

# NATURAL PRODUCTS CHEMISTRY 1950 TO 1980—A PERSONAL VIEW\*

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## ABSTRACT

In the field of natural products chemistry the decade of the 1950s still largely emphasized degradative structural chemistry, while the 1960s were dominated by the extensive use of newer physical methods, notably nuclear magnetic resonance and mass spectrometry. Concurrently, increasing emphasis was placed on sophisticated biosynthetic studies using tracer techniques. The present decade is seeing and will see refinements along similar lines, but, in addition to the continued search for natural products from terrestrial plants, ever-increasing attention is being paid to natural products from marine and insect sources. Many of these generalizations are exemplified in this article by work from the author's laboratory.

Since this must be a purely personal view—retrospectively and prospectively—of natural products chemistry, I propose to illustrate my views almost entirely through examples from our own research. This approach has the advantage of speaking on the basis of intimate knowledge.

Let us briefly analyse natural products chemistry in terms of source materials and of general approach. Initially, most of the starting materials were of terrestrial origin and overwhelmingly dominated by plant sources. Microbial products have become important during the past 25 years, and increasing attention to natural products from marine sources has only become noticeable during the past decade. Insects—one of the oldest and most diverse forms of life on earth—form a very special group which also has started to come to the fore only during the past decade, primarily because of recent methodological advances in separation and detection techniques. Even the over-all organization of this IUPAC symposium reflects the recent emphasis on natural products from marine and insect sources by dedicating separate sessions to them.

Of more fundamental significance is the general scientific approach to natural products chemistry. Until the middle of this century, the main emphasis centred on the elucidation of the gross structure of new natural products, and frequently these represented real chemical *tour de force* utilizing a minimum of physical methods and a maximum of chemical experimental skill and intuition. It was not uncommon to have investigators spend a life time (e.g. Hermann Leuchs with strychnine) on the structure elucidation of a single substance, although there were giants such as Robert Robinson, who left their imprint on many of them.

Selected personal statements by the author were removed by the editor without Professor Djerassi's consent. An uncensored version of this paper can be obtained by writing to Professor C. Djerassi, Department of Chemistry, Stanford University, Stanford, California 94305.

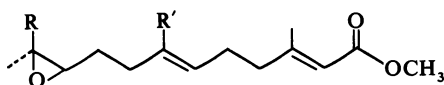
Major changes started to occur in the early 1950s. Increasing attention was being paid not just to gross chemical structure but also to the determination of relative and absolute configurations. The latter became increasingly significant as the details of biogenesis were examined. At the same time, the impact of new separation methods (countercurrent distribution; paper, thin layer and gas chromatography) and especially of new physical methods made itself felt and resulted in an enormous quickening in the rate of structure elucidations. It is frequently forgotten that, prior to about 1945, natural products chemists were essentially limited to column chromatography for separation and that their physical methods consisted primarily of absorption spectroscopy and monochromatic rotation measurements. Infra-red spectroscopy only became a routine tool in the late 1940s; nuclear magnetic resonance became a standard method in the late 1950s; and it was only in the 1960s that optical rotatory dispersion, circular dichroism and mass spectrometry became everyday components of the organic chemist's armamentarium. With these methods, which markedly speeded up the course of structure elucidation and at the same time permitted the use of much smaller quantities of material, the structures of many 'minor' products were established which frequently proved to be important missing links in theoretical biogenetic schemes. Robinson was one of the earliest and most brilliant practitioners of this art<sup>1</sup>, and by 1960 the emphasis had clearly swung from structure elucidation as an aim by itself to the recognition that elucidation of the natural biosynthetic pathways was of much more fundamental significance. The introduction of more powerful and automated x-ray diffractometers has in many instances reduced the structural chemist's role even further, and there is little doubt that some of the intellectual enjoyment associated with the chemical elucidation of a novel structure has been lost.

Experimental work on biosynthesis—in contrast to 'paper schemes' based on the isolation of 'missing links'—is crucially dependent on the use of isotopic markers, primarily radioactive ones. The technical difficulties of incorporating radioactive precursors into plants were such that serious work on a wide scale did not really start until about 15 years ago, while similar biochemical studies in animal tissues were carried out much earlier. At present, experimental work on the biosynthesis of plant natural products is a flourishing field, and the biochemical sophistication is rapidly reaching the level where the use of isolated enzyme systems will become common.

Biological activity has, of course, always been an important factor in selecting a given source for the isolation of natural products. The recent 'explosion' in insect chemistry is based almost exclusively on such motivation (viz. extensive work on pheromones)—much more so than is the case with plants. The chemical complexity of some of these compounds is comparatively trivial, but the expertise involved in handling minute amounts of material for complete structure elucidation is most impressive. A single recent example<sup>2</sup> from the insect field will suffice to illustrate this point.

Work by Röllner's group<sup>3</sup> and subsequently by Meyer *et al.*<sup>4</sup> has shown that the giant silk moth contains two juvenile hormones which have the unusual homosesquiterpenoid structures **A** and **B**. The question naturally arose whether all insects contain the same juvenile hormones or whether different families secrete different chemical types. Nothing was published about this

problem during the 5 years following the initial silk moth work<sup>3, 4</sup>, primarily because of the great experimental difficulties in collecting the large numbers of insects needed to isolate the minute amounts of hormone generated by them. The Zoecon group<sup>2</sup> attacked this problem by collecting 738 endocrine glands from the tobacco hornworm (*Manduca sexta*) and incubating them *in vitro* with radioactive methionine, which was incorporated into the methyl ester portion of the hormone. By separating the mixture by use of the new technique of high-pressure liquid chromatography, coupled with radioactive scanning and gas chromatographic—mass spectrometric analysis, they were able to demonstrate that the tobacco hornworm contained the earlier-isolated<sup>4</sup> juvenile hormone **B** as well as the new hormone **C**. Its structure and absolute configuration was established with a total of 5.3  $\mu\text{g}$  of material!



**A**  $R = R' = \text{C}_2\text{H}_5$

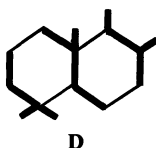
**B**  $R = \text{C}_2\text{H}_5$ ;  $R' = \text{CH}_3$

**C**  $R = R' = \text{CH}_3$

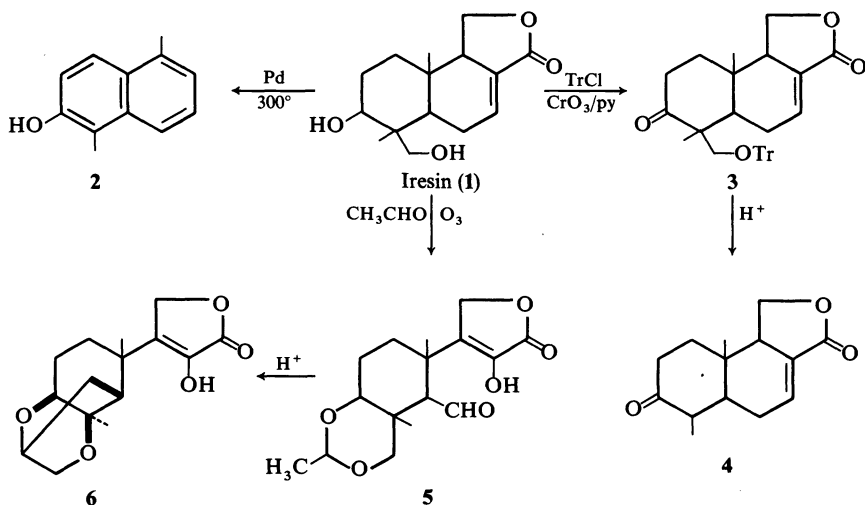
The timing of my own entry into the natural products field in the early 1950s was highly propitious. I still had a few years of pure chemical pleasure, only slightly diluted by help through physical methods; and when the latter started to play an increasingly dominant role, my research group was very actively involved in developing the use of such techniques and thus benefited intellectually as well as operationally from this trend. We have concentrated on steroids, terpenoids, antibiotics and alkaloids, which were isolated from terrestrial as well as marine sources. While we have not been active ourselves in biosynthetic tracer work, we have contributed our share of 'missing links' to various biogenetic schemes. I have decided to select a few examples from our work over the past 20 years which I considered scientifically exciting ones to illustrate the progress of natural products chemistry and to re-examine some of them in the light of recent advances. In other words, how would we have handled the problems of the 1950s 15 or 20 years later?

One of the great triumphs of 'paper biogenesis' which subsequently prompted an enormous amount of experimental biogenetic work has been the isoprene rule and its application in the terpenoid and steroid fields. This was a clear-cut case where the isolation and structure determination of a wide variety of natural products over a period of decades led to a hypothetical scheme, beautifully summarized by Ruzicka<sup>5</sup>, which was then subjected to verification both by organic synthesis 'under physiological conditions' and by actual biochemical experimentation using labelled precursors. The steroids are a classic case of the intimate detail in which the biosynthesis of a class of natural products can now be described with considerable certainty<sup>6</sup>. In his 1953 summary Ruzicka<sup>5</sup> called attention to the fact that, of the many sesquiterpenoids that follow the isoprene rule, none had been encountered that was based on the skeleton **D**. He concluded that 'this

appears to indicate that the biogenesis of the steroids, diterpenes and triterpenes differs in some fundamental detail from that of the monoterpenes and sesquiterpenes.<sup>7</sup>



Under the circumstances it should not be surprising that the sesquiterpene iresin (*Figure 1*) is one of my favourites, because 1 year after the appearance of Ruzicka's seminal paper<sup>5</sup> we were able to show<sup>7</sup> that iresin constitutes the missing link between the lower and higher terpenes. Since that time many other sesquiterpenes have been encountered which are based on the skeleton D.



*Figure 1.*

Except for the use of ultra-violet and infra-red spectroscopy, the gross chemical structure was established<sup>7</sup> by chemical degradations, some of which are summarized in *Figure 1*. In retrospect, it would have been interesting to determine what impact mass spectrometry and n.m.r. spectrometry might have had if the present stage of their instrumental and interpretative capability could have been applied to iresin. These measurements were carried out this year, and demonstrated that their effect would only have been marginal. The mass spectrum was relatively uninformative, with a minute molecular ion peak because of dominant loss of water. However, the successive loss of two methyl groups and the expulsion of the  $\text{CH}_2\text{OH}$  substituent from an  $\text{M}-\text{H}_2\text{O}$  precursor can be discerned. The 300 MHz p.m.r. spectrum is reproduced in *Figure 2*, and while even at 100 MHz valuable information

(e.g. methyl groups, olefinic proton, proton attached to hydroxyl-bearing carbon) could be deduced, the resolving capability of a 300 MHz instrument was necessary to offer unambiguous information about hydrogens attached at C-3, 6, 9 and 11.

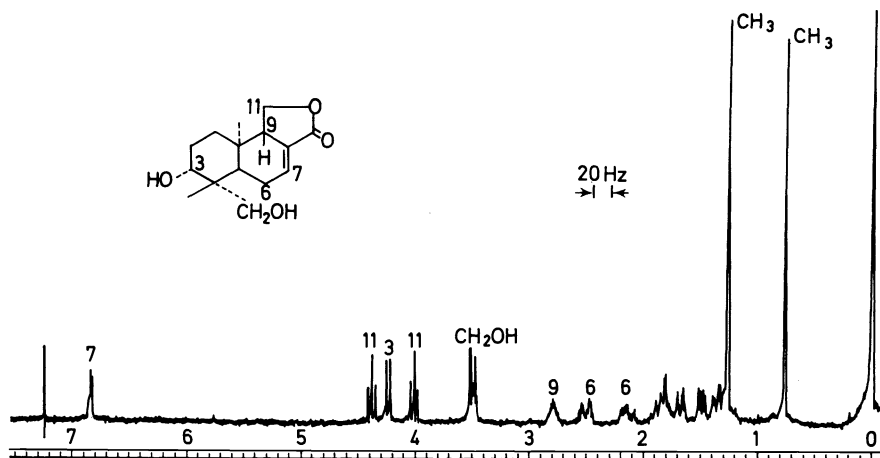


Figure 2.

