tronics and waves, occupies perhaps another 15 percent of the physicists. Microwave technology, developed for radar during the war, has generated several lines of research. On the one hand, it has greatly expanded the field of molecular spectroscopy, while, on the other hand, it has generated the maser technique, making possible optical feats which only 30 years ago would have been considered completely unfeasible.

The remaining 13 percent of the physicists are busy with miscellaneous activities connected with a great variety of subjects ranging from gravitation to acoustics, from the improvement of optical instruments to plasma physics and gas discharges.

Computer technology. Before I complete this brief review I must mention another development which is having a great impact on physics: the development of computing machines. These are deeply affecting the whole field of applied mathematics. In physics they make possible computations which were unthinkable before the war. They also process vast amounts of experimental material with unprecedented speed. They are becoming a standard tool, and most of our present students learn a certain amount of computer technique.

With this I have completed my task of briefly describing the postwar physics. I am well aware that I have omitted many important items, but space and time have their exigencies.

What are the prospects for the future? Here I know I am sticking my neck out in a dangerous way. On the other hand, you may be interested in hearing guesses, if only to be able, a few years from now, to show how wrong they were.

First of all, many illustrious men of science, physicists in particular, have made the mistake of thinking that the end of physics was in sight. They have consistently been proved wrong by the opening up of completely new fields. Hence, I must make allowance for possible radically new discoveries.

Of the fields where we already have some knowledge, I venture to say the field of elementary particles is the one most likely, in the foreseeable future, to produce intellectually interesting results. The task ahead is a great challenge and will probably test the forces of an entire generation. The outcome should be an understanding of the systematics of the particles, including their masses, quantum numbers, and interactions.

While nuclear physics will give increasingly refined results, it will reach a stage similar to the present state of molecular spectroscopy, where the interest is more in applications and systematics than in new fundamental ideas.

Solid-state physics will be of ever-increasing practical importance. The creation of new materials with unexpected and unprecedented properties will give us some first-class technological surprises. However, here I do not expect the discovery of new principles.

Spectacular results, leading to new deep insights amounting to a revolution, are in the making in biology. These results will be due in part to the applications of physics and may provide some big surprises, even for physics.

Finally, space exploration and the study of the interior of the earth are new departures. Here we do not yet see any new phenomena, but we are penetrating in unexplored regions. It is possible that these regions will not yield anything extraordinary, such as extraterrestrial life. However, they present phenomena on scales impossible to reproduce in the laboratory, and a change in orders of magnitude is a well-known source of surprises. Furthermore, we must not forget that particle physics originated with the study of cosmic rays.

Steroid Oral Contraceptives

The chemical developments which led to the currently employed steroid contraceptive agents are reviewed.

Carl Djerassi

The social, economic, and political problems associated with the "population explosion" have received great attention in recent years, as testified by the appearance of monographs (*1*), special reports (*2*), and numerous articles, including several in *Science* (*3*). It is generally agreed by most authors that control of conception constitutes an indispensable component of any solution of this world problem and that the extensive clinical use of steroid oral contraceptives has been one of the most spectacular and promising new approaches to such control. The biological and clinical work leading to the development of the steroid contraceptive agents now being used has been ably summarized by one of the pioneers in the field, Gregory Pincus, in *The Control of Fertility* (*4*), but neither in that book nor in the voluminous clinical literature, encompassing several hundred articles, is there any coverage of the history of the chemical developments which made these biological studies possible, or citation of the original chemical publications.

Every synthetic drug must, by definition, have its origin in a chemical laboratory. How this chemical entity ultimately becomes a drug depends on circumstances. Frequently, such substances are synthesized in connection with some chemical problem and, as an afterthought, submitted for wide pharmacological screening. Alternatively, a given substance may be con-

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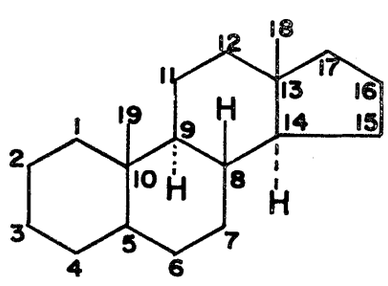
ceived and synthesized for a specific biological purpose, found to be inactive, and then exposed to wider pharmacological scrutiny. The literature of medicinal chemistry is filled with accounts of instances where accidental screening uncovered an unexpected biological activity, which provided the necessary impetus for further chemical, pharmacological, and clinical work.

It is not surprising that the sophisticated medicinal chemist is unhappy with this state of affairs and that, since the days of Ehrlich, he has attempted to establish relationships between chemical structure and biological activity which would lead to the a priori prediction of a potentially useful drug. Considerable progress has in fact been made by chemists along these lines, and since the steroid oral contraceptive agents represent a telling example of this approach, it seems worthwhile to recapitulate the little-known history of the chemical developments that led to the growth of this presently flourishing field.

