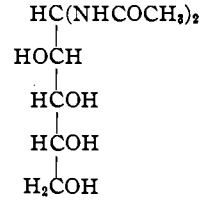
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 297]

Lead Tetraacetate Oxidations in the Sugar Group. VIII.[1] The Preparation and Proof of Structure of N-Acetyl-D-glucofuranosylamine[2]

BY ROBERT C. HOCKETT AND LEONARD B. CHANDLER[3]

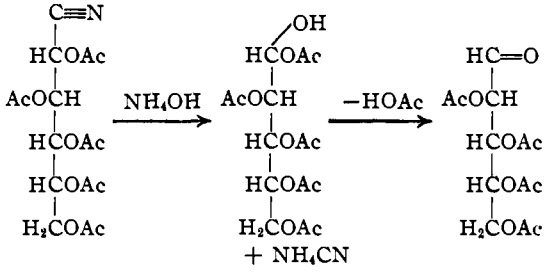
In 1893, Alfred Wohl[4] published his method of degrading an aldose to the next lower member of the series. The action of acetic anhydride and fused sodium acetate upon the D-glucose oxime which had been described by Jacobi[5] produced an acetylated D-gluconic acid nitrile which in turn lost CN^- when treated with an ammoniacal solution of silver oxide. This unusual hydrolysis of a cyanide group as a pseudohalogen instead of to the carboxyl group, produced a compound with one less carbon atom. However, instead of obtaining D-arabinose directly in a free state, Wohl obtained the pentose in a combination with two molecules of acetamide. This product, usually called by the unsatisfactory name "D-arabinose diacetamide," showed a composition and properties consistent with the formula



The open-chain structure was accepted as a matter of course in the era[4] when both sugars and their oximes were regarded as compounds of this type. As the realization grew, however, that the majority of sugar derivatives have cyclic structures,[6] these acetamide condensation products eventually became recognized as representatives of the relatively rare class of acyclic sugar derivatives.[7] The absence of a ring has been further confirmed in several cases by observation of the number of acetyl groups introduced on complete acetylation[8,9] as well as by study of the behavior of the substances toward lead tetraacetate.[10]

It was shown by Maquenne[11] that silver ions are not necessary for the removal of the cyanide group and that aqua ammonia alone will bring about the reaction in one instance. In this Laboratory Maquenne's observation has been confirmed and the effectiveness of 29% ammonia alone has been shown in a number of other cases.[8]

Interesting questions arise concerning the mechanisms of the several reactions which convert pentaacetyl-D-gluconic nitrile into "D-arabinose diacetamide." It is noteworthy that no tendency of free sugars to condense directly with acetamide has been observed either in this Laboratory or elsewhere[7] in spite of a number of efforts to effect such a combination under various conditions. The implication is that some form of sugar other than the pyranose is present at the instant of combination with acetamide. Such a form of D-arabinose could conceivably be the tetraacetyl *aldehydo*-D-arabinose which might be present in a transitory manner, *if* the hydrolysis of nitrile group proceeds at a greater speed than ammonolysis of the acetate groups. The latter, so long as present, will prevent cyclization to furanose or pyranose.



There are two objections to this theory. First, we have been unable to combine pentaacetyl *aldehydo*-D-glucose with acetamide in this Laboratory under any conditions found so far. Second, in the Wohl reaction no acetamide is present until it has been formed by the action of ammonia upon acetate groups in the molecule. We must therefore assume that two acetyl groups are converted to acetamide prior to condensation. If acetyl groups must also serve to prevent cyclization until after condensation has occurred, we must also assume that the groups at the two and three positions undergo ammonolysis more rapidly than those in the four and five positions. Thus 4,5-diacetyl *aldehydo*-D-arabinose may be the true intermediate

(1) Number VII of this series, THIS JOURNAL, **66**, 472 (1944).

(2) Parts of this paper are taken from a thesis submitted by Leonard B. Chandler to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in October, 1939. A similar paper was read before the Division of Organic Chemistry at the Cincinnati meeting of the American Chemical Soicety in April, 1940.

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(4) Wohl, *Ber.*, **26**, 730 (1893): *cf.* Wohl and List, *ibid.*, **30**, 3101 (1897); Wohl, *ibid.*, **32**, 3668 (1899).

