SYNTHESIS AND STRUCTURE OF YOHIMBINE ALKALOIDS

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New methods for the synthesis of yohimbine alkaloids - including both the normal and allo type - have been developed. The structure of alloyohimbine has been revised and some unnatural stereoisomers of yohimbine have also been obtained.

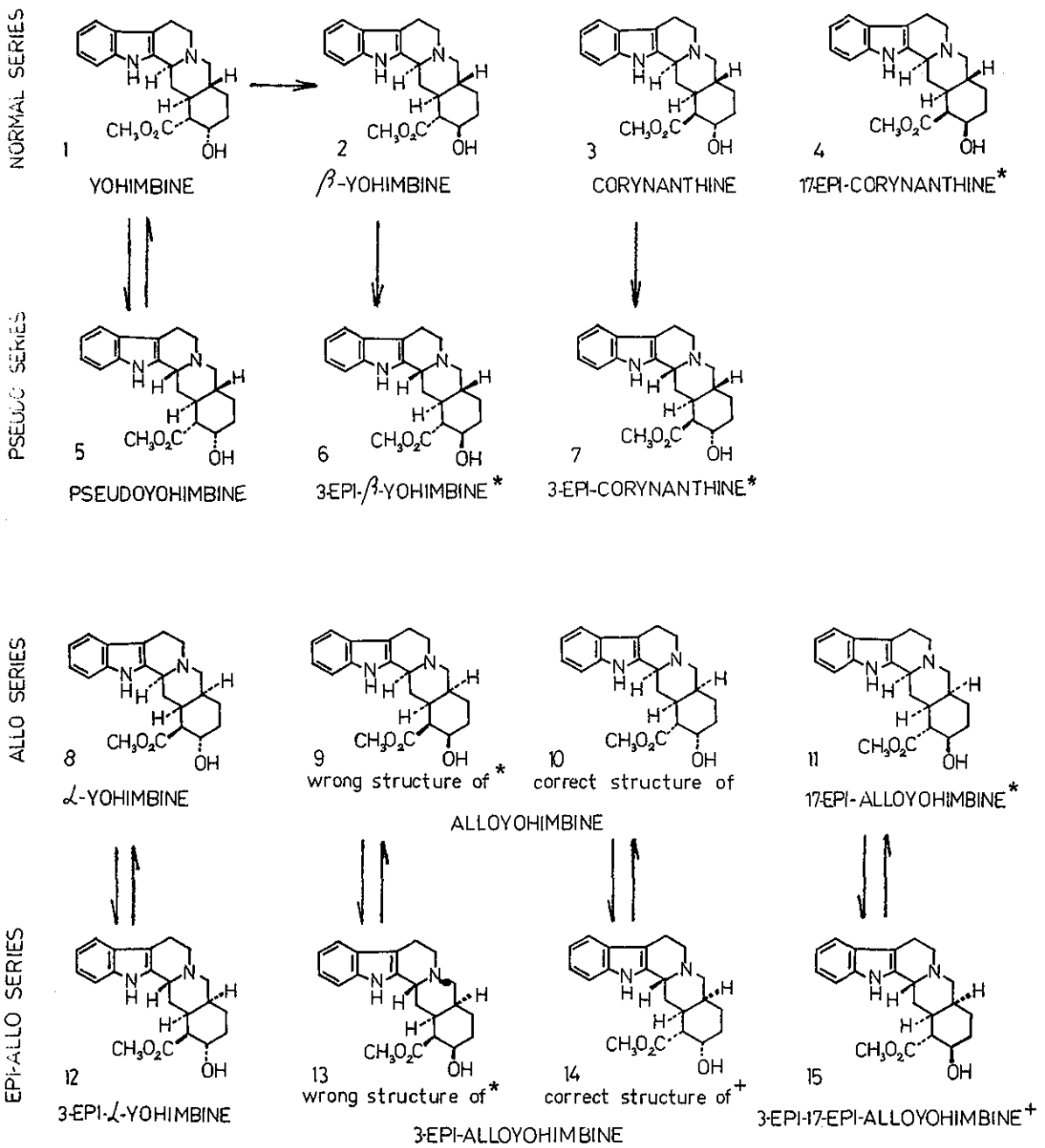
Excellent monographs on the synthesis and structure of yohimbine alkaloids are found in the literature.[1] Therefore the subject of the present review is primarily a discussion of the - in part, still unpublished - work on the synthesis of yohimbine alkaloids performed at the Institute of Organic Chemistry of the Technical University, Budapest. In the course of this work, the need to revise the structure of alloyohimbine has been shown.

1. A survey of yohimbine alkaloids

In the narrower sense, also used by us, the yohimbine alkaloids comprise yohimbine (1) and those of its stereoisomers which occur in plants. The structures of these bases, together with their isomers not occurring in nature (the latter marked with asterisks) are

shown in Figure 1.

Figure 1



The arrows in the figure indicate the directions where chemical transformations are relatively readily effected.

From the point of view of synthesis, it is expedient to distinguish two large groups of yohimbine alkaloids, depending on trans or cis annellation of the D/E ring. Let us first discuss the structure of the D/E trans-annellated type.

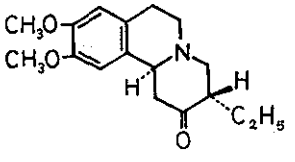
2. Synthesis of yohimbine and β-yohimbine

When our work was started, only a single yohimbine alkaloids synthesis was known. Van Tamelen and co-workers,[2a] in a preliminary paper, had reported a synthesis of pseudo-yohimbine (5) (this work was later published in detail[2b]). Since the conversion of pseudoyohimbine into yohimbine was already known, this approach simultaneously implied the synthesis of yohimbine.

2. 1 The construction of the indolo[2,3-a]quinolizidine system.

In planning our work, we applied a new, so-called linear, approach for building-up the yohimbine structure.

As starting material for the stereoselective total synthesis of Ipecacuana alkaloids,[3] ketone 16 is excellently suitable.[4] It can be prepared in about 90 % yield by the reaction of the salt of 3,4-dihydro-6,7-dimethoxyisoquinoline with ethylbutenone.[5]



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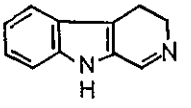

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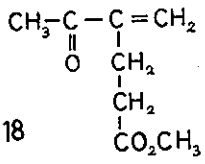
We wished to apply a similar procedure for building up the structure of yohimbine. For this purpose, we intended to utilize the reaction of 3,4-dihydro-β-carboline (17) with the unsaturated ketoester (18)[6] The latter compound was prepared by means of a Mannich reaction of acetylglutaric ester, yielding - in addition to 18 - the corresponding aminomethyl derivative[7] which can readily be identified in the form of the methiodide (19).



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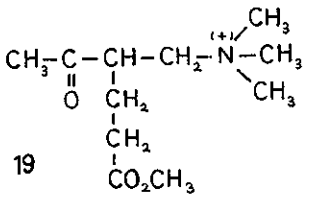

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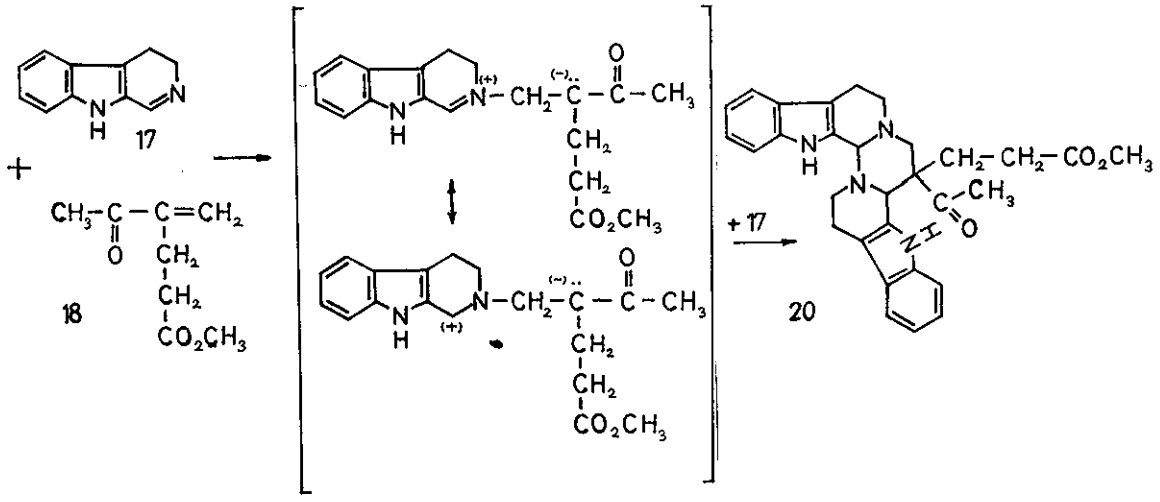
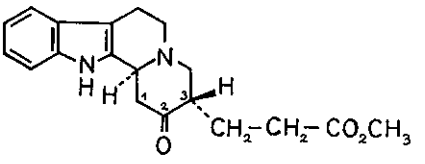
However, 3,4-dihydro-β-carboline reacts in a different manner with unsaturated ketones than the corresponding isoquinolines. Its hydrochloride does not react at all, whereas the free base, in cold alcoholic medium reacts by a 1,4-dipolar cycloaddition



process, yielding compound 20 as the major product.[8]

It clearly follows from this mechanism that the desired cyclization can take place if the 1,4-dipole is eliminated by proton addition. In agreement with this expectation, when the constituents were boiled in ethanol in the presence of a small amount of acid, the desired quinolizidine derivative (21) was obtained in satisfactory yield.[6,9] The same product can also be obtained by reaction with the methiodide (19).



