zene[15,16] in 50 ml. of refluxing absolute ethanol for 3 hr. After 48 hr. at 25° the orange solution was refluxed for an additional 3 hr. while ammonia was passed through. Evaporation gave an orange solid which was chromatographed in benzene on silica gel. A yellow band eluted rapidly and the eluate on evaporation yielded 1.6 g. which on recrystallization from aqueous ethanol gave 1.49 g. (82%) of 3,6-dibromo-2-nitroaniline as yellow needles, m.p. 73.5–74.5°, lit.[14] m.p. 75°.

Azidodibromonitrobenzenes.—The Hodgson and Walker procedure[3] for the diazotization of nitroamines was utilized for the conversion of 5,6-, 4,6-, and 3,6-dibromo-2-nitroaniline to the corresponding diazonium salts. Treatment of the diazonium salts with aqueous sodium azide led to the azidodibromonitrobenzenes. Thus, for the preparation of 1-azido-5,6-dibromo-2-nitrobenzene (IIIa), 1.16 g. (0.017 mole) of finely pulverized sodium nitrite was gradually added to 8 ml. of concentrated sulfuric acid with stirring at 0°. The suspension was heated to 50° and held at this temperature until the sodium nitrite dissolved. The solution was cooled and a finely divided suspension of 3.88 g. (0.013 mole) of 5,6-dibromo-2-nitroaniline in 40 ml. of glacial acetic acid was added gradually with stirring while the temperature was maintained below 15°. After the diazotization was complete, the pale yellow suspension was added dropwise to a solution of 1.16 g. (0.018 mole) of sodium azide in 20 ml. of water with vigorous stirring at 10°. The resulting precipitate was filtered, washed with water, and recrystallized from 95% ethanol. The yield of pale yellow, feathery needles, m.p. 71.5–72.5°, was 3.73 g. (88%).

Anal. Calcd. for $C_6H_2Br_2N_4O_2$: C, 22.38; H, 0.63; Br, 49.65. Found: C, 22.61; H, 0.84; Br, 50.07.

1-Azido-4,6-dibromo-2-nitrobenzene (IIIb) was obtained in 76% yield in the same manner from 4,6-dibromo-2-nitroaniline, forming pale yellow needles from 95% ethanol, m.p. 52–53°.

Anal. Calcd. for $C_6H_2Br_2N_4O_2$: C, 22.38; H, 0.63; N, 17.40. Found: C, 22.65; H, 0.84; N, 17.23.

1-Azido-3,6-dibromo-2-nitrobenzene (IIIc) was obtained in 86% yield from 3,6-dibromo-2-nitroaniline, forming colorless needles from *n*-hexane, m.p. 65.5–66.5°.

Anal. Calcd. for $C_6H_2Br_2N_4O_2$: C, 22.38; H, 0.63; Br, 49.65. Found: C, 22.31; H, 0.71; Br, 49.84.

Dibromobenzofurazan Oxides.—5,6-Dibromobenzofurazan oxide was prepared in 76% yield by the sodium hypochlorite oxidation[5] of 4,5-dibromo-2-nitroaniline, forming yellow needles, m.p. 128–128.5° (from 95% ethanol).

Anal. Calcd. for $C_6H_2Br_2N_2O_2$: C, 24.52; H, 0.69; N, 9.53. Found: C, 24.73; H, 0.75; N, 9.56.

The remaining dibromobenzofurazan oxides were prepared by the thermal decomposition of the corresponding *o*-nitroazides. For example, a solution of 1.0 g. of 1-azido-5,6-dibromo-2-nitrobenzene (IIIa) in 25 ml. of anhydrous toluene was refluxed for 29 hr. Evaporation gave a tan solid. Chromatography in benzene–*n*-hexane (1:1 v./v.) on silica gel gave a yellow band, which eluted readily to yield 4,5-dibromobenzofurazan oxide (IIa), which crystallized from 95% ethanol as pale yellow, feathery needles, m.p. 148–149°. The yield was 0.80 g. (88%).

Anal. Calcd. for $C_6H_2Br_2N_2O_2$: C, 24.52; H, 0.69; N, 9.53. Found: C, 24.57; H, 0.81; N, 9.90.

4,6-Dibromobenzofurazan oxide (IIb) was obtained in 82% yield in the same manner from IIIb, forming canary yellow platelets from 95% ethanol, m.p. 92.5–93°.

