PROGRESS IN DRUG RESEARCH
FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG
PROGRÈS DES RECHERCHES PHARMACEUTIQUES

VOL. 13

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Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progrès des recherches pharmaceutiques
Vol. 13

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PREFACE

Ten years have elapsed since the appearance of the first Volume and it is with great pleasure that the Editor is now able to present Volume 13. During these ten years various fields of drug research have undergone important, partly revolutionary, changes. A number of these have already been dealt with, so that the series PROGRESS IN DRUG RESEARCH contains a comprehensive review of a substantial part of our current knowledge. The Editor is particularly grateful for the opportunity of transmitting to those connected with the development of drugs the extensive knowledge of the Authors, who, without exception, are themselves actively engaged in research.

Drug research is currently in a state of transformation: reconsideration in the light of the past and reorientation with a view to the future. To a large extent this is due to the tumultuous developments in the last 20 years, developments which are unparalleled in the history of medicine and the consequences of which cannot yet be completely evaluated. Unfortunately, however, the current situation is not devoid of its unpleasant and even tragic aspects, aspects which fall outside the research worker's sphere of influence. Those connected with drug research, be they in industry, in universities or in clinics, are aware of these problems, and, as a result of this awareness, are all the more in need of an aid which will assist them in ascertaining the current position and in fixing future goals. The Editor and the Authors hope that in this respect also PROGRESS IN DRUG RESEARCH will be useful to research workers and further the development of our science.

In addition to thanking the Authors and the Publishers, the Editor would like to express the hope that the international collaboration, which has hitherto succeeded to such an exceptional extent to the benefit of all, will continue so that the value of this series as a reference work will steadily increase. Judging from the manner in which the series has thus far been received and from the Volumes currently in preparation, this hope appears to be justified.

VORWORT

Seit dem Erscheinen des ersten Bandes sind zehn Jahre vergangen, und der Herausgeber freut sich, der Fachwelt hiermit den 13. Band übergeben zu können. In dieser Zeitspanne haben auf verschiedenen Gebieten der Arzneimittelforschung wichtige, zum Teil umwälzende Entwicklungen stattgefunden; einzelne davon wurden in dieser Reihe bereits behandelt, mit dem Resultat, daß die FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG in ihrer Gesamtheit einen nicht unwesentlichen Teil unseres heutigen Wissens in zusammenfassender Darstellung enthalten. Der Herausgeber schätzt sich glücklich und ist dankbar für die Möglichkeit, mit diesem Werk das umfassende Wissen der Autoren, die ausnahmslos mitten in der aktiven Forschung stehen, zahlreichen in der Arzneimittelforschung Tätigen vermitteln zu dürfen.

Unser Forschungsgebiet befindet sich zurzeit in einer Phase des Umbruchs, der Besinnung auf Vergangenes und der Umorientierung auf die Zukunft. Diese Situation ist zum Teil der äussere Ausdruck und das Resultat der stürmischen Entwicklung der letzten 20 Jahre, die in der Geschichte der Medizin ohne Parallele dasteht, und deren Folgeerscheinungen noch gar nicht überblickt werden können. Zum Teil aber hängt die jetzige Lage mit unerfreulichen und auch tragischen Ereignissen zusammen, die außerhalb der Einflußsphäre der Arzneimittelforscher liegen. Die an der Arzneimittelforschung Beteiligten, seien sie Mitarbeiter der Industrie oder Forscher an Universitäten und Kliniken, sind sich der Problematik dieser Situation bewußt. Um so mehr bedürfen sie alle eines Hilfsmittels, das ihnen bei der Standortbestimmung und zur Neuorientierung dienen kann. Der Herausgeber und die Autoren hoffen, daß die FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG auch in dieser Hinsicht dem aktiven Forscher nützen und die Weiterentwicklung unserer Wissenschaft fördern können.

Zum Schluß dieser Betrachtungen möchte der Herausgeber nicht nur in gewohnter Weise den Autoren und dem Verlag danken, sondern darüber hinaus auch die Hoffnung aussprechen, daß die auf internationaler Ebene bisher so ersprießlich verlaufene Zusammenarbeit aller Beteiligten auch in Zukunft erhalten bleibt, um das Werk immer mehr zu einer wertvollen, viel benutzten Institution werden zu lassen. Die bisherige Aufnahme in Fachkreisen und die vorbereiteten weiteren Bände lassen diese Hoffnung als berechtigt erscheinen.

