An nmr spectrum of **3** revealed a singlet for the anomeric hydrogen at τ 3.85. This is consistent with a *trans* configuration[14] between H_1 and H_2, and it can be concluded that the chloro substituent was oriented in the β configuration.

Anal. Calcd for $C_{12}H_{19}ClO_5$: C, 51.70; H, 6.09; Cl, 12.72. Found: C, 51.78; H, 6.19; Cl, 12.84.

9-(2,3-*O*-Isopropylidene-β-D-gulofuranosyl)adenine (5).—6-Benzamidochloromercuripurine (7.15 g, 15.1 mmol) was coupled with 4.2 g (15.1 mmol) of the halogenose (**3**) in 400 ml of dry xylene.[8] After work-up[5] a foam weighing 8.4 g was obtained. This was subjected to acid hydrolysis in 150 ml of 70% aqueous acetic acid at 50° for 2.5 hr. The acetic acid was removed by evaporation, and absolnte ethanol was added and removed three times. Toluene was added and evaporated to remove a trace of acetic acid. The residue was dissolved in 135 ml of warm 0.15 *N* methanolic sodium methoxide solution, and the solution was refluxed for 1.5 hr. The solution was neutalized with glacial acetic acid,[19] and the solvent was evaporated. The syrup was dissolved in warm water, and the aqueous solution was decanted from an insoluble oil (methyl benzoate).[20] The water was evaporated using a few drops of nonyl alcohol to hold down foaming. The product (**5**) crystallized as clusters of hemispheres from a concentrated solution in methanol after it stood in an open flask overnight. Two crops of a tan-colored substance[21] were obtained, 3.33 g (71%). Two recrystallizations in the same manner gave the analytical sample as irregular white crystals, mp 154–160°. The crystallinity of this compond was verified under a polarizing microscope, $[\alpha]^{25}D$ −29.0° (*c* 1.37, H_2O). Uv and ir data were $\lambda_{max}^{H_2O}$ 259 mμ (ε 12,900); λ_{max}^{KBr} 3700–3150 (broad NH, OH), 1660–1612, 1590 (NH and purine ring), 1375 (*gem*-dimethyl), 1110–1048 cm^{-1} (plateau C–O–C, C–O–H).

A formaldehyde determination with dimedone reagent,[22] after treatment of **5** with excess periodate, yielded 0.80 mol of HCHO/mol of nucleoside.

Anal. Calcd for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.68; N, 20.76. Found: C, 49.61; H, 5.70; N, 20.64.

(19) More recently it has been found to be a better practice to remove sodium ion with an acid resin (IRC 50). Crystallization of **5** from concentrated methanol is made difficult by cocrystallization of small amounts of sodium acetate when acetic acid is used in the neutralization step.

(20) When attempts were made to partition the residue between water and chloroform as previously described for the case of the mannosyl nucleoside,[5] an emulsion formed which was impossible to break.

(21) This contained a small amount of sodium acetate which was apparent from an uv spectrum and an ash test. See ref 19.

(22) J. R. Dyer, *Methods Biochem. Analy.*, **3**, 111 (1956).

9-β-D-Gulofuranosyladenine (6).—To 100 ml of 0.1 *N* sulfuric acid solution was added 400 mg of **5**, and the mixture was swirled until dissolution occurred.[9] The flask was stored at room temperature for 5 days after which 1 equiv of barium hydroxide was added, and the mixture was stirred for 1 hr. Barium sulfate was removed by filtration through a pad of Celite on a sintered-glass funnel using light suction. The filtrate was evaporated to dryness and the product (**6**) was crystallized from ethanol–water in two crops to yield 180 mg (51%) of **6**. Recrystallization from water gave light feathery crystals, mp 227.5–228.5°. Admixture with an authentic sample[4] of 9-β-D-gulofuranosyladenine gave no depression of the melting point. The mobilities of **6** and the authentic sample were identical on both tlc and paper chromatography using 1-butanol–water (86:14) and 5% aqueous disodium hydrogen phosphate as solvents. The ir spectra were identical: $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,300), lit.[4] $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,400).

When acetic acid solutions at 100° were used to remove the isopropylidene group the yields of **6** varied from 36% with 12% aqueous acetic acid to 50% for 20–25% aqueous acetic acid.

In a separate experiment the entire synthetic route was repeated from **2** without isolation of any intermediate compounds. The crude chloride (**3**) was used without distillation. The *N*-benzoyl group was removed with methanolic sodium methoxide and both isopropylidene groups were removed simultaneously by hydrolysis for 3 hr at 100° in 25% aqueous acetic acid. The yield of **6** from **2** was 11%.

9-(2,3-*O*-Isopropylidene-α-L-lyxofuranosyl)adenine (8).—The preparation of **8** was carried out exactly as described for the preparation of the corresponding D compound from 9-(2,3-*O*-isopropylidene-α-D-mannofuranosyl)adenine.[11] From 127 mg of **5**, there was obtained 30 mg of pure **8**, which began to shrink at 163–165°, mp 182–184°, $[\alpha]^{22}D$ +29.1° (*c* 0.5, pyridine).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.88; H, 5.48; N, 22.71.

9-α-L-Lyxofuranosyladenine (9).—The preparation of **9** from **8** was carried out in a manner exactly as described for the preparation of the corresponding D compound from 9-(2,3-*O*-isopropylidene-D-mannofuranosyl)adenine.[11] By this procedure, pure 9-α-L-lyxofuranosyladenine (**9**) was obtained: mp 246–249°, $[\alpha]^{23}D$ −96.6° (*c* 0.2, H_2O). Uv and ir data were $\lambda_{max}^{H_2O}$ 259 mμ (ε 13,350); λ_{max}^{KBr} 2.9–2.95 (OH, NH), 6.1, 6.25, 6.8 (NH and purine ring) 8.9, 9.4–9.6 μ (C–O–C, C–O–H).

Registry No.—**3**, 16136-64-4; **5**, 16136-60-0; **6**, 10279-87-5; **8**, 16136-62-2; **9**, 16136-63-3.

Intramolecular Displacement by Neighboring *O*-Thionobenzoate. Synthesis of 3′-Thioadenosine[1]

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Received November 21, 1967

Internal displacement of a tosylate by adjacent *trans*-*O*-thionobenzoate as a new neighboring group has been used to convert the 3,5-di-*O*-tosylate 2-*O*-thionobenzoate **3** of methyl α-D-xylofuranoside into 3-thio-D-ribofuranoside derivatives. Attachment of sulfur and configurational inversion at C-3 occurred upon treatment of **3** with sodium benzoate–dimethyl formamide (DMF), which also converted the 5-*O*-tosylate into 5-*O*-benzoate. The initial product was a dimer **8** of novel structure, elucidated by spectral studies; a crystalline analog of **8** was obtained in the analogous 5-deoxy series. Acid treatment of **8** afforded solely the monomeric thiol **6**, which was protected by benzoylation. Acetolysis afforded crystalline 1-*O*-acetyl-2,3,5-tri-*O*,*S*,*O*-benzoyl-3-thio-β-D-ribofuranoside (**5**). Condensation of **5** (*via* the chloro sugar obtained with titanium tetrachloride) with chloromercuri-6-benzamidopurine afforded the tetrabenzoate of 3′-thio-D-adenosine. Debenzoylation afforded 3′-thioadenosine (**11**), which was precipitated as a mercury salt and then liberated. The β configuration of **11** and location of the sulfur at C-3 were proved by nickel desulfurization to form 3′-deoxyadenosine.

