OBITUARY NOTICE.

J. C. E. SIMPSON.

1908—1952.

JAMES CHARLES EDWARD SIMPSON was born in Wallasey, Cheshire, on August 14th, 1908, and died on February 7th, 1952, after a series of operations at Wrexham Hospital.

He was educated at St. Edward's School, Oxford, and at the University of Liverpool where he graduated in 1929, was awarded the Leverhulme Chemistry Prize and the Campbell Brown Fellowship, and began work under Professor (now Sir Ian) Heilbron on researches in the sterol group. These were chiefly concerned with the elucidation of the chemistry of ergosterol, and from studies on the oxidation of α- and β-ergostenol and their derivatives (Heilbron, Simpson, and Wilkinson, *J.*, 1932, 1699; Simpson and Morrison, *J.*, 1932, 1710; Heilbron, Morrison, and Simpson, *J.*, 1933, 302) additional convincing evidence was obtained concerning the nuclear identity of ergosterol and the bile acids (cf. also Heilbron, Simpson, and Samant, *J.*, 1933, 1410). Analysis of bromine-substitution products confirmed the C_{28} formula for ergosterol (Heilbron and Simpson, *J.*, 1932, 2400), and the isolation from the oxidation of ergostanol of a methyl ketone, $C_9H_{18}O$, distinct from the *iso*hexyl methyl ketone obtained from cholesterol under similar conditions, indicated that the additional carbon atom was present in the side chain (*loc. cit.*, p. 1699).

The importance of the researches on ergosterol in which Simpson played a prominent part is made clear in the account given before the Chemical Society in December 1932 (Heilbron, Simpson, and Spring, *J.*, 1933, 626).

In 1933 he was awarded a Commonwealth Fund Fellowship and spent the next two years with Dr. W. A. Jacobs at the Rockefeller Institute for Medical Research, New York. Simpson's earlier experience with sterols stood him in good stead in his collaboration on problems connected with the digitalis sapogenins. The first definite information that this group of sapogenins contains the typical steroid skeleton came with the isolation by Jacobs and Simpson (*J. Biol. Chem.*, 1934, **105**, 501) of Diels' hydrocarbon on selenium dehydrogenation of sarsasapogenin; the same hydrocarbon was obtained by similar treatment of gitogenin (*J. Amer. Chem. Soc.*, 1934, **56**, 1424). Other observations indicated a C_8 side chain in the sapogenins and this correlation of the general structure of sarsasapogenin and gitogenin was extended to that of tigogenin (Jacobs and Simpson, *J. Biol. Chem.*, 1935, **110**, 429).

Simpson became an Assistant Lecturer at King's College, London, on his return from America and began independent work on natural products, beginning with an investigation of Senega root (*J.*, 1937, 730) and the ether-soluble components from sarsaparilla root (Simpson and Williams, *J.*, 1937, 733; 1938, 2040).

Simpson's work between 1938 and 1944 was largely concerned with triterpenes. He showed (Simpson and Williams, *J.*, 1938, 686, 1712) that β-boswellic acid was a β-hydroxy-acid, and that its double bond was in a similar environment to that in α- and β-amyrin. Much effort was devoted to attempts to determine the detailed structure of rings C—E of the β-amyrin group of triterpenes (*loc. cit.*; *J.*, 1943, 477). Continuing his examination of natural products, and making use of chromatography on alumina—then a very novel procedure—he isolated three new alcohols from dandelion root: taraxol, taraxerol, and ψ-taraxasterol (Burrows and Simpson, *J.*, 1938, 2042). The last, together with a precursor, ψ-taraxastanediol, was also isolated from the minor constituents of Manila elemi resin. In this case a further alcohol, maniladiol, was obtained for the first time, whilst the technique for isolating brein was considerably improved (Morice and Simpson, *J.*, 1940, 795; *J.*, 1941, 181). Finally (*J.*, 1944, 283), *Lactucarium germanicum* yielded a new alcohol, germanicol, which was to become of considerable importance in the final elucidation of the stereochemistry of the β-amyrin group of triterpenes.

In 1939 Simpson was appointed to a temporary lectureship in Durham Colleges in the University of Durham. Soon after his arrival he became interested in the chemistry of cinnoline, a heterocyclic system which had been almost completely neglected since the discovery of the first derivative in 1883. Simpson's contribution to cinnoline chemistry was the generalisation of the existing fortuitous syntheses, the determination of the factors affecting the extent of cinnoline formation and hence a mechanism for the process, and, finally, a study of the properties of cinnolines.

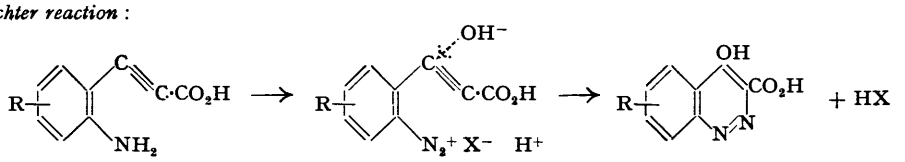
At this time cinnoline derivatives had been obtained by Richter (1883), Widman (1884), Stoermer (1909), and Borsche (1941).

