AUSTRALIAN NATURAL PRODUCT RESEARCH

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At a meeting of this kind, a considerable proportion of the papers delivered will inevitably be concerned with work carried out in the host country. I have assumed, therefore, that the purpose of the Organizing Committee in inviting me to speak to you about Australian natural product chemistry was to provide a framework for the picture which these papers will present. To do this it will be necessary for me to tell you a little about the historical background.

We are told that, in 1788, the first year of European settlement in Australia, the essential oil of *Eucalyptus piperita* was distilled and used medicinally as a substitute for oil of peppermint. But it seems unlikely that the enterprise shown by those early settlers had any significant influence on the utilization or study of the country's plant products[1]. It was not until 1852 that the distillation of essential oils was investigated seriously, and was later placed on a commercial basis, by a man named Joseph Bosisto, who set up a still, only a few miles from here, outside Melbourne. It is not clear whether the credit for this action is due solely to Bosisto, because at about the same time a second, and very significant, character appeared on the scene. This was Ferdinand von Mueller, a German from Rostock, who became Government Botanist of Victoria in 1853 and made a magnificent contribution to the botanical exploration of Australia and to the systematic study and description of the Australian flora. Without attempting to allocate credit as between Bosisto and von Mueller, we can certainly date to this period the foundation of interest in the study of natural organic products of Australian origin. Both Bosisto and von Mueller, the one with interests mainly commercial, and the other academic, had been trained in pharmacy which, in those times, of course, was a near equivalent to organic chemistry. Both saw the potential of the novel Australian flora—at a time when medicine and industry relied much more directly on natural products than they do now—and both contributed substantially to its exploitation. Each achieved eminence in his own sphere. Bosisto not only founded a firm of oil distillers and pharmacists which operated for nearly one hundred years, but he played a leading part both in State government and in the development of the pharmaceutical profession in Victoria. He distilled the essential oils from at least twenty-six species, representing the families Myrtaceae, Labiatae and Rutaceae, and reported the yields of oils and certain of their physical and medicinal properties. von Mueller, of course, achieved a world reputation as a botanist, was made a Fellow of the Royal Society of London, was knighted by the Queen of England, and made a hereditary baron by the King of Wurtemberg.

The work of these two men was a starting point for the study of Australian natural product chemistry. Inevitably, their interests and enthusiasm were transmitted to others, and notably to J. H. Maiden, whose link with von Mueller is clear and well documented. The setting up of the eucalyptus oil industry drew attention to the potentialities of other kinds of natural products, and the need for a broader basis for investigation was the theme ably expounded and developed by Maiden. Maiden, the first curator of what is now the Museum of Applied Arts and Sciences in Sydney, was a botanist, but one with well-defined chemical interests. We owe a great deal to him, but his main claim to fame, I think, is that he provided the stimulus for much of the early organic chemical research carried out in this country by H. G. Smith.

Smith made a systematic examination of the essential oils of numerous species of Eucalypts, of a number of other Myrtaceae, and also of the pines of Australia—*Callitris, Araucaria* and related genera. His organic chemical work was begun in 1895, at a time when terpene chemistry, though advancing rapidly in the hands of Wallach, Wagner and others, was still more or less in its infancy. Smith's researches, carried out in collaboration with R. T. Baker, a botanist, achieved a remarkable correlation between the chemistry and morphology of the genus *Eucalyptus*. He was a pioneer, not only from the purely chemical point of view, in the study of the constituents of essential oils but also, with Baker, in the broader field of the relation between chemistry and taxonomy, to which Professor Erdtman, the present President of the Organic Chemistry Section of the International Union of Pure and Applied Chemistry, has so ably contributed.

When H. G. Smith began his work there was only one chair of chemistry in each of the then four Australian universities, but while he was still active an important step was taken by the University of Sydney which, in 1913, established a separate chair of organic chemistry. The first holder of this chair was a young Englishman, a very remarkable young man. He is still young, and I am very happy that he is with us today—Sir Robert Robinson. Robinson was very interested in Smith's work, and he collaborated with him and stimulated him as he has so many others; but, unfortunately for Australian chemistry, he did not stay long in Sydney. Robinson's immediate successor, John Read, assimilated from H. G. Smith an interest in essential oils which persisted long after he left Australia. In like manner, personal contacts initiated the particular chemical interests of many others, and the transmitted influence of these earlier chemists on present-day work can still be traced from colleague to colleague, and from teacher to student.