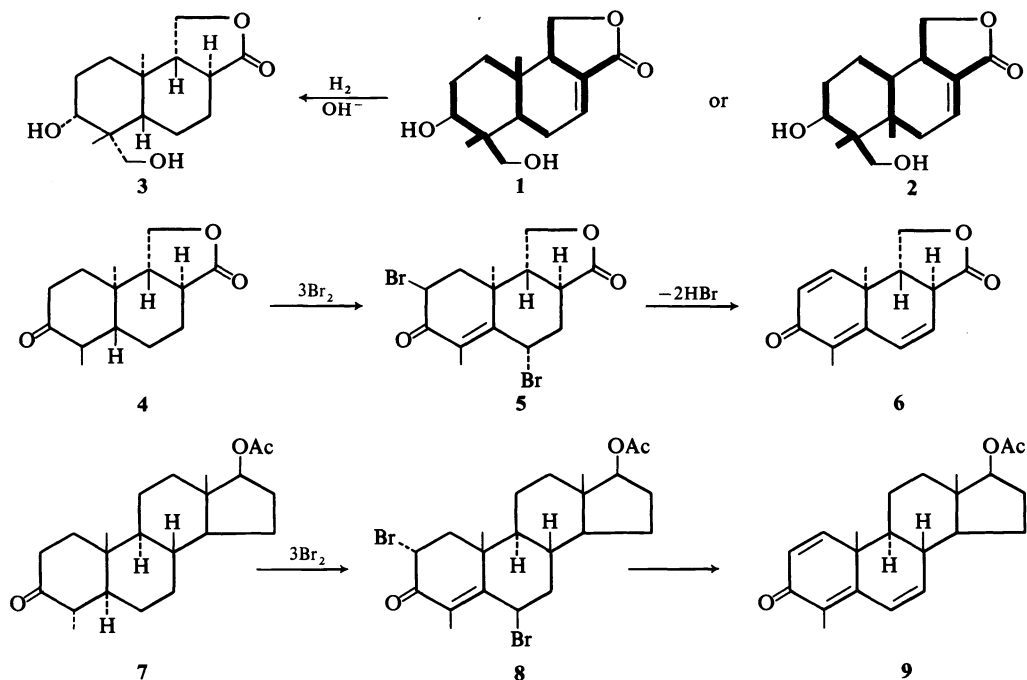
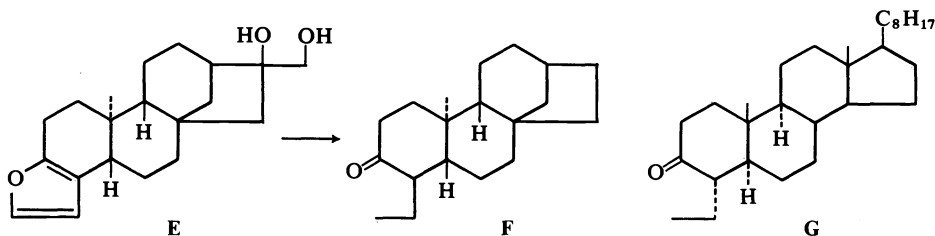
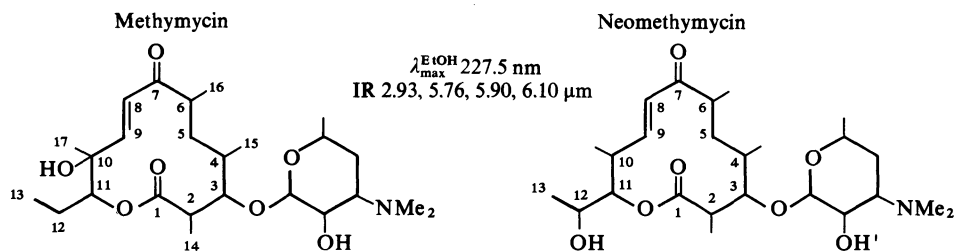


Figure 3.

Of considerably greater scientific relevance was the question of the absolute configuration of iresin (*Figure 3*). Two years earlier we had shown<sup>8</sup> that optical rotatory dispersion could be a powerful technique for the determination of the absolute configuration of organic molecules, and iresin was one of the first examples to which this method was applied. By comparing the rotatory dispersion curves of the iresin transformation products **5** and **6** (*Figure 3*) with those of the steroids **8** and **9** and noting a complete mirror image relationship of the appropriate Cotton effect curves, we concluded that iresin had the opposite, i.e. 'wrong', absolute configuration as compared with the steroids. In the same year we demonstrated that the diterpene cafestol **E** also belonged to the 'wrong' series, since its degradation product **F** and 4 $\alpha$ -ethylcholestan-3-one **G** displayed antipodal rotatory dispersion curves. Together with the diterpene eperuic acid<sup>10</sup>, these were the first three examples in which an absolute configuration opposite to that of the steroids and triterpenoids could be demonstrated, and in each instance the then newly developed technique of optical rotatory dispersion provided the missing information.



Let us turn to another series of natural products—the macrolide antibiotics<sup>11</sup>—whose structural pattern suggested<sup>12</sup> that they might arise by biological condensation of propionate units rather than by the conventional acetate mechanism. The first complete structure elucidation<sup>13</sup> of a macrolide antibiotic was that of methymycin (*Figure 4*), and was followed shortly thereafter by that of neomethymycin<sup>14</sup>. The validity of Woodward's propionate hypotheses<sup>12</sup> was soon established<sup>15</sup> by actual tracer experiments with methymycin.



Djerassi, Halpern, *Tetrahedron*, 3, 255 (1958)

*Figure 4.*

The complete structure determination of these two antibiotics was not a simple matter (see *Figures 5* and *6*), but here again only ultra-violet and infra-red spectroscopy were available at that time as physical tools, and extensive

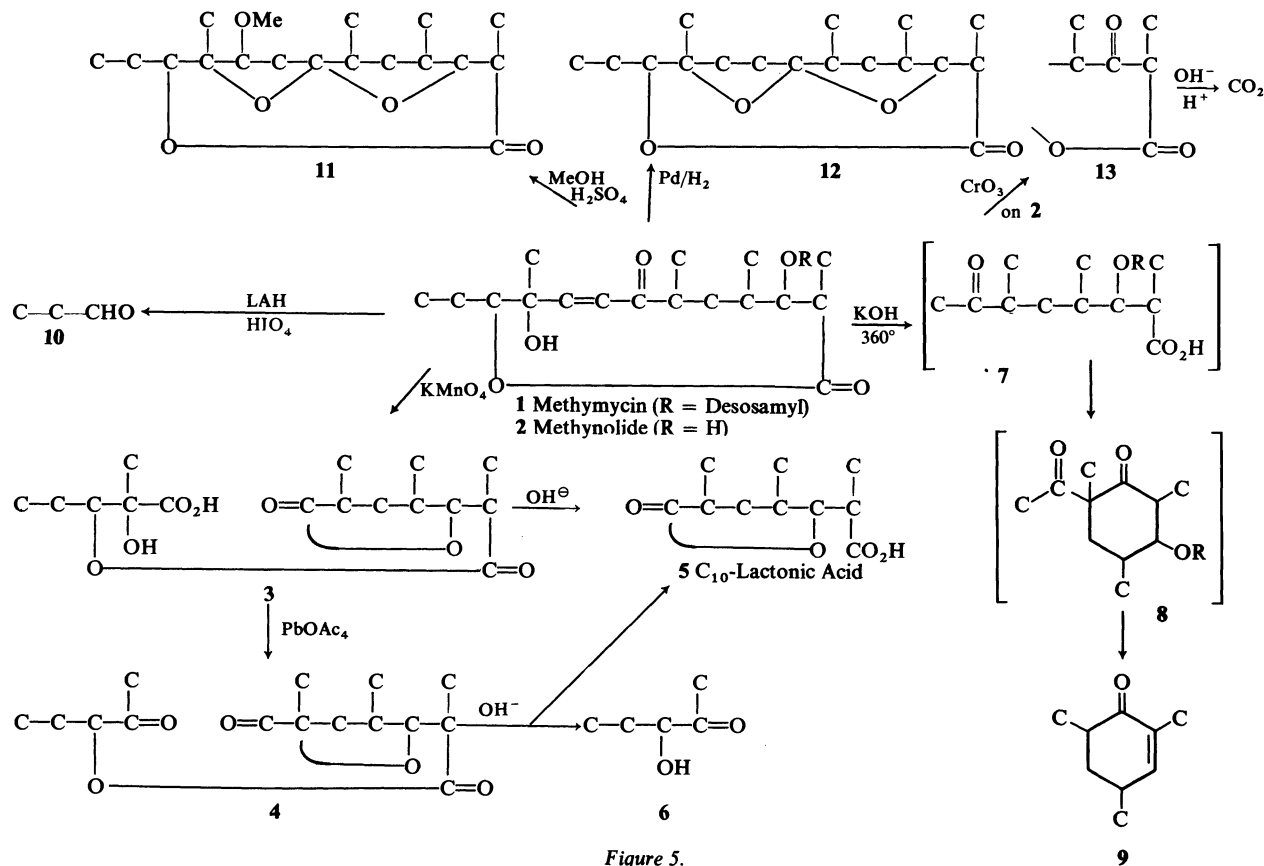


Figure 5.

