PROGRESS IN THE SYNTHESIS OF POLYCYCLIC NATURAL PRODUCTS

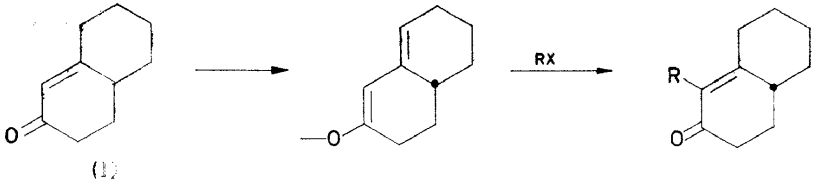
G. STORK

Columbia University, New York, U.S.A.

We will examine here two problems which have occupied our attention recently. Both of these are concerned with the construction of polycyclic natural products and represent some results of our efforts to design new synthetic methods of some generality.

The first of these problems concerns the fusion of a cyclohexenone ring on to a pre-existing system which will be assumed here to be cyclic. This is a synthetic operation which has proved of very great value in the elaboration of complex natural products. We will focus here on the particular approach which consists in utilizing an α, β- unsaturated ketone such as (I), *Figure 1* and introducing by alkylation a group R which has to be a suitable array capable of transformation into a 3-ketoalkyl group.

The interest in this particular method of annelation is first that the double bond of the enone serves to establish the position of alkylation, secondly that the proper 3-ketoalkyl precursor allows either reduction of the enone double bond or further alkylation reaction, should an angular substituent be required in the eventual annelated system (*Figure 2*). A



(I)

Figure 1

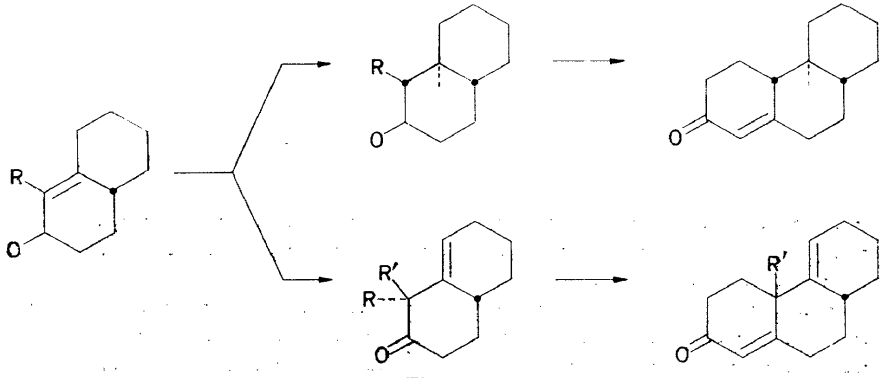


Figure 2

further flexibility follows from the possibility of reversing the order of introduction of the potential 3-ketoalkyl chain and the angular substituent, depending on the dictates of the relevant stereoelectronic factors (*Figure 3*).

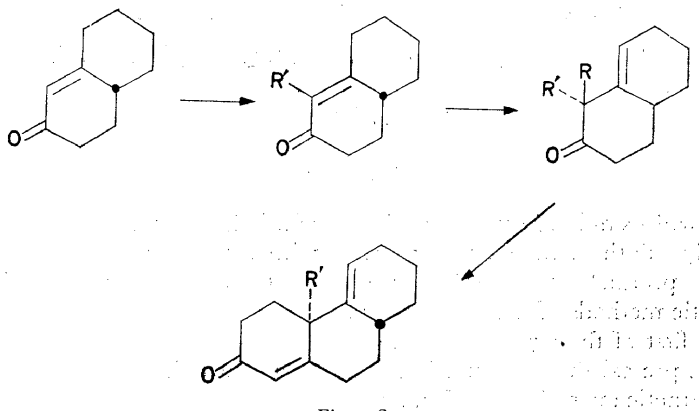


Figure 3

We do not, of course, wish to imply that the construction of an enone with a potential 3-ketoalkyl group on the double bond α to the carbonyl cannot be achieved by other means. We ourselves introduced, several years ago, another method for this purpose[1]. This is illustrated in *Figure 4*.

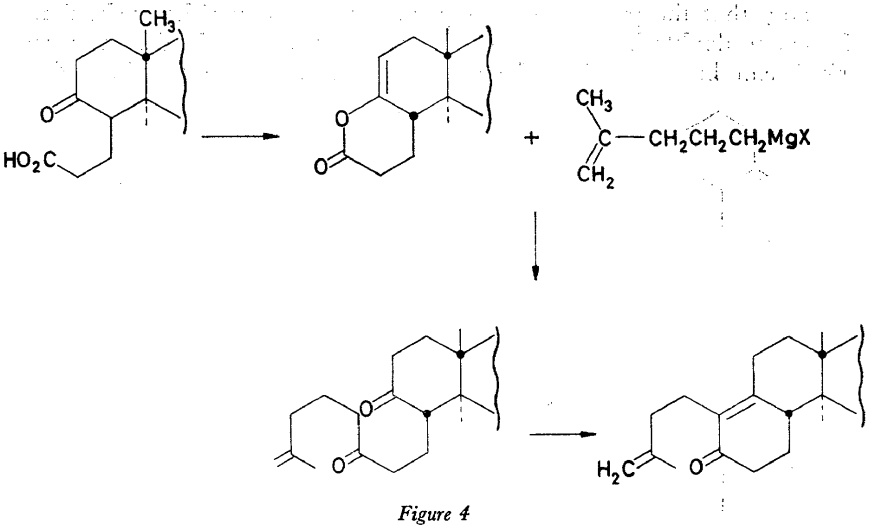


Figure 4

A useful variant of this method has recently been published[2]. We will not, however, consider these other approaches further here, and we now return to the enone alkylation procedure.