It is clear, therefore, that the first important steps in natural product chemistry in this country stemmed from the occurrence of numerous plant species of high essential oil content and the incentive for investigation that these oil-bearing species offered. It is not my purpose to review the chemical achievements of these investigations; suffice it to say that current interest in essential oils has a marked biological slant, and investigation hinges largely on recent advances in technique. Radiocarbon labelling has been made use of, for example by Birch[2], to investigate the biogenesis of essential oils. The development of gas chromatography has made possible very precise analysis of the oils, with the result that the study of inter-specific

relationships and varietal differences, such as were first made by Baker and Smith, can be placed on a much firmer basis. Likewise, studies of seasonal variation in the composition of essential oils and of variation according to the physiological age of the leaf can now be carried out on very small specimens with comparative simplicity. This, naturally enough, is the direction which the interests of H. G. Smith's successors at the Museum of Applied Arts and Sciences, notably H. H. G. McKern, have taken.

The volume of chemical work carried out in Australia (and, even more, overseas) on essential oils of Australian origin has been very great, but the economic significance of the industry was and is small, particularly when compared with that of the older-established pastoral industry. As time went on, the increasing attention given to improvement in the pastoral industry had its influence on chemistry, and one aim in the search for greater efficiency has been the elimination of losses due to the ingestion of plants poisonous to sheep, cattle and horses. An indication of the significance of such losses is to be seen in the publication of *The Poison Plants of New South Wales*[3] and, more recently, *The Toxic Plants of Western Australia*[4]. The preparation, no less than the publication, of Hurst's book was responsible for the examination of the toxic principles of a number of poisonous plants. The work of Finnemore on cyanogenetic glycosides was the first chemical outcome of such studies, and this was followed by the isolation of such substances as the unusual aliphatic azoxy-glycoside macrozamin[5] and, more recently, by the examination of the liver-damaging pyrrolizidine alkaloids. I shall have more to say about these later. Numerous poisonous species have been and are being examined, some of them not undesirable weeds but deliberately introduced pasture plants which have proved toxic in particular environments. The need for examining poisonous plants has constituted, therefore, a second factor promoting the study of natural products by organic chemists.

In the past fifteen or twenty years, there have been profound changes in the pattern of scientific research in this country. This has been due to several causes, an important one being the changing situation in the universities. Up to 1945, the amount of research work carried out in the chemistry departments of Australian universities was limited by small staffs, few research students and poor facilities. In the post-war period, university activities have expanded considerably, staffs have increased in size, research students in number, and despite the ever-present deficiencies there is a conspicuous improvement in research facilities. One result has been a considerable diversification of interests, and new fields of work have been tackled, some as a logical development from previous projects, others for reasons essentially the same as that of Sir Edmund Hillary for climbing Mount Everest—" because it is there ". As far as natural products are concerned, these new ventures, breaking right away from the traditional phytochemistry, may be exemplified by Professor Cavill's investigations of ant metabolites and by Dr Sutherland's examination of marine animal pigments.

A further stimulus to research has been provided by scientists coming to this country from overseas. Two such men who have made outstanding contributions to the chemistry of natural products are Lemberg, whose

work on the chemistry and biochemistry of porphyrins is too well-known to require any comment from me, and Gottschalk, likewise noted for his investigations of the sialic acids.

Another important factor has been the considerable expansion in governmental research, centred mainly as far as the subject of this Symposium is concerned, in the C.S.I.R.O. Chemical Research Laboratories. One field in which the Organic Chemistry Section of the Chemical Research Laboratories has been very active is the study of long-chain aliphatic compounds by Hatt, Murray and their colleagues. An outstanding feature of this work has been the level of instrumental development achieved by Murray which has made possible the separation of long-chain compounds in a high degree of purity, and also the deduction of structures following separation and identification of the components of complex mixtures of oxidation products. Hatt's group has made major contributions to the chemistry of wool wax and of sugar cane wax[6]; they have separated and identified the alcohols of carnauba wax, they have elucidated the structure of the novel nonadecenyl-hydroxycyclohexenones present in Tigaso oil from New Guinea[7], and are currently making considerable progress in the study of acetylenic compounds of local origin.

