

# Liversidge Research Lecture

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CHANCE AND DESIGN: AN HISTORICAL PERSPECTIVE  
OF THE CHEMISTRY OF ORAL CONTRACEPTIVES

A.J. BIRCH



The Royal Society of New South Wales



**Arthur John Birch**

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### ARTHUR JOHN BIRCH 1915-1995

**Arthur John Birch** was born in Sydney on 3 August, 1915. His secondary education was first at the Woollahra Superior Public School, and then at Sydney Technical High School. He began studying at the University of Sydney in 1933 and at the end of that year won the Levey Scholarship that financed succeeding years. He graduated B.Sc. (1st. class Hons.) in 1937 and M.Sc. in the following year, then with the award of an 1851 Exhibition Scholarship he proceeded to Oxford University (U.K.), where he worked with Robert (later Sir Robert) Robinson on the synthesis of long chain fatty acids with a quaternary carbon atom adjacent to the carboxyl group, and graduated D.Phil. in 1941. Between 1941 and 1948 he continued work in Oxford as a Research Fellow, then in 1949 he moved to Cambridge as Smithson Fellow of the Royal Society. In 1952 he was appointed to the Chair of Organic Chemistry at the University of Sydney, then at the end of 1955 he moved back to England to take up the Chair of Organic Chemistry at the University of Manchester. For the period 1965-67 he was Dean-Elect of the newly established Research School of Chemistry at the Australian National University, and in 1967, after 11 years at Manchester he took up the Foundation Chair of Organic Chemistry at the new Institution in Canberra. He was Foundation Dean of the Research School of Chemistry at A.N.U. from 1967 to 1970, and was again Dean from 1973 to 1976. He first won international fame for development of the alkali-metal / ammonia reduction of aromatic ring systems - the **Birch Reduction**. While he was at Sydney he began experimental work that subsequently (at Manchester) led to proof of his 'acetate hypothesis', the biosynthesis of phenolic aromatic compounds (polyketides) via polyacetate and / or polypropanoate intermediates. A later phase of his work, developed at the Research School of Chemistry, A.N.U., was the preparation and synthetic exploitation of iron complexes of cyclohexadienes generated by the Birch reduction of benzene derivatives.

In the 1970s and 1980s, Arthur Birch became involved with science policy and administration. In 1978 he was President of the Royal Australian Chemical Institute. He was a member of the Commonwealth Advisory Committee in Science and Technology; Chair of an independent inquiry into CSIRO, which produced the 'Birch Report'; Chair of the newly formed Australian Marine Sciences and Technologies Advisory Committee; OECD Examiner on Science and Technology Policy in Denmark; and, over a long period, Consultant to the UNESCO-UNDP project 'Strengthening Research and Teaching in Universities' in the People's Republic of China. He was President of the Australian Academy of Science for the period 1982-1986. For many years, beginning in the 1950's, he was a consultant to SYNTEX, a pharmaceutical company that led the way in the large-scale production of hormonal steroids from plant steroids. He died in Canberra on 8 December, 1995.

#### Honours and Awards

1953	FRACI
1954	FAA
1954	H.G. Smith Medal, RACI
1958	FRS

- 1960 FRIC
- 1972 Matthew Flinders Lecture / Award, Australian Academy of Science
- 1974 Liversidge Research Lecturer, Royal Society of New South Wales
- 1976 Full Foreign Academician of the U.S.S.R. Academy of Science
- 1977 D.Sc., *honoris causa*, University of Sydney
- 1979 Companion of the Most Distinguished Order of St. Michael and St. George
- 1980 A.E. Leighton Memorial Award, RACI
- 1980 Honorary Fellow, Royal Society of Chemistry
- 1982 D.Sc., *honoris causa*, University of Manchester
- 1982 D.Sc., *honoris causa*, Monash University
- 1983 Honorary Fellow, RACI
- 1987 Companion of the Order of Australia
- 1987 Tetrahedron Prize for Creativity in Organic Chemistry
- 1989 Foreign Fellow of the Indian National Science Academy
- 1992 Special Issue of the *Australian Journal of Chemistry*, 1992, **45**(1) dedicated to Arthur J. Birch.

### Bibliographical Sources

- (1) Rickards, R.W., 'Arthur J. Birch', *Aust.J. Chem.*, 1992, **45**, 1-3.
- (2) Rickards, R.W., obituary, 'Arthur John Birch', *Australian Academy of Science Year Book 1999-2000*, 1999, 99-101.
- (3) Birch, A.J., 'To see the Obvious' in the series *Profiles, Pathways, and Dreams; Autobiographies of Eminent Chemists*, Seeman, J.I., Series Editor, American Chemical Society, Washington, 1995.
- (4) Rickards, R.W., personal communication

### Scientific Publications of A.J. Birch

A list of more than 430 scientific publications of A.J. Birch will accompany the biographical memoirs that will be published in due course in *Historical Records of Australian Science*, and in *Biographical Memoirs of Fellows of the Royal Society*.

**CHANCE AND DESIGN: AN HISTORICAL PERSPECTIVE  
OF THE CHEMISTRY OF ORAL CONTRACEPTIVES\***

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ABSTRACT - The requirement of total synthesis of sex and cortical hormones is discussed in the historical context of evolution of ideas and techniques leading to biologically active analogues. In particular, the desire to make 18- and 19-norsteroids led to development of the technique of metal-ammonia reductions and eventually to the 19-norsteroid hormones used as oral contraceptives. This history is considered against a background of the role of chance and design in scientific research in general and pharmaceutical research in particular.

Most scientists are too busy to analyse why they carry out scientific work in the way they do. If they pause to consider how creative new discoveries are made they probably think in terms of the scientific method. This method involves collecting facts, drawing logical deductions from them and testing these deductions by experiment. It is usually thought to define the respectable way to discovery. The destructive testing of hypotheses once they are initiated is vitally necessary, but the real stories behind the origins of genuinely new and creative scientific theories are rarely told, and they often do not accord with the orthodox "official" scientific approach. Although a creative scientist operates instinctively by leaps of imagination, he often feels bound to make obeisance before the official tablets. The authentic process of discovery is often rationalized in recounting to what it *should* have been, usually unconsciously. Sometimes the motives are more conscious and less admirable, designed to confer apparently greater insight on the discoverer. There is no apparent sin attached, since the primary objective is thought to be to reach the facts and providing these are stated the process by which they are reached is often thought to be unimportant in any case. The pathway may even be forgotten and be later recounted in terms of what must have happened.

The high regard for the truth, which is an absolute necessity in testing scientific theories, is often strangely missing in defining the origins of the theories. A particular manifestation is the omission of discussion of previous ideas. It is perhaps incredible but true that one highly distinguished scientist, on being challenged on this score, replied "Am I not as good a scientist as he is; could I not have thought of this for myself?"

