Time (sec.)	0	780	3600	5400
x = mmoles NaOH	0.585	0.635	0.785	0.89
Time (sec.)	7200	9000	10800	Infinity
x = mmoles NaOH	0.98	1.07	1.15	2.34

From the slope of a plot of log (a–x) against time, the first-order rate was derived $k_1 = 3.55 \times 10^{-5}$ sec.$^{-1}$.

Hydrogenation of dibenzyl carbethoxy phosphate in dry ethanol in the presence of a 10% palladium catalyst (on carbon powder) yielded after several hours shaking at 30–40 lbs./sq. in. pressure of hydrogen an equivalent amount of carbon dioxide (collected in barium hydroxide). Similar results were obtained by treatment of the material with barium iodide in acetone,[6] and hydrogen bromide in acetic acid.[7]

Acknowledgment.—The authors are indebted to Dr. S. Pinchas for the infrared measurements. This investigation was supported in part by grant RG-5842 from the National Institutes of Health, U. S. Public Health Service.

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Potential Inhibitors of Cancerous Growth. III. Dibenzyl Acetals as Synthetic Intermediates

J. H. Jordaan and W. J. Serfontein

Department of Organic Chemistry, University of Pretoria, Pretoria, Republic of South Africa

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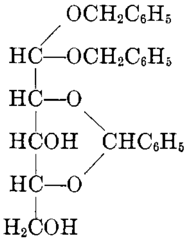
In the attempted synthesis of N,N-bis(2-chloroethyl)-3,5-cyclophosphamido-D-ribose, the corresponding dimethyl acetal[1] was hydrolyzed in dilute mineral acid. Although the cyclic phosphamide structure was apparently retained, the removal of the acetal grouping was unsatisfactory under these conditions. In a typical run, using 0.01 *N* hydrochloric acid in 50% aqueous dioxane, the amount of liberated aldehyde, estimated by the quantitative Benedict procedure, initially increased to 70% of the calculated value and then decreased for some unknown reason.

In view of the relative acid lability of cyclic phosphamides[2] and certain phosphate esters,[3] it seemed desirable to investigate the possibility of using an aldehyde blocking group in the above synthesis which could be removed by some reaction that does not involve the use of acid. The cleavage of O- and N-benzyl compounds by catalytic hydrogenation is a well known and widely used reaction in other fields for similar purposes.[4,5] In the carbohydrate field the cleavage of benzyl β-D-glycosides with hydrogen and metal catalysts has been described.[6] The dibenzyl acetal derivatives of D-ribose therefore appeared to be suitable intermediates for our projected synthesis, particularly in view of the reported stability of phosphate esters toward hydrogenolysis.[7] However, the dibenzyl acetals of D-ribose and its derivatives do not appear to have been described or used as synthetic intermediates. We have, therefore, prepared the dibenzyl acetal of D-ribose as well as that of D-ribose tetraacetate and 2,4-O-benzylidene-D-ribose.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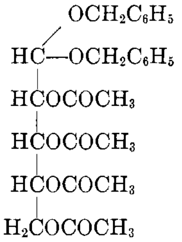
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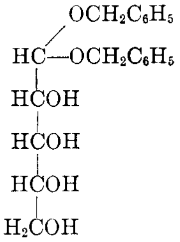
III

In order to determine the suitability of dibenzyl acetals as synthetic intermediates, we have studied the behavior of these compounds toward hydrogenation. By choice of a suitable catalyst,[6] O-benzyl groups can be removed selectively by hydrogenation. In the case of the above-mentioned dibenzyl acetals, 10% palladized charcoal was found to be a suitable catalyst for the preparation of the corresponding free aldehyde compounds by hydrogenolysis.

Experimental[18]

2,4-O-Benzylidene-D-ribose dibenzyl Acetal (I).—Yellow mercuric oxide (3.24 g., 15 mmoles) and anhydrous calcium sulfate (5 g.) were added to a solution of 2,4-O-benzylidene-D-ribose di-*n*-propyl dithioacetal[9] (1.86 g., 5 mmoles) in 68 ml. of pure anhydrous benzyl alcohol in a 500-ml. three-necked flask fitted with a mercury-sealed mechanical stirrer and a calcium chloride tube. The mixture was stirred vigorously with the flask submerged in a water bath maintained at 70°. A solution of 3.4 g. of mercuric chloride in 68 ml. of anhydrous benzyl alcohol was added slowly from a dropping funnel over a period of 5 min. Stirring was continued for a further 3 hr., the mixture filtered under suction onto 0.5 g. of yellow mercuric oxide, and the residue washed thoroughly with anhydrous benzyl alcohol. The benzyl alcohol was then removed from the combined filtrates as completely as possible in a rotary vacuum evaporator (0.5 mm., 65°). The residue was taken up in 100 ml. of chloroform, filtered, and washed with five 100-ml. portions of 10% aqueous potassium iodide and then with water until the washings were free from iodide ions. The chloroform solution was then dried over anhydrous sodium sulphate and evaporated to dryness. The remaining oil crystallized immediately on addition of 50 ml. of dibutyl ether. The crystals were filtered off and recrystallized from dibutyl ether; yield 1.6 g. (73%), m.p. 96–97°, $[\alpha]^{20}\text{D}$ +18.6 (*c* 8.75, methanol); $\lambda_{\max}^{\text{CH}_3\text{OH}}$ 258 mμ (a_m 570); $\lambda_{\max}^{\text{KBr}}$ 2.93, 9.05 μ.