The phytochemical activities of the C.S.I.R.O. rank—after the early influence of essential oils and the latter one of stock poison problems—as the third major factor determining the development of natural product chemistry in this country. This influence has not been due primarily to the calibre of the scientific work in the C.S.I.R.O. laboratories, nor to its volume, but to a quite different cause. During the 1939–45 war, sources of certain of the more essential imported drugs of plant origin were sought in the native flora. Though not successful, this search made evident the need for a systematic survey of the pharmacological potential. So, in 1944, the C.S.I.R.O. Division of Plant Industry planned such a survey to involve botanical, pharmacological and chemical collaboration. With one or two exceptions, such as the hyoscine- and hyoscyamine-containing *Duboisia* species, background pharmacological information was almost negligible. The starting point of the programme, therefore, was a preliminary botanical survey in the hands of Dr L. J. Webb[8]. This soon revealed that the volume of chemical work would be far beyond the capacity of the chemists available, so the co-operation of the universities was sought, those interested in natural product chemistry were encouraged, problems were suggested to them, and plant materials provided for their work. After a few years the number of chemists involved and the volume of work in progress was such that the survey, with its initial botanical impetus, acquired more and more a chemical flavour, and eventually full responsibility for it was assumed by the Chemical Research Laboratories. Nevertheless, the corner-stone of all this phytochemical work was and is the botanist in the field, who explores, collects and supplies materials for those in the laboratory, and it is largely through the provision of this collecting facility that the C.S.I.R.O. has influenced directly and indirectly natural product chemistry in this country. I should make clear, of course, that by no means all plant chemistry is dependent on the C.S.I.R.O.—the very active group in Western Australia, for example, is entirely self-contained. However, an average of something

like 200 requested species are collected and distributed here and abroad each year, and about 30 per cent of the papers presented by Australian chemists at this Symposium are directly associated with the survey. A further aspect of the activities of the C.S.I.R.O. Chemical Research Laboratories is the part played in encouraging the fullest use of physical methods in structural organic chemical studies; for the purpose of this Symposium the most important facet of this is the X-ray crystallographic work of Dr Mathieson carried out in the Division of Chemical Physics.

The study of alkaloids was the initial objective of the C.S.I.R.O. programme, because alkaloids were believed to offer the most promising approach to pharmacologically useful materials, and it was to alkaloids also that the first university collaborators turned. But the broader the scope of the information that can be obtained concerning the native flora the better, and the provision of plant materials to those interested in them is not limited to species thought to be of potential economic interest. Apart from alkaloids, then, considerable attention has been paid to the study of triterpenes, notably at the Universities of New South Wales, Western Australia and Queensland, of cardiac glycosides, cyclitols, colouring matters, coumarins and so on. All these activities, hinging to a large extent on the centralized collection of plant material and involving periodical informal meetings of those interested, have come to be known as the phytochemical survey, and I shall subsequently refer to it as such.

This historical account, brief though it has necessarily been, leaves little opportunity for discussion of chemical work. To review the whole field would be quite impossible, so I have chosen to mention three recent topics, each representing one of the three factors influencing Australian natural product chemistry to which I have referred.

Firstly, essential oils: activity in essential oil chemistry since 1945 has lacked coherence as compared with earlier years. Although many have contributed, much of the effort has gone into clearing up long-standing problems, while the rest has been thinly spread over a wide field. From the somewhat heterogeneous results I will draw attention to one point only, namely the increasing number of phloroglucinol derivatives which have been isolated and identified as components of essential oils, usually predominantly terpenoid. Examples of such substances are leptospermone (I) and evodionol (II), and the more recently established angustifolionol (III), alloevodionol (IV) and torquatone (V). The major interest of these phloroglucinol derivatives lies in their association with Birch's development of the " acetate " hypothesis.

