REVIEW ARTICLE

THE CHEMISTRY OF CORTISONE

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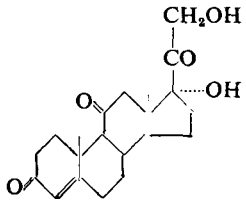
The introduction of cortisone into medical practice in 1949[1] had a great impact both on the general public, when it received the news through the newspapers, and on scientists; on the former because of the dramatic improvements that the drug effected in rheumatoid arthritis, a widespread and crippling disease, and on the latter because of the biological implications of the medical discovery and the difficulties implicit in the technical preparation of the drug. Cortisone is perhaps the most complicated of the synthetic organic compounds yet introduced into medical practice, not so much for the actual number of atoms in the molecule, but because of intrinsic difficulties arising from the specific nature of the substituents, the variety of stereochemical complications and the occurrence of a sensitive and highly reactive side chain.

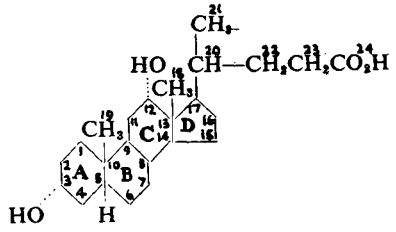
The substance now known as cortisone was originally discovered by three different groups of workers in the same year[2,3,4] during research into the biologically active constituents of the adrenal cortex. This contains a number of steroids, several of which have not only biological activity but activity of different types, which can be associated with the chemical constitution of the isolated materials. Because of the variety of compounds and the small amounts in the glands, the work was extremely complex. Furthermore, when compounds having important physiological actions were discovered, the glands were unsuitable as sources of further material, because the amounts available were too small, and synthetic or partially synthetic methods of preparation had to be devised.

As cortisone is known by several terms, apart from trade names, it may be helpful to give some of them. The original investigators isolated it as one of several substances in adrenal cortex, each of which was given an alphabetical letter, and cortisone is Kendall's compound E, Reichstein's compound Fa and Wintersteiner's compound F. Of these terms the first is the best known. The name 17-hydroxy-dehydrocorticosterone was also extensively used. More systematically it is described as Δ^4-pregnen-17α:21-diol-3:11:20-trione or 17α:21-dihydroxy-3:11:20-triketo-pregn-4-ene.

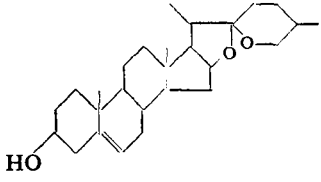
At first cortisone was prepared from desoxycholic acid, and until recently practically all the drug was obtained from this source. There are other naturally occurring sterols, shown below, from which it can be produced by partial syntheses, and a great deal of work has been done on them. Further, there is the possibility of total synthesis, and this has recently been brought about by brilliant investigations in three laboratories. In this article an attempt will be made to deal with most of the ways in which the drug can be prepared, by either partial or total



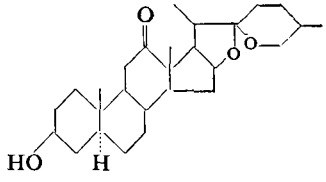
Cortisone



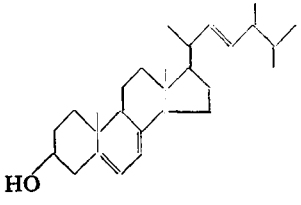
Desoxycholic acid



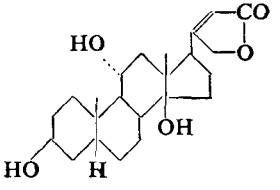
Diosgenin



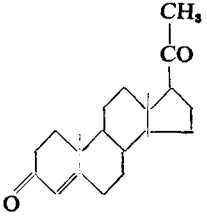
Hecogenin



Ergosterol



Sarmentogenin



Progesterone

synthesis, and to bring these methods into general relationship one with the other. Several of the methods of partial synthesis are of general application and may have been applied to sterols having, for instance, different side chains. In order to avoid confusion and complications, these methods are described by means of partial formulæ and only those portions of the molecule involved in the reactions are portrayed. In order to facilitate interpretation, the structure and numbering of desoxycholic acid are given in detail. Substituents in the α- or β-configurations are shown by dotted and full lines respectively.

The attractions of sarmentogenin as starting material for cortisone are clear enough from the formulæ. It is one of the very few presently known steroids, apart from those of the adrenal cortex itself, having an oxygen-containing substituent in position 11. Furthermore, the side

chain attached in position 17 is readily degraded to a pregnan-20-one, from which the cortisone side chain can be created, as will become apparent later on. Unfortunately, sarmentogenin, though occasionally found in *Strophanthus sarmentosus*, is present in only small quantities and the vine is not one that can readily be cultivated. The difficulties of obtaining the aglycone in quantity have so far defeated its application to the production of cortisone.

One of the other starting materials shown, namely progesterone, has the unsaturated ketonic grouping in ring A and a suitable side chain, but is devoid of any kind of substituent in ring C. Its application to the commercial synthesis of cortisone has been a recent occurrence and depends upon the introduction of an hydroxyl group in position 11 by fermentation methods using particular species of moulds. The largest volume of published work has been on partially synthetic methods from desoxycholic acid and ergosterol.

Early work has been surveyed in several places[5,6,7,8,9] and need not be discussed in detail here, although the major general methods will be summarised to bring them into relationship with newer ones. This review is principally concerned with the work published during the last 2 or 3 three years. A valuable historical review is given by E. C. Kendall, one of the original discoverers of the substance[10].

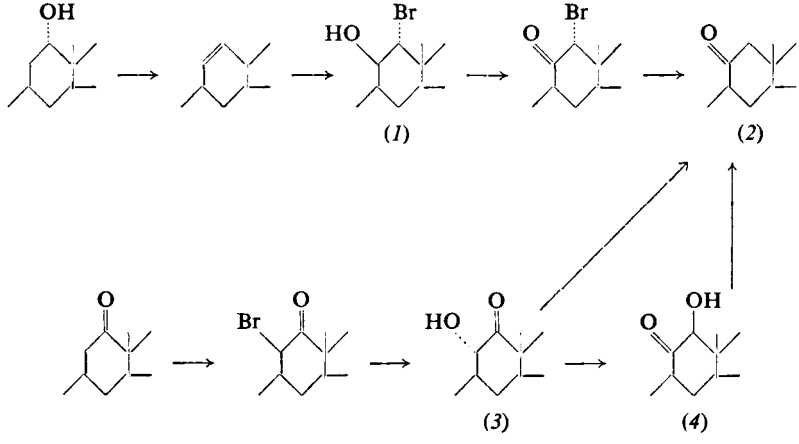
The synthesis of cortisone can be carried out by a variety of procedures from any of the naturally-occurring compounds referred to above and can be subdivided into four subsidiary groups of reactions: (i) introduction of a ketone group into ring C in the 11 position; (ii) degradation of the side chain, whether it be of a bile acid, ergosterol or a sapogenin, to that of a pregnan-20-one; (iii) construction of the dihydroxy acetone side chain present in cortisone from the above types of grouping; and (iv) the modification of ring A, which is usually saturated, to introduce the unsaturated ketone group.

In most instances the synthetic steps are carried out in the above-mentioned order, though in special instances this may be altered. As, however, the substituents present in the starting material determine to a large extent the methods within the above sections, it will be clearer if the processes used with each starting material are discussed in turn.

Desoxycholic Acid

Taking first the conversion of the 12-hydroxyl group of desoxycholic acid into the 11-ketone group, there are several different methods to be mentioned, of which the earliest were based on Δ^{11}-compounds, obtained by suitable elimination reactions from desoxycholic acid or one of its acyl derivatives. Addition of hypobromous acid, generated from N-bromacetamide, to the double bond gave a mixture of products from which the bromhydrin (*1*) was isolated. This was converted to an 11-ketone (*2*) by oxidation of the hydroxyl group and removal of the bromine atom by reduction. Yields on both double bond formation and addition of hypobromous acid were poor. In another early method a 12-ketone was brominated and the product hydrolysed to an α-ketol.

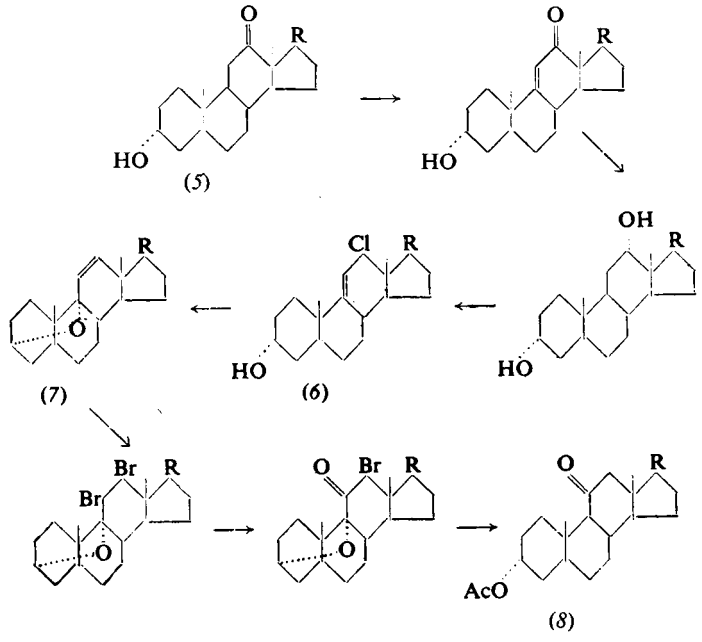
When the hydrolysis was carried out under very mild conditions an 11-hydroxy-12-ketone (*3*) was obtained, but under more strongly alkaline conditions this underwent rearrangement and the principal product was a 12-hydroxy-11-ketone (*4*). From this the hydroxyl could be removed by replacement with bromine[11] and debromination. The 11-hydroxy-12-ketone intermediates (*3*) can also be converted to 11-ketones by Kishner Wolff reduction and oxidation.



A more efficient method was discovered by Kendall and his co-workers[12,13] and depends upon the reactivity of the allylic system of a $\Delta^{9(11)}$:12-halogen compound. This is obtainable as shown (*5*) to (*6*); it gives on mild hydrolysis a neutral product, devoid of free-hydroxyl groups and subsequently found to be a Δ^{11}-3:9-oxide (*7*). Addition of bromine to the double bond followed by hydrolysis, oxidation, etc., completes the sequence of reactions to give an 11-ketone (*8*) as shown. Unlike the previous methods this one is very much influenced by the stereochemical configuration of the molecule, as the formation of the 3:9-oxide depends upon rings A and B being fused in the cis position and also on the 3-hydroxyl group being in the α- and not the β-configuration. Only in these circumstances does the oxygen atom at position 3 approach sufficiently closely to the 9-position to permit ring formation. The oxide ring when formed is stable enough to permit many reactions to take place, but can be reopened to give a 3α-acetoxy compound by the action of hydrogen bromide and acetic anhydride.

Many variations on all the above methods have been worked out, but it is not possible to discuss them all here and only one example of each is given. They are discussed more fully in Professor and Mrs. Fieser's valuable monograph[5].