Steroid Nomenclature

This brief section is included for readers who are totally unfamiliar with the symbolism employed by steroid chemists; more extensive discussions may be found in standard monographs dealing with steroid chemistry (*5*). The term *steroid* is a chemical rather than a biological term, since it is applied only to compounds possessing the skeleton shown below (or at times a slight modification of it).



The carbon atoms are numbered as indicated, and, as a chemical shorthand device, the lines projecting from positions 10 and 13 denote angular methyl groups. The molecule is essentially planar, and if it is visualized as lying in the plane of the paper, the dotted bonds denote substituents projecting below that plane, and the solid ones, substituents above it.

Structural Specificity Associated with Progestational Activity

The naturally occurring female hormone progesterone (structure I) has multiple biological functions (*4*), one of which is the inhibition of further ovulation during pregnancy. It is for this reason that it is frequently referred to as "nature's contraceptive," and, were it not for the fact that the substance is essentially inactive when given by mouth, it might very well have found practical application as an oral contraceptive. For a long time it was assumed (*6*) that such activity is extremely specific and limited to progesterone (I) and some analogs with additional double bonds in the 6-7 or 11-12 positions. This assumption was supported by the observation that even so close a relative as 17-isoprogesterone (II) (*7*), which differs from the parent hormone (I) in stereochemical detail at only one center (carbon atom No. 17), exhibits no noticeable progestational activity.

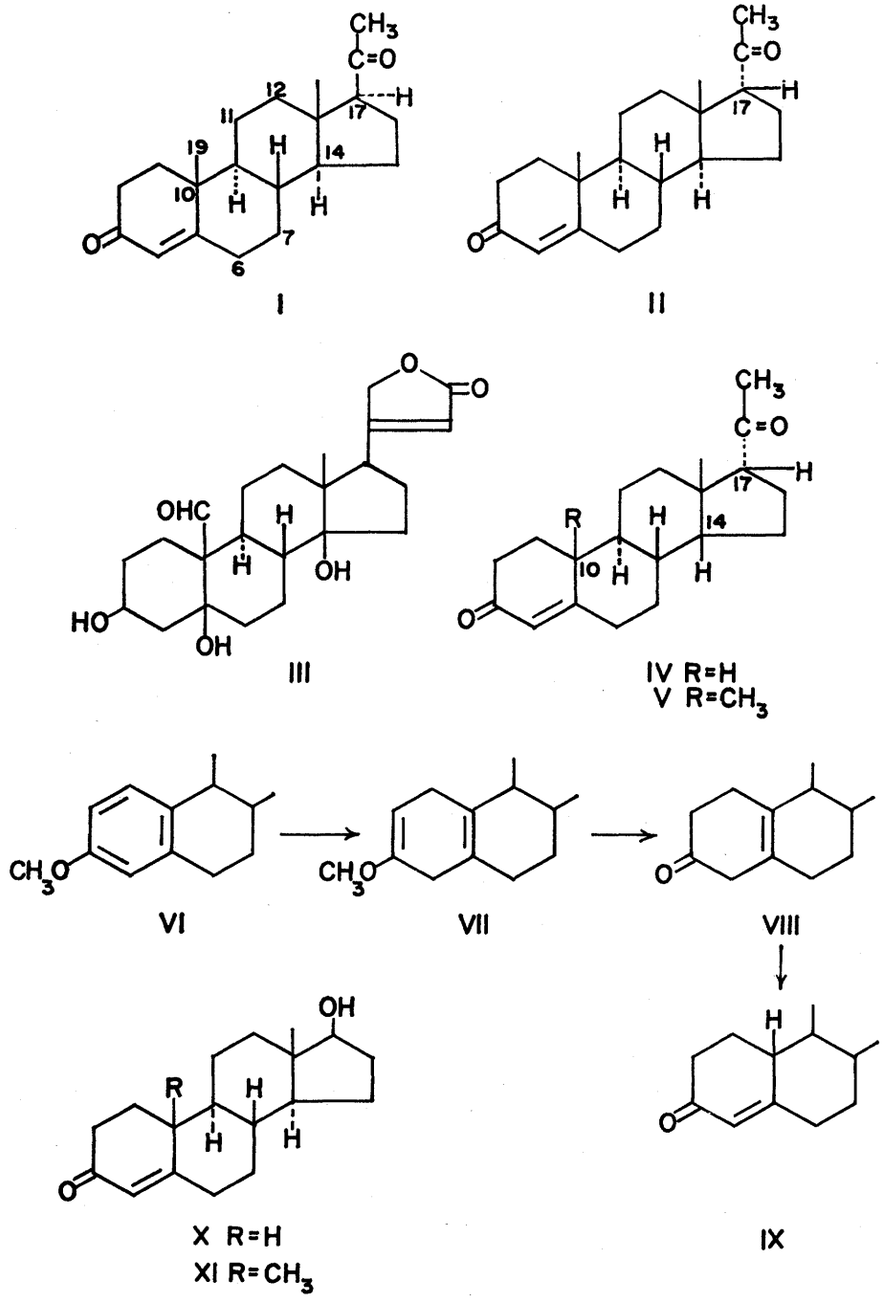
In 1944, Ehrenstein (*8*), at the University of Pennsylvania, reported the multistage transformation of the cardiac aglycone strophanthidin (III) to an oily mixture of stereoisomers of "19-norprogesterone." The purpose of that work was to remove the angular methyl group, carbon No. 19, attached to position 10 of structure I and to examine the effect of such a structural change upon progestational activity. The chemical steps involved isomerization of two and perhaps three asymmetric centers (positions 17, 14, and perhaps 10 in IV); this seemed unfortunate, since it had been shown earlier (*7*) that even inversion just at carbon No. 17 (see II) abolishes biological activity. It was most surprising, therefore, to find that this oily material, when tested in two rabbits (*9*), exhibited the same biological activity as progesterone itself. In view of the extremely poor overall yield (0.07 percent), insufficient material was available for further study (*10*).