Secondly, the chemistry of plants toxic to livestock: in every country pastoralists suffer to a greater or lesser degree from losses caused by poisonous plants. The plants causing these losses are usually known or are soon recognized because of an obvious association between the ingestion of the plant and the onset of symptoms. However, this is not always so, and it is now appreciated that there are at least three groups of plants which can cause heavy loss of stock—and in some parts of the world, of human life— as much as two years after ingestion, so that recognition of the responsible species was not at first easy. The three groups of plants are the genus *Senecio* and some closely related species, certain members of the genus
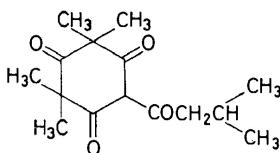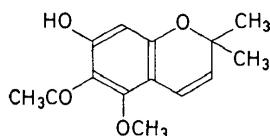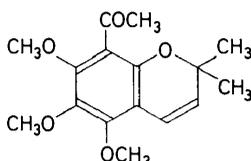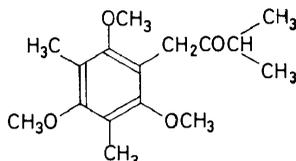
(I)   (II)
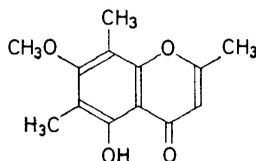
(III)   (IV)   (V)

Crotalaria, and a number of members of the family Boraginaceae. All three groups contain the liver-damaging pyrrolizidine alkaloids with the chemistry of which the names of Adams and Menshikov are closely associated. Investigation of these alkaloids in this country was inspired by Dr L. B. Bull and his colleagues of the C.S.I.R.O. Division of Animal Health, following their recognition that toxaemic jaundice, a disease causing serious loss of sheep in southern New South Wales and northern Victoria, was associated with the grazing of *Heliotropium europaeum*[9]. Chemical work on this species was commenced in the C.S.I.R.O. Chemical Research Laboratories with the object of isolating the constituent alkaloids, determining their structures, and providing pure substances for biological study. This has developed into an extensive collaborative programme, different aspects of the mode of action of the pyrrolizidine alkaloids being under investigation in several laboratories. Thus, the pathological effects of the alkaloids on the liver are being examined by Bull and Dick[10], who have already carried out detailed studies of the relation of damage by the alkaloids to the storage of copper in the liver. Professor Christie of the University of Melbourne has investigated the action of the alkaloids on liver cell enzyme systems in the intact animal, a major biochemical effect being on the diphosphopyridine nucleotide-dependent enzymes[11]. The effects on nucleoprotein synthesis are being studied by Professor Morton in the University of Adelaide. Dr Gallagher of the McMaster Animal Health Laboratory, Sydney, has investigated the neuro-muscular blocking action of the alkaloids and confirmed *in vitro* the inhibition of enzyme systems requiring pyridine nucleotides[12]. He has observed the formation of copper complexes by certain of the alkaloids, a point of some interest in relation to the part which copper can play in the disease in the field.

Because of the effects on liver cell nuclei, Christie suggested to Professor Clark of the University of Tasmania that investigation of the mutagenic activity in *Drosophila* might be opportune. This suggestion led to the particularly interesting discovery that the pyrrolizidine alkaloids are

strongly mutagenic[13] and, furthermore, at a dose rate lower relative to the toxic dose level of other mutagens. Further studies in this direction are also under way in the Botany Department, University of Melbourne, and requests are also being received from biologists in other countries for supplies of alkaloids for the study of chromosome breakage and mutagenic action. From these collaborative studies, coupled with work elsewhere, there is accumulating a body of information concerning the structural features necessary for the liver-damaging activity of the alkaloids.

