THE ISOLATION AND SYNTHESIS OF THE METHYL ESTER-METHYL α-GLYCOSIDE OF 3-O-β-D-GLUCURONOSYL-N-ACETYL-D-GLUCOSAMINE (HYALOBIURONIC ACID)[1]

Sir:

Polysaccharide components of animal connective tissue, such as hyaluronic acid, chondroitin sulfate and dermatan sulfate, are built of alternate units of uronic acid and hexosamine linked at positions 4 and 3, respectively. Isolation of a 3-*O*-β-D-glucuronosyl-hexosamine disaccharide, chondrosin, from chondroitin sulfate was reported already in 1914,[2] whereas a similar disaccharide, 3-*O*-(β-D-glucopyranosyluronic acid)-2-amino-2-deoxy-D-glucose (hyalobiuronic acid) (I) recently has been isolated from hyaluronic acid.[3,4] We wish to report the first synthesis of this type of disaccharide, isolated as the fully acetylated methyl ester-methyl-α-glycoside of I, namely, methyl 3-*O*-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)-2-acetamido-4,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside (II). The same compound II was obtained directly by degradative methanolysis of hyaluronic acid, then by acetylation, and from hyalobiuronic acid (I), by glycoside formation and acetylation.

Dried hyaluronic acid (1.10 g.) from human umbilical cord,[5] was refluxed with 6% methanolic hydrochloric acid for 24 hr. The resulting sirup, treated with pyridine and acetic anhydride gave, after purification by chromatography on silicic acid, 0.76 g. of crystalline material. Recrystallization afforded 0.22 g. of II, m.p. 236–238°, $[\alpha]^{26}D$ +30° (*c* 0.68, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{37}O_{17}N$: C, 49.13; H, 5.87; N, 2.20; OCH_3, 9.77. Found: C, 49.19; H, 5.95; N, 2.35; OCH_3, 10.36. Hydrolysis of *II* with barium methylate in methanol at 0° gave methyl 3-*O*-(β-D-glucopyranosyluronic acid)-2-acetamido-2-deoxy-α-D-glucopyranoside (III) in 95% yield, m.p. 207–210°, $[\alpha]_D$ +31° (*c* 0.74, CH_3OH). *Anal.* Calcd. for $C_{15}H_{15}O_{12}N \cdot H_2O$: C, 41.96; H, 6.34. Found: C, 41.94, H, 6.40. Esterification of III with diazomethane or methanolic hydrochloric acid afforded IV, identical with the compound described below. 3-*O*-(β-D-glucopyranosyluronic acid)-2-acetamido-2-deoxy-D-glucose,[6] obtained by *N*-acetylation of I, was refluxed with 1.5 *N* methanolic hydrochloric acid and gave, after purification by chromatography on silicic acid, methyl 3-*O*-(methyl β-D-glucopyranosyluronate)-2-acetamido-2-deoxy-α-D-glucopyranoside (IV) in 50% yield, m.p. 223–225°, $[\alpha]^{23}D$ +16° (*c* 1.09, CH_3OH). Acetylation of IV gave II in 80% yield.

Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[7] (V) was allowed to react with an excess of (methyl tri-*O*-acetyl-α-D-glucopyranosyluronate) bromide and mercuric cyanide in a mixture of nitromethane and benzene for 2 days. The resulting product was purified by chromatography on silicic acid, heated for 15 min. with 60% acetic acid, and acetylated with acetic anhydride in pyridine solution, to give II in 42% over-all yield, m.p. 237–238°, $[\alpha]^{23}D$ +30° (*c* 0.98, $CHCl_3$), identical with the product described above. *Anal.* Calcd. for $C_{26}H_{37}O_{17}N$: C, 49.13; H, 5.87; OCH_3, 9.77. Found: C, 49.27; H, 5.96; OCH_3, 9.91. Reduction of II with lithium borohydride in tetrahydrofuran, followed by acetylation, gave a product identical with VI, described below.

The product resulting from the reaction of V with equimolecular quantities of tetra-*O*-acetyl-α-D-glucopyranosyl bromide and mercuric cyanide in benzene–nitromethane at 30° for 3 days was deacetylated catalytically with sodium methoxide, and heated with 60% acetic acid. After purification through a charcoal–Celite (1:1) column, methyl 3-*O*-(β-D-glucopyranosyl)-2-acetamido-2-deoxy-α-D-glucopyranoside (VI) was obtained in 35% yield, m.p. 252–254°; $[\alpha]^{27}D$ +44° (*c* 1.00, H_2O). *Anal.* Calcd. for $C_{15}H_{27}O_{11}N$: C, 45.33; H, 6.85. Found: C, 45.88; H, 7.13. Acetylation of VI with acetic anhydride in pyridine solution gave the hexa-*O*-acetyl derivative in 75% yield, m.p. 236–237°, $[\alpha]^{28}D$ +24° (*c* 1.11, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{39}O_{17}N$: C, 49.92; H, 6.05. Found: C, 50.02; H, 6.08.

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(8) On leave of absence from the Weizmann Institute of Sciences Rehovoth, Israel.

DEPARTMENT OF BIOLOGICAL CHEMISTRY AND MEDICINE
HARVARD MEDICAL SCHOOL AND
MASSACHUSETTS GENERAL HOSPITAL ROGER W. JEANLOZ
BOSTON 14, MASS. HAROLD M. FLOWERS[8]

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THE CYCLOADDITION OF "SULFENE" TO KETENE DIETHYLACETAL

Sir:

Sulfenes as reactive intermediates have been proposed by various workers. Diphenylsulfene was suggested as an intermediate in the reaction of diphenyldiazomethane with sulfur dioxide which decomposed to form tetraphenylethylene.[1] Likewise a similar structure was postulated by Kloosterziel and Backer.[2] "Methylenesulfene" ($CH_2=SO_2$) was proposed by Hesse and Reichold[3] as formed by the interaction of diazomethane with sulfur

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(2) H. Kloosterziel and H. J. Backer, *Rec. trav. chim.*, **71**, 1235 (1952).