Anal. Calcd. for $C_{26}H_{28}O_6$: C, 71.55; H, 6.46. Found: C, 71.34; H, 6.34.

Hydrogenolysis of 2,4-O-Benzylidene-D-ribose Dibenzyl Acetal.—Two grams of 10% palladized charcoal[10] was saturated with hydrogen in 50 ml. of methanol. A solution of 2,4-O-benzylidene-D-ribose dibenzyl acetal (200 mg.) in 10 ml. of methanol was added and the hydrogenation continued. After approximately 3 hr., the calculated volume of hydrogen had been taken up. The catalyst was filtered off, washed with four 25-ml. portions of

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[8] Microanalyses were performed by the Microanalytical Section of the South African Council for Scientific and Industrial Research. Spectra of the compounds were measured with a Beckman DK 2 recording ultraviolet spectrophotometer and a Perkin-Elmer 21 infrared spectrophotometer. Paper chromatograms were run on Whatman no. 1 paper using acetone-butanol–water (7:2:1), butanol–acetic acid–water (4:1:5), butanol–pyridine–water (6:4:1), and water-saturated butanol as mobile phases.

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[10] A. I. Vogel "Practical Organic Chemistry," 3rd ed., Longmans. Green and Co., London, 1956, p. 950.

methanol, and then with five 10-ml. portions of distilled water. The combined filtrate was concentrated in vacuum at 40° and traces of water removed from the residue by repeated evaporation *in vacuo* with small quantities of absolute ethanol. Paper chromatography using acetone–butanol–water (2:2:1) as mobile phase revealed the presence of a high concentration of D-ribose (R_f 0.41) as well as traces of two nonreducing components (R_f 0.33 and 0.73) which could be revealed by periodic acid–benzidine coloration. Confirmation of the identity of the main component as D-ribose was obtained by means of comparative paper chromatography employing various other mobile phases as well as by conversion of the crude oily product into D-ribose di-*n*-propyl dithioacetal[11] (m.p. 81–82°).

2,3,4,5-Tetra-O-acetyl-D-ribose Dibenzyl Acetal (II). (a).—2,3,4,5-Tetra-O-acetyl-D-ribose diethyl dithioacetal[12] (6.37 g., 15 mmoles) was demercaptalated in the presence of yellow mercuric oxide (9.72 g., 45 mmoles), anhydrous calcium sulfate (15 g.), and anhydrous benzyl alcohol (100 ml.) by the addition of a solution of mercuric chloride (10.2 g., 37.5 mmoles) in 200 ml. of benzyl alcohol as described previously. After removal of the chloroform an oily residue was obtained. Traces of benzyl alcohol were removed by repeatedly dissolving the product in 25 ml. of ethanol and precipitating the oil with 400 ml. of water at 40°. Finally the product was repeatedly evaporated to dryness with small quantities of absolute ethanol to remove traces of water. The oily product, dried at 50° and 0.5 mm. for 3 hr., was soluble in methanol, ethanol, chloroform, ether, etc., and insoluble in water and petroleum ether. $[\alpha]^{20}D + 11.2$ (c 10, methanol); $\lambda_{max}^{CH_3OH}$ 258 mμ (a_m 346); λ_{max}^{film} 5.72, 8.20, 9.52 μ.

Anal. Calcd. for $C_{27}H_{32}O_{10}$: C, 62.78; H, 6.25. Found: C, 63.88; H, 6.32.

After unsuccessful attempts to purify the material by crystallization, the product was further characterized by conversion into the crystalline D-ribose dibenzyl acetal by deacetylation.

(b).—D-Ribose di-*n*-propyl dithioacetal[11] was acetylated as described by Zinner[12] for other D-ribose dithioacetals and 2,3,4,5-tetra-O-acetyl-D-ribose di-*n*-propyl dithioacetal obtained as an oil which could not be crystallized. Upon demercaptalation of the product in benzyl alcohol as described previyusly, 2,3,4,5-tetra-O-acetal-D-ribose dibenzyl acetal was obtained as an oil and was shown to be identical to the product obtained from 2,3,-4,5-tetra-O-acetyl-D-ribose diethyl dithioacetal (a), by infrared spectroscopy.