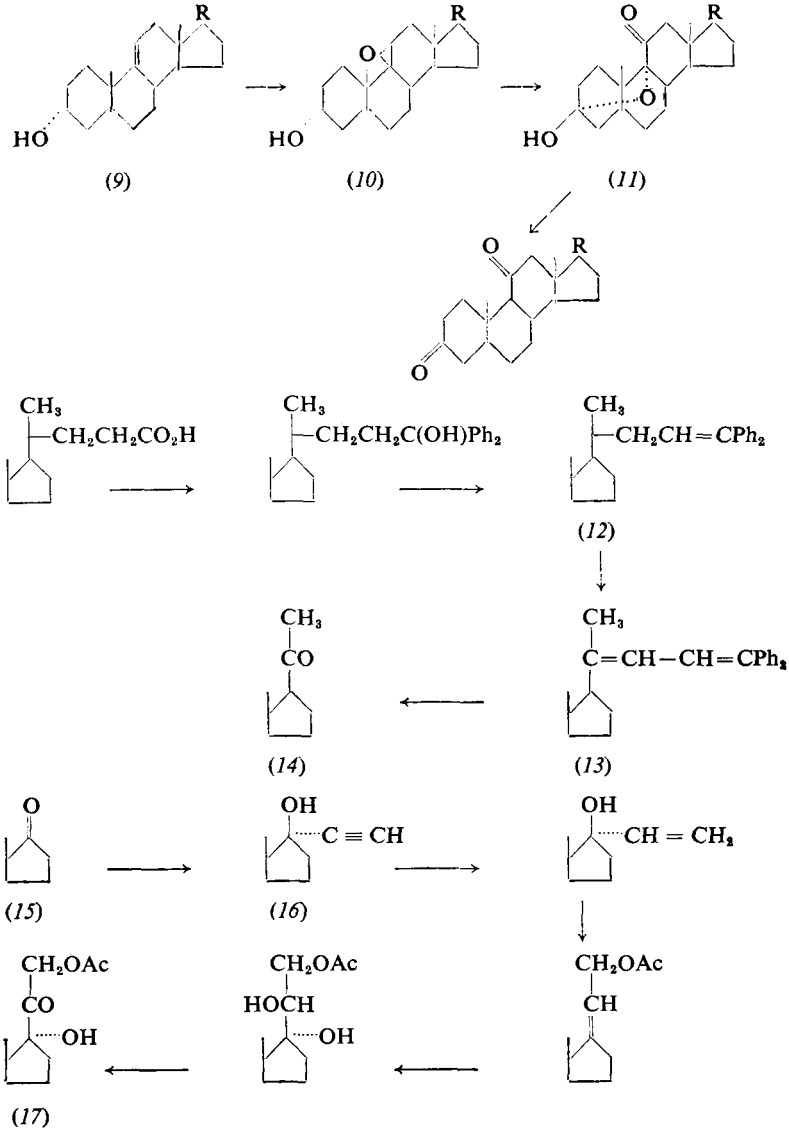
A recent method, introduced by Fieser[14,15], also depends on the formation of a 3:9-oxide. Here a double bond is first introduced (*9*) by selenium dioxide oxidation of a 12-ketone followed by removal of the keto group. On treatment with per-acid a 9:11-oxide is formed (*10*) and is stable to the action of various acids or reducing agents, but



on treatment with chromic acid is oxidised to a hemiketal (*11*). This can then be converted by treatment with hydrogen bromide and reduction, etc., to the type of intermediate required. Again the formation of the intermediate oxygen bridge depends upon the molecule having an A/B *cis* configuration. The change in configuration of the 3-hydroxyl group in (*11*) is due to the fact that a 3-ketone, which is formed as an intermediate, is attacked in the rear or α-position by the oxygen atom attached in position 9, with formation of a 3β-hydroxyl group.

Passing on to the modification of the bile acid side chain, the original method used was the well-known Barbier-Wieland degradation devised many years ago in Wieland's classical work on the structure of bile acids. It required a large number of steps and can be considerably shortened by the modification introduced by Meystre and Miescher[16,17], in which the diphenylcholene (*12*) formed after Grignard reaction on the cholic esters is treated with *N*-bromsuccinimide under conditions that permit removal of hydrogen bromide to form another double bond, the product being a diphenylchola-20:23-diene (*13*). This is directly oxidised by chromic oxide to a pregnan-20-one (*14*), which serves as starting material for the next phase of the synthesis, namely the creation of the dihydroxy-acetone side chain, which is one of the principal features of cortisone.

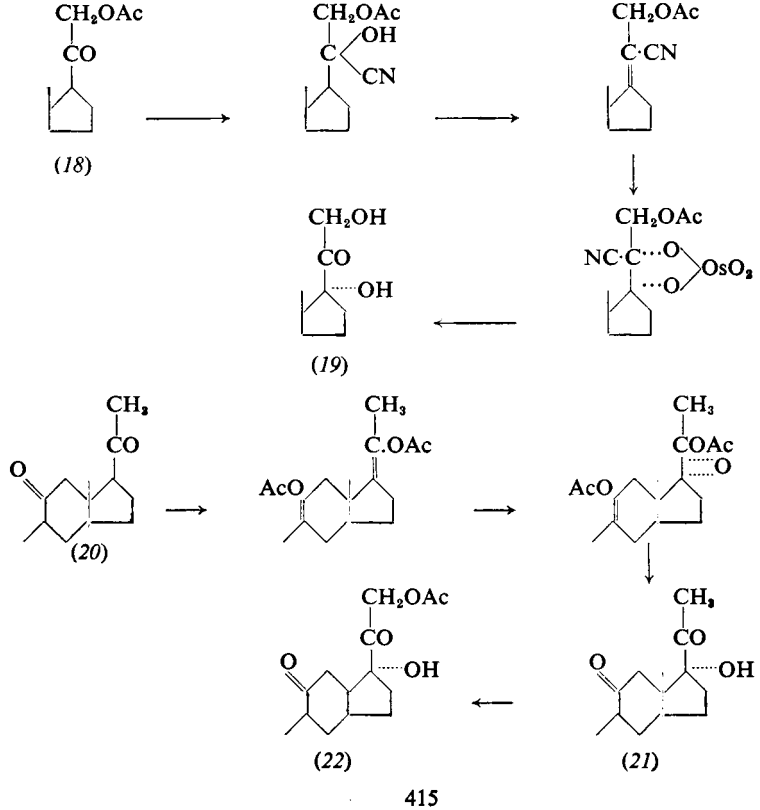
This is beset by one major difficulty. In all naturally-occurring sterols the side chain is 17β. When attempts are made to form a 17α-hydroxy compound from, for instance, a 17-ketone, the reaction invariably leads to a substance having the carbon side chain in the α-configuration together with a 17β-hydroxy group (e.g. *15* to *16*). This is the reverse of that present in the natural hormones and the positions must be inverted.

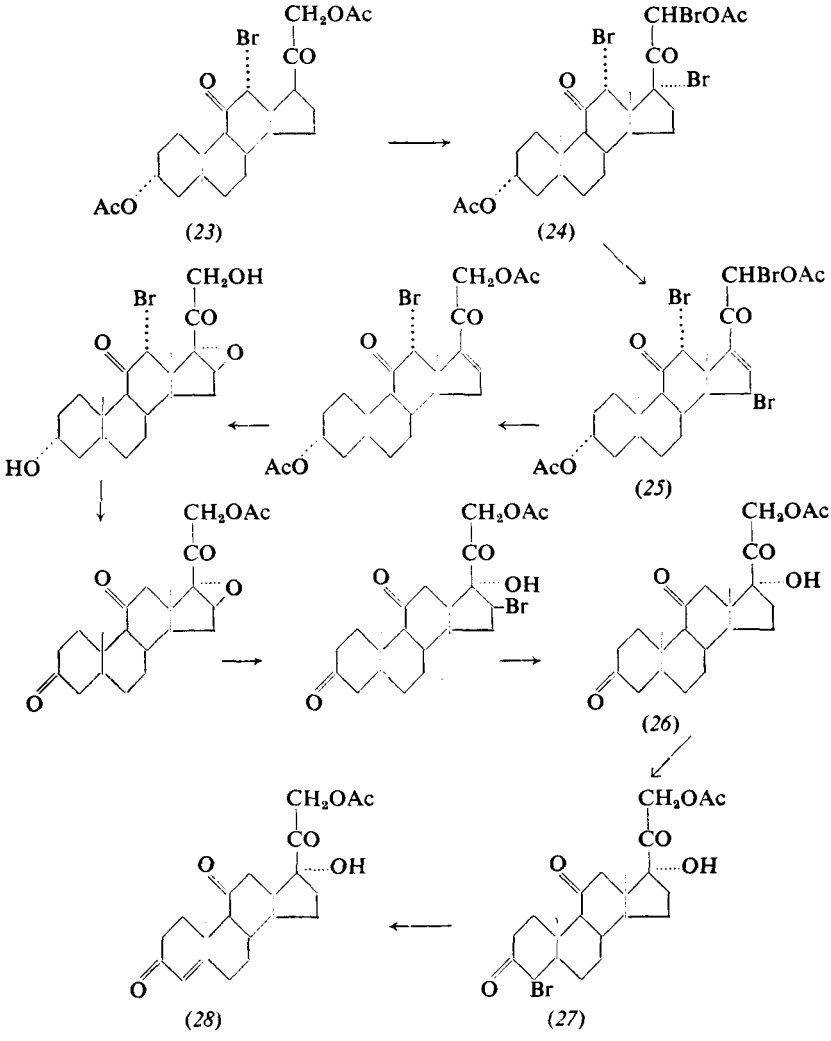


All the successful methods of building the required side chain have depended on an intermediate having a double bond at the 17-position. This can be done in several different ways (e.g. *15* to *17*; *18* to *19*). The second of these illustrates one of the methods used by Sarett[18,19] in the synthesis of cortisone. It depends on oxidation of the 17:20-double bond with osmium tetroxide, which produces a 17α:20α-glycol. The reagent always attacks the less hindered α face of the molecule, the angular methyl group at position 13 preventing attack from the other side. Modifications of the method are also described[20,21].

But osmium tetroxide is dangerous as well as expensive, and methods of avoiding its use have been sought. The most successful depends upon forming the double bond by enolisation of a pregnan-20-one. The procedures were introduced by Gallagher[22,23,24] and his co-workers and are illustrated by formulæ (*20* to *21*). They have been used on several intermediates, and it is noteworthy that both the 11- and 20-ketone groups are enolised and acetylated as shown, but at the next step only 17:20-double bond is attacked by perbenzoic acid and therefore on the subsequent hydrolysis the 11-ketone group is recovered unchanged and a 17α-hydroxyl group is introduced. The side chain is then completed by bromination at position 21 followed by hydrolysis or acetoxylation to (*22*).

In the above paragraphs major procedures are given in outline only; there are many opportunities for varying the order in which the different steps are carried out. By means of such a combination of methods (*23*) may be prepared and can be used as a means of introducing the 17α-hydroxyl group by a series of reactions quite different from any of those hitherto described[25,26]. Bromination in acetic acid forms a 12:17:21-tribromo compound (*24*) which after dehydrobromination and re-bromination yields (*25*). From this, dihydrocortisone (*26*) may be obtained in several steps by reduction, oxidation, etc., as shown. The





procedure is efficient, avoids the use of osmium tetroxide and makes use of a Δ^{16}-compound and a method introduced earlier by Julian[27]. Again attack by the reagent at the unsaturated 17-position is at the unhindered α face of the molecule.

The last phase of the synthesis is then carried out by brominating in the 4-position and removing hydrogen bromide to form the Δ^4:3-ketone. Yields on dehydrobromination with bases are poor, and a great improvement was affected by treating the 4-bromo ketone (*27*) with dinitrophenylhydrazine or semicarbazide whereby the appropriate derivative of the ketone is obtained and dehydrobromination takes place at the same time provided acetic acid is used as the solvent. The unsaturated ketone (*28*) (cortisone acetate) is generated from the derivative by treatment with

pyruvic acid. The method was discovered by Mattox and Kendall[28] and later modified and improved[29,30,31] and it is now commonly used for introducing double bonds into ring A in very satisfactory yield, provided rings A and B are *cis*. The need for this will become apparent later.

