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The Chemistry of Ecdysones

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Ecdysones ara a group of structurally similar steroid compounds with hormonal activity in the moulting and metamorphosis of insects. The review deals with the sources from which ecdysones are isolated, their structure determination, and methods for their partial synthesis. The principal features of the biological activity of ecdysones and their synthetic analogues are also briefly outlined.
The bibliography includes 193 references.

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I. INTRODUCTION

A group of polyhydroxylated sterols with related chemical structures, isolated from arthropods and plants, is combined under the name of ecdysones (see the relevant reviews[1-9]). The group is of interest from both chemical (their unusual structure distinguishes them from all previously known steroid compounds) and biological standpoints, since ecdysones exhibit an extremely interesting physiological activity. The most common characteristic of the biological action of ecdysones is their capacity to cause the moulting and metamorphosis of insects. Depending on the source from which they are isolated (from plants or animals), these substances are divided into zooecdysones and phytoecdysones.

Zooecdysones are present in the organisms of various insects[10-13] and crustaceans[14-16], but their amounts are negligibly small. Thus 25 mg of α-ecdysone[17] was isolated from 500 kg of the pupae of the silkworm moth *Bombyx mori* and 9 mg of ecdysterone was obtained from two tons of the pupae[18,19]. The isolation of α-ecdysone corresponds to enrichment by a factor of 2×10^7 compared with its content in the initial biological material; the substance isolated in a pure form constitutes about 50% of the amount of hormones present in the initial material (according to biological assay). Only 2 mg of ecdysterone could be isolated from one ton of the crayfish *Jasus lalandei*[15]. Both the total content of zooecdysones and the relative amounts of the various components in their mixture depend on the insect species and the stage of development of the insect; for example, in some cases up to five individual active fractions were obtained[20].

The postembryonic development of insects is controlled by several hormones the interaction of which may be represented as follows[6]. Ecdysones (the moulting and metamorphosis hormones—MMH) are produced in the prothoracic gland of insects or in the analogous Y-organ of crustaceans. The secretion of ecdysones is controlled by the polypeptide ecdysiotropic hormone (ETH, also called the activating hormone), produced by the neurosecretory brain cells. Finally, the type of moulting induced by the MMH is determined by the Juvenile Hormone (JH), which is produced in the so called corpora allata). In the presence of the Juvenile Hormone larval moulting takes place and in its absence the metamorphosis of the larva to the pupa and of the pupa to the adult form (the imago). Ecdysones induce the moulting not only of insects but also of other classes of arthropods[21,22]. Probably steroids of this type already controlled the moulting of the common ancestors of anthropods in the Precambrian period (600 million years ago), i.e. ecdysones are the oldest steroid animal hormones. The MMH activity of ecdysones is determined in assays developed on various insects (see Karlson's review[23]). The most sensitive assay is on the housefly *Musca domestica*[24,25] and the simplest assay involves the rice pest *Chilo suppressalis*[26]. However, the commonest assay involves the blow-fly *Calliphora erythrocephala*[4,23,27]; the amount of ecdysones is sometimes expressed in "Calliphora units"—CE (1 CE $\simeq$ 0.01 μg of α-ecdysone, varying somewhat depending on the strain of the fly). One should bear in mind that the relative MMH activities of ecdysones found in various assays are different[28-30]. Biological control using assays of MMH activity proved particularly useful in the isolation of ecdysones from natural sources.

Ecdysones control physiological processes in insects associated with moulting and metamorphosis; their role in the formation of the puparium in the sclerotisation of the larval cuticle in the pupation process has been most thoroughly investigated. Ecdysones influence the carbohydrate, proteins, and nucleic acid metabolism[31-38]. The primary site of the action of ecdysones is the cell nucleus, more precisely its genetic material (see the relevant reviews[39-45]). Initially specific regulator genes are activated, then messenger RNA is synthesised, and finally proteins, in particular enzymes involved in the sclerotisation of the cuticle are synthesised. This mechanism of their action is satisfactorily consistent with the sequence of events in time. α-Ecdysone penetrates the cell nucleus 15–20 min after injection, causes the formation of chromosome "puffs" (i.e. gene activation) after 30–60 min, and increases the rate of synthesis of messenger RNA after 1–2 h, of microsomal RNA after 3–4 h, and of sclerotisition enzymes after 6–8 h.

The biosynthesis of zooecdysones in insects begins with cholesterol obtained from food (the insect organism is incapable of independent synthesis of steroids); the first step is dehydrogenation to 7-dehydrocholesterol[46-48]. Hydroxylation of the side chain apparently precedes the formation of the structural elements of the steroid skeleton; the C-25 and C-26 positions are hydroxylated faster than C-20.[49] α-Ecdysone is the precursor of ecdysterone in insects and crustaceans[50]. Zooecdysones are rapidly inactivated (cleaved) in insect tissues, the principal site

of their metabolism being the fat body [51-53]. The mechanism of the enzymatic cleavage of zooecdysones has not been established; it has only been shown that one of the first stages in the metabolism of ecdysterone may be the dissociation of their C-22–C-23 bond [54].

Numerous reports [55-63] on the isolation from plants of substances with MMH activity (phytoecdysones) appeared in 1966–1967. It has now been established that these substances are present in the fruit, leaves, bark, and roots of more than 100 plant species-mainly evergreen trees and ferns [64-67]; in higher fungi and algae compounds with MMH activity were not detected [56]. General methods have been developed for the extraction of total phytoecdysones from plants and for the chromatographic isolation of their individual components [68-70]. The content of phytoecdysones in plants depends on the species and the part of the plant; it usually exceeds by several powers of 10 the content of zooecdysones in crustaceans. For example, the amount of ecdysterone in the inflorescence of the saw-wort (*Serratula inermis*) can reach 2% of the dry weight [71].

The physiological role of phytoecdysones has not so far been elucidated. They may be the final products of the metabolism of sterols in plants or they can play a role in their growth and development (analogously to zooecdysones in insects). The hypothesis of the protective role of phytoecdysones in relation to insect plant pests [55,72] is apparently not confirmed by direct tests on their toxicity [73,74]. The biosynthesis of phytoecdysones in *Podocarpus* and *Taxus* species involves the usual sterol mechanism—via mevalonate and cholesterol, and their subsequent biochemical modification. The hydroxy-group at C-25 of the side chain is introduced after the hydroxy-groups at C-20 and C-22. [75-79]

Ecdysones exhibit physiological activity in relation to many groups of organisms. It has been reported that α-ecdysone accelerates plant growth [67,70] and induces the sexual cycle in protozoan symbionts of the insect *Cryptocercus* sp. [81] The effect of ecdysones on mammals is of special interest. In the first place both zooecdysones and phytoecdysones are fairly active anabolic agents (their activity is at the level of 4-chlorotestosteron) [82-87] and there are no toxic effects even after their prolonged administration [88]. The anabolic effect is probably associated with the mechanism of the action of ecdysones, which includes stimulation of protein synthesis; this is evidence that the transmission and counting processes in genetic information are common to insects and mammals. *In vitro* ecdysones inhibit the growth of sarcoma-180 cells and of embryonic fibroblasts [89,90], but they do not affect the growth of the Yoshida ascitic sarcoma [91]. α-Ecdysone shows virtually no hypocholesterolemic activity [92]. It should be remembered that human tissues do not exhibit MMH activity [93].