Prompted by these unexpected biological results, a Swiss group (*11*) undertook the synthesis of 14-iso-17-isoprogesterone (V), since its "wrong" stereochemistry at positions 14 and 17 mimicked that of Ehrenstein's (*8*) material (IV) and it seemed conceivable that inversion of the stereochemistry of progesterone (I) at both carbon No. 17 and carbon No. 14 might have been responsible for the activity of Ehrenstein's substance (IV). However, the pure, crystalline 14-iso-17-isoprogesterone (V) proved (*11*) to be devoid of progestational potency and thus raised the intriguing possibility that it was the removal of the angular methyl group (compare IV with V) that was the key factor, and that progestational activity, therefore, was not as structure-specific as had been imagined.

Synthesis of 19-Nor Steroids

The likelihood that the absence of the angular methyl group was associated with high biological activity became more remote when, 2 years later, Birch (*12*) described the synthesis of 19-nortestosterone (X)—a substance which was identical in every stereochemical detail (*13*) with the natural male sex hormone testosterone (XI), but which exhibited considerably lower androgenic activity (*14*) than the parent hormone (XI). The key step in Birch's synthesis was the reduction, by the metal-liquid ammonia procedure, of an appropriate aromatic ether (for example, VI) to the dihydroanisole VII. Such enol ethers can be cleaved, upon mild treatment with acid, to the β,γ-unsaturated ketone VIII, while stronger acid or base results in complete conjugation to the α,β-unsaturated isomer (IX).

Birch's results (*14*) in the androgen series implied that removal (X → XI) of the carbon No. 19 angular methyl group in an intact steroid hormone is not necessarily associated with an increase in biological activity. Nevertheless, in view of our great interest at that time in progestationally more potent steroids, we decided to undertake the synthesis of authentic 19-norprogesterone (XIII) with the correct stereochemistry at all centers. The requisite starting material for such a synthesis by means of the general Birch metal-ammonia procedure (VI → VII → VIII → IX) is the progesterone analog XII, in which ring A is aromatic. Fortunately, this substance had been synthesized in 1950 in our laboratory (*15*) in connection with another investigation, and it proved to be a relatively simple matter to transform it into crystalline 19-norprogesterone (XIII) (*16*), which differed from the natural hormone (I)



only in the replacement of the angular methyl group by hydrogen. The substance was found (*17*), by injection, to possess between four and eight times the progestational potency of the natural hormone (I), as determined by the Clauberg assay, and thus constituted the most potent progestational substance known at that time.

Of particular interest, therefore, was the removal of the angular methyl group in 17α-ethynyltestosterone (XIV). Chemically (compare XI with XIV), this substance is a close relative of testosterone (XI), whose androgenic activity is apparently reduced (*14*) when its carbon No. 19 angular methyl group is eliminated (see X). However, biologically it should be classified among the progestational hormones, because the observation had been made (*18*) many years ago that 17α-ethynyltestosterone (XIV), given orally, was an effective progestational agent, although less active than progesterone (I) administered by the parenteral route. Since the biological potency of progesterone (I) was augmented greatly upon loss (I $\rightarrow$ XIII) of its angular methyl group (*16*), we argued that progestational activity of orally ingested 17α-ethynyltestosterone (XIV) might be similarly enhanced after elimination of its carbon No. 19 angular methyl group. This prediction was fully confirmed in late 1951, when we successfully transformed the estrogenic hormone estrone (XVI), in seven steps, into 19-nor-17α-ethynyltestosterone (XV) (*19*).