The methods used for the synthesis of cortisone from desoxycholic acid have never been brought together, but a possible complete synthesis has been suggested[32].

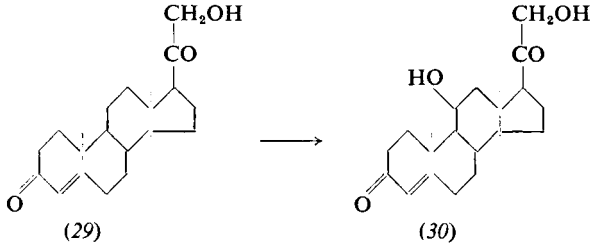
Progesterone

The use of this raw material is dealt with next, partly because complete information has been made available on its conversion to cortisone, and partly because, though it bears little superficial resemblance to desoxycholic acid it can, in a few stages, readily be converted to an 11:20-diketone derivable from it, and from which the rest of the synthesis has already been described. Progesterone itself can be prepared from a number of raw materials, and several different preparative methods are known, probably the best being that from diosgenin, although recently interest has also been shown in its preparation from stigmasterol[6,33,34,35].

While progesterone has an appropriate side chain for conversion to cortisone and already has an unsaturated ketonic group in ring A, it suffers from the obvious disadvantage of having no substituent at all in ring C and no evident means of introducing one. Great interest was therefore shown in a report[36] from Professor Pincus's laboratories that the perfusion of 11-desoxycorticosterone (*29*) or its acetate through isolated adrenal glands led to the formation of corticosterone (*30*), which was isolated and identified. This work was actively followed up, and it was later shown[37] that (*31*) could be converted to (*32*) by an extract of minced adrenal tissues containing the appropriate enzyme system. Note that the hydroxyl group at the 11-position appears in the β-configuration, which is that present in natural hormones, as would be expected from the method of preparation. However interesting these observations might be, they did not offer a practical large scale method for the introduction of oxygen at the 11-position into sterols, but this became feasible with the discovery by Peterson and Murray[38,39] that fermentative oxidation of several sterols by suitable species of moulds could accomplish similar reactions. They used a strain of *Rhizopus* and from the fermentation mother liquors containing progesterone (*33*) isolated 11α-hydroxyprogesterone (*34*). A 6:11-dihydroxyprogesterone was also isolated in these experiments. Other workers[40] using a strain of *Streptomyces* succeeded in converting Reichstein's compound S (*31*) into Kendall's compound F (*32*), the so-called hydrocortisone, though in poor yield. Note that in this case an 11β-hydroxyl group is again introduced. Hydroxylation of progesterone in the 16-position (*35*) has also been reported[41], along with several other similar oxidations, including simultaneous hydroxylation in the 6- and 11-positions[42].

The preparation of 11α-hydroxyprogesterone by these methods obviously made the synthesis of cortisone from that starting material a great deal more attractive, and the observations were rapidly followed up.

The methods became still more attractive when it was found[43] that hydrogenation of the 4:5-double bond, to protect it during subsequent operations, gives a normal pregnane derivative (*36*), whereas hydrogenation of similar compounds with either a ketone or a β-hydroxyl group



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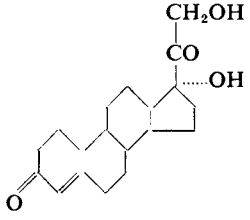
(*30*)



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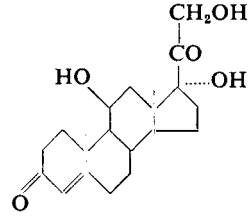

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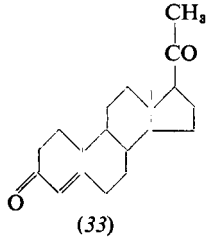

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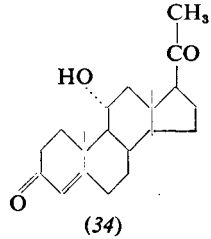

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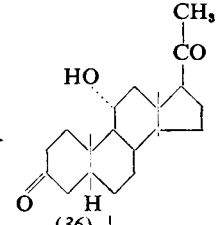

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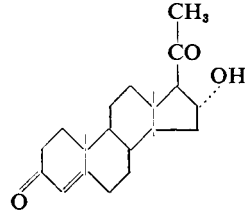

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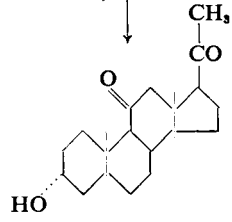


(*37*)

in the 11-position gives predominantly products belonging to the *allo*-pregnane series. It is thought that the additional steric hindrance at the rear of the molecule provided by the 11α-hydroxyl tips the balance of factors affecting the position of attack by the catalyst, so that hydrogenation takes place principally at the front or β-position, yielding an A/B *cis* compound on hydrogenation. By oxidation and preferential reduction of the thus formed 3:11:20-triketone with sodium borohydride in pyridine (*37*) is obtained, from which the preparation of cortisone has been described above[24].

Thus biological oxidation to obtain an 11-hydroxy compound, coupled with the unexpected hydrogenation of this particular type of derivative to a compound of the pregnane series, readily converts progesterone into a substance previously prepared from desoxycholic acid, permitting the complete conversion of progesterone to cortisone in about 10 stages.

Hecogenin

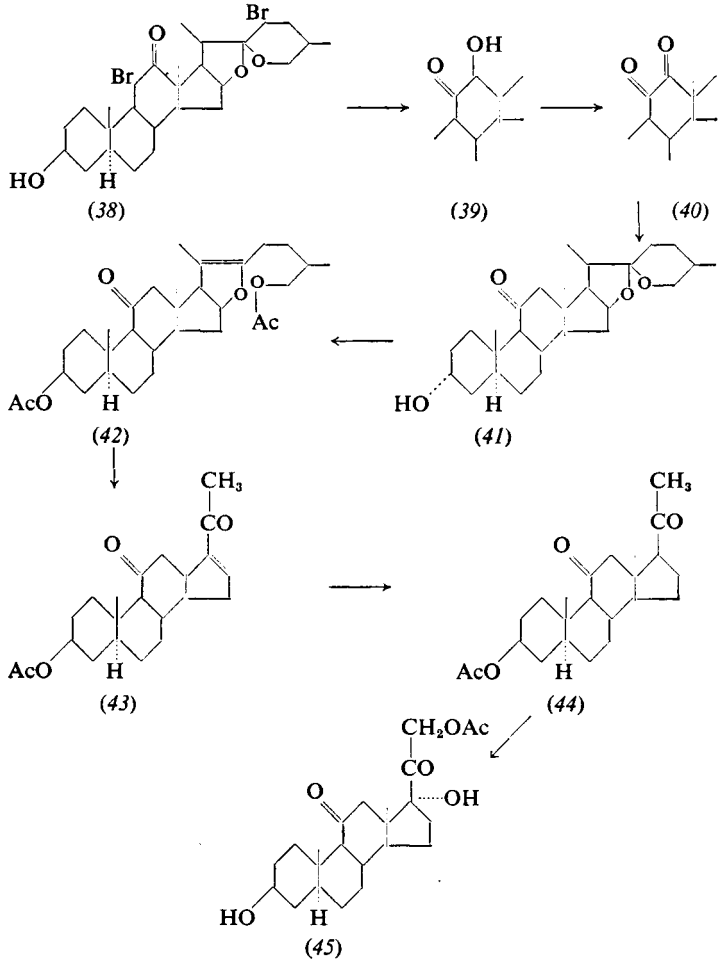
This, regarded as a starting material for the synthesis of cortisone, looks similar to desoxycholic acid, apart from the side chain, in that it has oxygen substituents in the 3- and 12-positions. The resemblance, however, is more superficial than real, and there is need for new methods at several different points. The A and B rings are fused in the *trans* configuration, rather than the *cis* as in bile acids, and this prevents the application of those methods of introducing an 11-ketone group that are dependent upon the use of 3:9-oxides. That same difference in configuration also necessitates a new process for the introduction of the 4:5-double bond. But the difficulties have been overcome and a complete synthesis has been described.

Hecogenin is the aglycone of a naturally-occurring saponin found in various species of agave. It was first isolated from a Mexican source[5] and has also been found in the sisal plant, which is cultivated on a very large scale in several parts of the world[44,45]. As the sapogenin can be isolated from waste fractions in the manufacture of the sisal fibre, it is an attractive starting material on which to found a manufacturing method.

Bromination of the sapogenin gives a dibromo compound[46,47] (*38*), which after hydrolysis and partial debromination leads to an 11-keto-12-hydroxy compound (*39*) similar to (*4*). In this case, however, removal of the 12-hydroxy group *via* the bromo compound gave very bad yields, and it was found better to oxidise the ketol with bismuth oxide, a reagent recently introduced for the oxidation of acyloins, to the 11:12-dione[48] (*40*), from which the 12-ketone group can be removed either by Kishner Wolff reduction or by conversion to a dithioketal and subsequent reduction with Raney nickel.

Degradation of the sapogenin side chain in the thus formed 11-keto compound (*41*) can readily be accomplished by methods that were well established for a number of sapogenins by Marker[5] and leads in good yield to (*43*)[49,50] from which 3β-acetoxy-*allo*-pregnan-11:20-dione (*44*) can readily be prepared by hydrogenation[51]. The first step in degrading the side chain, the conversion of (*41*) to (*42*), has been carried out on many sapogenins and compounds derived from them, by heating with acetic anhydride at about 200° C. Conversion to this unsaturated acetate, called the ψ-sapogenin, is usually accomplished in high yield. Recently a modification of the method was introduced; working with diosgenin it was found that its conversion to the ψ-sapogenin by acetic anhydride is catalysed by the use of a Lewis acid, such as aluminium chloride, and that the conversion can then be carried out at much lower temperatures[52].

These products all have rings A and B in the *trans* configuration and

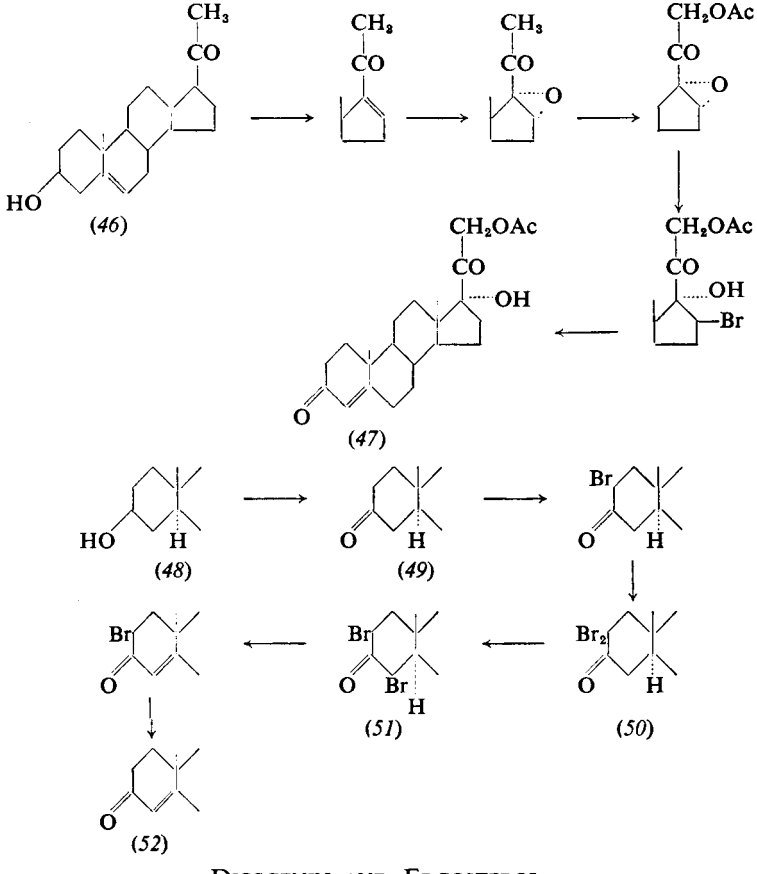


therefore the opposite of that to which Gallagher applied his methods of converting a pregnan-20-one to a substance having a cortisone side chain, but the same method can be applied to (*44*)[53,54,55] to give (*45*).

