Advances in Carbohydrate Chemistry

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PREFACE

With this Volume, "Advances in Carbohydrate Chemistry" comes of age through the completion of a series of ten issues. Herein, modern conformational analysis is applied to the carbohydrate field by J. A. Mills (Adelaide). The ever-recurrent and always puzzling subject of nitrogen chemistry is elaborated in a discussion of the glycosylamines and their rearrangement products by G. P. Ellis with J. Honeyman (London) and by J. E. Hodge (Peoria). The preparation and reactivity of the useful glycosyl halides is presented by L. J. Haynes (Edinburgh) and F. H. Newth (Cambridge). W. W. Binkley (Columbus) summarizes the present status of column chromatographic technique as applied to the sugar group. Our series of chapters on the methyl ethers is augmented by G. G. Maher (Clinton, Iowa). Polysaccharide chemistry is represented by a chapter on the non-cellulosic components of wood from the pen of W. J. Polglase (Vancouver) and by one on the biochemically significant subject of heparin from A. B. Foster and A. J. Huggard (Birmingham and Columbus). These, together with an obituary of the late, esteemed Dr. E. G. V. Percival of Edinburgh, complete this Volume and are offered as a contribution to the summarizing of progress in the ever-growing subject of carbohydrate chemistry.

M. L. WOLFROM

Columbus, Ohio

EDMUND GEORGE VINCENT PERCIVAL

1907–1951

The death of E. G. V. Percival at the early age of 43, when he was at the height of his powers as a scientist, was a severe blow to carbohydrate chemistry. He was born on 10th November, 1907, in the Midlands of England at Hinckley in the County of Leicester, being the younger son of Albert Henry and Elizabeth Percival. As a boy, he attended the King Edward VII Grammar School in the neighboring town of Coalville. His school record showed great promise, and in 1925 he entered the University of Birmingham where he studied for the honours degree in chemistry. His undergraduate career was one of unusual brilliance, and it was a foregone conclusion that he would obtain a First Class Honours in Chemistry at the end of the course in 1928. A research career was clearly indicated for him, but, before choosing a field in which to specialize, Percival wisely decided to gain as wide an experience as possible. In the fall of 1928, he joined William Wardlaw's group of workers in the Birmingham University laboratories and took part in work on the chemistry of metallic co-ordination compounds. A year later, he gained a Research Fellowship awarded by the Canadian Pulp and Paper Association, tenable at McGill University, Montreal, and there, in Harold Hibbert's laboratory, he investigated various physicochemical problems concerned with addition compounds of cellulose. Before returning to England, he made an extensive tour of research centers in Canada and the United States, gaining much experience which was of value to him in his later work, and making, as was the case wherever he went, many lasting friendships.

The experience in Montreal had given him a deep interest in carbohydrate chemistry, and this became his main field of work on his return to Birmingham University in October, 1930, as senior research assistant to W. N. Haworth (later Sir Norman Haworth). This period was one of rapid and successful progress, and at this stage he decided to seek a post which would enable him to pursue a career in the academic world. The opportunity came three years later (1933), when he was appointed to a lectureship in organic chemistry in the University of Edinburgh. Here, in the Department presided over by James P. Kendall, F.R.S., Percival settled happily, and during the next 18 years he built up a research school in carbohydrate chemistry which had an international reputation. He found conditions so congenial in Edinburgh that he made no serious attempt to gain promotion by moving elsewhere. In 1934, he married Ethel Elizabeth Kempson, herself a chemist, a graduate of the University of Birmingham where she had been a student in Sir Norman Haworth's laboratories. After her arrival in Edinburgh, she took an active part in the development of Percival's research activities, and assisted in the teaching of undergraduates. She and their two children survive him, and Mrs. Percival is continuing, as a member of the University staff, some of the work initiated by her husband.