D-Ribose Dibenzyl Acetal (III).—2,3,4,5-Tetra-O-acetyl-D-ribose dibenzyl acetal (7 g.) was dissolved in 90 ml. of anhydrous methanol in a 250-ml. round-bottomed flask fitted with a reflux condenser and a calcium chloride drying tube. Barium methylate solution (3 ml., 1.7 *N*) in anhydrous methanol was added, the mixture shaken well, and heated under reflux on a water bath for 2 hr., cooled to room temperature, and carbon dioxide bubbled through. The precipitated barium carbonate was filtered off and the yellow filtrate decolorised with activated charcoal. The solution was taken to dryness *in vacuo* at 40° and the oily residue redissolved in 50 ml. of hot benzene. Upon concentration of the benzene solution the product crystallized. A seeding crystal was retained and the product recrystallized from benzene; yield 3.0 g. (96%); m.p. 91–92°; $[\alpha]^{20}D + 10.0$ (c 10, methanol); $\lambda_{max}^{CH_3OH}$ 258 mμ (a_m 325); λ_{max}^{KBr} 2.94, 9.60 μ.

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.39; H, 7.12.

Hydrogenolysis of D-Ribose Dibenzyl Acetal.—D-Ribose dibenzyl acetal was hydrogenated in the presence of 2 g. of palladized charcoal in 60 ml. of methanol. After 4 hr. 32 ml. of hydrogen had been consumed (calcd. 32.18 ml.; press., 651.6 mm.; temp., 20°). The catalyst was filtered off and the filtrate taken to dryness *in vacuo*. The residue (77 mg., 90% as D-ribose) consisted of a viscous oil. The material was shown to be practically pure D-ribose by comparative paper chromatography using various mobile phases and by conversion into the crystalline D-ribose di-*n*-propyl dithioacetal (m.p. 81–82°).

Acknowledgment.—The authors are indebted to the African Explosives and Chemical Industries Ltd. for a research grant and to the South African Atomic Energy Board for financial Assistance.

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The Halogenation of 8-Hydroxy- and 8-Methoxyacridizinium Salts[1]

C. K. BRADSHER AND R. C. CORLEY

Department of Chemistry, Duke University, Durham, North Carolina

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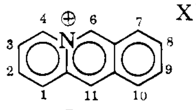
The aromatic nature of the acridizinium ion (I) results in an extensive delocalization of the positive charge. A consequence is that the system undergoes nucleophilic reactions,[2] but does not easily undergo electrophilic substitution. It has been reported[3] that the related quinolizinium iodides (II) react with bromine in acetic acid to yield dibromoiodides ($R^+IBr_2^-$) rather than substitution products.[4] The present communication describes the first examples of the electrophilic substitution of an acridizinium derivative, the halogenation of 8-hydroxy (III)- and 8-methoxyacridizinium (IV) salts.

The bromination of 8-hydroxyacridizinium bromide (III)[5] was carried out in refluxing acetic acid, using a onefold molar excess of bromine. The product (68% yield) had the composition of a monobromination product. Analogy suggested that bromination had occurred at the 7-position, and the synthesis of the 7-bromo-8-hydroxyacridizinium ion was undertaken. The bromination of 2-bromo-3-methoxytoluene[6] (VII) with N-bromosuccinimide gave crude 2-bromo-3-



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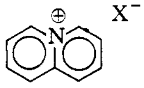

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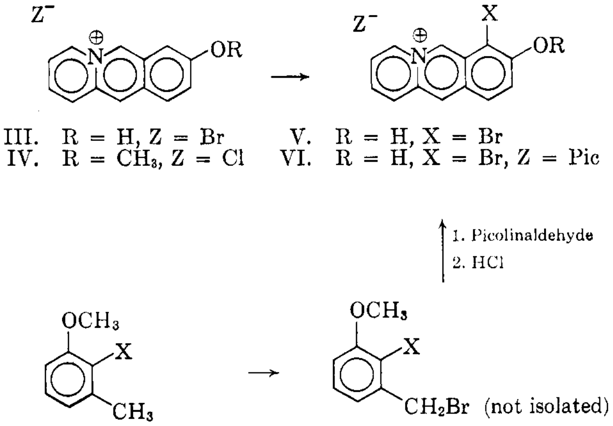

III. R = H, Z = Br
IV. R = CH₃, Z = Cl
V. R = H, X = Br
VI. R = H, X = Br, Z = Pic

VII. X = Br
VIII. X = Cl
IX. X = Br
X. X = Cl

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