The initial biological results, reported in 1952 (*19*), indicated an extremely high order of progestational potency of the compound when it was administered orally and thus prompted us to submit the substance to various investigators for extensive biological (*20*) and clinical (*21*) scrutiny. The clinical investigations completely supported the conclusion, based on the earlier animal studies, that removal of the carbon No. 19 angular methyl group from progestationally active steroids results in increased potency. 19-Nor-17α-ethynyltestosterone (XV) (*19*) was thus the first 19-nor steroid to find clinical application.

These results prompted us to undertake the more laborious synthesis of the 19-nor analogs of the adrenal cortical hormones deoxycorticosterone (XVIII) and hydrocortisone (XX). While removal of the angular methyl group (*22*) in the former (XVIII $\rightarrow$ XVII) caused an increase in the mineralocorticoid activity, a diminuition of glucocorticoid potency was observed when the angular methyl group of hydrocortisone (XX) was removed (XIX) (*23*). One can conclude, therefore, that removal of the angular methyl group—an apparently trivial change on paper though a highly involved one in the chemical laboratory—may increase or diminish biological activity, depending upon the type of steroid hormone with which one is dealing.

Chemical Structure and Oral Inhibition of Ovulation

Slightly more than a year after our initial report (*19*) of the synthesis and biological activity of 19-nor-17α-ethynyltestosterone (XV), Colton (*24*) recorded, in a patent application, the synthesis of its β,γ-unsaturated isomer (XXI), which is an intermediate (see VII $\rightarrow$ VIII $\rightarrow$ IX) in the usual Birch reduction (*12*). These two substances (XV and XXI) were the first 19-nor steroids to be studied by Pincus and his collaborators in animals (*25*) and

human females (*26*) as agents for inhibition of ovulation; they were found to be highly effective when administered by the oral route, as was to have been expected on the basis of assays, reported earlier (*19, 20*), of progestational activity in animals. This initial clinical paper by Rock, Pincus, and Garcia (*26*) led to a veritable flood of clinical studies and publications (for leading references, see *4*), which was followed by the introduction of these two substances into clinical practice—first as effective oral progestational agents and, a few years later, as specific oral contraceptive agents.

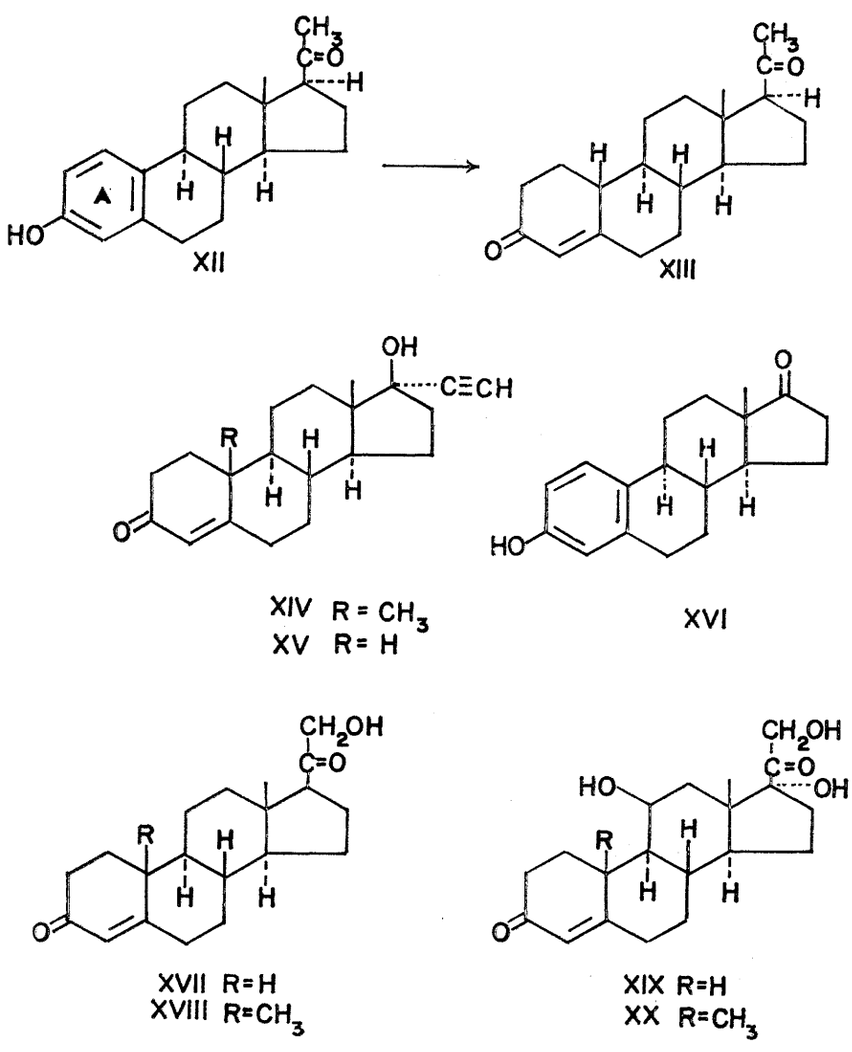
The fact that 19-nor-17α-ethynyltestosterone (XV) (*19*) and its β,γ-unsaturated isomer (XXI) (*24*) exhibit qualitatively the same type of biological activity is not surprising, since the conversion of the β,γ-unsaturated ketone XXI to the α,β-unsaturated isomer XV is usually effected in the laboratory with acid and also occurs to an appreciable extent upon exposure to human gastric juice (*27*). Similarly, the high progestational activity associated with the acetate at carbon No. 17 (XXII) (*28*) of 19-nor-17α-ethynyltestosterone (XV)—another clinically employed oral contraceptive (*29*)—is probably associated with in vivo fission of the ester linkage to the free alcohol XV.

