General Methods of Synthesis of Indole Alkaloids. 14.[1,2] Short Routes of Construction of Yohimboid and Ajmalicinoid Alkaloid Systems and Their ^{13}C Nuclear Magnetic Resonance Spectral Analysis

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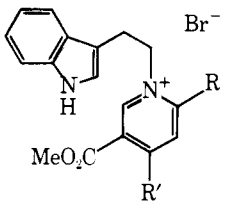
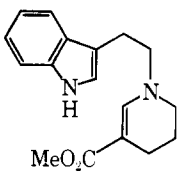
Received September 8, 1975

Abstract: Conceptually new schemes of synthesis of indole alkaloids are introduced. The yohimboid ring system is constructed by the sequential treatment of 1-tryptophyl-3-(β-ketobutyl)pyridinium bromide with base and acid. Hydrogenation of the product yields *d,l*-pseudoyohimbone. The ajmalicinoid ring system is formed by the exposure of 1-tryptophyl-3-acetylpyridinium bromide to sodio dimethyl malonate and then to acid, followed by hydrogenation. Subsequent reduction and dehydration of the products leads to the racemates of the alkaloids tetrahydroalstonine and akuammigine as well as isomers of ajmalicine. Complete carbon shift analyses of yohimboid and ajmalicinoid alkaloids of normal, pseudo, allo, and epiallo configuration have been executed. Shifts of specific carbons are found to be of stereochemically diagnostic value. A general shielding γ effect is observed for the interaction of carbon–hydrogen bonds with spatially rigid and directed electron pair orbitals.

The syntheses of the skeleta of a large number of structurally distinct alkaloids have been executed in recent years by the exploitation of a two-step, general scheme of quinolizidine construction—partial hydrogenation of 1-alkyl-3-acylpyridinium salts and acid-catalyzed cyclization of the resultant 2-piperideines.[4] In the field of indole alkaloids this procedure is illustrated most simply by the preparation of the naturally occurring indoloquinolizidine **3** through the reduction of the nicotinic ester salt **1a** and subsequent decarbomethoxylative cyclization of **2**.[5] The structure of the 2-piperideines used in the cyclization step is not limited to the tetrahydropyridine type, e.g., **2**. Thus, dithionite reduction of the pyridinium salt **1a** yields a 1,4-dihydropyridine derivative (**4**) which, without



1a, R = R′ = H
b, R = Me; R′ = H
c, R = H; R′ = Me



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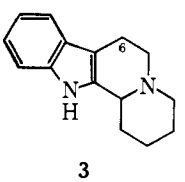

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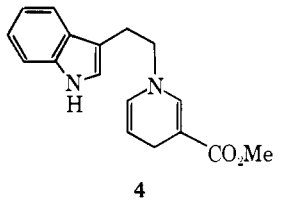

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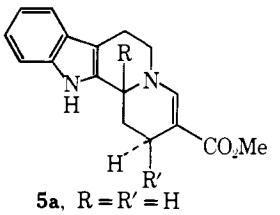
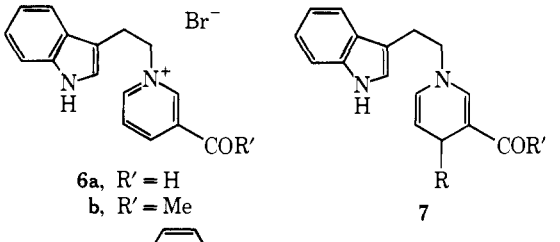


5a, R = R′ = H
b, R = Me; R′ = H
c, R = H; R′ = Me

isolation, is converted into tetracycle **5a** on mild acid treatment.[6] A similar two-step reaction sequence on salts **1b** and **1c**, prepared by the N-alkylation of methyl 6-methylnicotinate[7] and methyl 4-methylnicotinate,[8] respectively, with tryptophyl bromide, produces tetracycles **5b** and **5c**, respectively. The stereochemistry of **5c** was determined by ^{13}C NMR spectroscopy (vide infra). Despite the presence of two enamine units in the intermediates, e.g., **4**, the cyclization proceeds regiospecifically. The vinylogous amide moiety is much less acid sensitive than the unsubstituted enamine function and thus stable in the cyclization process.

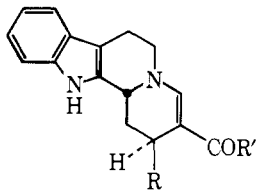
The two-step reaction sequence exemplified by the **1a** → **4** → **5a** transformation has excellent potential of application for the synthesis of yohimboid, ajmalicinoid, and corynanthoid indole alkaloids, if somewhere along the reaction route a proper substituent were introduced on the γ carbon of the original pyridine ring and this substituent and the carbomethoxy group or its equivalent exposed thereafter to chemical alterations necessary to lead to specific alkaloids. While, in principle, the γ substituent could be incorporated in the original pyridine ring prior to salt formation and the initiation of the two-step reaction sequence, a more pleasing and challenging approach would be replacement of the dithionite reduction by γ-substituent introduction as the first step of the two-reaction scheme. Since the reduction is the operational equivalent of nucleophilic hydride attack on the γ-carbon site of 1-alkyl-3-acylpyridinium salts, the alternative method requires nucleophilic carbanion involvement at the same reaction site. This type of reaction was investigated long ago in the form of base-catalyzed condensations of ketones with *N*-alkyl- and *N*-acylpyridinium salts[9-11] and used recently for the synthesis of vallesiachotamine models.[12] In the latter case base-induced condensations of acetone with salts **1a, 6a,** and **6b** and acid treatment of intermediates **7** had produced ketones **8a, 8b,** and **8c,** respectively. While the yields were low, the initial success in launching a new two-step scheme for general alkaloid synthesis led to the pursuit of γ substituents more amenable than the acetonyl unit to desired chemical alteration. After much experimentation exact reaction conditions for the addition of dimethyl malonate to salts **1a, 6a,** and **6b** and subsequent cyclization of compounds **7** were found, thus permitting the preparation of tetracycles **8d, 8e,** and **8f.** Not only was the first reaction difficult especially in view of its reversibility, but this tendency of fragmentation of **7** into the pyridine salt precursors plagued also the second reaction.[13] The stereochemistry of compounds **8a** and **8f** was elucidated by ^{13}C NMR spectroscopy and diester **8f** served as an excellent intermediate in the synthesis of a variety of admalicinoid alkaloids (vide infra).

^{13}C NMR analysis proved to be the simplest method for the determination of the stereochemistry of selected members of the class of tetracycles **5** and **8.** Carbon shift assignment of the least substituted compound **5a** is based on the ^{13}C NMR data



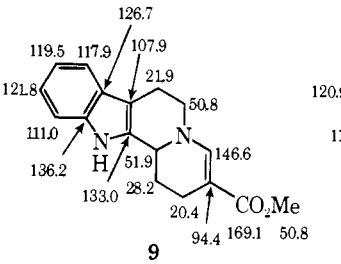
6a, R′ = H
b, R′ = Me

7



8a, R = CH_2Ac; R′ = OMe
b, R = CH_2Ac; R′ = H
c, R = CH_2Ac; R′ = Me
d, R = $CH(CO_2Me)_2$; R′ = OMe
e, R = $CH(CO_2Me)_2$; R′ = H
f, R = $CH(CO_2Me)_2$; R′ = Me

for alkaloid **3** and its relatives[14,15] and methyl 1-methyl-1,4,5,6-tetrahydronicotinate.[16] The benzylic methylene shift of 21.9 ppm is reminiscent of δ(C-6) = 21.8 ppm for compound **3**, a tetracycle possessing a *trans*-quinolizideine unit. The angularly methylated substance **5b** reveals flattening of the *trans*-quinolizideine ring system by the nuclear double bond of the vinylogous amide unit in the form of diminished γ effects of the angular methyl group on the aminomethylene and allylic methylene groups interacting 1,3-diaxially with it. The strong upfield shift of the bridgehead aminomethine and the unperturbed benzylic methylene shift of compound **5c** compared to the like carbon sites of **5a** is clear evidence of the axiality of the methyl group of the former tetracycle and hence of the stereostructure depicted in formula **5c**. Similar considerations establish the stereochemistry of substances **8a** and **8f**. The δ values of compounds **5a, 5b, 5c, 8a,** and **8f** are portrayed on formulas **9, 10, 11, 12,** and **13,** respectively.



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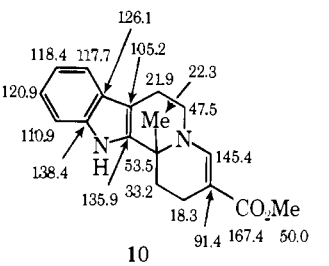

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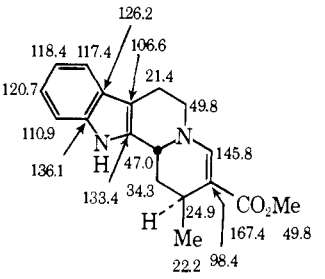

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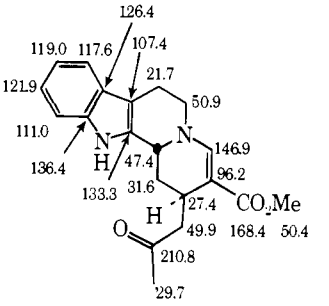

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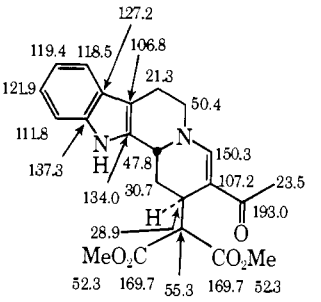

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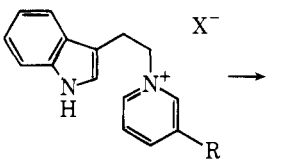
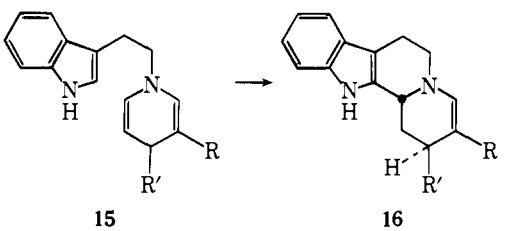
A Route to Yohimboid Alkaloids. Much of the success in the synthesis of amide vinylogs **5** and **8** is associated with the presence of the acyl function in the starting materials **1** and **6** and the intermediates **4** and **7**. The acyl substituent enhances the electrophilicity of the pyridine ring in the nucleophilic addition step, stabilizes one of the double bonds of the dienamine toward acid in the cyclization step, and prevents the remaining enamine unit in the final product from causing acid-catalyzed polymerization. Despite the healthy influence of the acyl group, the two-step reaction scheme would be even more impressive and less constrained in its applicability to alkaloid synthesis, were it operative on nonacylated pyridinium salts. In this event, a salt of structure **14,** for example, might undergo carbanion addition such as to produce dihydropyridine **15,** which, in turn, might be transformed into **16** on exposure to acid. Unfortunately this proposal suffers from deep-seated difficulties. Not only is the regiospecificity of both the addition and cyclization steps difficult to predict, but also the stability of **15** toward air oxidation and other environmental factors and of **16** toward the acid medium in which it is produced are dubious, lending a low probability of success to the reaction scheme. Indeed, no tractable products could be isolated from the reaction of **14** (R = Et) with sodio malonic ester under a large variety of conditions and from related reactions. However, the following exceedingly short synthesis of the yohimboid ring system by an intramolecular equivalent of the **14** → **15** → **16** reaction sequence shows the method under careful control to be successful.



