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The Biogenetic-Type Total Synthesis of Ajmaline

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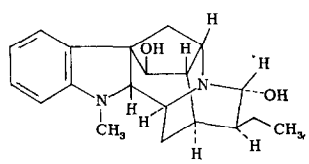
Chemical steps **14**→**15**→**20**→**21**→**22**→**23a**→**23b**→**24a**→**24b**→**25**→**29**→**30**→**42**→**43**→**44**→**45**→**46**→**1** constitute the first biogenetic-type total synthesis of the indole alkaloid ajmaline.

Possessing four heteroatoms, six rings and nine asymmetric centers, the well-known indole alkaloid ajmaline (**1**) presents a challenging opportunity for total synthesis patterned after the biochemical pathway which leads to this complex, naturally occurring system. Described herein is a sequence which features several chemical changes related to obligatory key steps in the biosynthesis and constitutes the first biogenetic-type total synthesis of **1** (*1*).



1

Subsequent to several preliminary suggestions by Robinson (*2*, *3*), the correct structure of ajmaline was proposed in 1956 by Woodward (*4*) and Schenker, who drew on a combination of biological and chemical evidence in arriving at their favored expression. In 1962, the stereochemistry portrayed in structure **1** was assigned (*5*) on the basis of additional chemical and spectral observations. In view of the biological incorporation of tryptophan (*6*) and loganin (*7*, *8*) into ajmaline, an overall biosynthesis scheme for the alkaloid can be put forth (Chart I). During the course of monoterpenoid indole alkaloid biosynthesis (*9–12*) from tryptophan (**2**) and secologanin (**3**), apparently in some cases the amino acid carboxyl is retained at the intermediary vincoside stage (**4**, $R' = 6O_2H$). Thus, a naturally occurring 5-carboxyisovincoside (**4**, $R' = CO_2H$, 3α-H) is in fact known (**13**); and the related epimeric lactams **8a** and **8b** have also been isolated from a plant source, following a work-up which included acetylation and methylation steps (*14*). Furthermore a C-5 acid with the *corynanthé* ring system, adirubine (**9**), has been uncovered (*15*). In ajmaline biosynthesis, preservation of the tryptophan carboxyl would be advantageous in that the α-amino acid unit could be used for specifically generating, through an oxidative decarboxylation process,

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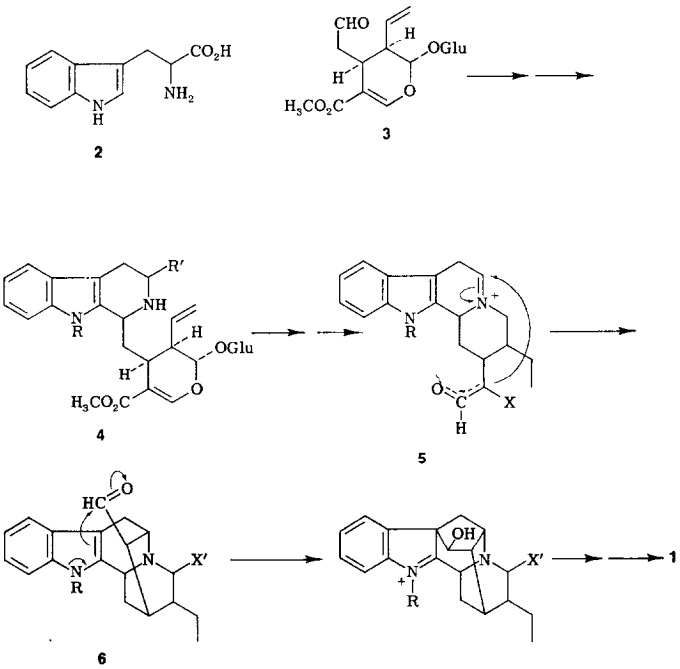
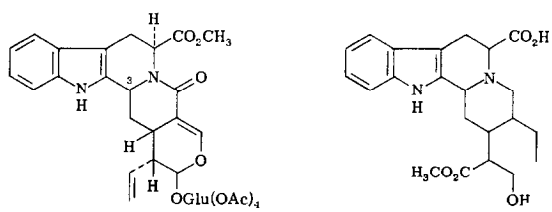
CHART I



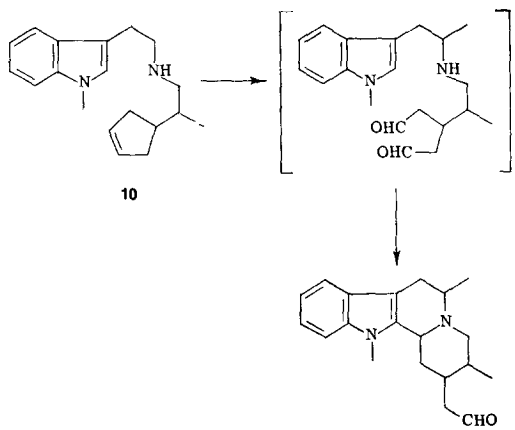
the $\Delta 4^{(5)}$ iminium ion (**5**) needed for the ensuing annulation step. Alternatively, intermediate **5** might derive by specific enzymic dehydrogenation of the C-ring in **4** or a related structure, in which case the chemically preferred oxidation to a $\Delta^{3(4)}$ imine must be avoided. Although recent feeding experiments indicate that tryptamine is the true biological precursor of ajmalicine and geissoschizine (**16**), whether it is tryptamine or tryptophan that biogenerates ajmaline remains unknown. In any case, starting with the iminium ion **5**, the next event would involve addition of, e.g., the side chain aldehyde ($X = H$) or aldehydo acid anion ($X = COOR$) to C-5, a reaction of the aldol type permitted only after C-3 and C-16 assume axial postures. Following appearance of the pentacyclic system **6**, nucleophilic attack, through the α-position of the indole ring, on aldehyde carbonyl would produce directly the required hexacyclic system (**7**) with reduction of indolinene to indoline, as well as introduction at some stage of the N_a methyl and the C-21 hydroxyl required for formation of the final naturally occurring product (**1**).