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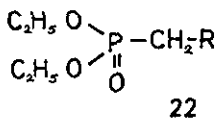
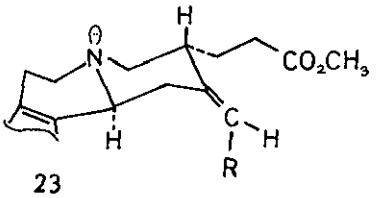
2.2 The synthesis of yohimbine and β-yohimbine through diester 24a.

The first step in building-up yohimbinone (26a) was to establish a methoxycarbonylmethyl group in the β-configuration in position 2 of ketone 21. Using the known procedure,[3,10] applied in the synthesis of emetine and dihydrocorynantheine, this was carried out in two



22

	R
a	CO_2CH_3
b	CN



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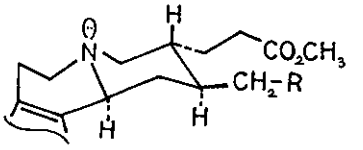

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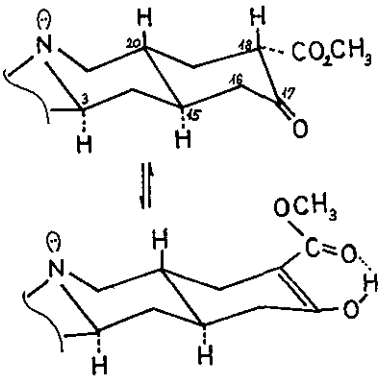
stages: the ketone (21) was reacted at 0° C, in the presence of an equivalent amount of potassium tert.butoxide, with phosphonoacetic ester 22a and the condensate obtained (23a) was catalytically hydrogenated to give diester 24a. From the diester (24a), by means of condensation in homogeneous medium (DMSO) in the presence of sodium dimsylate, the ketoester (25) was obtained in a regiospecific reaction as the only product. This compound is the thermodynamically more stable product, and is capable of enolization, but unsuitable for synthesis of yohimbine alkaloids. Yohimbinone (26a) is incapable of enolization,[11] owing to the steric hindrance, "peri-effect", of the hydrogen in position C_{14}. Therefore it appeared that the only way to obtain yohimbinone from these reactants was to utilize kinetic control. In fact the Dieckmann condensation, carried out in heterogeneous phase in hot benzene under the influence of sodium methoxide, yielded a mixture of the two ketoesters (25) and (26a) from which the desired isomer (26a)



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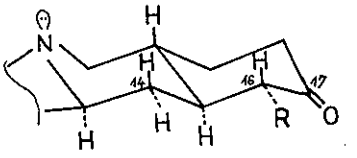


26

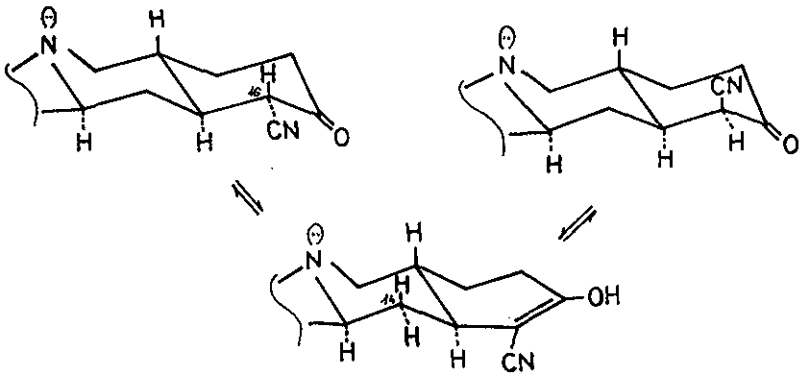
	R
a	CO_2CH_3
b	CN
c	H

could be isolated in a yield of 30 %.

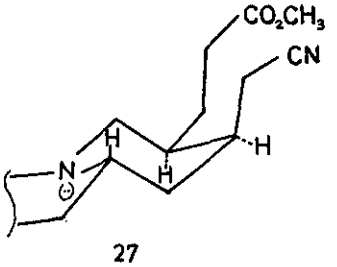
Acid hydrolysis accompanied by decarboxylation led, from both isomers, to yohimbone (26c). From yohimbinone, with sodium borohydride,[11] a 1 : 3 mixture of yohimbine (1) and β-yohimbine (2) racemates (2) is obtained, whereas the use of a platinum catalyst[12] results mainly in the formation of racemic yohimbine. The racemates were resolved into the optical antipodes by using the method of diastereomer salt pair formation. For yohimbine racemate, N-acetyl-L-leucin, for racemic β-yohimbine, L-camphorosulphonic acid was found to be the most suitable agent. The salts of the natural antipodes crystallize in pure form from the solution and their enantiomers could be obtained from the mother liquors.

2.3 Synthesis of yohimbine (1), β-yohimbine (2) and 17-epi-corynantine (4) through the cyanoester (27)

In order to control the Dieckmann condensation for obtaining the nitrile analogue of yohimbinone (26b) in good yields, the ketone (21) was made to react with phosphonoacetonitrile (22b) in the above-mentioned way, and the double bond of the product (23b) was subsequently reduced in the presence of palladium on bone black. Two products (24b and 27) - in conformity to the two directions of saturation - were formed in this reaction, in a ratio of 4 : 1. They could readily be separated by crystallization. The Dieckmann condensation of the isomer obtained in the higher amount (24b) in DMSO yielded the nitrile (26b) quantitatively.



26 b



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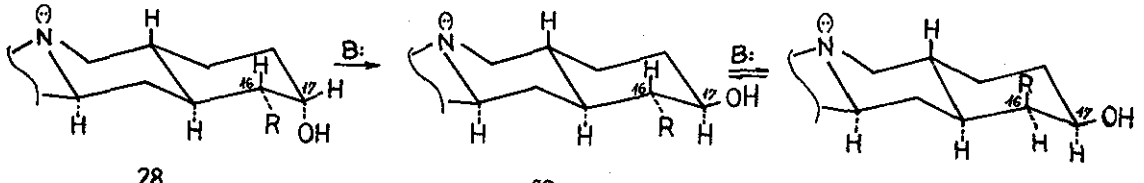
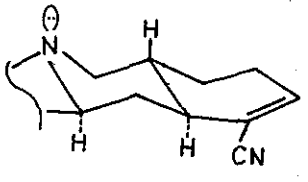
In contrast with its ester analogue, the nitrile enolizes both in solution and in the solid state, since no significant interference arises between the samll-volume nitrile group and the hydrogen atoms in the peri position even when the nitrile group is attached to a double bond.



