. equiv., 136.5 and 91.0. Found: C, 39.69; H, 3.91; N, 15.25. Neut. equiv., 135.7 and 91.5.

Tris(2-carboxyethyl) isocyanurate (X) (34.5 g.) refluxed with 200 ml. of 5*N* absolute ethanolic hydrogen chloride for 2 hr. gave 40.0 g. (yield 93%) of tris(2-carbethoxyethyl) isocyanurate (XI), m.p. 50–52° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{27}N_3O_9$: C, 50.35; H, 6.33; N, 9.80. Found: C, 50.16; H, 6.33; N, 9.78.

Hydrogenation of tris(2-cyanoethyl) isocyanurate (VIII). A stainless steel autoclave containing 50.0 g. of VIII, 17.1 g. Raney nickel and 61.3 g. anhydrous ammonia was pressurized to 1400 p.s.i.g. with hydrogen and heated to 80–82° for 5 hr. Additional hydrogen was added as the reaction proceeded until theoretical uptake was realized.

The autoclave was cooled, vented, and the product washed from the bomb with absolute ethanol and filtered from the catalyst. Evaporation of the alcohol solution gave a sirupy mass practically free of ammonia. Extraction of the sirupy mass with ethanol gave 23.9 g. of bis(3-aminopropyl) isocyanurate (XII), m.p. 212–215°; crystallized from water and then from *N*-methylpyrrolidone, m.p. 205–207°.

Anal. Calcd.: Mol. wt., 243. Neut. equiv., 121.5 and 243. Found: Mol. wt. by freezing point depression of water: 236. Neut. equiv., 126 and 252.

Reaction with dilituric acid gave a didilituric salt.

Anal. Calcd. for $C_{17}H_{23}N_{11}O_{13}$: C, 34.62; H, 3.90; N, 26.15. Found: C, 34.64; H, 3.77; N, 25.93.

A mixture of 43.0 g. of VIII, 100 ml. of ethanol, 15.6 g. of wet W-2 Raney nickel and 18.1 g. of ammonia was placed in a 320 ml. autoclave and heated to 155–160° for 3 hr. at 2000 p.s.i.g. hydrogen pressure. The autoclave was cooled, vented, and the contents washed out with ethanol. The catalyst was filtered and the solution concentrated to give 15.0 g. mono(3-aminopropyl) isocyanurate (XIII).

Anal. Calcd. for $C_6H_{10}N_4O_3$: C, 38.75; H, 5.38; N, 30.10. Neut. equiv., 186. Found: C, 39.05; H, 5.64; N, 30.08; Neut. equiv., 187.

Attempted isolation of the above amines *via* vacuum distillation gave appreciable quantities of tetrahydropyrimidinone-2 (XIV), m.p. 263–265° (lit.,[14] m.p. 263–265°). The identity of the pyrimidone-2 was established by hydrobromic acid hydrolysis to 1,3-diaminopropane and comparison of the dihydrochloride and the picrate salts of the latter with authentic materials. The known and the unknown salts gave identical infrared spectra.

Conversion of tris(2-cyanoethyl) isocyanurate (VIII) *to bis(2(cyanoethyl) isocyanurate* (VII). Heating VIII (50 g.) and 70 g. of anhydrous ammonia in a 320-ml. autoclave for 4 hr. at 80° gave 39.1 g. of VII (yield 96%), m.p. 216–218°. A mixed melting point with an authentic sample of bis(2-cyanoethyl) isocyanurate gave no depression. Infrared spectra of the compounds were identical.

HOPEWELL, VA.

(14) E. Fisher and H. Koch, *Ann* **232**, 224 (1886).