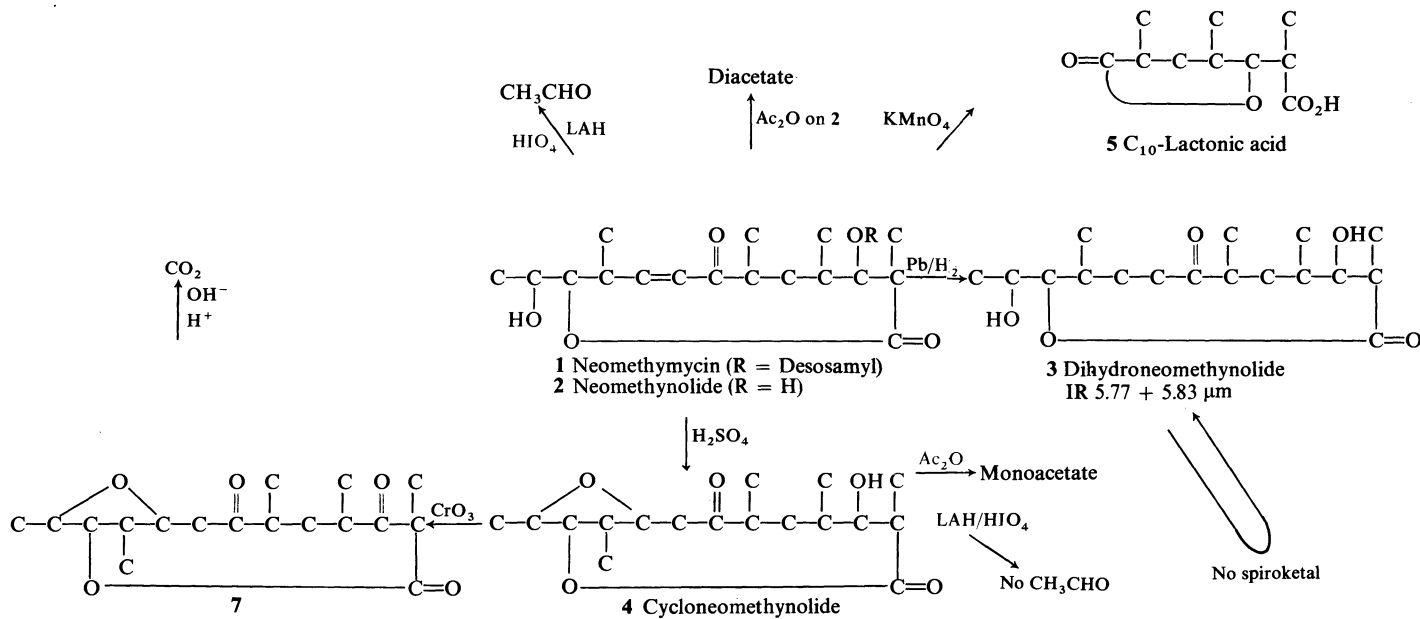


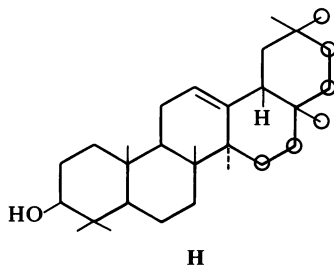
Figure 6.



degradative chemistry as well as chemical intuition were required for solution of these problems. It is interesting to examine the possible impact that n.m.r. spectroscopy and mass spectrometry might have had upon the structure elucidation of these two macrolides. In contrast to the above-cited experience with iresin (*Figures 1–3*), it is fair to state that these two techniques—notably p.m.r. and c.m.r. spectroscopy—would have facilitated the problem greatly. Thus, it is instructive to note that even the parent antibiotic methymycin with the intact desosamine glycosidic bond (see *Figure 4*) and its large number of heteroatoms displayed a molecular ion peak, which immediately yielded the exact molecular weight (469) corresponding to  $C_{25}H_{43}NO_7$ . The mass spectra\* of the two isomeric aglycones, methynolide (**2** in *Figure 5*) and neomethynolide (**2** in *Figure 6*), differed completely in the range  $m/e$  312 ( $M^+$ )–150. In fact, the most intense peak in the high mass range of each aglycone already shed some light on their main chemical difference—methynolide exhibiting a very intense  $M-C_3H_6O$  peak ( $m/e$  254), whereas neomethynolide displaying a moderately intense  $M-C_2H_4O$  peak ( $m/e$  267).

The p.m.r. spectrum of the  $C_{10}$ -lactonic acid **5**—a key degradation product of methymycin (*Figure 5*) and neomethymycin (*Figure 6*)—is reproduced in *Figure 7*, and the sequence of carbon atoms 1, 2, 3 and 14, as well as of 6 and 16, is readily deducible from the 100 and especially 300 MHz spectrum. Substantial structural information is also available from the p.m.r. spectrum (*Figure 8*) of the aglycone neomethynolide, and this is beautifully supplemented by its very informative c.m.r. spectrum (*Figure 9*). There is little doubt that if these techniques had been available in the middle 1950s, the structure elucidation of these macrolide antibiotics would have proceeded much faster, albeit with less chemical pleasure.

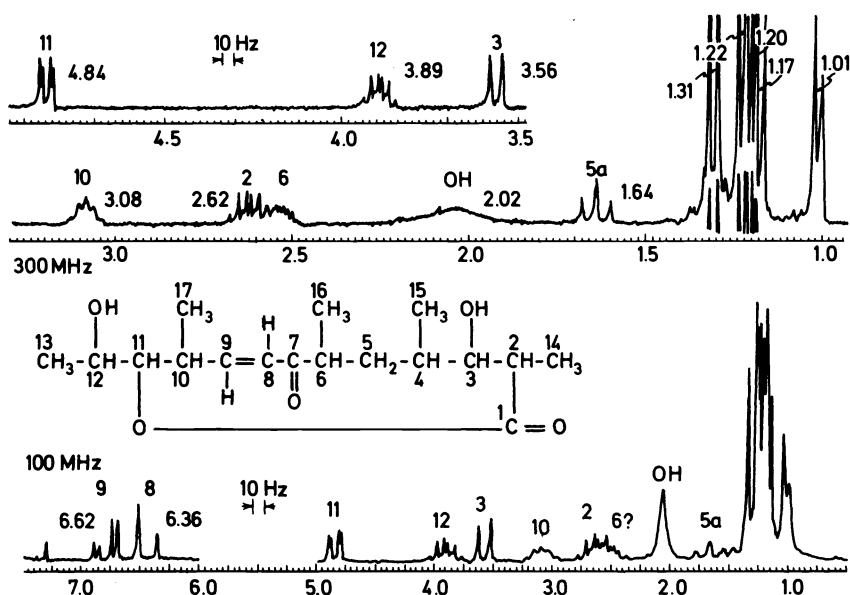
I turn now to our foray into cactus chemistry in the 1950s<sup>16</sup>. In this area we carried out a systematic investigation of a large number of related species of giant cacti from all over Central and South America. At the same time, it offered a most productive entry into triterpene chemistry, and in a period of approximately 6 years we established (primarily through chemical degradative work without recourse to p.m.r. or mass spectrometry) the structures of a dozen novel triterpenes (*Figure 10*), among which were found the first examples of naturally occurring triterpenoid lactones. It is interesting to note that, with the  $\beta$ -amyrin skeleton being used as a template **H**, aside from the



\* For an instructive recent example of the extensive use of mass spectrometry in the macrolide field, see D. E. F. Gracey, L. Baczynskyj, T. I. Martin and D. B. MacLean, *J. Chem. Soc. (Perkin I)*, 827 (1974).

Figure 1 displays the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compound **1**. The top spectrum is the  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) showing peaks at 4.60 (3H), 2.76 (2H), 2.53 (6H), 1.44 (5e), and 1.44 (5a). The bottom spectrum is the  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) showing peaks at 16, 15, 14, and 15. The chemical structure of **1** is shown below the spectra.

Figure 1 shows the  $^1\text{H}$  NMR spectrum of compound **1** in  $\text{CDCl}_3$ . The spectrum displays several peaks: a broad peak for  $\text{CO}_2\text{H}$  at 9.25 ppm, a multiplet for protons 3 at 4.60 ppm, and a complex set of peaks for protons 2, 6, and 5a in the aliphatic region between 1.0 and 3.5 ppm. A scale bar indicates 10 Hz.



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ubiquitous 3 $\beta$ -hydroxyl function, oxygenation is only observed on one contiguous chain of carbon atoms (circles in **H**), which implies that only that side of the molecule is exposed to enzymatic attack.

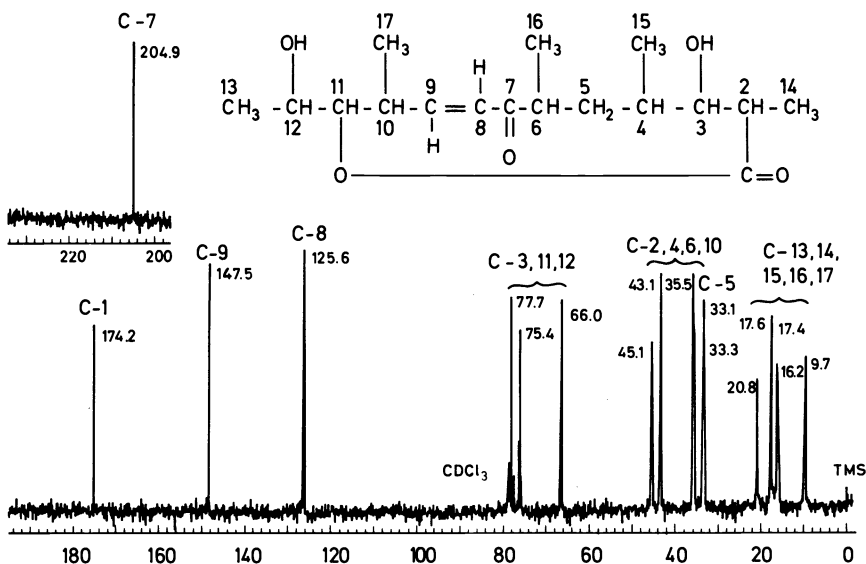


Figure 9.

Several years after we had terminated our systematic studies of novel cactus triterpenes, we examined the applicability of mass spectrometry to triterpenes. This work<sup>17</sup> led to the conclusion that retro-Diels-Alder fragmentation of  $\alpha$ - and  $\beta$ -amyrin triterpenes is a general phenomenon, which causes fragmentation of the molecule into two parts, as depicted schematically in Figure 11. The moiety retaining rings D, E and parts of C generally undergoes a second decomposition with loss of the substituent attached to C-17, so that it is a relatively simple matter to reduce the structural possibilities of newly discovered  $\alpha$ - and  $\beta$ -amyrins to just a few alternatives just from inspection of one mass spectrum. This paper<sup>17</sup> has been cited very frequently in triterpene chemistry, and the retro-Diels-Alder fragmentation shown in Figure 11 has proved to be a key element in the structure elucidation of many triterpenes during the past decade. The following example will show how chemical precedent among triterpenes led us down the garden path from which we were only rescued by mass spectrometry.

In collaboration with some Brazilian colleagues<sup>18</sup>, we investigated the toxic constituents of the Brazilian plant *Stryphnodendron coriaceum* and were able to show that its saponins were responsible for the reported toxicity to cattle. Acid hydrolysis led to two triterpenoid lactones ( $\text{B} = \text{C}_{30}\text{H}_{46}\text{O}_3$ ;  $\text{F} = \text{C}_{30}\text{H}_{46}\text{O}_4$ ) which were thought to be of a completely novel type because of the extreme ease (room temperature and atmospheric pressure) with which