The rationale for introducing a thiol function at C-3 of the D-ribose moiety of adenosine has been discussed in a recent communication[2] describing the synthesis of 3′-thioadenosine (**11**), and in earlier papers[3,4] from these laboratories describing some other studies toward this nucleoside. Structure–activity studies with the 3′-amino-3′-deoxy-D-ribo nucleoside

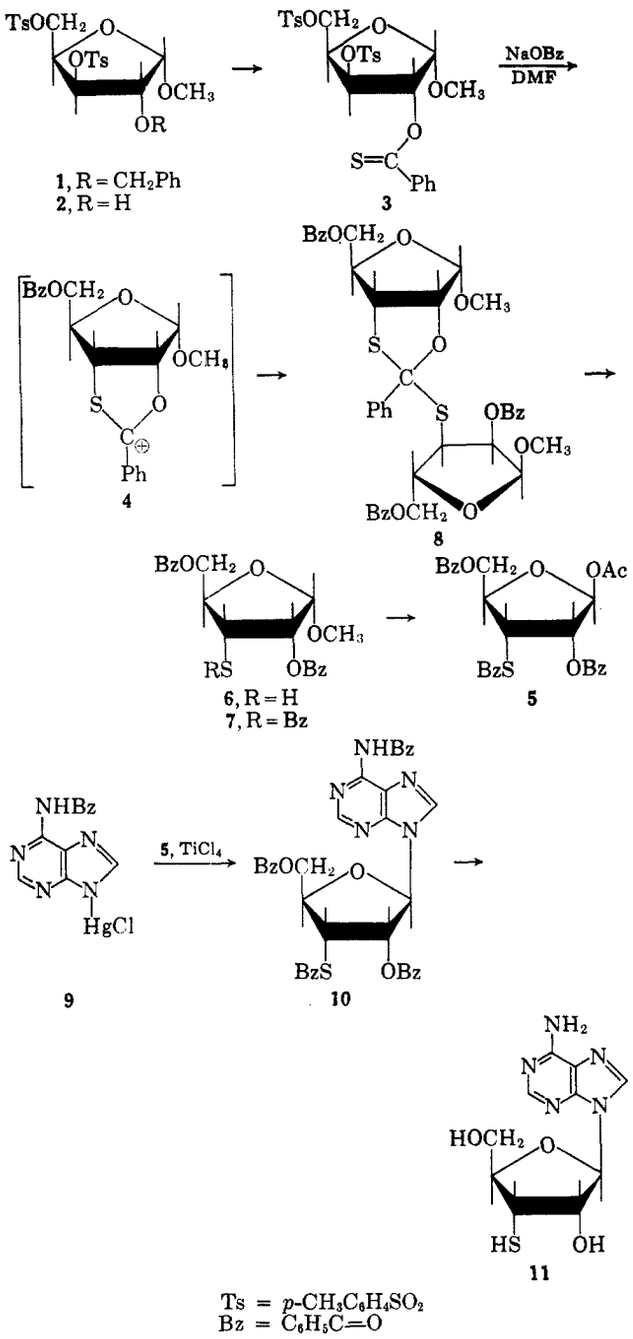
(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Contract No. PH-43-64-500. The opinions expressed are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

(2) E. M. Acton, K. J. Ryan, and L. Goodman, *J. Amer. Chem. Soc.*, **89**, 467 (1967).

(3) B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *ibid.*, **80**, 6577 (1958).

(4) L. Goodman, A. Benitez, C. D. Anderson, and B. R. Baker, *ibid.*, **80**, 6582 (1958).

SCHEME I



derived from puromycin showed that the amino group at C-3 and in the *ribo* configuration was essential for biological activity.[5] It seemed that similar substitution of a thiol sulfur might give a molecule with significant and useful biological properties. Though synthetic methods have been devised for *trans*-2,3-mercapto alcohol systems in furanose rings,[6,7] the requisite *cis*-2,3-mercapto alcohol for a thioribose has not hitherto been attained.[8] The successful synthesis of 3-thio-D-ribofuranose derivatives was accomplished by our method[9-11] for configurational inversion within furanose rings; this method requires the anchimeric assistance of a *trans* neighboring group. In attaching a thiol sulfur to the furanose ring by intramolecular displacement of a tosylate, the present synthesis demonstrates for the first time the utility of *O*-thionobenzoate as the neighboring group.

The synthetic sequence was that outlined in Scheme I. The *trans*-2-*O*-thionobenzoyl-3-*O*-tosyl system was obtained (compound **3**) from the 3,5-ditosylate **2** of methyl α-D-xylofuranoside, by acylation with thiobenzoyl chloride[12] in pyridine. The crystalline thionobenzoate **3** was frequently contaminated with a little of the corresponding benzoate, even when the acid chloride had been carefully freed of benzoyl chloride. Apparently, some loss of the sulfur can occur during the acylation step, but once formed the thionobenzoate was perfectly stable. Though slightly contaminated with benzoate, the thion ester **3** was suitable for use in the scheme without purification. The inversion was conducted in hot dimethylformamide (DMF) containing sodium benzoate, and the acetate tribenzoate **5** of 3-thio-D-ribose was eventually isolated (39% yield from **3**) as a readily crystallized and purified compound. Absence from **5** of the related 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose could be discerned from ir and nmr spectra. Had a fractional percentage of this compound remained undetected in **5**, the 3-oxy contaminant (*i.e.*, adenosine) would be lost at the nucleoside stage, since 3′-thioadenosine (**11**) was isolated by precipitation as a mercury salt. The thio nucleoside was regenerated with hydrogen sulfide in acetic acid. Thiol content of several samples was 90–95%, with the disulfide as the only contaminant by chromatographic analysis. Attachment of the sulfur at the C-3 of the sugar was confirmed by nickel desulfurization of **11** to form 3′-deoxyadenosine[13] (**12**). This confirmed the β orientation of the purine moiety as well which was expected from the "*trans*" rule.[5] Desulfurization of the sugar ester **5** was also carried out; the resultant crude 3-deoxy sugar **13** (some 1-OH was present) was treated with methanolic hydrogen chloride to form the methyl furanoside; this was treated with benzoyl chloride to restore any benzoyl groups which had been lost; and methyl 2,5-di-*O*-benzoyl-3-deoxy-β-D-ribofuranoside[13b] (**14**) was isolated by chromatography (Scheme II).

Structure of the Inversion Intermediate.—The nature of the inversion product obtained from **3** was studied at some length, since it was immediately apparent that the product was not the result of simple hydrolytic opening of the expected cyclic acylonium ion **4**. Simple hydrolysis was expected, as with reactions[9-11] of *trans*-3-*O*-tosyl-2-*O*-benzoyl sugars, where *cis*-hydroxybenzoates were obtained *via* the oxygen

(5) B. R. Baker in "The Chemistry and Biology of Purines," Ciba Foundation Symposium, Little, Brown, and Co., Boston, Mass., p 120.

(6) A. P. Martinez, W. W. Lee, and L. Goodman, *J. Org. Chem.*, **31**, 3263 (1966).

(7) (a) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **81**, 3967 (1959); (b) E. J. Reist, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, **32**, 2538 (1967).

(8) After our synthesis of 3′-thioadenosine was announced,[1] the preparation of a 3-deoxy-3-thiocyano-D-ribose derivative by a direct displacement was described: J. Defaye and J. Hildesheim, *Carbohyd. Res.*, **4**, 145 (1967). Much of this work confirmed our experience of difficulty of many direct displacements in this system. The method for *cis*-2-(acetylthio)cyclopentyl acetate (ref 4) has not been applied to sugars.

(9) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 2497 (1964).