A possible structure for the 3-ketoalkyl precursor to be introduced by this route has to meet a number of requirements. It must be an alkyl halide which is stable to the basic alkylation conditions; it must, as already

mentioned, permit either reduction of the enone double bond or further alkylation; and its latent 3-ketogroup should be easily unmasked.

The construction of ring *A* of the steroids from a tricyclic enone such as (II), *Figure 5*, is archetypal and the first successful use for this purpose of the enone-alkylation approach was reported by us several years ago[1],

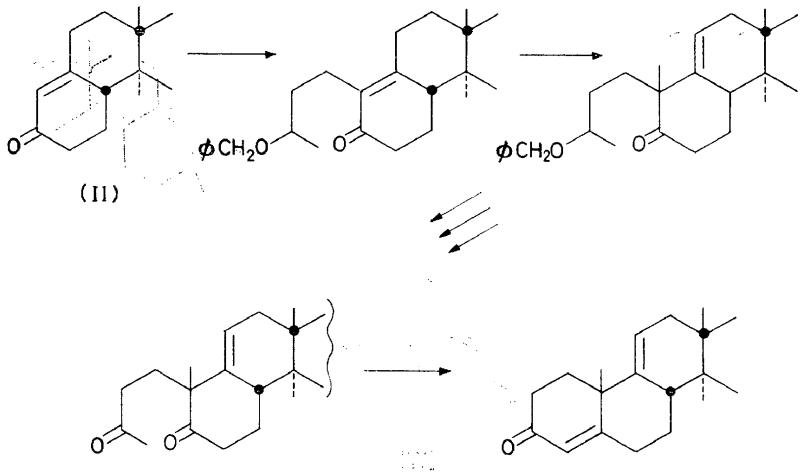


Figure 5

following the principles adumbrated above. The potential 3-ketobutyl group we then devised was 3-benzyloxybutyl bromide, the benzyloxy group being eventually cleaved with lithium-ammonia to a secondary alcohol which was then oxidized to the required carbonyl function. This is not a fully satisfactory method: the benzyloxybutyl group has the disadvantage of introducing an irrelevant, albeit temporary, asymmetric centre with the necessary production (unless the halide be initially resolved) of a diastereoisomeric mixture. An additional difficulty is the rather

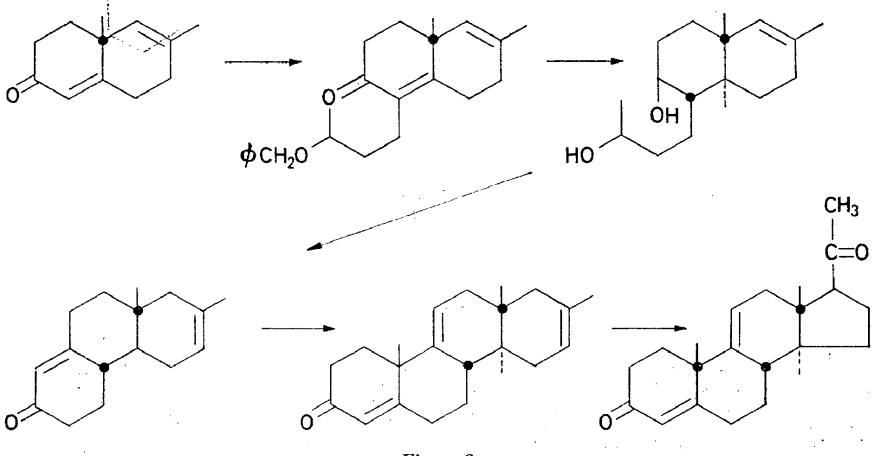
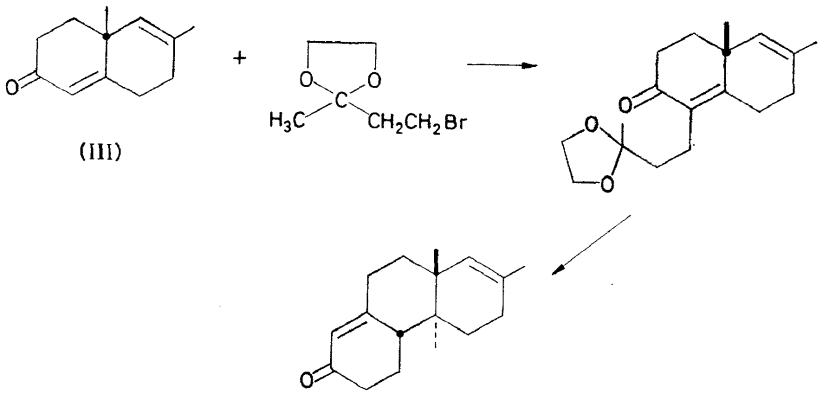


Figure 6

cumbersome generation of the side-chain keto group. We nevertheless used this method some years ago for a total synthesis of $\Delta^{9,11,16}$ bisdehydroprogesterone[3] (see *Figure 6*).

