# PROGRESS IN THE TOTAL SYNTHESIS OF STEROIDS

I. V. TORGOV

*Institute of the Chemistry of Natural Products, Academy of Sciences, Moscow, U.S.S.R.*

The total synthesis of steroids is undoubtedly one of the most important achievements in organic chemistry. It is not so long since 1939 when Bachmann, Cole and Wilds[1] carried out the first total synthesis of the simplest of the sex hormones, equilenin, but in this short period we have witnessed a tremendous development in the chemistry of steroids in general and of their total synthesis, in particular. Allow me to call to mind the principal landmarks: in 1948—the first synthesis of oestrone by Miescher[2]; 1950—the second, by Johnson[3]; 1952—synthesis of cholesterol, and of the sex and adrenocortical hormones by Woodward[4] and by Robinson[5]; 1952–1953—preparation of the cortical hormones by Sarett[6]; 1953–1954—modification of Woodward's synthesis by the Monsanto group[7]; production of ketoetianic acid by Wilds[8] and of lanosterol by Woodward and Barton[9]; 1955–56—preparation of epiandrosterone, testosterone and some 11-oxidized steroids by Johnson[10], the first synthesis of aldosterone by Wettstein[11]; 1957–58—syntheses of oestrone by Johnson and Christiansen[12] and by Johnson and Walker[13]; three syntheses of aldosterone (by Reichstein[14], by the Dutch group[15] and by Johnson[16]), synthesis of vitamin D by Inhoffen[17]; 1959–60—second modification of the synthesis of aldosterone by Wettstein[18]. four more routes to oestrone (Hughes and Smith[19], Torgov and Anan-chenko[20], Banerjee[21] and Velluz[22]), synthesis of testosterone by Johnson[23] and of androsterone by Velluz[22] and finally of the sapogenins (and steroid alkaloids) by Sondheimer[24]—a veritable torrent of syntheses! Finally, in 1961–1962 we have the production of pregnane derivatives by Nagata[25], preparation of conessine by Barton[26] and by Johnson[27] and the first synthesis of a cardiac aglycone by Sondheimer[28].

We thus see that both the pace and scale of work are ever increasing and chemists have now arrived at the threshold of industrial synthetic methods of steroid production. This, despite the fact that such a multi-stage, stereospecific synthesis has many pitfalls in its path and the failure of any stage may lead to collapse of the whole projected route.

To what are these gigantic strides due? First of all they result from the general advance in organic chemistry. The number of specifically directed reactions is constantly increasing, and most of them are capable of being carried out at low temperatures and in the absence of "drastic" reagents. It is difficult to imagine the synthesis of even the simplest of steroid compounds without the Arndt–Eistert reaction, without selective hydrogenation techniques, or without stereospecific reduction. Thus, in the Johnson–Christiansen synthesis[12] (*Figure 1*) hydrogenation under various conditions

solved the problem of ring B formation and of *trans*-fusion of the C and D rings.

Reduction by metal hydrides [$LiAlH_4$, $NaBH_4$, $AlH(O\text{-}t\text{-}C_4H_9)_3$] is now being used so widely that at present there is hardly any synthesis in which it does not play an important part.

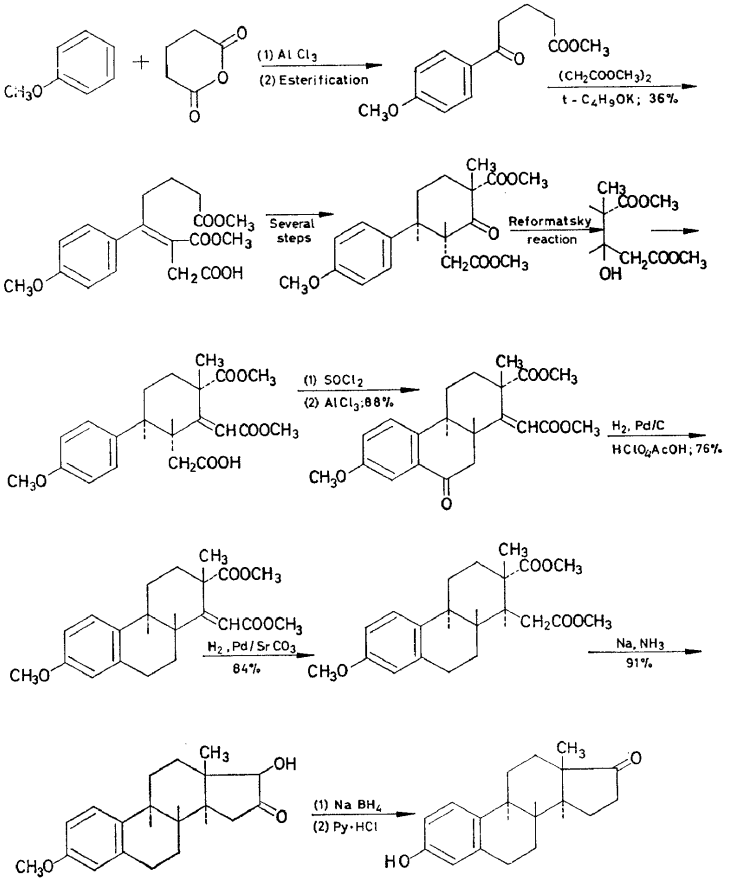


*Figure 1.* Johnson–Christiansen synthesis of oestrone

Reduction of styrenoid compounds by alkali metals in liquid ammonia has been a decisive factor, determining the success of the numerous syntheses by Johnson[10], Nagata's syntheses and those of Velluz[22].

Oppenauer oxidation and chromic anhydride oxidation in pyridine, extensively used in the synthesis of cortisone and corticosterone by Sarett[6], in the syntheses of aldosterone[11], and of the sapogenins, have contributed as much to these successes as has periodic acid oxidation utilized by Woodward[4], Sarett[6] and Nagata.

Stereospecific hydroxylation with the aid of osmium tetroxide, or of iodine in the presence of silver acetate, was also of great assistance in the same

syntheses. Special mention must be made of Fried and Sabo's method, allowing the 11-oxygen function to be incorporated in $\Delta^{9(11)}$ compounds, a technique made use of by the Monsanto group[7] (*Figure 2*), and by Velluz[22]. (*Figure 3*).

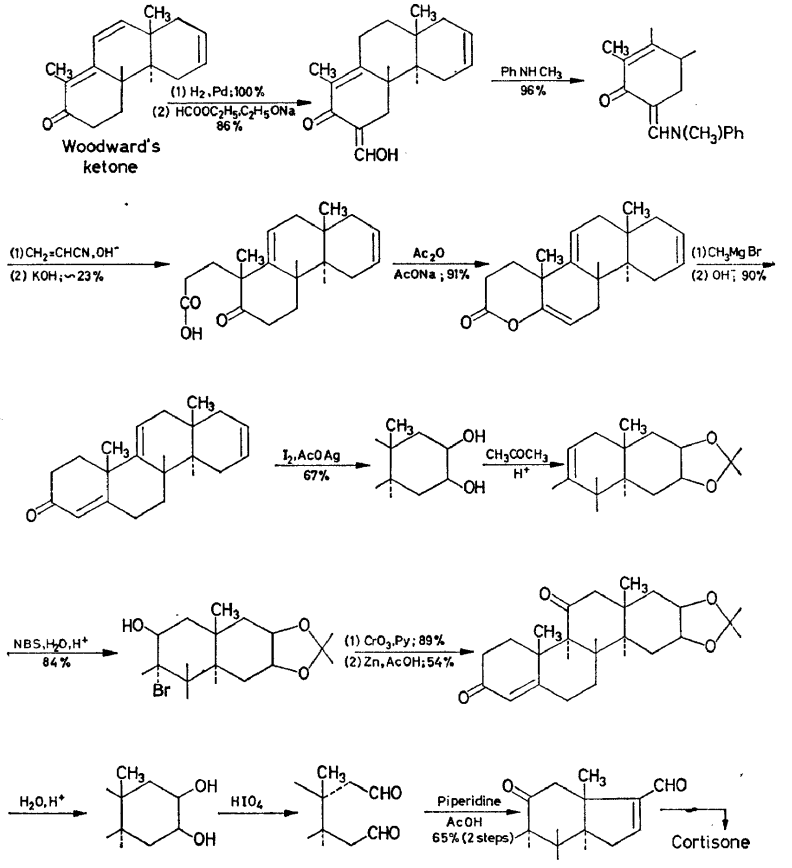


*Figure 2.* Synthesis of cortisone by the Monsanto group

Incorporation of the vinyl group by the Norman reaction was felicitously employed in the syntheses of oestrone by Johnson, Robins and Walker[13] and by Torgov and Ananchenko[20] (*Figure 4*).