(5) Jacobi, *ibid.*, **24**, 696 (1891); *cf.* Rischbieth, *ibid.*, **20**, 2673 (1887).

(6) Irvine and Gilmour, *J. Chem. Soc.*, **93**, 1429 (1908): *cf.* Wolfrom and Thompson, THIS JOURNAL, **53**, 622 (1931).

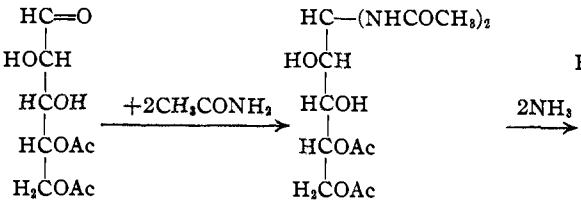
(7) Brigl, Mühlschlegel and Schinle, *Ber.*, **64**, 2921 (1931).

(8) Hockett, THIS JOURNAL, **57**, 2265 (1935); Hockett, Deulofeu, Sedoff and Mendive, *ibid.*, **60**, 278 (1938).

(9) Deulofeu, *J. Chem. Soc.*, 2973 (1932).

(10) Hockett, Dienes, Fletcher and Ramsden, THIS JOURNAL, **66**, 467 (1944).

(11) Maquenne, *Compt. rend.*, **130**, 1402 (1900).



The non-combination of the fully acetylated aldehydo sugars with acetamide may indicate either (1) that removal of acetyls from positions two and three activates the carbonyl in a necessary manner or, (2) that an alkaline medium is necessary for the condensation. If this is true, the "sugar diacetamide" is obviously formed as a result of a delicate balance among the rates of several concurrent reactions.

In either case, fully acetylated *aldehydo*-sugars ought to be converted by aqua ammonia into the open-chain diacetamide condensation products. Deulofeu[9] obtained "L-erythrose diacetamide" by the action of ammonia in ethanol upon triacetyl-aldehydo-L-erythrose and Brigl, Mühlschlegel and Schinle[7] obtained an analogous "D-glucose dibenzamide" by the action of ammonia in methanol upon pentabenzoyl-*aldehydo*-D-glucose. An attempt in this Laboratory, to prepare "D-xylose diacetamide" has resulted in failure. The action of aqua ammonia upon crystalline tetraacetyl-*aldehydo*-D-xylose,[12] has yielded no crystalline products. Neither have we been able to obtain D-gulose oxime or pentaacetyl-D-gulonic nitrile in a crystalline state.

Since "D-glucose diacetamide" had apparently not been described, we undertook to prepare this substance by two methods: the action of 29% aqua ammonia upon pentaacetyl-*aldehydo*-D-glucose[13] and by the action of the same reagent upon hexaacetyl-D-α-glucoheptonic nitrile[14] prepared from D-α-glucoheptose oxime. In both cases the same crystalline product, melting 192–194°, was obtained in yields of 56 and 26% of the theoretical, repectively. Nitrogen analysis showed at once that the substance was not a typical "aldose diacetamide." The analysis supported formulation as an N-acetyl-D-glucosylamine. Such a compound had previously been reported by Brigl and Keppler and by Niemann and Hays.[15] Their product, prepared by the action of ketene upon D-glucopyranosylamine, was shown by oxidation with periodic acid and hypobromite to a dibasic acid with one less carbon atom, to contain a pyranose ring.

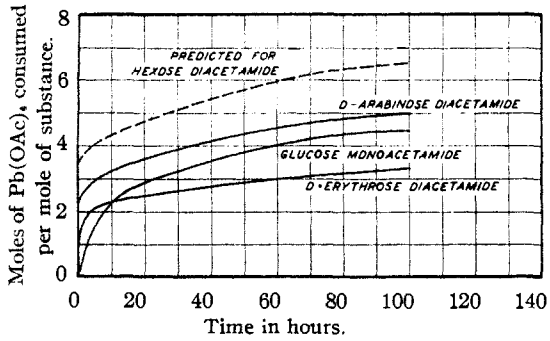


Fig. 1.