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

Potential Anticancer Agents.[1] XXXIX. An Alternative Synthesis of 9-(2′,3′-Anhydro-β-D-ribofuranosyl)adenine

ALLEN BENITEZ, OSBORNE P. CREWS, JR., LEON GOODMAN, AND B. R. BAKER

Received March 30, 1960

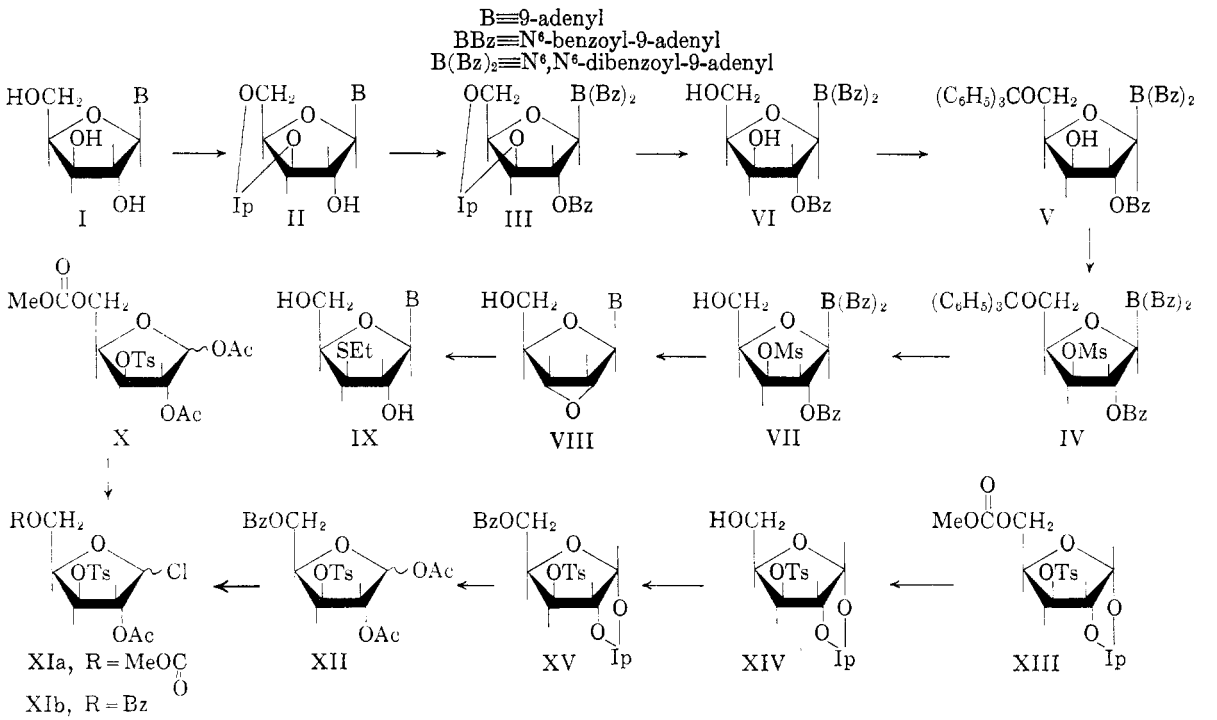
A seven-step synthesis of 9-(2′,3′-anhydro-β-D-ribofuranosyl)adenine (VIII) from 9-(β-D-xylofuranosyl)adenine (I) was accomplished. The direct coupling route to VIII using 2-*O*-acetyl-5-*O*-benzoyl-3-*O*-(*p*-tolylsulfonyl)-D-xylofuranosyl chloride (XIb) was explored but proved less satisfactory than the use of the 5-*O*-methoxycarbonyl analog (XIa) of XIb.

In a previous paper[2] from these laboratories, the synthesis of the anhydronucleoside (VIII) from 1,2-di-*O*-acetyl-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (X) was described. The over-all yield of this versatile intermediate (VIII) from X was only 8.9% with essentially all of the low yield being attributable to difficulties in the coupling reaction between the chlorosugar (XI) and chloromercuri-6-benzamidopurine. It was felt that better over-all yields of X might be obtainable by carrying out the necessary transformations on a suitable and more readily accessible preformed nucleoside. The coupling reaction between 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide and chloromercuri-6-benzamidopurine has been reported to give approximately 45% of 9-(β-D-xylofuranosyl)adenine (I)[3] and this nucleoside (I) appeared to be a suitable starting material for an alternative synthesis of VIII.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, K. A. Hyde, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, in press.

(2) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

(3) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).