An interesting route to highly unsaturated steroid systems was elaborated by Zavialov[16a] (*Figure 5*).

The Wittig reaction though as yet not used very often, was employed three times by Inhoffen[17] in his synthesis of vitamin $D_3$ (*Figure 6*).

An unexpectedly important rôle has been played by certain " nameless " reactions. Thus, the very simple method of protecting the carbonyl group by means of ethylene glycol greatly facilitated, and in some cases determined the success of, the synthesis of $\Delta^4$-3-ketosteroids and of sapogenins. The same holds true for the tosylation reaction. As is well known, the tosyloxy-group,

very similar to halogen, can take part in a variety of exchange reactions, a property which has aided in the solution of many complicated synthetic problems as, for example, the formation of ring D in the synthesis of corticosterone and of cortisone by Sarett's method (*Figure 7*), in Johnson's synthesis of aldosterone[16] (*Figure 8*), and in Barton's synthesis of conessine (*Figure 9*).

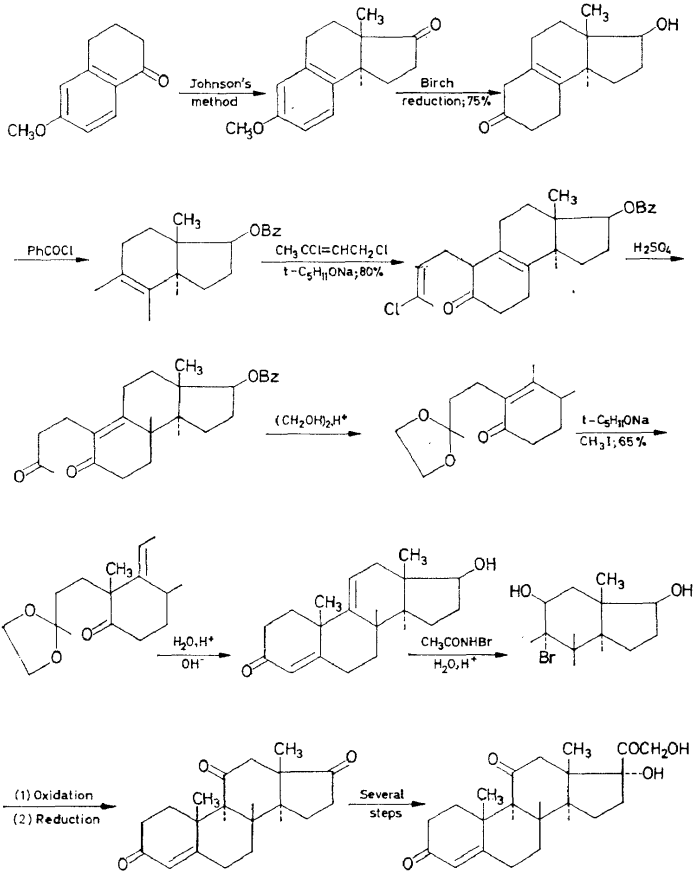


*Figure 3.* Velluz's synthesis of cortisone

One can expect that in the very near future extensive use will be made of radical reactions, hydroboration, *etc.*

Thus, the organic chemist has at his disposal an ever-increasing variety of specific and stereospecific reactions which serves as a mighty tool in the materialization of his ideas, as evidenced by the syntheses mentioned above.

In the total synthesis of steroids chemists have had to cope with certain specific problems dealing with formation of the steroid skeleton and the incorporation of functional groups.

The introduction of the angular methyl group was solved by Robinson and Johnson and is, in general, reduced to a Michael reaction and alkylation of a

ketone. Recently Stork has proposed, and verified on bicyclic systems, a novel method for incorporating the 18–$CH_3$ group, based on a Favorsky rearrangement of chloroketones (*Figure 10*). The chloroketones were prepared by condensing the ketones with chloronitriles.

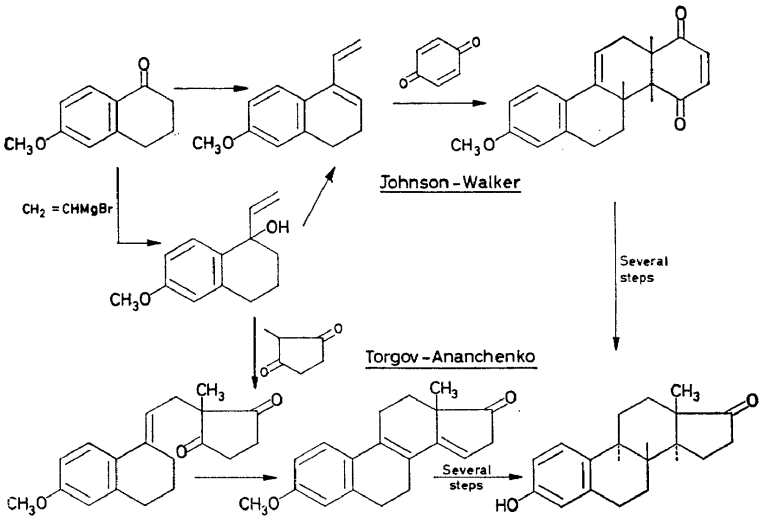


*Figure 4.* Syntheses of oestrone by Johnson, Robins and Walker, and by Torgov and Ananchenko

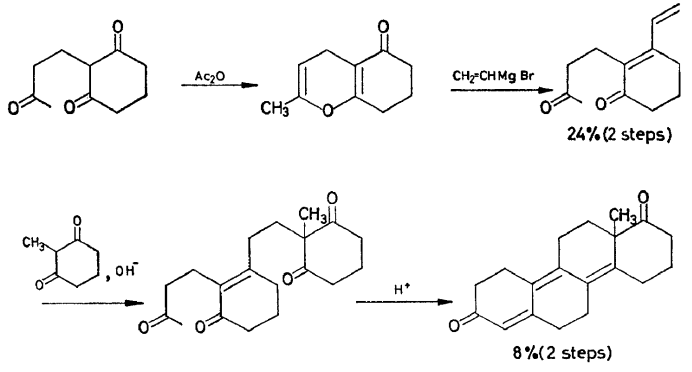


*Figure 5.* Zavialov synthesis

*Trans*-fusion of rings C and D was solved in two major ways, namely, catalytic hydrogenation of $\Delta^{14(15)}$-compounds (Miescher, Johnson and Christiansen, Hughes and Smith, Torgov and Ananchenko) or isomerization of D-homosteroid ketones of the type of *cis*-decalone to ketones of the type of *trans*-decalone (Woodward, Johnson) *cf. Figure 11.*