Percival entered fully into the scientific and social life of both the University and the City of Edinburgh. He took a keen and sympathetic interest in student welfare and activities, and amongst his University duties was that of Director of Studies. He was elected to membership in the Faculty of Science, and in 1948 was promoted to the status of Reader in the University. Shortly before his death he had been chosen to serve as a member of the Senatus Academicus. He gave his time and energy, with unselfish enthusiasm, to work for various scientific societies. For many years he had been interested in the work of the Pharmaceutical Society and in *British Chemical Abstracts*. He was concerned with work for the Institute of Brewing, he was one of the original pioneers in investigations on the chemistry of marine algal polysaccharides sponsored by the Scottish Seaweed Research Association, and he was an active member of this Association's Chemical Advisory Committee. He served also on the local district committees of the Royal Institute of Chemistry and of the Society of Chemical Industry, and in addition acted for two years as Chairman of the Edinburgh and South East Scotland section of the Royal Institute. He was the local representative in Edinburgh of the Chemical Society (London), and at the time of his death was a member of the Society's Council and of its Committee on Carbohydrate Nomenclature. His help was called for on all special occasions, and in 1948, when the Society of Chemical Industry held its annual general meeting in Edinburgh, and again in 1951, when he was Local Secretary for the Chemistry Section of the British Association for the Advancement of Science, his unselfish and unstinted efforts contributed in large part to the success of the meetings.

It was characteristic of Percival that, to everything he undertook, he brought enthusiasm and intensity of purpose, whether it was in playing tennis or cricket, discussing painting (in which art he was deeply knowledgeable), walking on the Cheviot Hills, or in teaching and research. He had a brain which acted with lightning rapidity, and he had the power to carry through with accuracy (and with every attention to detail) a phenomenal amount of work in a very short time. He was a clear lecturer and expositor, and in consequence he was frequently invited to visit other universities and chemical societies. These visits, especially those which involved traveling, he found highly congenial. He was at his best as a teacher with advanced students of quick perception, who could follow without difficulty the logical but rapid development of his theme. Friendly, generous, sympathetic, and approachable, he was an inspiring leader for postgraduate research workers, who found him full of ideas and suggestions, and marveled at his encyclopedic memory for details. All who had the privilege to work with him and enjoy his friendship will remember especially his kindliness, generosity, and unselfishness, his deep sense of loyalty, and his capacity to see and appreciate the humorous side of everyday happenings.

Percival's outstanding ability was soon recognized, and awards came to him at an early age—Fellowship of the Royal Institute of Chemistry in 1936, the D.Sc. degree of the University of Edinburgh in 1938, and, in 1941, election to the Fellowship of the Royal Society of Edinburgh.

Although Percival's main interest in chemistry lay in the carbohydrate field, his earliest research, carried out under William Wardlaw in Birmingham (1928–1929) was concerned with polynuclear co-ordination compounds of cobalt with amines.[1] During the following year, he held a Research Fellowship in Montreal, working with Hibbert on the constitution of soda-cellulose, the hydrolysis of polysaccharides, and the absorption of aluminum ions on cellulose. It was demonstrated that a chemical compound is formed between the sodium hydroxide and the cellulose, containing about 15% of alkali (or one molecule to each anhydro-D-glucose unit). Investigation of the rates of hydrolysis indicated that the lower rate for cellulose as compared with that of starch is a reflection of the comparative rates of hydrolysis of cellobiose and maltose.[2]

In the following three years (1930–33), working with Sir Norman Haworth, Percival began his studies in structural carbohydrate chemistry, and took part in the early work of the Birmingham School on the investigation of polysaccharides. Some of the most important results he obtained were concerned with the structures of starch and glycogen. Up to this time, strictly chemical evidence was lacking as to the presence of preformed maltose units in starch and glycogen, and concerning the nature of the ring present in the D-glucose residues. Percival developed a method of simultaneous deacetylation and methylation of the acetylated polysaccharides followed by acetolysis of the methyl derivatives. These yielded, amongst other products, a partially methylated maltose. The hexa-*O*-methylbiose was oxidized to the bionic acid and subjected to further methylation. The resulting methyl octa-*O*-methylmaltobionate was then

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(1) E. G. V. Percival and W. Wardlaw, *J. Chem. Soc.*, 1317, 1505, 2628 (1929).