As degradation of the side chain of a sapogenin leads to a Δ^{16}-20-ketone, an alternative to Gallagher's synthesis of the dihydroxy acetone group may be employed. It was first devised by Julian[27] for the conversion of pregnenolone (*46*) to compound S (*47*) as shown. A modification of the method has already been mentioned in the section on desoxycholic acid.

There remains the problem of introducing the 4:5-double bond into (*49*), obtainable from (*48*) by oxidation. In 3-keto-*allo*-pregnanes, bromine substitutes not in the 4- but in the 2-position. If, however, halogenation is continued further, a 2:2-dibromo compound (*50*) is formed that on treatment with hydrogen bromide in acetic acid solution

rearranges to give a 2:4-dibromo compound (*51*), from which, on removal of a molecule of hydrogen bromide and reduction, the required unsaturated ketone (*52*) is obtained. Several publications have appeared that claim successful application of this method[56,57,58], and various reagents may be used. For instance, removal of hydrogen bromide to form the 4:5-double bond may be accomplished by the use of either collidine or sodium iodide, and reduction of the remaining halogen, bromine or iodine in the 2-position may be carried out by treatment with sodium iodide, sodium bisulphite, chromous chloride or zinc. The method is not so efficient as when applied to simpler substances, such as cholestanone, but nevertheless served to complete the synthesis of cortisone from dihydro-*allo*-cortisone acetate[59].

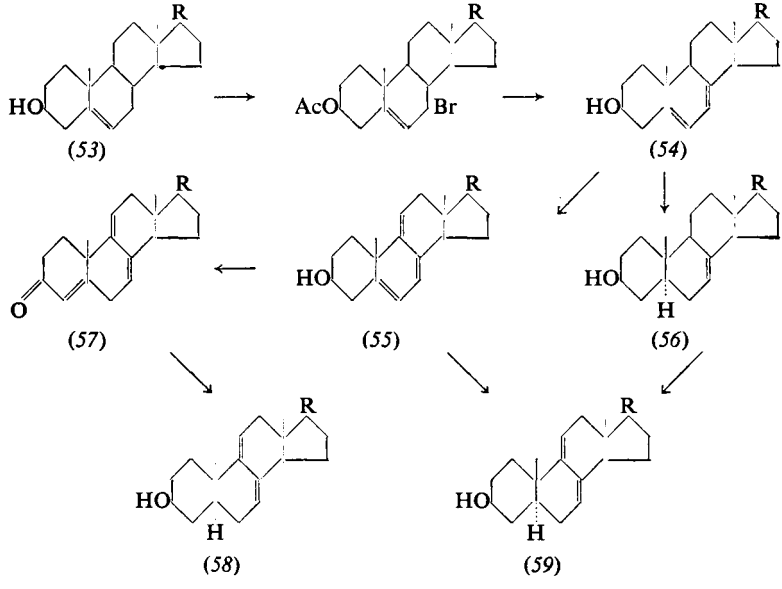


Diosgenin and Ergosterol

These two starting materials are dealt with together here because their use in the synthesis of cortisone invokes essentially the same problems, after a 5:7-diene system has been introduced into diosgenin. Neither compound has an oxygen substituent in ring C and both normally lead to intermediates of the *allo* series. It has been known for some time

that the diene system of ergosterol can be extended to dehydro-ergosterol, a 5:7:9(11)-triene system, by oxidation with selenium dioxide or mercuric acetate, of which the latter is preferred. This is essentially the reaction by which both the above starting materials are brought to the position of being useful intermediates in the synthesis of cortisone.

As a first step it is necessary to create a 5:7-diene system from diosgenin. The problem is the same as that of converting cholesterol into cholesta-5:7-dienol in the preparation of vitamin D_3 and may be solved in much the same manner by bromination at the 7-position with *N*-bromo-succinimide and subsequent elimination of hydrogen bromide on treatment with bases of various kinds (*53* to *54*)[60–65]. Other methods are also known[66,67]. Such dienes may be extended to 5:7:9(11)-trienes (*55*) by dehydrogenation as above or may be selectively reduced to Δ^7-compounds (*56*) with platinum oxide or, better, with Raney nickel[68,69].



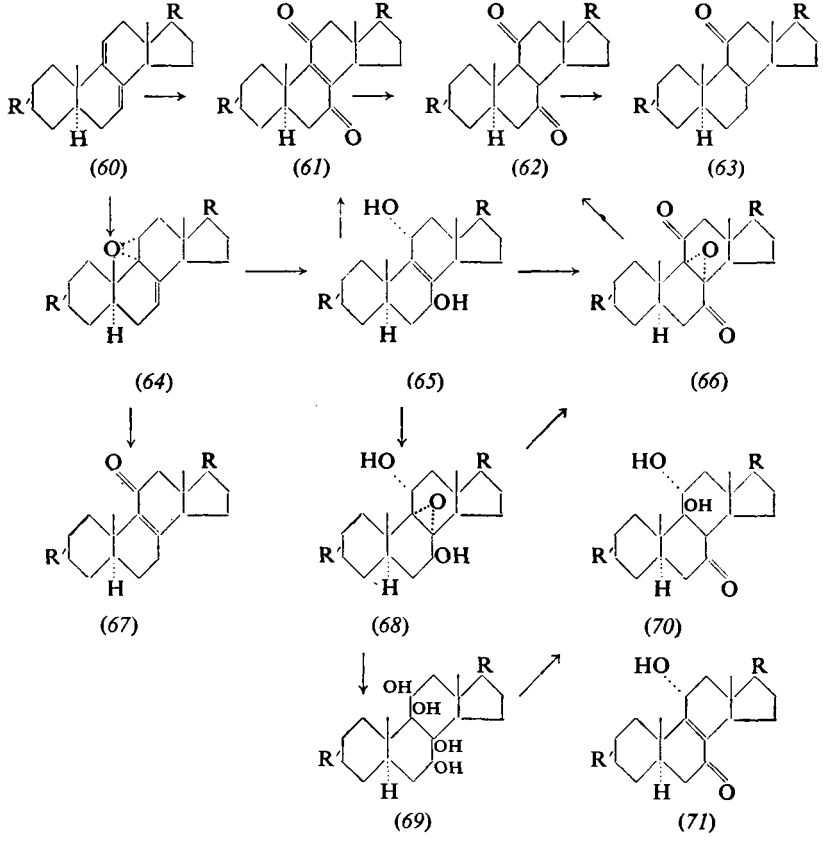
Whereas the direct reduction of (*54* and *55*) leads to *allo*-pregnenes, with which we are mostly concerned, it is possible to convert them to compounds of the normal series by oxidation to (*57*) followed by hydrogenation to (*58*)[70]. Below the emphasis is on the use of *allo* compounds (*59*); most of the reactions, though not all, take a different course in intermediates of the normal series (*58*).

Many different methods have been reported for the conversion of these 7:9-dienes to 11-ketones. Most of the reactions are self-explanatory when depicted in partial formulæ, though several were quite unexpected and, at the time of their discovery, new to sterol chemistry. The direct oxidation of (*60*) to the diketone (*61*) is accomplished by treatment with chromic acid[71], but in very poor yield; alternatively, a similar transformation is accomplished indirectly by bromination, hydrolysis and oxidation[72];

(*61*) is then reduced with zinc to (*62*) and thence by Kishner Wolff reduction to the desired 11-ketone (*63*).

In another method (*60*) is treated with perbenzoic acid[73] to give an oxide, later[74] shown to be the 9:11-oxide (*64*); this on hydrolytic rearrangement gives (*65*), which can be oxidised to (*61*), and this[74,75] is accompanied by the oxido ketone (*66*), itself directly reducible to (*62*). It has also been shown that (*64*) on reaction with a Lewis acid, namely boron trifluoride, rather than with a mineral acid, leads to an unsaturated ketone (*67*). Owing to steric hindrance its reduction to a saturated ketone is difficult, but can be accomplished[76,77], by the use of lithium in liquid ammonia, whereupon (*67*) is converted directly to (*63*) in good yield. A modification of this method, which is claimed to be efficient and is akin to another group of reactions yet to be discussed, is also available[78]. In this (*65*) is oxidised with perphthalic acid to the oxide (*68*), which can be directly oxidised to (*66*) or hydrolysed to (*69*); this on dehydration yields (*70*) and thence (*71*), convertible to (*63*) by methods to be mentioned below.

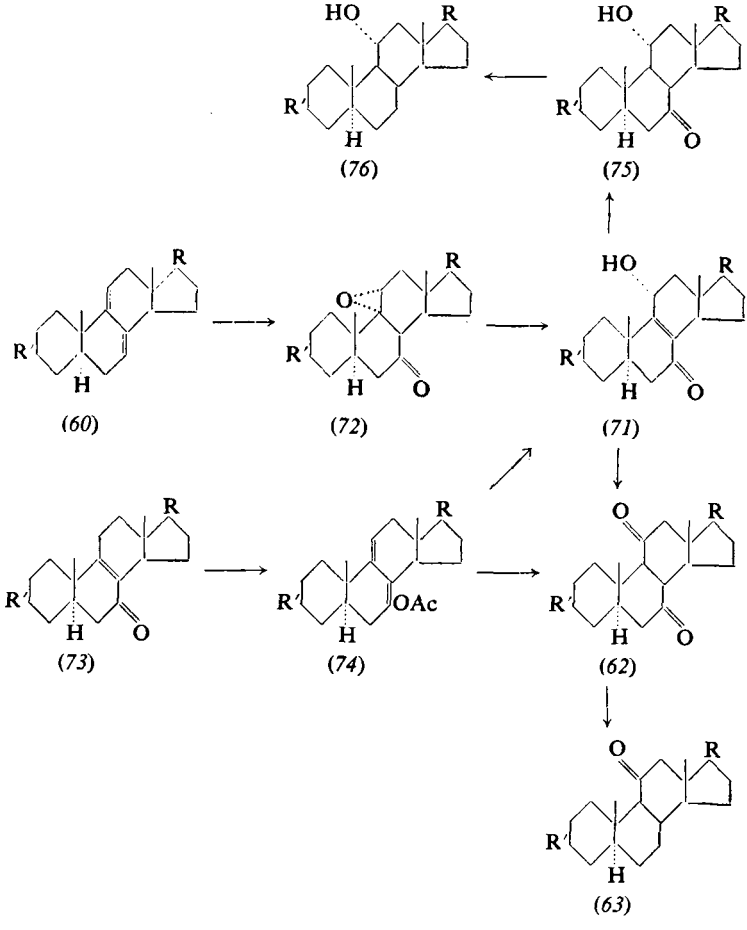
It is to be understood that these various transformations are not being discussed in the chronological order of their discovery and that for



clarity various groups of intermediates have been dealt with together. It is now necessary to go back to one of the earlier methods and follow its development.