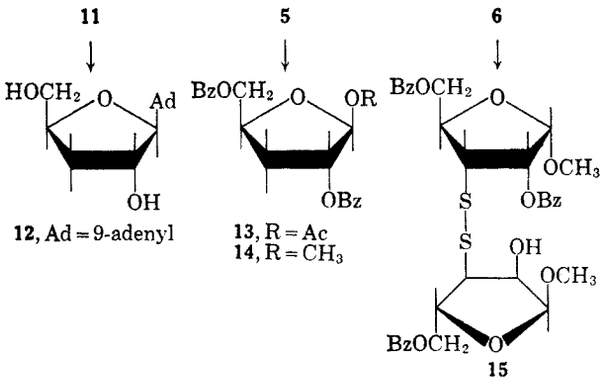
(10) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *ibid.*, **86**, 2503 (1964).

(11) E. M. Acton, K. J. Ryan, and L. Goodman, *ibid.*, **86**, 5352 (1964).

(12) E. J. Hedgley and H. G. Fletcher, Jr., *J. Org. Chem.*, **30**, 1282 (1965).

(13) (a) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **83**, 1906 (1961); (b) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965).

SCHEME II

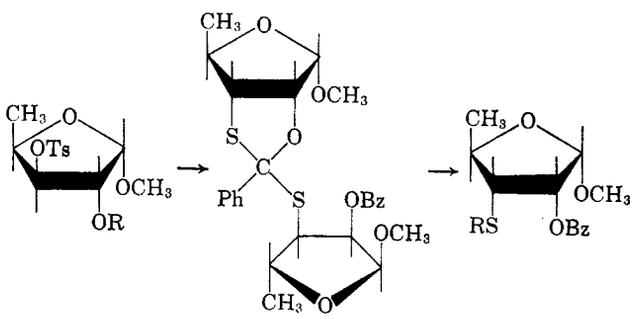


analog of **4**. Though the tosyl groups in **3** had been ejected, the inversion product was free of hydroxyl or thiol, according to the spectra. Benzoate carbonyl absorption (5.8 μ) was present in the ir, but thiolbenzoate carbonyl (6.0 μ) was unexpectedly missing. The nmr spectrum appeared to exhibit two equal singlets for C-1-OCH_3, two equal sets of doublets for C-1-H, and two equal sets of quartets for C-2-H. This was even more apparent after chromatographic purification to yield a homogeneous syrup. The pattern of the signals and the coupling constants were those found to be characteristic of 3-thio-α-D-ribofuranose derivatives, *i.e.*, a quartet for C-2-H, somewhat downfield from a doublet for C-1-H, with $J_{1,2}$ = 4 and $J_{2,3}$ = 8 cps. The facts seemed best explained by a dimer with structural differences in the two monomeric units, for which structure **8** was written. Osmometer molecular weight values varied from over 500 to nearly 700; there were indications here that the substance was slowly degraded in chloroform,[14] the solvent used, and consequently these values were regarded as consistent with a dimer such as **8**. The substance was stable to moisture and in methanol solution, but was converted in warm 80% acetic acid to the monomeric thioldibenzoate **6**, which was immediately protected by benzoylation to yield **7**. Apparently the postulated oxathiolane ring of **8** had opened exclusively to form **6**, as evidenced by thiol absorption in the ir, and by the complete absence of OH or *S*-benzoyl bands from the isomeric possibility, a 2-hydroxy-3-thiolbenzoate. It seems likely that during the inversion in DMF some opening of the ion **4** did occur, and that the resultant thiol **6** reacted further with the ion **4** (*i.e.*, alkylation of the thiol with the carbonium ion **4**) to form structure **8**.

The disulfide **15** was prepared from the thiol **6** for comparison with the intermediate **8**. The nmr spectrum of the disulfide **15**, as expected, and in contrast to **8**, showed for C-1-OCH_3, C-1-H, and C-2-H only one singlet, one doublet, and one quartet, respectively. Optical rotations of **15** and **8** were strikingly different. In a comparison of mass spectra,[15] the intermediate **8** showed a strong peak at *m/e* 371 (attributed to structure **4**, a likely fragment) where the disulfide showed none. Compound **8** was heat labile, and a parent peak at *m/e* 758 could not be observed; a weak peak at *m/e* 774 was attributed to a little disulfide **15** as impurity, since the spectrum of **15** showed the parent peak at 774.

5-Deoxy Analogs.—The credibility of structure **8** for the inversion intermediate was enhanced by the isolation of a similar, crystalline intermediate in the related 5-deoxy series (Scheme III). Methyl 5-deoxy-2-*O*-

SCHEME III

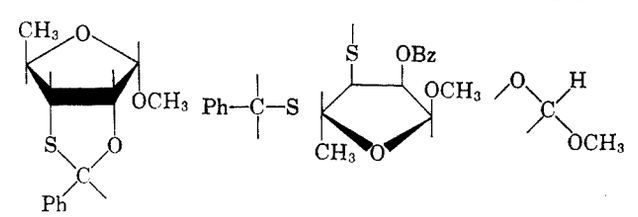


16, R = CH_2Ph
17, R = H
18, R = C(=S)Ph

19

20, R = H
21, R = Bz

thionobenzoyl-3-*O*-tosyl-α-D-xylofuranoside (**18**) was obtained by hydrogenolysis of the benzyl ether[9] **16** and acylation of the resultant 2-hydroxy compound **17**; **18** was purified chromatographically. The product **19** from sodium benzoate–DMF inversion of **18** crystallized; as with **8**, it was free of OH and *S*-benzoyl in the ir; occurrence of OBz bands showed that a benzoate was attached to the furanose ring (*e.g.*, at C-2). As with **8**, the nmr spectrum of **18** showed two sets (of equal intensity) of signals for C-1-OCH_3, C-1-H, and C-2-H. Excellent elemental analyses and molecular weight values for structure **19** could be obtained from a recrystallized sample. The high-resolution mass spectrum [15] of **19** gave only a very minor peak for the molecular ion at *m/e* 518 (*cf.* **8**, no molecular ion); a weak peak at *m/e* 534.138 was attributed to a little disulfide (disulfide of **20**) impurity. The main peaks, however, were consistent with structure **19**, and were inconsistent with the disulfide of **20**. The major peak, *m/e* 251.076, appeared to require structure **19a** (calcd for $C_{13}H_{15}O_3S$, 251.074); this indicated structure **19**, as did another strong peak,



19a 19b 19c 19d

m/e 121.011, assigned the structure **19b** (calcd for C_7H_5S, 121.011). Peaks for the loss of OCH_3 and Bz from *m/e* 518 were also seen. Strong peaks at 236 and 115 (medium resolution spectrum) were interpreted as the loss of OCH_3 and of OCH_3 plus OBz from structure **19c**, *m/e* 267, the half of **19** remaining after loss of **19a**. Another common process seemed to be loss of **19d**, *m/e* 60. A very minor fragment at *m/e* 268

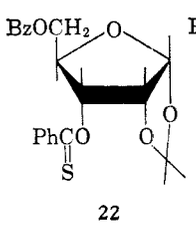
(14) In addition, when a deuteriochloroform nmr solution of **8** was stored for 2–3 days, the spectrum slowly changed with collapse of the two OCH_3 singlets into one; in the 5-deoxy series (Scheme III), progressive conversion of **19** into **20** in chloroform-*d* was clearly seen.

(15) Instrumentation was as described by R. F. Muraca, J. S. Whittick, G. D. Daves, Jr., P. Friis, and K. Folkers, *J. Amer. Chem. Soc.*, **89**, 1505 (1967); we are indebted to Dr. Muraca and Mrs. Whittick for the spectra and interpretations.

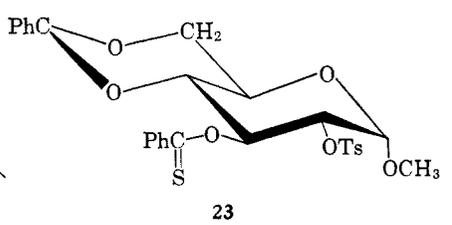
was attributed to the structure **20** (possibly formed by attachment of a hydrogen to **19c**).