Possibly the simplest and most desirable halide which might be considered, the ketal of 4-bromo-2-butanone, can sometimes be used[4]. We have, for instance, carried out the transformation (III) to (IV) (*Figure 7*) by its



(III)

(IV)

Figure 7

agency[5]. The low reactivity of that halide and its tendency to dehydrohalogenate, presumably both the result of the strong electron withdrawing effect of the ketal oxygens, preclude its general use.

In recent years, considerable success has been obtained with this approach

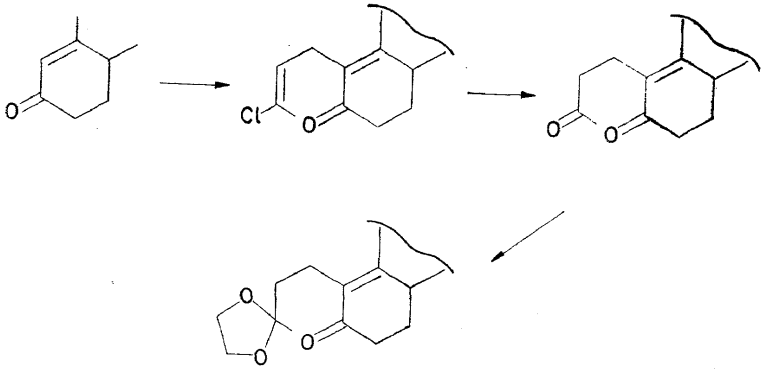
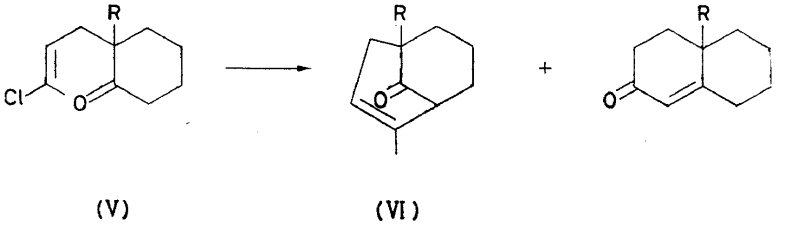


Figure 8

to the construction of the steroid ring *A* by the use of 1,3-dichloro-2-butene (see *Figure 8*), notably in connection with the enamine alkylation synthesis[6]. This method suffers from the need to use concentrated sulphuric acid for the hydrolysis of the vinyl chloride system. It has the further drawback

that with *saturated* ketones the sulphuric acid treatment leads to an undesired cyclization, sometimes as the main product[7] ((V) to (VI) in *Figure 9*).

We have devised a new way of "storing" the necessary 3-ketoalkyl group within a type of alkylating agent which is quite different from those previously used for this purpose. We will illustrate this first with the addition



(V) (VI)

Figure 9

of a ring to 9-methyl-1, 6-octalindione (*Figure 10*). For reasons which will become clear shortly, we came to the conclusion that 4-halomethyl-3-alkylisoxazoles could be excellent reagents for our purpose and we were very encouraged to find that these substances were, in fact, known and relatively easily available[8]. Alkylation of the sodium enolate of 9-methyl-1,

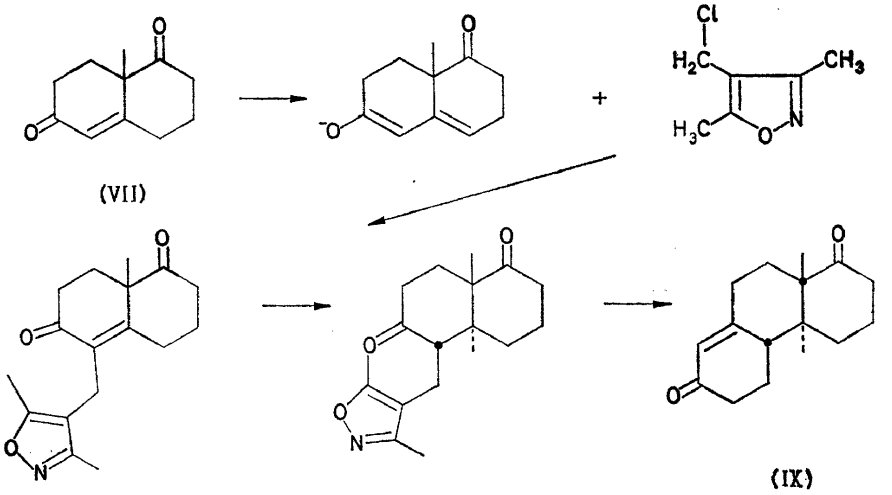


Figure 10

6-octalindione (VII) with 3,5-dimethyl-4-chloromethylisoxazole leads to the alkylated product (VIII) in good yield. The bulk of the alkylating agent undoubtedly helps reduce the extent to which undesirable dialkylation takes place.