PRÉFACE

L'éditeur a aujourd'hui le plaisir de remettre au public le volume 13 de l'ouvrage, dix ans après la parution du premier. Durant ce laps de temps, les recherches pharmaceutiques ont subi, dans différents secteurs, des développements considérables, voire même, en partie, révolutionnaires; d'aucuns ont été déjà traités dans la présente série, si bien que les PROGRÈS DES RECHERCHES PHARMACEUTIQUES, pris dans leur ensemble, contiennent une part importante de nos connaissances actuelles sous forme d'aperçus généraux. L'éditeur est heureux de pouvoir, par ce canal, faire bénéficier les nombreuses personnes occupées aux recherches pharmaceutiques de la vaste science des auteurs, tous engagés activement dans la recherche et auxquels il se sent profondément obligé.

Notre champ de travail se trouve en ce moment dans une phase de transformation, de réflexion sur le passé et d'orientation nouvelle pour l'avenir. Cette situation est, en partie, la manifestation et le résultat du développement impétueux des vingt dernières années, développement sans précédent dans l'histoire de la médecine et dont les conséquences ne peuvent encore être évaluées; mais elle provient aussi, pour une part, d'événements malheureux, tragiques même, qui échappent à la sphère d'action de la recherche pharmaceutique. Ceux qui y collaborent, que ce soit dans l'industrie ou dans les universités et les cliniques, sont pleinement conscients des problèmes que pose cette situation nouvelle. Ils ont d'autant plus besoin d'un instrument qui puisse les aider à déterminer leur position et à se fixer une orientation nouvelle. L'éditeur et les auteurs espèrent que les PROGRÈS DES RECHERCHES PHARMACEUTIQUES s'avéreront utiles aux chercheurs, à cet égard aussi, et contribueront au développement ultérieur de leur discipline.

Au terme de ces considérations, l'éditeur ne voudrait pas seulement remercier, comme d'habitude, les auteurs et la maison d'édition, mais il tient en outre à exprimer l'espoir que la collaboration de tous les participants, qui s'est réalisée jusqu'ici au plan international d'une façon si satisfaisante, se poursuivra à l'avenir, pour que l'ouvrage devienne toujours davantage un instrument précieux et d'emploi fréquent. L'accueil qu'il a reçu dans les milieux intéressés et les articles à paraître dans les volumes suivants, en préparation, permettent de penser que cet espoir sera justifié.

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VOL. 13

Biological Activity of the Terpenoids and Their Derivatives – Recent Advances

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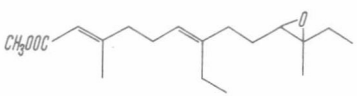
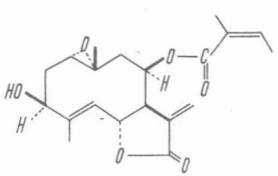
1. Introduction

The 6 years that have elapsed since the subject of biological activity in terpenoids and their derivatives was previously reviewed in this series [1] have witnessed many notable advances in our knowledge of the pharmacological, physiological and biochemical properties of this major group of compounds. For instance, a number of triterpene acids have recently been shown [2–6] to be potent uncoupling agents of oxidative phosphorylation, i.e. to inhibit the mitochondrial biosynthesis of adenosine-5′-triphosphate without inhibiting mitochondrial respiration – an action which is suggested [7] to be linked with their anti-inflammatory activity [8–13] and ability to heal gastric ulcers [14 to 19]. Again, it is now apparent that various lower terpenoids have a much greater physiological significance in insects and in plants than was realised at the time of the earlier survey and so the new approaches to insect control and weed control opened up by this knowledge can be expected to see intensive exploitation in the near future. In the case of insects, apart from the discoveries of further terpenoids as constituents of defensive secretions in various species, a number of mono- and sesqui-terpenoids have now been assigned their rightful place beside other relatively simple aliphatic compounds as pheromones and sex attractants of particular species [20–22]. Further, the fact that various sesquiterpenoids closely mimic the actions of the juvenile hormones of different insects [23–30] gives strong support to the view that at least some of these agents, such as the juvenile hormone, I [31] of the giant silkworm moth *Hyalophora cecropia*, are in fact sesquiterpenoid derivatives. In the plant kingdom,

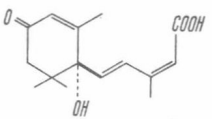


I

new horizons have appeared with the discovery that certain sesquiterpenoids are natural plant growth inhibitors. Specific examples are heliangin (II) [32, 33] and abscisin II (III) [34, 35], which was first characterised as one of two abscission-accelerating substances present in young cotton fruit [36] and later shown [37] to be identical with dormin, the dormancy factor of sycamore leaves. Indeed, subsequent discovery [38–42] of complex and apparently species-depen-