28 29 30



31

	R
a	CN
b	$CONH_2$

When reducing 26b with sodium borohydride at room temperature, three products were formed. The structures of two of these, namely 28a and 29a have been confirmed by their spectra - and by their transformation into yohimbine (1) and β-yohimbine (2) resp. As to the third product (30a), its IR and NMR spectra (Table 1) reveal that its hydroxyl group, similarly to that of the isomer 29a, is in an equatorial alignment and hence this product is

Table 1

	NMR /τ/			[a]: DMF-d_7 [b]; $CDCl_3$
Compound	C_{17}-H	C_{17}-OH	CO_2CH_3	O-CO CH_3
28[a]	5,75	4,50		
29[a]	-	4,33		
30[a]	-	4,33		
1[b]	5,77		6,2	
2[b]	6,18		6,18	
3[b]	6,02		6,47	
4[b]	6,20		6,40	
O-Acetyl derivatives of;				
1[b]	4,55			7,95
2[b]	5,02			8,00
4[b]	5,22			8,00

apparently the C_{16} epimer of compound 29a. This assumption was fully confirmed by the chemical behaviour of the compound in question: an equilibrium between compounds 29a and 30a is established even by the action of aqueous alkali. The position of this equilibrium, as calculated from the equilibrium constant, is defined by the conformation energy of the nitrile group (0.2

Kcal/mol). The acidic hydrogen at C_{16} is abstracted under these mild conditions and, as a result, the nitrile group passes into the axial and equatorial position, resp. The appearance of isomer 30a in the reaction mixture is due to the presence of the isomer containing the nitrile group in the axial position, the latter being formed by enolization in the solution of the ketonitrile (26a), followed by reduction. The ratio of isomers thus established is only slightly modified by the subsequent epimerization taking place during the reduction process. Under more severe conditions (potassium tert.butoxide + hot benzene), the less acidic hydrogen atom in position C_{17} of nitrile 28a can also be exchanged and the transformation of 28a to 29a effected. This epimerization is, however, unidirectional, and, owing to the stereoelectronic conditions of the E_2-type elimination, substantial amounts of apo-yohimbine-nitrile (31) are also formed in the reaction.

The transformation of the nitrile groups in isomers 28a, 29a, and 30a into ester groups was carried out in three stages. First, the nitrile group was converted into the amide, using alkaline H_2O_2, then the amides, 28b, 29b and 30b, were hydrolized to the corresponding acids, and finally the acids were esterified <u>in situ</u> by acid in methanol. In this way, one obtains yohimbine (1) from 28a, β-yohimbine (2) from 29a, and a yohimbine isomer, unknown in nature up to now, 17-<u>epi</u>-corynanthine, (4), from compound 30a. In the course of these transformations, the effects of the steric factors and the neighbouring groups on the rate of reaction could be studied: 30a in conformity with its axial nitrile group, reacts much slower with alkaline peroxide, and the amide (30b) with water,

than their isomers (28a, b) and (29a, b). A substantial difference between the rates of reaction of the latter two epimer pairs, was also observed: the rates are higher with 28a, b, containing an axial hydroxyl group than those of their equatorial (29a,b) analogues. NMR spectroscopic data of the compounds are listed in Table 1.

It may be seen from the table that the signal of the ester group of compound 4 - similarly to corynanthine (3) which also contains an axial ester group - appears at a higher field strength and differs from the chemical shift of the analogous protons of yohimbine (1) and β-yohimbine (2). On the other hand, the C_{17}-hydrogen of 4 is axial, and, hence, similar to the analogous hydrogen in β-yohimbine, but in contrast to that of yohimbine and corynanthine, absorption is ovserved at a higher field strength. Similar observations could also be made in the spectra of the O-acylated alkaloids.

3. Synthesis of D/E-cis-annellated yohimbine alkaloids

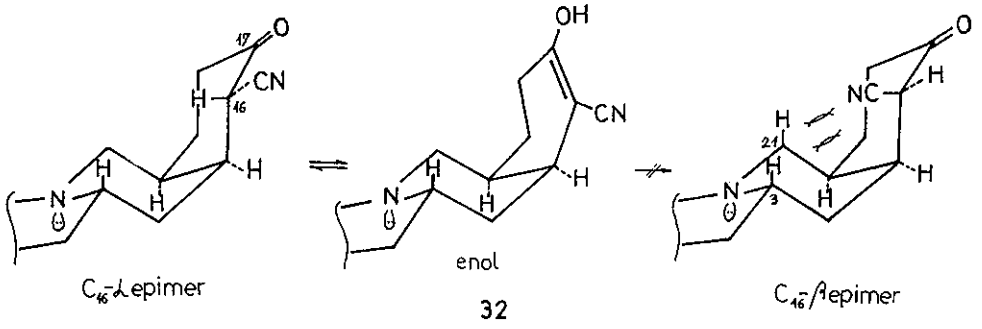
Throughout the world, several research groups are still continuing to study yohimbane-type compounds, and experiments are being carried out to produce yohimbine isomers with allo- and epi-allo yohimbane structures.[13,14]

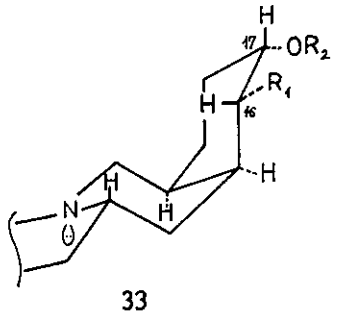
In the following paragraphs we report the successful synthesis of compounds of this type.[6,15]

3.1 Synthesis of yohimbine isomers with epi-allo-yohimbane structure. The steric structure of allo-yohimbine[15]

The utilization of the isomer (27) obtained in smaller amounts in the catalytic hydrogenation of compound 23b appeared to be

the simplest approach for synthesizing D/E-cis-annellated compounds. The compound (27) was transformed quantitatively into pentacyclic compound 32 by potassium tert.butoxide in DMSO. According to spectroscopic data, the prevailing form of this compound in both the solid state and in solution is the enol form, and the conformation of the structure is epi-allo-trans (E_t).[16] In contrast to the reduction of the analogous compound with the normal configuration (26b), reduction of ketone 32 with sodium borohydride in methanol yielded two, instead of three, products: 33a and 34a in a ratio of 2 : 3.





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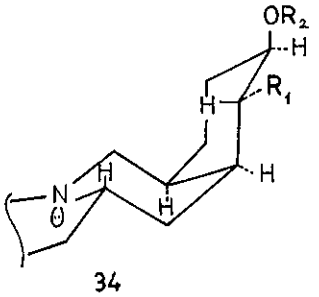


34

	R_1	R_2
a	CN	H
b	CN	Ac
c	CN	Ts
d	$CONH_2$	H
e	COOH	H

From the spectra, the conformation of the yohimbane skeleton is E_t in both products. NMR spectra also reveals the steric position of the C_{17}-hydroxyl group. This is based on the chemical shift of the C_{17}-proton which depends on its equatorial or axial position.[17] It was found that the C_{17}-hydrogen is equatorial in isomer 33a and axial in 34a (Table 2).

Table 2

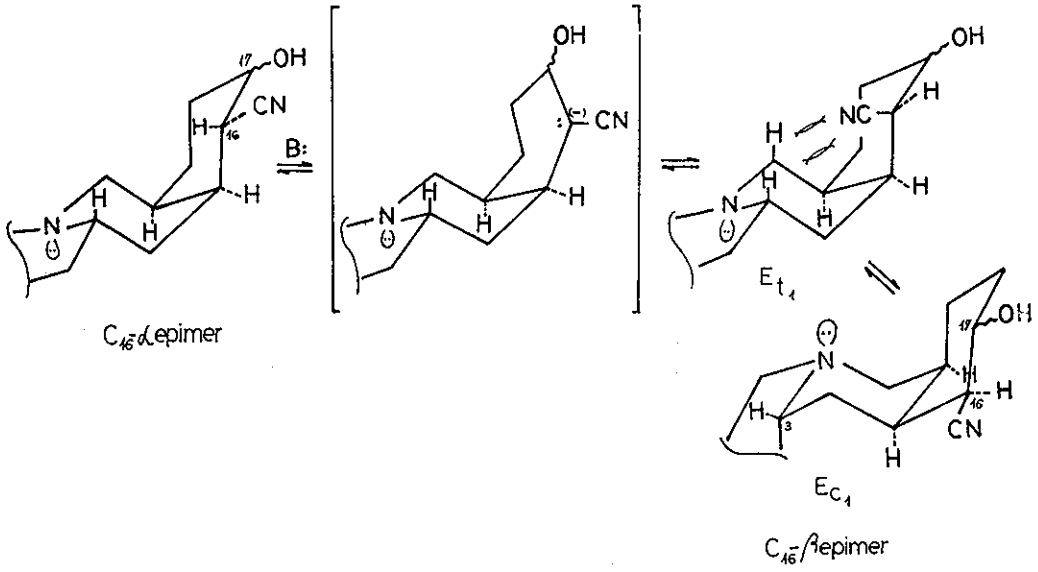
	NMR /τ/ DMSO-d_6			IR /cm^{-1}/ pyridine		
Compound	C_{17}-H	C_{17}-OH	NH	Bohlmann bands	OH	CN
33a	5,95	4,75 /d, J=6/	0,8	2750-2810 s	3450	2250
33b	4,6			- " -		
34a	6,45	4,55 /d, J=6/	0,9	- " -	3600-3000	2240
34b	5,2		0,9	- " -		

From the stable E_t conformations of the products, it follows that in 33a the hydroxyl group is located in the α-, and in 34a, in the β-hemispace. The spectra of the corresponding O-acyl derivatives (33b and 34b) as well as the differences in the rate of the O-acylation reaction (the reaction of 34a exceeds that of 33a by one order of magnitude) also confirm the correctness of these steric conclusions.