As described above, 7:9-dienes are oxidised to 7:11-diketones by chromic acid and to Δ^{7}:9:11-oxides by aromatic peracids; aliphatic peracids cause yet another reaction to take place, whereby (*60*) is oxidised to the oxido ketone (*72*)[79,80]. Hydrolysis with mild alkali converts this to an unsaturated hydroxy ketone previously encountered (*71*), while stronger alkali leads directly to the formation of (*62*). It was later found that this rearrangement gave much better yields when carried out in the presence of potassium tertiary butoxide[81].

Finally, some interesting transformations are recorded on $\Delta^{8(9)}$-7-ketones (*73*), already known as the major products of the direct oxidation of (*60*)[71] and also as one of the products of the rearrangement of (*64*) with mineral acid[74]. Since then it has been discovered[82,83] that, if (*73*) is converted to its enol acetate (*74*) and this oxidised with perphthalic

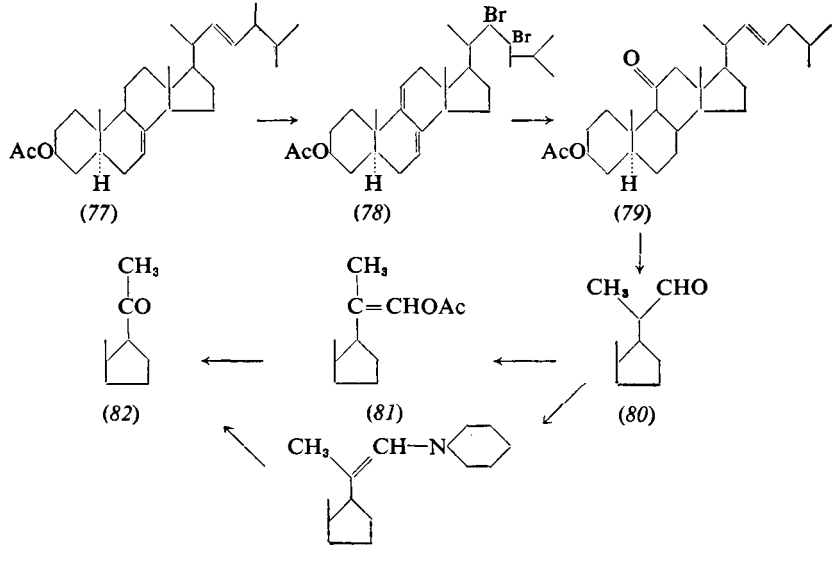


acid, (*71*) is formed directly, thus providing an interesting route from 7- to 11-ketones, or alternatively to 11α-hydroxy compounds (*76*) by catalytic hydrogenation of (*71*) to (*75*) followed by reductive removal of the 7-keto group.

Compounds represented by partial formulæ (*60*) to (*76*) have been derived from parent 7:9(11)-dienes, where R may have been an ergosterol, sapogenin, bile acid or *allo*-pregnan-20-one side chain.

A novel turn was given to this work as a result of a publication by Spring and his collaborators[69], who found that by brominating 5:6-dihydro-ergosteryl acetate (*77*) a crystalline tetra-bromide of unknown constitution could be obtained, from which the acetate of ergosterol D dibromide (*78*) was readily prepared by removal of two bromine atoms with sodium iodide under mild conditions. It will be seen from the above paragraphs that many of the reactions on the dienes involve oxidation and reduction, and much difficulty is occasioned by the need to find selective reagents or conditions. The bromination method at once provides the diene system and protects the double bond in the side chain from attack, and many of the above transformations have been carried out on ergosterol D dibromide[84–90]. When required the double bond in the 22-position is easily regenerated by debromination with zinc. Thus, 11-ketones may be obtained from diosgenin and ergosterol in several ways.

The next group of reactions, involving degradation of the side chain, is known in general for both intermediates. Degradation of the diosgenin side chain is similar to that already given for hecogenin, whereas that of 3β-acetoxy-11-ketoergost-22-ene (*79*) may be carried out in any of several different ways. In a simple and effective method, which has been used on similar compounds[91,92,93], the double bond is cleaved to the



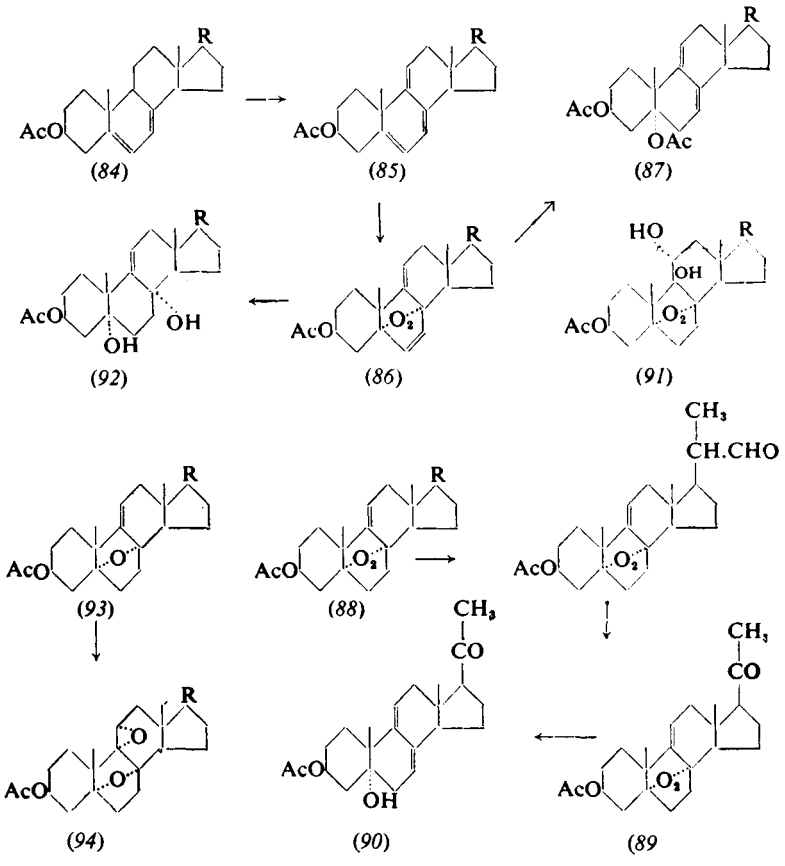
(*77*) (*78*) (*79*) (*80*) (*81*) (*82*) (*83*)

aldehyde (*80*) by ozone. The corresponding enol acetate (*81*) is then prepared and ozonised to give a pregnan-20-one (*82*). The method has been applied to the preparation of progesterone from stigmasterol[94]. In a modification, the double bond between the 20- and 22-positions is introduced by condensing the aldehyde (*80*) with a secondary amine to give (*83*), converted by ozonolysis to (*82*)[94].

Details of the degradation of 3β-acetoxy-11-ketoergost-22-ene to 3β-acetoxy-*allo*-pregnan-11:20-dione have not been published, and the above is only an indication of methods that might be used. It is known, however, that the complete synthesis of cortisone from ergosterol has been accomplished[53]. Thus several different processes from several starting materials all converge on 3β-acetoxy-*allo*-pregnan-11:20-dione, from which the synthesis of cortisone has already been discussed (see Hecogenin).

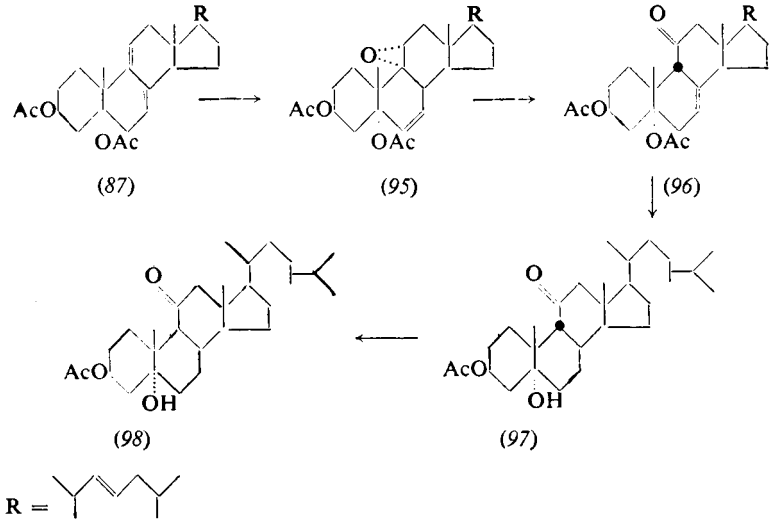
An entirely different approach to the problems was devised by E. R. H. Jones and H. B. Henbest and developed in conjunction with their associates. Ergosterol (*84*) is oxidised by mercuric acetate to dehydroergosterol (*85*), which forms an epi-dioxide (*86*) in air under the influence of light and a photo-catalyst such as eosin. It was thought that this known epi-dioxide could give access to 11-oxy compounds from the 9:11-double bond, and also that hydrogenation of the epidioxide group might provide a 5-hydroxy derivative to be available at the end of the synthesis for the introduction of the 4:5-double bond by dehydration. On examination it was found[95] that several products could be derived from (*86*) by different methods of catalytic hydrogenation or chemical reduction, among which the 7:9(11):22-triene (*87*) and 6:7-dihydro compound (*88*) are to be specially noted. The latter seemed to be of particular interest, and of the several possible methods of preparation the best was catalytic hydrogenation in the presence of hydrated platinum oxide, a novel catalyst. That compound is subsequently degraded[96], by the method already mentioned, to the corresponding 20-ketone (*89*) and thence by treatment with zinc and acetic acid to the 5-hydroxy-20-ketone (*90*).

Attempts to oxidise (*88*)[97] to obtain an 11-oxy compound were disappointing as it was slow to react with peracids; an unreactive oxide is obtained in poor yield by the action of perbenzoic acid and a glycol (*91*) by oxidation with potassium permanganate in acetic acid. Later work showed that the diol (*92*) is readily cyclised under the influence of weak acids to a 5:8-oxide (*93*); although the 9:11-bond in this compound can now readily be attacked with peracids to give a 5:8–9:11-diepoxide (*94*), the transformation of such compounds into useful 11-oxygenated steroids has yet to be achieved. Further progress was made by the use of the 7:9(11):22-triene (*87*) which is readily oxidised by perbenzoic acid to the oxide (*95*), and this, on treatment with boron trifluoride under mild conditions, gives the unsaturated ketone (96). Note that here the double bond has not moved into conjunction with the keto group and compare the conversion of (*64*) to (*67*). Further examination of (*96*) showed it to be a substance of much interest, for it was found to have



the abnormal *iso*-configuration at the 9-position; moreover, because of the effect of this unusual configuration on the geometry of the molecule as a whole, catalytic hydrogenation of the 7 : 8-double bond to the saturated ketone (*97*) was possible, though a Δ^7-steroid of the normal configuration at C_9 cannot be hydrogenated. Note also that reduction can often be carried out on 11-ketones without this feature of the molecule being affected. Because of the steric hindrance occasioned by the presence of the two angular methyl groups at positions 10 and 13, 11-ketones are particularly unreactive; they do not form any ketonic derivatives and are difficult to reduce. On treatment with strong alkali (*97*) isomerised to give the known saturated 11-ketone (*98*), but the sequence of reactions, though interesting, still did not provide a useful route to cortisone, as hydrogenation of (*96*) was not selective and the double bond in the side chain was invariably reduced.