The conversion of I to the 3′,5′-*O*-isopropylidene derivative (II)[3] in 68% yield was accomplished by reaction with acetone at room temperature using a large quantity of ethanesulfonic acid as a catalyst. Reaction of II with a large excess of benzoyl chloride in pyridine for three to five days gave a 66% yield of a crystalline compound whose analysis showed that three benzoyl groups had been introduced and whose infrared spectrum showed no —NH absorption; its structure seems to be best represented as the N^6,N^6-dibenzoyladenine derivative (III). Cleavage of the *O*-isopropylidene group from III with 70% aqueous acetic acid at 50°[4] gave a good yield of crude VI. A partial purification of VI was carried out by partitioning the product between the layers of a benzene-methanol-water mixture. The major fraction (74% calculated as VI), isolated from the benzene-rich layer, appeared from the infrared spectrum to be mainly the N^6,N^6-dibenzoyl compound (VI), although efforts to obtain it in analytically pure form were unsuccessful; it was the material used for the remainder of the synthetic sequence to VIII. The material isolated from the water-rich phase appeared to be mostly the N^6-monobenzoyl compound, corresponding to VI, and was probably a useful precursor of VIII although it was not used. The crude dihydroxy nucleoside (VI) was tritylated at 50–55° to form V and the reaction mixture was directly treated with excess methanesulfonyl chloride to form the mesylate (IV). The crude tritylated mesylate (IV) was detritylated by the procedure of Schaub, Weiss, and Baker[4] using 80% aqueous acetic acid at 80° for twenty-five minutes and the crude mesylate, benzoate (VII), was converted with sodium methoxide to the anhydronucleoside (VIII) by the procedure of Anderson, *et al.*,[2] in an over-all yield of 28% based on the acetonide (II).

As was described previously,[2] the procedure of Baker and Hewson[5] was used to precipitate the picrate of VIII, as a means of separating VIII from nonbasic materials. Regeneration of the picrate of VIII was studied using Dowex 2 (CO_3), Dowex 2 (OAc), and Dowex 2 (Cl); using a standardized and comparable procedure with each resin, the recovery of VIII was best with the acetate form of the resin, somewhat less with the chloride form, and poorest with the carbonate form. The same order of resin regeneration efficiency was found in the recovery of adenosine from adenosine picrate. Adsorptive losses on the resins are responsible for the lowered yields with the more basic resins.[5]

The over-all yield of VIII from 2,3,5-tri-*O*-benzoyl bromide was 6–8%, comparable with that from the direct coupling reaction with XIa.

In order to study the effect of the blocking group at the 5-position of the sugar on the coupling reaction with chloromercuri-6-benzamidopurine, 1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (XIII)[6] was cleaved with a catalytic quantity of sodium methoxide in methanol to the 5-hydroxy sugar (XIV), which was directly benzoylated to give the crystalline 5-*O*-benzoyl compound

(4) R. E. Schaub, M. J. Weiss, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 4692 (1958).

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

(6) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5247 (1958).

(XV). Acetolysis of XV to the diacetate (XII) and cleavage of the diacetate (XII) to give the chloro sugar (XIb) were carried out as described for the 5-*O*-methoxycarbonyl compound.[6] The coupling reaction of XIb with chloromercuri-6-benzamidopurine, however, gave a somewhat poorer crude yield of VIII than did the reaction of XIa, making it clear that the low yield of VIII from XIa could not be attributed solely to the 5-*O*-methoxycarbonyl blocking group.

A further investigation of the coupling reaction between XIa and chloromercuri-6-benzamidopurine on a large scale has shown that certain modifications of the procedure lead to a large improvement in the reaction, as shown by the nearly threefold increase in yield of the 3′-ethylthionucleoside (IX) isolated by using the crude anhydronucleoside (VIII) from the coupling reaction. These modifications are outlined in the Experimental.

EXPERIMENTAL[7]

9-(3′,5′-O-Isopropylidene-β-D-xylofuranosyl)adenine (II). To a well stirred mixture of 18.9 g. (70.6 mmoles) of 9-(β-D-xylofuranosyl)adenine (I)[3] and 530 ml. of dry acetone was added 29.0 ml. (*ca.* 0.35 mole) of ethanesulfonic acid. After being stirred for 7 hr. at room temperature, the mixture was poured into a cold stirred solution of 45 g. (0.53 mole) of sodium bicarbonate in 200 ml. of water. The resulting solution was stirred at room temperature for 2 hr. and was evaporated to dryness *in vacuo* (finally at 2 mm. and 50°). The thoroughly powdered residue was extracted with 700 ml. of chloroform for 22 hr. using a Soxhlet extractor. The extract was evaporated *in vacuo* to leave 14.85 g. (68%) of crystalline solid, m.p. 206.0–207.5°, suitable for use in the next step. Further crystallization of the product from methanol gave material, m.p. 212.5–214.0° (lit.[3] m.p. 204–207°); it was chromatographically homogeneous in solvent A with R_{Ad} 1.74.