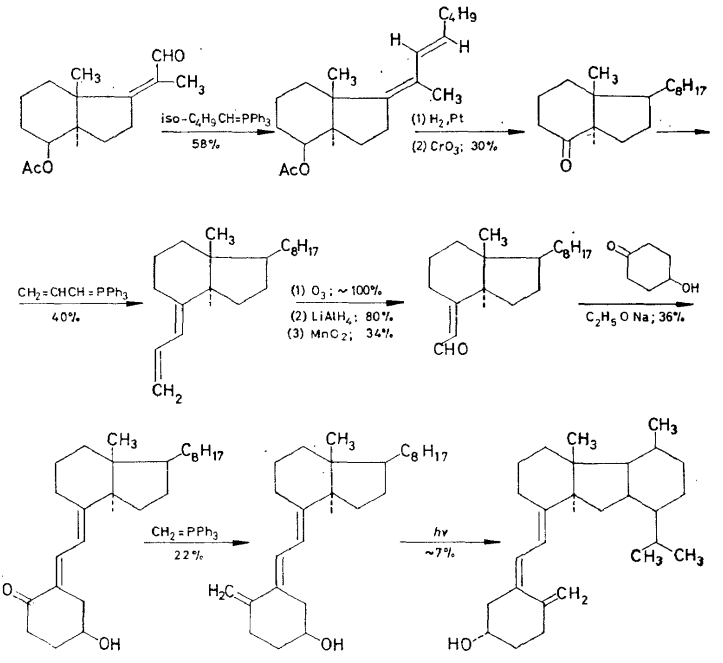


*Figure 6.* Inhoffen's synthesis of vitamin $D_3$

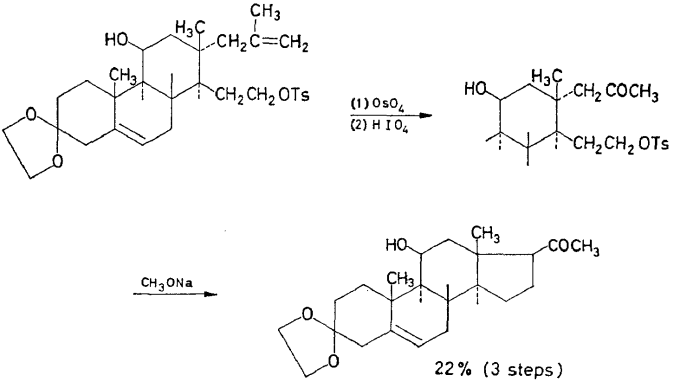


*Figure 7.* Part of Sarett's cor ticosterone synthesis

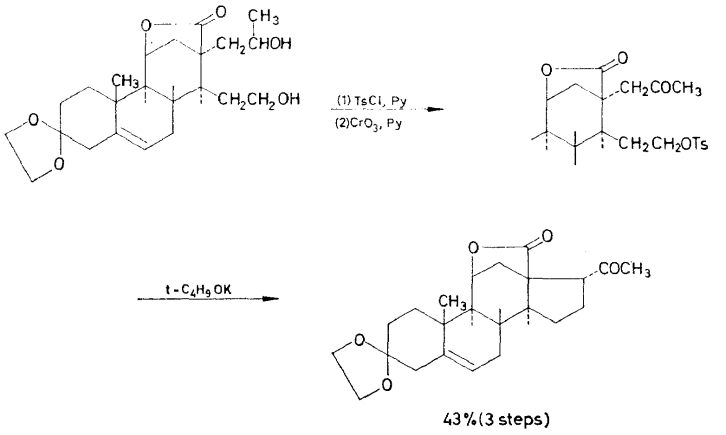


*Figure 8.* Part of Johnson's aldosterone synthesis

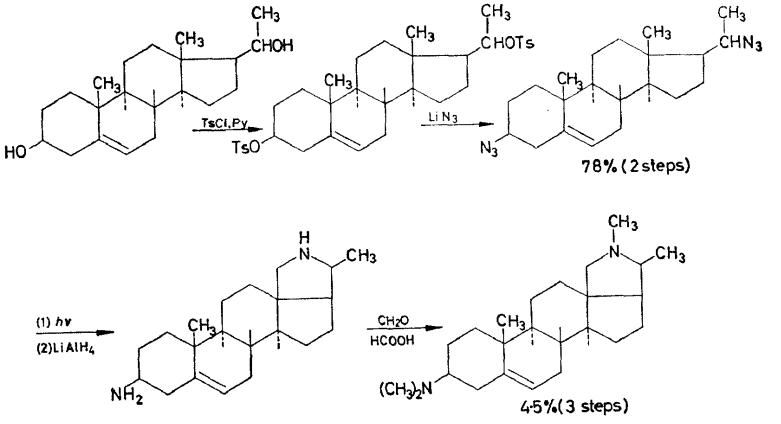


*Figure 9.* Barton's synthesis of conessine

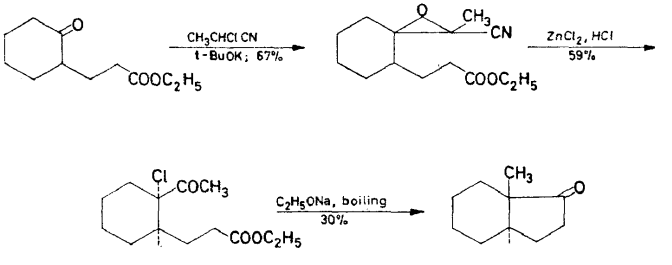


*Figure 10.* Stork's method for introducing angular methyl group

*Trans*-fusion of rings B and C was accomplished by hydrogenation of $\Delta^{9(11)}$-compounds, by use of the Fried–Sabo method (Woodward, Velluz) or by means of Birch reduction (Johnson and Walker synthesis). For the $\Delta^{8(9)}$-compounds as yet only the Birch method gives good results (syntheses by Johnson, by Hughes and Smith, by Torgov and Ananchenko); but this too is not completely stereospecific and yields some *cis*- together with the *trans*-compound (Nagata). Finally, in Sarett's synthesis isomerization of the *cis*-decalone to the *trans*-decalone system took place under conditions of Oppenauer oxidation[6] (*Figure 12*).

As for the incorporation of functional groups, with very few exceptions, this is at present readily accomplished.

Introduction of the oxygen function at C–18 ceased to be a difficult problem after the syntheses of aldosterone in 1955–58 [by Wettstein, by Reichstein, by Johnson, by the Organon group as well as the brilliant work by

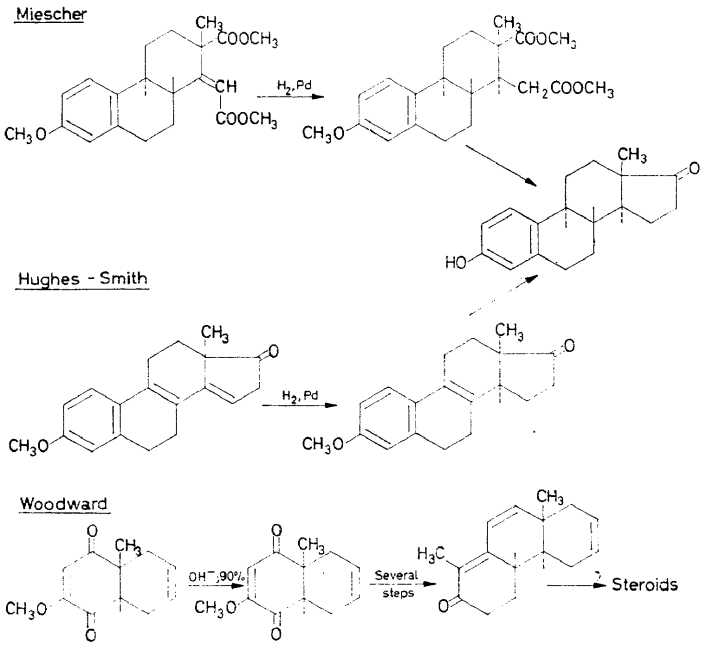


*Figure 11.* Syntheses leading to *trans*-fused CD rings

Barton and by the Swiss and French chemists (Eger–Vellus) who used radical reactions for this purpose[30]] (*Figure 13*).

Another difficult problem, the incorporation of an oxygen function at C–19, is nearing its practical solution. Thus, Barton, applying his method of nitrite photolysis to 6-hydroxy-steroids synthesized 19–carbonyl derivatives[31] (*Figure 14*).

To our mind a highly promising procedure is that in which the carbethoxy group is incorporated in a tricyclic ketone intermediate and ring A is formed subsequently.

The problem of introducing a nitrogen function at C–18 has been solved similarly as can be seen, for example, in the syntheses of conessine by Johnson[27] (*Figure 15*) and by Barton[26] (*Figure 9*) and in Corey's synthesis of dihydroconessine[32] (*Figure 16*).