Three principal factors are of interest in the chemistry of ecdysones—the determination of their structures, their synthesis from other groups of steroids, and finally the relation between activity and structure and the preparation of structural analogues of ecdysones which maintain or enhance the type of physiological activity of practical importance to man.

II. THE STRUCTURE OF ECDYSONES

The study of the structure of ecdysones began in the 1950's with their isolation from insects in a crystalline state. The main obstacle in this work was the exceptionally low content of zooecdysones in biological material.

The structure of α-ecdysone was the first to be determined. X-Ray diffraction analysis and mass spectra made it possible to establish its empirical formula as $C_{27}H_{44}O_6$. [94] Dehydration of α-ecdysone (II) gave a low yield of the so called "Diels hydrocarbon" (I), which demonstrates the presence of the steroid skeleton in (II).

Table 1. Proton signals in the NMR spectrum of α-ecdysone (in C_5D_5N). [94]

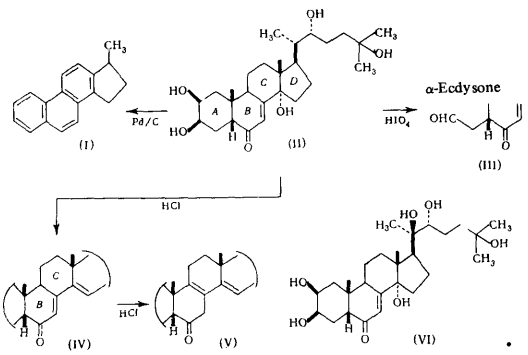
δ, p.p.m.	No. of protons	Functional groups
0.70	3	>C—CH_3 (angular methyl group)
1.05	3	>C—CH_3 (angular methyl group)
1.19	3	R—CH—CH_3 (doublet)
1.30		R—C(OH)—
1.38	6	R—$C(CH_3)_2$
1.92	21	CH and —CH_2—
4.18	1+2	HO—and HC<
5.75	4	HO
6.31	1	R—CO—CH=C(R)R
	44	

NMR spectroscopy proved to be particularly useful in the determination of the structure of α-ecdysone (Table 1) [94]—it made it possible to assign all 44 protons in the molecule to particular groups. The two angular methyl groups, the presence of which constitutes additional proof of the steroid structure of α-ecdysone, have the lowest chemical shifts. The third methyl group linked to a CH group, was assigned to the side chain (C-21). The two terminal methyl groups of the side chain were not found at a CH group as would be expected for a cholesterol derivative but at quaternary carbon atoms (six-proton singlet with δ = 1.38 p.p.m.). Hence it was concluded that, together with the two methyl groups, at C-25 there is also a hydroxy-group (if the methyl group were located at a double bond, the resonance signal would be observed at higher values of δ). This hydroxy-group gives rise to a hydroxyl proton signal at 4.18 p.p.m. In the NMR spectrum of α-ecdysone there is also a single signal corresponding to an olefinic proton (6.31 p.p.m.). It is suggested that this proton forms part of the structural element $RCOCH{=}CR_2$. The presence of a keto-group conjugated with a double bond in the α-ecdysone molecule is also confirmed by the ultraviolet ($\lambda_{max}^{CH_3OH}$ = 242 nm) and infrared (ν = 1657 cm^{-1}) spectra. The high degree of substitution of this group follows from the failure of its catalytic hydrogenation over palladium or platinum even under severe conditions [95]. The position of the $\alpha\beta$-unsaturated keto-groups in the ring system was established by comparing the spectra of a large number of model steroids [96] and by investigating their colour reactions [97]. These data led to the conclusion that the α-ecdysone molecule contains Δ^7-6-oxo-groups; this was confirmed in a study of the reactions of α-ecdysone under the influence of acids. When α-ecdysone is treated with HCl in

ethanol, a derivative with λ_{max} = 293 nm is formed initially and is then converted into a product with λ_{max} = 244 nm. These data were interpreted as indicating the initial dehydration of the readily eliminated tertiary 14-hydroxy-group with formation of a doubly unsaturated ketone (IV), which, as a result of the steric strain of the B ring, gradually isomerises to the unconjugated dienone (V).[95] These reactions also establish the position of the hydroxy-group at C-14; thus, of the six oxygen atoms in the α-ecdysone molecules, the positions of three were identified.

The ready cleavage of α-ecdysone by periodate to the corresponding dialdehyde (III)[95] demonstrates the presence in its molecule of a vicinal glycol group. The absence of volatile cleavage products in this oxidation indicates that the glycol group is in a steroid ring and not in a side chain. Biogenetic data suggest that one of the glycol hydroxy-groups is at C-3, as in all other natural steroids; then the second hydroxy-group can be at C-2 or C-4. The lack of similarity between model 3,4-diols and α-ecdysone[98] permits a choice in favour of a 2,3-diol. The position of the last hydroxy-group was established by studying the mass spectrum of α-ecdysone[94,95]. This yielded very intense peaks with m/e = 81 ($C_6H_9^+$) and m/e corresponding to $C_6H_{11}O^+$. Such fragments can be split off only from a side chain of the steroid molecule with dissociation of the C-20–C-22 bond, which establishes the location of the remaining hydroxy-group at C-22.

The final proof of the structure of α-ecdysone (II) was obtained by X-ray diffraction analysis, which confirmed all the conclusions arrived at above on the basis of chemical and spectroscopic data and in addition made it possible to establish the configuration of the hydroxy-groups in the steroid skeleton and in the side chain (2β-, 3β-, 14α-, 22R-) and the *cis*-junction of the A and B rings[99,100]:



Another representative of the group of ecdysones isolated from various natural sources[101,102] is ecdysterone (VI), which has one hydroxy-group more than α-ecdysone (II). Since according to the mass spectrum both hormones are identical up to C-19 and beyond C-22, this hydroxy-group can be located only at C-20. Comparison of the NMR spectra of ecdysterone and α-ecdysone leads to the same conclusion. The signals of the protons in the methyl groups at C-18 and C-21 in ecdysterone are displaced by 0.3–0.4 p.p.m. towards lower field compared with the analogous signals in the spectrum of α-ecdysone. Such changes are characteristic when a 20-hydroxy-group is introduced into a steroid molecule; this was confirmed by a comparative study of the NMR spectra of model compounds. The chemical properties and infrared and ultraviolet spectra of ecdysterone confirm the assignment of formula (VI).[103,104] On the basis of data for the interconversions of ecdysones in living organisms and the mode of their synthetic reactions, the 20*R*,22*R*-configuration of the hydroxy-groups in the side chain has been assigned to the majority of ecdysones, although it cannot be regarded as finally proved.

The structures of more than 30 zooecdysones and phytoecdysones have now been determined (Table 2). The elucidation of their structures is significantly aided by the knowledge of the structures of α-ecdysone (II) and ecdysterone (VI). Therefore in the determination of the structures of newly isolated ecdysones their structural similarity to (II) and (VI) is established on the basis of the infrared and ultraviolet spectra with the study of chemical reactions reduced to a minimum (usually only with HCl and HIO_4). The structural details are determined

Table 2. The structure of ecdysones.