Now, the isoxazole ring is quite useful because its stability to bases, acids, oxidizing agents, *etc*, could allow various transformations in other parts of the molecule, should such be required. In the present case, however,

we need only reduce the enone double bond, and this is readily achieved with palladium and hydrogen. The isoxazole ring can also be cleared by hydrogenation, and we will return to this later, but in this case hydrogenation was carried out only to saturation of the double bond with the production of the expected *trans*-decalone.

It is now merely necessary to transform the isoxazolylmethyl portion into the desired annelated system. This is readily done. Addition of triethyloxonium fluoroborate, followed by treatment with base, leads to the required tricyclic enone (IX). The presumed course of the reaction is shown in *Figure 11*. It will be noted that an intermediate is the symmetrical

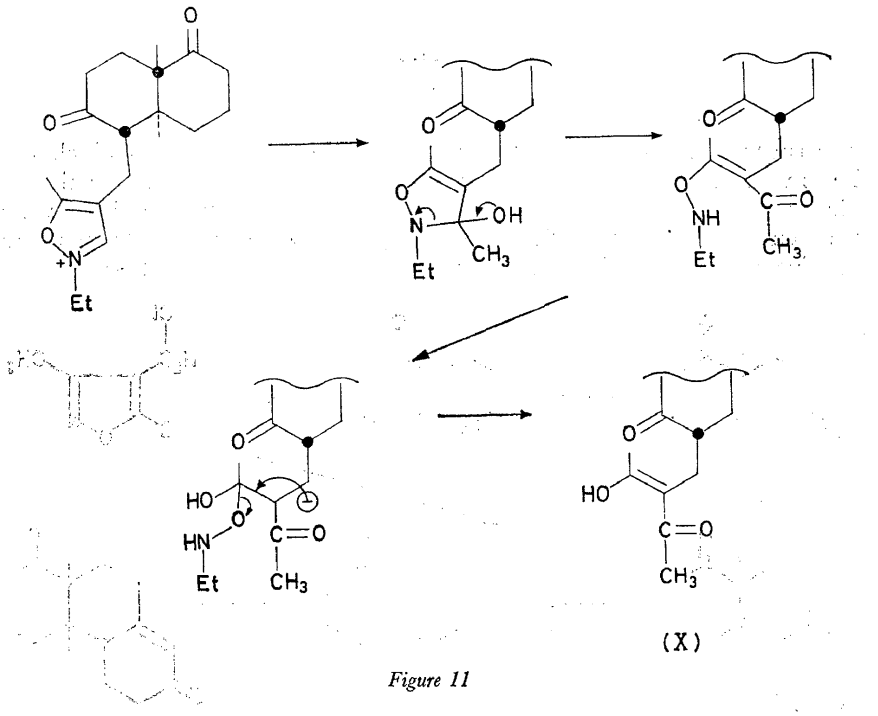


Figure 11

β-diketone (X). As shown on *Figure 12*, the latter could cleave either before or after cyclization. In the former case the result can only be the anticipated tricyclic enone (IX). In the second case, the β-diketone has become asymmetric and its cleavage can take place in two directions, leading not only to the desired annelated substance (IX) but also to the diketo acid (XI). The latter is an undesirable by-product although it also could be converted to (IX).

A number of modifications suggested themselves at this point. In one of these, alkylation was effected with another known substance, 3-methyl-4-chloromethylisoxazole, leading as before to the monoalkylated enone (XII), *Figure 13*. The lower degree of substitution of the isoxazole ring in this compound allows an even simpler annelation procedure. Palladium hydrogenation can readily be continued after the absorption of the first

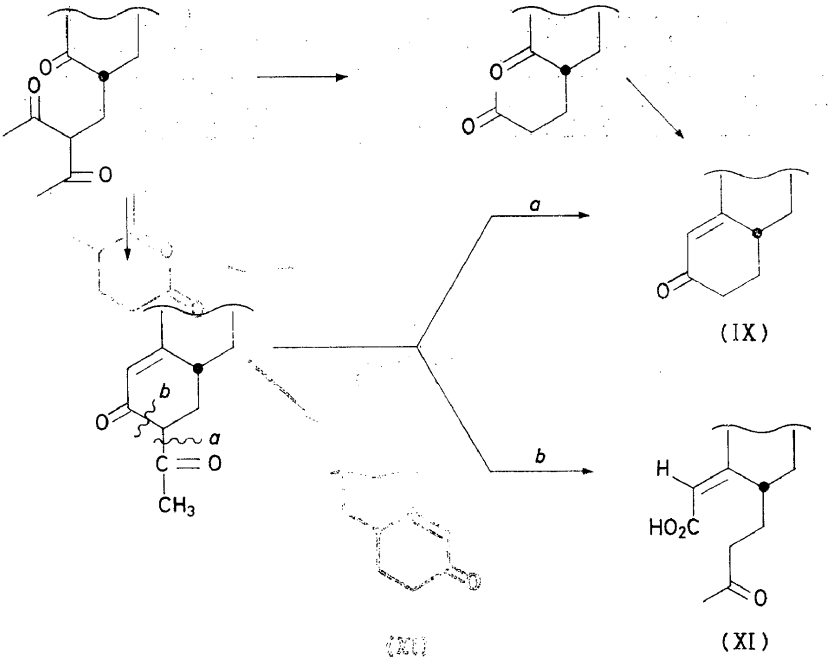
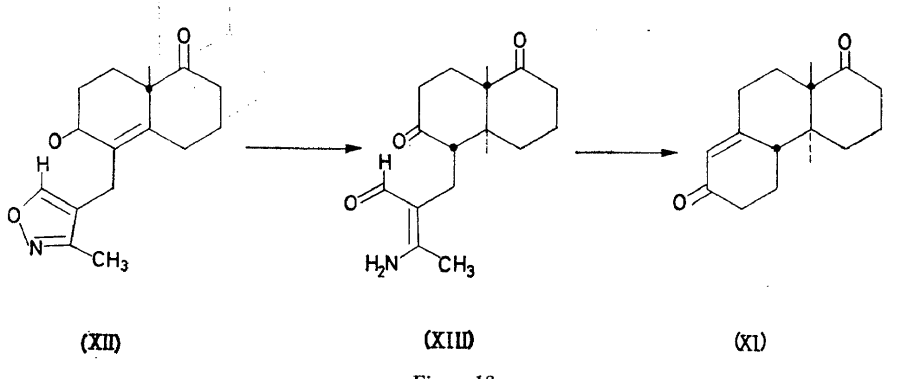