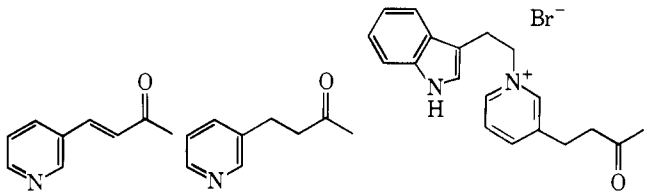
14



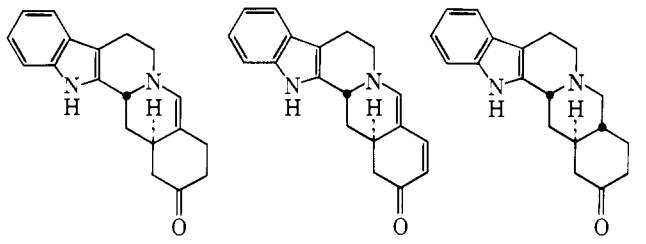
15 **16**

Condensation of nicotinaldehyde with acetone and hydrogenation of the product **17** yielded ketone **18,** whose N-alkylation with tryptophyl bromide gave salt **19.**[17] Careful treatment of the latter first with base and then with mild acid produced pentacyclic ketone **20,** albeit in only 14% yield. Oxidation of the latter with chloranil led to **21,** while hydrogenation yielded *d,l*-pseudoyohimbone (**22**). Identification of this product permitted the assignment of the stereochemistry of ketones **20** and **21.** It is noteworthy that the products of the acid-catalyzed cyclization of **7** and **15,** i.e., **5c, 8,** and **20,** possess uniformly a H(3)-H(15) trans configuration in accord with the notion of the need of a trans-diaxial addition across the double bond of the intermediate immonium salt and a consequent, initial trans-diaxial alignment of the indole ring and nitrogen electron pair in the product.

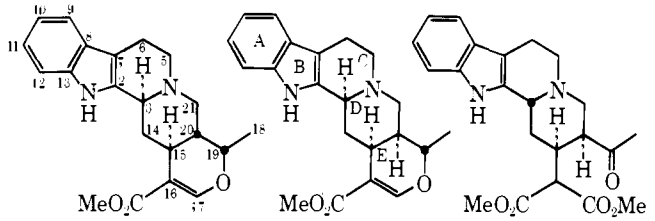
Synthesis of Ajmalicinoid Alkaloids. The tetracycle **8f** appeared to be an ideal intermediate for the synthesis of indole alkaloids of the ajmalicine (**23**) and tetrahydroalstonine (**24**) type. Platinum-catalyzed hydrogenation of **8f** in glacial acetic acid produced keto ester **25**[18] in 49% yield, its 20-epimer (**26**)[18-20] in 12% yield, and their overreduction compounds **27a**



17 18 19

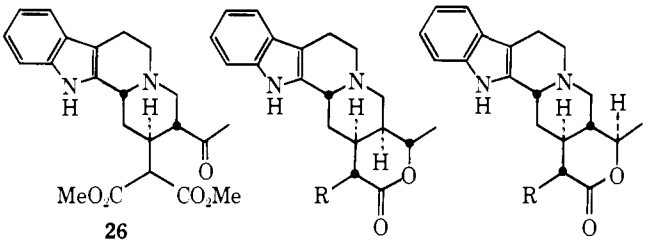


20 21 22



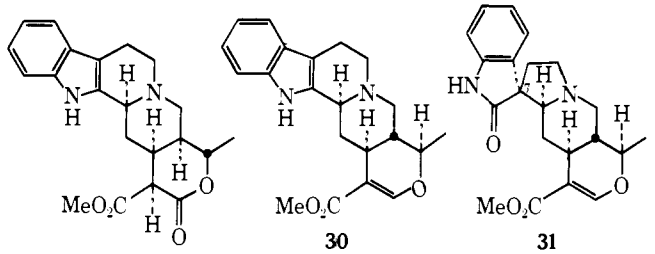
23 24 25

and **28a** in 20 and 5% yield, respectively. Since keto ester **25** is isomerized into **26** in up to 87% yield on contact with acid, the latter and **28a** probably were not direct products of reduction. Hydrogenation of **8f** for an extended period of time or at slightly elevated temperature led to lactone esters **27a** and **28a** as primary products and lactones **27b, 28b,** and **29** as minor products. Under these conditions more intermediate keto ester **25** had isomerized into **26,** increasing the yield of lactone ester **28a** at the expense of **27a.**[21] Lactones **28a** and **28b** proved to



26 27 28

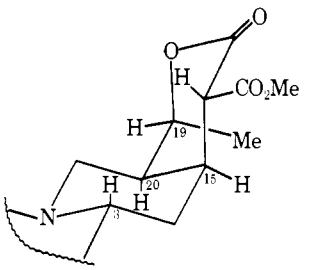
a, R = CO_2Me
b, R = H



29 30 31

be identical with the recently reported product of hydrogenation of keto ester **26** and its decarbomethoxylation product, respectively.[22,23] In view of the previous transformation of keto ester **26** into 3-isoajmalicine and the racemic form of the alkaloid ajmalicine (**23**)[22] and the conversion of 3-iso-19-epi-ajmalicine (3-iso-**30**)[23] into *d,l*-formosanine (**31**) and *d,l*-isoformosanine (7-iso-**31**),[22] the above construction of **26** and **28a** constitutes a formal, total synthesis of the racemates of ajmalicine (**23**)[24] and the two oxindole alkaloids (**31** and 7-iso-**31**).

Mild treatment of keto ester **25** with sodium borohydride produced lactone ester **27a,** the major product of overhydrogenation of the vinylogous amide **8f,** in 68% yield.[25] Acid-catalyzed hydrolysis and decarboxylation of **27a** yielded lactone **27b.** The relative stereochemistry of the lactones **27** was based in part on their derivation from keto ester **25** (i.e., the ring D configuration) and partly on the subsequent conversion of **27a** into *d,l*-akuammigine (i.e., the H-19 configuration) (vide infra). The carbomethoxy group of **27a** was assigned an α, equatorial orientation, thereby causing rings D and E to assume conformation **32** in order to accommodate a *trans*-quinolizideine structure, based on infrared[26] and ^1H NMR[27] spectral evidence regarding the H(3) conformation, and an H(19) equatorial conformation, founded on ^1H NMR coupling data.[27] Sodium borohydride reduction of lactone **27a** and acid-induced dehydration of the product yielded *d,l*-akuammigine (**34**). The intermediate could be isolated in 77% yield and was shown to possess the stereochemistry depicted in **33** on the basis of infrared and ^1H NMR spectral analyses.[18,25,28] The β-acetylpyridine → **6b** (→**7**) → **8f** (→**25**) → **27a** (→**33**) → **34** route constitutes a highly specific synthesis of racemic



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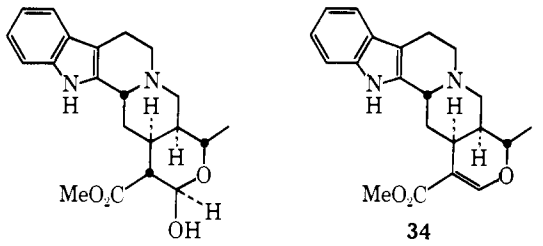
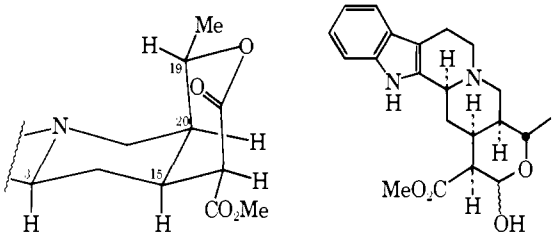


33 34

akuammigine[18,29] and represents the shortest construction of the alkaloid on record. Oxidation of **34** with mercuric acetate and reduction of the resultant 3-dehydro product with sodium borohydride yielded *d,l*-tetrahydroalstonine (**24**).[18,29-31]

Lactone ester **29,** a minor product of the extensive hydrogenation of vinylogous amide **8f** (vide supra), had been assigned the depicted stereochemistry on the basis of the following facts. The ring D configuration relied on the compound's later conversion into **24** (vide infra), and the infrared[26] and ^1H NMR[27] spectrally deduced *trans*-quinolizideine and the ^1H NMR[27] spectrally determined H(19)-H(20) transdiaxial relationship limited the 19-methyl group, and hence also the carbomethoxy unit, to equatorial conformations and the overall structure of **29** to conformation **35.** Sodium bor-

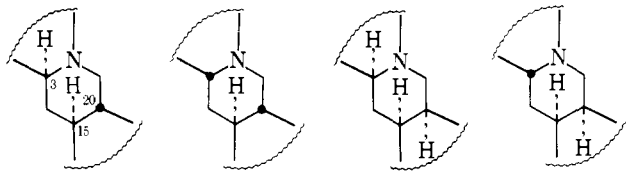


35 36

ohydride reduction of **29** yielded a 17-epimer mixture of hemiacetals (**36**) which, without isolation, was transformed into *d,l*-tetrahydroalstonine (**24**) on acid-catalyzed dehydration. The β-acetylpyridine → **6b** (→**7**) → **8f** → **29** (→**36**) → **24** sequence constitutes an exceedingly short, highly specific synthesis of racemic tetrahydroalstonine (24).[18,29]

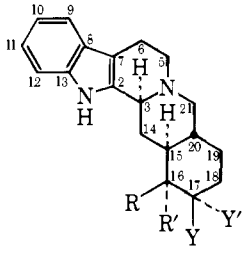
^{13}C NMR Analysis of Yohimboid and Ajmalicinoid Alkaloids.[32] During the period of intense research on the structure of the Rauwolfia alkaloids in the late 1950's and early 1960's, various physical and chemical methods of analysis of the stereostructures of yohimboid, ajmalicinoid, and corynanthoid substances were developed. Most importantly, infrared[26,33] and ^{1}H NMR[27,34] spectral procedures and oxidation-reduction operations[26,30,35] were introduced for the determination of the H(3) configuration of the alkaloids and their derivatives. As a consequence it is only natural that the advent of ^{13}C NMR spectroscopy would lead to the application of this powerful, new tool of structure analysis in this field of alkaloid chemistry. While the ^{13}C NMR interpretation of corynanthoid natural products has been executed already,[14,15,36] the following discussion represents an exhaustive ^{13}C NMR analysis of alkaloids of the yohimboid and ajmalicinoid types.[37,38]

The indole alkaloids under consideration have been categorized in the past on the basis of their ring D stereochemistry in terms of normal (**37**), pseudo (**38**), allo (**39**), and epiallo (**40**)

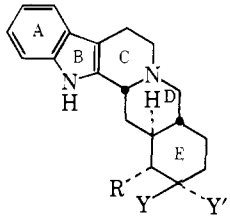


37 **38** **39** **40**

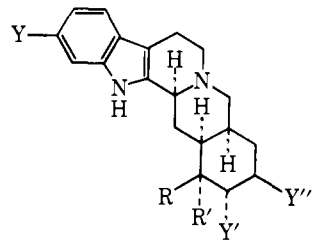
configurations. The ^{13}C NMR analysis of the yohimboid alkaloids of the normal type included yohimbine (**41a**),[39] β-yohimbine (**41b**), and corynanthine (**41c**).[39] Pseudoyohimbine (**42a**) represented the pseudo type, α-yohimbine (**43a**) and alloyohimbine (**43b**) represented the allo system, and 3-epi-α-yohimbine (**44a**), reserpine (**44b**),[39] raunescine (**44c**), and isoraunescine (**44d**) represented the epiallo configuration. Furthermore, the alkaloid derivatives fitted into the following series: normal, yohimbane (**41d**) and yohimbinone (**41e**); pseudo, pseudoyohimbone (**42b**); allo, alloyohimbane (**43c**) and isoreserpine (**43d**); epiallo, epialloyohimbane (**44e**) and methyl reserpate (**44f**).[40]