This remark is not as egocentric and irrelevant as it sounds. From the viewpoint of completeness in presentation, all previous ideas should be acknowledged, but frequently these play no part in a particular crucial development, since the developer was unaware of them despite their presence in the literature. A true picture of the evolution of his ideas can therefore apparently falsify the "true" historical development of the subject, as shown by complete documentation. The size of the literature and the fallibility of abstractors guarantee large areas of ignorance. Furthermore, Journal referees who presumably know their fellow scientists, tend not to accept any statements relative to independence of ideas which cannot be

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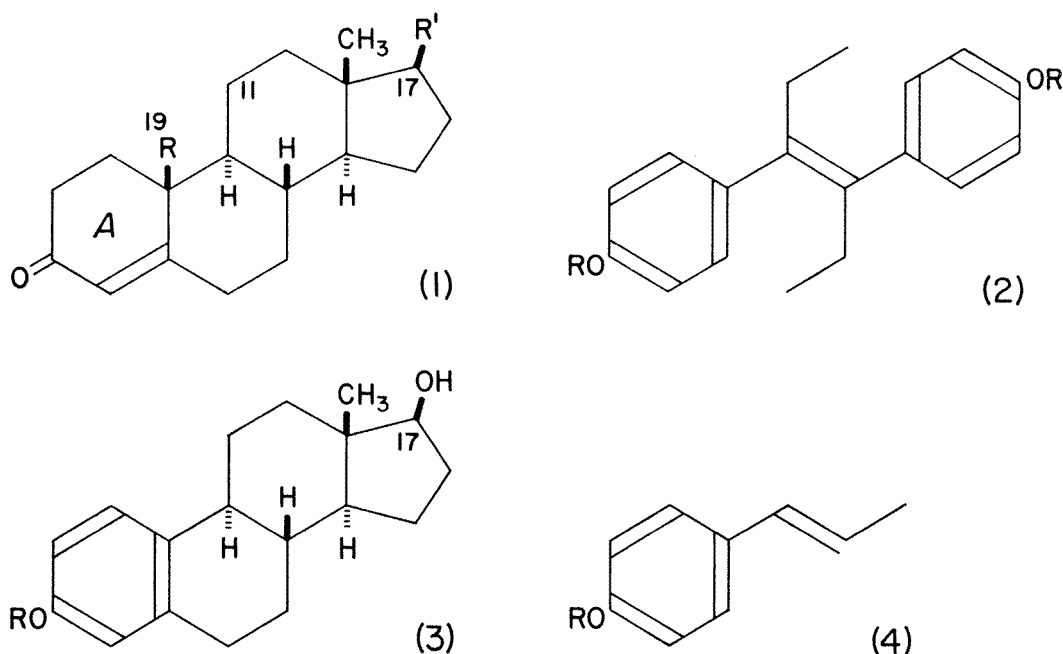
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demonstrably documented. That controversy is now barred under the heading of "polemics" is sometimes unfortunate, since resolutions of the origins of ideas have value, quite apart from bolstering egos. On a more practical plane, demands by Journal editors, and costs of publication are also factors leading to brief *logical* presentations of *facts*, presentations which not only obscure the intellectual processes involved but often falsify them.

Science is one of the most creative of intellectual activities, so falsifications, for whatever reasons, of processes of intellectual adventure, are very regrettable in cultural terms. They, are also misleading for young scientists, who pursue invalid approaches, or despair, because their work does not proceed in the smooth logical manner they are often led, by reading the Journals, to believe it should.

A story tracing the origins of an idea can be told authentically only by the discoverer. However, to recount it thus requires an interest in and awareness of the nature of the processes as they occur, considerable intellectual honesty and detachment, and a good memory. With these requirements very consciously in mind and with a long continued interest in historical processes in science as well as in results, I recount my own contact with the course of development of synthetic sex hormone analogues.

I finished a D.Phil. degree course at Oxford, with Sir Robert Robinson, in late 1940 and was asked to join a group attempting to synthesize steroid hormones, the structural group to which the cortical and sex hormones belong. A report from the Polish underground had suggested that Luftwaffe pilots were being given cortical hormones, which are involved, for example, in shock conditions. I still have no idea whether this was true, or whether they would have been useful, but in consequence, the R.A.F. wanted reasonable quantities of substances biologically active as corticoids.



The molecules of the sex hormones and those from the adrenal cortex contain the same basic carbon skeleton (1), variations in the types of group present and in their positions leading to substances with different kinds of biological activities (Fieser and Fieser, 1959*a*). For example (1, R = CH<sub>3</sub>, R' = OH) is the male sex hormone testosterone, and (1, R = CH<sub>3</sub>, R' = COCH<sub>3</sub>) is progesterone, one of the two types of female hormone. The molecules of cortical hormones are of the progesterone type but require for activity critical groups,

containing oxygen atoms, at certain positions, such as 3, 11, 17, 21 (*cf.* 1) notably the last is needed in the 17-side chain as  $R' = \text{COCH}_2\text{OH}$ . Many compounds of these series have several types of biological activity although one usually preponderates, for example, a cortical hormone can also be androgenic, and androgens normally have the generalized anabolic action (stimulation of protein formation) in addition to their specialized effects on male sex organs and secondary sex characteristics.

At this time, the natural hormones were, and still now are, available only in minute amounts by extraction from animal glands. The original work on cortical molecular structures by Reichstein and Kendall (Fieser and Fieser, 1959*a*) met with great difficulties because of the rarity of the substances and because of their presence in complex mixtures of twenty or more related compounds. The development of partial synthesis, that is of chemical modification of steroids which are available naturally in large quantities, still awaited the advent of the remarkable Russell Marker and his diosgenin from Mexican yams.

The answer, if any, then appeared to be a total synthesis, and it was a logical deduction that if the Germans had indeed succeeded in making a practical hormone, they were either producing the natural structure synthetically, or more likely were preparing a structurally simplified but biologically active analogue. The subject of sex hormone analogues was then much in mind because of recent work on stilboestrol (2,  $R = \text{H}$ ), a replacement for the oestrogenic female hormone oestradiol (3,  $R = \text{H}$ ).

The discovery of stilboestrol is an interesting illustration of the role of accident (Campbell *et al.*, 1938). When oestrone (the 17-ketone corresponding to (3,  $R = \text{H}$ ) and the first oestrogenic hormone discovered) was shown to be a phenol, Sir Charles Dodds and Sir James Cook commenced examination of other "natural" phenols. Among those to be tested was anole (4,  $R = \text{H}$ ) the phenol corresponding to anethole (4,  $R = \text{CH}_3$ ) the readily available flavouring matter of aniseed.

According to the literature, drastic alkaline treatment of (4,  $R = \text{CH}_3$ ) gives (4,  $R = \text{H}$ ), and the product of such a reaction was tested without adequate purification. It was powerfully oestrogenic. The activity was then found to be concentrated in mother liquors from the pure phenol and was thought possibly to be due to a dimer of anole. Sir Robert Robinson, who then with Leon Goldberg collaborated on the chemical side, synthesized possible dimers, the first being stilboestrol (2,  $R = \text{H}$ ) (Dodds *et al.*, 1939) which proved to be a very powerful hormone. It is still used in medicine and in veterinary practice. Later, Robinson rationalized the structural resemblance to oestradiol (3,  $R = \text{H}$ ) by writing the formula of (2,  $R = \text{H}$ ) as shown. This has led to the fairly general belief that it was synthesized because of this structural resemblance, although the authentic story is well documented.

A possible answer to the problem of supply of corticoids seemed to be the attachment of the highly characteristic cortical  $\text{COCH}_2\text{OH}$  side-chain to a nucleus of the stilboestrol type. Even at that time there were considerable doubts about the validity of such an approach because it was becoming clear that many aromatic compounds, particularly phenols, are oestrogenic, and that oestrogenic activity is less linked to exact structure than any other hormonal activity. However, I was asked to make aromatic compounds of the general type, basically because they were easy to make.