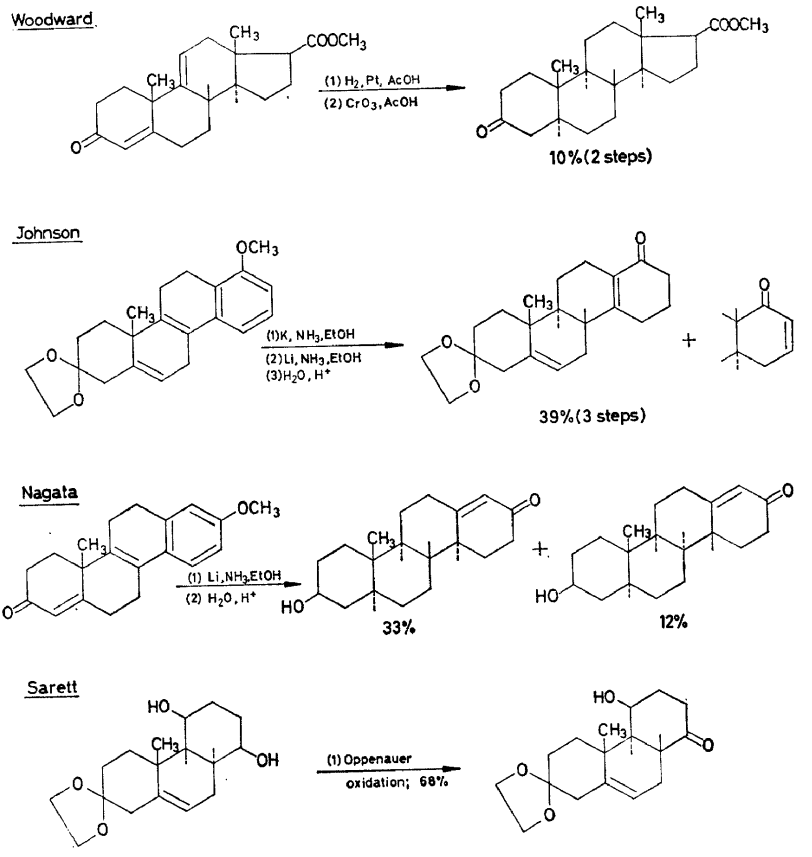


*Figure 12.* Syntheses leading to *trans*-fused BC rings

It is somewhat more difficult to place an OH–group at C–14 in order to build the cardiac aglycone system. In the total synthesis of digitoxigenin by Sondheimer[28] (*Figure 17*) the starting material was methyl-3$\beta$,14$\beta$-dihydroxyetianate, which Ruzicka[33] had prepared by hydrolysis of the 14,15$\beta$-epoxy compound. This ester was converted into a derivative of 20-keto pregnane. Reaction of the latter with ethoxyethynyl-lithium led to a carbinol which readily isomerized in acid medium to the ester of an $\alpha,\beta$-unsaturated acid. The decisive step was the last stage of the reaction when a hydroxy group was incorporated in position 21 by selenium oxide oxidation. The resultant hydroxyester cyclized under the reaction conditions to digitoxigenin acetate.

Another way of incorporating the 14–hydroxy group was that proposed by Eschenmoser and Julia[34] (*Figure 18*). Condensation of the cyclic dienone (I) with methyldihydroresorcinol yields the hydroxyketone (II). It was found that this reaction could be extended to tetracyclic steroid systems, in particular 19–norsteroids (Torgov)[35].

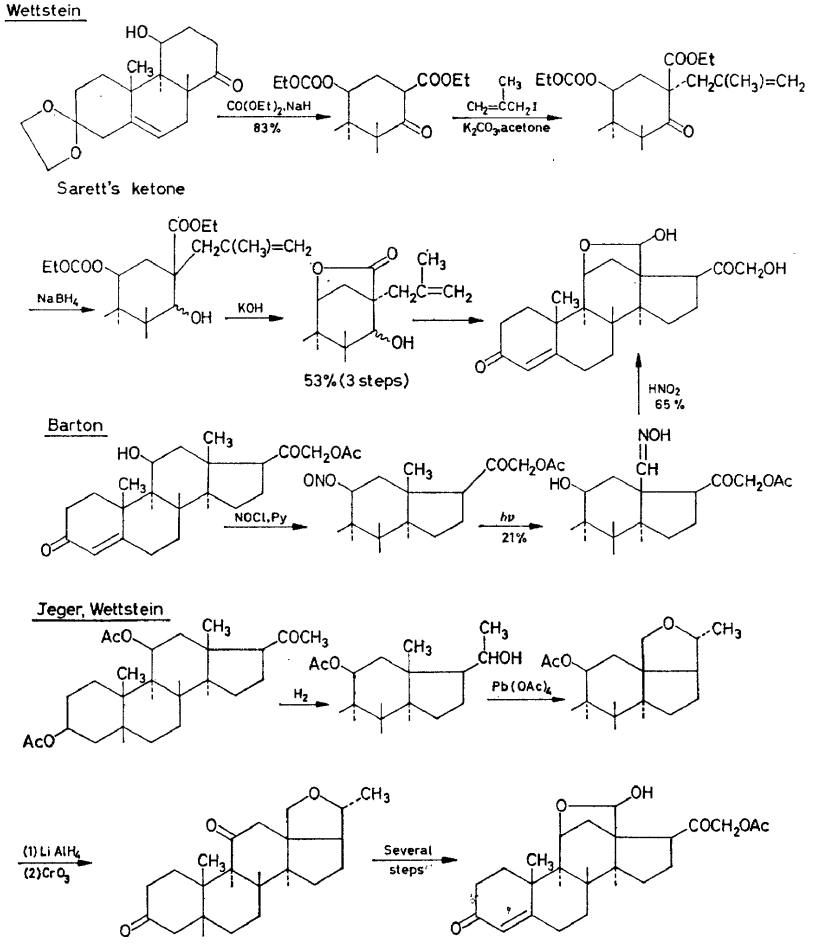


*Figure 13.* Syntheses of aldosterone

Another way, which has however not been tested, might be the preparation of 14–hydroxysteroids by cyclization of readily available hydroxyesters of the type A or B (*Figure 19*). If the cyclization could be accomplished, elimination of the extra keto or carboxyl group should present no difficulty, and the resultant compounds could also be used for incorporation of the 5β-hydroxy group and further for the synthesis of cardiac aglycones.

Until very recently, the total synthesis of steroids was only of scientific interest. Indeed the over-all yield of oestrone in Miescher's and Johnson's