Further conclusions can be made from the behaviour of the nitrile alcohols and their tosylates (33c and 34c). In contrast to their analogues in the normal series (29a and 30a), the nitrile alcohols

(33a and 34a) do not epimerize at C_{16} under the influence of cold aqueous or alcoholic alkali. The absence of such reaction can be understood from examination of molecular models. Fig. 2 shows that the conformational energy difference between the two possible C_{16} epimers in the epi-allo series is substantially higher than that found in the normal series.[18] In the trans conformer of the "β-epimer" containing the nitrile group in the β-hemispace, the nitrile group is so close to the axial C_3 and C_{21} hydrogens that the molecule can be built up only by a vigorous deformation of the chair form. Such interactions do not exist in the E_{c1} conformation. However, the energy content of the molecule is high, because, owing to the conformation change $E_t \rightarrow E_{c1}$, the large C_3 indole substituent gets into the axial position.

Figure 2



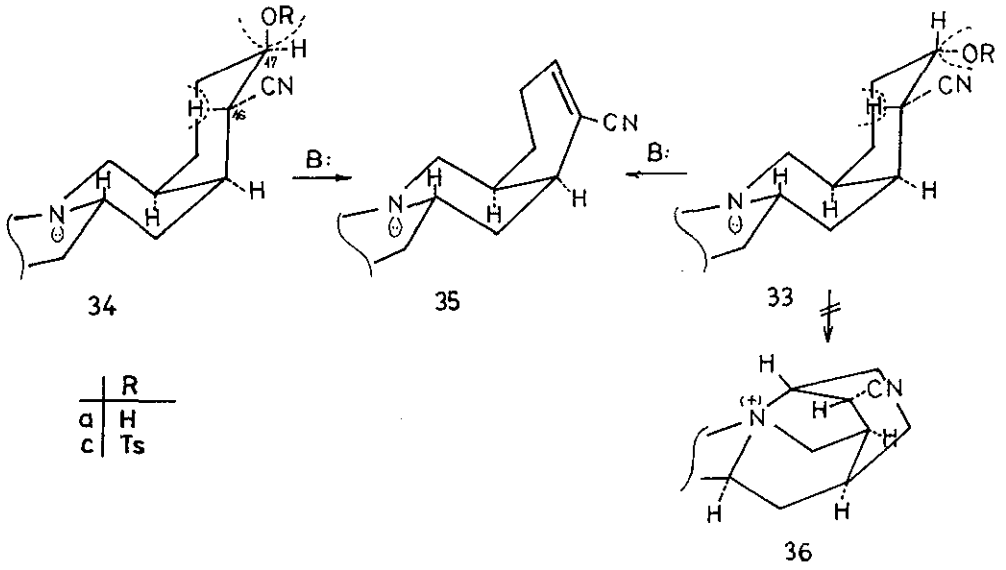
From what has been said, the assumption appears obvious that the

nitrile group is bound to the epi-allo-yohimbane structure having the E_t conformation, in the case of both nitrile alcohol isomers 33a and 34a in the α-hemispace, in the equatorial position, and the epimerization equilibrium is fully shifted towards the C_{16}-α-epimer.

It should be noted that 3-epi-α-yohimbine (12), in which the C_{16} ester group is in the ß-position, exists solely in the epi-allo-cis conformation E_{cl}, and the Bohlmann bands pointing to the E_t conformation are absent from its IR spectrum.

Thus, it is not surprising that even with hot sodium methoxide in methanol C_{16} epimerization of 33a and 34a can not be brought about. However, the elimination reaction does take place. The same unsaturated nitrile (35) is obtained from both compounds. The reaction is relatively rapid (30 minutes) with 33a and slower (about 8 hours) with 34a (Fig. 3).

Figure 3



The difference in the rate of elimination is in full agreement with the structures: the conditions for the energetically most favourable trans-diaxial elimination are present in the compound 33a, while compound 34a must first epimerize (this being the rate-controlling step) or else - this could also be imagined - the molecule is constrained to syn-type elimination.

We also prepared and studied the O-tosylates (33c and 34c) of the nitrile alcohols. These compounds are decomposed by alcoholic alkali even more rapidly than the nitrile alcohols. When their solutions in pyridine are heated, only the unsaturated nitrile (35) can be isolated. They show differences in the rate of elimination similar to the nitrile alcohols. Mass spectrometry of the tosylates allows similar observations: in contrast to its isomer pair, tosylate 33c totally decomposes at its boiling point (180°C), and only the molecular peak of the unsaturated nitrile (35) and ion peaks originating from its fragmentation can be observed in the spectrum. From the structure of the tosylate (33c) one would expect that - as with the tosylate of epi-α-yohimbine (12) - intramolecular N-alkylation would also take places on heating the solution in pyridine, and a quaternary salt would be formed (Fig. 3). However, no such compound could be isolated, probably because the rate of the elimination reaction leading to the unsaturated nitrile (35) is higher than the rate of the S_Ni reaction. Through a knowledge of the structures of the products, some conclusions can also be made on the reduction process of ketone 32 with borohydride. Hach and coworkers[29] studied the reduction of menthone and thujone derivatives, and stated that the asymmetric centre in the vicinity of the oxo

group, under the effect of the basicity of sodium borohydride, will epimerize prior to the reduction of the oxo group (i.e., the epimerization preequilibrium is more rapid than reduction), and hence all four isomeric alcohols theoretically possible will be formed in the course of the reduction.

This is the case also in the reduction of normal and allo-yohimbane ketonitriles 26b and 41a and allo-yohimbinone (41d) because the C_{16} epimer pair can always be found among the three (or four, resp.) reduction products (cf. below).

The picture is different in the reduction of compound 32, which has the epi-allo-yohimbane configuration, whose C_{16}-β epimer is not present in the reaction mixture, owing to its inability to enolise. The same finding is made in the reduction of yohimbinone (26a). As discussed earlier, only two isomeric alcohols are formed under the action of sodium borohydride and the two isomers are related to each other by C_{17} epimerism and not by C_{16} epimerism.

These findings can be explained by the same arguments discussed earlier in connection with the structure of 33 and 34.

According to molecular models, the existence of the "β-epimer" in the E_t conformation is improbable, owing to the interaction between the axial nitrile group and the axial C_3 and C_{21} hydrogens in the interior of the basket-like ring system. On the other hand, the energy of the E_{c1} conformation is higher than that of the α-epimer by approximately the conformation energy of the large C_3 substituent which must become axial.

Hence, only the "α-epimer" can be considered as a reaction partner in reduction. This is why we obtained the same result,

with regard to the number and stereochemical relation of the products, as in the reduction of simpler related compounds carrying no substituent in position C_{16}, e.g. epi-allo-yohimbone.[2/c]

Moreover, the ratio of the nitrile alcohols seems to indicate that the attack of the borohydride anion on the carbon atom of the carbonyl group is somewhat easier and requires surmounting of a smaller steric compression when it is directed against the convex side of the ring system ("steric approach control"). However, the attack in the opposite direction is also feasible.

As the final step of the alkaloid synthesis, we transformed the nitrile groups of compounds 33a and 34a into ester groups. Since direct hydrolysis or the Pinner reaction were unsuccessful, we chose the indirect path developed for the isomers of the normal series. We first prepared the amides 33d and 34d, then hydrolized these to the carboxylic acids 33e and 34e and subsequently, without purification, esterified the crude acids to 14 and 15.

The nitrile → amide reaction proceeded smoothly with alkaline methanol containing hydrogen peroxide. However, owing to the increased sensitivity of the epi-allo-compounds to oxidation and heat, we had to work at lower temperatures. With regard to the yield, it is of the utmost importance to achieve continuous precipitation of the amide from the reaction mixture. To ensure this, seed crystals must be added to the solution at the appropriate moment.

In the nitrile to amide and amide to carboxylic acid transformations, we again observed that the isomers 33a and 33d, containing the C_{16} and C_{17} substituents in the cis position, reacted more

rapidly than the trans compounds (34a and 34d), owing to the effect of the neighbouring hydroxyl group.

In the acid hydrolysis of amide 33d, C_3 epimerization also takes place. Therefore, after esterification of the mixture, in addition to the hydroxyester (14) belonging to the epi-allo series, a small amount of the yohimbine isomer (10) having the allo configuration could be separated. The ratio of 14 to 10 was 3 : 1. The compounds are C_3 epimers, since they can be mutually prepared from one another by the usual methods for C_3 epimerization. Oxidation with mercury (II) acetate results in a common intermediate product which, when reduced with zinc and acid, yields isomer 14, whereas reduction with sodium borohydride yields isomer 10 (initially formed in lower quantities) as the main product.