Compound **19**, like **8**, was converted with acid into a single monomeric product, the 3-thiol-2-benzoate **20**. Benzoylation afforded the crystalline dibenzoate **21**.

Properties of Thionobenzoates.—Only one sugar thionobenzoate[12] has, to the authors' knowledge, been recorded in the literature, and the chemistry of simple aliphatic or alicyclic thionobenzoates is rather little known. Ethyl thionobenzoate has been described both as distillable without change,[16] and as converted to ethyl benzoate on contact with air.[17] In the present work, sensitivity to oxygen seemed to be present only during the acylation step, and could be controlled. Benzoate by-product was formed along with the thionobenzoates prepared, but was limited to a few per cent when oxygen was excluded during the acylation and when no more than a 1–2% excess of the acyl chloride was used (it apparently mattered little if the thionobenzoyl chloride was freed of the last few per cent of benzoyl chloride). Once formed, the thionobenzoates were stable, crystalline compounds. There are comments in the literature as to the ease of rearrangement in the system —C(=S)O— to —C(=O)S—. Examination of the references dealing with thionobenzoates[16a,18–20] showed that these rearranged only in especially favorable cases, owing to other structural features and not to properties of the thionobenzoate alone. This was further exemplified with the ribose thionobenzoate **22**, which we found to be completely stable to temperatures of 250°, in an attempt to prepare a 3-thioribose derivative by rearrangement. Also, the 3-*O*-thionobenzoate **23** of methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside[21] was completely stable to heating with sodium benzoate–DMF, quite unlike **3**. Failure of **23** to undergo inversion



22



23

with displacement of the tosylate is not completely understood and requires further study. Inability of the fused-ring system to permit ring transition of the pyranose and thereby attain a 2,3-*trans*-diaxial arrangement seems to be an insufficient explanation; it has been our experience that these neighboring-group displacements are generally less favored in pyranose rings than in furanose rings.

Experimental Section[22]

Thiobenzoyl chloride was prepared by the method of Staudinger and Siegwart,[23] as improved by Hedgley and Fletcher.[12] An initial distillation removed a considerable nonvolatile residue and afforded a 53% yield (based on methyl dithiobenzoate), bp 65–70° (0.5 mm, bath 150–180°). Benzoyl chloride, which was generally present (up to 20%, estimated by infrared carbonyl intensity), could be removed by subsequent fractional distillation of a forerun. The undistilled oil then remaining (47% yield) contained little or no benzoyl chloride (0–5%) and crystallized on standing at −5°. It was stored in the cold. There were strong ir bands[17] at 6.30, 6.90, 8.0, 8.47, 9.5, 11.8, 13.1, and 14.7 μ (liquid); bands at 12.5 (weak) and 14.15 μ (medium) were recently[24] attributed to an impurity removable by repeated distillation.

Methyl 3,5-Di-*O*-*p*-Tolylsulfonyl-α-D-xylofuranoside (2).—Methyl 2-*O*-benzyl-3,5-di-*O*-tosyl-α-D-xylofuranoside[9] (**1**, 24 g, 0.043 mol) was hydrogenated by passing a slow stream of hydrogen through a stirred mixture (complete solution was attained as the hydrogenolysis proceeded) with 1250 ml of glacial acetic acid and 2 g of 10% palladium–carbon for 3 days. After removal of the catalyst by filtration through Celite, the acetic acid was removed *in vacuo*, and the residue was crystallized from 200 ml of ethanol to yield 19.1 g (94%), mp 97.5–99°. Hydrogenolysis at 50 psi in a smaller volume of acetic acid was incomplete. Complete reaction was observed by the absence of infrared bands at 10.75, 12.7, and 13.25 μ (present in **1**, medium intensity); nmr data, τ 2.27 d and 2.70 d (*p*-C_6H_4, J = 8 cps), 5.15 d (C-1-H, J = 4.5 cps), 6.63 s (OCH_3), 7.59 s (CH_3 of tosyl).

Anal. Calcd for $C_{20}H_{24}O_9S_2$: C, 50.8; H, 5.12; S, 13.6. Found: C, 51.2; H, 5.27; S, 13.8.

Methyl 3,5-Di-*O*-*p*-tolylsulfonyl-2-*O*-thionobenzoyl-α-D-xylofuranoside (3).—To a chilled solution, under nitrogen, of 34.2 g (0.0725 mol, dried *in vacuo*) of **2** in 340 ml of pyridine (dried by distillation from calcium hydride, in the presence of nitrogen) was added slowly 11.5 g (0.0735 mol) of thiobenzoyl chloride (as thawed liquid). The mixture was heated at 50° for 2 hr, stirred at room temperature for 3 days, and then poured into 600 ml of ice-cold 1 *M* hydrochloric acid. The product was extracted with two 300-ml portions of chloroform. The combined chloroform extracts were washed with 500 ml of saturated sodium bicarbonate solution, with 500 ml of water, were dried, and were concentrated. The residual dark red oil, by tlc, contained red and orange components in addition to the yellow thionobenzoate (R_f's 0.9, 0.5, 0.4, respectively, 0.5% ethyl acetate in chloroform) and a colorless, ultraviolet absorbing spot (R_f 0.3) assumed to be 3-*O*-benzoate. The oil was dissolved in 600 ml of hot 95% ethanol, the solution was chilled at 5% overnight, and the resultant yellow crystals were collected, 29 g (67%), mp 117.5–120°. Infrared carbonyl absorption at 5.77 μ indicated the presence of benzoate, *ca* 5–10%; this was observed even in experiments where the thiobenzoyl chloride used was free of carbonyl. A sample of the crude red oil was purified by preparative tlc; the yellow band was extracted with chloroform; and the product, freed of solvent, was recrystallized from ethanol to yield pure **3** (40%): mp 120.5–121.5; $[\alpha]^{22}D$ 152° (chloroform); $\lambda_{max}^{CHCl_3}$ 415 mμ (ε 147); ir data, 7.30, 7.35, 8.4, 8.5 (OTs), 8.22 (C=S), no bands at 5.78 or 13.95 μ (OBz); nmr data, τ 2.31 d and 2.68 d (*p*-C_6H_4 of 3-*O*-tosyl, J = 8 cps), 2.36 d and 2.94 d (*p*-C_6H_4 of 5-*O*-tosyl, J = 8 cps), 2.0–2.8 m (C_6H_5), 4.82 d (C-1-H, J = 4.5 cps), 6.76 s (OCH_3), 7.57 s (CH_3 of 5-*O*-tosyl), 7.77 s (CH_3 of 3-*O*-tosyl); tosyl signals which differed from those in the analogous benzoate were assigned to the 3-*O*-tosyl group.

Anal. Calcd for $C_{27}H_{28}O_9S_3$: C, 54.7; H, 4.76; S, 16.2. Found: C, 54.8; H, 4.73; S, 16.1.

(16) (a) S. A. Karjala and S. M. McElvain, *J. Amer. Chem. Soc.*, **55**, 2966 (1933); (b) S. G. Smith and M. O'Leary, *J. Org. Chem.*, **28**, 2825 (1963).

(17) R. Mayer and S. Scheithauer, *J. Prakt. Chem.*, **21**, 214 (1963).

(18) S. G. Smith, *J. Amer. Chem. Soc.*, **83**, 4285 (1961).

(19) S. G. Smith and J. P. Petrovich, *J. Org. Chem.*, **30**, 2882 (1965).