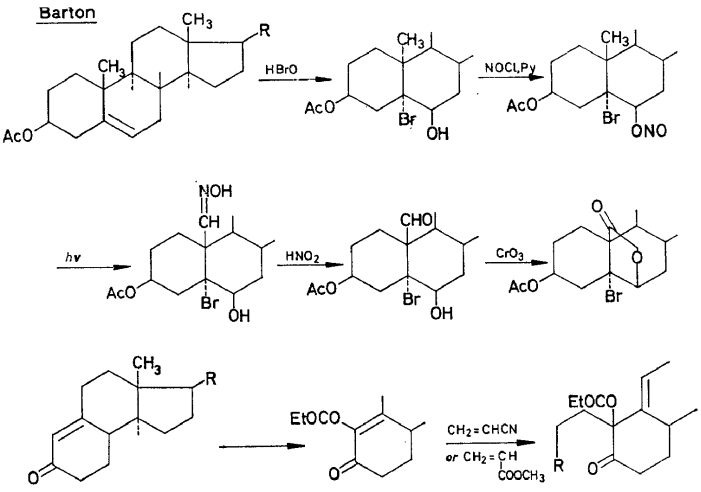


*Figure 14.* Introduction of C-19 oxygen function

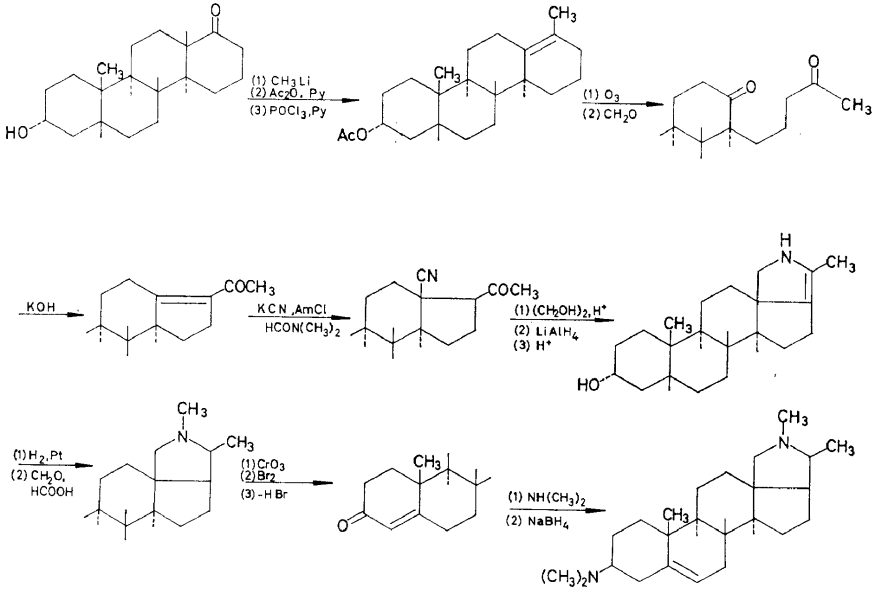


*Figure 15.* Johnson's synthesis of conessine

early syntheses amounted to only about 0·1 per cent, based on the naphthalene derivatives (used as starting materials). The yield of deoxycorticosterone acetate in Woodward's 30-stage route was only $7 \times 10^{-5}$ per cent. At the same time, the production of steroid hormones from natural sources (diosgenin, hecogenin, desoxycholic acid) has been brought to a high degree of perfection and at first glance it is difficult to visualize competition between natural sources and total synthesis favouring the latter, as occurred,

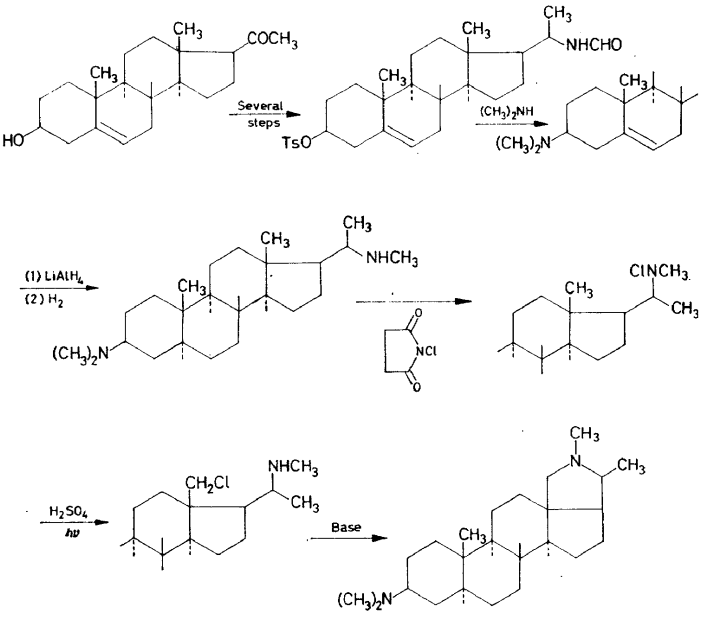


*Figure 16.* Corey's synthesis of dihydroconessine

for example, in the case of natural and synthetic indigo. Nevertheless, the total synthesis of steroids has an irresistible attraction for chemists, due to the possibility of starting from exceptionally cheap by-products. Moreover, the general trend in steroid chemistry is centered around the preparation of compounds with maximum activity and the methods of total synthesis offer more possibilities for modifying the molecules than when the latter are already in the final form. Furthermore, by partial synthesis it is easier to obtain derivatives of pregnane than of androstane or of oestrone, which are also of considerable medical significance.

Among the total syntheses published up to May 1962, the most promising from the industrial standpoint are those of oestrone.

Indeed, there are three routes to hydrocortisone: Sarett's synthesis (1952) starting with 3-ethoxypiperylene and quinone[6], that of the Monsanto group (a modification of Woodward's method) starting from methoxytoluquinone and methyl vinyl ketone[7] and Velluz's synthesis, from 6-methoxytetralone and dichlorobutene[22]. Each of these syntheses involves 25–28 stages and the over-all yield of the first two methods is about 0·04 per cent (the yield is not

given in Velluz's paper). Thus the total synthesis of hydrocortisone will hardly be attempted on an industrial scale until it has been considerably improved.

Five syntheses of aldosterone have been published. Johnson's method[16] comprises 30 stages with an over-all yield of 0·002 per cent based on 1,6-dihydroxynaphthalene. The four other methods (two by Wettstein[11, 18], one

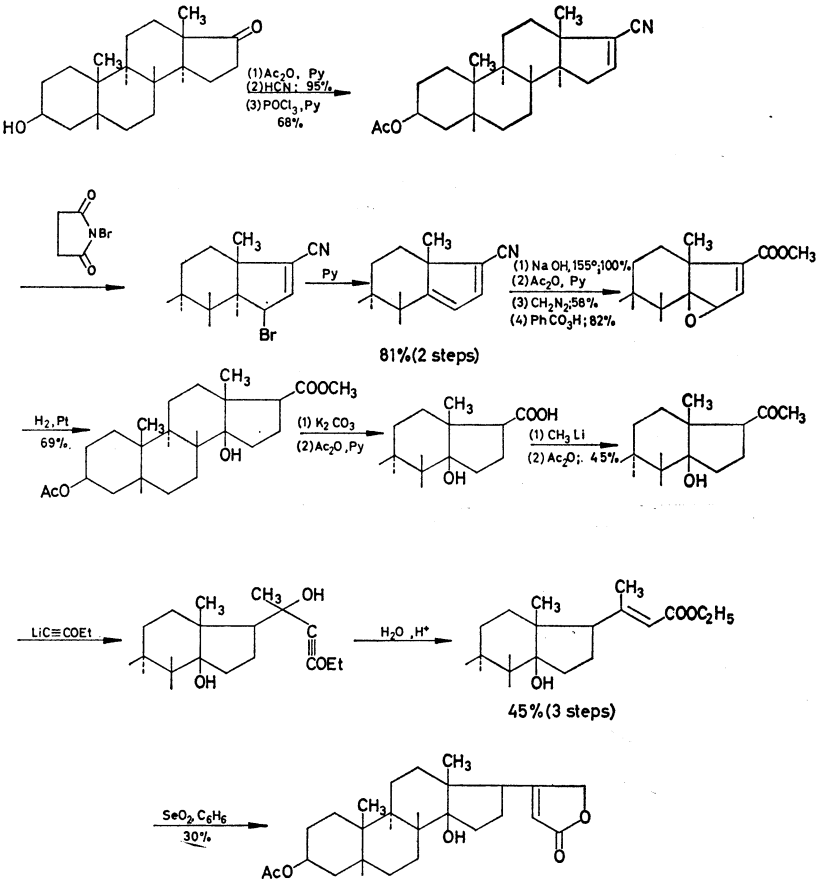


*Figure 17.* Sondheimer's synthesis of digitoxigenin

by Reichstein[14] and one by the Dutch " Organon " group[15]) all start from Sarett's hydroxyketone, *i.e.* in the long run from ethoxypiperylene and quinone. The highest yield is 0·22 per cent given by Wettstein's second method[18] comprising 27 stages (*Figure 20*).

It seems to us that the last method can already find industrial application, despite the competition from the partial synthesis developed by the Swiss group of chemists with the participation of Wettstein, himself.