(3) G. Hesse and E. Reichold, *Ber.*, **90**, 2106 (1957).

dioxide. Recently, Stork and Borowitz[4] and, independently, Opitz and Adolph[5] have formed four-membered-ring sulfones by interaction of enamines and methanesulfonyl chloride in the presence of base, presumably through a sulfene intermediate.

Methanesulfonyl chloride has now been found to react with ketene diethylacetal in the presence of triethylamine to give the cycloaddition product 3,3-diethoxythiacyclobutane-1,1-dioxide (I).[6] The structure of I was confirmed by elemental analysis, molecular weight, infrared and nuclear magnetic resonance spectrometry.

$$CH_2{=}C(OCH_2CH_3)_2 + CH_3SO_2Cl + (CH_3CH_2)_3N \longrightarrow$$

$$\begin{array}{l} CH_2{-}C(OCH_2CH_3)_2 \\ | \quad\quad | \\ SO_2{-}CH_2 \\ \quad I \end{array} + (CH_3CH_2)_3N{\cdot}HCl$$

A solution of methanesulfonyl chloride in ether was added dropwise to a solution of ketene diethylacetal and triethylamine in ether. An immediate precipitate of triethylamine hydrochloride formed. The amine hydrochloride was removed by filtration (96% yield) and the ether solution was evaporated under reduced pressure to give I in 79% yield, m.p. 49–50°. *Anal.* Calcd. for $C_7H_{14}O_4S$: C, 43.30; H, 7.22; S, 16.49; mol. wt., 194. Found: C, 43.59; H, 7.10; S, 16.74; mol. wt., 202. The infrared spectrum of I shows the presence of the sulfone grouping at 7.45 and 8.65 μ and the presence of ether linkages at 9.15–9.25 μ. There were no bands indicative of unsaturation or a carbonyl function. The n.m.r. spectrum (in carbon tetrachloride) is in full agreement with the structure of I. The peak for the six methyl hydrogens was centered at 8.76 τ (relative to tetramethylsilane) and the peak for the four methylene hydrogens of the ethoxy groups was centered at 6.55 τ. A single unsplit peak occurring at 5.93 τ was attributed to the four methylene hydrogens of the ring. The relative areas were 3:2:2. No vinyl protons were detected.

To date, attempts to isolate like products from methanesulfonyl chloride and the following unsaturated systems have been unsuccessful: ethyl vinyl ether, *p*-tolylmercaptoethene, ethoxyacetylene, diphenylketene, ketene-diethylmercaptal, vinylidene chloride and cyclopentadiene. It appears from these results that a facile polarization of the type

$$\left(\rangle C{=}C\langle^{X} \longleftrightarrow \rangle \overset{-}{C}{-}C\langle^{\overset{+}{X}}\right)$$

in the transition state is an important factor in allowing cycloaddition to occur.

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(4) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962).
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(6) ADDED IN PROOF.—The same product has been isolated by Stork and co-workers (private communication).

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

WILLIAM E. TRUCE
JEROME J. BREITER[7]
DONALD J. ABRAHAM
JOHN R. NORELL[8]

(7) Post-doctoral Research Associate.
(8) Phillips Petroleum Co. Fellow, 1961–1962.

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BOOK REVIEWS

Namenreaktionen der organischen Chemie. Ein Beitrag zur Terminologie der organischen Chemie, Biochemie und theoretischen organischen Chemie. By HELMUT KRAUCH and WERNER KUNZ. Dr. Alfred Hüthig Verlag, G.m.b.H., Heidelberg, Germany. 1961. 592 pp. 16 × 23 cm. Price, DM. 46,—.

However objectionable it may be, the custom of referring to organic reactions, even those which are uncommon, simply by the names of the chemists who discovered or developed them, is obviously too convenient and too well established a practice to be discontinued. Yet, it is a fact that the name of a chemist attached to the non-committal word "reaction" hardly conveys any more information about the nature of a reaction than an obsolete, nongeneric trivial name does concerning the structure of a substance. Consequently, it is the central thesis of this book that "name" reactions can be learned more easily, and remembered more effectively, if, along with the proper name, an appropriate descriptive or defining phrase is used which indicates something of the mechanism or nature of the reaction. In view of the great strides in chemical nomenclature that have taken place over the years, owing largely to our vastly increased knowledge of the structure, stereochemistry and conformation of molecules, it would seem all the more imperative to have a similar development of a systematic terminology for specific name reactions. Certainly when one considers the almost staggering number of such reactions, rules and definitions, which are continually being cited in today's literature, the pressing need for a more explicit system of nomenclature for them is all too evident.

In this compilation over 500 recognized name reactions and rules are treated, in alphabetical order, with the amount of discussion in each case being allocated on the basis of relative importance and frequency of use. Each entry opens with a concise definition of the reaction in question, followed by a brief outline of the reaction conditions and a short discussion of its scope and utility. Electronic mechanisms are employed extensively, and numerous examples from the newer as well as from the older literature are cited in over 5,000 references. Happily, a complete author index and a detailed subject index are also provided.

Comparison of the entries given here with the list of name reactions in the Seventh Edition of the "Merck Index," or with the more extensive tabulation in Gowan and Wheeler's "Name Index of Organic Reactions" (Longmans, 1960), discloses comparatively few omissions of any great importance. Thus, the failure to include such less commonly known reactions as the Akabori amino acid reactions, the