About eighteen months of frustrating work led only and, not unexpectedly, to oestrogenic compounds. These would merely have feminized R.A.F. pilots, which was not exactly what was needed. I started in 1942 to rethink the problem on the basis of possible rational, rather

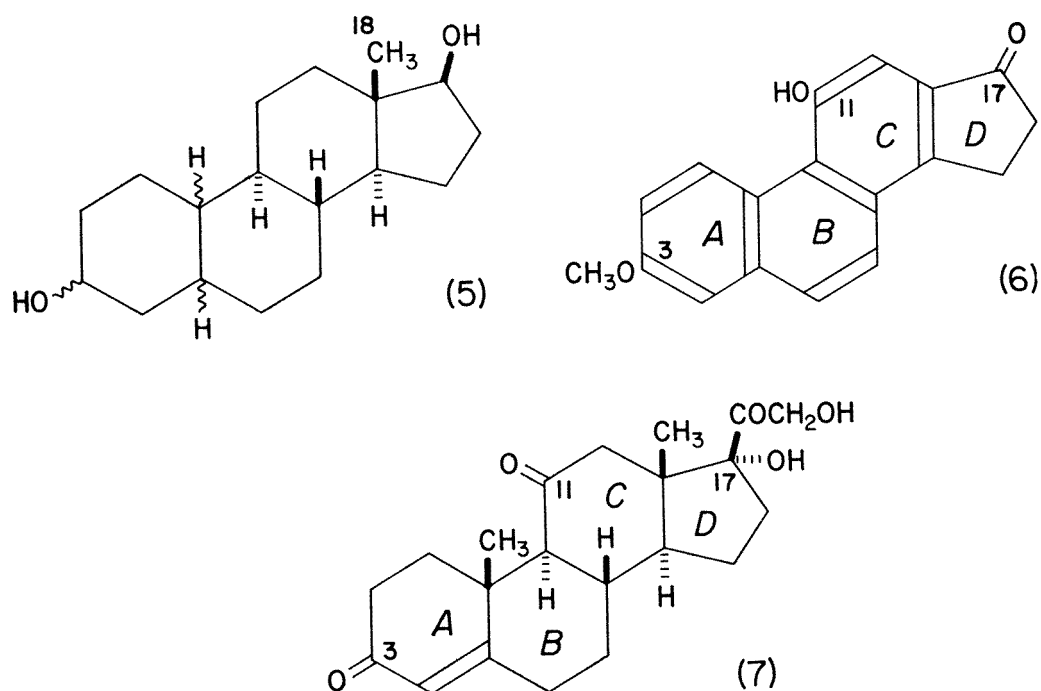
than accidental, modifications of the skeleton which might assist synthesis by simplification and yet result in structures with some possibility of retaining biological activity. In pharmacological-structural relations usually there are no predictable certainties, merely finite probabilities of finding activity which make the synthetic operations worthwhile. To see what simplifications might conceivably be made with profit, let us look at the difficulties to be surmounted in a total synthesis of the natural compounds, multiplied in their effects if the synthesis needs to be employed for making quantities for practical use, rather than formally to prove a scientific point. This need for a practical synthesis was an aspect which the origins of the work had impressed on me long after the original war necessity had vanished and it led to a continued preoccupation with the possibility of a given route for large-scale production. In all probability, I could have carried out a formal total synthesis earlier but for this; for example, an abandoned procedure published in 1951 (Birch, 1951*a*) was completed by others (Narasimha Rao and Axelrod, 1965).

The first problem is that of stereoisomerism. There are a number of asymmetric centres, e.g. for testosterone (1, R = CH<sub>3</sub>, R' = OH) there are 6, giving rise to the possibility of 2<sup>6</sup> = 64 isomers with different shaped but otherwise identical molecules. Normally only one isomer is likely to be highly active (the normal series shown) (8) although progestational activity seems from the subsequent results to be less linked to exact shape than is androgenic activity. The subject of steric specificity in synthesis of cyclic systems was then in its infancy, and made notable advances only from about 1950, with Sir Derek Barton's work on conformational analysis.

Some empirical correlations were then known (e.g. a relevant one was that the stable configuration of two six-membered fused rings is normally *trans* - as in the steroids). Much of the experimental work on steric specificities of reactions in complex molecules indeed grew out of the need for synthesis of steroids and other natural products.

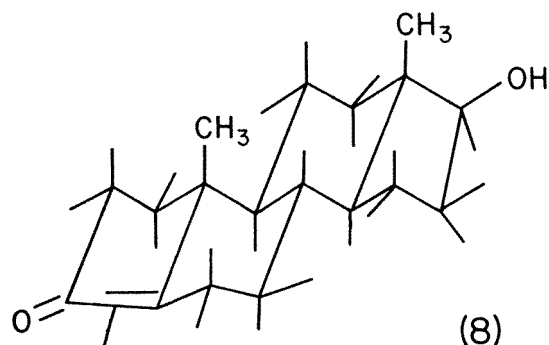
A further synthetic difficulty was due to the presence of two *angular* CH<sub>3</sub> groups at 18- and 19- (e.g. 1, R = CH<sub>3</sub>) the formation of which require the production of quaternary carbon atoms. This greatly limits tempting approaches through benzenoid precursors, made possible by the presence of the six-membered rings. Aromatic compounds are attractive because of the practical ease and known specificities of substitution and ring-closures. Reduction by direct or indirect addition of hydrogen to such benzenoid rings can lead to non-aromatic products [e.g. (5) from oestradiol (3, R = H)] (Discherl *et al.*, 1936), but the structural equivalent of addition of CH<sub>3</sub> rather than H required to produce the angular methyl group is more difficult, since it involves formation of new C-C rather than just C-H bonds. If CH<sub>3</sub> is present in the precursors it limits the number of possible synthetic procedures, although a possible one, the Robinson annelation, was known at the time. Robinson had also elaborated previously (Koebner and Robinson, 1938) a very simple route to (6) which seemed potentially capable of development for quantity production, particularly of corticoids, in view of the oxygenation at 3, 11, 17- [*cf.* corticosterone (7)]. Use of (6) would however, require elaboration of specific reduction processes. I had this route in mind, or one involving the precursors of (6), as a possible basis of our work. However, it was many years later before Subba Rao and I succeeded, as I note below, in completing such an approach.





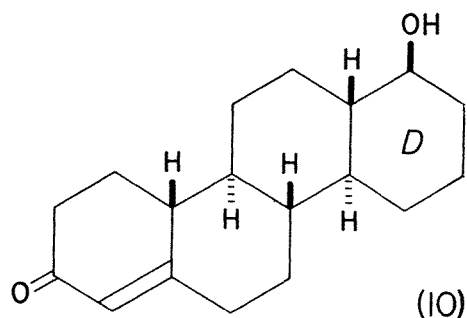
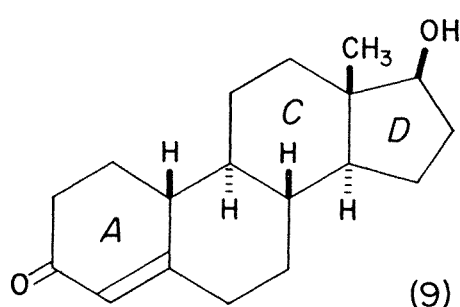
The effect of structural, including steric, difficulties on total synthesis are shown by the historical sequence: equilenin (14, R = H) in 1937 (Backmann *et al.*, 1937) (two aromatic rings and only one angular CH<sub>3</sub> and two asymmetric centres), oestrone (3, R = H) in 1948 (Anner and Miescher, 1948) (one aromatic ring, one angular CH<sub>3</sub> and four asymmetric centres) and finally, the non-aromatic steroids in 1951 (Cardwell *et al.*, 1951) (no aromatic rings, two angular CH<sub>3</sub> and six or more asymmetric centres).