These experimental modifications give a considerably higher yield than previously reported.[3]

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-3′,5′O-isopropylidene-β-D-xylofuranosyl)adenine (III). A solution of 4.00 g. (13.0 mmoles) of the acetonide (II) in 50 ml. of reagent pyridine was prepared by gentle heating. The solution was cooled in an ice bath and 11.0 g. (78.0 mmoles) of benzoyl chloride was added dropwise and with stirring over a period of 30 min. The reaction mixture was stored at room temperature for 96 hr. protected from moisture, then was poured into 70 ml. of cold water. The aqueous mixture was extracted with five 30-ml. portions of chloroform; the combined extracts were washed with two 60-ml. portions of saturated aqueous sodium bicarbonate solution and with one 100-ml. portion of water, then were dried over magnesium sulfate. After filtration, the filtrate was evporated to dryness *in vacuo* and re-evaporated *in vacuo* after the addition of 50 ml. of toluene. The final residue weighed 10.02 g. and was extracted with ten 50-ml. portions of boiling petroleum ether (b.p. 64–69°) decanting the hot solvent each time, to leave 7.94 g. of crystalline solid, m.p. 144–185°. The material was recrystallized from 60 ml. of benzene to give 6.34 g. of the benzene solvate, m.p. 125–140°. This solvate was then heated with 100 ml. of boiling petroleum ether (b.p. 64–69°) and gave, on cooling, 5.36 g. (66%) of crystalline solid, m.p. 195–196°, which was identical with the analytical sample described below.

A portion (0.407 g.) of the product was recrystallized from 10 ml. of benzene and it slowly deposited 0.399 g. of crystalline solid that was still solvated after drying at 2 mm. and 100° for 17 hr., m.p. 164.5–165.5°.

Anal. Calcd. for $C_{34}H_{29}N_5O_7 \cdot 0.75C_6H_6$: C, 67.7; H, 4.94. Found: C, 67.3; H, 5.04.

A portion (0.184 g.) of the benzene-recrystallized material was boiled with 20 ml. of petroleum ether (b.p. 64–69°). Filtration of the mixture gave 0.151 g. of solid, m.p. 194–196°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 5.90 (amide C=O), 11.77 (strong band related to isopropylidene group), 13.96 ($C_6H_5CO_2$), 14.30 [$(C_6H_5CO)_2N$]; there was no OH or NH absorption near 3.0 μ. The compound traveled as a single spot on paper in solvents C and A with R_{Ad} 1.56 and 3.14, respectively.

Anal. Calcd. for $C_{34}H_{29}N_5O_7$: C, 65.9; H, 4.72; N, 11.3. Found: C, 65.8; H, 4.86; N, 11.4, 11.6.

The above material could be recrystallized from ethyl acetate to give a material, m.p. 136–140°, which was evidently another crystal form.

Anal. Found: C, 65.5; H, 5.01; N, 11.3.

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-β-D-xylofuranosyl)adenine (VI). A solution of 5.36 g. (8.65 mmoles) of the benzoylated purine (III) in 75 ml. of 70% aqueous acetic acid was stirred at 50° for 4.75 hr., whereupon complete solution was effected. Stirring and heating (50°) was continued for 3.25 hr. more and the solution was allowed to stand 15 hr. at room temperature before being evaporated to dryness *in vacuo* at 35°. The residue weighed 5.58 g. and was triturated with three 50-ml. portions of boiling petroleum ether (b.p. 65–69°) and again evaporated to dryness *in vacuo* at 30°. The residue (5.47 g.) was partitioned using a mixture of 160 ml. of benzene, 96 ml. of methanol, and 64 ml. of water. The upper benzene-rich phase, on evaporation *in vacuo*, gave 3.71 g. (74% calculated as VI) of white solid, m.p. 90–120°; $\lambda_{max(\mu)}^{Nujol}$ 3.02 (OH), 5.80 (ester C=O), 14.00 ($C_6H_5CO_2$), 14.32–14.50 [$(C_6H_5CO)_2N$]. There was no isopropylidene absorption near 11.8 μ; the lack of amide C=O near 5.9 μ remains unexplained. On paper chromatography in solvents C and A, the material showed major spots with R_{AD} 1.65 and 3.20, respectively, which were not easily distinguished from starting material III; there were additional trace spots in each of these solvent systems. The material could be recrystallized from benzene or from water but the resulting solids had broad melting ranges and analytical values that did not fit any reasonable structure.