The allo-hydroxyester (10) can also be obtained from epimer 14 by boiling with acid and subsequence methylation. The composition of the isomeric mixture is identical with that obtained by boiling the amide (33d) with acid.

In view of the steric formulae derived from these considerations, it was unexpected that the chromatographic, spectral and chemical properties of compound 10 were found to agree with those of natural allo-yohimbine, to which formula 7 had been assigned in the literature.[1,19] This was based on the observation of Janot, Goutarel and coworkers that under the effect of strong bases like potassium tert. butoxide, the carbon atom C_{17} carrying the hydroxyl group will epimerize, so that β-yohimbine (2) can be obtained, e.g., from yohimbine (1). Since allo-yohimbine, in hot benzene and in the presence of potassium tert.butoxide is converted into the more stable α-yohimbine (8), the former was considered, per analogiam,

to be the C_{17}-epimer of the latter.[11]

However, our experiments demonstrate that this is not so. To bring about the allo-yohimbine to α-yohimbine reaction, the vigorous conditions used for epimerization of the carbon atom carrying the hydroxyl group are unnecessary. The reaction will take place even at ambient temperature in the presence of methanolic sodium methoxide, without yielding any by-products. In this case, however, only the inversion of the configuration of carbon atom C_{16} carrying the more acidic hydrogen can come into question. The result is understandable only on the basis of formula 10 since carbon C_{17} is incapable of epimerization under these conditions. The substance obtained in the larger amount by acid hydrolysis of amide 33d is, consequently, epi-3-allo-yohimbine (14).

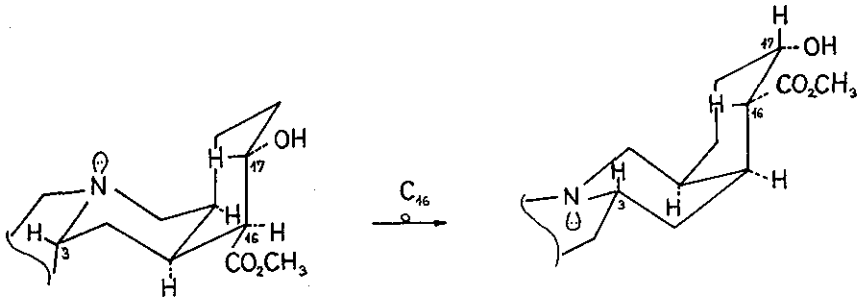
Spectra (Table 3) indicate that the basic structure of the alkaloid (10) has the E_t conformation. As a result, the molecule would appear in the C/D-cis annellated E_{cl} conformation (like epi-3-α-yohimbine (12)).

Table 3

	$CDCl_3$ NMR /τ/		IR /cm^{-1}/			
Compound	C_{17}-H	C_3-H	OH	NH	Bohlmann bands	CO_2CH_3
10	6,20	6,75	3280 3530	3400	2750-2810	1730
14	5,75	6,55	3320 3570	3460	2760-2850	1720
15	6,13	6,45	3200 3570	-	2780-2820	1740
11	6,20	6,05	3480	-	-	1725

Moreover, 3-epi-allo-yohimbine (14) can also be obtained - in full agreement with our formula - by a epimerization of epi-3-α-yohimbine (12) with methanolic sodium methoxide (Figure 4).

Figure 4



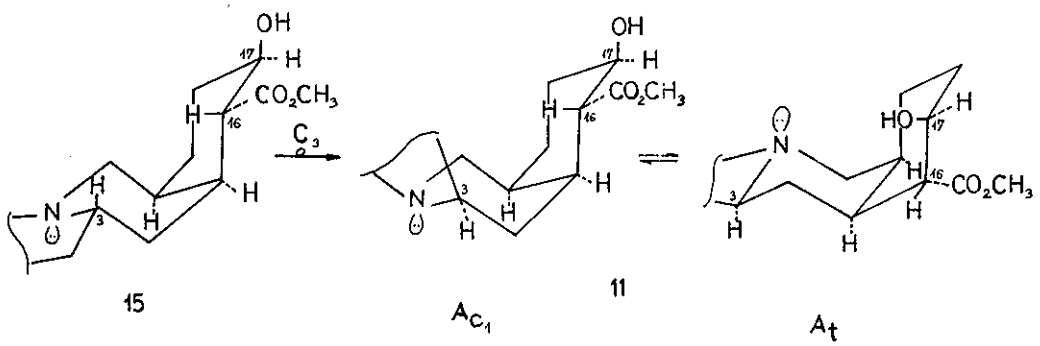
12 14

The driving force for the epimerization is the energy gain resulting from the difference in conformation energies for the two equilibrating constituents with respect to the C_3 substituent and the hydroxyl group. In the stable conformer of product 14, the C_3 substituent will occupy an equatorial position, and simultaneously the OH group will take the axial position. This epimerization experiment had already been performed by Weisenborn[20] in 1957. However, he termed the compound obtained as 3-epi-16-epi-α-yohimbine instead of epi-3-allo-yohimbine. Since that time, nobody had investigated the compound in question and nobody had compared it with epi-3-allo-yohimbine, presumably because this seemed unnecessary in the light of the steric structure put forward by Janot and coworkers several years later.[11]

Yohimbine isomer 15 has not been found in nature. In agreement with its stable steric arrangement (the substituents at C_3, C_{16}

and C_{17} are all equatorial) it does not epimerize when heated with acid, and even when C_3 epimerization is brought about by sequential treatments with mercury(II) acetate and sodium borohydride, substantial amounts of starting material (15) are recovered. These properties are to be expected from consideration of the formulae of epimers 15 and 11: the allo-yohimbane structure will be more labile, since either the large C_3 substituent (in conformation A_{c1}) or the two substituents on the E ring (in the conformation E_t) will occupy the axial position (Figure 5).

Figure 5



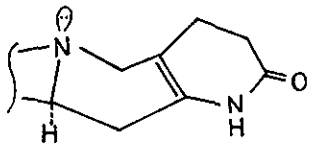
3.1 The stereoselective elaboration of the allo-yohimbane structure; synthesis of α- and allo-yohimbine[6]

3.2.1 Synthesis of key-intermediate 40h

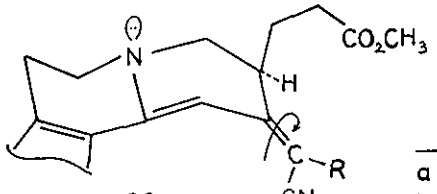
By-product 27 was utilized for the synthesis of the D/E-cis-annellated yohimbane structure. The particular starting product was ketoester 21. As the reagent required for further synthetic elaboration it was decided to use cyanoacetic ester and malonodinitrile, resp., since earlier experiences with other molecules[21,22] demonstrated that in such cases, the substituent next to the reaction centre will epimerize. The stereoselectivity of this re-

action is explicable[3] on the basis of the higher rate of reaction between the β-C_3 epimer which is always present in significant amounts in solutions of the ketone (21) and the malonic ester derivative as compared to the rate of reaction of ketone 21 itself. Steric compression between the substituents being incorporated and the substituent already present in position C_3 is minimized in this arrangement.

New experimental conditions, however, had to be developed for the Knoevenagel condensation, since the usual conditions (ammonium acetate catalyst, azeotropic removal of water with benzene) leads to the formation of lactam 37 instead. Evidently ammonia derived from the ammonium acetate adds to the keto function, and the adduct becomes stabilized by intramolecular acylation and loss of water.



37



38

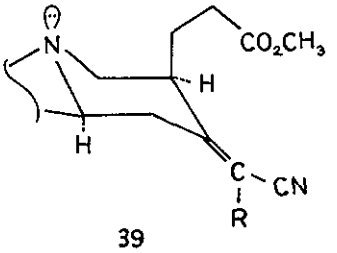
	R
a	CO_2CH_3
b	CN

When triethylamine acetate was used as catalyst, the desired reaction did take place, but the desired product was obtained in low yields only, on the one hand because the ester groups were partially hydrolyzed by the water formed in the condensation, and on the other hand, because another substantial part of the already formed condensate was oxidized during the long reaction time to the weakly basic dieneamine 38.