(2) A. C. Cuthbertson, H. Hibbert and E. G. V. Percival, *J. Am. Chem. Soc.*, **52**, 3257, 3448 (1930); H. Hibbert and E. G. V. Percival, *ibid.*, **52**, 3995 (1930).

hydrolyzed and the tetra-*O*-methyl-D-glucopyranose and tetra-*O*-methyl-D-gluconic 1,4-lactone were separated and identified, thus showing that the maltose structure must be present in starch and glycogen. Similar methods were applied to a di-*O*-methylxylan, in which the methoxyl groups were found to be attached to C2 and C3, showing that the linkage occurs at C4 and that the D-xylose is present in the pyranose form.[3] The methylation and hydrolysis technique was further applied to inulin, the methylated derivative of which gave rise to rather labile D-fructofuranose derivatives. In order to avoid unnecessary decomposition, the hydrolysis (after methylation) was carried out using aqueous methanolic oxalic acid, and the yield of tetra-*O*-methyl-D-fructofuranose indicated the presence of one terminal nonreducing D-fructofuranose unit in 32 residues.[4]

One of Percival's major contributions during his Birmingham period was the part he played, in collaboration with other members of the School, in determining the constitution of ascorbic acid (vitamin C). Oxidation studies were carried out which showed that L-threonic acid is one of the products of oxidation, indicating ascorbic acid to be a derivative of L-gulose. The nature of the ring system was investigated by methylation studies, and vitamin C was proved to be the enolic form of 2-keto-L-gulonic 1,4-lactone.[5] Confirmation was obtained for this structure by the synthesis of vitamin C by the same group of workers.

At this point in his career, Percival moved to Edinburgh (1933), where he continued his work in the carbohydrate field. During the succeeding 18 years, his numerous publications covered a wide variety of subjects. From among the early work in Edinburgh may be mentioned the study of the compounds of alkali-metal hydroxides with sugars and polysaccharides, as a result of which he suggested that the alkali–sugar complexes are definite compounds, and indicated how, by methylation, the points of attachment of the added hydroxides could be determined. Compounds of alkali-metal hydroxides with mono-, di-, and poly-saccharides were investigated.[6] The methylation studies resulted in the production of partially methylated sugars whose identification required reference compounds, and Percival proceeded to study various mono-*O*-methylhexoses not previously charac-

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(3) W. N. Haworth and E. G. V. Percival, *J. Chem. Soc.*, 1342, 2850 (1931); 2277 (1932).

(4) W. N. Haworth, E. L. Hirst and E. G. V. Percival, *J. Chem. Soc.*, 2384 (1932).

(5) R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J. Chem. Soc.*, 1270 (1933); R. G. Ault, D. K. Baird, H. C. Carrington, W. N. Haworth, R. W. Herbert, E. L. Hirst, E. G. V. Percival, F. Smith and M. Stacey, *ibid.*, 1419 (1933).

(6) E. G. V. Percival, *J. Chem. Soc.*, 1160 (1934); 648 (1935); E. G. V. Percival and G. G. Ritchie, *ibid.*, 1765 (1936); W. J. Heddle and E. G. V. Percival, *ibid.*, 1690 (1938).

terized; for example, 4-*O*-methyl-D-glucose and 2- and 6-*O*-methyl-D-galactose. He also devoted much attention to the structure of sugar osazones. By the methylation method, he decided that the previous assumption that osazones possess a straight-chain structure was erroneous, and that sugar osazones could exist in a ring form. In the case of D-*arabino*-hexose phenylosazone ("glucosazone"), the ring was shown to be of the 2,6 type. In the course of these studies, the hitherto-unknown 5-*O*-methyl-D-*arabino*-hexose phenylosazone was characterized for the first time by a single methylation of D-*arabino*-hexose phenylosazone, and the work was also extended to include the structures of several new anhydrohexose osazones of the Diels type.[7]

An entirely different approach to the structure of methylated and free sugars was made by the application of Böeseken's method, involving measurements of the conductivity of sugars in boric acid solution. In this way, the respective configurations assigned to the hydroxyl groups on C1 and C2 in α- and β-D-glucose were confirmed, the conductivity being considerably influenced by the *cis* or *trans* arrangement of the hydroxyl groups. The method was extended and applied to such methylated sugars as 3,4,6-tri-*O*-methyl-α-D-mannose, where the hydroxyl groups on C1 and C2 were shown to have the *trans* arrangement.[8]

The main portion of Percival's work in the years following 1936 was concerned with the structure of polysaccharides; in particular, of plant mucilages and seaweed polysaccharides. At this time, the polysaccharides of marine algae had been but little investigated; Percival was among the first in this field and became a recognized authority on the subject. One of the earliest studies he embarked on was that of the structure of agar, which presented an extremely difficult and complex problem. The results of the preliminary work on acetylation and methylation indicated that the basic structure consists of D-galactose units linked directly or indirectly through C1 and C3, as shown by the isolation of the hitherto-unknown 2,4,6-tri-*O*-methyl-α-D-galactose and of an unknown portion giving strong ketose reactions. Later work proved the presence also of 3,6-anhydro-L-galactose, but the complexity of the molecule precluded the solution of the detailed structure at that time. This study also entailed the synthesis of several anhydrogalactose derivatives used in the investigation as reference compounds.[9] At about the same time, work was commenced on other algal