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Treatment of 3 with Sodium Benzoate–DMF.—To a solution of 29 g (0.049 mol) of methyl 3,5-di-*O*-tosyl-2-*O*-thionobenzoyl-α-D-xylofuranoside (**3**, containing 5–10% of benzoate) in 1 l. of DMF (dried by storing over alumina of Brockman activity I) was added 25 g (0.17 mol) of sodium benzoate, and the mixture was heated under nitrogen at 120–125° for 5 hr. About half the DMF was removed *in vacuo*, and the residue (a solid mass of precipitated sodium benzoate) was diluted with 2 l. of water, with cooling to dissipate the heat of solution. The solution was extracted with two 400-ml portions of ether. The combined extracts were washed with three 500-ml portions of saturated aqueous sodium bicarbonate and 500 ml of water, were dried, and were concentrated to form 17.6 g (92% yield) of a residual dark oil. This crude product (crude **8**) was free of OH, SH, and SBz bands (expected near 3.0, 3.7, and 6.0 μ) in the infrared, but showed benzoate absorption at 5.78 (C=O), 7.85 (broad, C—O—C), and 14.05 μ (broad). Two singlets (τ 6.59 and 6.67, indicative of two kinds of C-1-OCH_3, of equal intensity) were readily apparent in the nmr; in a typical experiment, a weak singlet could be detected near τ 7.8, indicative of *ca.* 4% unreacted 3-OTs.

Purification of the Intermediate 8.—Preparative tlc (in chloroform containing 1% ethyl acetate) of a sample of the crude oil and elution with chloroform of the major band, R_f *ca.* 0.4, afforded a clear yellow oil (37% based on **3**): $[\alpha]^{23}D$ −79° (benzene); the ir was unchanged from that of the crude; nmr data, τ 1.8–3.0 m (20 ArH's), 4.57 q and 4.87 q (one H each, two kinds of C-2-H, $J_{1,2}$ = 4 cps and $J_{2,3}$ = 8 cps), 4.90 d and 5.20 d (one H each; two kinds of C-1-H; $J_{1,2}$ = 4 cps), 6.59 s and 6.67 s (total of six H's; two kinds of OCH_3). Incomplete purity was indicated by the failure of samples from two different experiments to give satisfactory analytical data for the proposed structure.

Anal. Calcd for $C_{40}H_{38}O_{11}S_2$: C, 63.3; H, 5.05; S, 8.45; mol wt, 758.8. Found: C, 60.6, 60.8; H, 5.34, 5.18; S, 7.12, 7.54; mol wt (osmometer, chloroform), 571, 680.

Methyl 2,5-Di-*O*-benzoyl-3-thio-α-D-ribofuranoside (6).—A solution of 17.6 g of crude intermediate **8** in 350 ml of 80% acetic acid was heated at 70° for 2 hr and then concentrated. The residual oil was twice dissolved in 30 ml of toluene and evaporated *in vacuo* to form 17.6 g of dark red oil. Presence of the thiol was indicated by a positive nitroprusside test and by absorption at 3.9 μ (–SH, weak) in the ir; *O*-benzoate bands were also present. Alternative opening to 2-hydroxy-3-thiolbenzoate was excluded by the absence of appreciable OH or SBz absorption (near 3.0, 6.0, and 8.25 μ). A doublet at τ 8.03 (J = 10 cps) in the nmr was attributed to –SH.

Disulfide 15 of 6.—A solution of 433 mg (1.22 mmol) of methyl 2,5-di-*O*-benzoyl-3-thio-D-ribofuranoside (**6**) in 5 ml of methanol was treated with 154 mg (0.61 mmol) of iodine and 0.3 g of potassium iodide in 5 ml of water solution. The resultant disulfide separated as a gum, so 20 ml of chloroform was added, and the mixture was stirred for 20 min. The excess iodine was titrated with sodium thiosulfate until the aqueous layer was decolorized; the chloroform layer was separated, washed with 20 ml of water, dried, and concentrated. The residual oil weighed 430 mg (100%). On tlc in chloroform, a contaminant of R_f 0.6 was observed in addition to the disulfide, R_f 0.4. Preparative tlc afforded 280 mg (65%) of homogeneous disulfide: $[\alpha]^{23}D$ +140° (chloroform, same in benzene); nmr data, τ 1.86–2.08 m and 2.4–2.8 m (ArH), 4.74 q (C-2-H; $J_{1,2}$ = 4 cps, $J_{2,3}$ = 8 cps), 4.86 d (C-1-H; $J_{1,2}$ = 4 cps), 6.22 q (C-3-H; $J_{2,3}$ = 8 cps, $J_{3,4}$ = 6 cps), 6.66 s (OCH_3); irradiation at τ 6.22 collapsed the quartet at τ 4.74 to a doublet (J = 4 cps), and irradiation at τ 4.74 collapsed the quartet at τ 6.22 to a doublet (J = 6 cps).

Anal. Calcd for $C_{40}H_{38}O_{12}S_2$: C, 62.0; H, 4.93; S, 8.28; mol wt, 775. Found: C, 61.4; H, 4.83; S, 8.06; mol wt (osmometer, in chloroform), 701.

Methyl 2,5-Di-*O*-benzoyl-3-*S*-benzoyl-3-thio-α-D-ribofuranoside (7).—To a stirred solution of 17.6 g of the thiol **6** in 150 ml of dry pyridine was added slowly, with chilling, 10 ml of benzoyl chloride. The mixture was stirred overnight at room temperature, treated with 2 ml of water, stirred 1 hr more, and poured into 400 ml of cold 1 *M* hydrochloric acid. The mixture was extracted with 300 ml of chloroform; the chloroform extract was washed with 300 ml of saturated $NaHCO_3$ and with 300 ml of water and was dried. Concentration afforded 21.1 g of red oil. In addition to OBz absorption, the ir spectrum showed SBz bands of medium intensity at 5.98, 8.25, 11.0, and 14.5 μ; it was free of OH or SH bands near 3.0 and 3.9 μ; nmr data, τ 1.7–2.9 m (ArH), 4.38 q (C-2-H, $J_{1,2}$ = 4 cps, $J_{2,3}$ = 8 cps), 4.66 d (C-1-H, $J_{1,2}$ = 4 cps), 6.67 s (OCH_3).

A sample purified (42% recovery) by preparative tlc (chloroform–ethyl acetate, 9:1) to remove impurities at the solvent front and at the origin was unchanged in the nmr and could not be induced to crystallize.

1-*O*-Acetyl-2,5-di-*O*-benzoyl-3-*S*-benzoyl-3-thio-β-D-ribofuranose (5).—A solution of 21 g of the crude methyl furanoside **7** in 300 ml of glacial acetic acid and 60 ml of acetic anhydride was treated dropwise, with chilling, with 18 ml of concentrated sulfuric acid, and stirred overnight at room temperature. The mixture was poured into 1.5 l. of ice and water and stirred for 15 min; the hyrdolysate was extracted with two 400-ml portions of chloroform. The combined chloroform solution was stirred with 1 l. of saturated sodium bicarbonate solution, was separated, was washed with two 600-ml portions of bicarbonate solution and with 600 ml of water, was dried, and was concentrated. The residue (21 g) was taken up in 500 ml of hot 95% ethanol, and the solution was chilled at 5° overnight. The resultant crystals weighed 10 g (39% over-all yield based on **3**), mp 136–137.5° (any further crops were gummy and not readily crystallized). When the starting methyl furanoside **7** was purified by chromatography, the yield of 1-acetate **5** was *ca.* 67% from **7**: mp 135.5–136.5°; $[\alpha]^{25}D$ +155° (chloroform); ir data, 5.73 (shoulder, acetate C=O), 5.78 (C=O, OBz), 6.00 (C=O, SBz), 8.25–8.30 (SBz), 11.0 (SBz), 14.1 (OBz), 14.5 μ (SBz); absence of the 3-*O*-Bz analog could be detected by absence of its characteristic bands at 10.5 (medium) and 14.3 μ (strong); nmr data, τ 1.75–2.22 m and 2.32–2.84 m (ArH), 3.59 s (C-1-H), 4.29 d (C-2-H, $J_{2,3}$ = 4 cps), 8.04 s (OAc); absence of any 3-*O*-Bz analog of **5** was observed by the absence of distinct signals for that compound at τ 3.50 s (C-1-H) and 3.9–4.2 m (C-2-H), although it was estimated 1 or 2% could have been detected.