Name	Side chain of C-17 substituent and hydroxy-groups in steroid skeleton	Sources and references
19C Ecdysones Rubrosterone	 2β, 3β, 14α-(OH)$_3$	Plants (Refs.119–121) Synthesis*
27C-Ecdysones Ajugasterone C	 2β, 3β, 11α, 14α-(OH)$_4$	Plants (Ref.122)
Viticosterone E	 2β, 3β, 14α-(OH)$_3$	Plants (123)
2-Deoxyecdysterone	 3β, 14α-(OH)$_2$	Crustacea (Ref.124)
Inokosterone (viticosterone B)	 2β, 3β, 14α-(OH)$_3$	Insects (Ref.49) Plants (Refs.123, 125)
Callinecdysone A	(inokosterone isomer?)	Crustacea (Ref.16)
26-Hydroxyecdysterone	 2β, 3β, 14α-(OH)$_3$	Insects (Ref.126
Podecdysone B	 2β, 3β-(OH)$_2$ ($\Delta^{8(9),14}$-)	Plants (Ref.127
Polypodine B (ajugasterone A, viticosterone C, 5β-hydroxyecdysterone)	 2β, 3β, 5β, 14α-(OH)$_4$	Plants (Refs.123,128–130)
Ponasteroside A (warabisterone)	3β-D-glucoside of ponasterone A	Plants (Refs.131–133)
Ponasterone A	 2β, 3β, 14α-(OH)$_3$	Insects (Ref.49 Plants (Refs.107,110,126) Synthesis*

Table 2 contd.

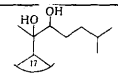
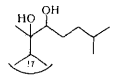
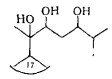
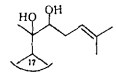
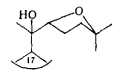
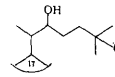
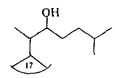
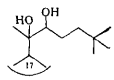
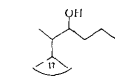
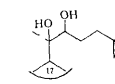
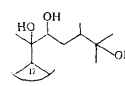
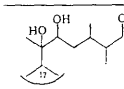
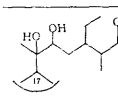
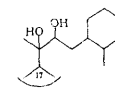
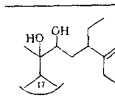
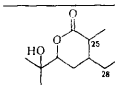
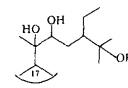
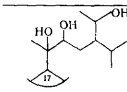
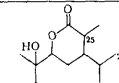
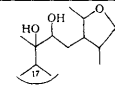
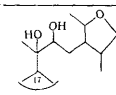
Name	Side chain of C-17 substituent and hydroxy-groups in steroid skeleton	Sources and references
Ponasterone B	 2α, 3α, 14α-$(OH)_3$	Plants (Refs.106, 107)
Ponasterone C	 2β, 3β, 5β, 14α-$(OH)_4$	Plants (Refs.106-108)
Pterosterone (viticosterone D)	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.123,124)
Stachysterone C	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.135)
Stachysterone D	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.135)
Cheilanthone A	 2β, 3β, 14α-$(OH)_3$ (7,8-dihydro-)	Plants (Ref.136)
Cheilanthone B	 2β, 3β, 14α-$(OH)_3$ (7,8-dihydro)	Plants (Ref.136)
Shidasterone (isomer of ecdysterone)	 2β, 3β, 14β-$(OH)_3$	Plants (Ref.137)
α-Ecdysone	 2β, 3β, 14α-$(OH)_3$	Insects (Refs.14,17,138 Plants (Refs.62,72,139,140) Synthesis*
Ecdysterone (viticosterone A, isoinokosterone, crustecdysone, 20-hydroxyecdysone, polypodine A, β-ecdysone)	 2β, 3β, 14α-$(OH)_3$	Insects (Refs.14,18,103,141, 142) Crustacea (Ref.141, 143) Plants (Refs.55,57,60) Synthesis*
28C-Ecdysones Calliecdysone B	(isomer of Makisterone A ?)	Crustacea (Ref.16)
Makisterone A (podecdysone D)	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.127,144)
Makisterone B	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.144,145)
29C-Ecdysones Amarasterone A	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.146

Table 2 contd.

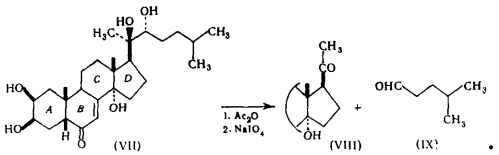
Name	Side chain of C-17 substituent and hydroxy-groups in steroid skeleton	Sources and references
Amarasterone B	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.146)
Ajugasterone B	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.147)
Capitasterone	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.148)
Lemmasterone (makisterone C, podecdysone A)	 2β, 3β, 14α-$(OH)_3$	Plants (Refs.83,139,145,149)
Makisterone D	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.145)
Precyasterone	 2β, 3β, 14α-$(OH)_3$	Plants (Ref.150)
Sengosterone	 2β, 3β, 5β, 14α-$(OH)_4$	Plants (Refs.115, 151)
Cyasterone	 2β, 3β, 14α-$(OH)_3$	Plants (Refs.113, 152)

*See Section III.

from the mass spectra, which yield information primarily about the structure of the side chain [105], and from NMR spectra, which in addition give information about the positions and configurations of the hydroxy-groups in the steroid skeleton†. A striking example is provided by the determination of the structure of the phytoecdysone ponasterone A. [107,109,110]. Apart from the corresponding

†It should be noted that such neglect of chemical methods for structural determinations can lead to significant errors. For example, a 2α,3α-configuration of the hydroxy-groups in the A ring of ponasterone C was assigned on the basis of spectroscopic studies [106,107]. A more careful reinvestigation [108] made it necessary to invert this configuration to 2β,3β- and moreover led to the detection in the ponasterone C molecule of an additional 5β-hydroxy-group, the presence of which had been overlooked as a result of the incorrect interpretation of the mass spectrum.

biological activity, its classification as an ecdysone is demonstrated also by ultraviolet and infrared spectra, which are similar to those of ecdysterone. Ponasterone A ($C_{27}H_{44}O_6$) has six oxygen-containing groups, one of which is part of the $\alpha\beta$-unsaturated ketone group (ultraviolet and infrared spectra and NMR signal of the olefinic proton at 6.17 p.p.m.). The formation of a diacetamide indicates the presence of four hydroxy groups in two vicinal diol groups; this is also confirmed by oxidation with $NaIO_4$, which involves the consumption of two moles of the oxidant. The location of the fifth hydroxy-group at C-14 follows (by analogy with α-ecdysone) from the successive formation of compounds with λ_{max} = 294 and 241 nm when ponasterone A is treated with HCl and its 14α-configuration follows from a comparison of the chemical shifts of the protons in the methyl groups at C-18 and C-19 in the NMR spectra of ponasterone A and ecdysterone. Ponasterone A readily forms a triacetate; the NMR spectrum of the latter ($CDCl_3$) has signals at 4.82, 5.05, and 5.32 p.p.m., which can be attributed to three carbonyl protons at C-22, C-2, and C-3. Therefore three hydroxy-groups are secondary and the remaining two are tertiary. Moreover, in the NMR spectrum of ponasterone A there is a doublet at 0.82 p.p.m. corresponding to the methyl groups at C-26 and C-27, which demonstrates the absence of a hydroxy-group at C-25 (in the spectra of α-ecdysone and ecdysterone these signals are at 1.38 and 1.34 p.p.m. respectively). Comparison of the signals due to the protons at C-18, C-19, and C-21 (at 1.16, 1.03, and 1.51 p.p.m. in ponasterone A and at 1.19, 1.06, and 1.55 p.p.m. in ecdysterone) leads to the conclusion that the corresponding methyl groups have the same environment and to the assignment of formula (VII) to ponasterone A. The formula is confirmed by the results of the oxidation of ponasterone A 2-monoacetate by $NaIO_4$ which results in the formation of the 20-ketone (VIII).[107] The identity of this ketone with the product of the analogous oxidation of ecdysterone and the intermediate in the partial synthesis of α-ecdysone [111,112] demonstrates unambiguously that the tetracyclic structures of all three ecdysones are the same up to C-21. The structure of the side chain of ponasterone A is confirmed by the isolation of isohexanal (IX) in oxidation with $NaIO_4$ and also by the presence in the mass spectrum of an intense peak with m/e = 83 corresponding to the $C_6H_{11}^+$ fragment formed on dissociation of the C-20–C-22 bond [107]. It should be noted that the structures of α-ecdysone, ecdysterone, ponasterone A, and also rubrosterone have been demonstrated by their synthesis (see section III).