Which analogues to synthesize might be decided by starting with the natural structures and working away from them (mentally and on paper) by progressive stages, omitting structures causing difficulties in the synthesis. Compounds with the resulting structures would then have to be made and their activities examined to find at what point of structural alteration activity disappeared in a given biological series. The then known structural factors necessary for activity were first summarized. A clear requirement for high activity in all series except the oestrogens was known to be the presence of the cyclohexenone ring-A (e.g. in 1). Hydrogenation of this unsaturation normally leads in the product to lowering or loss of biological activity in any hormonal series. Another clear factor was stereochemistry. Despite a remarkable exception in the progestational series noted below, activity, which depends on the shape of the main skeleton, normally is found only when this is identical with the natural one [e.g. (8) is a three-dimensional model of testosterone (1, R = CH<sub>3</sub>, R' = OH)]. Even a minor steric alteration such as that of the 17-OH from β- (above) to α- (below) the ring system can abolish activity in the androgenic series.



I decided from such considerations that a fairly direct method of making cyclohexenones from aromatic systems might be useful for ring-A synthesis. However, because of the practical difficulty of inserting the angular  $\text{CH}_3$  at position 19-, the question then arose whether the presence of this group is really necessary. Omission of the 18- $\text{CH}_3$  would also be desirable to facilitate a synthesis using an aromatic precursor of ring-C.

On searching the literature I found one clue that the 19- $\text{CH}_3$  might be omitted. Oestradiol (3,  $\text{R} = \text{H}$ ) had been catalytically hydrogenated (Dirschel *et al.*, 1936) to an octahydro-derivative of undefined stereochemistry (5) which was weakly androgenic. Since this structural type of A-ring even with the complete skeleton and in the authentic stereochemical series would not be expected to confer high activity, it seemed to me of great interest to make the 19-nor analogue (9) of testosterone which contained the cyclohexenone A-ring (nor implies loss of one carbon, in this case the 19- $\text{CH}_3$  attached to carbon 10). My second objective was to omit the 18- $\text{CH}_3$ , but this was liable to lead to stereochemical problems, since the C-D ring-junction is *trans* (e.g. in 9) and the stable junction is *cis*. Most syntheses would probably involve an intermediate carbonyl at the 17-position, which would permit equilibration of the stereoisomers and would almost certainly lead in consequence to the unnatural *cis* C-D junction. A six-membered D-ring would give a stable *trans* C-D junction. A practical objective was therefore to make 18,19-bisnor-D-homotestosterone (10), retaining a good deal of the overall shape of the natural molecule.



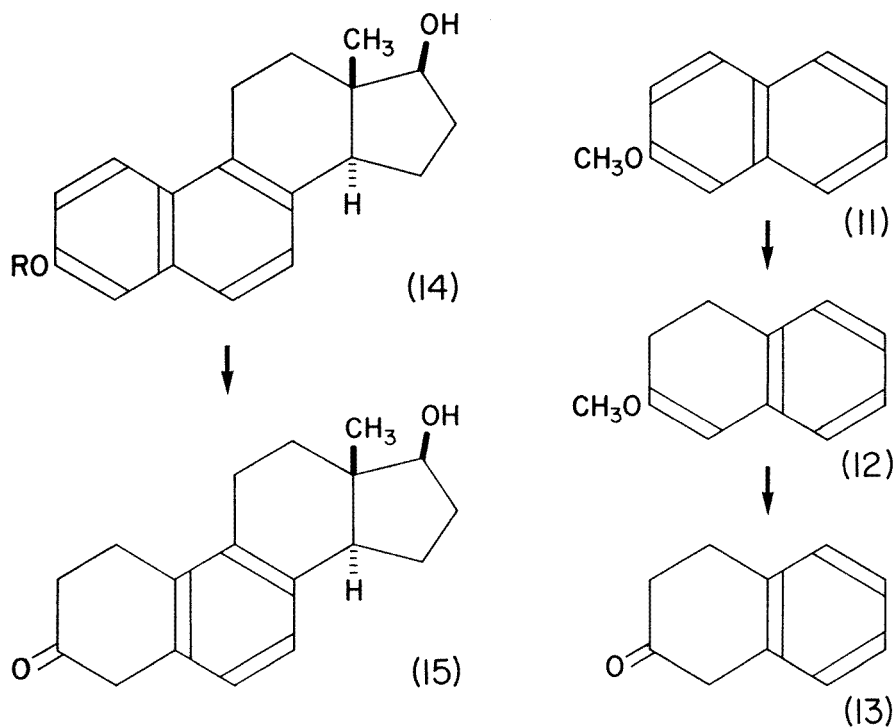
This intuitive approach is a characteristic example, leading merely to a suggestion of what should be submitted to experimental test. Such intuitions cannot be exercised in the absence of some known facts; frequently there are too many facts and the creativity lies in choosing which are significant in the context. In the present connection the cyclohexenone A-ring requirement was fairly obvious, but the Dirschel hydrogenation result, which was critical to the decisions, was rather obscure and was deliberately sought in the form of any information available on hydrogenated oestrones. The work of Ehrenstein, discussed below, apparently did not start from this same point, since he mentions it in none of his publications, despite an implication to the effect by Fieser (Fieser and Fieser, 1959b).

In 1942 oestrone was available only at a high price (about £25 per g) but it nevertheless seemed worthwhile to try to convert it into (9) to see whether androgenic activity resulted and whether consequently the further labour of total synthesis of this and other hormone analogues was justified. The initial synthetic problem was therefore how to obtain from the oestrone phenolic A-ring the required cyclohexenone A-ring. An objective which could more immediately be attacked experimentally, since the starting-material was available, was to modify the original approach via stilboestrol analogues to make corresponding cyclohexenones.

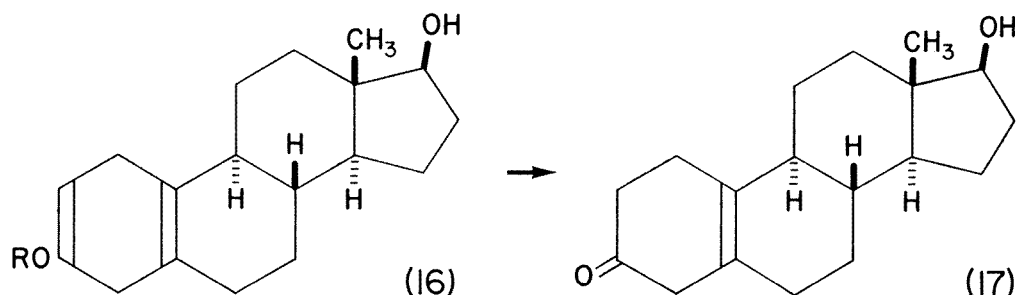
The reduction of aromatic rings had hitherto been by two methods: catalytic, using a transition metal and hydrogen gas, or by sodium and an alcohol. They both have severe drawbacks for the present requirements. Catalytic hydrogenations, such as used by Dirscherl, cannot usually be stopped short of saturation, stereochemistry is unpredictable and frequently resulting mixtures contain mostly *cis*-isomers, in this case undesirable. A further drawback is that oxygenated groups are frequently undesirably removed.