New examples of the Widman–Stoermer reaction (see below) were presented in " Cinnolines. Part I " (Simpson and Stephenson, *J.*, 1942, 353), and the effect of substituents R′ and R″

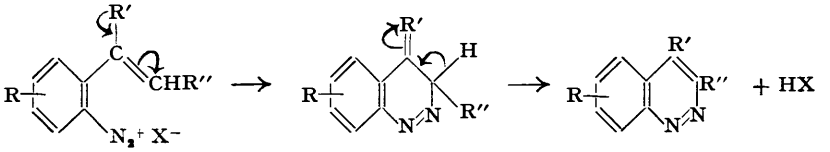
(see below) on the cyclisation of diazotised *o*-aminoarylethylenes was studied (*J.*, 1943, 447); the steric factors involved were also considered (*J.*, 1946, 673). Extension of the reaction to simple 4-methylcinnolines came later (Atkinson and Simpson, *J.*, 1947, 808).

Generalisation of the Richter reaction by Schofield and Simpson (Part III, *J.*, 1945, 512) was accompanied by suggested possible mechanisms for this reaction. This study was continued in Part IV (Schofield and Simpson, *J.*, 1945, 520) with extensions to the Borsche reaction, a number of *Bz*-substituted 4-hydroxycinnolines being prepared from the corresponding *o*-amino-acetophenones. Further, a most important conclusion was reached that the three main reactions were to be considered " essentially manifestations of the same fundamental process."

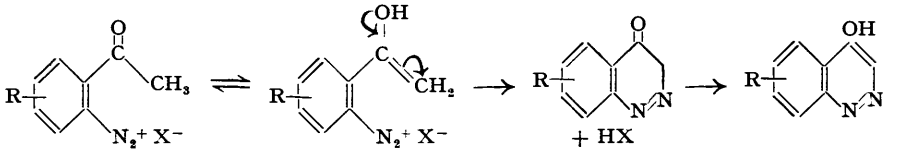
Richter reaction :



Widman–Stoermer reaction :



Borsche reaction :



The Borsche synthesis was considered the best route to 4-hydroxycinnolines and was exploited with much success by Simpson and his co-workers in the preparation of the following derivatives : 6 : 7- and 7 : 8-disubstituted (*J.*, 1947, 227), 7-chloro- (*J.*, 1947, 232), 3-methyl- (*J.*, 1948, 354), 8-nitro-, *Bz*-methyl- (*J.*, 1948, 1702), and 3-ethyl-4-hydroxy-cinnoline, and β-(4-hydroxy-3-cinnolyl)propionic acid (*J.*, 1948, 2318). A modified mechanism for the Borsche synthesis, involving acid-catalysed enolisation of the ketonic side chain, was advanced by Schofield and Simpson (*J.*, 1948, 1170) to account for the beneficial effect of high acid concentration on cinnoline formation in those cases where the *Bz*-substitution tends to reduce the electrophilic activity of the diazonium ion. In all this work much effort was expended in preparing intermediates of established structure. The importance of good routes to *o*-amino-ketones for other syntheses besides those of cinnolines led to Simpson's earlier publication of a critical survey of such routes (*J.*, 1945, 646).

Probably the most interesting reaction encountered in the cinnoline field, and apparently specific to it, is that discovered by Schofield and Simpson (*J.*, 1946, 472) when trying to acetylate 4-hydroxycinnoline-3-carboxylic acid with pyridine–acetic anhydride.

Methylation of several 4-hydroxycinnolines was studied and the nitration of 4-hydroxy-cinnoline itself was investigated (*J.*, 1946, 480; *J.*, 1947, 237). Reference has been made to 4-methylcinnolines (*J.*, 1947, 808), the methyl group of which was shown to be reactive and hence N^1 is the basic centre of the molecule; further studies (Simpson, *J.*, 1947, 1653) designed to confirm this point by alkaline degradation of cinnolinium salts showed the importance of the nature of the 4-substituent on such decompositions. The extent to which cinnolines may be regarded as cyclic azo-compounds was superficially examined (Atkinson and Simpson, *J.*, 1947, 1649) through the properties of some *N*-oxides and the reduction of cinnolines to indoles.

Some of the reactions studied by Simpson and his co-workers not only disclosed fundamental properties of the cinnoline ring system, but were valuable sources of materials for other researches. A particular example of this type of work was Simpson's war-time collaboration with Imperial Chemical Industries Limited on the preparation of potential antimalarials (Schofield and Simpson, *Nature*, 1946, **157**, 439; Keneford and Simpson, *J.*, 1947, 917; Keneford, Schofield, and Simpson, *J.*, 1948, 358).