Figure 12

mole of hydrogen. A second mole is taken up and the ring is cleaved to form the crystalline imino ketone (XIII) which is readily converted by treatment with base into the previous tricyclic ketone (IX).

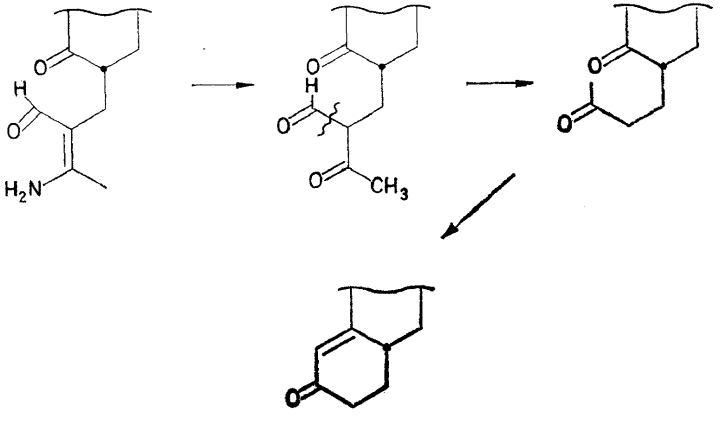


(XII) (XIII) (XI)

Figure 13

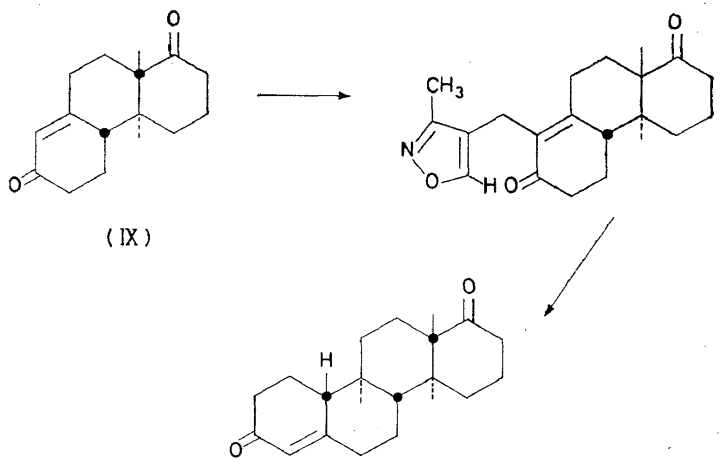
The mechanism of the hydrolysis is outlined in *Figure 14* and it will be noted that the β-dicarbonyl intermediate is no longer symmetrical. Since it is now a hydroxymethylene ketone it can be anticipated that, whether or not cleavage precedes cyclization, formic acid will be lost and no carboxylic acid by-product should be formed. This is indeed the observed result.

Repetition of the sequence on the tricyclic ketone (IX), as shown in *Figure 15*, now led to the known 19-nor-D-homoandrostenedione[9]. This is still not a complete solution, however: the yields in the alkylation step with the monomethylisoxazoles, in contrast to the dimethyl series, are often poor for reasons which are not yet fully understood. We are currently



(IX)

Figure 14



(IX)

Figure 15

pursuing our investigation of these and other isoxazole routes to annelation, in steroids and other areas.