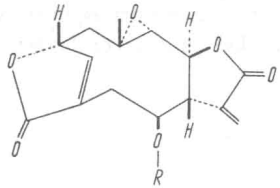
II



III

dent interplay of agonistic and antagonistic properties between abscisin II, indole acetic acid and the diterpenoid gibberellins (of which some twenty-five have now been fully characterised [43] including one member which occurs as

a glycoside [44]) has served to focus new attention upon the intricacies of growth control in plants and the important role played in it by terpenoids. Moreover, that repression of cell growth may, in fact, be a general characteristic of certain types of sesquiterpenoids is suggested by the anti-tumour properties recently shown to be associated with several representatives of this group [45 to 51], two of which, elephantin (IVa) and elephantopin (IVb) [48] are highly oxygenated germacrane derivatives somewhat similar in structure to heliangin.



a, R = $-COCH{=}CMe_2$: b, R = $-COCMe{=}CH_2$

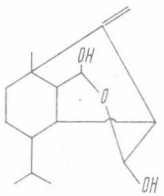
IV

An increasing number of fungal toxins are proving to be terpenoids, while the number of terpenoid antibiotics now known has increased significantly since the previous review was written although the somewhat controversial tendency in recent years to enlarge the original concept of an antibiotic as a chemical substance of microbial origin which possesses antimicrobial activity to embrace antimicrobial substances derived from higher plants and animals as well, is responsible to some extent for this increase in the size of the terpenoid group. Other recent advances include an increase in our knowledge, in biochemical terms, of the intimate modes of action of the vitamins A and K, the ubiquinones, and the plastoquinones. Potent pharmacological activities have been discovered in many newly prepared synthetic terpenoid derivatives, and it would seem that significant further advances will be forthcoming in this area in view of the ever-increasing rate at which terpenoids of novel structure are being isolated from natural sources and so becoming available, not only for biological evaluation in their own right, but also for conversion into synthetic derivatives possessing potentially interesting pharmacophoric groups. Indeed the present rate of discovery of new skeletal types within the terpenoid group has far outstripped the ability of the pharmacologists to subject all the naturally occurring compounds to detailed study in depth, let alone permit the medicinal chemist to investigate their full potentialities as new supporting moieties [52, 53], as hydrophobic units capable of giving adsorption on to enzyme surfaces at sites adjacent to the active sites, or as latentiating and protective functions, in an analogous manner to the recent intensive studies which have employed the adamantane skeleton in these capacities [e.g. 54–62].

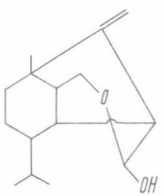
1.1 *The Bearing of Recent Biogenetic Studies*

Recent advances in the field of biogenesis have served to give a completely revised perspective to the spectrum of biological actions found within the ter-

penoids and their derivatives. In addition to providing further evidence for a monoterpenoid origin of the active principles of *Cannabis* resin (marihuana) [63, 64, 64a] and a sesquiterpenoid origin [65, 66] for the toxin produced by the fungus *Helminthosporium sativum* which has been responsible for widespread losses of cereal crops [67, 68] (although in this case it is now established that the compound helminthosporal which was previously considered to be the active principle, is in fact an artifact [66] with the true principles apparently being unstable complexes of prehelminthosporal (V) and prehelminthosporol (VI)), recent work has revealed that several very important groups of com-



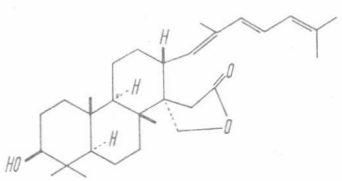
V



VI

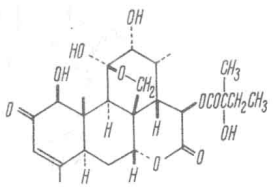
pounds, not formerly regarded as terpenoids or as originating in a mixed terpenoid biosynthesis, must now be included within the terpenoid group. As a consequence, a large number of compounds of well established biological importance, which were not considered in the previous review, must now be brought within the compass of the present review in order to secure a valid assessment of the biological activities found within the terpenoid group as a whole.

Prominent amongst the compounds newly recognised as having a terpenoid origin are the many compounds which appear to arise biogenetically via extensive oxidative degradation of tetracyclic triterpene precursors belonging to the tirucallane type [69–71]. These substances include the limonoid or meliacin group of tetranortriterpenoids where 26 carbon atoms of the original triterpenoid apoeuphol skeleton are retained, compounds having a skeleton of 25 carbon atoms such as simarolide, compounds having a skeleton of 20 carbon atoms belonging to the quassin group, and compounds having a skeleton of 19 carbon atoms as, for example, samaderin. Anticipation of the oxidative processes which have their ultimate conclusions in the biosyntheses of these compounds is to be found in the structures of natural products such as flindissol, melianone, the bourjotinolones and ebelin lactone (VII) which still retain the full true triterpenoid content of 30 carbon atoms. Certainly the extreme in vitro sensitivity to aerial oxidation of the conjugated triene side chain of

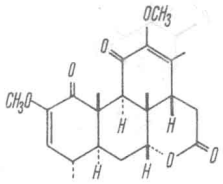


VII

ebelin lactone, which might serve to indicate a parallel facility of oxidative degradation in vitro, has been clearly demonstrated [72]. In the case of glaucarubinone (VIII), recent feeding experiments employing [2-^{14}C]mevalonate [73] and [5-^{14}C]mevalonate [74] have afforded conclusive proof of a biogenetic origin in an apoeuphol-like precursor.