The prerequisite for all these biological programmes is the availability of the pure alkaloids and this, of course, is contingent upon the activities of the chemist. At the chemical level, but closely linked with the biological work, the metabolism of heliotrine *in vivo* is being studied by Mr Dann in the Division of Animal Health, at present with unlabelled alkaloids as a preliminary to the use of labelled heliotrine. On the purely chemical side, the work hinged initially on the elegant application by Culvenor[14] of partition chromatographic methods for isolating the alkaloids and, with many species, on the recognition (following earlier work by Russian chemists[15] and by Warren[16] in South Africa) of the importance of the *N*-oxides which sometimes constitute over 90 per cent of the total occurrence. Culvenor has made a preliminary examination of over eighty species of plants which are potential producers of pyrrolizidine bases, isolated many previously un-described alkaloids and determined the structures of a number of them. As a result of the investigation of *Heliotropium europaeum*, the initial emphasis was on the Boraginaceae, which in general contains diester bases involving two esterifying acids, as compared with the more common macrocyclic diesters of dicarboxylic acids found in *Senecio* species. Of all this work, however, that which is probably of the widest academic interest has been concerned with a *Senecio* alkaloid, one of the longest-known pyrrolizidine alkaloids, jacobine. Jacobine was isolated by Barger[17] and others from *Senecio jacobea* or ragwort, which is responsible for stock losses in many parts of the world. Degradative studies were carried out in the C.S.I.R.O. laboratories by Bradbury[18], and from the results of these the main features of the structure were deduced by Geissman[19], then working temporarily in Melbourne. The complete stereochemical picture has now been revealed by X-ray crystallographic studies and will be discussed by Dr Mathieson.

Recently the emphasis in this pyrrolizidine field, on the chemical side, has shifted to the genus *Crotalaria*, several species of which are implicated in stock disease problems here and overseas. However, the main chemical interest is concentrated on the isolation of a number of unesterified bases, and these appear *not* to possess the power of causing liver damage. Examples of these are 1-methylenepyrrolizidine (VI), 7-hydroxy-1-methylene-pyrrolizidine (VII) and 1-methoxymethyl-1,2-dehydropyrrolizidine[20] (VIII).
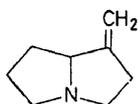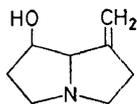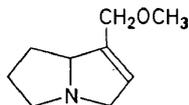

(VI)   (VII)   (VIII)

Table 1

	Quinolines	Furoquinolines	Acridines	Quinazolines	Indoloquin-azolines	Canthinones	Benzyl-iso-Quinolines	Imidazoles
Sub-Family I RUTOIDEAE	Orixa Lunasia **Galipea** **Cusparia**	**Fagara** **Zanthoxylum** Evodia **Orixa** Melicope Lunasia Medicosma Haplophyllum Boenninghausenia **Dictamnus**	Evodia Melicope Haplophyllum		Zanthoxylum **Evodia**	Zanthoxylum Pentaceras	**Fagara** **Zanthoxylum** Evodia	Pilocarpus
Sub-Family III FLINDERSIOIDEAE	Flindersia	Flindersia **Chloroxylon**						
Sub-Family V TODDALIOIDEAE	Casimiroa	Balfourodendron Casimiroa Acronychia Hortia **Skimmia**	Acronychia		Hortia		**Phellodendron** **Toddalia**	Casimiroa
Sub-Family VI AURANTIOIDEAE		Glycosmis **Aegle**		Glycosmis Aegle				

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My third example concerns the so-called phytochemical survey. As I mentioned previously, the objective of the C.S.I.R.O. survey was a search for alkaloids and this also became the starting point for a number of our university colleagues. For this reason more attention has been paid to the chemistry of alkaloids than to that of other types of plant constituents. Although no special emphasis has been placed on any one group of plants—except in so far as earlier work pointed to the likelihood of alkaloids being present—certain families have inevitably received more attention than others. One of these is the Rutaceae, a family which is widely distributed throughout the warmer parts of the globe. Taxonomic problems in the Rutaceae became evident very early in the survey, and as long ago as 1947 I had occasion to discuss with Dr L. J. Webb the possibility that, limited though they were, our chemical data might be of some value for taxonomic purposes. Despite the limitations, therefore, it seems to me worthwhile to illustrate some aspects of the phytochemical survey by examining the results in relation to what is known of the alkaloid pattern in the Rutaceae as a whole. I hope this will not only serve the primary purpose of the lecture, but will also stimulate others to fill in the numerous gaps in the chemistry of a most interesting group of plants.