In discussing his attraction by heterocyclic chemistry Simpson often referred to his intense

distaste for the subject as a student owing to " the presentation of an apparently endless series of syntheses of compounds having illogical names and systems of numbering, little mention being made of their properties." Consequently his work on cinnoline was always discussed with reference to comparable results in other heterocyclic types. This characteristic enthusiasm for correlating data from related topics found expression in a new series of papers including work on quinolines and quinazolines.

The first paper (Morley and Simpson, *J.*, 1948, 360) described reactions of 6- and 7-nitro-4-hydroxyquinazoline. The possibility of reaction between 4-chloroquinazolines and amines (Part II, Morley and Simpson, *J.*, 1949, 1014) was related to the pK_a values of the amines and, in heterocyclic amines, to the possibility of prototropy to the dihydroimino-form. In Part III (Morley and Simpson, *J.*, 1949, 1354) it was shown that the basic centre of 4-phenoxyquinazoline is N^1. Aspects of quinoline chemistry investigated (with Wright) were the synthesis of derivatives of 4-chloro- and 6-nitro-quinoline and the nitration of 4-aminoquinoline (*J.*, 1948, 1707, 2023); 3-nitroquinolines were also synthesised (Morley and Simpson, *J.*, 1948, 2024). Simpson's emphasis on comparative chemistry became dominant about this time, the basic strength of some 4-substituted cinnolines, quinolines, and quinazolines being determined (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356). The qualitative expressions of chemical reactivity which had been amassed by Simpson and his co-workers were summarised (*J.*, 1950, 1104) and discussed with reference to the predictions arising from the calculation of electron densities by Longuet-Higgins and Coulson in the parent systems. Simpson's earlier collaboration with Professor R. A. Morton was renewed in connection with this work, and ultra-violet absorption spectra of compounds in the three series, quinolines, quinazolines, and cinnolines, were interpreted (with Miss J. M. Hearn, *J.*, 1951, 3318).

Most of the antimalarial work was carried out at the Warrington Yorke Department of Chemotherapy in the Liverpool School of Tropical Medicine where Simpson held an I.C.I. Fellowship from 1945, the year in which he was awarded the D.Sc. of Liverpool University. In 1946 he was appointed to the staff of the Medical Research Council and began work in collaboration with Dr. E. M. Lourie (then Director of the Department) on the chemotherapy of trypanosomiasis; this was continued after 1949 in the Chemistry Department of Manchester University where Simpson was Director of the Council's Group for Research in Chemotherapy. The comparative work outlined above formed part of this project. The discovery of trypanocidal activity in crude preparations of 4 : 6-diaminocinnolinium salts and its absence in the pure compounds led to the hypothesis (Keneford, Lourie, Morley, Simpson, Williamson, and Wright, *J.*, 1952, 2595) that it was due to products of incomplete reduction such as the biscinnolinium azo-compounds. A few of these compounds (McIntyre and Simpson, *J.*, 1952, 2606, 2615) and the quinoline analogues (Macey and Simpson, *J.*, 1952, 2602) were prepared and the original assumption fully supported by the high activity of one form of the cinnolinium compounds. An extension of the hypothesis to include biscinnolinium salts with bridge groups other than $^-N{=}N^-$ (Morley and Simpson, *J.*, 1952, 2617) led to N^1N^3-di-(4-amino-6-cinnolyl)guanidine dimethiodide, a compound of the same order of activity as " Antrycide " (Morley, Lourie, Simpson, and Walker, *Brit. J. Pharmacol.*, 1951, **6**, 643). Other work in this field (with Atkinson, Brown, and Taylor, unpublished) was being actively pursued at the time of Simpson's death, but he regarded the synthesis of a highly active compound as something incidental in a programme designed to discover a fundamental relation between biological activity and chemical constitution.

Simpson's expert knowledge of cinnolines and his keen interest in related heterocylic types are evident in his volume on " Condensed Pyridazine and Pyrazine Rings " in the Interscience Series on Heterocyclic Compounds.

To his leisure hours he brought the same energetic qualities which characterised his research and teaching. He enjoyed a fast game of tennis or badminton and spent many of his holidays fell-walking in the Lake District. An early interest in bell-ringing at St. Mary's Church, Liscard, where his father, later Residentiary Canon of Chester Cathedral, was the Vicar, developed throughout his life. In this connection his expression as a conductor and his stamina and artistry in the handling of bells is fully described in " *The Ringing World* " (1952, **48**, 105); he was also well-known in choral societies.

The extent and quality of Simpson's publications are not only proof of his intense intellectual and physical energy but reveal the degree to which he was able to inspire in his research students, always small in number, the same enthusiasm for the problems in hand; that he was able, simultaneously, to gain their confidence as a friend is a measure of his personal qualities. Our loss of an able colleague and understanding teacher is indeed great and our sympathy is with his mother and brother who survive him.

C. M. Atkinson.