The water-rich phase was evaporated *in vacuo*, leaving 1.54 g. (32% calculated as the N^6-monobenzoyl purine corresponding to VI) of solid, m.p. 100–118°; $\lambda_{max(\mu)}^{Nujol}$ 3.02 (OH), 5.80 (ester C=O), 5.95 (amide C=O), 14.02 ($C_6H_5CO_2$); there was no isopropylidene absorption near 11.8 μ. On paper chromatography, the material showed three spots in solvent C with R_{Ad} 1.38, 1.54, and 1.64, and two spots in solvent A with R_{Ad} 2.74 and 3.18.

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-3′-O-methanesulfonyl-5′-O-trityl-β-D-xylofuranosyl)adenine (IV). A solution of 3.71 g. (*ca.* 7.8 mmoles) of the dihydroxy compound (VI) (material prepared as above and processed through partition in the benzene-methanol-water system) in 7 ml. of reagent pyridine was combined with a solution of 2.39 g. (8.57 mmoles)

(7) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus. Paper chromatograms were run by the descending technique on Whatman No. 1 paper in the following solvent systems: A, water-saturated *n*-butyl alcohol[8]; B, 5% disodium hydrogen phosphate[9] (without the usual organic phase); C, benzene-water-methanol (2:1:6).[10] Adenine was used as a standard (spot locations are expressed as R_{Ad} units with adenine at 1.00) and spots were detected by visual examination under ultraviolet light.

(8) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(9) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

(10) T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

of triphenylchloromethane in 10 ml. of pyridine and the resulting solution was stirred for 72 hr. at 50–54° with exclusion of moisture. Methanesulfonyl chloride (1.34 g., 11.7 mmoles) was then added and the mixture was stirred for an additional 16 hr. at the same temperature. The reaction mixture was diluted with 60 ml. of chloroform followed by 100 ml. of water. Solid sodium bicarbonate was added to the vigorously stirred mixture until the aqueous phase was just basic to litmus paper. The chloroform phase was separated, dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* at 30°. The residue was dissolved in 30 ml. of toluene and the evaporation repeated to leave 6.17 g. of a foam, m.p. 80–100°; $\lambda_{max(\mu)}^{Nujol}$ 5.78–5.90 (ester and amide C=O), 8.48 (—OSO_2—), 13.09 (mono substituted benzene), 14.10–14.25 (C_6H_5C=O). Paper chromatography in solvents C and A showed main spots with R_{Ad} 1.64 and 3.50, respectively, not easily distinguishable from the starting material (VI).

*N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-3′-O-methanesulfonyl-β-*D*-xylofuranosyl)adenine* (VII). A mixture of 6.17 g. of the crude 5′-*O*-trityl compound (IV) and 100 ml. of 80% aqueous acetic acid was heated at 80° for 25 min. (complete solution resulted in 5 to 6 min.). The reaction mixture was evaporated *in vacuo* at 30° and the residue was dissolved in 30 ml. of absolute ethanol and re-evaporated *in vacuo*. The evaporation with absolute ethanol was repeated twice more to remove actic acid. The final residue was triturated with six 50-ml. portions of hot (90°) petroleum ether (b.p. 64–69°) and one 40-ml. portion of boiling ether to leave 3.56 g. of residue, m.p. 105–125°, which was used directly for the preparation of the anhydronucleoside (VIII).

A portion (0.100 g.) of the residue was dissolved in 10 ml. of benzene, the solution was filtered to remove some insoluble solid, and the filtrate was diluted with 40 ml. of petroleum ether (b.p. 64–69°) and cooled. The precipitated solid (0.051 g.) was collected; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (OH, NH), 5.78–5.90 (ester and amide C=O), 8.45 (—OSO_2—), 14.03 (C_6H_5C=O); there was no monosubstituted benzene absorption (due to trityl group) near 13.0 μ.