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(7) Elizabeth E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 1398 (1935); 1320 (1937); 750 (1941); E. G. V. Percival, *ibid.*, 1770 (1936); 1384 (1938); 783 (1945); J. R. Muir and E. G. V. Percival, *ibid.*, 1479 (1940); W. J. Heddle and E. G. V. Percival, *ibid.*, 1511 (1940).

(8) H. T. Macpherson and E. G. V. Percival, *J. Chem. Soc.*, 1920 (1937).

(9) E. G. V. Percival and J. C. Somerville, *J. Chem. Soc.*, 1615 (1937); I. A. Forbes and E. G. V. Percival, *ibid.*, 1844 (1939); T. L. Cottrell and E. G. V. Percival, *ibid.*, 749 (1942).

polysaccharides, notably those forming the mucilaginous extracts of *Chondrus crispus* and *Gigartina stellata*, collectively known as Irish moss. The polysaccharides from the two algae are essentially similar, in that both contain a considerable number of ester sulfate groups and consist of galactopyranose residues linked through C1 and C3, a portion of the galactose being in the L-form in the *Chondrus* polysaccharide. The complete elucidation of the structure proved difficult owing to the presence of the sulfate groups which interfere with methylation.[10] In view of these difficulties and of the need for more knowledge of carbohydrate sulfuric esters, Percival then investigated the sulfates of D-glucose and D-galactose, their rates of hydrolysis with reference to the position of the sulfate group in the molecule, and the formation of 3,6- and 5,6-anhydro sugars on alkaline hydrolysis.[11]

With the collaboration of the newly-formed Scottish Seaweed Research Association, Percival commenced a further series of investigations in the marine algal field,[11a] the earlier work being concerned with the development of specific methods of analysis for the various constituents present in seaweed. Procedures were worked out for the estimation of D-mannitol, alginic acid, laminarin, and fucoidin.[12] At the same time, structural studies were instituted on the last three polysaccharides.[13] Laminarin[11a] was shown to consist essentially of (3 → 1) linked β-D-glucose units, and to occur in two forms, a soluble and an insoluble, depending on the species of seaweed used for extraction. In fucoidin,[11a] the principal sugar is L-fucose, along with sulfate groups, and a branched structure was proposed in which 2 → 1-α-L links predominate. Among other seaweed polysaccharides, the xylan from *Rhodymenia palmata* was found to be of unusual interest in that it was shown to contain both (3 → 1) and (4 → 1) linked D-xylose residues as part of the main structure of the polysaccharide. Percival had had previous experience with xylans while investigating the structures of the mucilages

[10] J. Buchanan, Elizabeth E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 51 (1943); E. T. Dewar and E. G. V. Percival, *ibid.*, 1622 (1947); R. Johnston and E. G. V. Percival, *ibid.*, 1994 (1950).

[11] Elizabeth E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 1585 (1938); 874 (1945); E. G. V. Percival and T. H. Soutar, *ibid.*, 1475 (1940); R. B. Duff and E. G. V. Percival, *ibid.*, 830 (1941); 1675 (1947); E. G. V. Percival, *ibid.*, 119 (1945); R. B. Duff, *J. Chem. Soc.*, 1597 (1949).

[11a] See also, T. Mori, *Advances in Carbohydrate Chem.*, **8**, 315 (1953).

[12] M. Christine Cameron, E. G. V. Percival and A. G. Ross, *J. Soc. Chem. Ind.* (London), **67**, 161 (1948); E. G. V. Percival and A. G. Ross, *ibid.*, **67**, 420 (1948); W. A. P. Black, W. J. Cornhill, E. T. Dewar, E. G. V. Percival and A. G. Ross, *ibid.*, **69**, 317 (1950).

