Summary

Aryl esters of *p*-toluenesulfonic acid when refluxed in toluene with arylmagnesium halides give sulfones and phenols. The reaction under like conditions with a large excess of alkylmagnesium halides gives some phenol, the aryl-alkyl sulfide and unidentified compounds which are probably sulfones formed by rearrangement.

AMES, IOWA

[CONTRIBUTION FROM THE POLARIMETRY SECTION, BUREAU OF STANDARDS, UNITED STATES DEPARTMENT OF COMMERCE[1]]

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. X.[2] THE CHLORO-, BROMO- AND IODO-ACETYL DERIVATIVES OF LACTOSE

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When it was shown in Part I[3] that the rotation of the end asymmetric carbon atom of a halogeno-acetyl aldose is approximately a constant quantity, namely, one of the coefficients A_F, A_{Cl}, A_{Br} or A_I, for nearly all the aldoses, it was stated that the value of A_{Cl} for chloro-acetyl lactose that was derived from Bodart's record of the specific rotation of this substance in chloroform ($[\alpha]_D = +72$) "is somewhat low and should be reëxamined." This revision has now been made and it has been found that Bodart's rotation is much too low, the correct $[\alpha]_D$ being $+84$, in good agreement with the calculated value. The specific rotation of carefully purified bromo-acetyl lactose has likewise been re-measured and found to be 109°, which is somewhat larger than previous determinations (105°) and agrees closely with the calculated value. The rotation of pure iodo-

TABLE I

THE VALUE OF THE QUANTITY A, THE ROTATION OF THE END ASYMMETRIC CARBON ATOM, FOR CHLORO-, BROMO- AND IODO-ACETYL LACTOSE

Lactose	Mol. wt.	$[\alpha]_D^{20-5}$ in $CHCl_3$	$[M]_D$	Rotation[a] of end carbon	A for corresponding derivative of	
					Cellobiose	Glucose
α-Chloro-acetyl	655	+ 84	+ 55,000	+38,100(A_{Cl})	+39,000	+40,200
α-Bromo-acetyl	699	+109	+ 76,200	+59,300(A_{Br})	+58,300	+60,700
α-Iodo-acetyl	746	+137	+102,200	+85,300(A_I)	+85,200	+87,800[b]

[a] $A = [M]_D - 16{,}900$. This number is the value of $B_{lactose}$ from the rotations of the alpha and beta forms of lactose octa-acetate (see Part I, p. 464).

[b] This value, which is somewhat larger than that recorded in Part I (+85,600) is obtained from the $[\alpha]_D$ of iodo-acetyl glucose in chloroform (+237), recently published by D. H. Brauns [THIS JOURNAL, **47,** 1280 (1925)].

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[1] Published by permission of the Director of the Bureau of Standards.

[2] Part IX was published in THIS JOURNAL, **47,** 872 (1925).

[3] *Ibid.*, **46,** 462 (1924); see also some corrections, *ibid.*, **46,** 2592, Footnote 5 (1924).

acetyl lactose, which has not previously been recorded, although the compound was prepared in 1912 by W. Sloan Mills, has been found to be $[\alpha]_D = +137$, in good agreement with that calculated. The newly measured rotations of these three halogeno-acetyl lactoses and the resulting values of the A coefficients are recorded in Table I. The values of A agree closely with those previously obtained from the rotations of the corresponding derivatives of cellobiose and glucose,[3] which proves that the halogeno-acetyl derivatives of lactose follow closely the generalization that was advanced in Part I. The positive values of A for these halogeno-acetyl sugars indicate that the substances are alpha forms, as was previously mentioned in Part I.

It seems very probable that α-fluoro-acetyl lactose, a substance that is now unknown, will be found to have the rotation that can be calculated in the usual manner by aid of the coefficient $A_F = +9{,}800$, which was found in Part I from the rotations of the fluoro-acetyl derivatives of xylose, glucose and cellobiose that D. H. Brauns has prepared. Thus, $[\alpha]_D = (B_{\text{lactose}} + A_F) \div \text{mol. wt.} = (16{,}900 + 9{,}800) \div 638 = +42°$ for fluoro-acetyl lactose in chloroform.