More recently, two other 19-nor steroids have been introduced into clinical practice as oral contraceptive agents—the 3-deoxo analog XXIII (*30*) and the diacetate XXIV (*31*)—but as yet there is no evidence available to indicate whether their activity is *sui generis* or due to prior in vivo conversion into 19-nor-17α-ethynyltestosterone (XV).

Once the myth of the supposed great chemical specificity of progestational action had been destroyed, a large number of divers steroids were screened for progestational and antiovulatory activity. A detailed survey of the relationship between these steroid structures and biological potency has been published by Kincl and Dorfman (*32*), but for the purposes of this review it is only necessary to consider those few compounds which have so far resulted in clinically utilized oral contraceptives.

In the foregoing discussion of 17α-ethynyltestosterone (XIV) (*18*) as the reference substance having progestational activity when given orally, it was noted that removal (*19*) of the angular methyl group attached at position 10 resulted in greatly increased activity. Another chemical manipulation which has a similar effect is the addition, rather than the removal, of a methyl group in certain selected loci. A relevant example is 6α,21-dimethyl-17α-ethynyltestosterone (XXV), which has been shown (*33*) to be superior to the unmethylated parent XIV in terms of progestational activity. It is now used as a clinically effective oral contraceptive.

Two other oral contraceptive agents (XXVII, XXVIII), which have been introduced into clinical practice in the United States only during the past year, represent chemical modifications of the progesterone (I) rather than the 17α-ethynyltestosterone (XIV) molecule. The development of these substances was prompted by the observation (*34*) that introduction of an acetoxyl substituent at carbon No. 17 of progesterone confers appreciable progestational activity, relative to that of the parent hormone (I), when the substances are administered orally. The resulting 17α-acetoxyprogesterone (XXVI) was not sufficiently active in the human to lead to production of a drug of wide clinical acceptability, but introduction of further substituents, such as a 6α-methyl group (*35*) and, especially, a 6-chlorine atom, together with an additional double bond (*36*), produced the highly active 6α-methyl-17α-acetoxyprogesterone (XXVII) and 6-chloro-6-dehydro-17α-acetoxyprogesterone (XXVIII), which are now used as oral contraceptive agents. There is little doubt that several other, related steroids, which have shown promise in laboratory experiments, will be added in the not-too-distant future to the list of clinically efficacious oral contraceptives. One of them—the analog of XXVII in which an additional double bond (*35*) is present between carbon atoms 6 and 7—has already been introduced in Europe.



Chemical Supply and Clinical Demand

At present, it is estimated, at least 7 million women are using steroid oral contraceptives. Of these, in the United States 19-nor-17α-ethynyltestosterone (XV) and its two chemical relatives, XXI and XXII, account for over 80 percent of the consumption, while the remainder is apportioned among XXV, XXVII, and XXVIII. The administration of oral contraceptives only received government approval in 1960, and it is very likely that the number of users will rapidly increase beyond the 7 million figure estimated for 1965. These prospects immediately raise two questions. (i) Can the chemist satisfy the demand? (ii) Is it worth while to synthesize additional compounds as potential candidates for oral contraceptives? The answer to both these questions is unqualifiedly in the affirmative, and it seems appropriate to end this historical survey with answers to both questions.