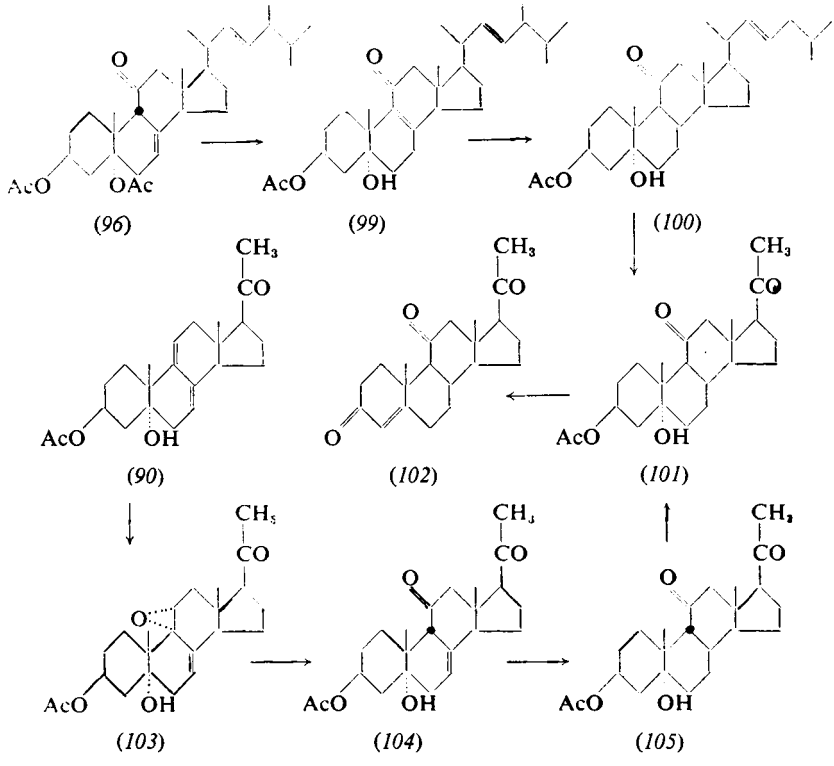
A large measure of success was finally achieved in two different ways. By treatment with zinc and acetic acid the unsaturated 9-*iso*ketone (*96*) was isomerised to the conjugated unsaturated ketone (*99*), which, like the analogous substances previously mentioned, is reducible by



lithium metal in liquid ammonia to the saturated ketone (*100*), in this instance without reduction of the double bond in the side chain. This feature of the molecule having been retained, degradation of the side chain can be carried out in the usual fashion to yield 3β-acetoxy-5α-hydroxy-*allo*-pregnan-11:20-dione (*101*). This can in its turn be converted by hydrolysis and oxidation to 11-ketoprogesterone (*102*), from which the synthesis of cortisone has virtually been completed (see Total Synthesis). Dehydration to introduce the 4:5-double bond may occur during oxidation of the 3β-hydroxyl group by the Oppenauer reaction with aluminium tertiary butoxide as the oxidising agent, or after oxidation with chromic acid, on treatment of the resulting 5-hydroxy-3-ketone with mild alkaline reagents.

An alternative method starts with a previously mentioned compound, 3β-acetoxy-5α-hydroxy-*allo*-pregna-7:9(11)-dien-20-one (*90*), which may be oxidised in the usual manner to the oxide (*103*). This is in turn converted to the Δ^7-ketone (*104*) by boron trifluoride, and the product is reduced catalytically to a saturated ketone. Here also reduction in the side chain takes place, but the secondary alcohol group at position 20 can conveniently be re-oxidised with chromic acid to the original ketone to give (*105*), which still has the 9-*iso*-configuration and can be isomerised by treatment with strong alkali, followed by reacetylation of the 3-hydroxyl group so formed to give 3β-acetoxy-5α-hydroxy-*allo*-pregnan-11:20-dione (*101*).

By these methods a complete synthesis of cortisone is developed from an ergosterol derivative having a 5α-hydroxyl group derived from the original 5:8-epidioxide. This work is now in the course of publication, and I am greatly indebted to Professor E. R. H. Jones of Manchester University, from whom I have received much of the information about it for his kind permission to publish it in this review.

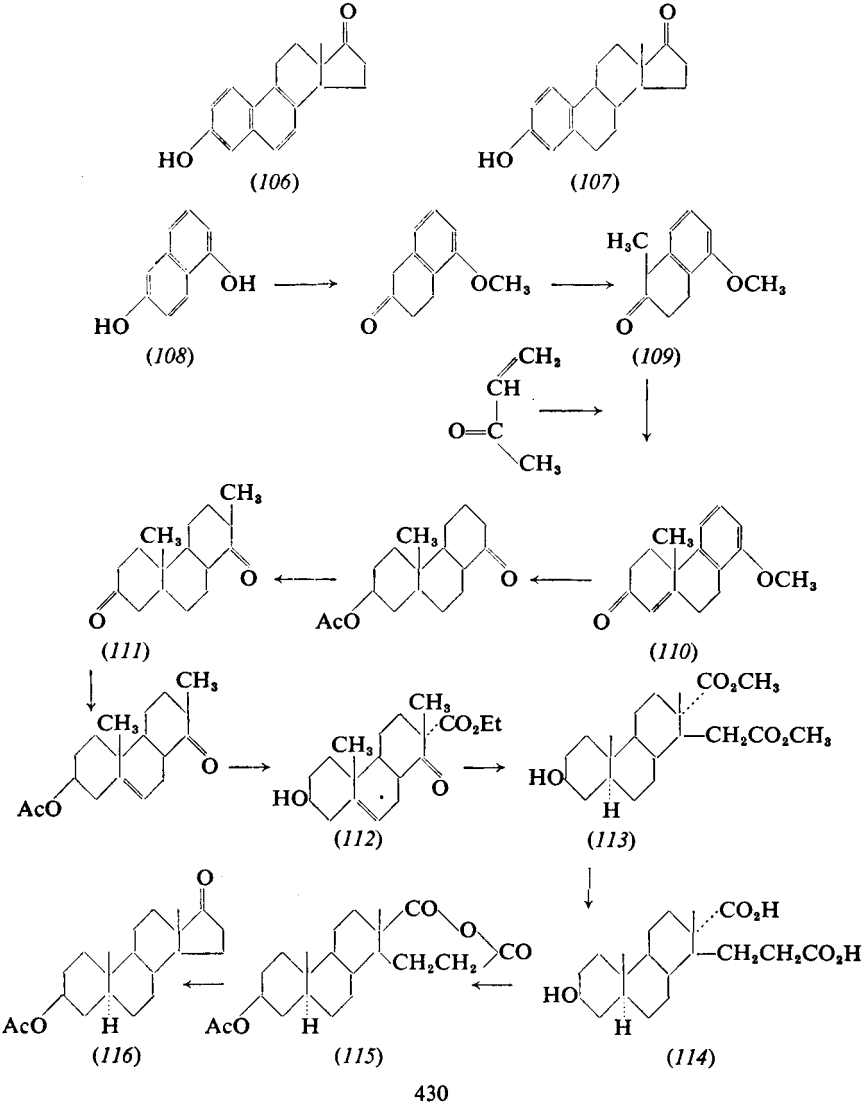


Total Synthesis

The problem of total synthesis of sterols has been a severe challenge to the ingenuity of organic chemists ever since the general formulation of the group was first arrived at in 1932 by Rosenheim and King in Britain and Wieland and Dane in Germany at almost the same time, after the intensive and brilliant research work of Wieland and Windaus and their collaborators in Germany over many years. The stereochemical complications are particularly acute, as can readily be seen by inspection of the graphic formula of desoxycholic acid, in which there are 10 centres of asymmetry, each of which must be correctly diagnosed and all of which must be assembled in the correct configurational relationship to each other during the synthesis: otherwise the product at the end will not be desoxycholic acid. These 10 asymmetric centres permit the existence of 2^{10} or 1024 stereoisomers. Cortisone has a smaller number of asymmetric centres but even so there are still 6 and therefore 64 possible stereoisomers. It is therefore not surprising that first attempts at synthesis were aimed at the simpler systems, equilenin (*106*) and œstrone (*107*), which have fewer centres of asymmetry because of their aromatic rings. The former was synthesised successfully by Bachmann, Cole and Wilds in 1939 and the latter by Anner and Miescher in 1948. There remained the problem of synthesising the complete *cyclo*-aliphatic

structure of which cortisone is a representative, and this has now been brought to a successful conclusion with full attention to stereochemical configuration by three groups of research chemists, one led by Sir Robert Robinson at Oxford University, one by Professor R. B. Woodward at Harvard University and the third by Dr. L. H. Sarett in the Merck laboratories at Rahway, New Jersey.

The first described here is that devised by Sir Robert Robinson and his collaborators, of whom Dr. J. W. Cornforth may be specially mentioned. The experiments had been continued at Oxford for many years and, though the early work was unsuccessful, it nevertheless contributed much useful information and several new reactions, later adopted by



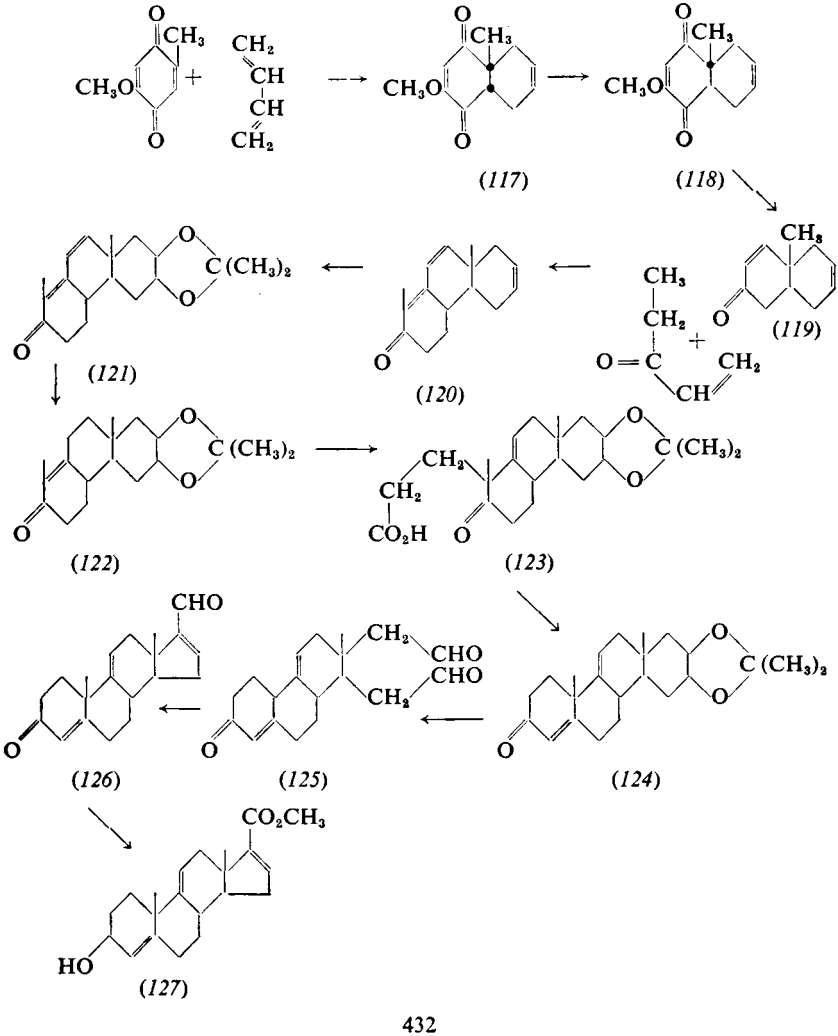
others, now forming part of all work on the incorporation of angular methyl groups or the formation of fused *cyclo*hexane structures.