The rotations that may be expected for the corresponding β-halogeno-acetyl lactoses can be calculated similarly. Thus, for β-chloro-acetyl lactose the calculated value is $[\alpha]_D = (B_{\text{lactose}} - A_{\text{Cl}}) \div \text{mol. wt.} = (16{,}900 - 38{,}100) \div 655 = -32°$ in chloroform.

Experimental Part

Acetylation of Lactose

Lactose octa-acetate, the material from which the halogeno-acetyl lactoses were prepared, was made by heating to a temperature near boiling 100 g. of commercial milk sugar (α-lactose monohydrate) with 600 cc. of acetic anhydride (96% strength) and 300 cc. of pure, dry pyridine, during half an hour, pouring the cooled solution into about 5 liters of ice water and washing the precipitated acetate with ice water. The granular, white material was filtered off, washed with ice water and dried in the air; yield, 168 g., or 89%. The rotation of the substance ($[\alpha]_D = +21$ in $CHCl_3$) indicates that it is a mixture of the α- and β-lactose octa-acetates, the beta form predominating slightly. It may be used without further purification for preparing the halogeno-acetyl lactoses in good yield and will be referred to as crude lactose octa-acetate.

Preparation of α-Chloro-acetyl Lactose ($C_{12}H_{14}O_{10}(C_2H_3O)_7Cl$)

Twenty g. of crude lactose octa-acetate was dissolved in 100 cc. of chloroform, 10 g. of phosphorus pentachloride and 5 g. of anhydrous aluminum chloride were added and the mixture was gently boiled 1.5 hours, after which it was cooled, washed thrice with ice water, dried with calcium chloride and evaporated under reduced pressure to about 25 cc. After the addition of 300 cc. of ether, crystallization of chloro-acetyl lactose took place rapidly; yield, 10 g., or 50%. The colorless needles gave $[\alpha]_D^{23} = +79°$ in chloroform. After four recrystallizations from chloroform and ether, $[\alpha]_D^{25} = +83.8$ (1.0318 g. of substance made up to 100 cc. of solution in pure chloroform rotated sodium light 5.19 to the right at 25°, the tube length being 6 dcm.). After another recrystallization, $[\alpha]_D^{22.5} = +84.0$ (0.9088 g. of substance, 100 cc. of solution in chloroform, 6dcm.

tube; rotation, 4.58 to the right). The average value, $[\alpha]_D^{20-5} = +83.9$, is accepted for the range 20–25° in dilute chloroform solution. The substance melts at 120–121° to a colorless liquid, which slowly decomposes. It is a very stable halogeno-acetyl sugar, as a sample of the crystals after six weeks' standing in a loosely stoppered bottle was unchanged, showing $[\alpha]_D^{22} = +84.4$ in chloroform (0.4895 g. of substance, 50 cc. of solution in chloroform, a 6dcm. tube; rotation, 4.96 to the right) and $[\alpha]_D^{23} = +68.2$ in benzene (0.4823 g. of substance, 50 cc. of solution in benzene, a 6dcm. tube; rotation, 3.95 to the right).

The only previous record of its rotation in chloroform is that of Bodart,[4] who found $[\alpha]_D^{20} = +72$ for a preparation melting at 119–121°. In benzene, E. Fischer and E. F. Armstrong[5] found $[\alpha]_D^{20} = +73.5$ for a material melting at 118–120° and $[\alpha]_D^{20} = +76$ for one melting at 57–59°, which they supposed to be an isomeric form. We have not met this supposed isomer of low melting point and our rotation in benzene for pure chloro-acetyl lactose is considerably different from either of Fischer and Armstrong's values.

On one occasion, upon the addition of petroleum ether to the mother liquor of an original crystallization of α-chloro-acetyl lactose, which had been prepared from 20 g. of crude lactose octa-acetate, there slowly separated about 1 g. of a crystalline substance in the form of prisms which showed $[\alpha]_D^{25} = +71.7$ in chloroform, melted at 160° and gave a strong chlorine reaction with silver nitrate. It seems to be a new chlorine derivative of lactose octa-acetate and is being examined further.