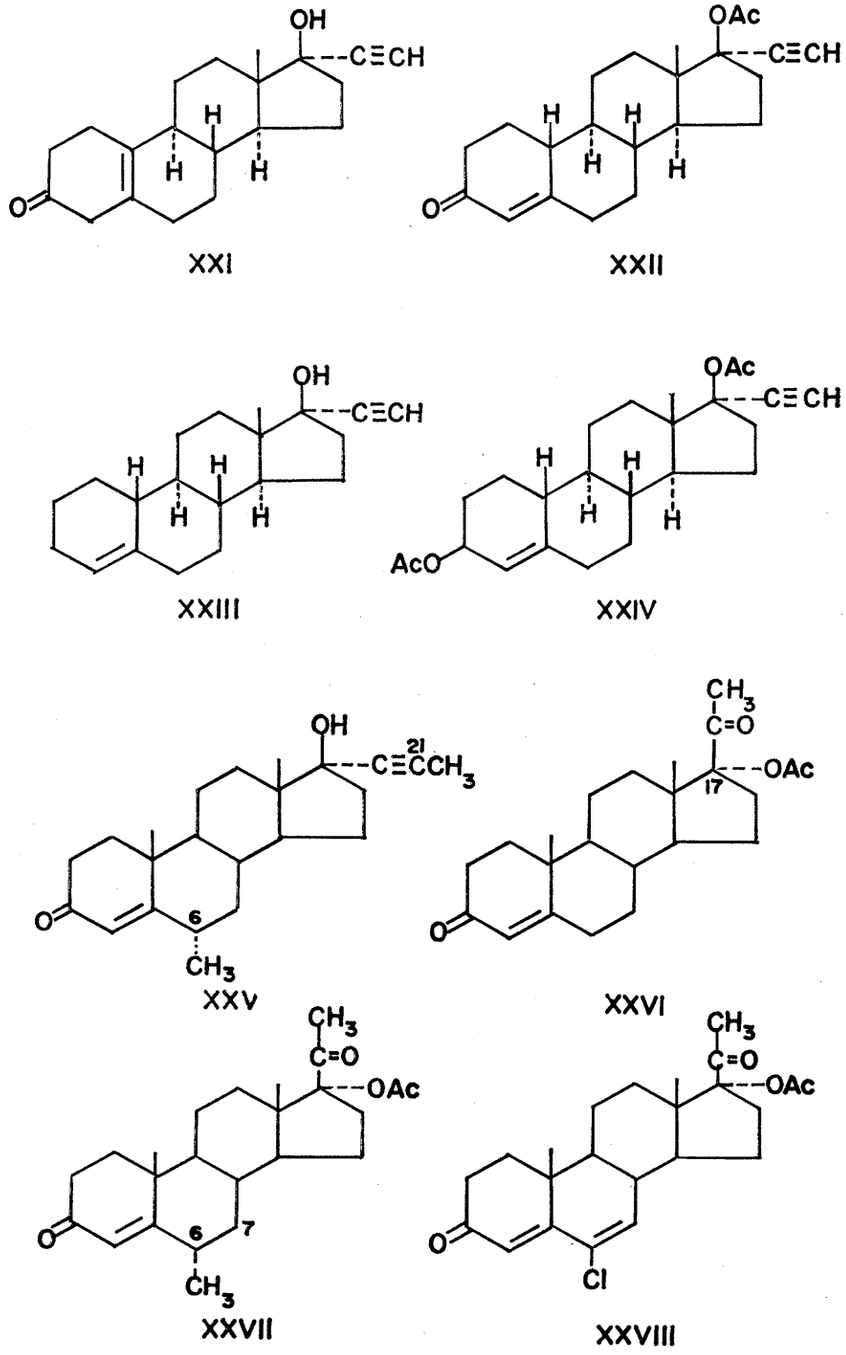
At present all the synthetic steroid drugs, irrespective of their ultimate clinical utility, are prepared by partial rather than total synthesis. The term *partial* implies that the chemist starts with one steroid and transforms it into another, while "total" synthesis refers to the *de novo* construction of the steroid skeleton, commencing with simple chemicals.