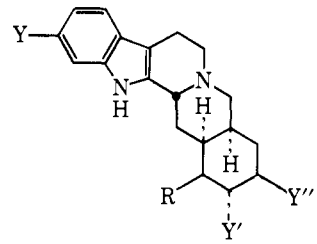
41a, R = Y = H; R′ = CO_2Me; Y′ = OH
b, R = Y′ = H; R′ = CO_2Me; Y = OH
c, R = CO_2Me; R′ = Y = H; Y′ = OH
d, R = R′ = Y = Y′ = H
e, R = H; R′ = CO_2Me; Y + Y′ = O



42a, R = CO_2Me; Y = H; Y′ = OH
b, R = H; Y + Y′ = O



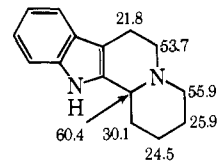
43a, R = CO_2Me; R′ = Y = Y″ = H; Y′ = OH
b, R = Y = Y″ = H; R′ = CO_2Me; Y′ = OH
c, R = R′ = Y = Y′ = Y″ = H
d, R = CO_2Me; R′ = H; Y = Y′ = OMe; Y″ = OTMB



44a, R = CO_2Me; Y′ = OH; Y = Y″ = H
b, R = CO_2Me; Y = Y′ = OMe; Y″ = OTMB
c, R = CO_2Me; Y = H; Y′ = OH; Y″ = OTMB
d, R = CO_2Me; Y = H; Y′ = OTMB; Y″ = OH
e, R = Y = Y′ = Y″ = H
f, R = CO_2Me; Y = Y′ = OMe; Y″ = OH

TMB = 3,4,5-trimethoxybenzoyl

The analysis started by the utilization of the carbon shifts of the tetracyclic alkaloid **45** obtained in a previous study.[14,37,42] For compounds of the normal series, e.g., yohimbane (**41d**), consideration had to be given to the effect expected for the imposition of a trans-fused four-carbon bridge onto C(15) and C(20) of tetracycle **45**.[43] The symmetry of substitution is revealed by the Δδ (**41d**-**45**) value of 6 ppm for



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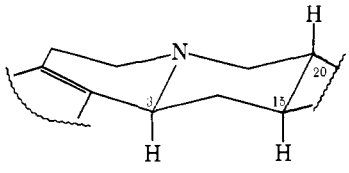
C(14) and C(21). The ring E methylenes of yohimbane (**41d**) fit into two sets of shifts, those of C(17) and C(18) which are most cyclohexane-like and the others deshielded by the neighboring ring carbons. The close shifts of C(17) and C(18) and the initially surprising, more widely separated C(16) and C(19) shifts were differentiated by the analysis of the 16,16,18,18-tetradeuterio derivative of yohimbane (**41d**), prepared by the exhaustive α-deuteration of yohimbone followed by deoxygenation. The 2.4-ppm shielding of C(19) relative to C(16) is an example of the now well-recognized γ-anti-periplanar heteroatom effect[44] exerted by N_b. The ring C carbon shifts of yohimbane (**41d**) and **45** are similar, indicating both substances to possess *trans*-quinolizideine structures.[14]

The introduction of a hydroxy and carbomethoxy group into ring E of yohimbane (**41d**) causes predictable shift changes in exclusively rings D and E. A γ-anti-periplanar effect[44] of ca. −2 ppm by the equatorial 17-hydroxy group is observed in the C(19) shift of β-yohimbine (**41b**). It it be assumed that the same magnitude of the effect is felt by C(15), the β effect of the alkaloid's equatorial 16-carbomethoxy group is ca. 2 ppm. This β effect is maintained in yohimbine (**41a**), as witnessed

by the difference of the γ effects of the compound's axial 17-hydroxy group on C(15) and C(19). Comparison of yohimbine (**41a**) with corynanthine (**41c**) shows the axial 16-carbomethoxy group of the latter to exert γ effects on C(18) and C(20). The shielding of C(14) by the carbomethoxy group of the three alkaloids is independent of the configuration of the C(16) substituent.

Assignment of the proper shifts to the carbons of pseudoyohimbine (**42a**) requires prior recognition of the dramatic change of the ring conformations of normal (**46**) vs. pseudo (**47**) systems, While thus the H(3) configurational alteration



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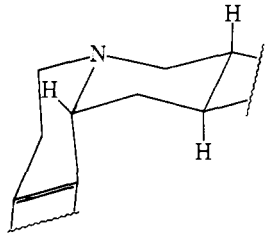

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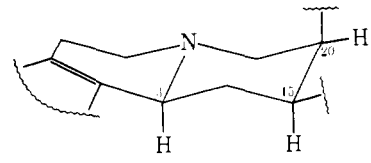
results in negligible shift modification of all ring E carbons except C(15), carbons 3, 6, and 21 experience large shielding in pseudoyohimbine (**42a**) relative to yohimbine (**41a**). The *cis*-quinolizideine form (**47**) of pseudoyohimbine (**42a**) imposes a γ effect on C(15) and C(21) by C(2), axially disposed to ring D, and reciprocal γ effects on C(6) and C(21). In view of its benzylic nature C(6) is distinguished from other methylenes in pseudoyohimbine (**42a**) as well as the other alkaloids by the difference of its one-bond, carbon-hydrogen coupling characteristics in single-frequency, off-resonance decoupled spectra.[45] The strong shielding of C(21) in pseudoyohimbine (**42a**) makes its shift similar to that of the other aminomethylene group. Their differentiation depends on the invariancy of the C(5) shift in pseudoyohimbine (**42a**) and 3-iso-19-epiajmalicine (**50**) (vide infra), a pseudo system in which the C(21) shift is perturbed by a ring E substituent. Despite the C(3) shift similarity with the δ value for C(16) in pseudoyohimbine (**42a**), the C(3) resonance can be identified by its retention in pseudoyohimbone (**42b**).

The yohimboid compounds of allo configuration show ring C carbon shifts nearly identical with those exhibited by the normal series of substances, thereby revealing the presence of a *trans*-quinolizideine conformation (**48**). Comparison of the shift data for α-yohimbine (**43a**) and isoreserpine (**43d**) and taking cognizance of the γ-anti-periplanar,[44] α and β effects exerted on the introduction of an equatorial aroyloxy group at C(18) permit complete ring E shift allocation in the two allo compounds. In particular, the γ-anti-periplanar effect distinguishes the D/E bridgehead carbons.

The difference of the configuration of the 16-substituent in α-yohimbine (**43a**) and alloyohimbine (**43b**) is obvious from the shielding of C(18) and C(20) induced by the axial carbomethoxy group of the latter alkaloid, the constancy of the C(19) shift in both bases, and the deshielding of C(14) on removal of the carbomethoxy-C(14) peri interaction, i.e., a γ effect. The expected similarity of the C(20) shift of α-yohimbine (**43a**) and alloyohimbane (**43c**) differentiates the δ values of the D/E bridgehead carbons of the latter. The ring E methylenes of the unsubstituted pentacycle (**43c**) fall into the following cyclohexane shift pattern: C(18), an unperturbed cyclohexane carbon shift; C(17), one feeling a γ effect from C(14); C(16), deshielded by an axial β effect; and C(20), experiencing opposing shift contributions.

While the ease of N_b inversion and the H(15)-H(20) cis configuration requires consideration of two all-chair D/E *cis*-perhydroisoquinoline conformations for allo and epiallo compounds, conformation **48** is distinctly the more favorable



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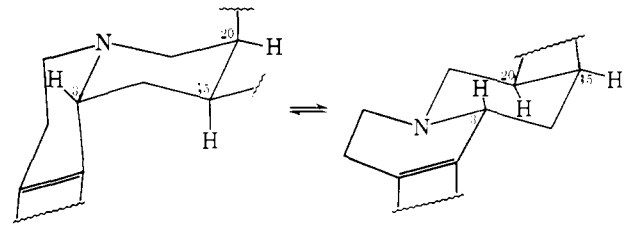
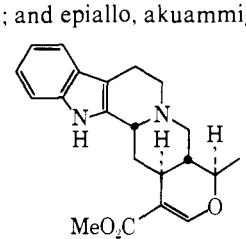


a 49 b

one for alloyohimbane (**43c**) and is not upset by too many axial ring E substituents among the allo compounds inspected above. Contrastingly, the unsubstituted epiallo pentacycle, epialloyohimbane (**44e**), is expected to be portrayed best by conformation **49b**, whereas the alkaloids of epiallo configuration (**44**) are represented best by formula **49a**, since otherwise their two or three ring E substituents would be constrained to an axial conformation. The chemical shifts of the ring C carbons 5 and 6 of epialloyohimbane (**44e**) reflect a *trans*-quinolizideine structure, thus precluding **49a** as the conformation of this epiallo derivative. The C(3) shift differs from that in yohimbane (**41d**) and alloyohimbane (**43c**) (cf. **46** and **48**, respectively) by an added γ effect from C(16). The ring E methylenes reflect by their shifts their mirror image relationship with those of alloyohimbane (**43c**).

The ring C carbon shifts of the natural, epiallo bases (**44**) show them to possess a *cis*-quinolizideine structure (**49a**) equivalent to that characteristic of pseudo compounds (**47**). Since as a consequence the perhydroisoquinoline unit of 3-epi-α-yohimbine (**44a**) and reserpine (**44b**) possesses the same conformational disposition as in α-yohimbine (**43a**) and isoreserpine (**43d**), respectively, the ring E carbon shifts of the two alkaloids of epiallo configuration are nearly the same as the δ values of the allo equivalents, except C(15). Carbon 15 is shielded by a γ effect from C(2). The C(21) shift of **43a** and **43b** differs from that of pseudoyohimbine (**42a**) by a modified β effect from C(19) and the C(14) shift by added γ effects from C(17) and C(19). Comparison of the shift data of raunescine (**44c**), isoraunescine (**44d**), and methyl reserpate (**44f**) with those of reserpine (**44b**) shows the expected changes of δ values on substituent modification.[43] In past ^{13}C NMR studies[38] of reserpine (**44b**),[39] deserpidine,[39] rescinnamine,[40] and methyl reserpate (**44f**)[40] the chemical shifts of C(3), C(5), C(21), and the 17-methoxy group were assigned incorrectly to C(21), the 17-methoxy function, C(5), and C(3), respectively. The shifts of all yohimboid substances are listed in Table I.