Of the eight routes to oestrone, the ones of greatest interest are those which utilize as starting material the easily available 6-methoxytetralone. Johnson and Walker employed diene condensation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene (I) and quinone (*Figure 21*). The *cis* diketone (II) obtained in good yield was reduced to the diketone (III) in which the 17a-keto group proved to be the more reactive, yielding in methanol the ketal

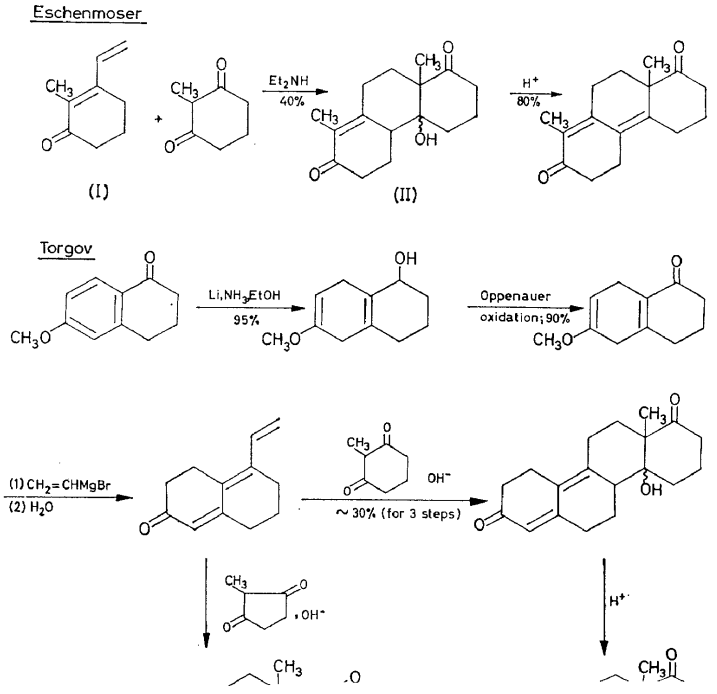


*Figure 18.* Introduction of 14-hydroxy groups

(IV). Removal of the 15-keto group by Kishner's method was accompanied by inversion at C–14 and hydrolysis then led to the *trans*-ketone (V). After methylation according to Johnson, and ring cleavage, the authors arrived at the acid (VI), which was reduced by sodium in liquid ammonia to a derivative of D-homomarrianolic acid (VII). Conversion of the acid (VII) to (±)-oestrone methyl ether (VIII) and then to (±)-oestrone was carried out in the ordinary way. The entire synthesis involves 12 stages and the over-all yield of (±)-oestrone methyl ether was about 3·8 per cent, and of (±)-oestrone about 3·2 per cent.

In 1960–62, Torgov and Ananchenko[20] carried out a synthesis of (±)-oestrone and (±)-D-homo-oestrone also starting from 6-methoxytetralone (*Figure 22*). The basic reaction underlying this synthesis is condensation of 1-vinyl-6-methoxytetralole (IX) with cyclic diketones, for example with methyldihydroresorcinol. The reaction takes place in the presence of

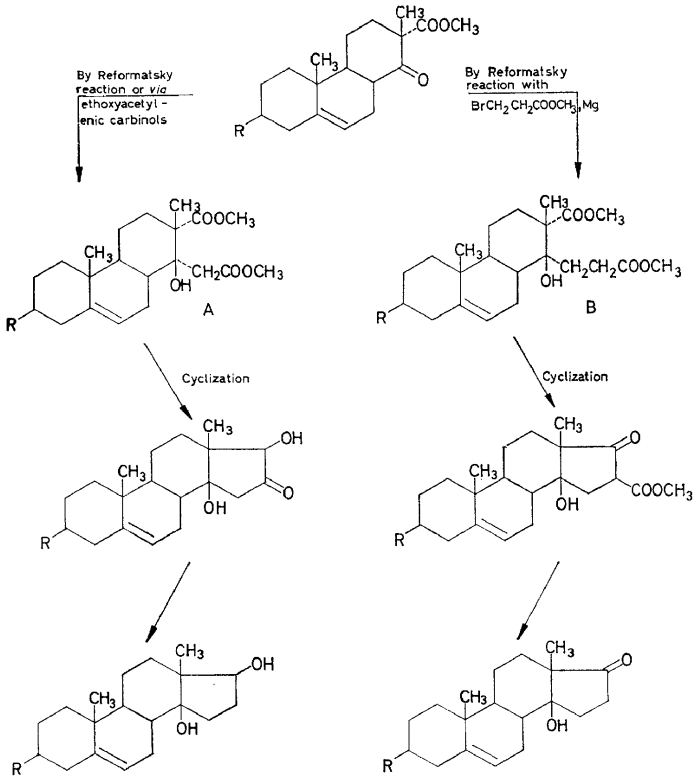


*Figure 19.* Tentative schemes for introduction of 14-hydroxyl groups

alkaline agents, such as potassium hydroxide, alcoholates, or, better still, trimethyl benzylammonium hydroxide. This results in the formation of the tricyclic ketone (X), which is easily cyclized to the D-homosteroid compounds (XI) and (XII).

Heated with a small amount of phosphorous anhydride, the diketone (X) is transformed into the ketone (XI) which on hydrogenation yields mainly the ketone (XIa) with *trans*-fused C and D rings. Reduction of the $\Delta^{8(9)}$-bond with the formation of the " natural " configuration is accomplished with the aid of potassium in liquid ammonia. The resultant ester of D-homo-oestrone (XIII) is converted into the methyl ester of (±)-oestrone (XIV) by Johnson's method.

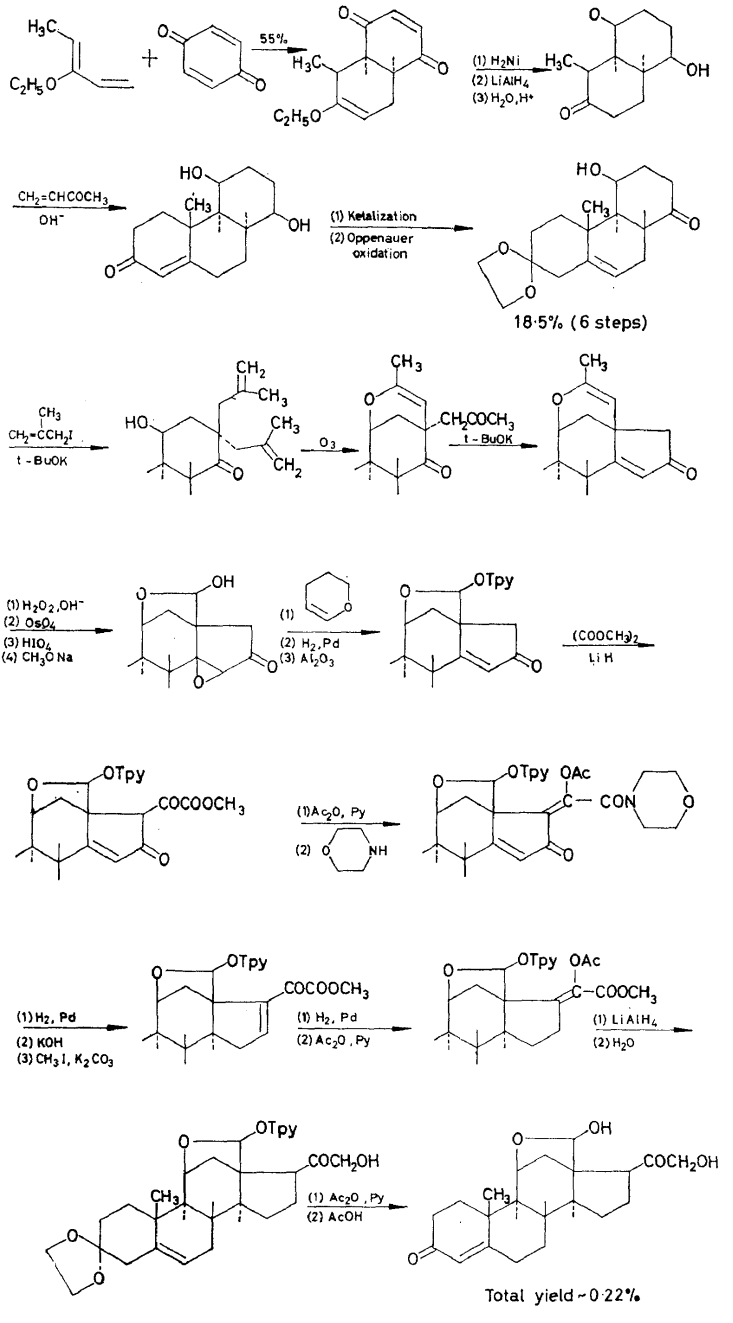


*Figure 20.* Wettstein's synthesis of aldosterone

The synthesis, involving 10 stages, gives (±)-oestrone methyl ether in 7·8 per cent yield and (±)-oestrone in 6 per cent yield. It is noteworthy that (±)-D-homoequilenin is formed on heating the diketone (X) with pyridine hydrochloride, *i.e.* cyclization, isomerization and demethylation, all take place in a single stage.