Anal. Calcd. for $C_{25}H_{23}N_5O_8S.C_6H_6$: S, 5.08. Found: S, 4.08, 4.03.

*9-(2′,3′-Anhydro-β-*D*-ribofuranosyl)adenine* (VIII). To a cold (0°), filtered solution of 3.52 g. (*ca* 6.4 mmoles) of crude VII in 175 ml. of methanol was added a cold solution of 0.345 g. (6.38 mmoles) of sodium methoxide in 15 ml. of methanol. The reaction mixture was stored at 3° for 6 days protected from moisture, then was filtered and the filtrate adjusted to *p*H 7 with glacial acetic acid. The solution was evaporated *in vacuo* at 30° and the residue was partitioned between 200 ml. of water and 100 ml. of chloroform. The aqueous layer was evaporated to dryness *in vacuo* at 35° to leave 2.00 g. of residue which was shown by paper chromatography in solvents A and B to contain VIII. The residue (2.00 g.) was dissolved in 100 ml. of water and to this solution was added a warm (30°) solution of 2.56 g. (9.5 mmoles) of picric acid in 120 ml. of water. The solution containing the precipitated picrate was maintained at 3° for 18 hr., filtered, and the picrate washed with 10 ml. of cold water. The damp picrate was suspended in 125 ml. of water and damp Dowex 2 (OAc) was added portionwise to the stirred suspension until the supernatent liquid had become essentially colorless. Stirring was continued for 6 hr. and the resin was removed by filtration and washed with three 20-ml. portions of water. The combined filtrate plus washings were decolorized with Norit A, filtered with the aid of Celite, and the filtrate evaporated to dryness *in vacuo* (30° and 1 mm.) to leave 0.82 g. (28% over-all yield from the acetonide II) of solid that decomposed gradually on heating[11] and that had $[\alpha]_D^{26}$ −18.3° (0.6% in 20% aqueous pyridine). The infrared spectrum of the material agreed well with that of VIII prepared previously[2] and paper chromatography in solvents A and B showed main spots with the proper R_{Ad}[2] but with several trace spots as contaminants. The solid was recrystallized twice from absolute ethanol (150 ml./g.) to give finally 0.16 g. of solid which darkened near 185° but showed no definite melting point, $[\alpha]_D^{26}$ −16.0° (0.6% in 20% pyridine), $[\alpha]_D^{30}$ −32.8° (0.53% in water). Its infrared spectrum was identical with that previously reported[2] and on paper chromatography in solvents A and B, it moved as a single spot with R_{Ad} 0.81 and 1.32, respectively.

In a study of the regeneration of the picrate of VIII with several types of Dowex 2 resin, a damp picrate (1.67 g.) from crude VIII prepared as above was divided into three equal portions which were regenerated with Dowex 2 (OAc), Dowex 2 (Cl), and Dowex 2 (CO_3). The acetate resin (2.21 g.) gave 0.122 g. of good nucleoside (VIII), the chloride resin (1.40 g.) gave 0.110 g. of VIII, and the carbonate resin (1.24 g.) gave 0.104 g. of VIII. A similar study of the regeneration of adenosine from its picrate showed that Dowex 2 (OAc) gave a 94% recovery, Dowex 2 (Cl) a 90% recovery, and Dowex 2 (CO_3) a 77% recovery of adenosine.

*1,2-O-Isopropylidene-3-O-(p-tolylsulfonyl)-*D*-xylofuranose* (XIV). To a solution of 10.0 g. (24.9 mmoles) of the 5-*O*-carbomethoxy compound (XIII)[6] in 300 ml. of cold (0°) methanol was added 0.134 g. (2.48 mmoles) of sodium methoxide dissolved in 5 ml. of methanol. The reaction mixture was allowed to stand for 16 hr. at room temperature in a stoppered flask and was then evaporated to dryness *in vacuo* at 30°. To the residue was added 50 ml. of chloroform and 50 ml. of water. The mixture was adjusted to *p*H 7 with glacial acetic acid and the chloroform layer was separated. The aqueous phase was extracted with two more 50-ml. portions of chloroform, then the combined chloroform extracts were dried over magnesium sulfate and filtered. The filtrate was evaporated *in vacuo* at 30°, leaving 8.96 g. (105%) of product; $\lambda_{max(\mu)}^{film}$ 2.81 (OH), 7.25, 8.37, 8.48 (—OSO_2—), 11.74 (isopropylidene), 12.23 (*p*-disubstituted benzene); there was no C=O absorption in the 5.5–6.0 μ region.