Preparation of α-Bromo-acetyl Lactose ($C_{12}H_{14}O_{10}(C_2H_3O)_7Br$)

The substance was prepared from crude lactose octa-acetate and a 40% solution of hydrogen bromide in glacial acetic acid according to E. Fischer and H. Fischer's directions,[6] except that the temperature was kept low by an ice-bath in an effort to increase the yield. However, the same yield that they found was obtained, 80–85%. Two crystallizations from chloroform by the addition of ether were sufficient for purification to constant rotation, which was $[\alpha]_D^{23} = +108.7$ (1.0118 g. of substance made up to 100 cc. of solution in pure chloroform rotated sodium light in a 6dcm. tube 6.60° to the right at 23°). It melted at 145° with decomposition. E. Fischer and H. Fischer record $[\alpha]_D^{22} = +104.9$ in chloroform; m. p., 141–142°. Ditmar[7] records $[\alpha]_D^{14} = +108.17$ in chloroform; m. p., 138°.

Preparation of α-Iodo-acetyl Lactose ($C_{12}H_{14}O_{10}(C_2H_3O)_7I$)

Ten g. of crude lactose octa-acetate was dissolved in 50 cc. of a 20% solution of hydrogen iodide in glacial acetic acid and the solution was kept at room temperature (20–25°) for 45 minutes. On pouring the solution into ice water a yellow precipitate separated. It was filtered off, dissolved in chloroform and the solution washed with dil. sodium thiosulfate solution, which decolorized it, and then washed again with ice-water. It was dried with calcium chloride and evaporated under reduced pressure to about 10 cc. On the addition of ether, crystallization took place immediately; yield, 6.5 g., or 59%. Recrystallization from chloroform by the addition of ether did not change the rotation, which was $[\alpha]_D^{23} = +136.9°$ (0.9475 g. of substance made up to 100 cc. of solution in pure chloroform rotated sodium light in a 6dcm. tube 7.78 to the right at 23°). The iodine percentage was found to be 17.3 in comparison with 17.01 calculated for iodo-acetyl lactose (0.1730 g. of substance yielded 0.0516 g. of silver iodide). The

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[4] Bodart, *Monatsh.*, **23**, 5 (1902).

[5] Fischer and Armstrong, *Ber.*, **35**, 833 (1902).

[6] E. Fischer and H. Fischer, *Ber.*, **43**, 2521 (1910).

[7] Ditmar, *Monatsh.*, **23**, 865 (1902).

melting point was 145° with decomposition. W. Sloan Mills,[8] who first prepared iodo-acetyl lactose, found a melting point of 142°, but did not record a rotation.

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Summary

The specific rotation of pure iodo-acetyl lactose has been measured, and the specific rotations of chloro- and of bromo-acetyl lactose have been remeasured; all have been found to agree with the theoretical requirements.

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[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO AND THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE]

THE MERCURATION OF METHYLENE BLUE[1,2]

BY LYMAN CHALKLEY, JR.

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Introduction

In the course of the work on tuberculosis which is being carried out by the Sprague Institute[3] it was early found that tubercle bacilli are readily stained in vitro by methylene blue and a few closely related compounds.[4] It was also shown that tubercle bacilli were quite sensitive to poisoning by mercury salts.[5] Since the discovery of these reactions various attempts have been made to prepare an organic mercury derivative of methylene blue.

A double salt of methylene blue and mercuric chloride is mentioned in the literature.[6] Dr. Sidney M. Cadwell[7] purified this substance and obtained it in a well crystalline form, which Dr. Louis M. Larson[7] showed by analyses to have the formula, $C_{16}H_{18}N_3ClS.HgCl_2$. Moreover, Larson showed that it was a double salt by extracting mercuric chloride with ether from its aqueous solution.[7] Cadwell tried to mercurate methylene-

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[8] W. Sloan Mills, *Chem. News*, **106**, 165 (1912).

[1] This is an abstract of a portion of a dissertation submitted by the author in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago.

[2] Read at the New Haven meeting of the American Chemical Society, April, 1923.

[3] See the series of "Studies on the Biochemistry and Chemotherapy of Tuberculosis," *J. Infectious Diseases*. The first article is by Wells, **11**, 349 (1912).

[4] Corper, *ibid.*, **11**, 373 (1912). DeWitt, *ibid.*, **12**, 68 (1913); **13**, 378 (1913); **14**, 498 (1914). Sherman, *ibid.*, **12**, 249 (1913).

[5] DeWitt and Sherman, *ibid.*, **15**, 245 (1914).

[6] Koch, *Ber.*, **12**, 594 (1879).

[7] Private reports to the Sprague Institute in the hands of Dr. DeWitt.