Anal. Calcd. for $C_6H_2Br_2N_2O_2$: C, 24.52; H, 0.69; N, 9.53. Found: C, 24.67; H, 0.79; N, 9.65.

4,7-Dibromobenzofurazan oxide (IIc) was obtained in 71% yield from IIIc, forming yellow prisms from 95% ethanol, m.p. 133–133.5.°, lit.[1] m.p. 132°.

Dibromobenzofurazans.—The dibromobenzofurazans were prepared by reduction of the furazan oxides with hydroxylamine followed by steam distillation of the alkaline solution of the dioximes.[1] For example, a solution 5.88 g. (0.02 mole) of 5,6-dibromobenzofurazan oxide in 100 ml. of hot 95% ethanol was cooled rapidly in an ice bath to produce a finely divided suspension. A solution of 2.2 g. (0.032 mole) of hydroxylamine hydrochloride in 12 ml. of water was added followed by 25% aqueous potassium hydroxide with stirring and cooling until nitrogen evolution ceased. Steam distillation of the deep red alkaline solution gave 3.88 g. (69%) which was chromatographed in *n*-hexane on silica gel. Evaporation of the eluate and crystallization of the residue from *n*-hexane gave 5,6-dibromobenzofurazan as long colorless needles, m.p. 87–87.5°.

Anal. Calcd. for $C_6H_2Br_2N_2O$: C, 25.93; H, 0.73; N, 10.08. Found: C, 26.27; H, 1.04; N, 9.78.

4,5-Dibromobenzofurazan was obtained in 43% yield from IIa, forming colorless needles from 95% ethanol, m.p. 123–124°.

Anal. Calcd. for $C_6H_2Br_2N_2O$: C, 25.93; H, 0.73; N, 10.08. Found: C, 26.02; H, 0.95; N, 9.83.

4,6-Dibromobenzofurazan was obtained in 55% yield from IIb, forming long colorless needles from 95% ethanol, m.p. 71.5–72°.

Anal. Calcd. for $C_6H_2Br_2N_2O$: C, 25.93; H, 0.73; N, 10.08. Found: C, 26.23; H, 0.93; N, 9.98.

4,7-Dibromobenzofurazan was obtained in 69% yield from IIc, forming colorless needles from 95% ethanol, m.p. 112–112.5°, lit.[1] m.p. 113°.

Conversion of Tetrabromotetrahydrobenzofurazan Oxide (I) to Dibromobenzofurazan Oxide. A. With Pyridine.—A solution of 4.56 g. (0.01 mole) of I, m.p. 169–170°,[1] in 25 ml. of pyridine was allowed to stand at 25° for 2 hr. The suspension was poured into cold water and the resulting yellow precipitate was filtered, washed with water, and dried. The yield was 2.62 g. (89% based on conversion to dibromobenzofurazan oxide). Recrystallization twice from *n*-hexane and once from 95% ethanol gave 0.70 g. of yellow needles, m.p. 148–149°. This material was identical (mixture melting point and infrared spectrum) with 4,5-dibromobenzofurazan oxide obtained by the decomposition of IIIa as previously described.

The hexane filtrates were combined and evaporated to a small volume to yield 0.96 g., m.p. 70–89°. Recrystallization from aqueous dioxane and then from 95% ethanol gave 0.55 g. of yellow plates, m.p. 92.5–93°. This material was identical (mixture melting point and infrared spectrum) with 4,6-dibromobenzofurazan oxide obtained by the decomposition of IIIb, previously described.

B. With Potassium Acetate in Acetic Acid.—A mixture of 22.8 g. (0.05 mole) of I and 22 g. of potassium acetate in 200 ml. of glacial acetic acid was refluxed for 24 hr. The suspension was poured into water and the resulting solid was filtered, washed with water, and recrystallized twice from 95% ethanol and once from acetic acid. The yield of high-melting isomer, m.p. 148–149°, was 4.4 g.

The acetic acid filtrate was evaporated to a small volume giving 2.2 g., m.p. 77–80°, which after recrystallization from methanol weighed 1.4 g. Two recrystallizations from *n*-hexane gave an additional 0.17 g. of the high-melting isomer. The *n*-hexane filtrates were combined and evaporated to a small volume; the resulting solid was recrystallized from aqueous dioxane and then 95% ethanol. The yield of the low-melting isomer, m.p. 92.5–93°, was 0.59 g.