*5-O-Benzoyl-1,2-O-isopropylidene-3-O-(p-tolylsulfonyl)-*D*-xylofuranose* (XV). To a cold (0°) stirred solution of 1.0 g. (2.9 mmoles) of the 5-hydroxy compound (XIV) in 10 ml. of reagent pyridine was added, dropwise, 0.61 g. (4.34 mmoles) of benzoyl chloride. The stoppered reaction mixture was allowed to stand at room temperature for 17 hr., then 0.1 ml. of water was added to the solution followed by stirring for 30 min. The mixture was diluted with 25 ml. of chloroform and the resulting solution was washed with two 25-ml. portions of water, three 25-ml. portions of 1*M* aqueous sodium bicarbonate solution, and one 25-ml. portion of water. After drying over magnesium sulfate, the solution was filtered and the filtrate evaporated *in vacuo*, leaving 1.15 g. (89%) of crystalline product. The solid was recrystallized from 120 ml. of petroleum ether (b.p. 64–69°), yielding 0.88 g. (68%) of product, m.p. 94.5–95.5°. Another similar recrystallization gave the analytical sample, m.p. 96.0–96.5°, $[\alpha]_D^{38}$ −63° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 5.78 (ester C=O), 7.82 (ester C—O—C), 8.39, 8.48 (—OSO_2—), 11.78 (isopropylidene), 12.29 (*p*-disubstituted benzene), 14.12 (C_6H_5C=O).

Anal. Calcd. for $C_{22}H_{24}O_8S$: C, 58.9; H, 5.39; S, 7.15. Found: C, 59.1; H, 5.62; S, 7.03.

*1,2-Di-O-acetyl-5-O-benzoyl-3-O-(p-tolylsulfonyl)-*D*-xylofuranose* (XII). Using the procedure described for the 5-*O*-methoxycarbonyl compound (XIII),[6] 7.38 g. (16.5 mmoles)

(11) In reference 2, the melting point of VIII was given as 200–203° dec. and $[\alpha]_D^{25}$ as −3° (0.6% in 20% aqueous pyridine). The melting point behavior of this compound, however, is completely dependent on the rate of heating and only with a very rapid rate can any kind of a melting behavior be observed. With normal heating rates, decomposition begins near 125° and darkening and softening continue up to 300°. When the optical rotation of the analytical sample[2] was redetermined, it was found to be $[\alpha]_D^{26}$ −17.5° (0.4% in 20% aqueous pyridine) and $[\alpha]_D^{26}$ −35.2° (0.33% in water).

of XV was converted to the diacetate (XII) which was recovered as 8.42 g. (104%) of a syrup; $\lambda_{max(\mu)}^{film}$ 5.68 (acetate C=O), 5.78 (benzoate C=O), 7.27, 8.39, 8.49 (—OSO_2—), 7.84 (benzoate C—O—C), 8.07, 8.21 (acetate C—O—C), 12.24 (*p*-disubstituted benzene), 14.00 (C_6H_5C=O).

2-O-Acetyl-5-O-benzoyl-3-O-(p-tolylsulfonyl)-D-xylofuranosyl chloride (XIb). The above diacetate (XII), 8.42 g., was converted to the chloride (XIb) by the procedure described for the preparation of XIa. A white, solid residue remained which showed none of the 8.07 μ absorption attributed to the C—O—C of the 1-*O*-acetate. The residue was directly coupled with chloromercuri-6-benzamidopurine using the procedure described for the coupling of XIa.[2] The solid product from the coupling and deblocking procedure, after regeneration of the picrate, weighed 0.43 g. and contained the anhydronucleoside (VIII), adenine, and some other purine-containing materials, as shown by paper chromatography in solvents A and B. If the residue had been pure VIII, the yield would have been 10.5% based on the isopropylidene compound (XV).