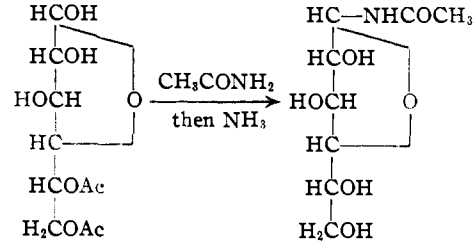
COMPARISON OF N-ACETYL-D-GLUCOSYLAMINES

	Melting point, °C. (uncor.)	Specific rotation
Hockett and Chandler	192–194	+86.9 (*C*, 1.584; H_2O; 25°)
Niemann and Hays (Brigl and Keppler)	255	−22.4 (*C*, 1.24; H_2O)

COMPARISON OF PENTAACETYL-D-GLUCOSYLAMINES

Hockett and Chandler	82.5–84.5	+32.7 (*C*, 1.062; $CHCl_3$; 25°)
Niemann and Hays (Brigl and Keppler)	160–161	+17.7 (*C*, 0.76; $CHCl_3$; 22°)

To determine the nature of the ring in our isomer, we applied the lead tetraacetate oxidation method.[16] Formaldehyde was produced and an oxidation curve of type IV was obtained (Fig. 1). The substance is therefore considered to be an N-acetyl-D-glucofuranosylamine. It is impossible to judge at present whether this product is formed by loss of acetamide from a typical "hexose diacetamide"[17] or by direct condensation of a glycofuranose with acetamide.



We describe D-α-glucoheptose oxime apparently for the first time. It was previously prepared in this Laboratory by Mr. André Laus (unpublished research) in 1936.

We wish to thank Professor M. L. Wolfrom of The Ohio State University for seed crystals of three compounds used in this study and Dr. Morris Zief of this Laboratory for optical measurements on glucoheptose oxime.

Experimental

N-Acetyl-D-glucofuranosylamine from Pentaacetyl-*aldehydo*-D-glucose.—A sample of 6.9 g. (0.0177 mole) of

(12) Wolfrom, Newlin and Stahly, THIS JOURNAL, **53**, 4379 (1931)
(13) Wolfrom, *ibid.*, **51**, 2188 (1929).
(14) *Cf.* Zemplén and Kiss, *Ber.*, **60**, 165 (1927).
(15) Brigl and Keppler, *Z. physiol. Chem.*, **180**, 38 (1929); Niemann and Hays, THIS JOURNAL, **62**, 2960 (1940).
(16) Hockett, Reeder and Nickerson, *ibid.*, **66**, 472 (1944).
(17) *Cf.* Schneider, Sepp and Stiehler, *Ber.*, **61**, 220 (1918); Pacsu, *ibid.*, **58**, 509 (1925); Montgomery, Hann and Hudson, THIS JOURNAL, **59**, 1124 (1937).

pentaacetyl-*aldehydo*-D-glucose (m. p. 116–118°), prepared by the method of Wolfrom[13] was treated with 110 cc. of 29% aqua ammonia at 50–60° for three hours. The solvents were then removed under reduced pressure and the remaining sirup was treated again with 110 cc. of ammonia solution. After concentration to a sirup, the latter was treated with 50 cc. of absolute ethanol which caused separation of fine crystals weighing 2.2 g.; yield, 56%. Recrystallized from about five parts of water with addition of eighteen parts of absolute alcohol, the crystals reached a maximum melting point of 189–191° (uncor.) (with decomposition) when heated at the rate of two degrees a minute. They rotated[18] +86.7° (*C*, 3.937; H_2O; 22.4°). A slow mutarotation[18] to +85.8° occurred in ten days. The compound is moderately soluble in hot water, slightly soluble in ice-cold water and in hot dry methanol, and insoluble in absolute ethanol, ether, pyridine, acetone and chloroform. It reduced Fehling solution only slowly on continued boiling.

Anal. Calcd. for $C_8H_{15}O_6N$: C, 43.3; H, 6.84; N, 6.34. Found: C, 42.4, 42.2, 43.2; H, 6.39, 6.73, 6.26; N, 6.34, 6.49.