Although unsaturation could theoretically be reinserted after complete hydrogenation, this would almost certainly be an inefficient procedure and direct partial hydrogenation would clearly be better. In some respects, laziness can be equated with efficiency: the smaller the number of stages in a synthesis, the more likely is it to be efficient. Calculated on the basis of reverse compound interest: a four-stage synthesis at 80% per stage gives an overall molecular efficiency in the product of 41% and even two further similar stages reduce this to 26%. Yields of 80% per stage are normally very good, and a continued run of them would be unusual except in the very best synthetic sequences.

The sodium method cannot be used with monobenzenoid compounds, but its existence gave the clue to the solution of the problem. At this time Cornforth and Robinson were beginning their work on steroid total synthesis which culminated in 1951 (Cardwell *et al.*,

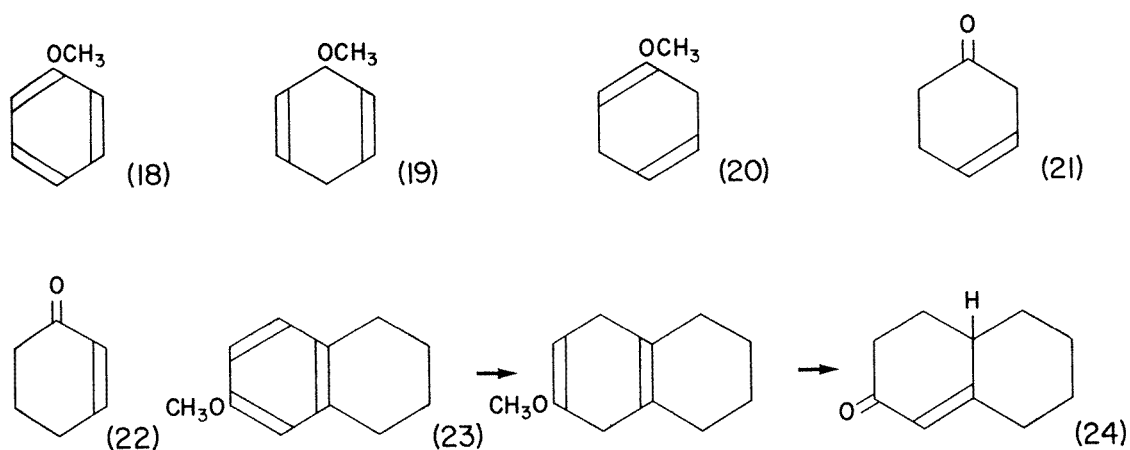


1951). A key model process was the reduction by sodium and ethanol of 2-methoxynaphthalene (11) into a dihydro-derivative (probably mostly 12) which, as an enol-ether, was hydrolysed by acid to give the ketone (13) (Cornforth *et al.*, 1942). A similar reduction of equilenin methyl ether (14, R = CH<sub>3</sub>) gave finally (15). I thought at the time that my problem would be solved if a similar process could have been carried out on an oestradiol ether (e.g. 3, R = CH<sub>3</sub>) through (16), reaction of which with acid would yield first (17) and then the more stable 19-nortestosterone (9). Unfortunately, it was known that similar reductions of monobenzenoid compounds do not take place. This is now known to be because of the lower electron affinity of a benzene compared with a naphthalene; the first stage of electron-addition to the aromatic ring does not take place. A search was then made of the literature, greatly assisted by a review then recently published (Campbell and Campbell, 1942) to see whether any chemical rather than catalytic reduction of monobenzenoid compounds had been reported other than the special case of benzoic acids which were well known to be reducible with sodium. Several very hopeful results were found.



In 1916 Dumanskii and Zvyerava (Dumanskii and Zvyerava, 1916) showed that benzene was converted into cyclohexa-1,4-diene by an ammoniate of calcium, produced by the action of ammonia gas on the metal. Kazanskii (Kazanskii and Glushner, 1938) later examined the reaction further, but obtained mainly cyclohexene with some unidentified diene. Alkylbenzenes similarly were found to give chiefly 1-alkylcyclohexenes. Unconjugated dienes could have been intermediates in the process since he also showed that these are further conjugated and reduced, e.g. cyclohexa-1,4-diene gives cyclohexene. I had initially intended to examine control of this type of process in an attempt to isolate intermediates, but a more exciting prospect was based on an observation of C. B. Wooster (Wooster and Godfrey, 1937).

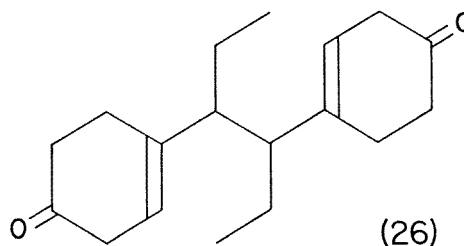
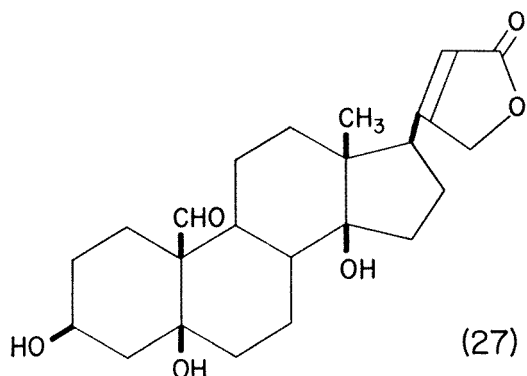
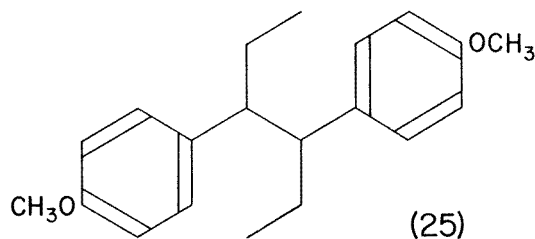
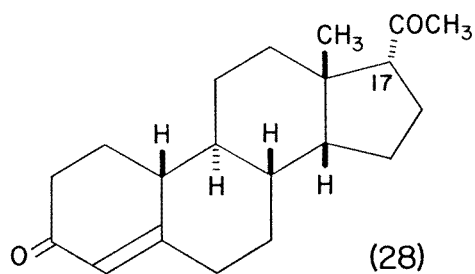
Sodium in liquid ammonia, which reacts with addition to naphthalenes, does not react with benzenes but Wooster found that if water or ethanol is added to such a solution containing benzene, toluene or anisole [methoxybenzene (18)] reduction occurs. The basic observation was "accidental". Toluene was intended to be a solvent for adding other substances he wished to react with sodium in ammonia but which were insoluble in the reagent. He recovered the product by adding water, still in the presence of dissolved metal, and the hydrogen gas given off was found to be deficient by 2H for every molecule of toluene used as solvent. This deficiency also occurred with benzene and with anisole on similar treatment, and he correctly deduced that dihydro-aromatic products are formed, although he proved only the structure of the 1,4-dihydrobenzene. Measurement of gas evolution was probably made originally to measure the metal consumption of his substrate, not of the admixed solvent, but the observation and deduction were crucial. Many workers would probably have dismissed the anomaly, since it was not closely related to the primary objective.



Wooster stated the anisole product to be "1,4-dihydroanisole" which is (19), and which on reaction with acid would probably give benzene. I thought it more likely to be 2,5-dihydro-anisole (20), precisely the type of enol-ether required. Perhaps Wooster merely intended to indicate an opinion that the hydrogens had added *para*- to each other as with benzene. He published no more work in the area.