From the point of view of alkaloid production, the Rutaceae are one of the most versatile of plant families. Dividing the alkaloids into arbitrary structural types there are now eight categories*, and data are available for
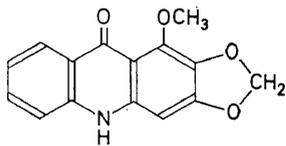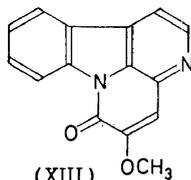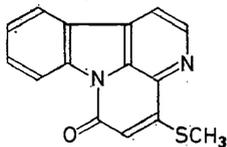
(IX)
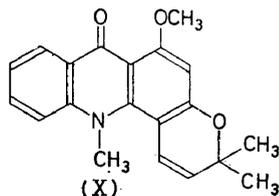
(X)
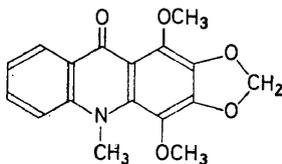
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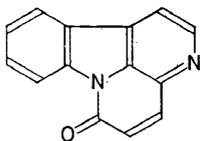
(XII)

(XIII)

(XIV)

* Excluding the amides *N*-(2-*p*-anisylethyl)-*N*-methylcinnamamide, fagaramide, neoherculin and aegeline.

four of the seven sub-families listed by Engler and Prantl[21]. The remaining three sub-families are monogeneric and for our present purpose may be disregarded. The names printed in **bold** type in *Table 1* show the distribution of alkaloid-containing genera as it was known about 1946 when the programme in this country was getting under way.

Additions to these categories were soon made by the isolation and identification firstly of a number of acridine derivatives—5-acridones—exemplified by (IX), (X) and (XI), and shortly afterwards of three canthinone alkaloids, (XII), (XIII) and (XIV), the last having a methylthio-substituent[22]. Subsequently, Russian chemists have isolated from the rutaceous genus *Haplophyllum* what appears to be an acridine derivative[23], co-occurring, as in the Australian genera, with furoquinolines.

The structures of two novel types of quinoline derivative were established, a dimethylpyrano-2-quinolone (XV) from *Flindersia australis*[24] and the 2-phenyl-4-quinolone (XVI) from *Lunasia quercifolia*[22]. The latter was later isolated by Goodwin, Smith, Velasquez and Horning[25] from another *Lunasia* species, *L. amara*, and from *Casimiroa edulis* by Sondheimer[26].
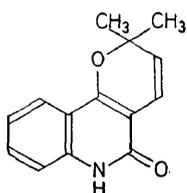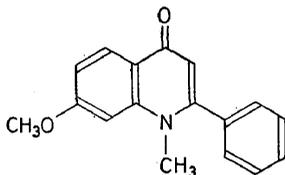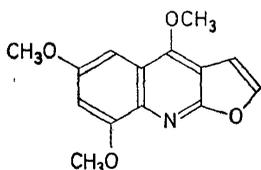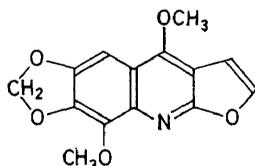

(XV)   (XVI)

Less novelty, but much more variety, has been encountered among the furoquinoline group, initially represented by three alkaloids but now numbering at least fifteen, exclusive of several dihydrofuroquinolines[22, 27]. Examples are (XVII), (XVIII), (XIX) and (XX).


(XVII)   (XVIII)

Our knowledge of the alkaloid distribution in the Rutaceae has been supplemented considerably by these results and also, of course, by work elsewhere, of which I would mention particularly that on the quinazolines by our Indian colleagues, and on the furoquinolones by Japanese chemists. The present position is shown in *Table 1*.