We now turn to the second topic which I would like to discuss. It is concerned with some problems which we encountered in the total synthesis[10]

of the large group of indole alkaloids which is represented by aspidospermine[11] (*Figure 16*). We face here a structural problem coupled with the stereochemical difficulties occasioned by the presence of four asymmetric centres. Both of these problems had to be solved essentially *ab ovo* since no

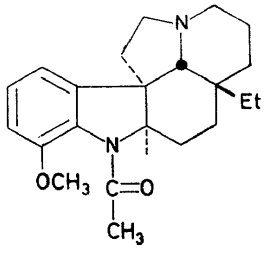
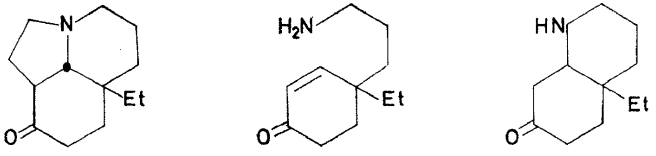


Figure 16

previous synthetic work had been done on this series of alkaloids. The goal of the first part of this investigation was a tricyclic quinolone (*e.g.* (XIV), *Figure 17*) on which the Fischer indole synthesis might be expected to proceed with the desired result. As a suitable precursor of this tricyclic system we



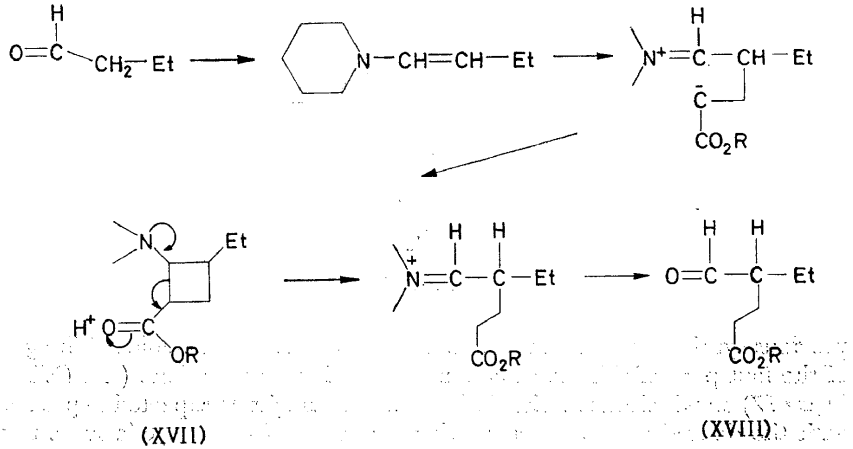
(XIV) (XV) (XVI)

Figure 17

selected the angularly ethylated quinolone (XVI). It appeared to us that a general synthesis of such a system would follow if a simple path to the aminoalkylcyclohexenone (XV) could be devised. This is again a problem involving the construction of a cyclohexenone ring. We were especially interested in it because our earlier discovery that enamines derived from aldehydes readily undergo alkylation with electrophilic olefins[12] appeared to provide an answer as simple as it might be general.

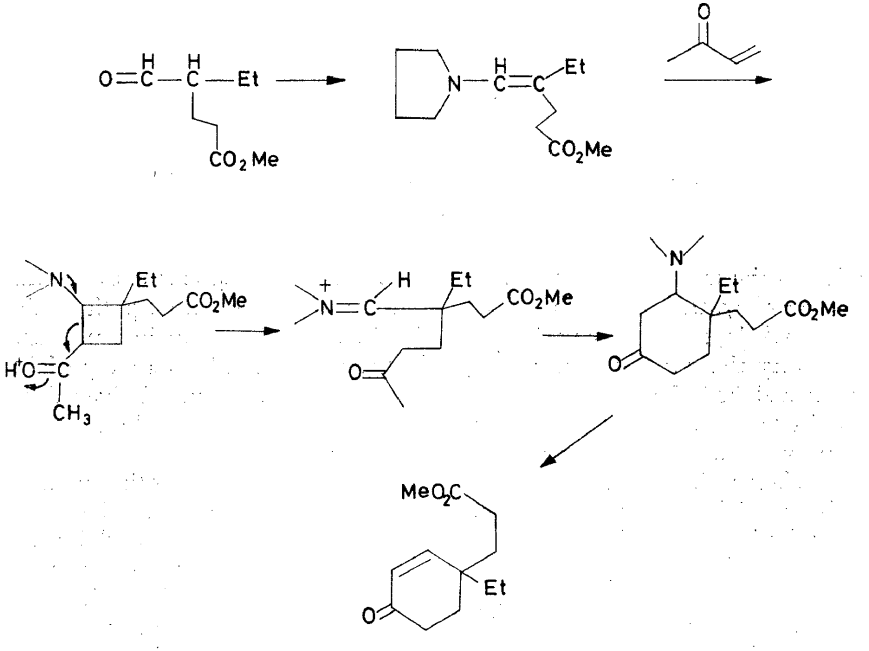
We began the construction as shown in *Figure 18*, by treating the enamine of butyraldehyde with ethyl acrylate. The intermediate in this condensation is undoubtedly, as has been observed in other cases, the cyclobutane derivative (XVII). The latter is readily opened, upon treatment with aqueous acid, to the expected product of this first enamine alkylation reaction, the glutaric half aldehyde (XVIII). Base-catalysed annelation with methyl vinyl ketone might have served to form the desired cyclohexenone, but this was not successful. We were pleased, however, to find that annelation was readily achieved by utilizing again the enamine

alkylation reaction, as shown in *Figure 19*. This now led, after treatment of the adduct with acetic acid, to the cyclohexenone (XIX). Transformation of the propionic ester group to a propylamine (*Figure 20*) is then followed by the anticipated closure to the angularly ethylated hydroquinolone (XX) which is thus obtained as a single crystalline isomer.