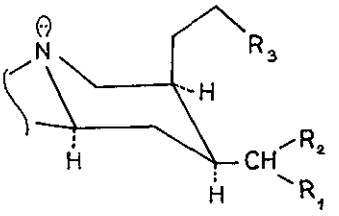
It is noteworthy that the NMR spectrum of compound 38 shows two

indole-NH signals whose joint intensity correspond to that of one proton. One of these signals disappears at about 180°C and merges into the other indole-NH signal. This phenomenon - similar to other analogous cases[23] - is due to the dieneamine in question being a mixture of cis-trans isomers relative to the double bond in position $\Delta^{2,\alpha}$ and these isomers are interconverted at 180°C.

The problems caused by the liberated water and oxidation were solved by bringing the reaction partners together in triethylamine acetate solvent in the presence of phosphorus pentoxide. Under such conditions, the condensation takes place rapidly at ambient temperature, and the pure product (39) is formed almost in quantitative yield.



39



40

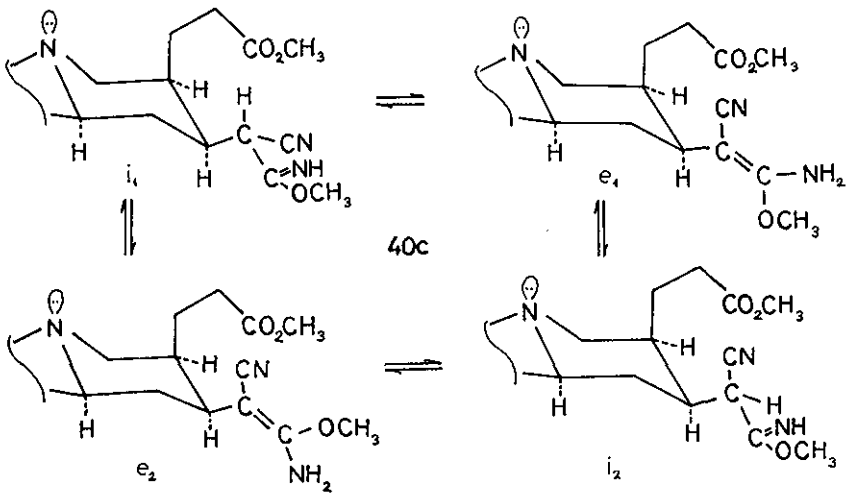
	R
a	CO_2CH_3
b	CN

	R_1	R_2	R_3
a	CO_2CH_3	CN	CO_2CH_3
b	CN	CN	CO_2CH_3
c	$C(=NH)OCH_3$	CN	CO_2CH_3
d	$C(=NH)OC_2H_5$	CN	CO_2CH_3
e	$CONH_2$	CN	CO_2CH_3
f	COOH	CN	COOH
g	H	CN	COOH
h	H	CN	CO_2CH_3
i	H	CO_2CH_3	CO_2CH_3

The next step, viz.hydrogenation, did not cause any problems, since the electron-poor exocyclic double bond can be saturated selectively and free of by-products to 40a and 40b, resp., by using sodium borohydride.

In the course of the reduction, two asymmetric centres are simultaneously formed leading to the formation of two diastereomeric racemates. NMR spectra reveal that compound 40a is in fact a mixture, since the methoxy protons present in the cyanoester function appear as a doublet signal which - even at higher temperatures - does not merge. Separation of these diastereomers is, however, unnecessary , since the asymmetric centre at the carbon atom in the cyano-ester function will disapper in the course of the subsequent reactions. The stable iminoether bases 40c and 40d are obtained from dinitrile 40b by an alkali-catalyzed reaction with alcohol. The iminoether bases were found to be capable of transformation (in solution) into the tautomeric enamines, and an equilibrium is reached.[24] NMR spectra distinctly demonstrate that a simultaneous equilibrium of not two, but four molecular species are present in the solution: owing to the tetrasubstituted C=C double bond, the enamine form occurs in cis and trans isomers $\underline{\underline{e}}_1$ and $\underline{\underline{e}}_2$, while the iminoether form, owing to the asymmetric centre at the carbon atom in the side chain, will appear in the form of two diastereomers $\underline{\underline{i}}_1$ and $\underline{\underline{i}}_2$ (Figure 6).

Figure 6



The position of the equilibrium depends on the nature of the solvent, the temperature, and the substituents. The iminoether 40c, in agreement with the properties of compounds of this type, can be converted into the ester 40a by addition of one mol equivalent of water in an inert solvent. However, without acid catalysis, the conversion is very slow. In methanol saturated with gaseous hydrochloric acid, in the absence of water, the iminoether reacts in another direction. The product crystallizing from the hot solution is the amide (40e). The reaction is readily controllable and quantitative. Therefore it appears expedient to prepare this intermediate product first, even in the preparation of the cyano-ester (40a) if the dinitrile (40b) is used as the starting material.

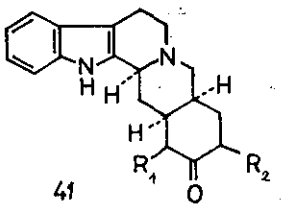
The iminoether to amide reaction is a process of the A_{al} type. This was experimentally confirmed by the finding that the imino-

ether, in dimethylformamide solution and in the presence of mineral acids, act as alkylating agents and convert carboxylic acids at ambient temperature into esters. Recently Kantlehner and Funke[25] also reported such a utilization of iminoethers. Both ester groups of compound 40a are readily hydrolizable. Dissolution in alkali at 0°C and acidification leads to the dicarboxylic acid (40f). Rapid hydrolysis is presumably due to the effect of the neighbouring group. The dinitrile (40b) behaves similarly with alkali, but in this case, in addition to the dicarboxylic acid (40f), the amide (40e) can also be isolated.

A short period of boiling 40f in DMF results in its decarboxylation to the cyanocarboxylic acid (40g), which, by methylation with diazomethane, yields the nitrile ester (40h), and by treatment with methanol and hydrochloric acid, the diester (40i).

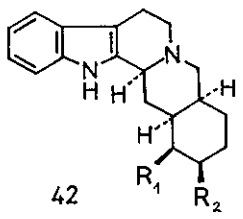
3.2.2. Alloyohimbane-type alcohols from nitrile ester 40h.

Under the effect of DMSO and potassium tert.butoxide, nitrile ester 40h is transformed into a pentacyclic compound (41a). This



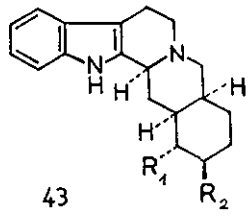
41

	R_1	R_2
a	CN	H
b	H	CO_2CH_3
c	H	H
d	CO_2CH_3	H



42

	R_1	R_2
a	CN	OH
b	CN	OAc
c	$CONH_2$	OH



43

product yields two nitrile alcohols (42a and 43a) in ratio of 4 : 1 after reaction with sodium borohydride. A third isomer could also be separated by thin-layer chromatography, but in very small amount, so that its stereochemistry was not investigated in detail.

According to the spectra of 42a and 43a as well as their acetyl derivatives (42b and 43b)(Table 4), the hydroxyl group and the acetoxy group, resp., are found in all compounds in the β-hemi-space i.e, these compounds are C_{16} epimers. Consequently under the characteristically mild conditions required for epimerization of C_{16} containing the acid hydrogen, an equilibrium can be established in which both constituents are present in a ratio close to 1 : 1.

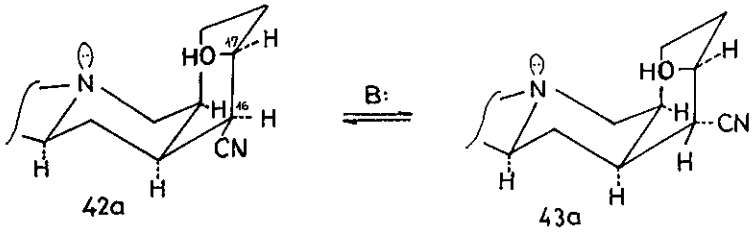
Table 4

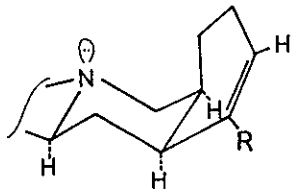
	NMR /τ/ DMSO-d_6			IR /cm^{-1}/ pyridine		
Compound	C_{17}-H	C_{17}-OH	NH	Bohlmann bands		CN
42a	5,95	4,90 /d, J=5/	-0,85	2760	2810	2240
42b	4,90		-0,90	2760	2810	2250
43a	5,95	4,85	-0,90	2770	2810	2250
43b	4,85		-0,90	2770	2815	2250

The relative steric structure of the carbon atom carrying the nitrile groups was determined by correlation experiments: all properties of the nitrile alcohol obtained in the smaller quantity (43a) agreed with those of the compound obtained from 34a, belonging to the epi-allo series, after C_3 epimerization.