Pentaacetyl-D-glucofuranosylamine.—A sample of 1.56 g. (0.00707 mole) of N-acetyl-D-glucofuranosylamine was treated with a mixture of 7.5 cc. (0.0789 mole) of acetic anhydride and 6 cc. (0.0740 mole) of pyridine at 75–80° for three hours. Solution was complete in thirty minutes and then slight discoloration occurred. After three hours, 5 cc. of pyridine was added and the solution was concentrated under diminished pressure (bath temp., 55°) to a sirup. This sirup was several times dissolved in absolute alcohol and reconcentrated to get rid of pyridine. The resulting yellow sirup was dissolved in 10 cc. of acetone and filtered through carbon to decolorize. The filtrate was treated with 10 cc. of dry ether and then with petroleum ether to turbidity. Crystals weighing 1.46 g. (53% of the theoretical) separated in a refrigerator. These prisms, once recrystallized from the same solvents, melted 82.5–84.5° (uncor.) and rotated[18] +32.7° (*C*, 1.620; $CHCl_3$; 25°). They are readily soluble in acetone, chloroform, methanol and ethanol, somewhat soluble in warm water, very slightly soluble in boiling ether or cold water, and insoluble in petroleum ether.

Anal. Calcd. for $C_{16}H_{23}O_{10}N$: N, 3.60; acetyl, 44.3. Found: N, 3.76, 3.77; acetyl, 44.2.

Pentaacetyl-D-glucofuranosylamine was also made by heating at 90° for ninety minutes with four parts of acetic anhydride and one-quarter part of anhydrous sodium acetate. The mixture was poured on ice, and the product was dissolved in chloroform, which was shaken repeatedly with sodium bicarbonate solution, was washed with water, dried over sodium sulfate and evaporated. The sirup remaining was crystallized as described above.

Attempted Condensation of Pentaacetyl-*aldehydo*-D-glucose with Acetamide.—After ten hours of boiling under reflux, a solution of the glucose derivative and of acetamide in chloroform was found to contain the starting materials unchanged.

D-α-Glucoheptose Oxime.—Nineteen grams (0.0906 mole) of D-α-glucoheptose (m. p. 188–190°) made as described by Haworth, Hirst and Stacey,[19] was treated with a methanol solution of 0.129 mole of hydroxylamine overnight at room temperature. A little unreacted sugar remaining the next morning was dissolved by warming a short time on the steam-bath. The solution was then concentrated to a sirup (diminished pressure) and was dissolved in a minimum volume of dry methanol. A crystalline product weighing 17 g. (85% of the theoretical) soon separated which melted at 89–91.5°. Recrystallized from water, it melted at 100–101° (uncor.).

Anal. Calcd. for $C_7H_{15}O_7N$: N, 6.22. Found: N, 6.33, 6.30.

The substance shows a slight mutarotation in water. The initial rotation[18] of −6.3° (*C*, 1.589; H_2O; 22°) reaches 0.9° in seventy hours. Because of the low magnitude of these rotations, no accurate rate constant has been obtained.

Hexaacetyl-D-α-glucoheptonic Nitrile.—Thirteen grams (0.0578 mole) of D-α-glucoheptose oxime (m. p. 89–91°) was treated with 69 cc. of acetic anhydride and 5 g. of anhydrous sodium acetate. Heat was evolved as the oxime dissolved. Finally the mixture was digested for an hour at 100° and then poured on ice. The precipitated gum soon solidified after excess acetic acid had been neutralized with sodium bicarbonate. Filtered, decolorized, and recrystallized from hot ethanol, 13.5 g. of product (51% of the theoretical) was obtained. After recrystallization to constant properties, the elongated prisms melted 85.5–87.5° (uncor.) and rotated[18] +24.3° (*C*, 3.893; $CHCl_3$; 24.8°). Zemplén and Kiss, who prepared the compound by another method,[14] reported a melting point of 112.5–113.5° but a closely agreeing rotation +24.6° at 21°. Possibly two crystal modifications exist.

Anal. Calcd. $C_{19}H_{25}O_{12}N$: C, 49.5; H, 5.44; N, 3.05. Found: C, 49.8, 49.8; H, 5.47, 5.47; N, 3.26. Acetyl determination by the method of Kunz and Hudson[20] resulted in hydrolysis of the cyanide group as well as the acetyls: calcd. for seven CH_3CO, 65.6; found, 63.6 (60 min.), 64.7 (75 min.) and 65.6 (120 min.).