Accidentally, in connection with another projected steroid synthesis (Birch and Robinson, 1944b) I fortunately had a cylinder of ammonia in the laboratory. In 1942 it took three months or more to obtain a cylinder from ICI (Billingham) and I might otherwise well have decided not to bother to test the possibility in view of other urgent tasks. After reaction of anisole (methoxybenzene) with sodium and ethanol in ammonia, the product, which already had a different sharp smell, was reacted directly with Brady's reagent. This was calculated to hydrolyse any enol-ether and to form the 2,4-dinitrophenylhydrazone of the cyclohexenone directly. There was an immediate orange precipitate [the derivative of (21)] which slowly changed to vermilion, rapidly on heating, to give the beautifully crystalline derivative of (22). It was a very satisfying moment.

The scope and specificity of the reduction process was then further examined with available substituted anisoles. Among the reductions reported was that of (23), the simple model for oestrone methyl ether, shown to give (24) the model for 19-norsteroids. This was published 1944 (Birch, 1944) without mention of steroid work for a number of reasons, one being that I hoped to continue the steroid line myself. However, thenceforth it must have been apparent to a steroid chemist "skilled in the art" who made the correct selection from the available literature what the application to steroids might be. Despite the large amount of work I carried out to generalize the procedure as a synthetic method, its genesis lay in steroid chemistry as outlined and it was not more or less accidentally later applied in that area. Its specificity and the simplicity and cheapness of the experimental procedure have led to wide use in sophisticated synthesis in other connections, e.g. (Birch and Subba Rao, 1972).



With the steroids themselves I had run into two types of problem: political and practical. The practical difficulties were the unavailability of oestrone, or rather of funds to buy it since I was officially still working on ring-opened analogues, and the insolubility in ammonia of the methyl ether, when I finally obtained 500 mg. Such low solubility was true also of hexoestrol dimethyl ether (25) which I wished to convert into (26). Insolubility defeated all reduction attempts. The political problems were concerned with whether I should have been carrying out such reductions at all. ICI (Dyestuffs Division, Blackley) which for some curious reason was connected with the organization of the project, was technically my employer. I was ordered to stop the reductions because of a cartel agreement with Dupont, who held a Wooster patent. I recall sorting this out at Blackley with the kind assistance of Dr. H. A. Piggott, on my first visit to Manchester in 1943, when the centre of the town was a smoking ruin, but continuation of the work was not viewed with favour.

In 1944 a tremendous impetus was given to the topic by M. Ehrenstein (Ehrenstein 1944). His starting point was also the desire to simplify the skeleton but he set out to make 19-norprogesterone from the natural material digitoxigenin (27), which differs from most other natural steroids by having the 19-CH<sub>3</sub> oxidized to CHO. Simple mechanisms for its removal and replacement of H can therefore be devised. Although it was not known for certain at the time, the conversion procedures produce an unnatural C-D *cis* ring-junction and the COCH<sub>3</sub> at 17- consequently becomes stabilized in the unnatural  $\alpha$ - instead of the  $\beta$ -configuration (28). The product initially obtained was amorphous and a mixture, but was claimed to be as biologically active as progesterone. Work much later, published in 1957 (Barber and Ehrenstein, 1957) reported obtaining the major product as pure (28) which, although of unnatural configuration (*cf.* 1), is more biologically active than progesterone itself. Because of the cost and rarity of digitoxigenin, the process is not a practical one, but the result led to an expectation that compounds of the natural stereochemical series would be of notable biological interest. Following this demonstration, a number of steroid chemists realized the desirability of making authentic 19-norprogesterone but were unable to devise methods to make it either by total or partial synthesis.

Up to the end of the war, and for some time afterwards, partly in collaboration with Robinson, I was still pursuing methods which might be practical ones for the synthesis of oestrone. The closest approach, based on precursors of (6), was that of isoequilenin methyl ether (Birch *et al.*, 1945).

Our original wartime project had folded by this time and I was employed on research fellowships in Oxford which permitted me to undertake work independently of Robinson's interests. Accordingly, I was mainly engaged on examination of the reduction method, rather than with steroids which Robinson was still pursuing. Also I had no oestrone, and no research assistance. About 1946, William S. Johnson, then at Madison, wrote to me indicating that he had also made the appropriate deductions from the reduction work and was interested in making 19-norsteroids. With his usual generous approach, he desisted on learning of my progress. In 1947, following the first IUPAC Conference held after the war, I met Gilbert Stork (now at Columbia University) and explained my situation. With characteristic generosity he gave me 5 g of oestrone which he had obtained from industrial sources.

Efforts to reduce oestrone methyl ether [or oestradiol methyl ether (3, R = CH<sub>3</sub>) into which it is converted initially by the reduction process] had been initially defeated by lack of solubility in ammonia. The ammonia was used direct from the cylinder, when it usually contains impurities such as iron which were later found to catalyse decomposition of the reducing agent. Only soluble compounds can compete with this loss. A.L. Wilds and N.A. Nelson, as the result of several years' study of the experimental conditions, evolved a technique using lithium instead of sodium which can cope with this impure ammonia. Using this technique (Wilds and Nelson, 1953), they were eventually able to reduce oestrone methyl ether. Providing purified ammonia is used, the original technique, particularly with sodium and *tert*-butanol (Birch, 1944), is effective and an industrial process resulted (Colton *et al.*, 1957).

In the first synthesis of 19-nortestosterone I solved the problem in a different way. Alcohols are usually soluble in ammonia, and using the  $\beta$ -hydroxyethyl (1, R = CH<sub>2</sub>CH<sub>2</sub>OH) or glyceryl ethers of oestrone, reduction proceeded readily. The nature of the ether group is unimportant since it is removed by the acid hydrolysis. I was able also to make greater progress because, for the first time I received research assistance in the form of a collaboration with Dr. S.M. Mukherji, now Professor at Kanpur. With Stork's oestrone we were able to carry out the sequence (3, R = OCH<sub>2</sub>CH<sub>2</sub>OH or OCH<sub>2</sub>CHOHCH<sub>2</sub>OH) to (16, R = OCH<sub>2</sub>CH<sub>2</sub>OH, etc.) to the  $\beta\gamma$ -unsaturated ketone (17) and thence to the objective (9) (Birch and Mukherji, 1949*a*) about July 1948. We also prepared (about May 1948) the dione (26) from hexoestrol dimethyl ether (Birch and Mukherji, 1949*b*). For structural reasons this undergoes only partial conjugation, and neither pure (26) nor the partially conjugated material has androgenic activity. This result appears to dispose finally of the initial ring-open approach based on stilboestrol.

19-Nortestosterone was the first synthetic potent androgen (Birch, 1950*a*), in fact it was the first synthetic hormone other than an oestrogen if we neglect the weakly active compound of Dirscherl. Oestrone had been synthesized in 1948, so according to the rules of the game, anything made from it counted as synthetic. Unfortunately this biological activity was not known when the chemical work was published in 1950 (Birch and Mukherji, 1949*a*). The compounds (17) and (9) were both sent to ICI for testing but were withdrawn at the urgent request of Sir Robert Robinson and sent to Sir Charles Dodds at the Courtauld Institute. This action was unfortunate for two reasons: it delayed the testing by several years (until late 1950)

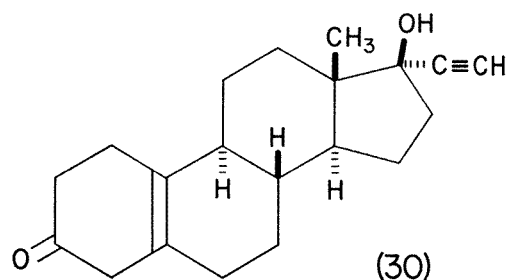
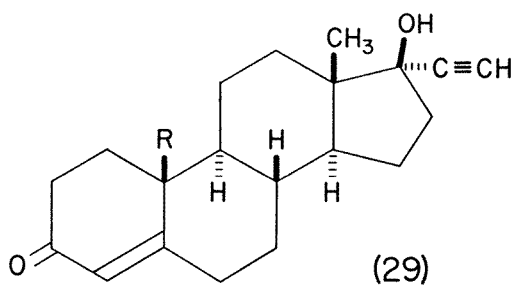
and also publication of the chemical paper which finally was submitted without the biological results. It also removed the series from an industrial atmosphere where exploitation of the biological breakthrough might have been favoured. One ketone (17) was found to be slightly oestrogenic (Birch, 1950*a*), but 19-nortestosterone (9) has a marked androgenic activity although this is somewhat lower than that of testosterone.