The ^{13}C NMR analysis of ajmalicinoid alkaloids and synthetic relatives consisted of the chemical shift assignment of five substances representing the four different structure patterns: normal, ajmalicine (**23**); pseudo, 3-iso-19-epiajmalicine (3-iso-**30** ≡ **50**); allo, tetrahydroalstonine (**24**) and rauniticine (**51**); and epiallo, akuammigine (**34**).[46]



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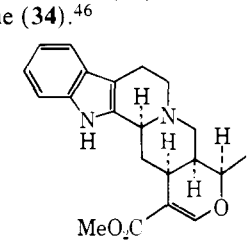

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Table I. ^{13}C Chemical Shifts of Yohimboid Substances[a]

	41a	41b	41c[b]	41d	41e[b]	42a[b]	42b[b]	43a	43b	43c	43d[c,d]	44a[e]	44b[c,d]	44c[d]	44d[d,e]	44e	44f[c]
C(2)	134.3	134.0	135.8	134.7	135.1	134.0	132.1	134.3	134.4	135.7	132.9	131.7	130.2	131.3	131.3	135.5	131.1
C(3)	59.8	59.0	60.5	60.1	58.7	53.7	53.4	60.1	60.1	60.4	59.6	53.7	53.6	53.5	53.4	54.6	53.8
C(5)	52.1	52.3	52.6	52.8	52.3	50.7	50.6	53.2	52.8	53.4	52.8	50.8	51.1	50.8	50.6	53.3	51.3
C(6)	21.5	21.3	21.6	21.4	21.6	16.4	16.7	21.7	21.3	21.7	21.6	16.5	16.7	16.4	16.3	21.9	16.8
C(7)	107.5	107.4	106.3	107.1	106.3	105.9	107.8	108.1	107.1	108.4	107.6	107.3	107.7	107.5	106.8	108.4	108.0
C(8)	127.0	126.9	127.0	127.0	126.5	127.2	127.6	127.1	126.8	127.7	121.4	127.2	121.9	127.3	127.0	127.7	122.4
C(9)	117.7	117.7	117.5	117.6	117.4	117.2	117.9	117.9	117.5	117.9	118.2	117.6	118.2	117.6	117.3	117.7	118.5
C(10)	118.8	118.8	118.4	118.7	118.2	118.1	119.5	119.1	118.6	119.2	108.4	118.9	108.7	119.1	118.7	119.4	109.0
C(11)	120.8	120.9	120.4	120.6	120.2	120.1	121.6	121.1	120.5	121.0	155.6	121.0	155.8	121.2	120.8	121.2	156.2
C(12)	110.6	110.7	111.1	110.6	110.8	111.1	111.0	110.6	110.6	110.5	94.8	110.8	95.0	110.7	110.8	110.7	95.5
C(13)	135.8	135.8	136.1	135.8	135.8	135.5	135.8	135.7	135.8	136.2	136.5	135.6	136.1	135.5	135.6	136.2	136.6
C(14)	33.8	33.8[f]	33.6	36.3	34.5	32.2	34.8	27.6	31.0	31.6	27.6	23.6[f]	24.1	23.7	23.5	35.7	24.3
C(15)	36.4	41.6	34.7	41.3[f]	43.3	32.4	36.6	37.9	37.4	34.8	37.0	32.5	32.2	31.9	32.5	34.8	32.7
C(16)	52.6	57.1	51.1	32.5	61.8	52.4	47.4	54.6	50.6	30.5	51.7	54.1	51.6	52.1	49.9	21.9	51.5
C(17)	66.9	71.6	65.9	26.2	205.7	66.6	210.7	66.0	66.7	20.8	77.5[f]	65.7	77.8[f]	68.3	73.8[f]	26.5	81.6
C(18)	31.4	33.5[f]	28.2	25.8	40.3	30.9	40.8	33.2	30.2	26.5	77.8[f]	33.5	77.7[f]	76.9	72.9[f]	26.5	75.2
C(19)	23.1	27.5	23.5	30.1	29.0	23.0	30.0	24.5	24.8	26.5	30.3	23.9[f]	29.6	29.1	32.5	29.6	32.7
C(20)	40.2	39.1	36.5	41.6[f]	37.9	39.5	39.9	36.4	32.0	36.7	34.6	35.6	33.8	33.7	34.1	34.2	34.7
C(21)	61.0	60.5	62.0	61.7	59.9	51.5	51.2	60.4	59.6	61.9	59.6	49.4	48.8	48.7	48.6	55.1	49.5
C=O	175.1	175.0	172.7		169.5	172.9		174.4	174.0		172.2	174.7	172.5	172.8	171.8		173.5
OMe	51.7	51.6	51.1		51.6	51.2		51.8	51.5		51.7	51.7	51.6	51.7	51.7		51.5

[a] The δ values are in ppm downfield from Me_4Si. Unless otherwise indicated, the spectra are from $CDCl_3$ solutions; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] In Me_2SO-d_6 solution; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. [c] δ(11-OMe) = 55.6 and δ(17-OMe) = 60.5 ppm. [d] The carbon shifts of the 3,4,5-trimethoxybenzoyl group are as follows: δ(C-1) = 124.9, δ(C-2) = 106.7, δ(C-3) = 152.5, δ(C-4) = 141.9, δ(3-OMe) = 56.0 and δ(4-OMe) = 60.6 ppm. The carbonyl shift in **43d** and **44b** is 165.0 ppm, while in **44c** and **44d** it is 165.8 ppm. [e] A trace of ethanol added to increase solubility. [f] Signals in any vertical column may be reversed.

Table II. ^{13}C Chemical Shifts of Ajmalicinoid Substances[a]

	23	50	24	51	34	34-52	34-53
C(2)	134.0	132.4	134.4	134.3	132.8[c]	134.0	130.9
C(3)	59.8	53.8	52.6	58.0	54.5	55.2	53.5
C(5)	52.7	50.9	53.3	52.8	52.2	52.8[e]	51.7[e]
C(6)	21.3	16.8	21.7	21.1	19.2[c]	21.3	16.3
C(7)	106.1[b]	107.4[b]	107.6	107.1[b]	106.8[b]	107.4	106.5
C(8)	126.6	127.3	126.9	127.0	127.2	126.6	126.6
C(9)	117.3	117.6	117.8	117.7	117.7	117.8	117.8
C(10)	118.4	119.1	119.0	119.1	119.1	118.7	118.7
C(11)	120.5	121.3	120.9	121.0	121.2	120.8	120.8
C(12)	110.6	111.1	110.6	110.6	110.8	110.5	111.2
C(13)	135.9	135.7	135.8	135.8	135.7	135.5	135.1
C(14)	32.1	31.2	34.2	32.5	30.6	30.3	30.3
C(15)	30.1	30.8	31.2	29.5	25.7	24.8	25.7
C(16)	106.5[b]	107.7[b]	109.3	107.7[b]	107.6[b]	103.8	109.2
C(17)	154.5	155.9	155.5	154.3	154.8	154.8	155.6
C(18)	14.5	18.0	18.4	19.1	18.4	18.2	18.7
C(19)	73.3	75.3	72.3	76.4	73.2	74.7	71.4
C(20)	40.2	43.8	38.3	34.2	37.2	36.3	36.8
C(21)	56.2	46.8	56.0	53.7	50.3[d]	55.2	44.4
C=O	167.3	167.2	167.8	168.0	167.5	167.8	167.8
OMe	50.6	50.9	51.0	51.0	50.9	51.7	51.7

[a] The δ values are in ppm downfield from Me_4Si; $CDCl_3$ solutions, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Signals in any vertical column may be reversed. [c] Broad, low-intensity signal. [d] Signal missing; shift taken from high-temperature spectrum. [e] Signals may be interchanged.

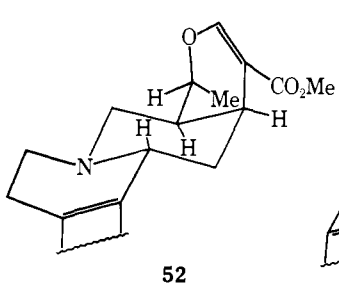
Carbons 16, 17, 18, and 19 of all ajmalicinoid substances reveal ^{13}C NMR signals of characteristic field position and multiplicity,[43] while the ring C carbon shifts, except those for akuammigine (**34**) (vide infra), fit into the patterns of either *trans*- or *cis*-quinolizideine structures. Comparison of the shift data for the normal with the pseudo bases and the allo with the epiallo alkaloids permits allocation of the C(15) and C(20) shifts. The shifts of all ajmalicinoid compounds appear in Table II.

The extensive broadening of the C(2) and C(6) signals in the spectrum of akuammigine (**34**), the unexpected absence of the C(21) signal, and the incompatibility of the C(6) shift with a structure based on either of the two stable conformations of an epiallo system, **49a** and **49b**, suggested that the alkaloid might be involved in a fast equilibrium of conformers in deuteriochloroform solution at room temperature. As a consequence, a study of the temperature dependence of the ^{13}C NMR spectrum of akuammigine (**34**) was undertaken. Above room temperature the C(2) and C(6) signals sharpen and a C(21) signal appears, while at cold temperatures each carbon is represented by two signals, indicative of the presence of two conformers in solution. Since some of the signals are charac-

Table III. Characteristic Shift Ranges of Yohimboid and Ajmalicinoid Substances

			Epiallo	
	Normal or allo	Pseudo or epiallo (C/D cis)	C/D trans	C/D cis and trans
C(3)	60 ± 1	53.5 ± 0.5	54.5 ± 0.5	54 ± 1
C(6)	21.5 ± 0.5	16.5 ± 0.5	21.5 ± 0.5	16–22

teristic of a *trans*-quinolizideine system and others of the cis equivalent, it is reasonable to assume the conformers to be represented by formulas **52** and **53.** On this assumption the shifts of all carbons for both conformers can be assigned (cf. Table II). Thus, for example, the 19.2-ppm methylene signal at room temperature correlates with the 21.3- and 16.3-ppm signals at low temperature, which are identifiable as C(6) shifts for *trans*- and *cis*-quinolizideine units, respectively [cf. δ(C-6) of 21.3 ppm for ajmalicine (**23**) and 16.8 ppm for 3-iso-19-epiajmalicine (**50**)]. Similarly, the 50.3-ppm aminomethylene signal, observed at high temperature, is associated with the low-temperature 55.2- and 44.4-ppm signals, recognizable as belonging to C(21) in *trans*- and *cis*-quinolizideine structures, respectively. While there is a small shift dependence on temperature, it is possible to analyze the conformer ratio at room temperature from the three sets of shift data. With the use of the shifts of C(6), C(19), and C(21), carbons which exhibit large Δδ values between conformers, an equilibrium constant of 1.3 ± 0.1 for the **52**:**53** ratio and a ΔG value of 150–200 cal/mol at 25° are obtained.



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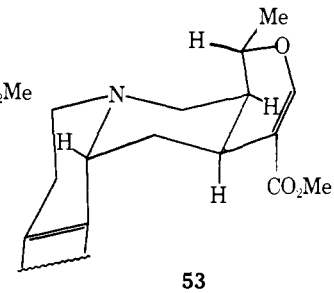

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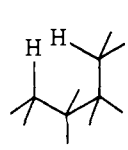
Several facts of interest in alkaloid chemistry emerge from the above, overall ^{13}C NMR analysis of yohimboid and ajmalicinoid substances. The chemical shifts of C(3) and C(6) can be used for configurational and conformational assignments. For D/E trans compounds δ(C-3) and δ(C-6) values of 59–61 and 21–22 ppm, respectively, reflect a normal configuration, while values of 53–54 and 16–17 ppm, respectively, mirror a pseudo configuration. The shielding of C(6) among pseudo compounds is a consequence of this carbon's 1,3-diaxial involvement with C(21). Among D/E cis substances the δ(C-3) and δ(C-6) values of normal substances are characteristic also of allo compounds.[47] In view of the facile equilibrium **49a** ⇌ **49b** the two carbon shifts are variable for epiallo compounds, but diagnostic of their conformational state. The δ(C-3) and δ(C-6) values are those of pseudo compounds in case of conformation **49a,** 54–55 and 21–22 ppm, respectively, in the event of preference of **49b** or 53–55 and 16–22 ppm, respectively, in case of a mixture of conformers. These correlations, summarized in Table III, show that two carbon shifts identify the stereochemistry of the C/D ring juncture. Since the signals of these carbons are easily recognizable, C(3) being the lowest field methine[48] and C(6) being the highest field methylene,[49] their shifts can be of serious aid in the structure analysis of indole alkaloids of the yohimboid, ajmalicinoid, and corynanthoid types. While, finally, C/D trans and conformationally impure epiallo compounds can be identified by their C(3) and C(6) shifts alone, differentiation of D/E trans from D/E cis systems, i.e., normal from allo and pseudo from C/D cis epiallo arrays, rests on their C(14) shifts.