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Methyl 4-Deoxy-4-mercapto-D-ribofuranoside[1]

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This laboratory and others have been engaged in producing modified sugars wherein the ring oxygen is replaced by another atom such as sulfur, selenium, or nitrogen. Most work has dealt with the placement of sulfur in the sugar ring. Many of the thiosugars thus far produced are of biological interest, such as the ana-

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logs of D-glucose,[2] D-fructose,[3] D-xylose,[4-7] L-arabinose,[8] D-ribose,[4,9] and 2-deoxy-D-ribose.[4] In all of these sugars the sulfur atom is a part of a six-membered pyranose ring. It is now of interest to prepare 4-deoxy-4-mercapto-D-ribose since this sugar would be useful in making nucleosides. A report of 4-deoxy-4-mercapto-L-ribose has been given[10] recently.

The starting material for the synthesis of the D analog is α-L-lyxose[11] which initially is converted to methyl 2,3-*O*-isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-L-lyxopyranoside (I) by the method of Kent and Ward[12] and also to the methyl 2,3-*O*-isopropylidene-4-*O*-(methylsulfonyl)-α-L-lyxopyranoside (II).

Displacements of the tosyloxy from I and the mesyloxy from II by thioacetate anion in N,N-dimethylformamide (DMF) were compared. The ratio of sugar derivative to thioacetate was 1:4 in both instances and reactions were conducted at an oil-bath temperature at 154–156°. After 2 hr., compound I gave methyl 4-deoxy-2,3-*O*-isopropylidene-4-thioacetyl-β-D-ribopyranoside (III) in 50% yield while even after 3 hr. of reaction time compound II gave only 30% of compound III. These results are as expected and confirm the general observation that the tosyloxy group is a better leaving group than mesyloxy. Compound III showed the characteristic absorption[13] for thiolacetate at 230–240 mμ.

Methanolysis of III gave sirupy methyl 4-deoxy-4-mercapto-D-ribofuranoside (IV) which was purified by paper chromatography. The product showed no thiol activity in the ultraviolet or with sodium nitroprusside (SNP)[14,15] or 2,3,5-triphenyl-2*H*-tetrazolium chloride (TTC)[16] reagents, indicating preferential ring formation on sulfur.

Deacetylation of III in methanolic sodium methoxide produced the free mercapto derivative which was converted to the disulfide by oxygen and iodine oxidation in refluxing methanol. The disulfide on treatment with Amberlite IR 120(H) gave bis(methyl 4-deoxy-β-D-ribopyranoside) 4,4′-disulfide.

Experimental

Analytical Methods.—Chromatographic separations of sugar derivatives were made at 25° on Whatman No. 3 MM filter paper developed in irrigants (A) 1-butanol–ethanol–water (40:11:19 v./v.) or (B) ethyl acetate:pyridine:water (25:1:25 v./v.). Spray indicators employed were (C) potassium permanganate–periodate[17] and (D) silver nitrate–sodium hydroxide.[16] Location of components on the paper was determined by spraying guide strips cut from the edges and center of each paper. The bands were excised and eluted with several portions of solvent. Purity of crystalline products was determined by thin layer chromatography on silica gel G[18] coated microscope slides irrigated with (E) chloroform–acetone (12:1 v./v.) or (F) butanol–ethanol–water (3:1:1 v./v.). Location of components was obtained by spraying with 5% sulfuric acid in ethanol and charring. Sugar flow rates are reported relative to that of D-ribose (R_r values). Molecular weights were measured in a Mechrolab vapor phase osmometer with water as solvent.

Methyl 2,3-*O*-Isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-L-lyxopyranoside (I).—This compound was made by the procedure of Kent and Ward.[12] It had m.p. 105–106°, $[\alpha]^{25}D$ +16.7° (*c* 2.81, ethanol).

Anal. Calcd. for $C_{16}H_{22}O_7S$: C, 53.6; H, 6.19; S, 8.95. Found: C, 53.3; H, 6.14; S, 9.2.

Methyl 2,3-*O*-Isopropylidene-4-*O*-(methylsulfonyl)-α-L-lyxopyranoside (II).—Methylsulfonyl chloride (5 ml., 0.063 mole) was dissolved in 30 ml. of dry pyridine and the solution was cooled to −5 to −10°. To this was added, dropwise with stirring, a solution of methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside[19] (10.2 g., 0.05 mole) in 20 ml. of dry pyridine. The mixture was stirred at −5 to −10° for 4 hr., then 25 ml. of water was added slowly. The mixture was extracted four times with 50-ml. portions of chloroform and the combined extracts were washed with water and dried over sodium sulfate. The dry chloroform solution was concentrated to a thick sirup which was dissolved in methanol and concentrated to dryness. The compound was crystallized from hot ethanol to give 13 g. (92%) of compound II: m.p. 92–93°, $[\alpha]^{25}D$ −14.7° (*c* 1.3, ethanol).