The method finally adopted starts with 1:6-dihydroxynaphthalene (*108*), which is methylated: the dimethyl ether is reduced under special conditions, the product being again methylated to give (*109*), in which there first appears a resemblance to the structure ultimately sought[98,99]. The two rings of the dihydroxynaphthalene are later to form rings B and C of the complete sterol. Ring A is then added to (*109*) by condensing it with methyl vinyl ketone or a substance that will produce it *in situ*, a method first devised at Oxford and now one of the classical procedures in the synthesis of sterols, common to all work undertaken in this field. The tricyclic ketone so produced (*110*) is again reduced and methylated to give (*111*). This substance is of considerable significance, for it was already known as a product of the degradation of desoxycholic acid; the identity of the two compounds, one natural and one synthetic, gave assurance that at least up to that point the required stereochemical relationships had been achieved. After reduction, carbonylation of the ketone led to (*112*), of which the carbethoxy group forms the embryonic limb bud of the final ring[100]. Reformatsky reaction followed by dehydration and reduction gave (*113*), an ætio-*allo*-bilianic acid derivative identical with a product of the oxidation of cholesterol. Extension of the acetic acid side chain to the corresponding propionic acid (*114*) is then carried out by Arndt Eistert reaction. Conversion of this last to the anhydride (*115*) followed by pyrolysis gave (*116*). This is an example of the principle that anhydrides of substituted adipic acids give ketones on pyrolysis, while those of substituted glutaric acids do not, the well-known Blanc's rule, which played an historic role in determining the constitution of sterols, because dicarboxylic acids of various types were often encountered as products in stepwise degradation; the rule gave valuable information on whether the rings from which these dicarboxylic acids were derived had originally been 5-membered or 6-membered. The final product (*116*) is *epi*androsterone acetate, which contains all the features of a naturally-occurring sterol and is readily derived by a simple process from *epi*dehydroandrosterone, the major product of the oxidation of cholesterol[101].

Does it seem simple? Maybe, but appearances are very deceptive and a brief and eclectic review of this nature bears insufficient testimony to the novel methods used, to the tedious discernment of selective reaction conditions and the painstaking separation of isomers involved. *Epi*-androsterone acetate could be converted to cortisone by methods such as those previously mentioned in this review, but this has not been done. The synthesis is included here as one of the only three known total syntheses of sterols.

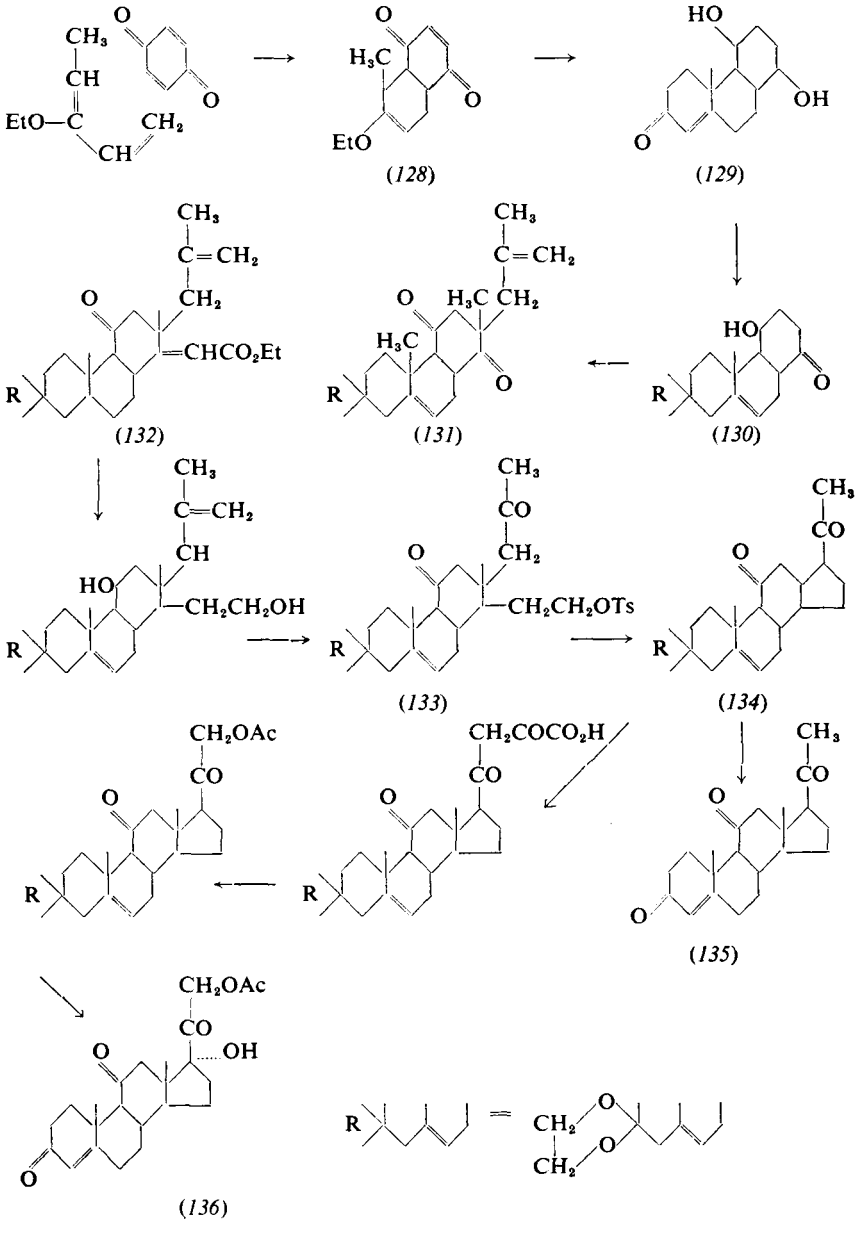
An alternative method evolved at Harvard University by Professor R. B. Woodward and his associates was first described by him in his centenary lecture to the Chemical Society in London in 1951. A preliminary summary of the work has been published[102] and was followed later by a communication describing the complete details of the methods

used[103]. In this scheme (*117*) is first prepared by reaction between butadiene and methoxy-toluquinone, a Diels-Alder condensation. In (*117*) the two rings are *cis* but they ultimately become rings C and D, which are *trans*. The point is, however, that the Diels-Alder reaction always gives *cis* products and, therefore, the configuration of (*117*) is known; because of the carbonyl group present it can be isomerised by treatment with alkali to the other configuration, (*118*), which must therfore be *trans*. Thus at one ingenious stroke, two of the stereochemical centres are disposed of without the need for laborious separations or determinations of structure. Reduction of the carbonyl groups, which among other things prevents a re-isomerisation of the carefully-designed *trans* ring structure, and hydrolysis of the enol ether later leads to (*119*). To this the third ring is added by condensation with ethyl vinyl ketone



in the normal manner; here the ethyl- rather than the more usual methyl-vinyl ketone is used, the additional carbon atom becoming the angular methyl group between rings A and B (*120*). Before proceeding to the construction of ring A, and because of the method to be employed, it was necessary to modify the double bond system in this last intermediate. The isolated double bond is protected by oxidation to a glycol and acetonylation to (*121*), thereby beginning a series of reactions that lead ultimately to ring D. The double bond present in ring C and conjugated to the ketone is removed selectively by hydrogenation with a palladised strontium carbonate catalyst in dry benzene giving (*122*). After blocking the α-methylene group the addition of acrylonitrile followed by hydrolysis leads to (*123*). This product was that expected on theoretical grounds, which are set out at considerable length in the publication, though there is not space to repeat them here. For the first time in this synthesis the reaction is not stereo specific and the mixture of products obtained has to be separated. Thereafter (*124*) is formed by known processes and the only remaining problem is that of converting the fourth 6-membered ring into the 5-membered ring D. This is accomplished by oxidising the glycol derived from (*124*) to the dialdehyde (*125*), which is self-condensed to (*126*), at which point all the features of a steroid are present. For identification with one of unimpeachable structure it was oxidised and esterified to (*127*), which was found to be identical in all respects with that derived from a bile acid. Resolution of the racemic product was also carried out. This *ætio* acid was converted to several important steroids by methods already known, but here we are only concerned with its further progress towards cortisone. This is brought about by reducing the double bond in ring D and introducing the 11-keto group by the method originated by Fieser and described earlier in this review. The synthesis of cortisone is then completed by methods already discussed. This synthesis of cortisone is the only one that has so far been fully described.

The third total synthesis has been devised in the Merck research laboratories under the leadership of Dr. L. H. Sarett[104–108], himself responsible in earlier years for the first partial synthesis of cortisone from bile acids. A two-ring system is built up, which is finally to represent rings B and C of the sterol, and here also the Diels-Alder reaction is used, so that the original product is *cis*, and a ketone group is provided to enable isomerisation to the *trans* configuration to be accomplished by treatment with alkali when required. Benzoquinone is condensed with 3-ethoxypenta-1:3-diene to give (*128*). Reduction of the ketone groups, hydrolysis of the enolic ether system and condensation with methyl vinyl ketone lead to formation of the tricyclic compound (*129*). Protection of the ketone and selective oxidation of one of the hydroxyl groups, followed by isomerisation of the so-formed ketone, gives (*130*), in which the ring junctions are now *trans*. The 11-oxy group and the potential unsaturated 3-ketone group are all present and also an additional carbonyl group is available to use as a point of attack for introducing the second angular methyl group and for creating ring D. This synthesis



is remarkable for the swiftness with which the major needs are introduced by ingenious selection of the starting materials and for the avoidance of superfluous blocking reactions. Double alkylation of the α-methylene group with first a methyl- and then a methylallylhalide gives (*131*). Condensation of this with ethoxy-acetylene magnesium bromide followed by anionotropic rearrangement brings about the formation of (*132*)

which, after reduction of the carbethoxy group, tosylation and oxidation of the unsaturated side chain, leads to (*133*) in which all the groups are present in a suitable state for condensation with alkali to the steroid (*134*). Into this, a derivative of the known compound 11-keto-progesterone (*135*), an acetoxyl group can be introduced into the side chain, as shown, to give ultimately cortisone (*136*). The ethylene dioxy group (R) has not only protected the ketone group, but has also afforded protection to the 5:6-double bond, which has survived several different types of oxidation, reduction and substitution reactions since its original formation much earlier in the synthesis. Unlike the first two methods described, this one was aimed particularly at the synthesis of cortisone, and therefore the potential 11-ketone group has been present from the beginning.

This review mentions the salient features of all the most important work on the synthesis of cortisone. There has not been space to go into the detail of any investigation and in particular earlier attempts at total synthesis have not been considered, being more appropriate for review in other circumstances. Also, discussions about the interpretation of physical constants, reaction mechanisms and the invaluable evidence brought forward by spectroscopy have been omitted. Nevertheless, it is hoped that an adequate picture has been presented of the excellent work carried out in this field.