Anal. Calcd for $C_{28}H_{24}O_8S$: C, 64.6; H, 4.64; S, 6.16. Found: C, 64.6; H, 4.66; S, 6.17.

6-Benzamido-9-(2′,5′-di-*O*-benzoyl-3′-*S*-benzoyl-3′-thio-β-D-ribofuranosyl)-9H-purine (10).—To a solution of 8.5 g (16 mmol) of 1-acetate **5** in 600 ml of ethylene chloride was added a mixture of 8.2 g (17 mmol) of chloromercuri-6-benzamidopurine (**9**) and 4.6 g of Celite. The suspension was heated to boiling and dried by azeotropic distillation to remove 100 ml of ethylene dichloride. The mixture was cooled and treated with a solution of 2.5 ml (23 mmol) of titanium tetrachloride in 20 ml of dried ethylene dichloride. The yellow-green reaction mixture was refluxed for 20 hr, cooled, and poured into 400 ml of saturated sodium bicarbonate solution. After stirring for 2 hr at 25°, the hydrolyzed mixture was filtered through Celite, and the ethylene dichloride layer was separated from the filtrate; the Celite filter cake was washed with two 250-ml portions of hot chloroform; and the combined ethylene dichloride–chloroform solutions were concentrated. The residue in 400 ml of chloroform solution was washed with 200 ml of 30% aqueous potassium iodide and with 300 ml of water, was dried, and was concentrated. The residual foamed glass weighed 10 g (88%): λ_{max}^{EtOH} 232 mμ (ε 50,800), 274 (23,900); tlc in acetone–ethyl acetate (1:1) indicated only trace contamination with 6-benzamidopurine. A sample of complete purity was not obtained by preparative tlc.

3′-Thioadenosine (11).—A solution under nitrogen of 10 g (14.3 mmol) of the tetrabenzoate (**10**) in 600 ml of methanol containing 5 g of sodium methoxide was refluxed for 2 hr, was cooled, and was neutralized with 5.6 g of glacial acetic acid. A solution of 20 g of mercuric acetate in 300 ml of warm methanol was added[6] slowly with stirring, the mixture was chilled and stirred for 30 min, then the precipitate was collected. This **3′-*S*-acetoxymercuri salt** weighed 14.4 g, 6.23 μ (ir, ionic acetate); elemental analysis (sample from another experiment) indicated that the salt contained an additional 2 mol of $Hg(OAc)_2$ (yield 85% on this basis).

Anal. Calcd for $C_{12}H_{15}O_5HgS \cdot 2Hg(C_2H_3O_2)_2$: C, 20.4; H, 2.22; Hg, 51.1; N, 5.94; S, 2.72. Found: C, 19.2; H, 4.53; Hg, 51.1; N, 6.12; S, 2.77.

The salt (14.4 g) was suspended, with stirring, in 400 ml of 80% acetic acid, and the mixture was saturated with a slow stream of hydrogen sulfide for 1 hr, while the lumpy gray salt dissolved and a fine black precipitate of mercuric sulfide was formed. The mixture was filtered through Celite and the filtrate was concentrated. The residual solid was dissolved in 40 ml of hot methanol. The solution was clarified by filtration and chilled for 1 hr, clarified again of a small amount of dark precipitate, and chilled overnight. The precipitated product was collected

on a filter. It weighed 1.0 g (21% yield based on 1-acetate **5**): mp 160–190°; tlc in water showed one major spot (R_f 0.8) and a faint spot (R_f 0.6) attributed to disulfide; SH found by iodine titration, 83%; N found, 22.4%, indicating hydration. Recrystallization from 10 ml of water containing a few milligrams of dithioerythritol[25] afforded 0.72 g (16% from **5**): mp 178–186°; SH found, 89%; N, found, 24.1%; as before, tlc indicated disulfide was the only contaminant. The uv spectrum was identical with that of a chromatographically homogeneous, analytical sample (18% yield from **5**), similarly obtained in another experiment: mp 179–181°; $[\alpha]^{25}D$ −13° (water); SH found, 95%; $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,400), $\lambda_{max}^{pH\ 7}$ 259 (14,500), $\lambda_{max}^{pH\ 13}$ 259 (15,100).

Anal. Calcd for $C_{10}H_{13}N_5O_3S$: C, 42.4; H, 4.62; 24.7; O, 16.9; S, 11.3. Found: C, 42.3; H, 4.83; N, 24.4; O, 16.9; S, 11.4.

3′-Deoxyadenosine (12). Desulfurization of 11.—3′-Thioadenosine (**11**) in DMF solution was desulfurized by heating with sponge nickel overnight, as described[6,7b] for isomeric deoxynucleosides. The product was recrystallized twice from water (*ca.* 50 ml/g) to afford a sample for analysis (22% yield), mp 223–226°. It was characterized as the hydrate with 0.8 mol of H_2O (*i.e.*, mol wt taken as 251.2 plus 14.4): $[\alpha]^{24}D$ −50.1° (*c* 0.5, in water); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 15,200), $\lambda_{max}^{pH\ 7}$ 260 (15,300), $\lambda_{max}^{pH\ 13}$ 260 (15,400); it was chromatographically homogeneous and identical (on Whatman No. 1 paper, R_{Ad} 1.36 in 5% disodium phosphate; R_{Ad} 0.93 in 1-butanol saturated with water *vs.* R_{Ad} 0.65 for adenosine) with an authentic sample (lit.[13] mp 224–225°, 223–225°, wherein optical rotation and uv data were not adjusted for hydration).

Anal. Calcd for $C_{10}H_{13}N_5O_3 \cdot 0.8H_2O$: C, 45.2; H, 5.54; N, 26.4. Found: C, 45.0; H, 5.46; N, 26.6.

Methyl 5-Deoxy-3-*O*-*p*-tolylsulfonyl-α-D-xylofuranoside (17).—Methyl 2-*O*-benzyl-5-deoxy-3-*O*-tosyl-α-D-xylofuranoside[9] (**16**) was debenzylated as described above for the 3,5-ditosylate **2**. The oily product (91% yield) could not be induced to crystallize: nmr data, τ 8.22 d and 8.68 d (*p*-C_6H_4 of tosyl, J = 8.5 cps), 5.12 d (C-1-H), 5.25 q (C-2-H), 5.68 q (C-4-H), 5.82 q (C-3-H), 6.62 s (OCH_3), 7.60 s (CH_3 of tosyl), 8.85 d (C-5-H_3); $J_{1,2}$ = 5 cps, $J_{2,3}$ = 3.2 cps, $J_{3,4}$ = 5 cps, $J_{4,5}$ = 6.5 cps. Absence of starting material could be determined by absence of any singlet near τ 5.5 due to OCH_2Ph.