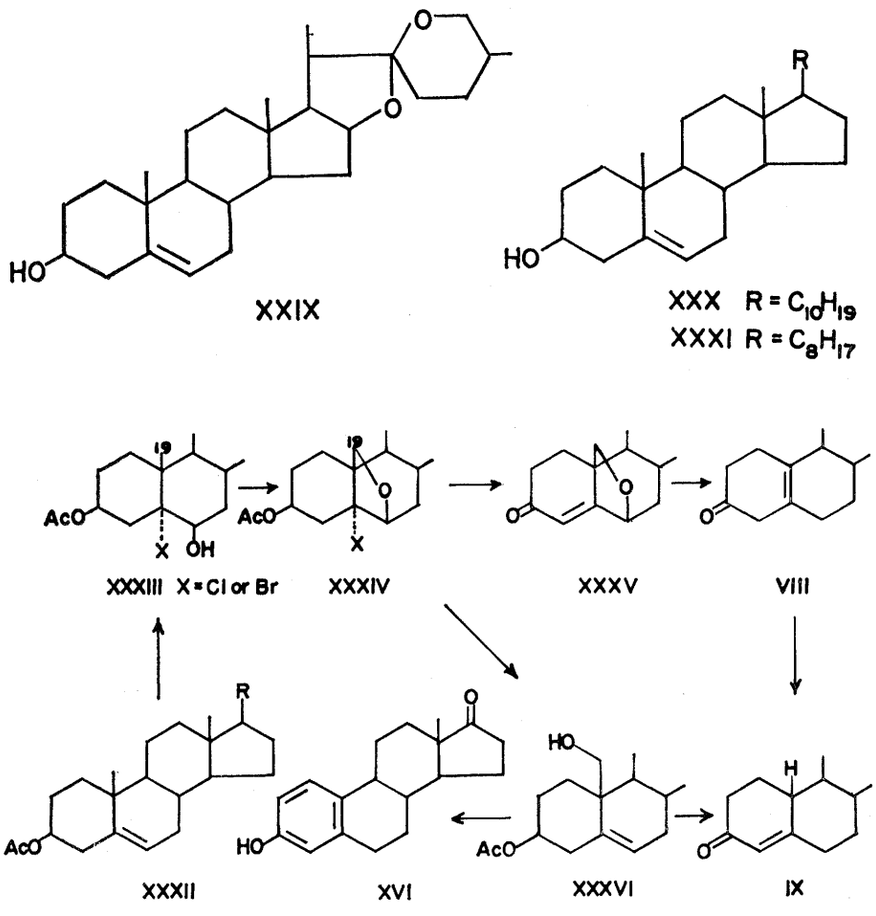
In the field of oral contraceptives, the most common starting material is diosgenin (XXIX), a naturally occurring plant sapogenin; steroids such as the soya sterol stigmasterol (XXX) and, to a lesser extent, the animal sterol cholesterol (XXXI) are also used.

As noted above, over 80 percent of the presently employed oral contraceptive agents are 19-nor steroids; until recently, all of them were synthesized by a modified Birch reduction (see VI → VII → VIII → IX), which required the female sex hormone estrone (XVI) as starting material. This is another illustration of the familiar theme in steroid chemistry that a given hormone (in this instance, estrone) eventually becomes an intermediate in the synthesis of a chemically more complex drug. Several multistage chemical transformations of diosgenin (XXIX) to estrone (XVI) have been worked out in the past (*5*), but in view of the complexity of the operations and the necessity of several subsequent steps to 19-nor steroids [notably, the metal-liquid ammonia reduction (VI → VII)], doubt has been expressed from time to time that such partial syntheses could keep up with the rapidly increasing demand, and it has been thought that total synthetic procedures would have to be introduced. This conclusion proved to be false, and it is very unlikely that the situation will change during the next few years, in spite of the fact that many total syntheses (*37*) of estrone (XVI) and of 19-nor steroids have been accomplished in the laboratory. The reasons for this prognosis are threefold.

First, as the demand for such contraceptive agents rose, continuing clinical experimentation demonstrated that the effective dose was much lower than had been assumed originally. Thus, while the daily regimen in 1960 was based on a 10-milligram pill, current work has demonstrated that 1 milligram and, very probably, even lower dosages are equally effective. Therefore, the demand, in kilograms of steroids, did not rise at all in proportion to the rapidly increasing number of users.

Second, the commercial importance





of steroid oral contraceptives prompted extensive work on alternate partial syntheses, which would obviate the use of estrone (XVI) as an intermediate. A very efficient procedure (*38*) was discovered virtually simultaneously by two groups working independently in Mexico and in Switzerland, who approached the problem through chemical functionalization of the angular methyl group at position 10. Addition of hypobromous or hypochlorous acid to the double bond of cholesterol acetate (XXXII, R = C_8H_{17}) or other readily available steroids (XXXII, R = O or $COCH_3$) afforded the halohydrins XXXIII, which, upon oxidation with lead tetraacetate, led to the versatile oxide intermediate XXXIV, in which functionalization of the angular methyl group had thus been effected. By simple chemical steps, such oxides as XXXIV can be transformed into the intermediates XXXV and XXXVI, which in turn are convertible into the 19-nor steroid types VIII and IX. The need for metal-ammonia reductions is thus avoided.