Anal. Calcd. for $C_{10}H_{18}O_7S$: C, 42.5; H, 6.4; S, 11.4. Found: C, 42.3; H, 6.5; S, 11.2.

Methyl 4-Deoxy-2,3-*O*-isopropylidene-4-thioacetyl-β-D-ribopyranoside (III).—Compound II (5.7 g., 0.02 mole) and 9.2 g., 0.08 mole, of recrystallized potassium thioacetate were dissolved in 70 ml. of dry DMF and the mixture was heated in an oil bath at 154–156° for 3 hr. The reaction mixture was poured with stirring into 300 ml. of xylene and the precipitated salts were filtered and washed with xylene. The combined solutions were evaporated under reduced pressure to dryness and the residue extracted twice with 100-ml. portions of heptane. The combined heptane extracts were concentrated to a volume of 15 ml. and cooled. The crystals which formed were separated by filtration and suspended in 50 ml. of petroleum ether (b.p. 30–37°). The crystals which did not dissolve were filtered to give 0.5 g. of unreacted compound II which was used for further displacements. The mother liquor, when concentrated to 10 ml., deposited crystals. The crystalline product was recrystallized several times from heptane giving a total yield of 1.42 g. (30%) of material: m.p. 91–92°, $[\alpha]^{25}D$ −26.8° (*c* 0.75, ethanol). The mixture melting point of II and III was 68°.

Anal. Calcd. for $C_{11}H_{18}O_5S$: C, 50.4; H, 6.9; S, 12.2. Found: C, 50.6; H, 7.2; S, 11.9.

This compound showed characteristic absorption for thiolacetate at 230–240 mμ and also gave a strong positive test with TTC and SNP.

Compound III was also prepared from compound I. Compound I (5.5 g., 0.154 mole) and 8 g., 0.07 mole of potassium thioacetate were dissolved in 50 ml. of dry DMF and the solution was heated in an oil bath at 154–156° for 2 hr. It was worked up as described above with 200 ml. of xylene. Initial crystals from heptane had m.p. 76–85°. These were recrystallized several times from petroleum ether (30–37°). The final product had the same constants as given above. The yield was 2.0 g. (49.6%).

Methyl 4-Deoxy-4-mercapto-D-ribofuranoside (IV).—Compound III (1.0 g., 0.0038 mole) was dissolved in 10 ml. of 0.7 *N* methanolic hydrogen chloride and the solution was refluxed for 24 hr. Thiol activity was determined periodically by testing an aliquot of the reaction mixture with TTC. No thiol test was found after 24 hr. The reaction mixture was cooled and was neutralized by passing it through a column of Amberlite IR-45 cationic resin. The effluent was concentrated under reduced pressure to a thin sirup (0.6 g.). The glycoside was purified by paper chromatography with irrigant A. Elution of a compound with R_r 2.03 (R_r 2.1 in irrigant B) with water followed by

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concentration of the extract, produced a sirup (IV) which gave $[\alpha]^{25}D$ −118° (*c* 1.58, methanol).

Anal. Calcd. for $C_6H_{12}O_4S$: S, 17.8; OCH_3, 17.3; mol. wt., 180. Found: S, 17.5; OCH_3, 17.6; mol. wt., 178.

Periodate oxidation[20] showed 2 molar equiv. of periodate consumed, 0.2 molar equiv. of total acids produced, but with no formic acid produced.[7] The excess periodate consumed was probably due to the oxidation of the sulfur to a sulfone or sulfoxide.[21] Compound IV showed no thiolacetate adsorption or free mercapto groups with TTC and SNP. Hydrolysis of IV in 0.5 *N* hydrochloric acid resulted in a change of the specific optical rotation from −118° to +38° in 30 min. at 75°. This is suggestive that the glycoside is predominantly in the β-D-configuration. After hydrolysis was complete, the product was isolated by passing the solution through a column of Amberlite IR-45(OH) resin and concentrating to a sirup. This material, 4-deoxy-4-mercapto-D-ribofuranose, gave a positive test for reducing groups and had R_f 1.36 in irrigant A and 1.5 in irrigant B.