N-Acetyl-D-glucofuranosylamine from Hexaacetyl-D-α-glucoheptonic Nitrile.—A sample of 10.5 g. (0.0229 mole) of the nitrile was heated for three hours at 50° with 125 cc. of 29% aqua ammonia. The solution was then concentrated to a sirup (diminished pressure) which was given a second treatment with ammonia. The sirup obtained by a second concentration was dried by adding absolute alcohol and redistilling solvent-free. The dried sirup was dissolved in a little absolute ethanol and ether was added to turbidity. Crystals separated in a yield of 1.3 g. or 26%. Recrystallized as described above, the small prisms attained a melting point of 192–194° (uncor.) and rotated[18] +86.9° (*C*, 1.584; H_2O; 25.1°). The two samples when mixed showed no depression of melting point.

Anal. Calcd. for $C_8H_{15}O_6N$: C, 43.4; H, 6.84; N, 6.34. Found: C, 43.4, 43.8; H, 6.94, 7.12; N, 6.25.

Rate of Oxidation of N-Acetyl-D-glucofuranosylamine by Lead Tetraacetate.—The measurement was carried out under the standard conditions described by Hockett, Dienes and Ramsden.[21]

Detection of Formaldehyde on Oxidation of N-Acetyl-D-glucofuranosylamine by Lead Tetraacetate.—A sample of 0.10 g. (0.0005 mole) of the glucose derivative was dissolved in 10 cc. of water in a small distilling flask. A volume of 15 cc. of approximately 0.05 molar lead tetraacetate in glacial acetic acid was added from a buret. After ten minutes, a receiver was attached and packed in dry-ice. The liquids were distilled under reduced pressure into this receiver. To the distillate was added 30 cc. of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid (about 0.2 g. of the hydrazine). The precipitate of formaldehyde 2,4-dinitrophenylhydrazone melted at 166° (cor.).

Summary

An N-acetyl-D-glucofuranosylamine has been prepared in two ways: by the action of aqua ammonia upon pentaacetyl-*aldehydo*-D-glucose and upon hexaacetyl-D-α-glucoheptonic nitrile. The physical properties of the new compound are recorded along with those of the corresponding pentaacetyl-D-glucofuranosylamine and of D-α-glucoheptose oxime.

(18) All rotations in this paper refer to specific rotations of the D line of sodium at 20° unless otherwise stated. Concentrations are stated in grams of solute in 100 cc. of solution.

(19) Haworth, Hirst and Stacey, *J. Chem. Soc.*, 2864 (1931); *cf.* Fischer, *Ann.*, **270**, 64 (1892), and Philippe, *Ann. chim. phys.*, **26**, 289 (1912).

(20) Kunz and Hudson, THIS JOURNAL, **48**, 1932 (1926).

(21) Hockett, Dienes and Ramsden, *ibid.*, **65**, 1474 (1943).

The ring structure of N-acetyl-D-glucofuranosylamine has been determined by its behavior when oxidized by lead tetraacetate. The new reactions give further insight into the mechanism of the Wohl degradation of sugars.