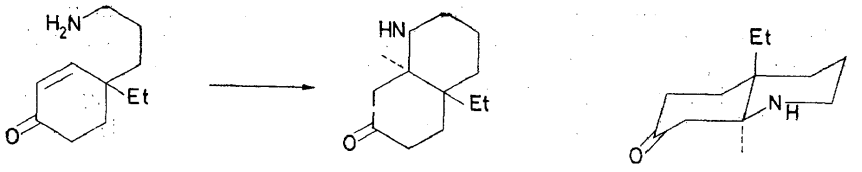
(XVII) (XVIII)

Figure 18



(XIX)

Figure 19



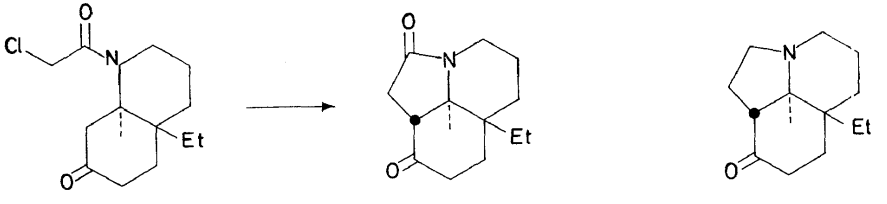
(XX)

Figure 20

The ring fusion of the hydroquinolone can be confidently assigned a *trans* stereochemistry: addition of the amino group to the enone is obviously reversible under the conditions of its formation, and conformational analysis shows that the *trans* system should be the more stable.

It will be noted that this is not the stereochemistry required of the hydroquinoline fusion in the aspidospermine alkaloids, but for reasons which will become clear shortly, this difficulty is only temporary.

The addition of the third ring to our bicyclic system requires alkylation to be carried out selectively on one side of the carbonyl group. We have encountered this problem earlier in connection with annelation in the steroid field. Here, however, a different solution was chosen (*Figure 21*)



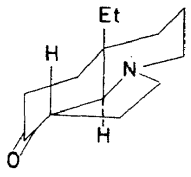
(XXI) (XXII) (XXIII)

Figure 21

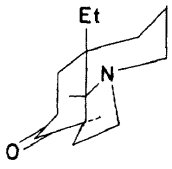
This took advantage of the directed cyclization which initial attachment of the required chain to the nitrogen atom allowed: in the cyclization of (XXI) to (XXII), alkylation is selective on the desired side because it thus involves forming a five- rather than a seven-membered ring. The tricyclic amino ketone (XXII) is obtained in its most stable form: it is recovered unchanged from vigorous acid or base treatment. Reduction of the amide then gives (XXIII).

The system is now more complex than that of the *bicyclic* precursor, but here again conformational analysis leads to the conclusion that the stereochemistry shown in (XXIII), *Figure 22*, should be more stable than that of (XXIV) (by about 1 kcal). It is more difficult to choose between (XXIII) and (XXV) merely on conformational grounds. The decision can, however, be based on the nuclear magnetic resonance (measured on the amide (XXII)) of the tertiary hydrogen next to the nitrogen atom. This shows a 12-cycle splitting by the adjacent hydrogen atom and is consistent with (XXIII) but not with (XXV)[13].

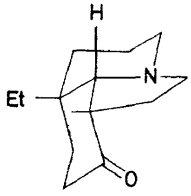
We now return to the stereochemistry required of the final product. The Fischer indole synthesis (*Figure 23*) in the presence of acetic acid, to the extent that it produces angular phenylation, could lead *a priori* to either axial or equatorial addition of the phenyl group to the ring double-bond. We illustrate here the result of axial entry (*cf.* XXVI). Loss of



(XXIII)

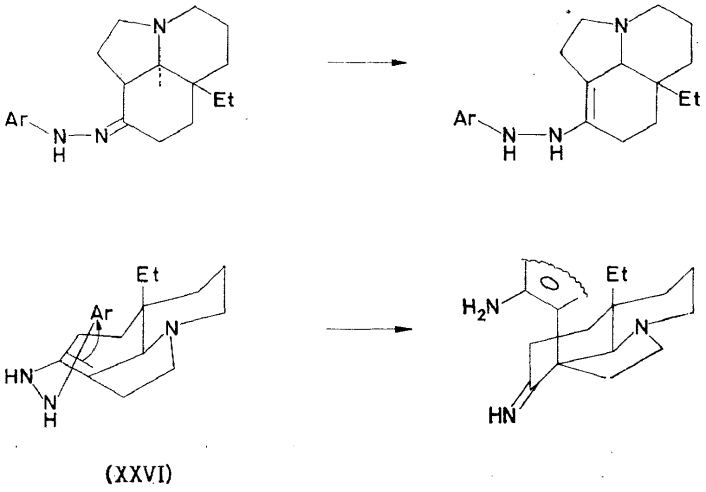


(XXIV)



(XXV)