[13] E. G. V. Percival and A. G. Ross, *J. Chem. Soc.*, 717 (1950); 720 (1951); J. Conchie and E. G. V. Percival, *ibid.*, 827 (1950); J. J. Connell, E. L. Hirst and E. G. V. Percival, *ibid.*, 3494 (1950).

from the seeds of various members of the plantain family (*Plantago lanceolata*, *Plantago arenaria*, and *Plantago ovata*). All these xylans are complex in structure and contain, in addition to D-xylose, other pentoses, hexoses, and uronic acid residues; for example, the mucilage from *Plantago arenaria* contains D-xylose, L-arabinose, D-galactose, and D-galacturonic acid. The mode of attachment of the uronic acid is not clear, and the structure of the main D-xylopyranose chain includes various types of linkage and is highly branched. In the mucilage from *Plantago lanceolata*, for example, the following types of D-xylose residue were found[14] to occur as building units: D-Xyl*p* 1, 3 D-Xyl*p* 1, 4 D-Xyl*p* 1, ${}^{4}_{2}$D-Xyl*p* 1, ${}^{4}_{3}$D-Xyl*p* 1, and ${}^{3}_{4}$D-Xyl*p* ${}^{2}_{1}$.

Further studies were carried out on the xylans from esparto and from pear cell-wall. In the former, the xylan was shown to be free from L-arabinose and to consist of a singly-branched molecule, the main chain containing about 75 D-xylopyranose units linked through the 4 position, the branching point occurring on C3. For the pear cell-wall polysaccharide, the general structure was found similar, but with the modification that the terminal residue consists of a D-glucuronic acid unit and the main chain is rather longer (*ca.* 115 D-xylopyranose units).[15]

Percival also applied himself to the study of the polysaccharides from lichens, as, for example, the complex product of alkaline extraction of Iceland moss (*Cetraria islandica*). As a result of this work, he concluded that the polysaccharide consists of β-D-glucose residues united by various linkages: 1,2, 1,3, 1,4, and 1,6, and includes also terminal D-galacto- and D-gluco-pyranose end groups. It was not possible to decide whether these linkages all occur in one polysaccharide.[16]

In the later stages of his career, Percival published papers dealing with barley starch[17] and wood starches,[18] the former being found to be, in the main respects, similar to other cereal starches. Fructans also attracted his attention, and those from couch grass and perennial rye grass were particularly investigated; it was shown that the fructan from couch grass has both 2,1 and 2,6 linkages in the molecule, whereas that from rye grass is essentially a 2,6-linked, straight-chain polysaccharide.[19] Finally, mention may be made of the inulin from dahlia tubers, in which the presence of

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(14) J. Mullan and E. G. V. Percival, *J. Chem. Soc.*, 1501 (1940); W. A. G. Nelson and E. G. V. Percival, *ibid.*, 58 (1942); R. A. Laidlaw and E. G. V. Percival, *ibid.*, 1600 (1949); 528 (1950); E. G. V. Percival and I. C. Willox, *ibid.*, 1608 (1949).

(15) S. K. Chanda, E. L. Hirst and E. G. V. Percival, *J. Chem. Soc.*, 1240 (1951).

(16) H. Granichstädten and E. G. V. Percival, *J. Chem. Soc.*, 54 (1943).

(17) I. C. MacWilliam and E. G. V. Percival, *J. Chem. Soc.*, 2259 (1951).

(18) W. G. Campbell, J. L. Frahn, E. L. Hirst, D. F. Packman and E. G. V. Percival, *J. Chem. Soc.*, 3489 (1951).

(19) P. C. Arni and E. G. V. Percival, *J. Chem. Soc.*, 1822 (1951).

D-glucose as an integral part of the molecule was demonstrated and possible structures were suggested[20] in which one D-glucose residue occurred as an end group, linked to D-fructose by a sucrose type of link, whilst the second D-glucose residue was in the middle of the chain, linked through C1 and C3.

Only a few days before his death, Percival took a prominent part in a conference on grass, sponsored by the Nutrition Society, at which he read a paper[21] on the "Carbohydrate Constituents of Herbage." In this paper, he emphasized the importance of the fructans as reserve carbohydrates in the metabolism of the plant, and expressed the opinion that they would be found to play a considerable part in the chemistry of the preservation of grass in the form of silage.

E. L. HIRST
A. G. ROSS

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(20) E. L. Hirst, D. I. McGilvray and E. G. V. Percival, *J. Chem. Soc.*, 1297 (1950).
(21) E. G. V. Percival, *Brit. J. Nutrition*, **6**, 104 (1952).