The family of indole alkaloids under consideration consists of substances of enough structural complexity to require the application of most known electronic and steric effects[43] to their ^{13}C NMR analysis. Whereas the steric γ effect is associated commonly with hydrogen-hydrogen nonbonded interactions of the type **54,**[50] the present study reveals examples of γ shifts arising from hydrogen-π bond (**55**)[51] and hydrogen-lone pair (**56** and **57**) interactions. These involvements of a hydrogen with a proximate electron pair are the consequence of the rigid ring system directing the electron pair orbital toward the hydrogen. The following represent illustrations of γ shifts induced by hydrogen-π bond interactions: the shielding of C(15) by C(2) and of C(21) by C(2) and C(6) in pseudoyohimbine (**42a**), 3-epi-α-yohimbine (**44a**), and reserpine (**44b**), as compared with yohimbine (**41a**), α-yohimbine (**43a**), and isoreserpine (**43d**), respectively,[52] and the shielding of C(2) by C(15) and C(21) in all epiallo, C/D cis compounds contrasted with epialloyohimbane (**44e**). As the strong similarity of the C(3) shift in the C/D trans conformer of akuammigine (**34–52**) and epialloyohimbane (**44e**) indicates, the same γ effect is induced by C(16) in either trigonal or tetrahedral form. Related γ effects at C(16) caused by C(3) and C(21) are observed in the C(16) shift of the C/D trans conformer of akuammigine (**34–52**) when compared with that of its alternate conformer (**34–53**). An example of the approximate equality of γ effects emanating from carbon-hydrogen bonds (**54**), π bonds (**55**), and oxygen lone pairs (**56**) is the similarity



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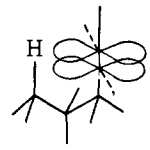

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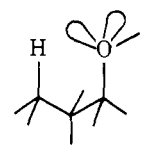

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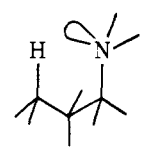
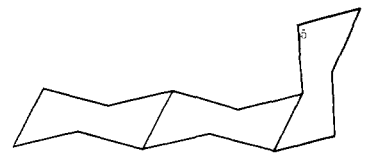


57

of the C(21) shift in the C/D trans conformer of akuammigine (**34–52**) and epialloyohimbane (**44e**). Finally, the identity of the 27 ppm shift for C(19) of alloyohimbane (**43c**) and C(5) of *cis,trans*-perhydroanthracene (**58**),[53] two substances of like



58

overall conformation, shows the γ effect of a nitrogen lone pair (**57**) to be equal to that of a carbon-hydrogen bond. While the γ effect of an electron pair acting on a carbon-hydrogen bond need not be similar in magnitude to that of the well-known hydrogen-hydrogen interaction, the above correlations suggest that an average 4–5 ppm shielding contribution for structural units **54–57** can be used in the analysis of natural products of complex constitution.[55]

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared and ultraviolet spectra were recorded on Perkin-Elmer 137 and Cary 14 spectrophotometers, respectively. Mass

spectra were obtained on Varian CH-7, AEI MS-9, and CEC 21-110 spectrometers. Unless otherwise noted, ^{1}H NMR spectra were run on deuteriochloroform solutions with Me_4Si as internal standard (δ = 0 ppm) and registered on Varian A-60 and HR-220 spectrometers. The ^{13}C NMR spectra were taken on a Varian XL-100-15 FT-NMR spectrometer and a Varian DP-60 spectrometer modified for Fourier transform operation. The δ values denoted on formulas **9** and **12** and those on **10**, **11**, and **13** are based on deuteriochloroform and hexadeuteriodimethyl sulfoxide solutions, respectively.

The conformational equilibrium constant for akuammigine (**34**) was determined by the use of the equation $\delta_{34} = A\delta_{52} + (1 - A)\delta_{53}$, in which A is the mole fraction of conformer **52**.

Pyridinium Salts (1). A solution of 1.34 g of tryptophyl bromide and 0.90 g of methyl 6-methylnicotinate[7] in 5 ml of methanol was kept at room temperature for 24 h. Evaporation of the solution and crystallization of the residue from methanol led to 1.35 g of salt **1b**, mp 224–225 °C. Anal. ($C_{18}H_{19}O_2N_2Br$) C, H, N.

The identical procedure for the interaction of tryptophyl bromide and methyl 4-methylnicotinate[8] gave an 86% yield of salt **1c**, mp 204–205 °C. Anal. ($C_{18}H_{19}O_2N_2Br$) C, H, N.

1,2,6,7-Tetrahydroindolo[2,3-*a*]quinolizines (5). A solution of 0.72 g of salt **1a**[5] in 70 ml of water was covered with 50 ml of ether and purged with nitrogen. Sodium dithionite (4.0 g) was added in portions to the vigorously stirring mixture and the stirring continued for 0.5 h. The aqueous layer was separated, saturated with potassium carbonate, and extracted with ether. The combined ether solutions were dried over anhydrous potassium carbonate and evaporated. A solution of the residue and 2 ml of concentrated hydrochloric acid in 20 ml of methanol was kept for 10 min, then diluted with water and extracted with methylene chloride. The extract was dried over potassium carbonate and evaporated. Crystallization of the residue from chloroform–ether led to 0.34 g (60%) of **5a**, mp 157–158 °C: ir (Nujol) NH 3.01 (m), C=O 6.02 (s), C=C 6.20 (s), 6.28 (m) μ; ^{1}H NMR ($CDCl_3$) δ 1.7–3.7 (m, 8, methylenes), 3.72 (s, 3, Me), 4.3–4.6 (m, 1, NCH), 7.0–7.4 (m, 4, aromatic H's), 7.51 (br s, 1, olefinic H); *m/e* 282 (parent, base), 281, 251, 223, 169, 156; exact mass: *m/e* 282.1375 (calcd for $C_{17}H_{18}O_2N_2$: 282.1368). Anal. ($C_{17}H_{18}O_2N_2$) C, H, N.

The identical procedure executed on salt **1b** gave a 50% yield of **5b**, mp 256 °C: ir (Nujol) NH 3.02 (m), C=O 6.05 (s), C=C 6.20 (s), 6.28 (s) μ; ^{1}H NMR ($CDCl_3$–trace CF_3CO_2H) δ 1.44 (s, 3, Me), 1.7–3.9 (m, 8, methylenes), 3.74 (s, 3, OMe), 7.0–7.6 (m, 4, aromatic H's), 7.70 (br s, 1, olefinic H); *m/e* 296 (parent), 281 (base), 265, 221. Anal. ($C_{18}H_{20}O_2N_2$) C, H, N.

The same procedure enacted on salt **1c** produced a 35% yield of **5c**, mp 240–241 °C: ir (Nujol) NH 3.05 (m), C=O 6.05 (s), C=C 6.24 (s), 6.34 (s) μ; ^{1}H NMR ($CDCl_3$–trace CF_3CO_2H) δ 1.20 (d, 3, J = 7 Hz, Me), 1.7–3.8 (m, 7, methylene, CH), 3.75 (s, 3, OMe), 4.5–4.7 (m, 1, NCH), 7.0–7.6 (m, 4, aromatic H's), 7.70 (br s, 1, olefinic H); *m/e* 296 (parent), 295, 281, 265, 237, 170, 169, 156 (base). Anal. ($C_{18}H_{20}O_2N_2$) C, H, N.

1,2,6,7-Tetrahydroindolo[2,3-*a*]quinolizines (8). Salt **1a**, (2.00 g) was added to a solution of the sodio salt of dimethyl malonate, prepared from 400 mg of sodium hydride and 1.11 g of dimethyl malonate, in 25 ml of 1,2-dimethoxyethane (DME) and the mixture stirred under nitrogen at room temperature for 5 h. The mixture was filtered and the filtrate diluted with 20 ml of dry benzene and cooled to 10°. A solution of 20 ml of dry benzene saturated with dry hydrogen bromide gas was added slowly with stirring and the mixture was stirred at room temperature for 1 h. It then was poured into 150 ml of dry ether, shaken well, and filtered. The filtrate was concentrated to dryness at room temperature and the residue taken up in 5% sodium bicarbonate solution and extracted with chloroform. The extract was washed with saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. Trituration of the oily residue with methanol yielded 780 mg of crystals, mp 213–216 °C, whose crystallization from methanol led to malonate **8d**, mp 217–219 °C: ir (Nujol) NH 3.04 (m), C=O 5.75 (s), 6.05 (s), C=C 6.20 (s), 6.28 (m) μ; uv (MeOH) λ_{max} 224 (ϵ 31 300), 282 (35 000), 291 (36 900) nm; ^{1}H NMR (Me_2SO-d_6) δ 3.48 (s, 3, Me), 3.54, 3.68 (s, 3 each, malonate methyls), 4.49 (dm, 1, J = 11 Hz, NCH), 6.7–7.4 (m, 4, aromatic H's), 7.49 (br s, 1, olefinic H); *m/e* 412 (parent), 381, 353, 282, 281 (base), 280, 279, 221. Anal. ($C_{22}H_{24}O_6N_2$) C, H, N.

A mixture of 2.24 g of tryptophyl bromide and 1.07 g of nicotinaldehyde in 4 ml of absolute methanol was heated at 72° for 1 h and then evaporated. The residual oil was washed with ether. Trituration with 4:1 ether–methanol precipitated 2.50 g of a solid, mp 228 °C, whose crystallization from ether–methanol gave salt **6a**, mp 230 °C dec: ir (Nujol) NH 2.95 (w), C=O 5.87 (s), C=C 6.13 (m), 6.32 (m) μ; uv (MeOH) λ_{max} 218 (ϵ 36 400), 263 (7300), 282 (4600), 288 (3500) nm; ^{1}H NMR (Me_2SO-d_6) δ 3.27 (t, 2, J = 7 Hz, CH_2), 4.82 (t, 2, J = 7 Hz, NCH_2), 6.7–7.5 (m, 5, indole H's), 8.02 (dd, 1, J = 6, 7.5 Hz, pyridine β'-H), 8.46 (br s, 1, pyridine α-H), 8.75 (dt, 1, J = 7.5, 1.2 Hz, pyridine γ-H), 8.97 (dt, 1, J = 6, 1.2 Hz, pyridine α'-H). The procedure for the conversion **1a** into **8d** was applied to 1.66 g of salt **6a.** It yielded 209 mg of a solid whose crystallization from ether–methanol gave tetracycle **8e**, mp 188–191°C; ir (Nujol) NH 2.90 (m), C=O 5.78 (s), C=O, C=C 6.38 (s) μ; uv (MeOH) λ_{max} 224 (ϵ 32 600), 294 (42 700) nm; ^{1}H NMR (Me_2SO-d_6) δ 3.55, 3.69 (s, 3 each, Me), 4.68 (br d, 1, J = 11 Hz, NCH), 7.37 (s, 1, olefinic NCH), 8.67 (s, 1, aldehyde H); *m/e* 382 (parent), 353, 351, 350, 251, 250, 249 (base), 221. Anal. ($C_{21}H_{22}O_5N_2$) N.

Salt **6b:**[54] mp 216–217 °C; ir (Nujol) NH 3.03 (w), C=O 5.87 (s), C=C 6.18 (m), 6.33 (m) μ; uv (MeOH) λ_{max} 219 (ϵ 33 700), 274 (6440), 288 (4010) nm; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3, Me), 3.38 (t, 2, J = 7 Hz, CH_2), 4.95 (t, 2, J = 7 Hz, NCH_2), 6.7–7.5 (m, 5, indole H's), 8.02 (dd, 1, J = 8, 6 Hz, pyridine β'-H), 8.73 (dt, 1, J = 8, 1.5 Hz, pyridine γ-H), 9.00 (dt, 1, J = 6, 1.5 Hz, pyridine α'-H), 9.31 (br s, 1, pyridine α-H). Anal. ($C_{17}H_{17}ON_2Br$) N.