Other physicochemical research methods have proved very helpful in the determination of the structure of ecdysones. The optical rotatary dispersion (ORD) curves are used mainly to determine the type of junction between A and B rings. The Δ^7-6-oxo-group of ecdysones exhibits a Cotton effect at about 240 nm ($\pi \rightarrow \pi^*$ transition) and at about 340 nm ($n \rightarrow \pi^*$ transition). In both cases the amplitude for the *trans*-A/B isomers is much higher than for the *cis*-A/B isomers [102,106,107,109,113]. Apart from the amplitudes, there is a significant difference (by 8–10 nm) between the positions of the peaks in the ORD curves for the *cis*- and *trans*-isomers. Thus in the region of the $n \rightarrow \pi^*$ transition natural α-ecdysone has peaks at 377 and 361 nm, while its *trans*-A/B isomer has peaks at 366 and 351 nm.[114]

The circular dichroism (CD) curves also show a shift of the maximum by 7–8 nm towards longer wavelengths on passing from the *trans*- to the *cis*-A/B junction [114]. A similar shift is observed when a 5β-H atom in the ecdysone molecule is replaced by a 5β-hydroxy-group, which makes it possible to determine the position of the latter [108,115]. The CD curves for the α-glycol dibenzoates of the ecdysone series have been used to determine their chirality in the elucidation of the structures of ponasterones A–C, polypodine B, and ajugasterone [108,116,117]. The use of the fluorescence spectra of ecdysterone and inokosterone for the analysis of a mixture of these compounds, which occur together in many plants, is also noteworthy [118].

The names and formulae of the ecdysones known at the present time are given in Table 2. According to the number of carbon atoms in the molecule they can be divided into four groups 19C-, 27C-, 28C-, and 29C-ecdysones. Phytoecdysones belonging to all four groups have been found, but zooecdysones occur only in the second group (with the sole exception of callinecdysone B, which apparently has 28 carbon atoms). The majority of ecdysones have the same characteristic set of substituents in the steroid skeleton: 2β, 3β, 14α-hydroxy-groups, a Δ^7-6-oxo-group, and a *cis*-A/B junction. The side chain always contains (except in rubrosterone which has no side chain) a hydroxy-group at C-22 and frequently at C-20; in certain cases oxygen-containing substituents occur at C-24, C-25, C-26, C-28, or C-29 carbon atoms of the side chain. Thus not only the MMH activity but also the common features of the chemical structures of the known ecdysones justify their classification as a special group of natural compounds.

The deviations from the above typical structure are comparatively small. Polypodine B, ponasterone C, and sengosterone have an additional 5β-hydroxy-group and ajugasterone C an 11α-hydroxy-group. The 2α,3α-configuration of the hydroxy-groups in the A-ring of ponasterone B has been demonstrated, instead of the 2β, 3β-configuration characteristic of the remaining ecdysones, and shidasterone apparently has a 14β- and not a 14α-hydroxy-group. In cheilanthones A and B there is no Δ^7-linkage and podecdysone B has a $\Delta^{8(9),14}$-diene system, which may be formed during its isolation as a result of the scission of the 14α-group.

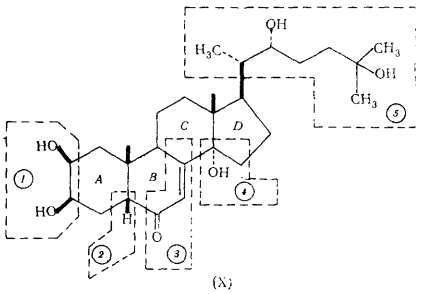
In natural sources so far only two ecdysone derivatives substituted at a hydroxy-group have been found—viticosterone E (ecdysterone 25-acetate) and ponasteroside A (ponasterone A 3β-glyucoside).

III. SYNTHESIS OF ECDYSONES

The synthesis of ecdysones, which was achieved almost immediately after the determination of their structure, is evidence of a high level of development and considerable

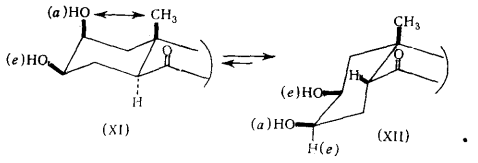
advances in steroid chemistry. Several groups of investigators have now developed four schemes for the partial synthesis of ecdysones (X). Unfortunately none of the investigators quote the yields in all the stages, which precludes an exact quantitative comparison of the effectiveness of these schemes.

In the ecdysone (X) molecule it is possible to isolate five principal structural elements, which distinguish this group of natural compounds from other steroids. These are the vicinal 2β,3β-diol group in the A ring (1), the 5β-hydrogen atom between the A and B rings (2), the Δ^7-6-oxo-group in the B ring (3), the 14α-hydroxy-group between the C and D rings (4), and finally the side chain in the 17β-position of the D ring (5).



(X)

These structural elements are introduced by various methods depending on the structure of the initial compound. For example, the 2β,3β-diol group is introduced into Δ^2-compounds by the *cis*-hydroxylation of the double bond and into 3-oxo-5α-steroids either by bromination in the 2α-position with subsequent replacement of bromine by a 2β-acetoxy-group (with silver acetate) or by auto-oxidation in an alkaline medium and subsequent reduction of the resulting 2,3-diketone with $NaBH_4$.[153] The Δ^7-bond is as rule introduced on bromination–dehydrobromination of 6-oxosteroids, but the Δ^7-6-oxo-group can be formed also directly by the oxidation of $\Delta^{5,7}$-steroids[154,155]. The 14α-hydroxy-group is likewise introduced into the molecule by several methods. The most common is the allylic oxidation of Δ^7-6-oxosteroids with SeO_2.[156] The pathway via the formation of enol acetates of these compounds with subsequent oxidation by peracids is also used[157]. Finally, microbiological hydroxylation[158] and photochemical oxidation of $\Delta^{8(14)}$-6-oxosteroids for this purpose have been described[159,160]. The reaction of steroid 20-ketones or 22-aldehydes with lithium or magnesium derivatives of the corresponding acetylene alcohols containing all the necessary substituents serves as the usual method for the introduction of the side chain. The problem of ensuring the 5β-configuration, i.e. the *cis*-junction of the A and B rings merits special attention. In the usual 6-oxosteroids the 5α-isomer is much more stable than the 5β-isomer[161]. However, in 2β,3β-dihydroxy-6-oxosteroids, specific examples of which are ecdysones, the *meta*-diaxial interaction between the 2β-hydroxy-group and the methyl at C-19 in the 5α-isomer (XI) lowers its stability compared with the 5β-isomer (XII), where such interaction is absent. Therefore the 5β-isomer predominates in the equilibrium mixture [the ratio 5β : 5α = (2 – 4) : 1, depending on the structure of the steroid]; this fact is used in the synthesis of ecdysones from 5α-steroids.