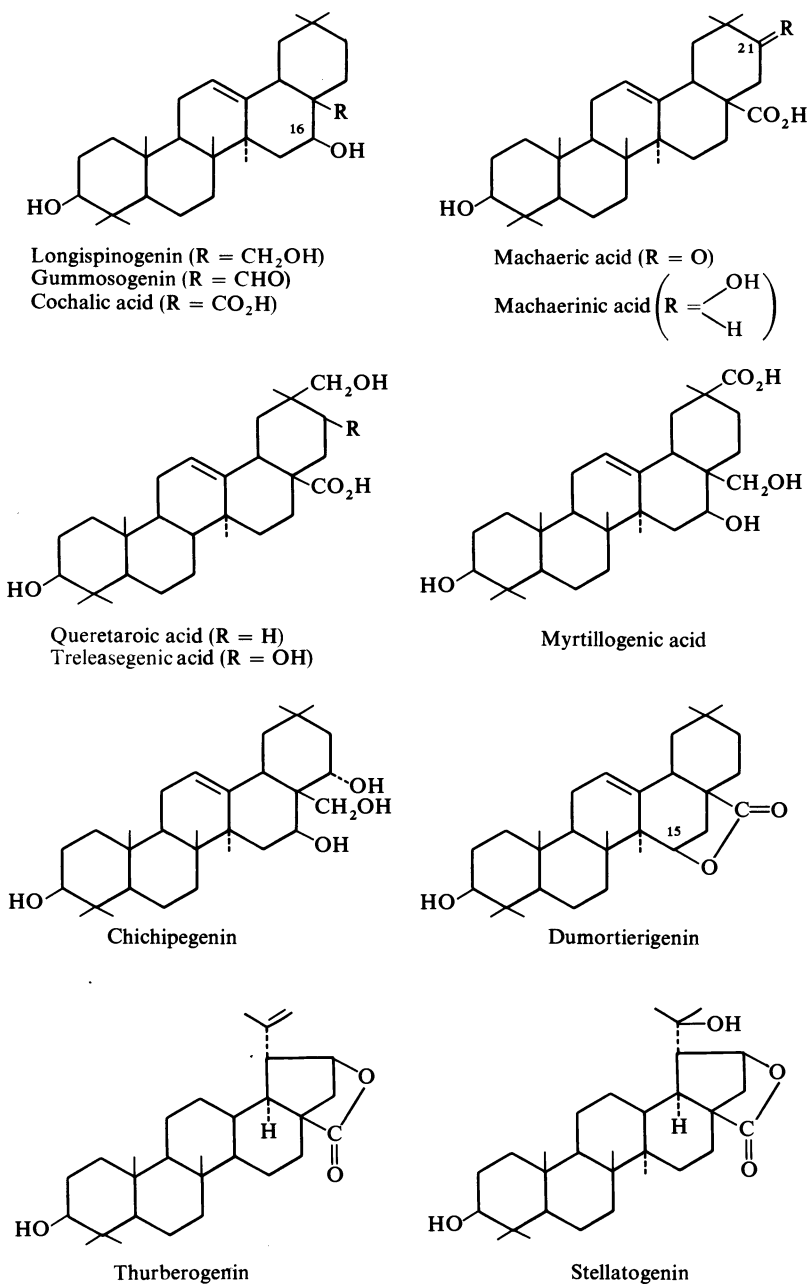


Figure 10.

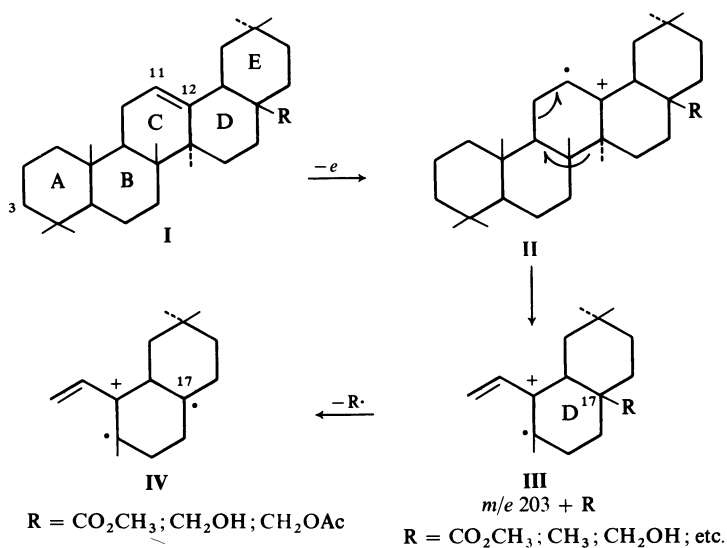


Figure 11.

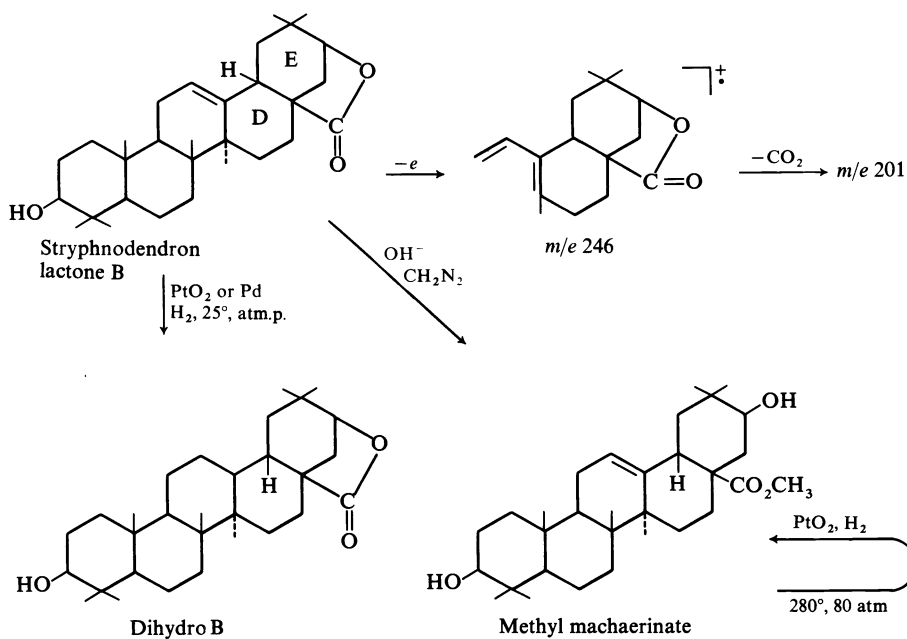
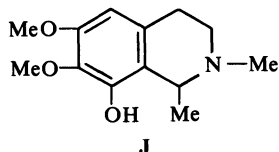
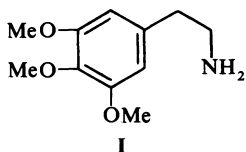


Figure 12.

the double bond could be reduced. Until that time one of the tenets of triterpene chemistry had been the non-reducibility of the  $\Delta^{12}$  double bond in  $\alpha$ - and  $\beta$ -amyrins. However, when the mass spectrum of lactone B was examined (see *Figure 12*), it was immediately noted that it underwent the typical retro-Diels–Alder fragmentation<sup>17</sup> to yield a diene fragment of mass 246, which still retained the lactone ring, as shown by its subsequent loss of carbon dioxide with production of an  $m/e$  201 peak. This observation encouraged us to ignore the unprecedented ease of hydrogenation and to assume that the substance might after all be a member of the  $\alpha$ - or  $\beta$ -amyrin class of triterpenes. To our embarrassment, we found that sapogenin B was simply the lactone of machaerinic acid—a cactus triterpene whose structure (*Figure 10*) had been established in our own laboratory<sup>19</sup> 7 years earlier. Apparently, lactone formation is associated with a drastic conformational distortion of rings D and E, which now exposes the otherwise sterically hindered double bond to ready catalytic hydrogenation.

Our investigations of cactus alkaloids offer another illustration of the powerful help that mass spectrometry and n.m.r. provide in areas of structure elucidation that would appear to be otherwise well suited to conventional chemical degradative methods. By the early 1950s a chemical study of cactus alkaloids appeared to be of only slight interest because of the relatively simple structures<sup>20</sup> of most of them (e.g. mescaline **I** and pellotine **J**)—most of the attention being centred on the biological (hallucinatory) properties of mescaline.



Given these circumstances, it was not surprising that we were extremely interested in pursuing the structure elucidation of a new cactus alkaloid, pilocereine, since its apparent empirical formula,  $C_{30}H_{42}O_4N_2$ , suggested that it was of much greater complexity than the hitherto known bases (**I**, **J**) from these plants. Our work<sup>21</sup>, summarized in *Figure 13*, led to the dimeric structure **1** (*Figure 13*), which appeared to us quite unequivocal, since we had synthesized the individual monomeric components (**2**, **3**, **4**, **5** in *Figure 13*) arising from the potassium–ammonia cleavage of the alkaloid. Five years later<sup>22</sup> we had occasion to measure the mass spectrum of pilocereine and to our surprise found that its molecular ion peak occurred at  $m/e$  757 ( $C_{46}H_{67}N_3O_6$ ) rather than at the expected value of 496 ( $C_{30}H_{44}N_2O_4$ ). Similarly, integration of the n.m.r. signals of pilocereine acetate (*Figure 14*) demonstrated that the alkaloid actually had to be a trimer rather than a dimer—a conclusion which was finally confirmed by further chemical experiments summarized in *Figure 14*. One of the monomeric fission products (**4** in *Figures 13* and *14*) had also been isolated by us from the cactus and apparently is the biogenetic precursor in a biological phenol oxidation terminating at the trimeric stage.

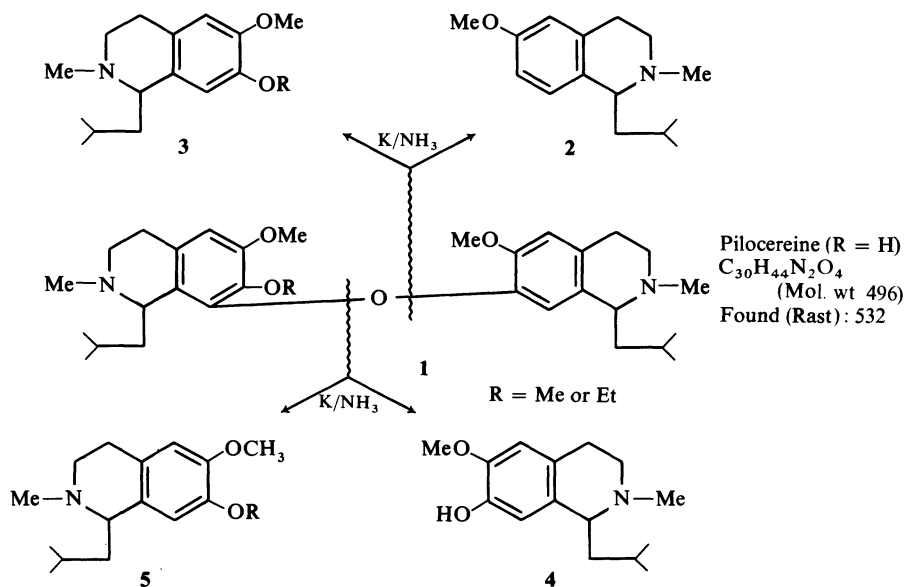


Figure 13.