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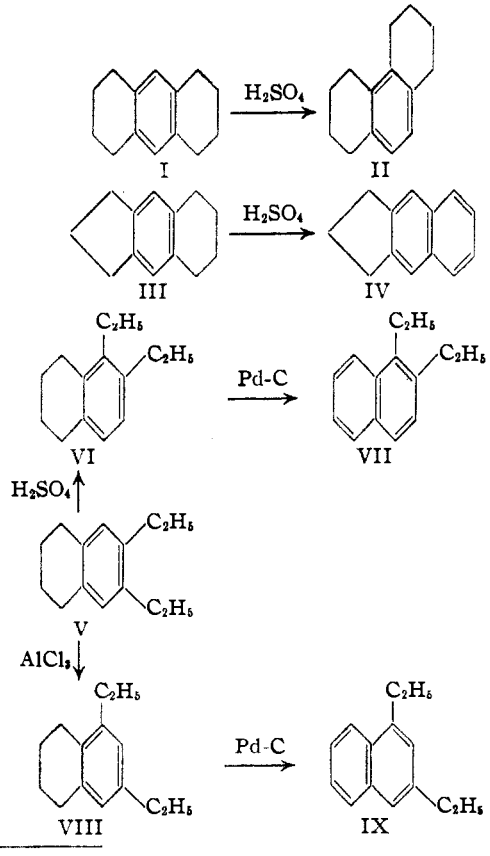
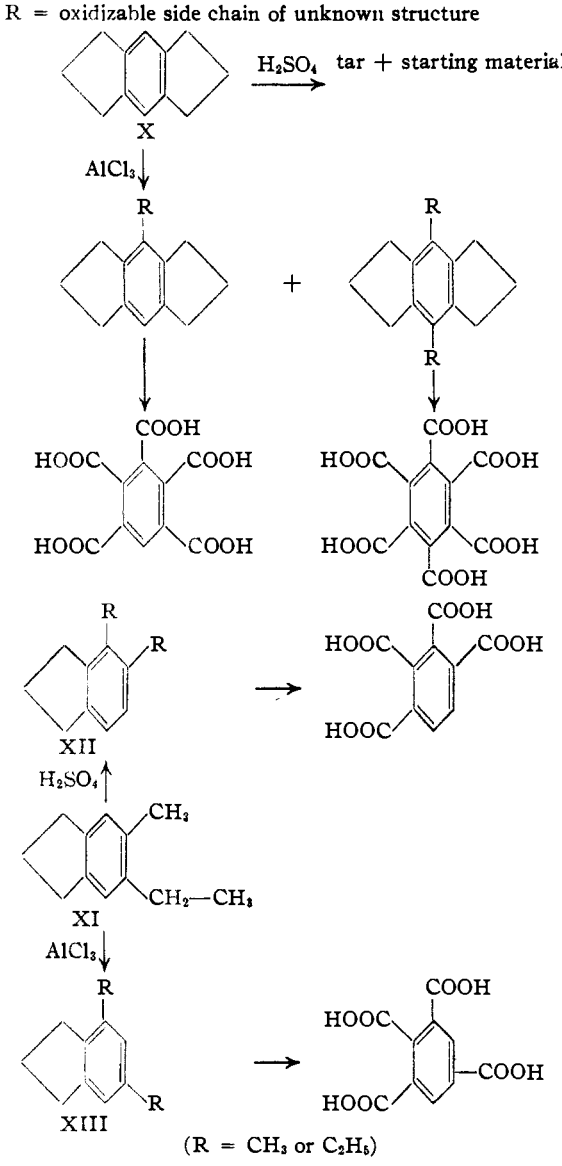
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Jacobsen Rearrangement. VIII.[1] Cyclic Systems; Mechanism

BY RICHARD T. ARNOLD AND RODERICK A. BARNES[2]

For many purposes it is convenient to regard hydrindene and tetralin as *o*-dialkylbenzenes. If this view is accepted, then one might suppose that the tri- and tetramethylene rings in these substances would undergo rearrangement when the molecule is subjected to conditions which bring about a migration of simple alkyl groups. Therefore it was of interest to study the Jacobsen rearrangement of hydrocarbons derived from tetralin and hydrindene. During the course of this investigation octahydroanthracene (I), 5,-6,7,8-tetrahydrobenz[f]indan (III),[3] 6,7-diethyltetralin (V), 5-ethyl-6-methylhydrindene (XI), and *s*-hydrindacene (X) (Ring Index 1459) have been prepared and their reactions with sulfuric acid and aluminum chloride (in three cases) investigated.





The only example of a Jacobsen rearrangement involving a cyclic system which so far has been

(1) VII, THIS JOURNAL, **62**, 2631 (1940). The Authors desire to thank Dr. Lee Irvin Smith for his interest in this work and for the authentic samples of benzene tetracarboxylic acids used as reference compounds.

(2) Abstracted from a thesis by Roderick A. Barnes, presented to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, November, 1943.

(3) Sen-Gupta, *J. Ind. Chem. Soc.*, **16**, 89 (1939).