CONTENTS

The Stereochemistry of Cyclic Derivatives of Carbohydrates

By J. A. Mills, *Department of Biochemistry and General Nutrition, Commonwealth Scientific and Industrial Research Organization, Adelaide, Australia*

Column Chromatography of Sugars and Their Derivatives

By W. W. Binkley, *Department of Chemistry, The Ohio State University, Columbus, Ohio*

Glycosylamines

By G. P. Ellis and John Honeyman, *Department of Chemistry, King's College, University of London, England*

The Amadori Rearrangement

By John E. Hodge, *Northern Utilization Research Branch, Agricultural Research Service, U. S. Department of Agriculture, Peoria, Illinois*

The Glycosyl Halides and Their Derivatives

By L. J. Haynes, *The University, Edinburgh, Scotland* and F. H. Newth, *The University, Cambridge, England*

The Methyl Ethers of the Aldopentoses and of Rhamnose and Fucose

By George G. Maher, *Research Laboratories, Clinton Foods Inc., Clinton, Iowa*

The Methyl Ethers of D-Galactose

By George G. Maher, *Research Laboratories, Clinton Foods Inc., Clinton, Iowa*

Polysaccharides Associated with Wood Cellulose

By W. J. Polglase, *Department of Biochemistry, University of British Columbia, Vancouver, British Columbia, Canada*

CONTENTS

The Chemistry of Heparin

By A. B. Foster, *Chemistry Department, The University, Birmingham, England* and
A. J. Huggard, *Chemistry Department, The Ohio State University, Columbus, Ohio*

THE STEREOCHEMISTRY OF CYCLIC DERIVATIVES OF CARBOHYDRATES*

By J. A. Mills

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Contents

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* This review is based on literature available to the author up to July, 1954.

I. Introduction

The chief aim of this article is to make a comparison between carbohydrates and analogous alicyclic compounds, with emphasis on the stereochemistry of the ring systems involved. In alicyclic chemistry, notable additions have recently been made to our knowledge of the stereochemistry of saturated rings, particularly six-membered rings.[1-9] This new information already has had a considerable impact on carbohydrate chemistry, but has been restricted to a few topics.[2, 5, 8, 10-13] The wider application attempted here will, it is hoped, assist in the coordination of considerable parts of the voluminous and diverse information available about carbohydrates, and may possibly lead to further development of stereochemical theory.

It is of interest to recall the development of the chemistry of terpenoids and steroids. Initially, these compounds were studied as problems in structural chemistry, but it was later realized[14] that terpenoids of established structure provided first-class material for the study of the mechanisms of reactions, their availability in optically active forms being a notable advantage. Stereochemical theory has also greatly benefited in recent years from studies on steroids, largely because of the wider range of structural types available through the complexity of steroid molecules. Carbohydrates also possess the desirable features of optical activity, crystallinity, and availability, and display a diversity in structural types and reactions that cannot be matched in other fields. The writer, whose interests have lain mainly in the alicyclic field, has been greatly impressed by the scope that

(1) C. W. Beckett, K. S. Pitzer and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (1947).

(2) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).

(3) O. Hassel, *Research* (London), **3**, 504 (1950).

(4) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(5) S. J. Angyal and J. A. Mills, *Revs. Pure and Appl. Chem.* (Australia), **2**, 185 (1952).

(6) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(7) O. Hassel, *Quart. Revs.* (London), **7**, 221 (1953).

(8) H. C. Brown, J. H. Brewster and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(9) Further discussions are given by (a) R. B. Turner, in "Natural Products Related to Phenanthrene," L. F. Fieser and Mary Fieser, eds., Reinhold Publishing Corp., New York, N. Y., 3rd Edition, 1949, p. 620; (b) V. Prelog, *J. Chem. Soc.*, 420 (1950); (c) W. Klyne, in "Progress in Stereochemistry," W. Klyne, ed., Academic Press Inc., New York, N. Y., Butterworths Publications Ltd., London, 1954, p. 36.

(10) R. E. Reeves, *J. Am. Chem. Soc.*, **72**, 1499 (1950); and preceding papers in the series.

(11) R. E. Reeves, *Advances in Carbohydrate Chem.*, **6**, 107 (1951).

(12) R. J. Dimler, *Advances in Carbohydrate Chem.*, **7**, 37 (1952).

(13) R. C. Cookson, *Chemistry & Industry*, 223 (1954).

(14) See, for example, W. Hückel, *Die Chemie*, **55**, 227 (1942).