In January 1949, I went to Cambridge as Smithson Fellow of the Royal Society. Lord Todd there generously obtained for me a grant in 1950 from the Nuffield Foundation and also gave me an exceptionally able Ph.D. student, Herchel Smith. By then it was probably basically too late for us to compete with industrial laboratories since both objectives and methods had become obvious. Our first objective was 19-norprogesterone followed by 19-norcortisone, foreshadowed in the paper of 1949 (Birch and Mukherji, 1949*a*) and also in the Report of the Smithson Fellow (September 1950) in the Royal Society Yearbook 1951 (issued in January 1951) (Birch, 1951*b*). It is perhaps worth quoting (it first discusses making  $\alpha\beta$ -unsaturated cyclohexenones from phenol ethers). "Almost all of the active hormones of the cyclopentenophenanthrene group, including testosterone, progesterone and cortisone, contain such a cyclohexenone group, and the method thus provides a method of synthesizing analogues from aromatic starting materials. It cannot, however, directly provide the 19-methyl group and experiments have been carried out to determine whether this group is in fact necessary for physiological activity. The reduction of the  $\alpha$ -oestradiol glyceryl or hydroxyethyl ether followed by acid hydrolysis and bond-migration with alkali has provided 10-nortestosterone\* (\*naming by the Editor, Chemical Society, now 19-nor). Since this compound is physiologically active, the methyl group is not necessary, at least in this case, and the method is being extended to make 10-nor derivatives of progesterone and desoxy-corticosterone". These other 19-nor derivatives specifically, of natural configuration, were therefore conceived in print although not then made.

Physically, our starting material was still oestrone and we were in process of adding the 17-COCH<sub>3</sub> via the 17-C $\equiv$ CH when Carl Djerassi of Syntex, who had the aromatic progesterone already available, reported (Miramontes *et al.*, 1951) the reduction of its methyl ether by metal-ammonia solutions, using the Wilds-Nelson technique, to 19-norprogesterone, and also the high progestational activity of the product. This work is dated May 21st, 1951. Further industrial interest was evinced by Byron Riegel, then recently appointed research director of Searle, who visited Herchel Smith and me in Cambridge in, I think, 1950 to discuss our work and ideas.

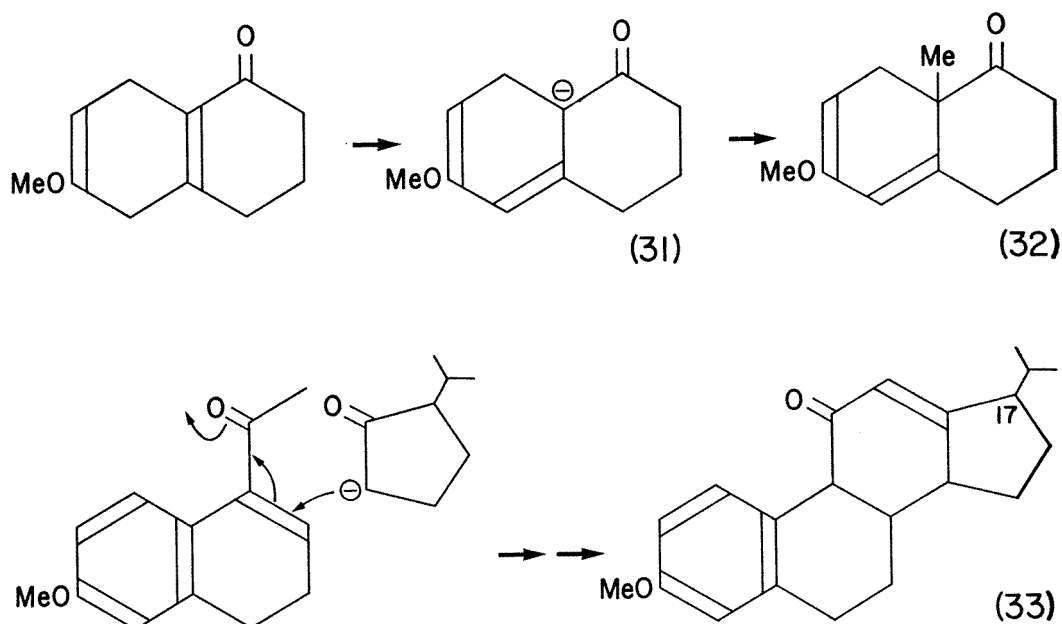
It was in retrospect a mistake for us to drop the 17-acetylene work because our initial objective had been reached by others. The progestational activity of 17 $\alpha$ -ethynyltestosterone (29, R = CH<sub>3</sub>) was well known and the substance had been used medically because it is more active than natural progesterone, when given by mouth (Stavely, 1939). It was therefore logical to attach this known activating group to the 17-position in the 19-nor series and also to hope for oral activity. The Syntex work (Djerassi *et al.*, 1954) on (29, R = H) and the Searle work (Colton, 1955) for the isomer (30) are dated 1954. Both compounds are potent oral progestational agents, and were adopted as oral contraceptives, chiefly as the result of investigations by Gregory Pincus. It was well known that progesterone prevents ovulation but has to be injected. The compounds norethindrone, norethisterone (29, R = H) and norethynodrel (30) were, accidentally apart from the clue noted, highly active when given by mouth. It is of interest that initially traces of aromatic oestrogen were left, from incomplete reduction, which potentiate the activity and later were deliberately added (norinyl, enovid).





In another account of the industrial development (Djerassi, 1966), Djerassi makes the statement "The likelihood that the absence of the angular methyl group was associated with high biological activity became more remote when . . . Birch described the synthesis of 19-nortestosterone . . . which exhibited considerably lower androgenic activity than the parent hormone". This is a misunderstanding of the resulting situation. In fact Djerassi notes elsewhere (Djerassi *et al.*, 1954) after mentioning the lower activity of 19-nortestosterone "Since the mechanism of androgenic and progestational activity is not necessarily comparable it appeared of very considerable interest to synthesize 19-norprogesterone". The importance of the 19-nortestosterone activity was that it indicated that the 19-nor series, the first with an altered carbon nucleus, showed very considerable activity in at least one hormonal series with highly structure-sensitive relationships. It was well-known that a change in activity produced by a particular structural alteration in one hormonal series is not usually parallel to change in another series. The matter of higher or lower activity in the progestational and cortical series was thus completely open, and it was clear that what was needed experimentally was to attach known activating groups for different hormonal series to the 17-position, followed by biological tests. In the 19-nor series compared with the natural series the progestational analogues were found to have higher activities, the anabolic analogues to be about as active, and the cortical analogues to have almost no activity. However important in other areas, the work would not have led to anything useful for fighter pilots.