Methyl 5-deoxy-2-*O*-thionobenzoyl-3-*O*-*p*-tolylsulfonyl-α-D-xylofuranoside (18) was prepared from 3.40 g (11.3 mmol) of **17** in 50 ml of cold, dry pyridine and 1.80 g (11.5 mmol) of thiobenzoyl chloride, by the procedure for **3** above. The crude product (84% yield) was a residual red oil which exhibited weak carbonyl absorption in the infrared. Preparative tlc on silica gel (18 plates) with 1% ethyl acetate in chloroform afforded 2.0 g (42%) of a yellow oil, free of carbonyl: nmr data, τ 1.9–3.1 m (ArH), 4.37 t (C-2-H), 4.67 q (C-3-H), 4.79 d (C-1-H, $J_{1,2}$ = 5 cps), 6.75 s (OCH_3), 7.82 s (CH_3 of tosyl), 8.61 d (C-5 H_3, $J_{4,5}$ = 6.5 cps). Crystallization from 10 ml of methanol yielded 1.3 g (27%): mp 66.5–67.5°; $[\alpha]^{22}D$ +185° (chloroform); ir data, 7.30, 8.38, 8.46, 12.25 (OTs), 8.23 (C=S), 14.58 μ (thionobenzoate); bands at 11.6, 12.82, and 13.32 μ distinguished the spectrum from that of a second form, below.

Anal. Calcd for $C_{20}H_{22}O_6S_2$: C, 56.9; H, 5.24; S, 15.2. Found: C, 56.6; H, 4.99; S, 14.8.

A second crop (0.3 g, 6% yield) occurred in a different crystal form: mp 82–83°; ir data, 7.25, 8.40, 8.48, 12.25 (OTs), 8.20 (C=S), 14.50 μ (thionobenzoate); bands at 11.80, 12.90, 13.40 μ distinguished the spectrum from that of the previous form.

Anal. Found: C, 56.5; H, 5.14; S, 14.9.

Treatment of 18 with Sodium Benzoate–DMF to Form the Crystalline Intermediate 19.—To a solution of 0.95 g (2.2 mmol) of methyl 5-deoxy-2-*O*-thionobenzoyl-3-*O*-tosyl-α-D-xylofuranoside (**18**) in 50 ml of dried DMF was added 0.35 g (2.4 mmol) of sodium benzoate, and the solution was heated under nitrogen at 110–115° for 6 hr. The volume was reduced *in vacuo* to a few milliliters and the residue was partitioned between 50 ml of ether and 50 ml of water. The ether layer was washed with two 50-ml portions of saturated aqueous sodium bicarbonate and 50 ml of water, was dried, and was concentrated to form 0.55 g (95%, calcd as **19**) of a residual oil that partly crystallized. The ir spectrum was free of OH or SH bands near 3.0 or 3.9 μ and showed benzoate bands at 5.76, 7.83, 14.22 μ; a strong unassigned band was at 13.46 μ. Recrystallization from 5 ml of methanol afforded 0.26 g (39%), mp 145–148° with softening at 140°. A second recrystallization yielded a sample (27%) for analysis, mp 146–149° with softening at 139°, $[\alpha]^{22}D$ +213° (chloroform), $\lambda_{max}^{95\%\ EtOH}$ 227 mμ (ε 18,300). The ir spectrum was virtually unchanged from that of the crude; nmr data, τ 1.75–2.85 m (10 ArH's), 4.55–5.0 m (two C-2 H's), 5.06 d and 5.28 d (two equal C-1-H's, $J_{1,2}$ = 4 cps), 6.59 s and 6.68 s (two equal OCH_3's), 8.90 d and 9.23 d (two equal C-5-H_3's, $J_{4,5}$ = 6 cps).

Anal. Calcd for $C_{26}H_{30}O_7S_2$: C, 60.2; H, 5.83; O, 21.6; S, 12.7; mol wt, 518. Found: C, 60.3; H, 5.86; O, 21.5; S, 12.4; mol wt (osmometer), 504 (in benzene), 488 (in chloroform).

Methyl 2-*O*-Benzoyl-5-deoxy-3-thio-α-D-ribofuranoside (20).—A solution of 80 mg (0.15 mmol) of the crystalline intermediate **19** in 15 ml of 70% aqueous acetic acid was heated at 50° for 2 hr, and then concentrated. To remove all acetic acid, the residual oil was twice taken up in 10 ml of toluene and concentrated, and the final weight was 80 mg (98%). The ir spectrum showed benzoate bands (5.78, 7.83, and 14.05 μ) and an –SH band at 3.88 (weak), but no –OH near 3.0 μ; the strong band observed in **19** at 13.46 μ was also absent; nmr data, τ 1.8–2.0 m and 2.4–2.7 m (C_6H_5–), 4.5–4.9 m (C-2-H and C-1-H), 5.9 q (C-4-H, $J_{4,5}$ = 6 cps), 6.61 s (OCH_3), 6.97 m (C-3-H), 8.28 d (–SH, J = 11.5 cps), 8.60 d (C-5-H_3, $J_{4,5}$ = 6 cps).

Methyl 2-*O*-Benzoyl-3-*S*-benzoyl-5-deoxy-3-thio-α-D-ribofuranoside (21).—The thiol **20** (30 mg, 0.11 mmol) in 5 ml of anhydrous pyridine was treated with 0.5 ml of benzoyl chloride, and the mixture was stirred for 17 hr at room temperature. Water (0.5 ml) was added, the mixture was stirred 1 hr, was poured into 15 ml of ice-cold 1 *M* hydrochloric acid, and extracted with 25 ml of chloroform. The extract was washed with 25 ml of saturated sodium bicarbonate solution, with 25 ml of water, was dried, and was concentrated. The residual oil crystallized on scratching (41 mg, 98% yield) and was crystallized from 5 ml of methanol to yield 29 mg (70%): mp 106–107°; ir data, 5.79, 7.77, 7.85, 14.0 (OBz), 5.98, 8.30, 10.98, 14.5 (SBz) μ; nmr data, τ 1.9–2.15 m and 2.4–2.8 m ($2C_6H_5$'s), 4.51 q (C-2-H, $J_{1,2}$ = 4 cps, $J_{2,3}$ = 8 cps), 4.78 d (C-1-H, $J_{1,2}$ = 4 cps), 5.6–5.9 m (C-3-H and C-4-H), 6.63 s (OCH_3), 8.57 d (C-5-H_3, $J_{4,5}$ = 6 cps).

Anal. Calcd for $C_{20}H_{20}O_5S$: C, 64.5; H, 5.41; S, 8.60. Found: C, 64.5; H, 5.41; S, 8.75.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*O*-thionobenzoyl-D-ribofuranose (22).—A solution of 0.80 g (2.7 mmol) of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose[26,27] in 15 ml of anhydrous pyridine was treated with 0.5 ml (use of a carefully controlled 1–2% excess would probably optimize the yield of **22**) of thiobenzoyl chloride. The mixture was stirred at room temperature for 3 days and was poured into 30 ml of water. The product was extracted with 30 ml of chloroform. The extract was washed with 30 ml each of cold 5 *M* hydrochloric acid, saturated sodium bicarbonate, and water, was dried, and was concentrated. The residual dark red oil (1.2 g, 108%) showed greater C=O intensity in the ir than expected for a mono-*O*-benzoate; tlc (0.5% ethyl acetate in chloroform) disclosed red, orange, and yellow components (R_f's 0.9, 0.5, and 0.4, respectively) and an uv-absorbing spot (R_f 0.3, assumed to be 3,5-di-*O*-benzoate). The yellow thionobenzoate was isolated by preparative tlc (as for **3**) and was recrystallized from 2-propanol to form 0.11 g (11%): mp 79–81°; $[\alpha]^{21}D$ 175° (chloroform); $\lambda_{max}^{CHCl_3}$ 416 mμ (ε 159); ir data, 8.11 (C=S), 14.51 μ (thionobenzoate); benzoate bands at 5.82, 7.9, and 14.02 μ.

Anal. Calcd for $C_{22}H_{22}O_6S$: C, 63.8; H, 5.35; S, 7.74. Found: C, 63.4; H, 5.53; S, 7.54.