REFERENCES

1. Recent Review: Velluz, Petit and Mathieu, *Bull. Soc. Chim.*, 1952, 1; Hench, Kendall, Slocumb and Polley, *Proc. Mayo Clinic*, 1949, **24**, 181.
2. Mason, Myers and Kendall, *J. biol. Chem.*, 1936, **114**, 613; 1936, **116**, 267.
3. Wintersteiner and Pfifner, *ibid.*, 1936, **116**, 291.
4. Reichstein, *Helv. chim. Acta*, 1936, **10**, 1107.
5. Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold, 1949.
6. Pincus and Thimann, *The Hormones* (Vol. 1), Academic Press, 1948.
7. Spring, *J. chem. Soc.*, 1950, 3352.
8. Petrow and Skrimshire, *Reports on the Progress of Applied Chemistry*, 1950, **35**, 316.
9. Petrow, *ibid.*, 1951, **36**, 167.
10. Samuels and Reich, *Ann. Ber. Biochem.*, 1952, **21**, 129; Kendall, *Chem. Engng News*, 1950, **28**, 2074.
11. Hershberg, Herzog, Coan, Weber and Jevnik, *J. Amer. chem. Soc.*, 1952, **74**, 2585.
12. McKenzie, Mattox, Engel and Kendall, *J. biol. Chem.*, 1948, **173**, 271.
13. McKenzie, Mattox and Kendall, *ibid.*, 1948, **175**, 249; U.S.Pat. 2,541,074; Turner, Mattox, McGuckin and Kendall, *J. Amer. chem. Soc.*, 1952, **74**, 5814; Mattox, Turner, McGuckin, Chu and Kendall, *ibid.*, 1952, **74**, 5818.
14. Fieser, Heymann and Rajagopalan, *ibid.*, 1950, **72**, 2306.
15. Heymann and Fieser, *ibid.*, 1951, **73**, 4054 and 5252; Heymann and Fieser, *ibid.*, 1952, **74**, 5938.
16. Meystre, Frey, Wettstein and Miescher, *Helv. chim. Acta*, 1944, **27**, 1815.
17. Meystre, Ehmann, Neher and Miescher, *ibid.*, 1945, **28**, 1252.
18. Sarett, *J. biol. Chem.*, 1946, **162**, 601.
19. Sarett, *J. Amer. chem. Soc.*, 1948, **70**, 1454.
20. Sarett, *ibid.*, 1949, **71**, 2443
21. Heer and Miescher, *Helv. chim. Acta*, 1951, **34**, 359.
22. Kritchevsky and Gallagher, *J. biol. Chem.*, 1949, **179**, 507.
23. Koechlin, Garmaise, Kritchevsky and Gallagher, *J. Amer. chem. Soc.*, 1949, **71**, 3262.

24. Kritchevsky, Garmaise and Gallagher, *ibid.*, 1952, **74**, 483.
25. Colton, Nes, Van Dorp, Mason and Kendall, *J. biol. Chem.*, 1952, **194**, 235.
26. Colton and Kendall, *ibid.*, 1952, **194**, 247; U.S.Pat. 2,541,074.
27. Julian, Meyer, Karpel and Waller, *J. Amer. chem. Soc.*, 1950, **72**, 5145.
28. Mattox and Kendall, *ibid.*, 1948, **70**, 882.
29. Koechlin, Kritchevsky and Gallagher, *J. biol. Chem.*, 1950, **184**, 393.
30. Mattox and Kendall, *ibid.*, 1951, **188**, 287.
31. Hershberg, Gerold and Oliveto, *J. Amer. chem. Soc.*, 1952, **74**, 3849; McGuckin and Kendall, *ibid.*, 1952, **74**, 5811.
32. Bavin and Seymour, *Mfg. Chemist*, 1951, **22**, 137.
33. Ehrenstein, *Chem. Rev.*, 1948, **42**, 457.
34. Heyl and Herr, *J. Amer. chem. Soc.*, 1950, **72**, 2617.
35. B.Pat. 679,775.
36. Hechter, Jacobsen, Jeanloz, Levy, Marshall, Pincus and Schenker, *J. Amer. chem. Soc.*, 1949, **71**, 3261.
37. Sweat, *ibid.*, 1952, **73**, 4055.
38. Peterson and Murray, *ibid.*, 1952, **74**, 1871; Meister, Peterson, Murray, Eppstein, Reineke, Weintraub and Leigh, *ibid.*, 1953, **75**, 55.
39. Peterson, Murray, Eppstein, Reineke, Weintraub, Mesiter and Leigh, *ibid.*, 1952, **74**, 5933.
40. Colingsworth, Brunner and Haines, *ibid.*, 1952, **74**, 2381.
41. Perlman, Titus and Fried, *ibid.*, 1952, **74**, 2126.
42. Fried, Thoma, Gerke, Herz, Donin and Perlman, *ibid.*, 1952, **74**, 3962.
43. Mancera, Zaffaroni, Rubin, Sondheimer, Rosenkranz and Djerassi, *ibid.*, 1952, **74**, 3711.
44. Callow, Cornforth and Spensley, *Chem. Ind.*, 1951, 699.
45. Spensley, *ibid.*, 1952, 426.
46. Djerassi, Martinez and Rosenkranz, *J. org. Chem.*, 1951, **16**, 303.
47. Mueller, Stobaugh and Winniford, *J. Amer. chem. Soc.*, 1951, **73**, 2400.
48. Djerassi, Ringold and Rosenkranz, *ibid.*, 1951, **73**, 5513; Martinez, Ringold, Rosenkranz and Djerassi, *ibid.*, 1953, **75**, 239.
49. Wagner, Moore and Forker, *ibid.*, 1950, **72**, 1856.
50. Djerassi, Batres, Romo and Rosenkranz, *ibid.*, 1952, **74**, 3634.
51. Chamberlain, Royle, Erickson, Chemerda, Aliminosa, Erickson, Sita and Tishler, *ibid.*, 1951, **73**, 2396.
52. Gould, Shaeudle and Hershberg, *ibid.*, 1952, **74**, 3685.
53. Chemerda, Chamberlain, Wilson and Tishler, *ibid.*, 1951, **73**, 4052.
54. Rosenkranz, Pataki and Djerassi, *ibid.*, 1951, **73**, 4055.
55. Pataki, Rosenkranz and Djerassi, *ibid.*, 1952, **74**, 5615.
56. Djerassi and Scholz, *ibid.*, 1947, **69**, 2404.
57. Rosenkranz, Mancera, Gatica and Djerassi, *ibid.*, 1950, **72**, 4077; Rosenkranz, Pataki, Kaufmann, Berlin and Djerassi, *ibid.*, 1950, **72**, 4081.
58. Oliveto, Gerold and Hershberg, *ibid.*, 1952, **74**, 2248.
59. Rosenkranz, Djerassi, Yashin and Pataki, *Nature, Lond.*, 1951, **168**, 28.
60. Rosenkranz, Romo and Berlin, *J. org. Chem.*, 1951, **16**, 290.
61. Rosenkranz, Romo, Batres and Djerassi, *ibid.*, 1951, **16**, 298.
62. Djerassi, Romo and Rosenkranz, *ibid.*, 1951, **16**, 754.
63. Bide, Henbest, Jones, Peevers and Wilkinson, *J. chem. Soc.*, 1948, 1783.
64. Bernstein, Binovi, Dorfman, Sax and Subbarow, *J. org. Chem.*, 1949, **14**, 433.
65. Ringold, Rosenkranz and Djerassi, *J. Amer. chem. Soc.*, 1952, **74**, 3441.
66. Dauben, Eastham and Micheli, *ibid.*, 1951, **73**, 4496.
67. Djerassi, *Chem. Rev.*, 1948, **43**, 271.
68. Laubach and Brunings, *J. Amer. chem. Soc.*, 1952, **74**, 705.
69. Anderson, Budziarek, Newbold, Stevenson and Spring, *Chem. Ind.*, 1951, 1035; Ruyle, Chamberlin, Chemerda, Sita, Aliminosa and Erickson, *J. Amer. chem. Soc.*, 1952, **74**, 5929.
70. Yashin, Rosenkranz and Djerassi, *ibid.*, 1951, **73**, 4654.
71. Feiser, Herz and Huang, *ibid.*, 1951, **73**, 2397; Feiser, Huang and Babcock, *ibid.*, 1953, **75**, 116; Feiser and Herz, *ibid.*, 1953, **75**, 121; Feiser, Schneider and Huang, *ibid.*, 1953, **75**, 124.
72. Feiser, Babcock, Herz, Huang and Schneider, *ibid.*, 1951, **73**, 4053.
73. Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita and Tishler, *ibid.*, 1951, **73**, 2396.
74. Heusser, Eichenberger, Kurath, Dallenbach and Jeger, *Helv. chim. Acta*, 1951, **34**, 2106.
75. Heusser, Heusler, Eichenberger, Honegger and Jeger, *ibid.*, 1952, **35**, 295.

76. Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda and Tishler, *J. Amer. chem. Soc.*, 1952, **74**, 2696.
77. Sondheimer, Yashin, Rosenkranz and Djerassi, *ibid.*, 1952, **74**, 2696.
78. Heusser, Anliker, Eichenberger and Jeger, *Helv. chim. Acta*, 1952, **35**, 936.
79. Stork, Romo, Rosenkranz and Djerassi, *J. Amer. chem. Soc.*, 1951, **73**, 3546.
80. Djerassi, Batres, Velasco and Rosenkranz, *ibid.*, 1952, **74**, 1712.
81. Romo, Stork, Rosenkranz and Djerassi, *ibid.*, 1952, **74**, 2918.
82. Djerassi, Mancera, Stork and Rosenkranz, *ibid.*, 1951, **73**, 4496.
83. Djerassi, Mancera, Velasco, Stork and Rosenkranz, *ibid.*, 1952, **74**, 3321.
84. Budziarek, Newbold, Stevenson and Spring, *J. chem. Soc.*, 1952, 2892.
85. Anderson, Stevenson and Spring, *ibid.*, 1952, 2901.
86. Budziarek, Johnson and Spring, *ibid.*, 1952, 3410.
87. MacEwan and Spring, *ibid.*, 1952, 3646.
88. Budziarek, Stevenson and Spring, *ibid.*, 1952, 4874.
89. Budziarek, Johnson and Spring, *ibid.*, 1953, 534.
90. Budziarek, Hamlet and Spring, *ibid.*, 1953, 778.
91. Bergmann and Stevens, *J. org. Chem.*, 1948, **13**, 10.
92. Levin, Wesner and Meinzer, *J. Amer. chem. Soc.*, 1948, **70**, 2834.
93. Antonucci, Bernstein, Giancola and Sax, *J. org. Chem.*, 1951, **16**, 1356.
94. Herr and Heyl, *J. Amer. chem. Soc.*, 1952, **74**, 3627.
95. Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, Wood and Woods, *J. chem. Soc.*, 1952, 4883.
96. Bladon, Henbest, Jones, Wood and Woods, *ibid.*, 1952, 4890.
97. Henbest, Jones, Wood and Woods, *ibid.*, 1952, 4894.
98. Cornforth, Cornforth and Robinson, *ibid.*, 1942, 689.
99. Cornforth and Robinson, *ibid.*, 1946, 676.
100. Cornforth and Robinson, *ibid.*, 1949, 1855.
101. Cardwell, Cornforth, Duff, Holtermann and Robinson, *Chem. Ind.*, 1951, 389; *J. chem. Soc.*, 1953, 361.
102. Woodward, Sondheimer and Taub, *J. Amer. chem. Soc.*, 1951, **73**, 4057.
103. Woodward, Sondheimer, Taub, Heusler and McLamore, *ibid.*, 1952, **74**, 4223.
104. Sarett, Lukes, Poos, Robinson, Beyler, Vandegrift and Arth, *ibid.*, 1952, **74**, 1393.
105. Beyler and Sarett, *ibid.*, 1952, **74**, 1397.
106. Lukes, Poos and Sarett, *ibid.*, 1952, **74**, 1401.
107. Beyler and Sarett, *ibid.*, 1952, **74**, 1406.
108. Sarett, Arth, Lukes, Beyler, Poos, Johns and Constantin, *ibid.*, 1952, **74**, 4974.