Salt **6b** (5.00 g) was added to a stirring solution of the sodio salt of dimethyl malonate, prepared from 1.04 g of sodium hydride and 3.16 g of dimethyl malonate, in 60 ml of DME under nitrogen and the mixture stirred at 35–40° for 24 h. The precipitated sodium bromide was filtered, and the filtrate was treated slowly with 70 ml of benzene saturated with hydrogen bromide gas, stirred, and heated at 60° for 1 h. After cooling the mixture was filtered and 5% sodium bicarbonate solution and 20:1 chloroform–methanol added to the filtrate. The chloroform extract was washed with saturated brine solution, dried over anhydrous sodium sulfate, passed through a thin layer of anhydrous, powdered magnesium sulfate, and evaporated. The residue was washed with ether leading to 1.67 g of a solid, mp 237–240 °C, whose crystallization from acetone gave ester **8f**, mp 250–253 °C; ir (Nujol) NH 3.09 (m), C=O 5.78 (s), C=O, C=C 6.13 (m), 6.16 (m), 6.34 (s) μ; uv (MeOH) λ_{max} 222 (ϵ 33 200), 302 (36 900) nm; ^{1}H NMR (Me_2SO-d_6) δ 2.08 (s, 3, Me), 2.74 (m, 2, benzyl CH_2), 3.55 (m, 2, NCH_2), 3.57, 3.63 (s, 3 each, OMe), 4.59 (dm, 1, J = 11 Hz, NCH), 6.9–7.5 (m, 4, indole H's), 7.77 (s, 1, olefinic NCH); *m/e* 396 (parent), 395, 364, 363, 353, 266, 265, 264 (base), 221, 131. Anal. ($C_{22}H_{24}O_5N_2$) C, H, N.

All aqueous solutions in the above preparation of **8f** were combined and acidified with 48% hydrobromic acid solution. The resultant precipitate was filtered and mixed with the precipitates which appeared during the chloroform extraction process, and the mixture was air-dried. A hot methanol solution of the solid was treated with Norit, filtered, and then treated with aqueous sodium bromide solution. This work-up sequence led to the recovery of 3.15 g of starting salt **6b.**

Modification of the initial condensation by the substitution of DME by a 3:2 mixture of dimethylformamide and tetrahydrofuran and variation of the subsequent acid-catalyzed cyclization by the use of benzene saturated with dry hydrogen chloride gas produced a 28.4% yield of **8f.** Modification of only the second reaction by the use of 1:1 DME–benzene saturated with hydrogen bromide, 3:2 DME–benzene saturated with hydrogen chloride, 1:1 chloroform–benzene (HBr), 1:1 chloroform–benzene (HCl), dry methanolic hydrogen chloride, and glacial acetic acid led to yields of **8f** of 27.4, 25.3, 28.1, 26.8, 0, and 0%, respectively. Recovery of starting salt **6b** amounted to 60–70% in the first four cases and 94.3 and 85.6% in the last two cases, respectively.

4-(β-Pyridyl-)3-buten-2-one (17). A solution of 6.0 g of freshly distilled nicotinaldehyde and 4.5 ml of 20% aqueous potassium hydroxide in 100 ml of acetone was kept at room temperature for 3 h. Saturated brine solution (200 ml) then was added and the mixture was extracted with chloroform. The extract was washed with 5% sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residual oil over neutral alumina and elution with ether gave 5.2 g of a pale yellow oil of ketone **17:** ir (neat) C=O 6.00 (s), C=C 6.20 (s), 6.31 (m), 6.39 (m) μ; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3, Me), 6.77 (d, 1, J = 18 Hz, H-3), 7.52 (d, 1, J = 18 Hz, H-4), 7.35 (dd, 1, J = 8, 5 Hz, pyridine β'-H), 7.88 (dt, 1, J = 8, 2 Hz, pyridine γ-H), 8.60 (dd, 1, J = 5, 2 Hz, pyridine α'-H), 8.75 (d, 1, J = 2 Hz, pyridine α-H); crystalline red 2,4-dinitrophenylhydrazone, mp 211–213 °C. Anal. ($C_{15}H_{13}O_4N_5$) C, H.

Pyridinium Salt 19. A mixture of 1.1 g of ketone **17** and 150 mg of

10% palladium/charcoal in 50 ml of 95% ethanol was hydrogenated under a pressure of 17 lb/in.^{2} at room temperature for 3 h. Filtration of the catalyst and evaporation of the filtrate yielded 1.1 g of colorless liquid β-(3-ketobutyl)pyridine (**18**): ir (neat) C=O 5.85 (s), C=C 6.27 (w), 6.34 (m) μ; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3, Me), 2.86 (m, 4, CH_2CH_2), 7.15 (dd, 1, J = 8, 5 Hz, β′-H), 7.50 (dt, 1, J = 8, 2 Hz, pyridine γ-H), 8.38 (dd, 1, J = 5, 2 Hz, pyridine α′-H), 8.43 (d, 1, J = 2 Hz, pyridine α-H). A solution of 1.00 g of the latter and 1.00 g of tryptophyl bromide in 5 ml of methanol was kept under nitrogen at room temperature for 60 h. Evaporation of the mixture yielded gummy salt **19**, which was used without further purification in the next reaction (vide infra), but was characterized as a perchlorate by extraction with hot water, addition of sodium perchlorate to the cooled solution, and crystallization of the resultant pale yellow precipitate (1.10 g) from water. This procedure led to the perchlorate equivalent of **19**, mp 112–113 °C: ir (Nujol) NH 3.00 (m), C=O 5.82 (s) μ. Anal. ($C_{19}H_{21}O_5N_2Cl$) C, H, N.

***d,l*-20,21-Didehydropseudoyohimbone (20).** A solution of 5.50 g of salt **19** and 40 ml of 5% sodium bicarbonate was rinsed twice with 30 ml of ether and added to 600 ml of ether. Nitrogen was bubbled through the two-phase system and the mixture stirred during the addition of 60 ml of 40% potassium hydroxide solution. The ether layer gradually turned amber, was decanted from the aqueous phase after 15 min, and stored temporarily over potassium carbonate at 0°. New ether was added to the basic aqueous solution and the procedure repeated three times over a 1.5-h period. The drying agent was filtered from the combined ether solutions and nitrogen bubbling and stirring resumed. Concentrated hydrochloric acid (5 ml) was added slowly and after 2 min the mixture neutralized with saturated sodium bicarbonate. The ether solution was separated and dried over sodium sulfate. An amber solid, which had separated, was dissolved in 9:1 chloroform–methanol and the resultant solution used to extract the aqueous solution. The extract was dried over sodium sulfate, combined with the ether extract, and evaporated. Chromatography of the brown, gummy residue over neutral alumina (activity IV) and elution with methylene chloride yielded a pale yellow solid whose crystallization from ether–chloroform led to 602 mg of ketone **20**, mp 223–224 °C: ir (Nujol) NH 3.00 (m), C=O 5.90 (s), C=C 5.99 (s) μ; ^{1}H NMR ($CDCl_3$) δ 4.16 (m, 1, H-3), 5.98 (s, 1, H-21); ^{13}C NMR (Me_2SO-d_6) C(2) 134.3, C(3) 49.4 (or 49.2 or 50.1), C(5) 50.1 (or 49.2 or 49.4), C(6) 21.2, C(7) 106.8, C(8) 126.7, C(9) 117.3, C(10) 120.4, C(11) 118.2, C(12) 110.9, C(13) 135.7, C(14) 32.6 (or 30.0 or 31.9), C(15) 30.0 (or 32.6 or 31.9), C(16) 31.9 (or 30.0 or 32.6), C(17) 207, C(18) 42.6, C(19) 49.2 (or 49.4 or 50.1), C(20) 110.1, C(21) 131.8 ppm; *m/e* 292 (parent, base), 291, 170, 169, 168, 156; *m/e* (calcd for $C_{19}H_{20}ON_2$: 292.1576) 292.1577.

***d,l*-18,19,20,21-Tetradehydropseudoyohimbone (21).** A solution of 169 mg of ketone **20** and 166 mg of chloranil in 25 ml of dry benzene was stirred under nitrogen for 12 h. The resultant precipitate was filtered and chromatographed on neutral alumina (activity IV) yielding 78 mg of yellow, crystalline solid, mp 249–251 °C, whose sublimation at 175–180° (0.001 Torr) led to **21**, mp 252–253.5 °C: ir (Nujol) C=O, C=C 6.12 (m), 6.30 (s), 6.50 (s) μ; uv (MeOH) λ_{max} 225 (ε 5800), 275 (1400), 400 (3900) nm; ^{1}H NMR ($CDCl_3$) δ 4.90 (s, 1, H-3), 5.50 (d, 1, J = 10 Hz, H-18), 6.59 (s, 1, H-21), 6.89 (d, 1, J = 10 Hz, H-19); *m/e* (calcd for $C_{19}H_{18}ON_2$: 290.1419) 290.1424. Anal. ($C_{19}H_{18}ON_2$) C, H, N.

***d,l*-Pseudoyohimbone (22).** A mixture of 40 mg of ketone **20** and 10 mg of 10% palladium/charcoal in 10 ml of methanol was hydrogenated at atmospheric pressure for 15 h. It was filtered and the filtrate was evaporated. The residue was chromatographed over neutral alumina (activity IV) and eluted with chloroform. Crystallization of the eluted solid from ether–chloroform yielded 34 mg of **22**, mp 249–251 °C: ir (KBr) NH 3.05 (m), C=O 5.91 (s) μ, identical with the spectrum of authentic pseudoyohimbone; ^{1}H NMR ($CDCl_3$) 4.49 (m, 1, H-3); *m/e* 294 (parent), 293 (base), 184, 170, 169, 156. Anal. ($C_{19}H_{22}ON_2$) C, H, N.

Keto Esters 25 and 26. A mixture of 600 mg of ester **8f** and prereduced Adams catalyst (from 300 mg of platinum oxide) in 40 ml of glacial acetic acid was hydrogenated at 15–18° for 9 h, during which time 1.8 equiv of hydrogen had been absorbed. The mixture was filtered and the filtrate evaporated under reduced pressure at room temperature. A methylene chloride solution of the residual oil was washed with 5% sodium bicarbonate solution and with water, dried over sodium sulfate, and evaporated. Crystallization of the oily residue (626 mg) from methylene chloride and from 1:1 methylene chloride–ether yielded 53 mg (9%) of starting ester **8f.** The mother liquors were evaporated and the residue subjected to fractional crystallization in various solvents. Acetone–ether gave 68 mg (12%) of lactone ester **27a**, mp 206–208 °C, (vide infra) and ether yielded 219 mg (37%) of keto ester **25**, mp 161–162 °C, and 57 mg of a mixture containing mostly **25.** The mother liquors and the latter mixture were separated by preparative TLC on Brinkmann silica gel PF-254 and plate development with 12:1:1 benzene–acetone–*n*-propyl alcohol. After exposure of the plates to air for a week, each band was extracted with acetone at room temperature. The R_f 0.70 band gave 75 mg of a mixture whose crystallization from ether afforded 51 mg (9%) of more keto ester **25**, mp 162–163 °C (lit.[18] mp 162 °C); ir and ^{1}H NMR spectra identical with literature values.[18] The crystallization mother liquor revealed by TLC the presence of a 3:2 mixture of **25** and **26.** The R_f 0.65 band yielded 33 mg (6%) of more lactone ester **27a**, mp 207–210 °C, (vide infra) on crystallization from acetone–ether. Crystallization of the solid extracted off the R_f 0.60 band from ether gave 68 mg (11%) of keto ester **26**, mp, mmp 199–201 °C [lit.[18] mp 198.5 °C], identical in all respects with an authentic sample.[20] The R_f 0.36 band led to 37 mg (5%) of lactone ester **28a**, mp 208–211 °C, (vide infra) on crystallization from acetone–ether.