Figure 22

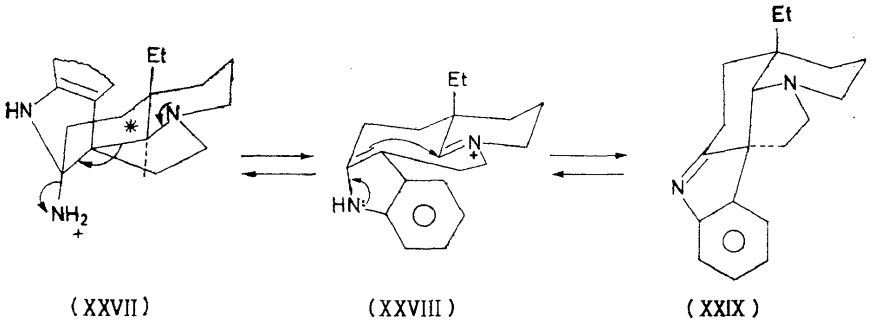


(XXVI)

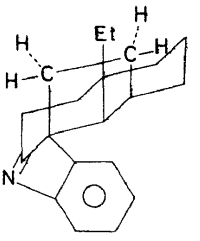
Figure 23

ammonia with the formation of a trigonal carbon atom to produce the final indolenine is possible only if the starred ring (*Figure 24*) becomes a boat. This boat now results, however, in an impossibly strained arrangement of the five-membered nitrogen ring. Under such circumstances, the fragmentation reaction shown in (XXVII) to (XXVIII) would be expected to supervene. It is apparent that the open form (XXVIII) can now reclose to produce any of the possible relative arrangements of the three asymmetric centres. Such a closure would also be reversible, and it is then to be anticipated that the actual indolenine produced will be the *most stable* of the various possible isomers. Since the attachment of the benzene ring *must* be by an equatorial bond in the indolenine, we only have two possibilities, one of which involves a *trans* hydroquinoline system, and the other the desired *cis*.

The further development of this synthesis depends on the fact that the *trans* hydroquinoline system is now the less stable. The necessary equatorial attachment of the phenyl ring in such a *trans* system would require either some strained boat conformation, as already mentioned or, the axial

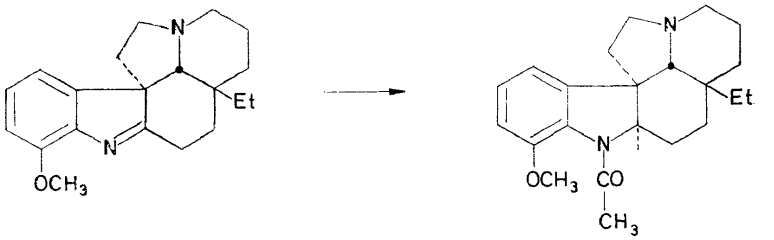


(XXVII) (XXVIII) (XXIX)



(XXVII a)

Figure 24



(XXX)

(XXXI)

Figure 25

orientation of the two carbon bridge to nitrogen as in (XXVIIa) (with consequent very unfavourable interaction with the axial ethyl group).

The expected system, under equilibrium conditions, is then (XXIX) and it is only necessary to reduce it with lithium aluminum hydride and acetylate the product to establish the validity of the conclusion (*Figure 25*). The product is indeed *dl*-aspidospermine (XXX) as shown by various physical measurements, and especially by its mass spectrum. Similarly, using the known sodium borohydride[14] trapping of the open form of the relevant indolenine, the simpler *dl*-quebrachamine[14] (XXXI) could also be synthesized.

In conclusion, it is a pleasure to acknowledge the most important contributions of those whose work I have described: The work on the "isoxazole annelation" was begun by Dr Samuel Danishefsky and is being carried on by Dr Clayton Heathcock. Dr Joseph Dolfini is responsible for the work on the aspidosperma alkaloids.

References

[1] G. Stork, H. J. E. Loewenthal, and P. C. Mukharji. *J. Am. Chem. Soc.* **78,** 501 (1956).
[2] L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède. *Compt. Rend.* 3086 (1963).
[3] Unpublished work by Dr Y. W. Chang.
[4] *cf.* G. Stork and R. Borch. *J. Am. Chem. Soc.* **86,** 935 (1964).
[5] Unpublished work by Dr P. Rosen and J. Pugach.
[6] *cf.* L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and Ph. Dufay. *Tetrahedron Letters* **1961,** 127;
L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and J. Tessier. *Compt. Rend.* **252,** 3903 (1961).
[7] S. Julia. *Bull. Soc. Chim. France* **1954,** 780.
[8] N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskiis. *Zh. Obshch. Khim.* **28,** 2736 (1958).
[9] S. N. Ananchenko, A. V. Platonova, V. N. Leonov, and I. V. Torgov. *Izv. Akad. Nauk, SSSR* **1961,** 1074.
[10] G. Stork and J. Dolfini. *J. Am. Chem. Soc.* **85,** 2872 (1964).
[11] *Inter alia cf.* C. Djerassi. *Pure Appl. Chem.* **6,** 575 (1963).
[12] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell. *J. Am. Chem. Soc* **85,** 207 (1963).
[13] M. Karplus. *J. Chem. Phys.* **33,** 941, 1842 (1960).
[14] K. Biemann and G. Spiteller. *J. Am. Chem. Soc.* **84,** 4578 (1962).