9-[3'-Deoxy-3'-(ethylthio)-β-D-xylfuranosyl]adenine (IX).[2] The conversion of 353 g. (0.79 mole) of diacetate (X) to the chloro sugar (XIa) was carried out as described previously.[2] Coupling of the chloro sugar (XIa) with 560 g. (0.785 mole) of 66.7% chloromercuri-6-benzamidopurine mixed with Celite was run for 2.25 hr.; it was found necessary to extract the filter cake with five 900-ml. portions of boiling chloroform to remove all the product. The crude, blocked nucleoside (345 g.) was converted to the anhydronucleoside (VIII) by dissolving it in 1600 ml. of methanol, cooling the solution to 10°, and adding a cold (10°) solution of 35 g. (0.65 mole) of sodium methoxide in 500 ml. of methanol. The resulting, stoppered solution, after standing at room temperature 14–15 hr., was adjusted to *p*H 7.4 with glacial acetic acid, then evaporated *in vacuo* at 55°, leaving 311 g. of crude VIII. A solution of the residue in 600 ml. of methanol was heated under reflux for 20 hr. with a methanolic sodium ethyl mercaptide solution (prepared from 227 g. (4.2 moles) of sodium methoxide, 340 ml. (4.6 moles) of ethanethiol, and 900 ml. of methanol) with exclusion of moisture. The solution was cooled to room temperature and adjusted to *p*H 8 with glacial acetic acid while cooling the mixture with an ice bath and maintaining the temperature below 45°. After evaporating the solution *in vacuo* at 50°, the residue was dissolved in 1500 ml. of water and continuously extracted with chloroform for 3.5 days to give 54.2 g. of crude IX. Recrystallization was effected by dissolving the material in 1500 ml. of 95% ethanol, evaporating the solution to 700 ml., and chilling to give 43.8 g. of a first crop, m.p. 183–185° (prior melting and resolidification 130–160°), whose infrared spectrum and paper chromatographic behavior were in excellent agreement with the previous analytical sample,[2] and a second crop of 3.1 g., m.p. 180° (with prior melting and resolidification 130–150°). The total product, 46.9 g., constituted a 19% over-all yield from the diacetate (X).

The main changes in the procedure from that of reference 2 are: (1) thorough extraction of the Celite residues from the initial coupling reaction with chloroform, (2) shorter reaction time in the deblocking to form VIII (3) neutralization of the reaction mixture from the reaction of VIII with sodium ethyl mercaptide before evaporation.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and his staff for the paper chromatography.

MENLO PARK, CALIF.

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

Potential Anticancer Agents.[1] XLIV. Some Derivatives of Uracil-5- and -6-carboxylic Acid

LEONARD O. ROSS, LEON GOODMAN, AND B. R. BAKER

Received May 9, 1960

The reaction of the butyl esters of uracil-5- and 6-carboxylic acid with hydrazine, butylamine, and with 2-aminoethanol gave the expected amides. The hydrazide of uracil-6-carboxylic acid was converted with nitrous acid to uracil-6-carboxazide.

In a continuation of interest in derivatives of uracil as potential anticancer agents,[2,3] attention was focused on some transformations of uracil-5-carboxylic acid and orotic acid (uracil-6-carboxylic acid). The latter compound is a key intermediate in the *de novo* synthesis of pyrimidine ribonucleotides and deoxyribonucleotides[4] and, as such, represents an interesting area for the synthesis of possible antimetabolites.

The principal objective in these studies was to prepare a number of new amides from the uracil-5- and 6-carboxylic acids. One of the common routes to amides, *via* an acid chloride, was not feasible because of the unavailability of the acid chlorides of the two uracil acids. A few attempts in this work to prepare these acid chlorides were unsuccessful, probably because of the insolubility of the acids; no mention of the two acid chlorides appears in the literature. Accordingly, the preparation of the amides *via* the esters of uracil-5-carboxylic acid and orotic acid was investigated.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, *J. Org. Chem.*, in press.

(2) A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press, paper XXXVI of this series.

(3) W. A. Skinner, M. G. M. Schaelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, 149 (1960), paper XXVIII of this series.

(4) J. N. Davidson, *The Biochemistry of the Nucleic Acids*, Methuen & Co., Ltd., London, 1957, p. 161.