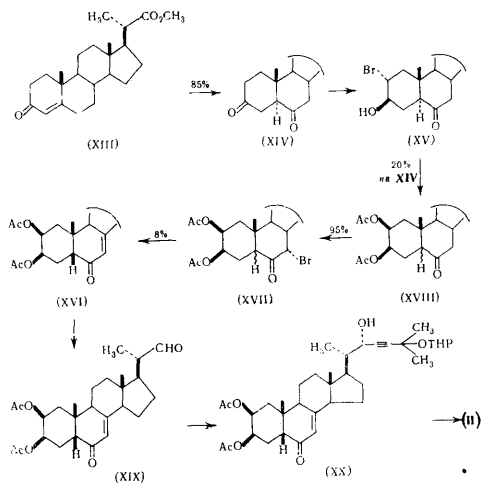
(XI) (XII)

The schemes for the synthesis of ecdysones which have not been developed differ not only in the types of reactions used to introduce various structural elements but also in the order of their introduction. In considering them particular attention must be paid to the syntheses of α-ecdysone, since these were in fact used to develop the main synthetic procedures. The syntheses of ecdysterone usually differ only in the methods of introduction of the side chain and the syntheses of rubrosterone, a metabolite of active ecdysone, are not usually of independent importance‡. In addition plants constitute a rich source of the last two ecdysones, whereas the requirements for α-ecdysone are mainly satisfied by the synthetic product.

In 1966 a group of Swiss chemists described a partial synthesis of α-ecdysone (II) in which the structural elements [see formula (X)] were introduced according to the scheme *1* → *3* → *2* → *4* → *5*.[163–167] The initial compound in this synthesis is the methyl ester of bisnorcholenoic acid (XIII) obtained from ergosterol or stigmasterol. The formation of ethyleneketal, the epoxidation of the Δ^5-bond with peracetic acid to a mixture of 5ξ,6ξ-epoxides, and the isomerisation of this mixture under the influence of perchloric acid led to the 3,6-diketone (XIV). The bromination and selective reduction of the 3-oxo-group with $LiAl(t\text{-}C_4H_9O)_3H$ yielded the 2α-bromo-3β-hydroxy-compound (XV), the acetylation of which and the replacement of bromine by an acetoxy-group led to a mixture of the 2β,3β-diacetates (XVIII) epimeric at C-5. The Δ^7-bond was introduced by bromination under acid conditions; the mixture of 5- and 7-bromoketones formed initially isomerises to the 7α-bromo-derivative (XVII). The elimination of HBr from the latter yields the Δ^7-6-oxo-compound, which is also a mixture of isomers at C-5. Alkaline isomerisation at the C-5 centre is accompanied in this case by epimerisation also at the C-20 centre and the shifte of the Δ^7-bond to the $\Delta^{8(14)}$-position; therefore halogenolysis (LiI in boiling lutidine) was employed to obtain the 5β-isomer (XVI). The 22-methoxycarbonyl group of compound (XVI) was reduced to the corresponding aldehyde (XIX) by allowing $LiAl(t\text{-}C_4H_9O)_3H$ to react with the carbonyldi-imidazole derivative. The side chain was introduced by a Grignard reaction with the MgBr derivative of the tetrahydropyranyl (THP; C_4H_9O) ether of 2-methylbut-3-yn-2-ol. This reaction yielded a mixture of the required 22*R*-isomer (XX) and the corresponding 22*S*-derivatives, which were separated by chromatography on silica and were treated separately. Catalytic hydrogenation of the triple bond in the side chain, the introduction of the 14α-group by the action of SeO_2 in dioxan, and acid hydrolysis of the

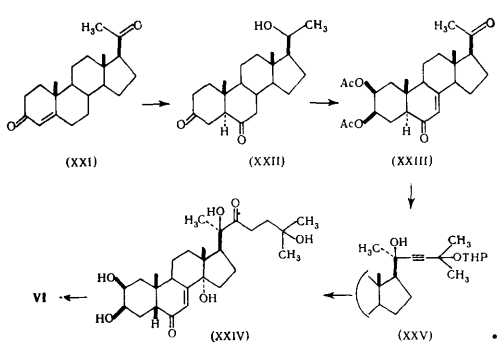
‡A novel synthesis of rubrosterone via *i*-steroids was developed recently[162], but it has not been extended to active ecdysones.

protecting groups (acetate, THP ether) yielded α-ecdysone (II). Analogous treatment of the 22*S*-epimer (XX) made it possible to obtain 22-iso-α-ecdysone. Rubrosterone was synthesised according to the same scheme [168].



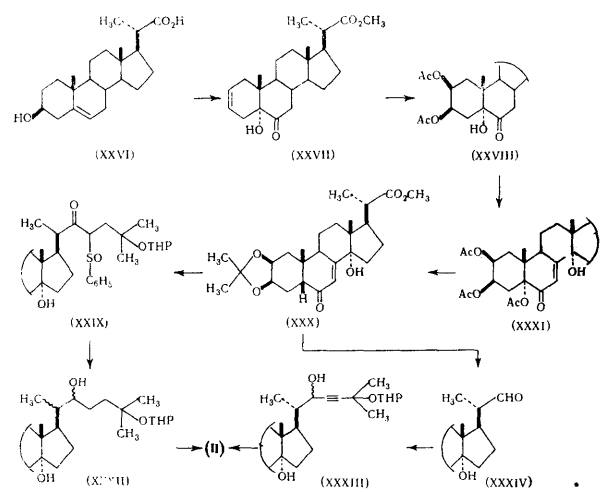
The chief disadvantage of the above method of synthesis is a low yield in the (XVII) → (XVI) isomerisation stage. Therefore in the synthesis of ecdysterone by the same group of investigators the formation of the 5β-configuration was transferred to the end of the synthesis and was combined with the alkaline hydrolysis of the protecting groups.

Ecdysterone (VI) was synthesised according to the following scheme [169]. The 3,6-diketone (XXII) obtained in four stages from progesterone (XXI) as in the synthesis of α-ecdysone [the (XIV) → (XV) → (XVIII) → (XVII) → (XVI) transition], was converted in seven stages into the intermediate (XXIII) containing the 2β,3β-diol and Δ^7-6-oxo-groups. The side chain was introduced into this compound by the reaction with the MgBr derivative of the THP ether of 2-methylpent-4-yn-2-ol.