Looking more closely at the information in this table, it is clear that in so far as any structural type might be regarded as characteristic of the Rutaceae

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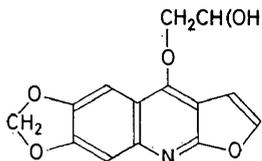
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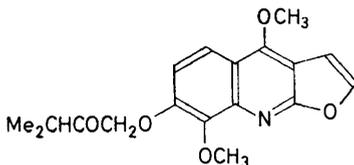
(XX)

it is the furoquinolines, which have not been reported from any other family*. But the acridines, likewise, are restricted to the Rutaceae and are always accompanied in the plant by furoquinolines; with certain exceptions, the quinoline alkaloids are confined to the Rutaceae and are often found together with furoquinolines, while in the genera containing quinazolines (*Glycosmis* and *Aegle*) furoquinolines are also present. It seems only reasonable, therefore, to regard these four as a biogenetically homogeneous group based formally on the " anthranilic acid " unit (XXI) common to all of them.
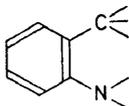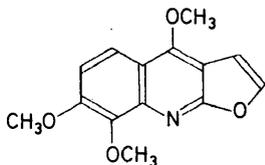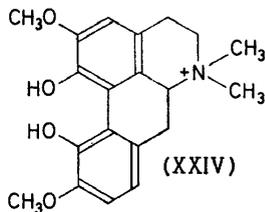
(XXI)

In addition to these four, we have the biogenetically distinct groups represented by the imidazoles, the benzylisoquinolines (themselves showing considerable structural variation) and indole derivatives, such as the canthinones, related to tryptophan. The versatility of the family becomes
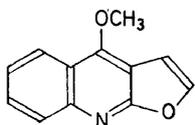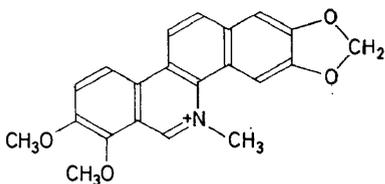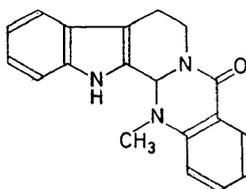
(XXII)

(XXIII)

(XXIV)

(XXV)

(XXVI)

* Since this paper was written, furoquinoline alkaloids have been reported from several additional rutaceous genera.

even more apparent when it is seen that not only are there certain genera, such as *Evodia*, capable of producing alkaloids by several of these biogenetic pathways, but an individual may make use of more than one route. Thus, from *Zanthoxylum ailanthoides*, Tomita and Ishii[28] isolated the furoquinolines dictamnine (XXII) and skimmianine (XXIII) and the quaternary aporphine magnoflorine (XXIV), while from *Zanthoxylum rhetsa*, Chatterjee, Bose and Ghosh[29] isolated chelerythrine (XXV) and three indoloquinazolines of which evodiamine (XXVI) is one.

Looked at against the complexity of the over-all metabolic picture, this versatility of alkaloid production is perhaps not especially surprising, but nevertheless it does distinguish the Rutaceae from other families and so deserves notice. It may suggest that the family is a rapidly evolving one, but, in any event, the data presented by the twenty-four genera so far known to contain alkaloids clearly make it desirable that as many as possible of the one hundred and twenty or so remaining genera be examined. Some, of course, have been examined without alkaloids being detected; others are known to produce alkaloids and work already in progress bears out the promise of much more interesting chemistry to come.

One further aspect of the chemistry of the Rutaceae warrants mention. Among the alkaloids to which I have referred have been several in which an isopentane unit is attached as an addendum to the type skeleton, for example, acronycine (X) in the acridine group, flindersine (XV) in the quinoline group and acronidine (XXVII) in the furoquinoline group, while there are several furoquinolines with isopentane ether substituents. There are in the Rutaceae numerous other examples of this kind, notably among the coumarins, representatives of which have been isolated from at least twelve rutaceous genera. Of those twelve genera, ten provide examples of courmarins involving the combination of one or more isopentane units. There are also a number of furocoumarins analogous to the furoquinolines. Among the flavanoids, recent examples are the flavanone isoprenoid ether
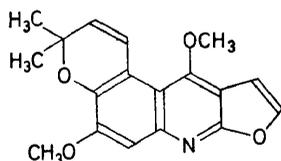
(XXVII)
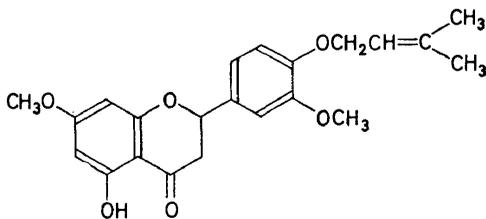
(XXVIII)   (XXIX)
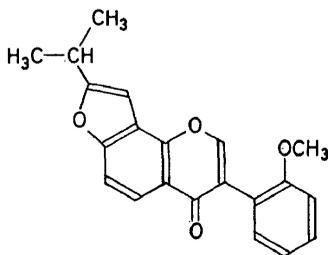
(XXVIII) reported by Geissman[30] from *Evodia sarcocca* and the isoflavone munetone (XXIX) isolated from *Mundulea suberosa* by Dutta[31].