Stirring of a methanolic suspension of silica gel and keto ester **25** at room temperature for 20 h produced a 3:1 mixture of isomers **25** and **26**, respectively. This ratio dropped to 3:2 on keeping a methanol solution of **25**, containing a trace of hydrogen chloride, at room temperature for 20 h and became 1:2 on mild heating of a solution saturated with hydrogen chloride for 12 h. An acetone solution of 100 mg of **25** was spotted on a silica gel TLC plate. After being dried in a desiccator for 12 h the chromatogram was developed for a 2-cm distance with 11:1:1 benzene–acetone–*n*-propyl alcohol and dried for 3 h (product isolation after one development led to 59 mg of **26** and a mixture of **25** and **26**). Further development to 4 cm, followed by 3 h drying and, finally, total development and extraction with acetone led to an oil whose crystallization from ether gave 87 mg of **26**, mp 200–201 °C.

Lactones 27. A solution of 40 mg of keto ester **25** and 25 mg of sodium borohydride in 2 ml of 2:1 absolute methanol–dry tetrahydrofuran was kept at −35 to −30° for 90 min, i.e., until by TLC all starting material had disappeared. The mixture was poured onto ice and water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated. Crystallization of the oily residue with acetone–ether yielded 27 mg of lactone ester **27a**, mp 207–210 °C: ir ($CHCl_3$) NH 2.87 (m), CH[26] 3.49 (m), 3.53 (m), 3.58 (m), C=O 5.77 (s), 5.78 (s) μ; uv (MeOH) λ_{max} 224 (ε 29 800), 282 (6580), 290 (5480) nm; ^{1}H NMR ($CDCl_3$) δ 1.48 (d, 3, J = 7 Hz, Me), 3.79 (s, 3, OMe), 4.50 (dd, 1, J = 7, 3 Hz, H-19); *m/e* 368 (parent, base), 367, 309, 251, 223, 184, 169. Anal. ($C_{21}H_{24}O_4N_2$) C, H, N.

A solution of 30 mg of lactone ester **27a** and 0.15 ml of 2 N hydrochloric acid in 3 ml of glacial acetic acid was refluxed for 2.5 h and then evaporated. A methylene chloride solution of the residue was washed with 5% sodium carbonate solution, dried over anhydrous magnesium sulfate, and evaporated. Crystallization of the residue with methanol–chloroform gave 14 mg of a crystalline solid, mp 277–278 °C, whose recrystallization from methanol led to lactone **27b**, mp 283–285 °C: ir (Nujol) NH 2.95 (m), CH[26] 3.45 (m), 3.47 (m), C=O 5.78 (s) μ; uv (MeOH) λ_{max} 224 (ε 38 000), 283 (7300), 290 (5960) nm; *m/e* 310 (parent), 309 (base), 223, 221, 181, 170, 169, 155, 143. Anal. ($C_{19}H_{22}O_2N_2$) C, H, N.

Lactones 28 and 29. A mixture of 800 mg of ester **8f** and prereduced Adams catalyst (from 400 mg of platinum oxide) in 50 ml of glacial acetic acid was hydrogenated at 18–20° for 62 h, during which time 6.0 equiv of hydrogen had been absorbed. The mixture was filtered and the filtrate evaporated under vacuum at room temperature. A methylene chloride solution of the residue was washed with 5% sodium bicarbonate solution and with water, dried, and evaporated. The residual oil (836 mg) was separated by preparative TLC (Brinkmann silica gel PF-254, 8:1:1 benzene–acetone–*n*-propyl alcohol). All chromatographic components were extracted with acetone except for the R_f 0.15 fraction, which was extracted with 2:1 acetone–methanol.

An ether solution of the oily R_f 0.80 fraction was filtered through anhydrous magnesium sulfate powder. Concentration of the filtrate and crystallization of the solute produced 29 mg (4%) of lactone ester **29**, mp 154–156 °C: ir ($CHCl_3$) NH 2.88 (m), CH[26] 3.49 (m), 3.54 (m), 3.59 (m), C=O 5.75 (s), 5.82 (s) μ; uv (MeOH) λ_{max} 224 (ε 33 050), 279 (7500), 290 (5680) nm; ^{1}H NMR ($CDCl_3$) δ 1.45 (d,

3, J = 6.5 Hz, Me), 3.80 (s, 3, OMe), 4.98 (dd, 1, J = 9.5, 6.5 Hz, H-19); *m/e* 368 (parent, base), 367, 337, 336, 310, 309, 253, 223, 184, 170, 169, 168, 156. Anal. ($C_{21}H_{24}O_4N_2$) C, H, N.

Crystallization of the R_f 0.74 fraction (350 mg) from acetone–ether gave 250 mg (34%) of lactone ester **27a**, mp 207–210 °C (vide supra), while crystallization of the R_f 0.61 fraction from methanol produced 6 mg (1%) of lactone **27b**, mp 282–284 °C (vide supra). Crystallization of the R_f 0.30 fraction (211 mg) from acetone–ether yielded 192 mg (26%) of lactone ester **28a**, mp, mmp 208–211 °C (lit.[22] mp 203 °C dec): identical ir, uv, and ^{1}H NMR spectra with those of an authentic sample prepared by the hydrogenation of keto ester **26**[20] according to a known procedure.[22] Crystallization of the R_f 0.12 fraction from methanol led to 19 mg (3%) of lactone **28b**, mp, mmp 283–285 °C (lit.[22] mp 230 °C sublimed); ir, uv, and ^{1}H NMR spectra identical with those of an authentic sample prepared by the hydrogenation of keto ester **26**[20] followed by acid-catalyzed hydrolysis and decarboxylation according to a prescribed scheme.[22]

Another hydrogenation of ester **8f** in the same mixture as above was carried out at 30° for 42 h, at which time 4 equiv of hydrogen had been absorbed. This reaction yielded 42 mg (6%) of lactone ester **29**, 160 mg (22%) of lactone ester **27a**, 18 mg (3%) of lactone **27b**, 220 mg (28%) of lactone ester **28a**, and 48 mg (7%) of lactone **28b**.

***d,l*-17β-Hydroxy-16β,17α-dihydroakuammigine (33).** Sodium borohydride (80 mg) was added portionwise to a stirring solution of 200 mg of lactone ester **27a** in 10 ml of 2:1 absolute methanol–dry tetrahydrofuran at −30 to −25° and the mixture kept at this temperature for 8 h. It then was poured into ice water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated. Separation of the residual oil (182 mg) on preparative TLC, extraction with acetone, and crystallization of the solute from methylene chloride gave 155 mg of hemiacetal ester **33**, mp, mmp 179–181 °C (lit.[18] mp 198 °C); melting point and ir and ^{1}H NMR spectra identical with those of a sample of **33** prepared by a literature procedure[18] for the one-step reduction of keto ester **25**: ir ($CHCl_3$) OH 2.80 (m), NH 2.95 (m), CH[26] 3.48 (w), 3.52 (w), 3.59 (w), C=O 5.78 (s) μ; ^{1}H NMR (Me_2SO-d_6) δ 1.28 (d, 3, J = 6.5 Hz, Me), 3.73 (s, 3, OMe), 3.78 (dq, 1, J = 6.5, 3 Hz, H-19), 4.95 (dd, 1, J = 7.5, 6 Hz, H-17), 6.25 (d, 1, J = 6 Hz, OH); ^{1}H NMR ($CDCl_3$, trace Me_2SO-d_6) δ 1.30 (d, 3, J = 6.5 Hz, Me), 3.73 (s, 3, OMe), 3.85 (dq, 1, J = 6.5, 3 Hz, H-19), 5.07 (d, 1, J = 7.5 Hz, H-17). Anal. ($C_{21}H_{26}O_4N_2$) C, H, N.

***d,l*-Akuammigine (34).** Treatment of ester **33** with polyphosphoric acid in DME by the literature procedure[18] yielded the racemic alkaloid **34**, mp, mmp 143 °C, 199–200 °C (lit.[18] mp 203 °C sublimed); ir and ^{1}H NMR spectra were identical with those of an authentic sample.[20] Anal. ($C_{21}H_{24}O_3N_2$) N.

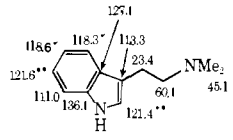
***d,l*-Tetrahydroalstonine (24).** Treatment of 50 mg of **34** with 266 mg of mercuric acetate by the 1956 procedure[30] gave 33 mg of 3-dehydro-**34** perchlorate, whose reduction with 93 mg of sodium borohydride in 4 ml of absolute methanol by the published procedure[30] gave a mixture. Purification of the latter by preparative TLC on Brinkmann silica gel PF-254 with 18:1:1 benzene–acetone–isopropyl alcohol yielded a R_f 0.75 band and a R_f 0.40 band from which 5 mg of *d,l*-akuammigine (**34**), mp 142–144 °C, could be isolated. Crystallization of the R_f 0.75 solid from ethanol produced 27 mg of *d,l*-tetrahydroalstonine (**24**), mp, mmp 200–201 °C (lit.[18] mp 222 °C); ir and ^{1}H NMR spectra identical with those of an authentic sample.

A solution of 45 mg of lactone ester **29** and 10 mg of sodium borohydride in 2 ml of 2:1 absolute methanol–dry tetrahydrofuran was stirred at −30 to −20° for 3 h. More hydride (7 mg) was added and the stirring continued for an additional 2 h. The mixture was poured into ice water and extracted with methylene chloride. The extract was dried and evaporated. Purification of the residual oil by preparative TLC on silica gel, development of the chromatogram with 18:1:1 benzene–acetone–*n*-propyl alcohol, and extraction of the R_f 0.5–0.6 band with acetone led to 40 mg of an oil, which consisted of a ca. 8:7 mixture of hemiacetal ester epimers **36**: ir ($CHCl_3$) OH 2.80 (w), NH 2.90 (m), CH[26] 3.49 (m), 3.53 (m), 3.60 (m), C=O 5.78 (s), 3.83 (s) μ; ^{1}H NMR ($CDCl_3$) δ (major isomer) 1.21 (d, 3, J = 7 Hz, Me), 3.73 (s, 3, OMe); δ (minor isomer) 1.27 (d, 3, J = 7 Hz, Me), 3.81 (s, 3, OMe). This oil was used in the next reaction without further purification.

A mixture of 30 mg of **36** and 1 drop of polyphosphoric acid in 1 ml of dry DME was kept at 60° for 1 h. The mixture was poured into ice water, neutralized with 5% sodium bicarbonate solution, and extracted with methylene chloride. The extract was washed with water, dried, and evaporated. Purification of the residual oil (27 mg) by preparative TLC in the above manner and crystallization of the R_f 0.75 solid from ethanol yielded 17 mg of *d,l*-tetrahydroalstonine, mp, mmp 200–201 °C; ir and ^{1}H NMR spectra identical with those of an authentic sample.