This yielded a 4 : 1 mixture of the 20*R*-isomer (XXV) and the 20*S*-isomer. The oxygen-containing substituent at C-22 was introduced by the catalytic hydration of the triple bond in the side chain [in the presence of $Hg(OAc)_2$]. The subsequent introduction of the 14α-hydroxy-group by oxidation with SeO_2 and alkaline hydrolysis of the protecting groups, accompanied by inversion at C-5 led to compounds (XXIV), which differs from ecdysterone (VI) only by the presence of an oxo-group at C-22. The reduction of this oxo-group with $LiAl(t\text{-}C_4H_9O)_3H$ led to a mixture of natural ecdysterone (VI) and its 22-isomer, which were separated chromatographically. Direct catalytic hydrogenation of compound (XXV) with subsequent treatment according to the above scheme made it possible to obtain 22-deoxy-ecdysterone, which is used in the study of the biosynthesis of ecdysterone [170,171].

Another synthesis of α-ecdysone and ecdysterone according to the *1* → *3* → *4* → *2* → *5* scheme was proposed in 1966 by a group of chemists in the USA. [172-175] The synthesis began with a derivative of bisnorcholenoic acid (XXVI), which was converted by acetylation and treatment with diazomethane into the 3-acetate of the methyl ester. Hydroxylation of the latter and the Δ^5-bond, hydrolysis of the 3-acetoxy-group, oxidation at C-6 with *N*-bromosuccinimide, tosylation, and the elimination of TsOH by treatment with Li_2CO_3 led to compound (XXVII) with an overall yield up to 50% with respect to the initial acid (XXVI). *Cis*-hydroxylation of the Δ^2-bond with silver acetate and molecular iodine in acetic acid and subsequent acetylation gave compound (XXVIII), in which a Δ^7-bond was introduced by bromination in an acid medium and subsequent elimination of HBr by treatment with Li_2CO_3. The acid-catalysed acetylation of the tertiary 5α-hydroxy-group and the introduction of the 14α-hydroxy-group by allylic oxidation with SeO_2 yielded compound (XXXI), which already contains three fragments of the α-ecdysone structure. The introduction of the next fragment (a 5β-hydrogen atom) was achieved in four stages. The 5α-acetoxy-group was removed by reduction with $CrCl_2$; next the alkaline hydrolysis of the 2,3-diacetate was carried out, the diol group was protected by the formation of an acetonide, and finally isomerisation at C-5 by heating with an aqueous-methanolic solution of potassium carbonate gave a 1 : 3 mixture of the 5α- and 5β-isomers. The pure 5β-isomer (XXX) was isolated from this mixture by chromatography on silica.

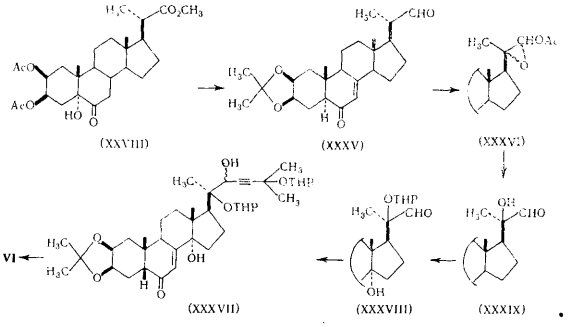


The introduction of the side chain characteristic of α-ecdysone into compound (XXX) was achieved by two methods. In the first version [173] the 6-oxo-group was reduced with $LiAl(t\text{-}C_4H_9O)_3H$ to a mixture of 6α- and 6β-hydroxy-derivatives; its alkylation at C-22 with the

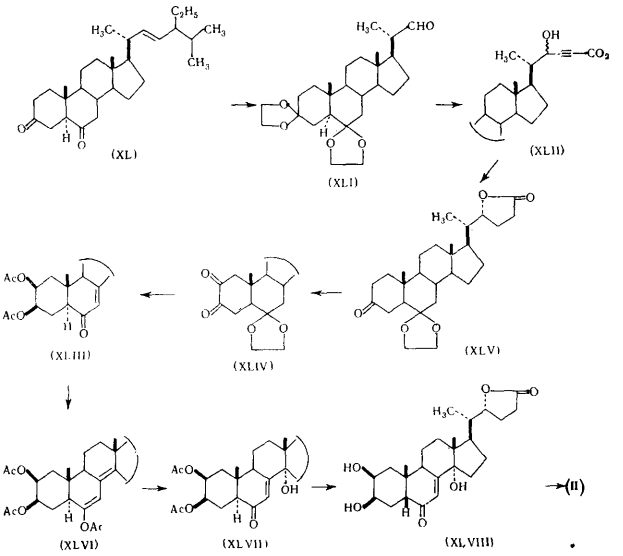
lithium salt of the THP ether of 2-methyl-4-sulphoxyphenylbutan-2-ol by the method of Corey and Chaykowsky[176] led to compound (XXIX). Hydrogenolysis of the sulphoxyphenyl group of this compound with aluminium amalgam and reduction of the 22-oxo-group with $LiAlH_4$ (the 6-oxo-group is reduced at the same time) gave the 22-hydroxy-derivative (XXXII), which is a mixture of epimers at C-20 and C-22. Resynthesis of the 6-oxo-group by oxidising this mixture with MnO_2 (only the allylic 6ξ-hydroxy-group is affected) and hydrolysis of the protecting groups with dilute HCl led to a mixture of the corresponding isomers of α-ecdysone, from which the natural hormone (II) was isolated in 12% yield with respect to compound (XXX) by chromatography on silica.

The inadequate stereospecificity of this synthesis made necessary a modification in which the introduction of the side chain into compound (XXX) does not involve isomerisation at the C-20 centre[11]. The methyl ester (XXX) was converted into the aldehyde (XXXIV) by a fairly complex procedure. Reduction of the 6-oxo-group with $LiAl(t\text{-}C_4H_9O)_3H$, reduction of the 22-carboxymethyl group with $LiAlH_4$, and resynthesis of the 6-ketone by oxidation with MnO_2 made it possible to obtain from (XXX) the corresponding 22-hydroxy-derivative. Its oxidation to the aldehyde (XXXIV) was achieved by treatment with dicyclohexylcarbodi-imide in dimethyl sulphoxide in the presence of trifluoroacetic acid as a catalyst[177]. The reaction of the aldehyde (XXXIV) with the lithium derivative of the THP ether of 2-methylbut-3-yn-2-ol gave a mixture of 22-hydroxy-compounds (XXXIII) epimeric at C-22. Its separation by preparative thin-layer chromatography on silica, catalytic hydrogenation of the triple bond, and hydrolysis of the protecting groups yielded α-ecdysone (II) and 22-iso-α-ecdysone.