To convert the nitrile into the ester, the amide intermediates (42c and 43c) were prepared by the alkaline hydrogen peroxide method. To suppress C_{16} epimerization and the elimination reaction that

would yield the unsaturated compounds 44a and 44b, resp., the work was carried out at ambient temperature.





44

	R
a	CN
b	$CONH_2$
c	CO_2CH_3

It should be noted that in contrast to the nitrile alcohol, amide 43c exists predominantly in the allo-cis(A_{cl}) conformation. In this conformation, both large substituents on the E ring are equatorial. The hydroxyesters (9) and (11) were obtained from the amides with hydrochloric acid in methanol. The by-product of this reaction is apo-α-yohimbine racemate (44c).

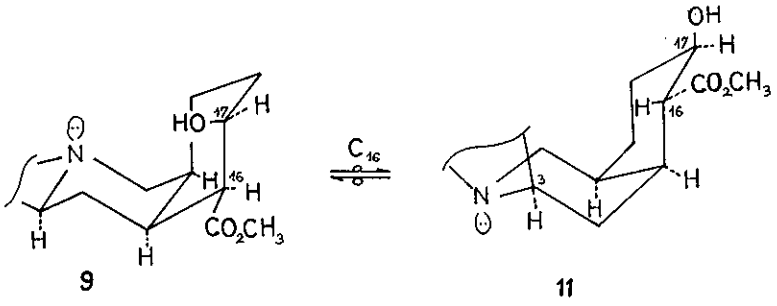
Hydroxyesters 9 and 11 have not yet been identified in nature, but their preparation is useful in structure elucidation of the stereoisomers of this series. The major spectral data of the four isomers are summarized in Table 5.

Table 5

	NMR /τ/ $CDCl_3$		IR /cm^{-1}/					
Compound	C_{17}-H	C_3-H	Bohlmann bands		CO_2CH_3	OH	C_{17}-OH	C_3-ind skeleton
10	6,20	6,65	2740	2830	1720	3470	ekv.	ekv. A_t
11	6,20	6,05			1725	3480	ekv.	ax. A_{c_1}
9	5,73	6,95	2740	2830	1720	3480	ax.	ekv. A_t
8	6,00	6,85	2750	2840	1725	3480	ekv.	ekv. A_t

As to the epimerization of 9 and 11, an epimerization equilibrium, similar to that involving the nitrile alcohols 42a and 43a, can be obtained at ambient temperature with methanolic sodium methoxide (Figure 7).

Figure 7



9 11

Epimerization is again accompanied by an elimination reaction, yielding apo-α-yohimbine (44c). Both hydroxyester constituents are present in the equilibrium in almost equal proportions. The conformation change accompanying epimerization in the case to the hydroxyesters represents an essential difference as compared to the equilibrium between the hydroxynitriles 42a and 43a. The A_t conformation in 9 changes into A_{c1} in 11, and hence, the methoxy-

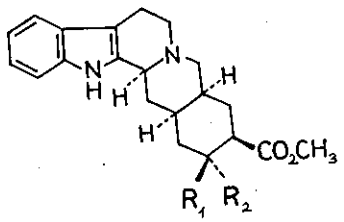
carbonyl group, which is substantially larger than the nitrile group, can be equatorial.

Incidentially, 11 is one of the very rare substances in which C/D-cis annelation of the allo-yohimbane structure occurs.

As discussed in detail in the foregoing, no conformation change takes place in the transformation of allo-yohimbine (10) to α-yohimbine (8) (the dominating conformer in both cases is A_t), and the equilibrium is almost completely shifted towards α-yohimbine, because the C_{16} methoxycarbonyl group passes in the course of this transformation from the axial position into the equatorial position.

3.2.3. Preparation of allo-yohimbinone (41d) and its reduction.

In hot toluene, in the presence of sodium methoxide or sodium hydride, diester 40i yields a single product (41b). Its hydrolysis with hydrochloric acid is accompanied by decarboxylation, and racemic allo-yohimbone (41c), already known in the literature,[26] is formed. The position of the ester group is confirmed by the formation of two hydroxyesters (45a and 45b) on reduction of 41b with borohydride, neither of them being identical with the already known isomers having an allo-yohimbine structure.



45

	R_1	R_2
a	OH	H
b	H	OH

The stereochemistry of these two products was not studied in detail, but it may be assumed that in this case too, steric approach controls the reduction, and hence structure 45a can be assigned to the substance obtained in the higher proportion and structure 45b to that obtained in the lower proportion.

The direction of the Dieckmann condensation of ester 40i changes at ambient temperature. In addition to the already known substance (41b), another isomeric ketocarboxylic ester can be isolated in yields of about 30 %. Keto-enol tautomerism appears with this isomer, too, and its acid hydrolysis yields allo-yohimbone, (41c). Thus, racemic allo-yohimbinone (41d) was also formed.

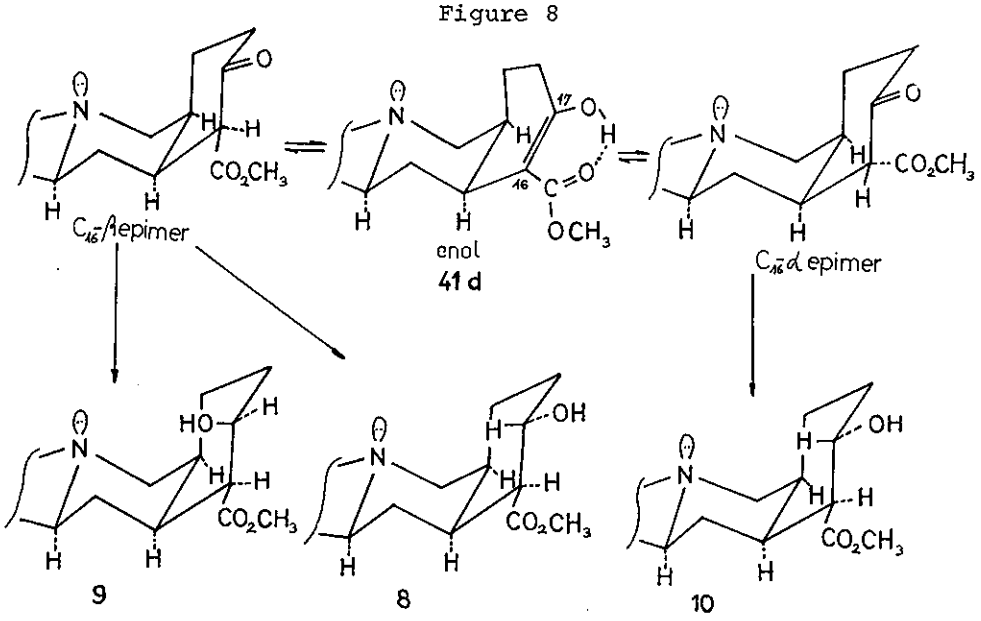
The optically active form of allo-yohimbinone is known in the literature.[27] It was prepared by oxidation of α-yohimbine. The authors claim that the compound exists only in the enol form. This statement is true for the solid state but, in pyridine or chloroform, the keto form is present to the extent of about 80 %. The conformation of the basic structure is At.

In the reduction of 41d with sodium borohydride, three hydroxyesters are formed. The main product is identical with hydroxyester 9 not occurring in nature, the second product with racemic allo-yohimbine (10), and the third product, formed in the smallest amount, with racemic α-yohimbine (8). The ratio of 9 to 10 to 8 is 7 : 3 : 2.

The proportion and steric structures of the products can readily be explained - as may be seen from Figure 8. - by the principle of steric approach control. By utilizing this principle, the results of reduction of ketoesters with normal yohimbane, epi-allo-yohimbane and the earlier thoroughly investigated berbane[28] structures

can also readily be interpreted.

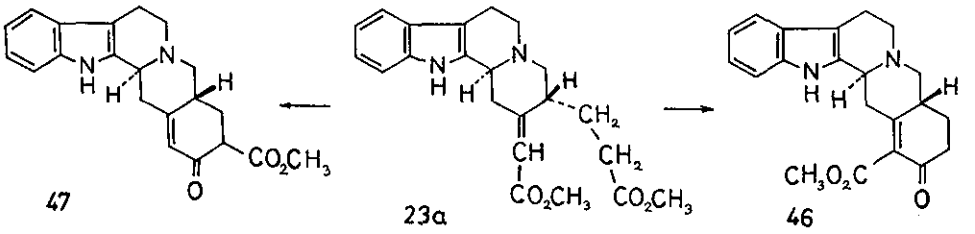
Figure 8



4. Synthesis of yohimbine alkaloids via product 23a. Dieckmann ring closure with unsaturated esters.

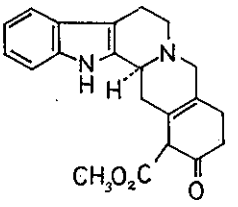
The cyclisation of the diester (24) obtained by reducing ester 23a could not be made satisfactorily regioselective. However, the presence of the double bond offers a specific opportunity for differentiating between the two ester groups. The limited data in the literature concerning the Dieckmann reaction of mixed esters[30a-f] are rather contradictory both as to the feasibility of ring closure and as to which of the two theoretically possible structures will arise.