Compound IV gave a crystalline tri-*p*-nitrobenzoate[10]: m.p. 193–194°, $[\alpha]^{25}D$ +85.5° (*c* 0.38, chloroform).

Bis(methyl 4-deoxy-β-D-ribopyranoside) 4,4′-Disulfide (V).—Compound III (1.0 g.) was dissolved in 20 ml. of 2 *N* methanolic sodium methoxide and allowed to stand at 25° for 16 hr. The solution was passed through a column of Amberlite IR-120(H) resin for neutralization and removal of the isopropylidene group. To the effluent was added a few crystals of iodine and the mixture was refluxed for 3 hr. with oxygen bubbling through it. The cooled solution was concentrated to a thick sirup which was dissolved in 10 ml. of water and extracted twice with 25-ml. portions of chloroform to remove the excess iodine. The aqueous solution was concentrated under reduced pressure to dryness and the residue was crystallized from hot ethanol to give m.p. 152°, $[\alpha]^{25}D$ −229° (*c* 0.43 water), yield 0.41 g. (60%). Titration of the product with 0.1 *N* iodine solution[22] showed no thiol activity. Reaction with TTC and SNP gave no color test until after reduction of the disulfide bond with lithium aluminum hydride[23] in diethyl ether. The R_f for V in irrigant A was 1.90, in irrigant B, 2.3.

Anal. Calcd. $C_{12}H_{22}O_8S_2$: S, 17.8. Found: S, 17.5.

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Sodium–Liquid Ammonia Debenzylations in Nucleoside Synthesis[1]

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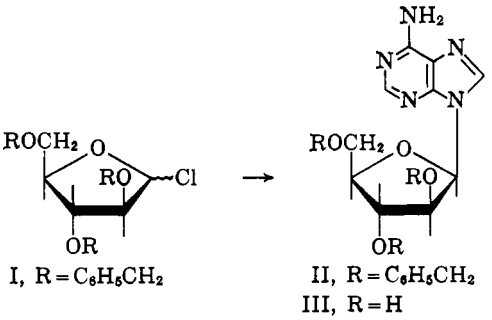
Recent publications[2] concerning spongoadenosine [(9-β-D-arabinofuranosyl)adenine, III], a nucleoside first synthesized in these laboratories,[3] have disclosed some interesting biological activities for the compound.



I, R = $C_6H_5CH_2$

II, R = $C_6H_5CH_2$

III, R = H

Accordingly the synthesis of III in quantity has become important both for further biological evaluation and for conversion to potentially useful analogs.

The description by Glaudemans and Fletcher[4] of the condensation of 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride (I) with 6-benzamido purine to give, after deblocking, the desired β-nucleoside (III) offered a practical, direct route to III. However, the final step in the synthesis, the catalytic hydrogenolysis of the intermediate II, was convenient only when small quantities of II were employed.

An alternative technique for removal of the benzyl blocking group of II was sought and the use of sodium in liquid ammonia was investigated. The numerous examples of debenzylation of S- and N-benzyl groups with sodium in ammonia made this a logical choice; surprisingly, however, there is virtually no mention in the literature of the use of this method for cleaving O-benzyl groups.[5] Recent work in this laboratory[6] described the smooth removal of both the O- and S-benzyl group of 6-amino-3-O-benzyl-5-S-benzyl-6-deoxy-1,2-O-isopropylidene-5-thio-L-idofuranose through the action of sodium in liquid ammonia. We wish to draw attention to this method of O-debenzylation because of its convenience and its applicability in situations where previously described methods of O-debenzylation are inappropriate.[7] It was possible to effect the conversion of II to III in high yield using sodium in liquid ammonia; this modification of the Glaudemans–Fletcher procedure[4] is especially convenient for large-scale synthesis of III. The stability of the adenine ring to the action of sodium in ammonia is noteworthy; there are numerous references to the reduction of nitrogen-containing heterocycles by this reducing agent.[9]

Experimental

To a stirred suspension of 3.75 g. (6.98 mmoles) of 9-(2′,3′,5′-tri-O-benzyl-β-D-arabinofuranosyl)adenine (II)[4] in 160 ml. of liquid ammonia was added a total of 600 mg. (26 mg.-atoms) of sodium in portions over 10–12 min. by which time the characteristic deep blue color persisted. At this point, the blue color

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