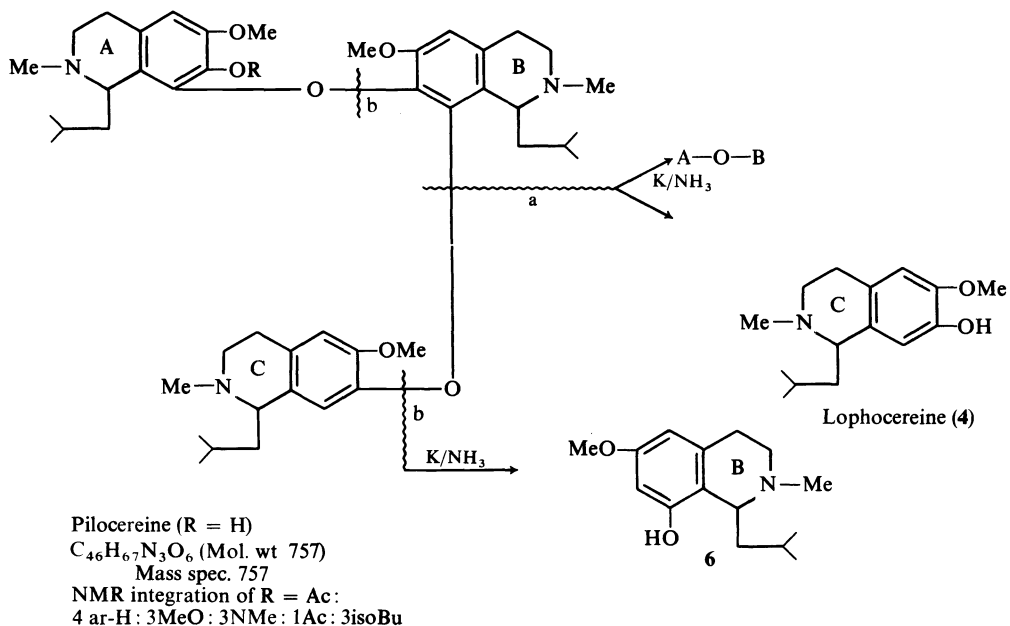


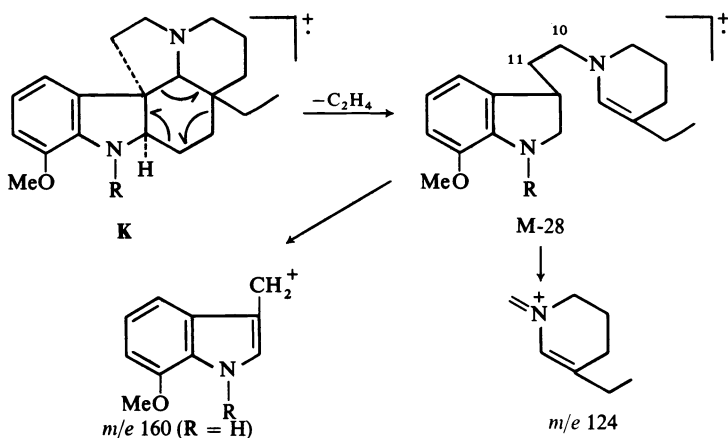
Figure 14.

Our work on triterpenes and alkaloids from giant cacti was terminated in the late 1950s, when we approached the point of diminishing returns by encountering largely products whose structures we had already established. Since our interest was primarily of a chemical rather than chemotaxonomic nature, we shifted our emphasis to another plant family, the *Apocynaceae*, which occupied us during most of the 1960s. These studies reflect rather accurately one of the significant events of that decade, namely the indole alkaloid explosion. This 'explosion' had an unusual quantitative as well as a qualitative component. Quantitative, in that a few hundred new alkaloids—many of them of amazing complexity—were isolated and their structures established<sup>23</sup> in a remarkably short time. Qualitative, in that the character of the structure elucidation work and of the biosynthetic investigations<sup>24</sup> had changed greatly. In all of natural products chemistry, the 1960s can clearly be considered to be the decade when the full impact of mass spectrometry and p.m.r. spectroscopy was felt, and in no area was this as noticeable as among indole alkaloids. The large numbers of diverse structural types which were reported almost bi-weekly offered superb material for the biosynthetic speculator, but this time tracer experimentation did not lag far behind, so that many hypotheses could soon be discarded or modified. In my opinion, this will be very much the model of the present decade for all of natural products chemistry: continued demonstration of the indispensability of mass spectrometry and p.m.r. for structure work coupled with greatly increased use of c.m.r. and especially of x-ray diffraction work (increasingly to be practised by organic chemists themselves rather than by x-ray crystallographers); continued and even more sophisticated biochemical experimentation centred at elucidating the more intimate details of the biogenesis of many presently known series (e.g. indole alkaloids); and increasing attention to new types that have so far not yielded to biosynthetic precursor incorporation.

An excellent example of the power of mass spectrometry can be provided by the *Aspidosperma* alkaloids—a group in which we became very interested because of our systematic investigation of Brazilian species of this important genus of the *Apocynaceae* plant family. At the time that we initiated this work, only five types of *Aspidosperma* alkaloids were known, which are summarized in Figure 15. While neither mass spectrometry nor p.m.r. played any significant role in the structure elucidation of the alkaloids shown in Figure 15, Biemann's<sup>25</sup> elucidation of the mass spectral fragmentation mode of aspidospermine ( $K, R = Ac$ ) marked a milestone which started a veritable flood of papers illustrating the power of this technique to the structure elucidation of indole alkaloids. The speed with which this occurred is best demonstrated by the fact that while Biemann's first paper<sup>25</sup> appeared only in 1961, by 1964 it was already necessary for us to summarize all of the accomplishments in this field in book form<sup>26</sup>. Biemann and collaborators<sup>25</sup> showed that aspidospermine ( $K, R = Ac$ ) and its relatives decomposed upon electron impact with loss of ethylene to provide an M-28 species, which then underwent further fission of the labile 10-11 bond with production of an intense peak at  $m/e$  124, encompassing the piperidine moiety of the alkaloid, and another peak at  $m/e$  160, due to the indole portion.

The over-all course of this mass spectrometric fragmentation is not greatly affected by substitution, as demonstrated, for instance, by our structure





elucidation<sup>27</sup> of the highly oxygenated *Aspidosperma* alkaloid aspidospermine (Figure 16). An even more dramatic illustration was the structure elucidation of the *Vinca* alkaloid vincadifformine, which was accomplished in a joint investigation with Janot's and Le Men's group<sup>28</sup>. The structure was established for all practical purposes by two mass spectra (Figure 17), those of the parent alkaloid and its dihydro analogue. Both spectra exhibited an intense *m/e* 124 peak, highly suggestive of the piperidine portion of aspidospermine (K, R = Ac), but instead of the latter's M-28 peak there occurred now the

#### Typical *Aspidosperma* alkaloids

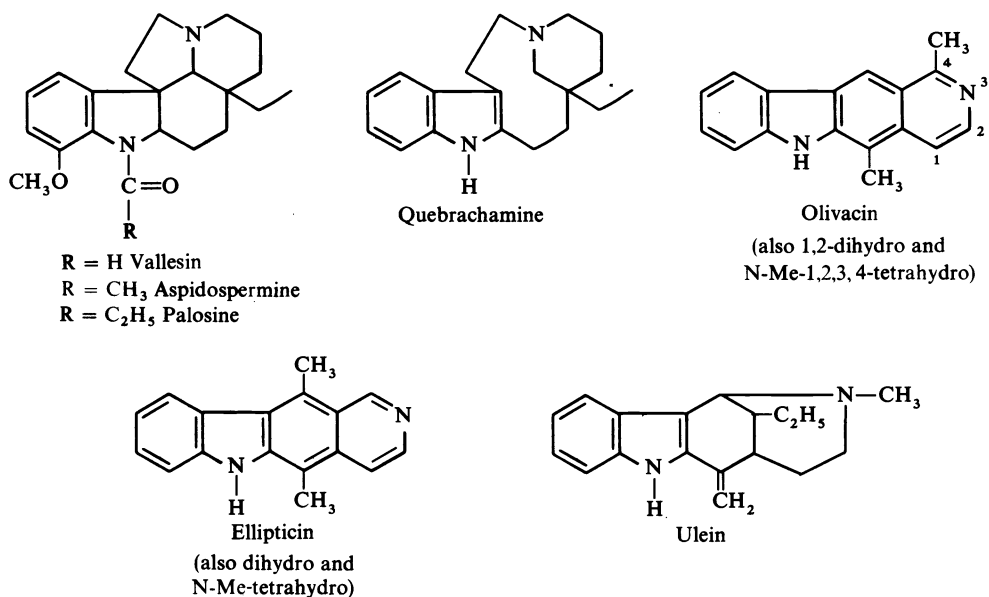


Figure 15.

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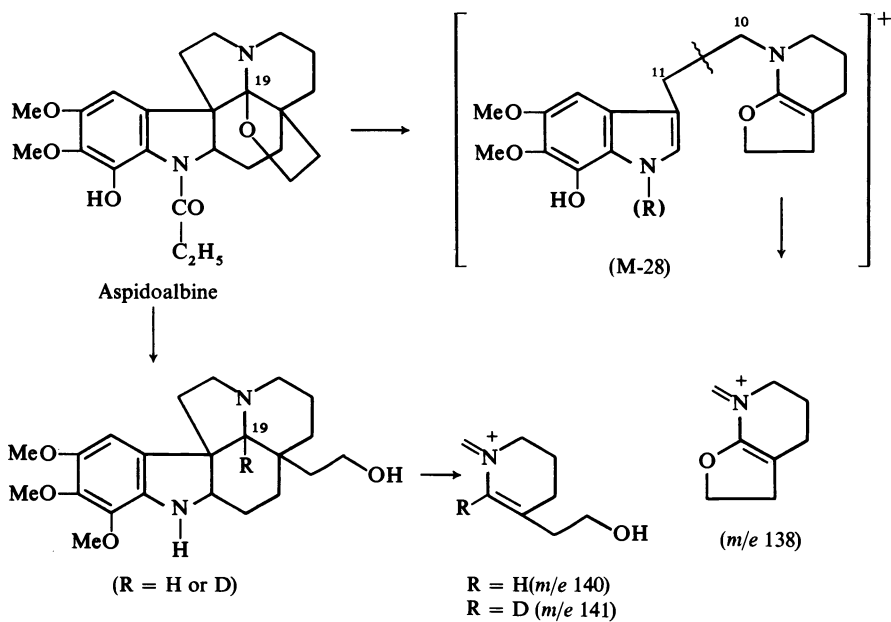


Figure 16.

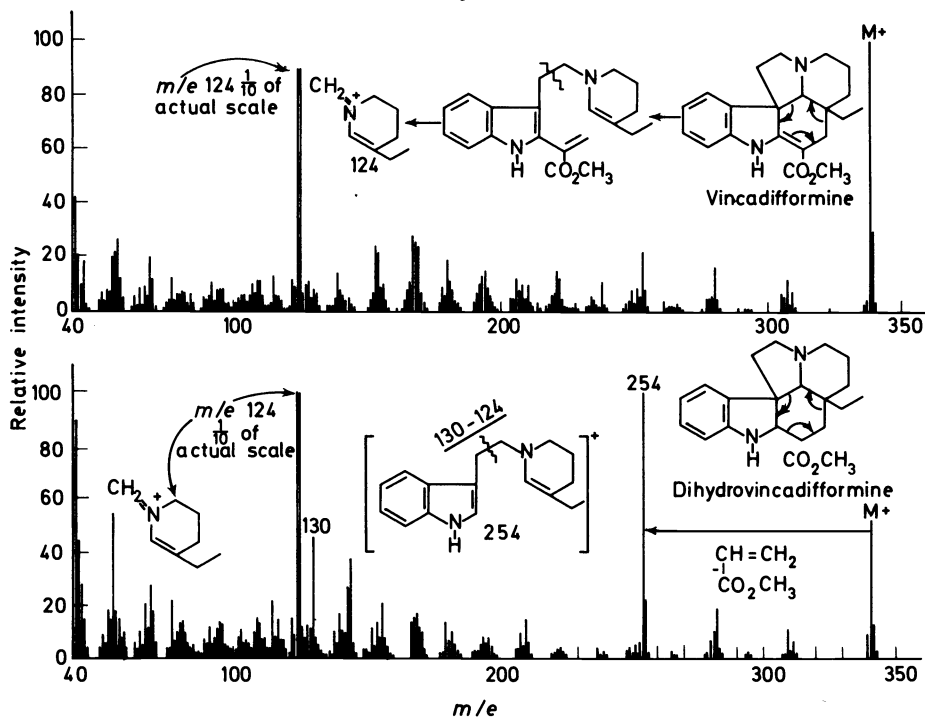
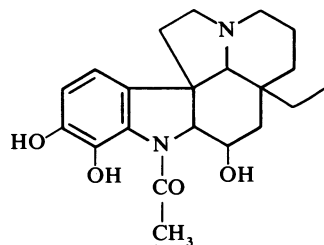
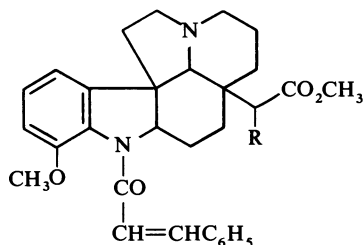


Figure 17.