In the case of ketone 23a, if kinetic control is valid, it is presumed that ester 46 must be formed, as opposed to the alternative structure (47).



47 23a 46

'Under the conditions of the reaction, the isomerization of the double bond in 46 to yield unsaturated compound 48 is, of course, also possible:



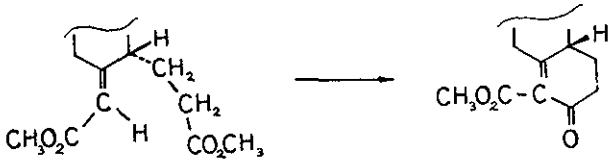
48

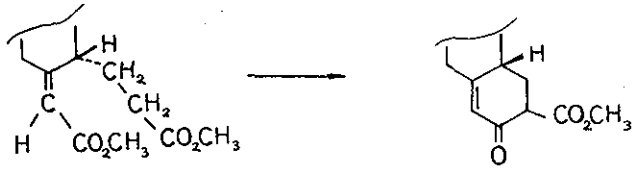
Various reaction conditions were studied and it was found that the homogeneous reaction in DMSO, in the presence of potassium tert. butoxide, yields a mixture. The formation of 48 is preferred, however, when the reaction is carried out in suspension in THF containing NaH, or in benzene in the presence of potassium tert. butoxide. Even at ambient temperature 46 is formed with a crude yield of 90 %, and subsequent treatment of this product with cold methanol yields 65 % of the pure product. From the mother liquor, compound 48 can also be isolated. This compound can, moreover, be obtained from the pure isolated compound 46 by treatment with pota-

ssium tert.butoxide in DMSO.

It is noteworthy that the rate of Dieckmann ring closure for the unsaturated ester (23a) is higher by one order of magnitude than that for the corresponding saturated ester (24). This finding also confirms the validity of kinetic control.

However, investigations on benzo[a]quinolizidine model compounds revealed the significance of the geometry of the carbon-carbon double bond, too.[32] An important condition for the desired regioselectivity is the proper orientation, otherwise the reaction proceeds in the other direction:

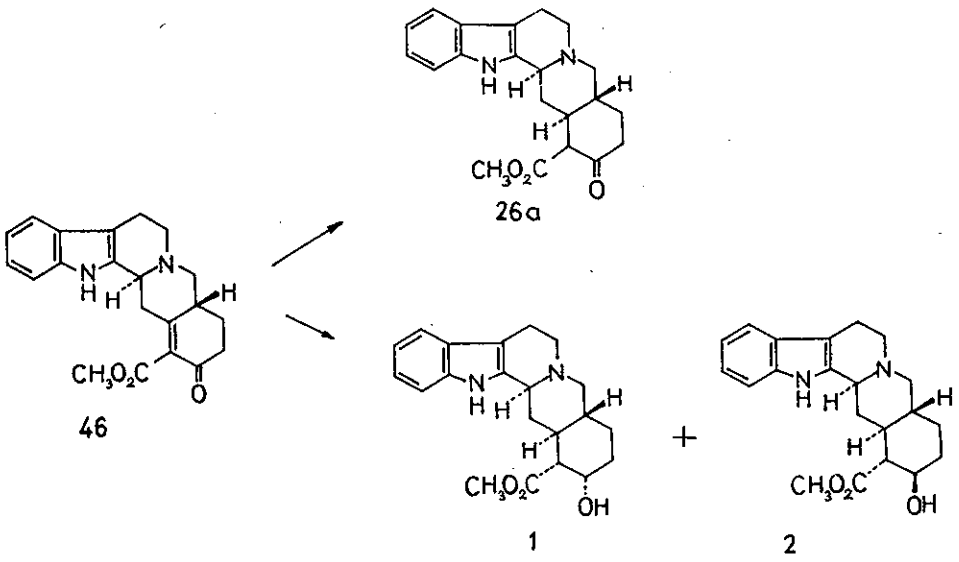




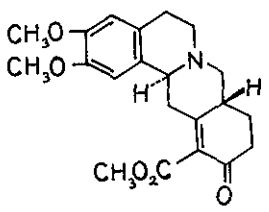
One source of the contradictions noted in earlier publications[30a-f] may originate in the undetermined geometry of the double bond.

The catalytic reduction of yohimbinenone (46) in acid medium, in the presence of Pd on carbon black, led to yohimbinone (26a)[31] in 75 % yield with high stereoselectivity. When Pt catalyst was used instead of Pd, yohimbine (1), besides β-yohimbine (2), was

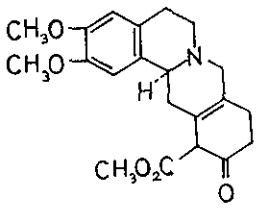
obtained directly, in one step. β-Yohimbine (2) is obtained with particularly high stereoselectivity when the unsaturated ketoester (46) is reduced with sodium borohydride in pyridine. Thus in the latter two cases, three asymmetric centres are being built-up in a single reduction operation, with high stereoselectivity.



The reduction of the double bond in alkaline media is a much more complex reaction. To study this problem the corresponding benzo[a]quinolizidine derivatives, i.e. berbanes,[32] were first used as model compounds.



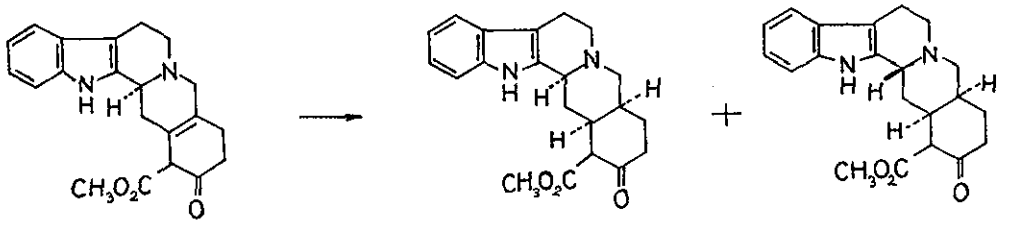
49



50

The double bond of compound 49, the analogue of 46 is readily isomerized, and reduction of the derivative formed (50) yields allo- and epi-allo berbanes whose relative proportions depend on the conditions of the reaction. Isomerization of the double bond in a separate step is unnecessary since, in alkaline medium, this isomerization proceeds at a higher rate than reduction, so that C/D-cis-annellated substances can be obtained directly.

Owing to its greater sensitivity to oxidation, the reduction of indole derivative 48 in alkaline medium is a more delicate operation. The structures and proportions of the product depend greatly on the conditions applied.[33] After catalytic reduction with Pd in alkaline medium, eight substances were isolated using preparative thin layer chromatography. Attempts were made to identify them in order to elucidate the effect of reaction conditions.



48 41d 51

The main product was found to be D/C-cis-annellated allo-yohimbinone (41d) and its C_3 epimer, epi-allo-yohimbinone (51). Surprisingly, we did not find the corresponding trans compound, namely yohimbinone. The reason is that the latter compound is incapable of enolization in alkaline medium, and hence ring-opening occurs in a retro-Dieckmann reaction. The product of this reaction (24a) was also found in the mixture. Small amounts of yohimbine and allo-yohimbine were found. These are not formed from the yohimbinones under the same conditions, so they must be the products of direct reduction of 48. This applies also to the unnatural yohimbine-alkaloid isomer, 17-epi-corynanthine (4), which we were able to isolate also from the reaction mixture. It is not possible to obtain the latter compound by direct reduction of yohimbinone.

From a preparative point of view the preferred procedure is to perform the reduction immediately after the Dieckmann-ring closure without isolation of the unsaturated intermediates. Using highly active Pd catalyst and an elevated (10 atm) pressure, allo-yohimbinone (41d) and epi-allo-yohimbinone (51) are formed in high yields. These compound can be transformed into one another readily, by known methods. Other researchers have also been concerned with the synthesis of yohimbine alkaloids. Among these we particularly wish to mention the excellent work of Winterfeldt and coworkers,[34] Stork and coworkers,[14] and Kametani and coworkers.[35]

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