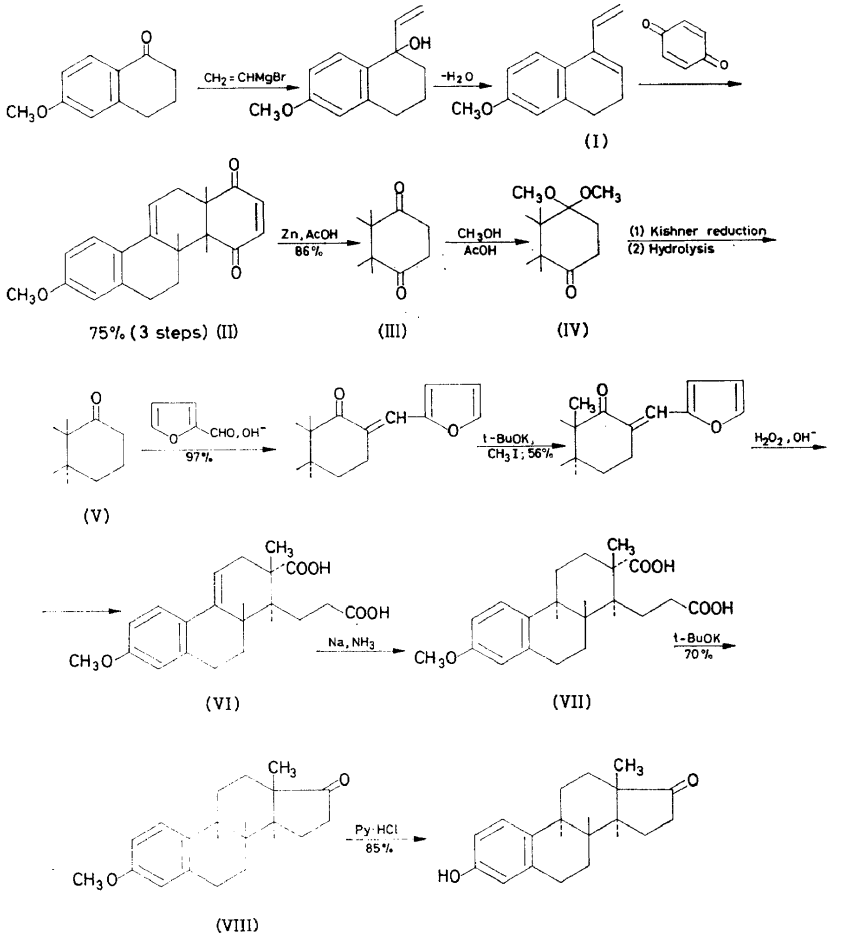


*Figure 21.* Synthesis of (±)-oestrone by Cole, Johnson, Robins and Walker

On substituting methylcyclopentanedione for methyldihydroresorcinol it is no longer necessary to convert the 6-membered into a 5-membered ring, and the synthesis can, thus, be somewhat shortened (*Figure 23*).

Condensation of carbinol (IX) with methylcyclopentanedione leads to the diketone (XV) which under the influence of toluene-*p*-sulphonic acid cyclizes to the methyl ester of bis-dehydro-oestrone (XVI). Consecutive hydrogenation and reduction of the latter gave (±)-oestrone methyl ether.

This second method comprises 7 stages and is so far the shortest synthetic route to oestrone. The total yield of oestrone methyl ether amounts to 12 per cent and of oestrone to 10 per cent. It should be mentioned that the main value in the syntheses described above is not so much the preparation of oestrone itself as the synthesis of 19-norsteroids[36] of the 19-nortestosterone type (or its D-homologue), which are anabolic agents, *i.e.* compounds stimulating protein synthesis in the body.

In the synthesis by Johnson and Christiansen described above the overall yield with respect to anisole or glutaric anhydride was 1·7 per cent. After

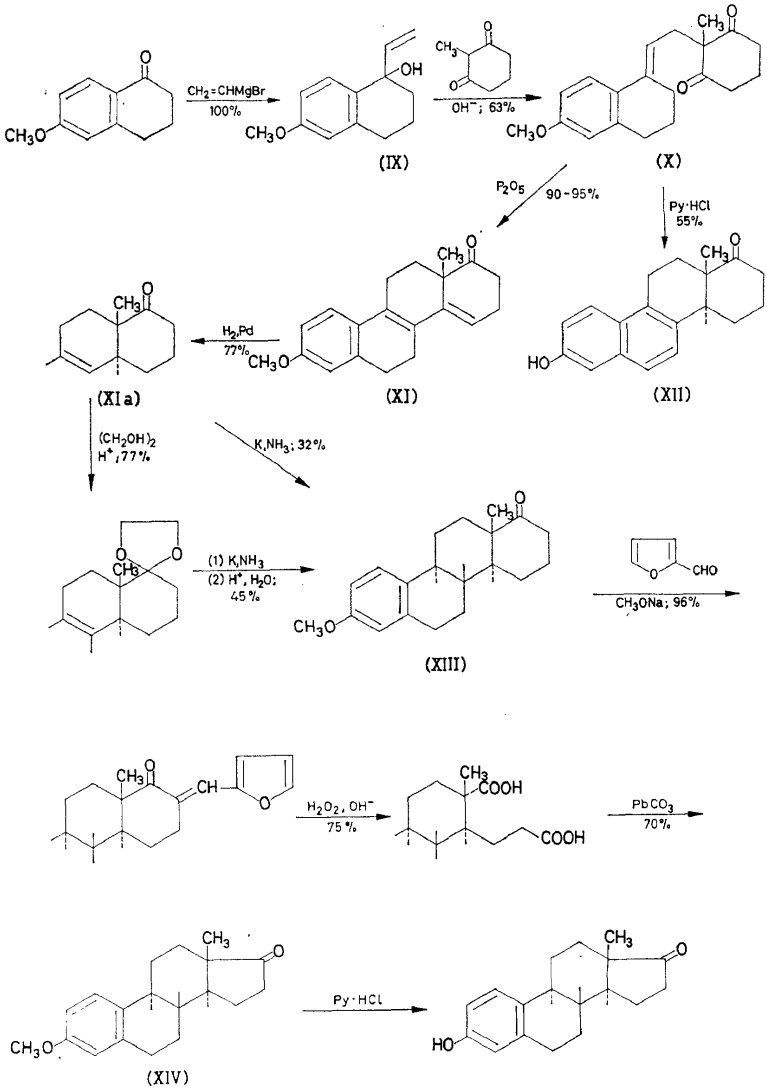


*Figure 22.* Synthesis of (±)-oestrone by Torgov and Ananchenkov

some improvement, this method may also prove to be of industrial significance.

There is no doubt that the large scale total synthesis of steroid hormones will become a reality in the near future. This will embrace, of course, not only the natural hormones, but to a still greater extent the " transformed " steroids (perhaps of as yet unknown classes), possessing augmented physiological activity and specificity. Here almost unlimited possibilities are open to the chemist.