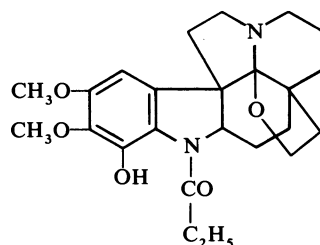
Typical *Aspidosperma* alkaloids



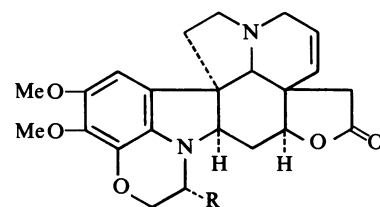
Spegazzinidine  
[*J. Amer. Chem. Soc.* **84**, 3480 (1962)]



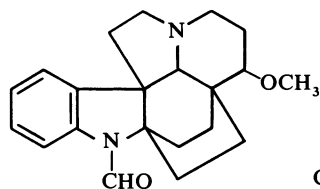
Cylindrocarpine (R = H)  
[*Tetrahedron*, **16**, 212 (1961)]  
R = OH [*J. Chem. Soc.(C)* 417 (1969)]



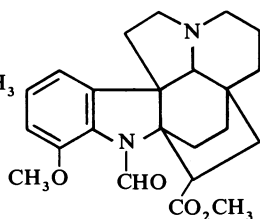
Aspidalbine  
[*Tetrahedron Letters* 1001, (1962)]



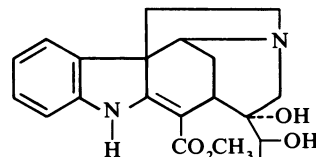
Obscurinervine (R = Et)  
Obscurinervidine (R = Me)  
[*J. Amer. Chem. Soc.* **86**,  
2451 (1967);  
*Tetrahedron Letters*,  
2527, (1971)]



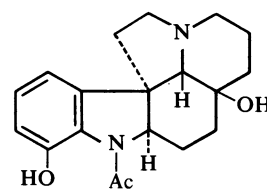
Refractidine  
[*Tetrahedron Letters* 59 (1962)]



Refractine  
[*J. Amer. Chem. Soc.* **84**, 1499 (1962)]

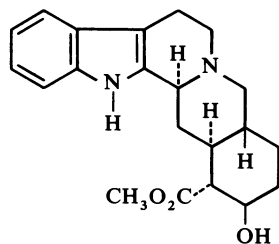
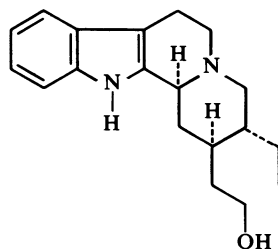


Compactinervine  
[*Experientia*, **19**, 467 (1963)]

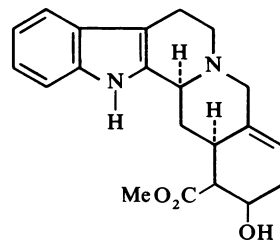


Aspidodispermine  
[*Tetrahedron Letters*, 5837 (1968);  
3015 (1970)]

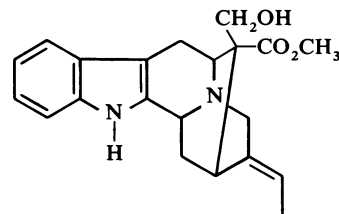
Figure 18.

Typical *Aspidosperma* alkaloids $\beta$ -Yohimbine[*J. Amer. Chem. Soc.* **84**, 2161 (1960)]

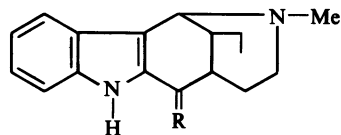
Dihydrocorynantheol

[*J. Org. Chem.* **27**, 4702 (1962)]

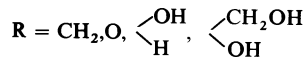
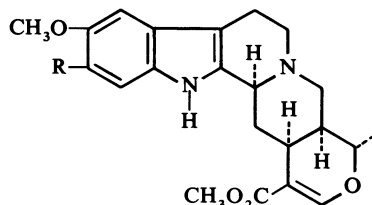
19-Dehydroyohimbine

[*Experientia*, **21**, 566 (1965)]

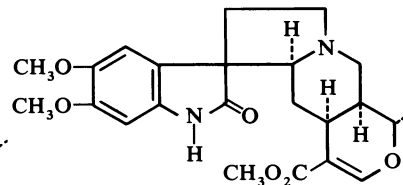
Polynuridine

[*J. Amer. Chem. Soc.* **84**, 2161 (1960)]

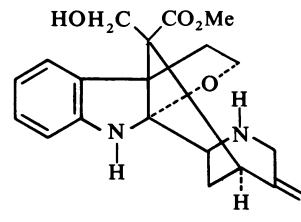
Uleine types

[*Tetrahedron* **21**, 1717 (1965)]

R = H: Aricine

[*J. Org. Chem.* **27**, 4702 (1962)]R = OCH<sub>3</sub>: Isoreserpiline[*Experientia*, **19**, 585 (1963)]

Carpanaubine

[*J. Amer. Chem. Soc.* **85**, 1523 (1961)]

Aspidodasycarpine

[*Tetrahedron Letters* 3899 (1964)]

Figure 19.

# NATURAL PRODUCTS CHEMISTRY 1950 TO 1980

## Some alkaloids from *Vallesia dichotoma*

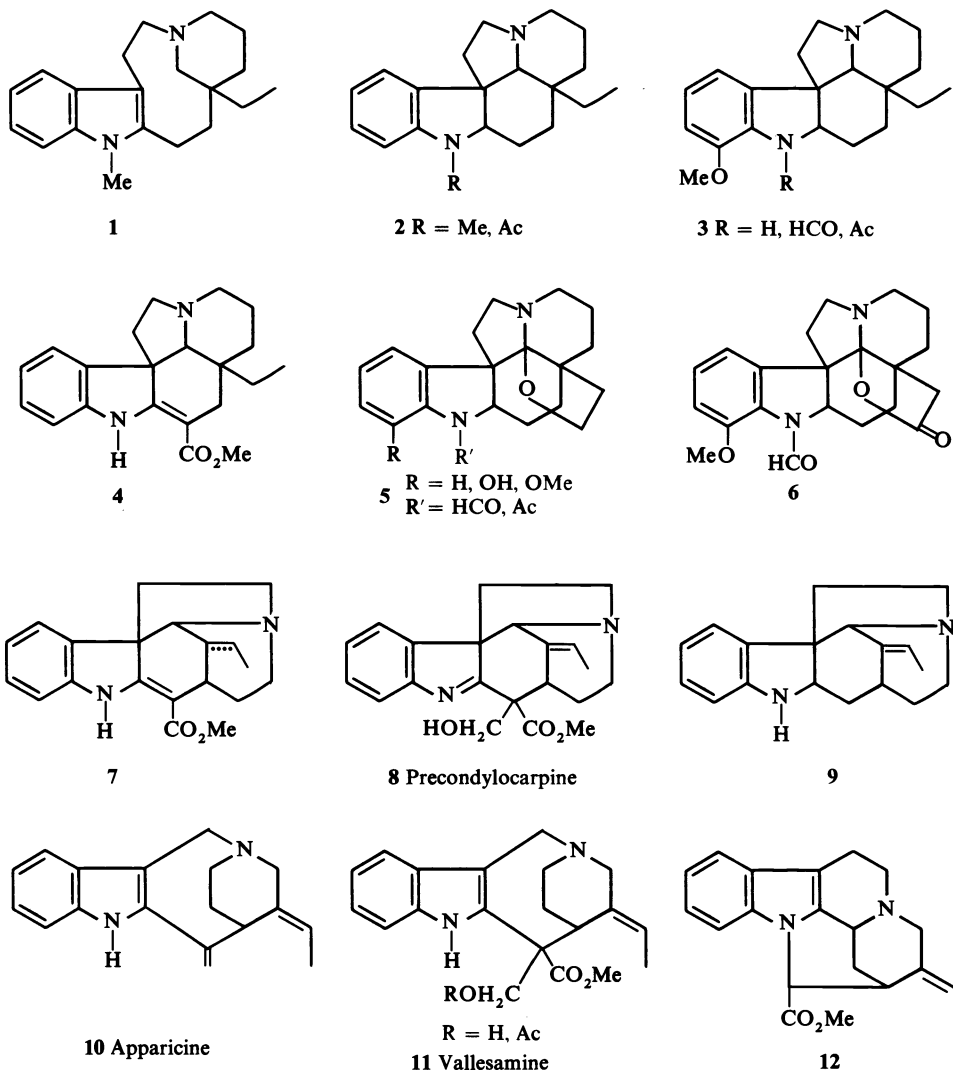
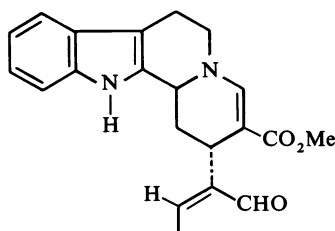


Figure 20.

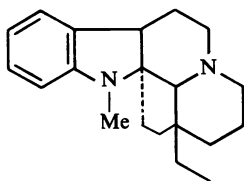
loss of the elements of methyl acrylate. Such a loss of methyl acrylate was not observed in the mass spectrum (Figure 17) of vincadifformine itself, presumably because this molecule underwent initial opening of the C ring by a retro-Diels–Alder reaction followed by fission of the 10–11 bond. This was the first demonstration of an aspidospermine-like skeleton in a *Vinca* species—an observation that was duplicated numerous times in the following years.

Figures 18 and 19 summarize only a few of the alkaloids isolated during the early 1960s in our laboratory from various Brazilian *Aspidosperma* species; with a few exceptions (e.g.  $\beta$ -yohimbine, dihydrocorynantheol), their structures were unknown. The speed with which these structures were established could to a large extent be attributed to the very extensive utilization of mass spectrometry (coupled with judicious deuterium labelling) and p.m.r. spectroscopy in our laboratory.

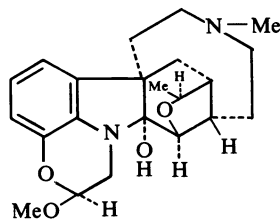
Some alkaloids from *Vallesia dichotoma*



Vallesiachotamine  
(with Monteiro, Walser)  
[*J. Amer. Chem. Soc.* **88**, 1792 (1966)]



Vallesamidine  
(with S. Brown)  
[*J. Amer. Chem. Soc.* **90**, 2445 (1968)]



Dichotine  
(with Ling)  
[*J. Amer. Chem. Soc.* **92**,  
222, 6019 (1970)]

Figure 21.

Another alkaloid gold mine was the Peruvian plant *Vallesia dichotoma*, from which nearly 30 new alkaloids were isolated in our laboratory. The structures of some of the more interesting members are reproduced in Figures 20 and 21. Even the non-specialist in the alkaloid field will realize from a perusal of Figures 18–21 that biogenetic relations among many of these alkaloids can be postulated purely on the basis of chemical intuition. Many of these have been verified by sophisticated tracer studies<sup>24</sup>, and several of the alkaloids encountered by us for the first time—for instance, precondylocarpine (8 in Figure 20)—have proved to be key intermediates in well-established biogenetic schemes<sup>24</sup>.