In telling this history there is an element of selection on the basis of what became important. Other ideas and lines of work to overcome synthetic problems discussed above were simultaneously conducted. The major lines concerned the introduction of angular methyl groups and the stereospecific synthesis of ring-A aromatic steroids with useful 17-substituents including new methods of closing rings. In line with my interest in general methods rather than in specific syntheses the reactions were initially more successful than the resulting syntheses. Three early methods of producing quaternary carbon atoms of scope beyond the original intention, emerged: (i) the methylanilino-methylene blocking group which I devised in 1943 (Birch and Robinson, 1944a) which permits substitution in the angle of rings at the CH centre of  $-\text{CHCOCH}_2-$  (rather than in the  $\text{CH}_2$ ) which led in our hands to isoequilenin (Birch *et al.*, 1945); (ii) the copper-catalyzed addition of Grignard reagents (Birch and Robinson, 1943), developed from an observation of Kharasch (Kharasch and Tawney, 1941), which gave *cis*-9-methyldecalone from 2-octalone. The wrong stereochemistry of the process led to its neglect in the steroid connection, but later work, especially in the  $\text{LiCuR}_2$  development, has had many uses; (iii) the alkylation of the correct enolate anions of  $\alpha,\beta$ -unsaturated ketones, e.g. (31) $\rightarrow$ (32) (Birch *et al.*, 1952), developed from my initial work on this type of deconjugation process, the prototype being the conversion of cholest-4-en-3-one into cholest-5-en-3-one (Birch, 1950b), a necessary step in the total synthesis of cholesterol.



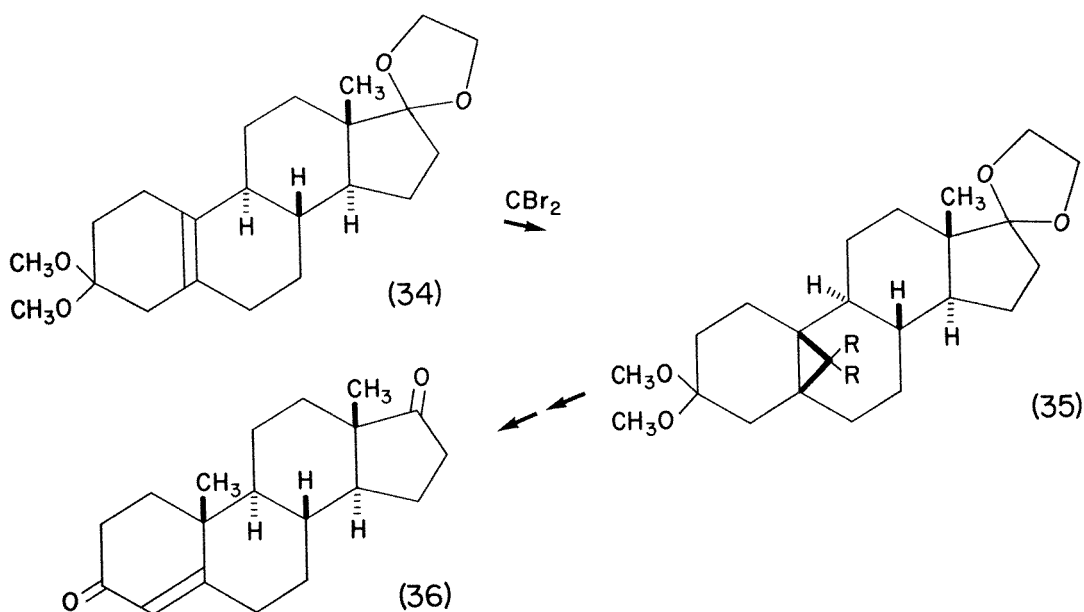
The ideas of stereochemical control were still rather primitive and based on equilibration of 6-6 ring junctions to the *trans* or steroid configuration. One example is the synthesis of (33), in which all of the asymmetric centres (8, 9, 14, 17) are equilibratable (adjacent or vinylic to carbonyl) (Birch and Robinson, 1944*b*). This is not pursued for two reasons: the problem of placing a useful group at 17- and the failure of additions to the unsaturated carbonyl system.

A ring-closure process which can only be briefly noted, but the discovery of which was also accidental in an interesting way, was the first use of polyphosphoric acid as a general cyclising agent for arylpropionic and butyric acids (Birch *et al.*, 1945). It was later rediscovered in an equally interesting and accidental manner (Snyder and Werber, 1950).

Also, Herchel Smith and I continued to make the 18-nor and 18,19-bisnor and D-homo- series (Birch and Smith, 1956). Our work and that of others, particularly of Gilbert Stork (Stork *et al.*, 1959) showed that removal of the 18-CH<sub>3</sub> even with the correct stereochemistry is catastrophic for any kind of activity. Two out of the three of our original bases for action thus proved to be invalid. Much later Herchel Smith (Smith *et al.*, 1964), taking into account the loss of activity by removal of the 18-CH<sub>3</sub> and effectively standing the 19-nor result on its head, inserted an *extra* CH<sub>3</sub> on the 18-carbon (to give an ethyl group). The resulting series, related to norethindrone, proved to be the most highly progestational known, and the compound norgestrel forms a very successful low-dosage contraceptive pill.

As a matter of some pride, although at present of no practical importance, in completing the original task I did eventually succeed in finding out how to insert the missing CH<sub>3</sub> groups and how to make use of intermediates in the original Robinson synthesis of (2). Inserting the 19-CH<sub>3</sub> turned out to be very simple (Birch *et al.*, 1964). The type of process used for (16) was employed to make (34) which on reaction with dichlorocarbene gave (35, R = Cl) which was reduced to (35, R = H), converted by acid into androstenedione (36). Since oestrone is now readily synthesized by a process due to Ananchenko, and Torgov (Ananchenko and Torgov, 1959) in Russia and to Herchel Smith in Manchester (Douglas *et al.*, 1963), this efficient procedure, or related ones, could be used for practical total syntheses of non-aromatic steroids. Our insertion of the 18-CH<sub>3</sub> and consequent synthesis of oestrone from precursors of (6) (Birch and Subba Rao, 1970) is of no practical interest compared to the Torgov-Smith

procedure but completes the sequence back to the original Robinson synthesis with which we started in 1941.



What general points are there to make? One is the obvious role of accident, although to interpret Goethe and Pasteur, accident tends to favour only those who have the attitude of mind to take advantage of it. The creative process involves the choice of significant features from numbers of facts, and I have tried to indicate the conscious part of this process in the present connection. It is also a demonstration of the oblique nature of attainment of unpredictable objectives. The initial conscious objective, the synthesis of useful corticoids, was not achieved, but the need generated in that area was transferred to a new but related area. The requirement was to simplify synthesis, and a logical analysis of the situation led to a selection of literature results culminating in the metal-ammonia procedure. This in turn had much more general application, including at least one initially unexpected impact back in the steroid field due to its stereospecificity. The high oral activity in the progestational series of the new nucleus was accidental, although Ehrenstein's work was a good indicator of probable high activity. The fact that I was not encouraged initially to pursue this line of work is an indication of how difficult it was to foresee developments. No patents were taken out initially on 19-norsteroids chiefly because it appeared that they were likely to be much more expensive than the 19-Me series. Probably universities should be better organized to take advantage, materially, of breakthroughs of this type.

However, accidentally, I am pleased that, to quote a Chemical Society Christmas competition, the Birch Reduction ultimately became a birth reduction.

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