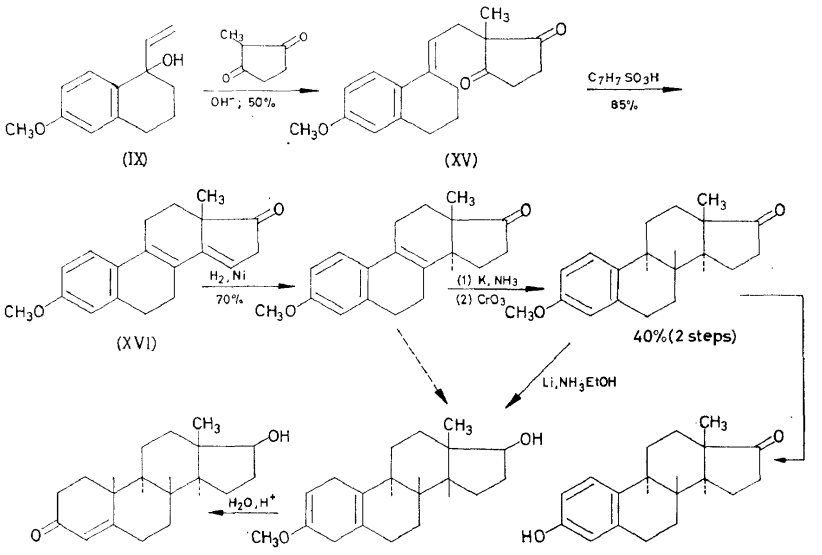


*Figure 23.* Second synthesis of (±)-oestrone and 19-norsteroids by Torgov and Ananchenko's second route

Bile acids, cardiac aglycones, toad poisons, alkaloids, *etc.* are now awaiting their turn. While the synthesis of cardiac aglycones has its specific difficulties, as mentioned above, we believe that the path to bile acids is open, since the incorporation of the oxygen function in position 12 is already feasible. I venture to say that if chemists needed desoxycholic acid then, within a year, we should have 3–5 original methods for the preparation of this important compound. But even without the total synthesis of this compound I am sure that the next few years, or perhaps even months, will give us many brilliant new examples of the powerful impact of novel synthetic methods on steroid chemistry.

## References

[1] W. E. Bachmann, W. Cole, and A. L. Wilds. *J. Am. Chem. Soc.* **61**, 974 (1939).
[2] G. Anner and K. Miescher. *Helv. Chim. Acta* **31**, 2173 (1948); **32**, 1957 (1949).
[3] W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg, and L. F. Chinn. *J. Am. Chem. Soc.* **72**, 1426 (1950); **74**, 2832 (1952).
[4] R. B. Woodward, F. Sondheimer, D. Taub, K. Heussler, and W. McLamore. *J. Am. Chem. Soc.* **73**, 2403, (1951); **74**, 4223 (1952).
R. B. Woodward, F. Sondheimer, and D. Taub. *J. Am. Chem. Soc.* **73**, 3547, 4057 (1951).

[5] H. Cardwell, O. Cornforth, S. Duff, H. Holterman, and R. Robinson. *Chem. & Ind. (London)* **1951**, 389; *J. Chem. Soc.* **1953**, 361.
[6] L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns, and J. M. Constantin. *J. Am. Chem. Soc.* **74**, 4974 (1952);
L. Sarett, R. M. Lukes, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandergrift, and G. E. Arth. *J. Am. Chem. Soc.* **74**, 1393, 1401, 1406 (1952); **75**, 422 (1953).
[7] L. B. Barkeley, M. W. Farrar, W. S. Knowles, and H. Raffelson. *J. Am. Chem. Soc.* **75**, 4110 (1953); **76**, 5014 (1954);
A. J. Speziale, J. A. Stephens, and Q. E. Thompson. *J. Am. Chem. Soc.* **76**, 5011 (1954).
[8] A. L. Wilds, J. W. Ralls, D. A. Tyner, R. Daniels, S. Kraychy, and M. Harnic. *J. Am. Chem. Soc.* **75**, 4878 (1953).
[9] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly. *J. Am. Chem. Soc.* **76**, 2852 (1954).
[10] W. S. Johnson. *J. Am. Chem. Soc.* **78**, 6278 (1956);
W. S. Johnson, J. Szmuszkovicz, E. R. Rogier, H. J. Hadler, and H. Winberg. *J. Am. Chem. Soc.* **78**, 6285, 6289, 6302, 6312, 6322, 6331, 6339, 6354 (1956).
[11] J. Schmidlin, G. Anner, J.-R. Billeter, and A. Wettstein. *Experientia* **11**, 365 (1955);
J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Überwasser, P. Wieland, and A. Wettstein. *Helv. Chim. Acta* **40**, 1034, 1438 (1957).
[12] W. S. Johnson, R. G. Christiansen, and R. E. Ireland. *J. Am. Chem. Soc.* **79**, 1995 (1957).
[13] J. E. Cole, Jr., W. S. Johnson, P. A. Robins, and J. Walker. *Proc. Chem. Soc.* **1958**, 114; *J. Chem. Soc.* **1962**, 244.
[14] A. Lardon, O. Shindler, and T. Reichstein. *Helv. Chim. Acta* **40**, 666 (1957).
[15] W. J. Van der Burg, D. A. van Dorp, O. Schindler, C. M. Siegman, and S. A. Szpilfogel. *Rec. trav. chim.* **77**, 171 (1958).
[16] W. S. Johnson, J. C. Collins, R. Pappo, and M. B. Rubin. *J. Am. Chem. Soc.* **80**, 2585 (1958).
[16a] S. J. Zavialov, G. V. Kondrateva, and L. F. Kudryartseva. *Izvest. Akad. Nauk, S.S.S.R.* OXH, 529 (1961).
[17] H. H. Inhoffen, K. Irmscher, H. Hirscheld, U. Stache, and A. Kreutzer. *Chem. Ber.* **91**, 2309 (1958);
H. H. Inhoffen, S. Schutz, P. Rossberg, O. Berges, K. H. Nordsiek, H. Plenio, and E. Höroldt. *Chem. Ber.* **91**, 2626 (1958); **90**, 1283 (1957).
[18] K. Heusler, P. Wieland, and A. Wettstein. *Helv. Chim. Acta* **42**, 1586 (1959).
[19] G. A. Hughes and H. Smith. *Chem. & Ind. (London)* **1960**, 1022.
[20] S. N. Ananchenko, V. N. Leonov, A. V. Platonora, and I. V. Torgov. *Doklady Akad. Nauk S.S.S.R.* **135**, 73 (1960).
[21] D. K. Banerjee and K. M. Sivanandaiah. *Tetrahedron Letters* No. 5, 20 (1960).
[22] L. Velluz, G. Nominé, and J. Mathieu. *Angew. Chem.* **72**, 725 (1960).
[23] W. S. Johnson, W. A. Vredenburgh, and J. E. Pike. *J. Am. Chem. Soc.* **82**, 3409 (1960).
[24] Y. Mazur, N. Danieli, and F. Sondheimer. *J. Am. Chem. Soc.* **81**, 3161 (1959); **82**, 5889 (1960).
[25] W. Nagata, S. Hirai, T. Terasava, I. Kikkawa, and K. Taked. *Chem. and Pharm. Bull.* **9**, 750, 769 (1961).
[26] D. H. R. Barton and L. R. Morgan. *Proc. Chem. Soc.* **1961**, 206.
[27] J. A. Marshall and W. S. Johnson. *J. Am. Chem. Soc.* **84**, 1485 (1962).
[28] N. Daniely, Y. Mazur, and F. Sondheimer. *J. Am. Chem. Soc.* **84**, 877 (1962).
[29] G. Stork, W. S. Worral, and J. J. Pappas. *J. Am. Chem. Soc.* **82**, 4315 (1960).
[30] K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni, and O. Jeger. *Experientia* **16**, 21 (1960).
[31] M. Akhtar and D. H. R. Barton. *J. Am. Chem. Soc.* **84**, 1496 (1962).
[32] E. J. Corey and W. R. Hertler. *J. Am. Chem. Soc.* **80**, 2003 (1958).
[33] L. Ruzicka, P. A. Plattner, H. Heusser, and K. Meier. *Helv. Chim. Acta* **30**, 1342 (1947).
[34] A. Eschenmoser, J. Schreiber, and S. A. Julia. *Helv. Chim. Acta* **36**, 482 (1953).
[35] N. A. Gaidamovich and I. V. Torgov. *Izvest. Akad. Nauk S.S.S.R.* OXH, 1803 (1961).
[36] A. Birch. *J. Chem. Soc.* **1950**, 367;
J. Iriarte, C. Djerassi, and H. J. Ringold. *J. Am. Chem. Soc.* **81**, 436 (1959).