The utility of isolating novel types from closely related botanical species in terms of suggesting possible experimental approaches to the elucidation of biosynthetic pathways can be illustrated by two examples among indole alkaloids. One of them is the question of the biogenesis of uleine (Figure 15)—an alkaloid lacking the usual tryptamine bridge. The isolation of diverse alkaloids (see Figure 22) together with various uleine types in *Aspidosperma dasycarpon* led us to propose<sup>29</sup> a hypothetical scheme which involves oxidative fission of the tryptamine bridge next to N<sub>6</sub> (see, for instance, aspidodasycarpine structure), followed by oxidative attack at C-3 and fragmentation, as indicated in Figure 22, of the two-carbon bridge with its oxygen substituent. Clearly, such a hypothesis is amenable to biochemical verification, although Kutney's<sup>24</sup> experiments with labelled precursors have not yet settled this question.

Another pertinent example is our attempt<sup>30</sup> (see Figure 23) to rationalize the existence of the unique carbon skeleton of vallesiachotamine (Figure 21). If

one postulated enzymatic hydroxylation next to  $N_b$  of a precursor such as geissoschizine or sitsirikine, the carbinolamine **I** could then open to the aldehyde ammonia form **II**\*. Rotation around the latter's 14, 15-bond would provide **III**, which could now cyclize to vallesiachotamine.

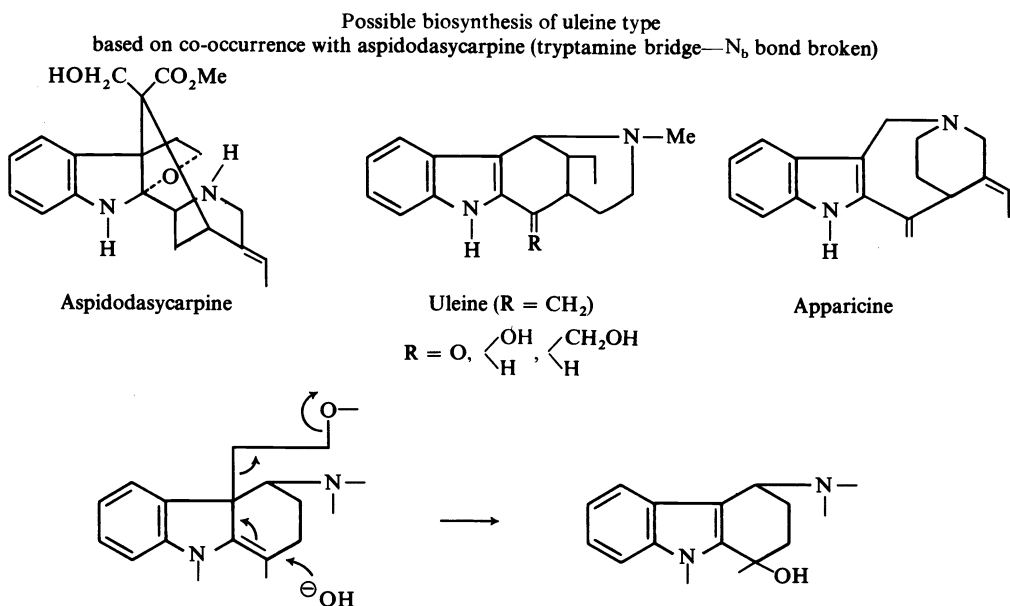


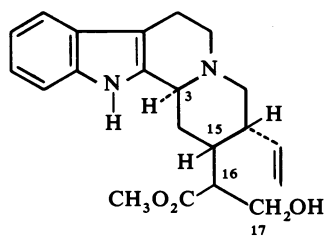
Figure 22.

Such biosynthetic speculation involving alternative forms of aldehyde ammonia intermediates is, of course, not limited to indole alkaloids. A recent investigation<sup>31</sup> of a lupine species growing near our laboratory utilizing gas chromatography coupled with mass spectrometry uncovered the presence of a variety of simple alkaloid types (Figure 24), aside from the usual lupine alkaloid, lupinine. These included the 'pomegranate' alkaloid, *N*-methylnelutrine, and the tobacco alkaloid, anabasine, as well as hystrine and ammodendrine. While the structures of all of these bases were known, their co-occurrence in a lupine species is of some biogenetic interest, but it can be readily accommodated in the context of experimentally well established schemes starting with lysine. This is not necessarily true of smipine (Figure 24), a simple but hitherto unknown alkaloid. Its co-occurrence with ammodendrine (Figure 25, 1, R = Ac) raises the interesting possibility, schematically depicted in Figure 25, that singlet oxygen attack upon ammodendrine may lead to an aldehyde intermediate **3**, which may cyclize to the eight-membered carbinolamine (**4**). Opening in the alternative direction

\* This is really the aglycone of strictosidine which was reported (G. N. Smith, *Chem. Comm.* 912 (1968) to yield vallesiachotamine during 'routine extraction' of the alkaloids. It is conceivable, therefore, that Figure 23 depicts portions of the *in vitro* rather than *in vivo* generation of vallesiachotamine.

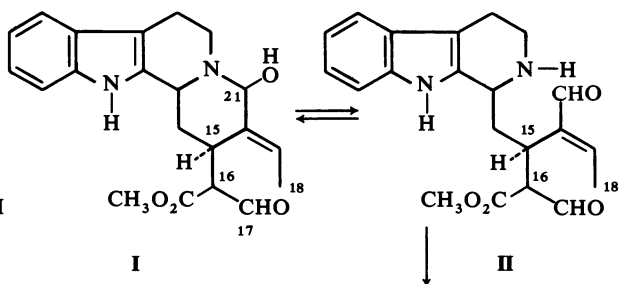
# CARL DJERASSI

## Possible biogenesis



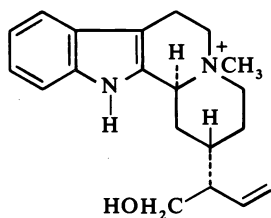
Sitsirikine

[Kutney, Brown,  
*Tetrahedron Letters*, 1815 (1963)]



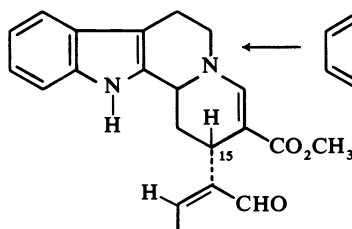
I

II

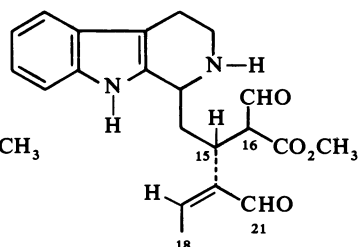


Hunterburnine

[Robertson, Sim, Taylor  
*et al.*, *Proc. Chem. Soc.* 72 (1962)]



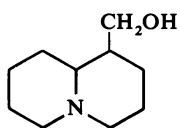
Vallesiachotamine



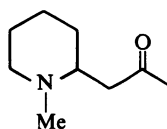
III

Figure 23.

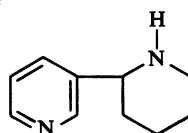
## Alkaloids of *Lupinus formosus*



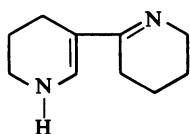
Lupinine



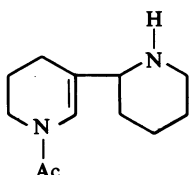
N-Me Pelletierine



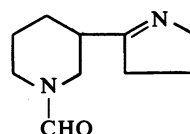
(-)-Anabesine



Hystrine



(+)-Ammodendrine



(±)-Smipine

Figure 24.



to **5** and recyclization with the keto function of **5** would then provide the smipine skeleton (**6**). The reason why such a variety of alkaloids was encountered from one lupine species is probably not the uniqueness of *Lupinus formosus* but rather the fact that very sensitive separation and detection techniques (gas chromatography coupled with mass spectrometry) were employed. It is likely that similar re-investigations of previously studied plant materials by more modern techniques will become more prevalent and will prove useful in outlining likely biogenetic schemes, which could then be examined experimentally.

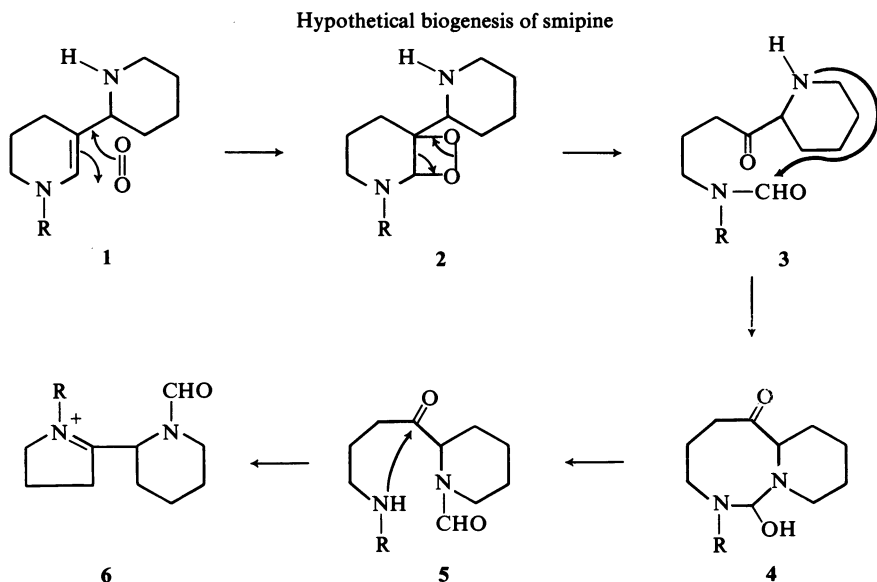


Figure 25.

In the introductory paragraphs of this paper I called attention to the fact that, in addition to changes in methodology, there has also occurred a noticeable increase in activity on natural products from marine sources. These will be covered in other sections of this symposium, but since our own emphasis has shifted to a considerable extent from plant to marine sources, a few recent trends in this field will be illustrated through results from our own laboratory with steroids and terpenoids.