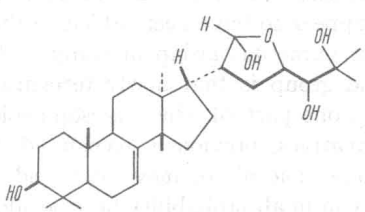


VIII



IX

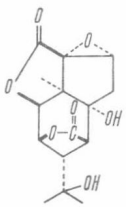
In actual fact there would appear to be relatively few reports in the literature of pharmacological studies with the meliacin group, although in the case of the C_{20} group, quassin (IX) [75, 76] has seen detailed pharmacological investigation [77, 78] on account of its use as a bitter principle in pharmacy and as an insecticide [79], but it would appear [80] to have low efficacy in this latter capacity. The main pharmacological actions would seem to be depression of the amplitude of the heart-beat, slowing of the heart rate and depression of intestinal smooth muscle. In anaesthetised cats and dogs quassin produces a fall in blood pressure. Interestingly however, the triterpenoid meliantriol (X), which can be regarded as being closely akin in structure to possible precursors of the meliacin group, has been claimed [81] to be the principle present in the fresh fruit of *Melia azedarach* L. and in the oil of *Melia azadirachta* L. responsible for inhibiting feeding in the desert locust, *Schistocerca gregaria* Forsk, although other workers [82] have shown that very potent activity can be attributed to another compound, azadirachtin, which was isolated from the seeds of *M. azadirachta* and which does not seem to be chemically related to meliantriol.



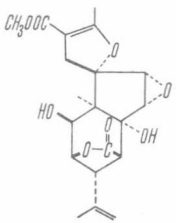
X

It would now seem likely that picrotin (XI), picrotoxinin, coriamyrtin and tutin (and hence mellitoxin), the biological properties of which were discussed in the earlier review, together with the closely related alkaloids dendrine [83], dendrobine [84] and nobiline [84], could in fact also be oxidatively degraded higher terpenoids rather than true sesquiterpenoids, as evidenced by the co-occurrence [85] of tutin and capenicin (XII) [86] in *Toxicodendron capense*.

Analogously there exist in Nature various oxidatively degraded lower terpenoids and examples of nor- and bisnor-diterpenoids are afforded by the inumakilactones [87] and the nagilactones [88]. Interesting examples of what

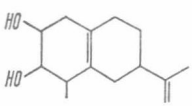


XI

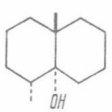


XII

appear to be degraded sesquiterpenoids derived from a eudesmane-type precursor are afforded by rishitin (XIII), an antifungal compound obtained from potato tubers infected with *Phytophthora infestans* [89] and the compounds geosmin (XIV) [90] and mucidone which are the principles responsible for the earthy or musty odours of various actinomycetes [91–95].



XIII



XIV

At the same time, several new compounds which would appear to be homoterpenoids have been discovered. Presumably the extra methyl groups present in compounds of this type are inserted into a terpenoid precursor in an analogous way to the in vivo elaboration of the ergostane-type and stigmastane-type side chains in various plant sterols from the cholestane-type side chain [96, 97]. A probable example of the homoterpenoid group is the juvenile hormone (I) of the giant silkworm moth, where, formally at least, two additional methyl groups would appear to have been added to the farnesane skeleton.

However, the most numerous group of compounds which must now be added to the terpenoid group is that newly recognised as arising in Nature by a mixed biogenesis, one part of which is isoprenoid. To the lysergic acid and chanoclavine derivatives, previously recognised [98–102] as arising via the incorporation of one molecule of mevalonic acid, i.e. incorporation of a single isoprenoid unit, can in all probability now be added the anthraquinones of the Rubiaceae, Verbenaceae and Bignoniaceae together with their closely related anthrones and anthrone dimers, since it has been shown using radiolabelled mevalonic acid [103, 104] that the substituted benzenoid ring C in representative members of this class occurring in *Rubia tinctorum* arises from the condensation of a mevalonic acid-derived unit with a 1,4-naphthoquinone [105] (itself formed from shikimic acid [106]) in accord with earlier proposals [107, 108]. This work makes it seem highly probable, therefore, that a clear