Methyl 4,6-*O*-benzylidene-3-*O*-thionobenzoyl-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (23) was prepared by acylation, as for **22**. Ethanol recrystallization of the crude product (a brown solid, 91% yield) gave a yellow solid, mp 215–216°, containing 50% of the 3-*O*-benzoate (according to S analysis, and the presence of ir C=O). Purification was completed by preparative tlc (as for **3** and **22**) and a final recrystallization: mp 218–219°; $[\alpha]^{21}D$ +92° (chloroform); $\lambda_{max}^{CHCl_3}$ 420 mμ (ε 141); ir data, 8.17, 8.27 (C=S), no benzoate bands at 5.8 or 14.0 μ; nmr data, τ 4.55

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s ($PhCHO_2$), 4.92 d (C-1-H, $J_{1,2}$ = 4 cps), 6.53 s (OCH_3), 7.83 s (CH_3 of tosyl).

Anal. Calcd for $C_{28}H_{28}O_8S_2$: C, 60.4; H, 5.07. Found: C, 60.2; H, 4.80.

Registry No.—**2**, 16136-65-5; **3**, 16136-66-6; **5**, 16136-67-7; **7**, 16136-68-8; **8**, 16136-69-9; **11**, 16136-70-2; **12**, 73-03-0; **15**, 16136-72-4; **17**, 16136-73-5; **18**, 16136-77-9; **19**, 16136-78-0; **20**, 16136-74-6; **21**, 16136-75-7; **22**, 16136-76-8; **23**, 16170-23-3.

Acknowledgment.—The authors are indebted to Dr. Peter Lim and staff for infrared and ultraviolet spectra and for optical rotation data. The authors are indebted to Mr. O. P. Crews and staff for large-scale preparation of intermediates.

Branched-Chain Sugar Nucleosides. III. 3′-*C*-Methyladenosine

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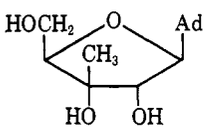
Received August 4, 1967

The synthesis of 3′-*C*-methyladenosine (**1**), the first example of a branched-chain sugar nucleoside, is described. The required derivative of the previously unknown 3-*C*-methyl-D-ribofuranose was prepared starting with 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**3**). Oxidation of **3** with RuO_4 produced 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (**4**) which when treated with methyl Grignard led to 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**9**). Removal of the 1,2-*O*-isopropylidene moiety of **9** in acidic methanol gave methyl 5-*O*-benzoyl-3-*C*-methyl-D-ribofuranoside (**11**). Benzoylation of **11** produced methyl 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-D-ribofuranoside (**13**). Conversion of **13** into 2,3,5-tri-*O*-benzoyl-3-*C*-methyl-D-ribofuranosyl bromide (**19**) followed by reaction with chloromercuri-6-benzamidopurine gave the acylated nucleoside (**22**) which was deacylated to yield 3′-*C*-methyladenosine (**1**). The β anomeric configuration of **1**, assigned on the basis of the *trans* rule and rotational properties, was proved through oxidation studies as well as by conversion of **1** into a 3,5′ cyclo nucleoside. Some reactions and properties of several 3-*C*-methyl-D-ribofuranose derivatives are described. As part of a short discussion of some conformational aspects of the 3-*C*-methyl-D-ribofuranosyl moiety based on nmr spectral measurements and construction of molecular models, it is suggested that the carbohydrate part of **1** exists in a T_3^2 conformation.

We became interested in the synthesis of nucleosides of branched-chain sugars[1] through earlier work on 3′-deoxyadenosine (**2**),[2] a potent inhibitor of RNA synthesis in Ehrlich ascites cells.[3] Available biological evidence[4] indicates that it is incorporated into the RNA chain where, having no 3′-hydroxyl group, it acts as a chain terminator. The biological properties of 3′-deoxyadenosine led us to undertake the synthesis of an adenosine analog having a 3′-hydroxyl group, but one of altered chemical reactivity. This was accomplished by the substitution of a methyl group for the proton at C-3′ of the ribose moiety thereby converting the normal secondary 3′-hydroxyl into a tertiary alcohol. The resultant nucleoside, 3′-*C*-methyladenosine (**1**), is the first[5] synthetic nucleoside containing a branched-chain sugar. This is not surprising in view of the rather limited availability of branched-chain sugars.[6]



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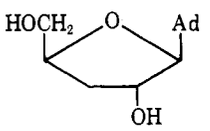

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It was felt that the change of the normal secondary 3′-hydroxyl of adenosine into the tertiary 3′-hydroxyl group in 3′-*C*-methyladenosine represented a more subtle alteration at the 3′-carbon than that in 3′-deoxyadenosine (**2**) where the 3′-hydroxyl is absent. The presence of the 3′-hydroxyl in **1** may permit certain enzymic reactions for which it is required; on the other hand, its reduced chemical reactivity might be expected to interfere with other biological processes. It is apparent that, in addition to changing the chemical reactivity of the 3′-hydroxyl group, the branching at C-3′ will have other consequences. The methyl group occupies more space above the furanose ring as depicted in **1** than does the C-3′ proton of adenosine. It also introduces an additional bulky-group eclipsing interaction with its predictable effect on the conformation of the furanose ring. Both of these factors would be expected to play a role in the biochemistry of 3′-*C*-methyladenosine.

For the synthesis of 3′-*C*-methyladenosine (**1**), a suitable derivative of the unknown 3-*C*-methyl-D-ribose was required. The key intermediate for its synthesis was 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (**4**), the synthesis of which was described recently[7] by us and earlier by Oka and Wada.[8] In both cases, the osulose **4** was obtained by the oxidation of the unblocked 3-hydroxyl group in

(1) (a) E. Walton, F. W. Holly, and R. F. Nutt, Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966, Abstract 37C; (b) E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Amer. Chem. Soc.*, **88**, 4524 (1966); (c) R. F. Nutt and E. Walton, *J. Med. Chem.*, **10**, 151 (1967).

(2) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *ibid.*, **8**, 659 (1965).

(3) (a) H. Klenow and S. Frederickson, Abstracts, the VIth International Congress of Biochemistry, New York, N. Y., July 1964, p 66; (b) H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, **240**, 806 (1965).

(4) H. T. Shigeura and G. E. Boxer, *Biochem. Biophys. Res. Commun.*, **17**, 758 (1964).

(5) After our preliminary report (ref 1b and 1c) on the synthesis of **1**, F. W. Lichtenthaler and H. Zinke [*Angew. Chem.*, **78**, 774 (1966)] described the synthesis of 1-(3-deoxy-3-*C*-methyl-3-nitro-β-D-glucopyranosyl)uracil from "uridine dialdehyde" and nitroethane.

(6) The chemistry of naturally occurring branched-chain sugars was reviewed by R. Shaeffer, *Advan. Carbohyd. Chem.*, **11**, 263 (1956). Since that time notable progress has been made in the synthesis of branched-chain sugars; for example, the synthesis of the streptoses by J. R. Dyer, W. E. McGonigal, and K. C. Rice [*J. Amer. Chem. Soc.*, **87**, 654 (1965)], the synthesis of hamamelose by W. G. Overend and N. R. Williams [*J. Chem. Soc.*, 3446 (1965)] and also by J. J. K. Novak and F. Šorm [*Collect. Czech. Chem. Commun.*, **30**, 3303 (1965)], and the synthesis of noviose by B. P. Vaterlaus, J. Kiss, and H. Spiegelburg [*Helv. Chim. Acta*, **47**, 381 (1964)], among others.

(7) R. F. Nutt, B. Arison, F. W. Holly, and E. Walton, *J. Amer. Chem. Soc.*, **87**, 3273 (1965).

(8) K. Oka and H. Wada, *Yakugaku Zasshi*, **83**, 890 (1963); *Chem. Abstr.*, **60**, 1825 (1964).