Largely through the pioneering studies of Bergmann during the 1940s, the structures of many marine sterols<sup>32</sup> were established. All of them were variants of the cholesterol skeleton, often with one or two carbon units attached to C-24. Three typical examples (brassicasterol, fucosterol and chondrillasterol) are reproduced in Figure 26, and while very little is known about their biogenesis in marine organisms, they clearly fall into the exceedingly well studied pattern of sterol side chain biosynthesis<sup>6, 33</sup>. After an

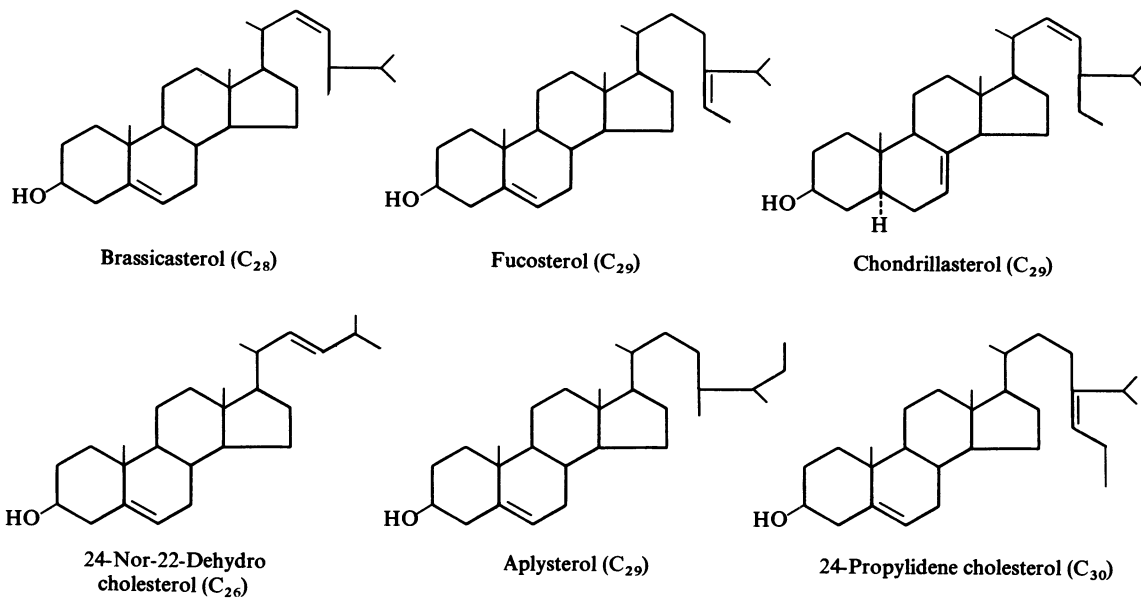


Figure 26.

interregnum of nearly two decades when few exciting advances in marine sterol chemistry occurred, suddenly several exceedingly interesting new sterols were detected. In each instance mass spectrometry played a crucial role, which is not surprising, since this technique really entered the steroid field only during the last decade<sup>34</sup>. Of the other three sterols shown in *Figure 26*, aplysterol<sup>35</sup> and 24-propylidencholesterol<sup>36</sup> constitute examples of new methylation sites (C-26 and C-29, respectively), while 24-nor-22-dehydrocholesterol<sup>37</sup> is particularly intriguing, since it represents the first naturally occurring C-26 sterol.

## Capnellanes

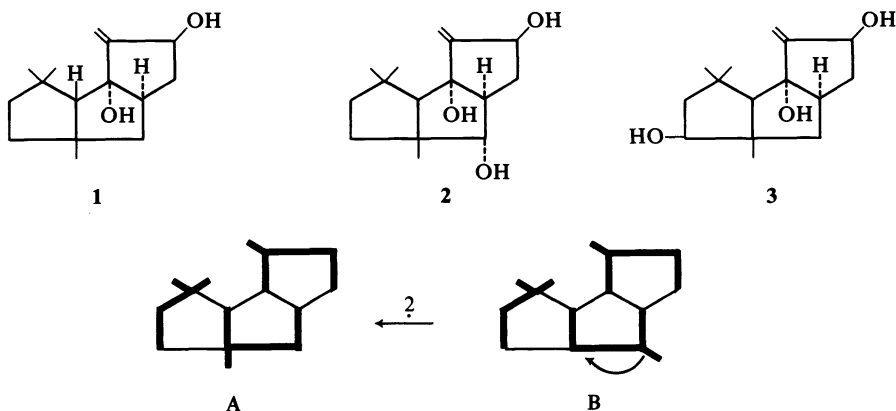
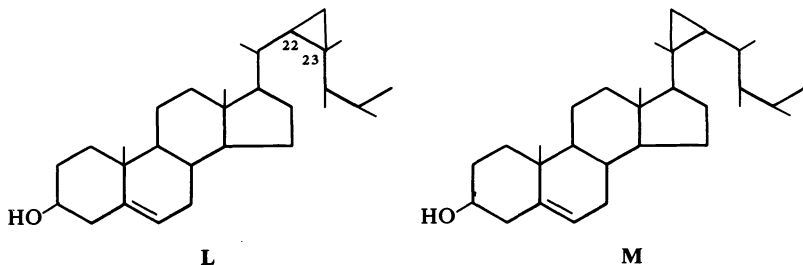


Figure 27.

Even more interesting is gorgosterol, a sterol first encountered by Bergmann in 1943. Seventeen years later we were able to show<sup>38</sup> through a combination of mass spectrometric and p.m.r. measurements as well as appropriate chemical reactions of its cyclopropane ring that gorgosterol had to possess either structure **L** or **M**. A rigorous decision in favour of **L** was reached<sup>39</sup> by x-ray crystallography, which has already reached such a stage of instrumental and interpretative simplicity that organic chemists themselves (in this case, N. C. Ling of our laboratory) can solve such structures in a period of weeks. Gorgosterol is unique in that it not only represents the first sterol with a cyclopropane ring in the side chain but also the first one that displays alkyl substitution at positions 22 and 23.



The isolation of these new marine sterols illustrates two facets of marine chemistry. First, in numerous instances novel structural types are encountered, which are of great biogenetic interest and which have not yet been found in terrestrial sources. Another recent example from our own work<sup>40</sup> are the capnellanes—a novel class of sesquiterpenoid alcohols (1, 2, 3 in *Figure 27*)—which are based on the hitherto unknown skeleton A. It is conceivable that this unusual sesquiterpenoid structure may have arisen in the *Alcyonarian* by *in vivo* methyl migration (e.g. B  $\rightarrow$  A in *Figure 27*). The second feature of marine chemistry is that at this stage we are just at the beginning of experimental biosynthetic studies. Just as such work in plants followed earlier work in animals by over a decade because of experimental difficulties, similar delays are being encountered in biosynthetic studies with marine organisms. This is not only due to the complications associated with radioactive precursor incorporation but also because frequently it is not even clear where and by whom the natural product is biosynthesized. For instance, gorgosterol L has been isolated from many soft corals which live symbiotically with unicellular algae (zooxanthellae), and nobody has so far been able to incorporate radioactive precursors of gorgosterol into either component. Another possible exogenous source of many marine products may be the plankton, and it remains to be seen how the biosynthesis of natural products of planktonic origin will be attacked experimentally. These are clearly areas of great potential in the coming years.

Other interesting steroid types which have been studied recently in our laboratory are summarized in *Figure 28*. They are derived from sea cucumbers and starfish and have one feature in common, namely a  $\Delta^{9(11)}$  double bond, which offers a potential hemisynthetic route to 11-oxygenated steroids. Indeed, one of the starfish aglycones proved to be  $\Delta^{9(11)}$ -pregnen-3 $\beta$ , 6 $\alpha$ -diol-20-one<sup>41</sup> which could be converted<sup>42</sup> into cortical hormones such as hydrocortisone. In retrospect, it may be fortunate that this discovery was not made two dozen years earlier, when there was a world-wide search for plant precursors suitable for corticosteroid synthesis (viz. African expeditions in search for sarmentogenin<sup>43</sup>). It is conceivable that considerable ecological damage would have been caused by indiscriminate large-scale harvesting of starfish for such purposes.

## EPILOGUE

What is my prognosis for natural products chemistry for the remainder of this decade? While the decade of the 1960s differed drastically from the 1950s—primarily because of the major impact of sophisticated physical methods and separation techniques—I predict a much smaller qualitative difference between the 1960s and the present decade. Physical methods will continue to play the dominant role in structure elucidation, and the major advances along these lines to be expected during the next few years are the much wider use by organic chemists themselves (rather than by x-ray crystallographers) of x-ray crystallography and the routine use of c.m.r. spectroscopy. In fact, the most significant contribution that could probably be made to natural products methodology in the near future is an instrumental one—the availability of

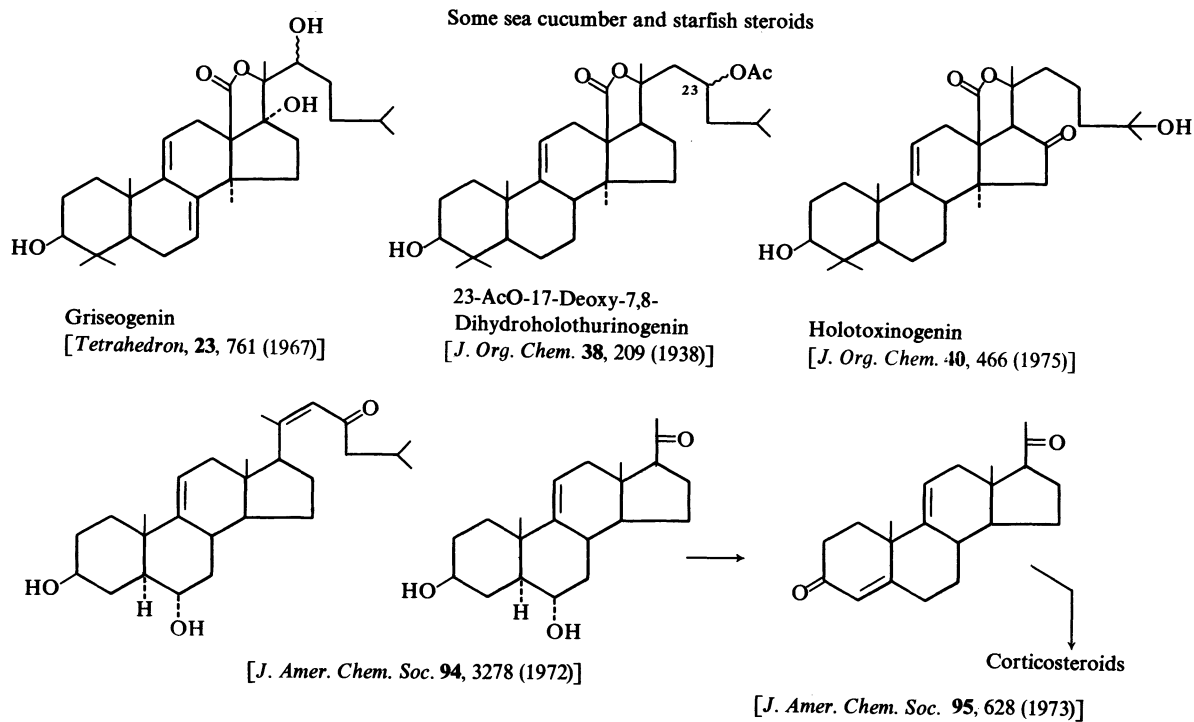


Figure 28.

c.m.r. instrumentation that would permit the routine obtention of c.m.r. spectra on 1–5 mg of substance.

Experimental biosynthetic studies will continue to flourish, and much greater attention will be paid along these lines to natural products from marine sources. What about practical applications? There is always the hope that another reserpine may be found. Considering the extensive screening programmes of natural products in the cancer field, at least statistically there exists a sporting chance that a practical therapeutic agent may emanate from such empirical searches. The greatly increased activity in the insect chemistry field may offer the most immediate practical results. Insect pheromones—an academic novelty 10 years ago—are already being sold for extensive monitoring of insect infestations, and the present field trials on the possible control of some insect pests through the use of confusion or mass trapping techniques with pheromones point towards a second use of even greater potential. The isolation and structure elucidation of the insect juvenile hormones provided the impetus for the synthesis of hormone analogues<sup>44</sup> which are about to be introduced as practical insect control agents, and similar leads are likely to arise from other lines of insect chemical research.

## ACKNOWLEDGEMENT

The work from our laboratory reviewed in this paper has of course not been done by one person. I consider myself simply a spokesman for a large group of predoctoral and postdoctoral collaborators—the latter from many different countries—whose names are listed in the attached bibliography.

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