The synthesis of ecdysterone (VI) was achieved by a similar scheme[178,179]. The starting material in this synthesis is compound (XXVIII), already described, which was converted in eight stages into the 22-aldehyde (XXXV) [similarly to the conversion (XXVIII) → (XXXI) → (XXX) → → (XXXIV) in the synthesis of α-ecdysone by the method of the same group of investigators]. Acetylation of the enol of the aldehyde (XXXV) and oxidation of the resulting enol acetate with *m*-chloroperbenzoic acid gave a mixture of isomers of the 20ξ,22ξ-epoxide (XXXVI). Its hydrolysis with $KHCO_3$ in aqueous methanol yielded the 20*R*-hydroxy-22-aldehyde (XXXIX) and its 20*S*-isomer in proportions of 5 : 3; the isomers could be separated by chromatography on silica. Protection of the 20-hydroxy-group by the THP ether and the introduction of the 14α-hydroxy-group by oxidation with SeO_2 led to compound (XXXVIII), which was used directly to introduce the side chain. Reaction with the MgCl derivative of the THP ether of 2-methylbut-3-yn-2-ol and its isomerisation at C-5 (K_2CO_3–H_2O–CH_3OH) led to compound (XXXVII) (in $5\alpha : 5\beta = 1 : 3$ equilibrium mixture). Finally, catalytic hydrogenation of the triple bond in the side chain (5% Pd/C)§ and hydrolysis of the protecting groups with dilute HCl gave ecdysterone (VI). An advantage of this method of synthesis of ecdysones is the use of the convenient procedure for the introduction of the 2β,3β-diol group by the *cis*-hydroxylation of the Δ^2-bond; the disadvantages include primarily the unsatisfactory choice of bisnorcholanoic acids as starting materials (in view of the laborious nature of the method of their conversion into the 22-aldehydes selected by the authors).



The third method of synthesis of ecdysones according to the scheme *5a* → *1* → *3* → *4* → *2* → *5b* (the side chain is built up in two stages) was published in 1967–1968 by a group of Japanese chemists. The starting material for the synthesis of α-ecdysone[181] was the 3,6-diketone (XL) obtained from stigmasterol and converted by ketalisation, ozonolysis, and the reduction of the ozonide with zinc dust in acetic acid into the diketal of the 22-aldehyde (XLI). Partial synthesis of the side chain was achieved through the introduction of the ethynyl group by reaction with BrMgC≡CH and subsequent reaction of the MgBr derivative of the resulting ethynylmethanol with carbon dioxide. Catalytic hydrogenation and acid hydrolysis of the acetylenic hydroxyacid (XLII) gave a mixture of 3,6-diketones epimeric at C-22, in which the required 22*R*-isomer predominated. Selective reduction of the 3-oxo-group with $NaBH_4$, ketalisation of the 6-oxo-group, and oxidation of the 3-hydroxy-group to the 3-ketone by the CrO_3 complex of pyridine resulted in the 6-monoketal (XLV) required for further synthesis. Auto-oxidation of this compound in the presence of $t\text{-}C_4H_9OK$ gave an oily mixture of the two possible enolic forms of the 2,3-diketone (XLIV). Reduction of this mixture with $NaBH_4$ and subsequent chromatographic separation made it possible to isolate the 2β,3β-diol, which was converted into the corresponding diacetate.

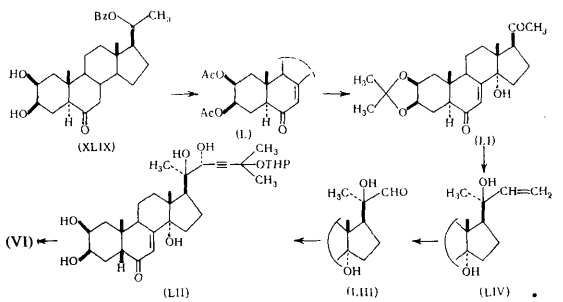


§The hydrogenation is also accompanied by the hydrogenolysis of the 25-hydroxy-group and the 25 deoxy-derivative of ecdysterone (ponasterone A) is formed as a side product[180].

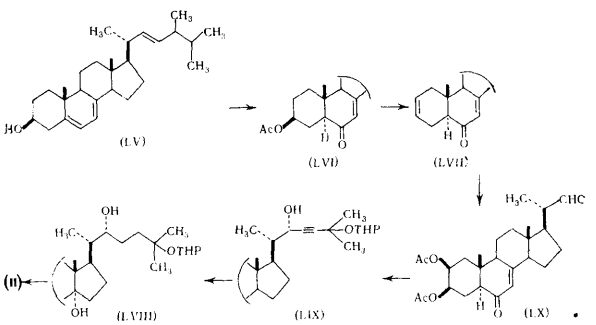
Bromination at C-7 with subsequent dehydrobromination by treatment with Li_2CO_3 yielded the Δ^7-6-oxosteroid (XLIII). The 14α-hydroxy-group was introduced into the latter by conversion into the enol acetate (XLVI) (acetic anhydride and perchloric acid) and its oxidation with monoperphthalic acid. The acetate groups in the resulting product (XLVII) were hydrolysed on heating under mild alkaline conditions (K_2CO_3–H_2O–CH_3OH) and there was inversion at C-5 with formation of compound (XLVIII). For conversion into α-ecdysone (II), this compound required only the attachment of the side chain, which was achieved by a Grignard reaction via the lactone group with a large excess of CH_3MgBr. 22-iso-α-ecdysone was synthesised according to a similar scheme from the 22*S*-lactone, which is isomeric with compound (XLV).[182] The scheme for the synthesis of the ecdysone nucleus described in the above studies has also been applied in the synthesis of rubrosterone[183].

The synthesis of ecdysterone (VI) by the same group of investigators[184] begins with pregnenolone, which was converted in nine stages into compound (XLIX) (the introduction of the 2β,3β-diol group was achieved via the 3,6-diketone, as in the synthesis of α-ecdysone[35]). Acetylation, bromination, and dehydrobromination made it possible to obtain from (XLIX) the Δ^7-6-oxosteroid (V) into which the 14α-hydroxy-group was introduced by oxidation of the enol acetate with monoperphthalic acid. Alkaline isomerisation at C-5, protection of the diol group in the A ring by the formation of an acetonide, and oxidation at C-20 with the CrO_3–pyridine complex yielded the 20-ketone (LI), which has all the structural elements of ecdysterone except for the side chain. The latter was built up in five stages. The Normant reaction and the corresponding ozonolysis of the resulting vinylmethanol (LIV) gave the aldehyde (LIII), which was introduced into a Grignard reaction with the MgBr derivative of the THP ether of 2-methylbut-3-yn-2-ol, forming compound (LII). Hydrogenation of the triple bond, hydrolysis of the protecting groups, and chromatographic separation of the C-22 isomers formed yielded ecdysterone (VI), which was identical with the natural hormone.

The third scheme for the synthesis of ecdysones described above begins directly with 22-aldehydes, which facilitates the introduction of the side chain. Its principal disadvantage is the large number of stages involved in the introduction of the 2,3-diol group and the side chain.