Third, a most significant development occurred in 1965 which promises to change the supply problem drastically and to make total synthetic procedures (*37*) a very unlikely practical route to synthesis of the presently employed oral contraceptive agents. Sih and his collaborators (*39*) discovered that the intermediate XXXVI, available (*38*) in three steps (XXXII → XXXIII → XXXIV → XXXVI) from cholesterol acetate (XXXII, R = C_8H_{17}), was transformed by a soil microorganism in 72-percent yield directly to estrone (XVI). Alternatively, the same organism could convert in one step the chloroepoxide (XXXIV) of the cholesterol series (R = C_8H_{17}) into the unsaturated keto epoxide (XXXV) of the 17-ketoandrostane series (R = O). These two chemical-microbiological syntheses thus offer by far the shortest and most efficient routes to 19-nor-17α-ethynyltestosterone (XV) and to the related steroid contraceptive agents XXI, XXII, XXIII, and XXIV.

The second question which I posed was whether it is worthwhile, from a scientific standpoint, to synthesize additional potential oral contraceptives, in view of the fact that nine different chemical entities are already being employed for such purposes in clinical practice. Of the numerous arguments that can be advanced in support of an affirmative answer, the following is probably the most cogent one.

The relatively recent introduction of steroid oral contraceptive agents and the surprisingly rapid acceptance of these substances by women has greatly stimulated research in this area of conception control. The development of nonsteroidal chemicals, which would probably be cheaper than the present steroids, may be desirable, although cost of the biologically active ingredient is not the problem which is currently inhibiting the use of these agents. At present, it is assumed that all the oral contraceptives work through inhibition of ovulation. That this is not the only biological mechanism whereby they can operate was recently demonstrated clinically (*40*) when it was found that 6-chloro-6-dehydro-17α-acetoxyprogesterone (XXVIII) can prevent conception when given in doses that do not inhibit ovulation. Pincus (*4*) and more recently Rudel and Kincl (*41*) have summarized the diversity of biological effects of progesterone (I) and other steroidal progestational agents. There is no reason to believe that it will not be possible to synthesize substances, steroidal or nonsteroidal in nature, in which the two activities can be separated—substances which may thus offer alternative and possibly preferable means of oral contraception. It is likely that, as in the past, the next major advance in this area of conception control will originate in the chemical laboratory.

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NEWS AND COMMENT

The Krebiozen Case: What Happened in Chicago

Chicago. The main question left standing in the Krebiozen case after 15 years of controversy and a 9-month criminal trial ending in acquittal for all the principals is how so many people could spend so much time on a problem so limited and come up with so little. The federal government prosecuted Andrew Ivy, Stevan Durovic, and two of their associates, Durovic's brother Marko and a Chicago physician, William Phillips, with all the zeal of the crusaders pursuing infidels. But, despite the government's efforts, the record is thin and full of contradictions. Immediately after the trial the Food and Drug Administration and the American Medical Association issued statements stressing that the verdict in no way altered their scientific judgment that the alleged anticancer agent is therapeutically worthless. Whether the public will accept that view, however, is open to doubt. As a challenge to public policy, the question of Krebiozen is plainly not yet settled.

To understand what happened at the trial it is important to realize how badly the government wanted to win the Krebiozen case. The passion was generated in part by certain characteristics of the Food and Drug Administration, in part by the peculiar intractability of the Krebiozen problem. The FDA has long had difficulty maintaining its scientific capability and in navigating the tricky shoals of drug regulation. But it has been unfailingly proud of its record against quackery: the agency is happiest when it is left to the fight against frauds.

In the case of Krebiozen, the FDA had much at stake. Throughout the 1950's, while Krebiozen, already controversial, was being distributed as an experimental drug, the agency took the position that the problem belonged in other hands. But in 1963 it became engaged in a full-scale investigation of the drug. FDA's involvement began as an effort to help the National Cancer Institute gather data on Krebiozen-treated patients to determine whether a long-sought official test of the drug seemed indicated (*Science* 21 June, 28 June, 5 July, 1963). It soon spread into an ambitious campaign to reconstruct all aspects of the drug's clinical, financial, and chemical history.

By the fall of 1963, FDA had reached its scientific conclusions. The Krebiozen powder, the agency announced, had been identified by several chemical tests as creatine. The contents of Krebiozen ampules were identified as mineral oil, with minute amounts of two other substances, amyl alcohol and 1-methylhydantoin, found in ampules shipped in 1963. FDA's chemical analysis was soon supported by the findings of the National Cancer Institute that Krebiozen "does not possess any anticancer activity in man."

These announcements had two effects. First, they put FDA's scientific reputation on the line: if Krebiozen were ever demonstrated to be something other than creatine, the agency, fighting hard for a progressive image, would find itself aligned instead with all the discredited reactionaries in the history of science. Second, no bureaucracy is sensitive to ambiguity, but the findings completely obliterated whatever appreciation of the complexities of the Krebiozen mystery FDA officials had previously been able to muster. From then on, they treated it as an open-and-shut case. If Krebiozen was creatine, it was obviously fraudulent. If it was fraudulent, the men marketing it were not erring scientists but crooks.