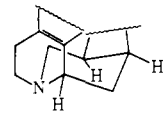
References and Notes

(1) Support by the U.S. Public Health Service acknowledged gratefully.
(2) Part XIII: E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and D. E. Rearick, *J. Org. Chem.*, **39**, 1662 (1974).
(3) U.S. Public Health Service Predoctoral Fellow, 1967–1971.
(4) E. Wenkert, *Acc. Chem. Res.*, **1**, 78 (1968).
(5) E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, **87**, 5461 (1965).
(6) Cf. J. H. Supple, D. A. Nelson, and R. E. Lyle, *Tetrahedron Lett.*, 1645 (1963).
(7) K. Isagawa, M. Kawai, and Y. Fushizaki, *Nippon Kagaku Zasshi*, **88**, 553 (1967).
(8) E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.*, **38**, 4305 (1973).
(9) E. Ghigi, *Ber.*, **73**, 677 (1940); **75**, 764 (1942).
(10) W. v. E. Doering and W. E. McEwen, *J. Am. Chem. Soc.*, **73**, 2104 (1951).
(11) F. Krohnke, K. Ellegast, and E. Bertram, *Justus Liebigs Ann. Chem.*, **600**, 176, 198 (1956).
(12) E. Wenkert and G. D. Reynolds, *Synth. Commun.*, **3**, 241 (1973).
(13) Even attempts of hydrogenation of **7** over platinum or palladium led to products from which the malonic ester residue had been extruded.
(14) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974).
(15) M. C. Koch, M. M. Plat, N. Préaux, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, **40**, 2836 (1975).
(16) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).
(17) These compounds were produced first by R. G. Lewis, Ph.D. Dissertation, Indiana University, 1966.
(18) Cf. E. Winterfeldt, H. Radunz, and T. Korth, *Chem. Ber.*, **101**, 3172 (1968).
(19) The numbering system is based on that customarily used for the ajmalicinoid alkaloids.
(20) The authors acknowledge gratefully the kind gift of a sample of this substance by Professor Winterfeldt.
(21) While the acid medium must have been responsible for the hydrolysis and decarboxylation of **27a** and **28a** and resultant formation of lactones **27b** and **28b**, respectively, the H(3) isomerization inherent in the production of lactone ester **29** could have been the consequence of acid-catalyzed C(2)–C(3) bond cleavage and re-formation or platinum-induced C(3)–H oxidation–reduction.
(22) E. Winterfeldt, A. J. Gaskell, T. Korth, H.-E. Radunz, and M. Walkowiak, *Chem. Ber.*, **102**, 3558 (1969).
(23) Compound **28a** has been converted into the as yet unnatural ajmalicinoid substances 3-iso-19-epiajmalicine and 19-epiajmalicine (**30**).[22]
(24) For other syntheses of *d,l*-ajmalicine (**23**) see E. E. van Tamelen and C. Placeway, *J. Am. Chem. Soc.*, **83**, 2594 (1961); E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, *ibid.*, **91**, 7359 (1969); J. Gutzwiller, G. Pizzolate, and M. Uskoković, *ibid.*, **93**, 5907 (1971).
(25) Borohydride reduction of **25** has been reported previously to yield 17-dihydro-**27a** of inverted H(16) and H(17) configuration.[18,28]
(26) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956); **80**, 1613 (1958).
(27) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Am. Chem. Soc.*, **83**, 5037 (1961); *Tetrahedron Lett.*, 822 (1961).
(28) Hemiacetal **33** appears to be identical with the substance reported for the reduction of **25**.[18,25] The previous incorrect assignment of the stereochemistry of H(16) and H(17)[18] stems from the lack of appreciation of the presence of a weak C–H stretching band in the infrared spectrum of **33**, characteristic of a *trans*-quinolizideine structure,[26] and from the mistaken identification of the 4.37- and 5.00-ppm ^{1}H NMR signals as representing H(17) and H(3), respectively.
(29) For another synthesis of *d,l*-akuammigine (**34**) and *d,l*-tetrahydroalstonine (**24**), see J. Gutzwiller, G. Pizzolate, and M. Uskoković, *J. Am. Chem. Soc.*, **93**, 5907 (1971).
(30) E. Wenkert and D. K. Roychaudhuri, *J. Org. Chem.*, **21**, 1315 (1956).
(31) The transformation of racemic **34** into *d,l*-**24** has been accomplished previously by lead tetraacetate oxidation followed by sodium borohydride reduction of the resultant ring C tetradehydro product.[18]
(32) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXVIII. For the preceding paper see R. C. Cambie, I. R. Burfitt, T. E. Goodwin, and E. Wenkert, *J. Org. Chem.*, **40**, 3789 (1975).
(33) The first description of the presence of characteristic 3.4–3.7 μ carbon–hydrogen stretching vibration bands in the infrared spectra of Rauwolfia alkaloids of certain H(3) configuration appeared in 1956.[26] The same infrared bands were discovered soon thereafter among alkaloids of the sparteine type [F. Bohlmann, W. Weise, H. Sander, H.-G. Hanke, and E. Winterfeldt, *Chem. Ber.*, **90**, 653 (1957); F. Bohlmann, *ibid.*, **91**, 2157 (1958); **92**, 1798 (1959)] and were considered to be characteristic of *trans*-quinolizidine structures. The infrared method of analysis has found general acceptance, especially in the alkaloid field, during the last twenty years. For unexplained historical and sociological reasons the unique infrared absorption has become known as the "Bohlmann bands".
(34) W. E. Rosen and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 4816 (1961); E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962).
(35) F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956).
(36) The indole α-carbon shift of *N,N*-dimethyltryptamine was reported erroneously as 128.2 ppm. It actually is as indicated on formula i, which denotes the δ values of all carbons of the alkaloid.



i

(37) D. W. Cochran, Ph.D. Dissertation, Indiana University, 1971.
(38) Three investigations on the carbon shift assignments of a limited number of Rauwolfia alkaloids were published[39-41] some time after completion of the 1971 study.[37]
(39) R. H. Levin, J.-Y. Lallemand, and J. D. Roberts, *J. Org. Chem.*, **38**, 1983 (1973).
(40) T. Kametani, T. Higa, M. Ithara, K. Fukumoto, M. Kajiwara, Y. Fujimoto, and G. Tanaka, *J. Heterocycl. Chem.*, **12**, 259 (1975).
(41) G. van Binst and C. Tourwe, *Heterocycles*, **1**, 257 (1973).
(42) G. W. Gribble, R. B. Nelson, G. C. Levy, and G. L. Nelson, *J. Chem. Soc., Chem. Commun.*, 703 (1972); 148 (1973).
(43) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(44) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(45) E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, in "Topics in Carbon-13 NMR Spectroscopy", Vol. II, G. C. Levy, Ed., Wiley-Interscience, New York, N.Y., 1976.
(46) The ^{13}C NMR spectrum of a sixth substance, reserpiline (10,11-dimethoxyakuammigine), was inspected also. Its nonaromatic carbons exhibit shifts identical with those of like carbon centers of akuammigine (**34**), while its extra methoxy shifts are 56.0 and 56.4 ppm and the shifts of its indole carbons 2, 7, 8, 9, 10, 11, 12, and 13 are 131.9, 107.2, 120.2, 100.4, 146.3, 144.7, 95.2, and 130.1 ppm, respectively.
(47) This is based on conformation **48** always representing the allo configuration. There is, however, the remote possibility of conformationally unfavorable substitution of ring E leading to the alternate conformation ii. The low δ(C-3) value of rauniticine (**51**) probably is the consequence of a low concentration of conformer ii for this alkaloid in deuteriochloroform solution.



ii

(48) In yohimboid compounds possessing a 16-carbomethoxy group the α-ketomethine signal appears in the 50–57-ppm range. While the C(3) signal of pseudo and epiallo systems lies within this region, no confusion arises in the ^{13}C NMR analysis, since the absence of a 60 ± 1 ppm methine signal negates a normal or allo configurational interpretation.
(49) While the ring E unsubstituted bases may exhibit an additional upfield methylene signal, the C(6) signal is recognized easily by virtue of its unique coupling characteristics (benzylic $^{R}J_{CH} \neq$ alicyclic $^{R}J_{CH}$).[45]
(50) Cf. D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **94**, 5318 (1972).
(51) Cf. F. Näf, B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, and E. Wenkert, *Helv. Chim. Acta*, **58**, 1567 (1975).
(52) The reciprocity of the γ effect is difficult to assess in the case of **42a** in view of its spectrum having been run in Me_2SO-d_6 solution, wherein the shift of the aminocarbon, C(2), is affected strongly by the polar solvent.
(53) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **96**, 1827 (1974).
(54) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965).
(55) NOTE ADDED IN PROOF. A recent ^{13}C NMR analysis of **45** and its derivatives [G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, **40**, 3720 (1975)] necessitated the revision of the C(9) and C(10) shifts of ring A unsubstituted, tetrahydrocarboline-based alkaloids and derivatives, initially proposed by R. G. Parker and J. D. Roberts, *J. Org. Chem.*, **35**, 996 (1970). The analysis contains an incorrect assignment of the aminomethylene shifts of the H(3)–H(15) cis isomer of 15-*t*-Bu-**45**. The interchange of the δ values for C(5) and C(21) removes the apparent anomaly of the C(5) shift.

Synthesis of Thymidine Oligonucleotides by Phosphite Triester Intermediates[1]

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Abstract: A synthetic procedure for building phosphotriester derivatives of oligothymidylates is described which involves four chemical steps for addition of each nucleotide unit: (1) reaction of $ROPCl_2$ with 5′-*O*-phenoxyacetylthymidine in tetrahydrofuran at −78° (5 min); (2) reaction of the resulting phosphoromonochloridite with 3′-*O*-mono-*p*-methoxytritylthymidine or a related oligonucleotide phosphotriester which possesses a 5′-OH group, also in tetrahydrofuran at −78° (10–20 minutes); (3) oxidation of the resulting phosphite with iodine and water (a few minutes at −10 to 0°); and (4) hydrolytic cleavage of the phenoxyacetic ester at the terminal 5′ position by ammonium hydroxide in aqueous dioxane (10 min). Best results were achieved with R = Cl_3CCH_2–; yields at the di, tri, tetra, and penta stage of synthesis were 95, 69, 75, and 69%, respectively. The corresponding phosphodiesters, dTpT, dTpTpTpT, and dTpTpTpTpT were obtained from the triesters by reaction with sodium–naphthalene in hexamethylphosphoric triamide (94, 69–71, and 59% yield, respectively). *o*-$ClC_6H_4OPCl_2$ was also employed as the phosphorylating agent. This reagent was satisfactory for the synthesis of triesters related to dithymidine phosphate, but did not prove suitable for synthesis of longer chains.

In spite of extensive experimental work and numerous improvements in methodology,[2] the stepwise synthesis of arbitrarily defined oligonucleotides remains a difficult and time consuming operation. Ideally, one would hope to automate repetitive step syntheses of the type required in preparing oligonucleotides. To date, however, the yields in condensation reactions conducted on insoluble supports, which offer the best opportunity for automation, have not been sufficiently high to afford a practical synthetic procedure.[3]

In pursuing this problem we have explored new approaches to generating internucleotide links. We report in this paper a novel coupling procedure that involves intermediate phosphite links. Although the potential and limitations of the method have not yet been fully investigated, the short reaction times and the relatively good yields are distinctive features of considerable promise.

The basis for this approach was the observation that phosphorochloridites, such as $(C_2H_5O)_2PCl$ and $C_6H_5OPCl_2$, react very rapidly at the 3′-OH of nucleosides in pyridine, even at very low temperatures.[4] By contrast, the reactions of the analogous chloridates $(RO)_2POCl$ and $ROP(O)Cl_2$ require several hours at room temperature.[5,6] The latter condensations can be accelerated by *N*-alkylimidazoles;[7] however, such reactions are complicated by the fact that the base ring (e.g., the thymine or *N*-benzoyladenine moiety) may be attacked as well as the sugar hydroxy groups.[8] Two subsequent findings of importance were: (1) dinucleoside monophosphite triesters can be oxidized essentially quantitatively to the corresponding