I have drawn attention to these substances, because this capacity to add an isopentane unit to a wide variety of molecular types is widespread through the Rutaceae and appears to be a biochemical characteristic of the family. It also gives rise to structural correlations which may have some biogenetic significance. For example, in the genus *Lunasia*, occurring together with simple furoquinolines, there are a number of isopropyldihydrofuro-quinolines such as (XXX) and (XXXI), while *Orixa japonica* contains several
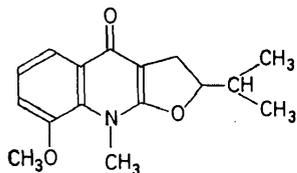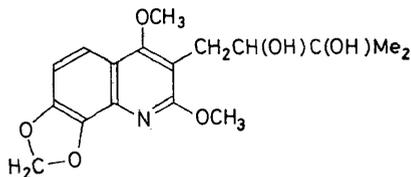

(XXX)
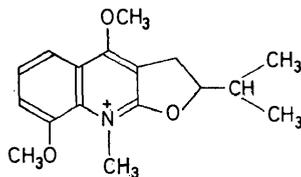
(XXXI)
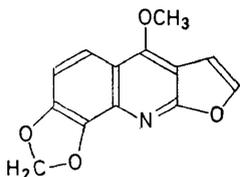
(XXXII)

(XXXIII)

furoquinolines, such as kokusagine (XXXII), together with the alkaloid orixine which has recently been shown by Terasaka[32] to have the structure (XXXIII).

In his book *The Structural Relations of Natural Products*, Robinson[33] writes of the furoquinolines that there is no good clue to the origin of the furan group. He outlines three possibilities—that it is a residue of the tryptophan side chain, that it arises by degradation of an aromatic ring of the acridones, or that it is formed by condensation of a suitable intermediate with a 2,4-dihydroxyquinoline derivative. I should like to refer to a fourth possibility which I suggested in 1948 in a lecture to the Sydney University Chemical Society, namely, that the furan ring represents a degraded isopentane unit. Since that time, of course, the origin of the isopentane unit from acetate units has been established, and it may well be that the furan ring represents, as in Robinson's third suggestion, no more than union with one acetate unit. However, the more devious route remains a possibility which is not rendered any less probable by the co-occurrence of kokusagine and orixine—the loss of the isopropyl group by a retro-aldol change can so easily be visualized. This view, foreshadowed by Haworth[34], has also been put forward, and possible mechanisms have been discussed, by Birch[35] and Seshadri[36].

To sum up, the abundance of essential oil-bearing species in the Australian flora provided the background for the chemical work of H. G. Smith. But Smith could not and would not have achieved what he did without the botanist, R. T. Baker, and, behind him, J. H. Maiden. The importance of stock poisoning by plants led Finnemore and others to investigate their chemistry, but these investigations would not have gone far without the stimulus provided by the veterinary scientists. The current interest in plant chemistry associated with the C.S.I.R.O. phytochemical programme hinges on the initial botanical survey, on the pharmacological incentive for the study of alkaloids, and on the botanical collections. Likewise, the work of Gottschalk and of Lemberg undoubtedly owes much to its medical contacts and environment.

If a moral is to be drawn from the development of Australian natural product chemistry it is surely that the study of natural products flourishes best when there is the closest collaboration between chemist and biologist.

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