The synthesis of α-ecdysone (II) from ergosterol (LV) with introduction of the structural elements according to the scheme *3 → 1 → 5 → 4 → 2* developed by Swiss chemists is free from the majority of the disadvantages of the schemes for the synthesis of ecdysones discussed above[154,155]. Oxidation of ergosteryl acetate with CrO_3 gives the 5α-hydroxy-6-oxo-derivative, which on reduction with zinc dust in acetic acid is converted into compound (LVI) in which the Δ^7-6-oxo-structure is already formed[185]. Further synthesis was performed via several pathways, of which only one proved to be successful. The two-stage substitution of the 3β-acetoxy-group in compound (LVI) by the 3β-methanesulphonyloxy-group with subsequent cleavage of the methanesulphonate with Li_2CO_3 gave the Δ^2-steroid (LVII). *cis*-Hydroxylation of the Δ^2-bond (silver acetate and iodine), protection of the resulting 2β,3β-diol group by formation of the diacetate, and ozolysis under controlled conditions resulted in the stereospecific formation (without inversion at C-20) of the 22-aldehyde (LX). Treatment of this aldehyde by the Grignard reagent obtained from the THP derivative of 2-methylbut-3-yn-2-ol led to a mixture of isomeric 22ξ-hydroxy-derivatives in which the required 22*R*-component (LIX) predominated; the mixture was separated by chromatography on silica. Catalytic reduction of the triple bond in the C-23–C-24 position¶ and subsequent introduction of the 14α-hydroxy-group by treatment with SeO_2 yielded compound (LVIII). Isomerisation at C-5 and hydrolysis of the acetoxy-groups under mild alkaline conditions (K_2CO_3–H_2O–CH_3OH) gave the corresponding 2β,3β-diol with the *cis*-junction of the A and B rings and hydrolysis of the THP group with dilute HCl yielded α-ecdysone (II). The above scheme constitutes the simplest procedure for the synthesis of ecdysones: the conversion of ergosterol (LV) into α-ecdysone (II) requires 14 stages in this scheme. The yield of compound (LVIII) is 0.063% with respect to ergosterol[155] (the yields in the last two stages are not indicated).



In the other versions of this scheme for the synthesis of α-ecdysone, the order of introduction of the principal structural elements of the molecule was altered[155]. For example, an attempt was made to achieve the isomerisation at C-5 already in the stage of the 2β,3β-diol obtained by the hydroxylation of the Δ^2-steroid (LVII); however, this involves also isomerisation at C-14 to the *cis*-C/D derivative. Evidently, before isomerisation at C-5 it is necessary to protect the C-14 position by introducing a 14α-hydroxy-group into the molecule. At the same time

¶The use of tritium instead of hydrogen in the hydrogenation of compound (LIX) (and other intermediates with a triple bond in the side chain obtained by other procedures) leads to α-ecdysone and its 25 deoxy-derivative (formed as a side product), labelled with tritium at C-23 and C-24; these compounds have been used in biological studies[49,180].

the introduction of this group before constructing the side chain caused an undesirable alteration in the stereochemistry of the Grignard reaction: the 14α-hydroxy-analogue of the aldehyde (LX) gave rise only to the 22*S*-isomer, which was converted in two stages as in the synthesis described above, into 22-iso-α-ecdysone. Thus in this case it is necessary to introduce initially the side chain into the molecule, then the 14α-hydroxy-group, and the isomerisation at C-5 must be carried out only in the last stage (i.e. the structural fragments must be introduced according to the scheme *5* → *4* → *2*). This is evidence of a considerable importance of the correct choice of the sequence of stages in the synthesis.

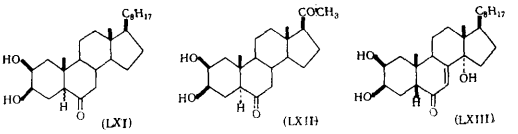
IV. ANALOGUES OF ECDYSONES

The study of analogues of ecdysones is of great practical importance, since these substances, which act as insecticides and chemosterilants, make it possible to control the numbers of insect pests. In the first place it is necessary to examine the effect of the structure of ecdysones on their MMH activity, which permits the elucidation of the relative importance of various structural elements of the molecule for its biological activity.

At the present time, the role of the hydroxy-groups in the steroid skeleton and in the side chain of ecdysones has been mainly investigated. The importance of the hydroxy-groups in the A ring of the ecdysone molecule can be assessed from the following facts: while the activity of 2-deoxyecdysterone, which has a 3β-hydroxy-group, is equal to that of ecdysterone [124], its 3α-epimer is three times less active [186]. Thus the hydroxy-group at C-2 is of no importance for MMH activity, while the presence of the hydroxy-group at C-3 and its equatorial configuration play a significant role. The importance of the 14α-hydroxy-group is even greater, its removal lowering the activity by a factor of 15 compared with α-ecdysone [187]. The introduction of an additional 5β-hydroxy-group into the molecule (polypodine B) greatly increases the MMH activity [128].

The presence in the steroid molecule of a long side chain at C-17 is necessary for MMH activity, since rubrosterone and its analogue with an acetyl side chain (VIII) do not show this activity [112, 120]. The complete absence of a hydroxy-group from the side chain also sharply reduces the activity (by a factor of 50 compared with α-ecdysone [187]). The removal or isomerisation of the 22*R*-hydroxy-group leads to a sharp fall or complete disappearance of MMH activity [111,155,170]; the introduction of an additional 26-hydroxy-group has the same consequences [126]. On the other hand, an additional 24-hydroxy-group or a Δ^{24}-bond do not have a significant effect on the activity, while a 20*R*-hydroxy-group increases it somewhat [134,135]. The presence of an ethyl-group at C-24 in 29C-ecdysones does not affect the activity [139,149]; nor is the activity reduced in the presence in the side chain of lactone groups (capitasterone, cyasterone) [113,148]. At the same time an epoxy-group in the side chain (stachysterone D) virtually eliminates the MMH activity of the compound [135].

Many synthetic analogues of ecdysones can inhibit the moulting and metamorphosis in the development of insects (i.e. they can act as ecdysone antagonists); also they can have a general toxic effect on adult forms. The toxic effect of ecdysone analogues—derivatives of androstane, pregnane, and cholestane—was investigated on the bug *Pyrrocoris apterus* [188-190] and certain other insects [174]. Compounds (LXI)-(LXIII) proved to be the most active.



Compounds with a low MMH activity are the most toxic for insects and conversely. The presence of a hydroxy-group at C-2 and the configuration of the hydrogen atom at C-5 proved to be unimportant for toxicity. The toxicity fell somewhat on introduction of a Δ^7-bond and disappeared completely on acetylation of the 3-hydroxy-group or on reduction of the 6-oxo-group. At the same time it was not possible to establish a definite link between toxicity and steroid structure: probably in this case there is a superposition of various toxic effects, which depend in different ways on the structure. The direct cause of the death of *P. Apterus* larvae proved to be the breakdown of the integrity of the cell membranes in consequence of a change in the surface tension of the haemolymph caused by the introduction of the steroid [189]. It is noteworthy that the susceptibility of different insect species to steroid insecticides is variable [67,74]. This necessitates a large-scale programme of tests in each case and at the same time leads to the possibility of choosing compounds which selectively supress a given insect species.

The observation of a sterilising effect by many ecdysone analogues on the females of the housefly and other Diptera is also of considerable interest [74,191,192]. It was not possible to observe rigorous correlations between structure and activity in this case either, but the presence of a 6-oxo-group in the steroid molecule is apparently necessary both for sterilising activity and for toxicity. Synthetic analogues of ecdysones are a new class of specific insect chemosterilants, which are safe for warm-blooded animals [193].

Thus synthesis of ecdysone analogues gives rise to the possibility of fundamentally new hormonal insecticides. One may expect that, apart from their high activity, these compounds will exhibit selectivity of action in relation to a chosen insect species and that insect pests will be unable to adapt to these insecticides.

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