8 a, 3β-H
b, 3α-H

9

As in nature, our laboratory synthesis features early linkage of a nitrogeneous moiety with a unit having the nine carbons needed for the rest of the alkaloid system. At the appropriate point, a biomimetic operation akin to step 5→6 was planned; and in order to provide for the required 4(5) imine function, a precursor 5-carboxylated C-ring was desired. Accordingly, the synthesis was initiated, not with a tryptamine but with ind-*N*-methyl tryptophan (**2a**). In regard to the second component, we planned to follow lines laid down earlier in the construction of other indole alkaloid systems (*17*): incorporation of a cyclopentene ring (**10**), which, on oxidative cleavage, would provide



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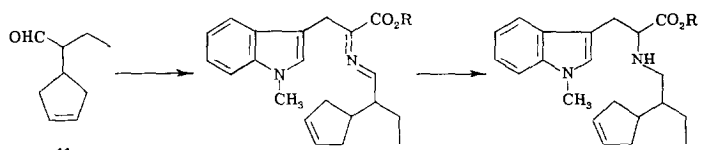
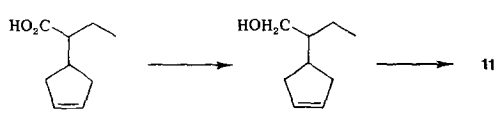
two equivalent acetaldehyde units, one used for Pictet–Spengler cyclization to the C–D ring system and the other remaining as a functionalized substituent at C-15 (*18*).

In the simplest conceivable version of this approach, ind-*N*-methyl tryptamine would be condensed with aldehyde **11**, giving imine **12**, which then could be reduced with



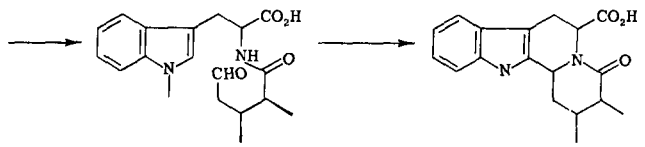
11 12 13

borohydride to amine **13**. Aldehyde **11** was made available by lithium aluminium hydride reduction of the acid **14** (*19*), followed by Collins oxidation of the resulting primary alcohol (**15**). Unfortunately, although tryptamine smoothly condenses with many aldehydes to give the corresponding imines, tryptophan **2a** (or its sodium salt) failed to react with aldehyde **11**, both starting materials being recovered. Substitution



14 15

of the ester for the acid resulted only in diketopiperazine formation. Alkylation of the tryptophan using bromide corresponding to alcohol **15** was also unsuccessful. Furthermore, although cyclopentene oxidation followed by a Pictet–Spengler-type cyclization can be realized with an appropriate tryptamide (*17*), in the corresponding *N*-acyl tryptophan case (**16**) conversion of the resulting piperidone carboxylic acid **17** to piperidine carboxylic acid would be complicated by the presence of the carboxyl group, a function subject to attack by any reducing agent likely to be utilized.

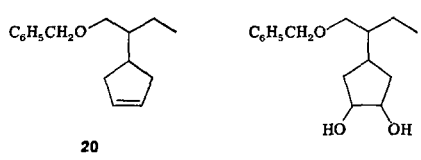


16 **17**

In view of the foregoing considerations, we resorted to still a different method for linkage of the two major building blocks, namely, catalytic reductive *N*-alkylation (*20*) of tryptophan **2a** with an appropriate C_9 aldehyde. In this approach, a cyclopentene unit in the starting aldehyde would most likely be converted in the process to cyclopentane and therefore the double bond in the starting cyclopentene aldehyde had to be hydroxylated prior to attachment of tryptophan. Osmium tetroxide oxidation of alcohol **15** proceeded quantitatively; however, the resulting water-soluble triol could not be selectively further oxidized to dihydroxyaldehyde and could not be protected by derivatization only at the *vic*-glycol center. The unsaturated aldehyde **11** also could be readily hydroxylated, product consisting of equal amounts of (i) diol aldehyde possessing the structure and stereochemistry shown in **18** and (ii) bridged acetal **19** derived

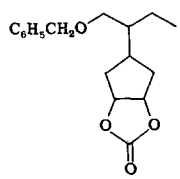
18 **19**

from the all *cis*-diolaldehyde, the latter compound being of no use in the projected alkaloid synthesis. Because of these difficulties, the primary alcohol function was merely protected at the start by conversion of **15** to the benzyl ether **20**, carried out in 83% yield by treatment at 100°C with benzyl chloride and powdered potassium hydroxide. Oxidation with osmium tetroxide in pyridine-THF proceeded in 79% yield,



20 **21**

providing diol **21**,[2] presumably a mixture of the two racemates which could result from *cis*-hydroxylation. Base-induced transesterification with dimethyl carbonate afforded (87%) the cyclic carbonate **22**, so constituted that, without disruption of the ester unit, the benzyl group could be removed, and liberated primary alcohol oxidized to aldehyde. After catalytic (Pd-on-C) hydrogenolysis of **22**, the resulting alcohol (**23a**) (95%) was treated with chromic acid–pyridine in CH_2Cl_2 (*21*), giving aldehyde **23b** in 98% yield.



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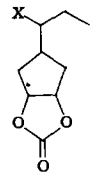
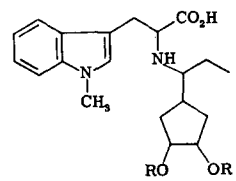


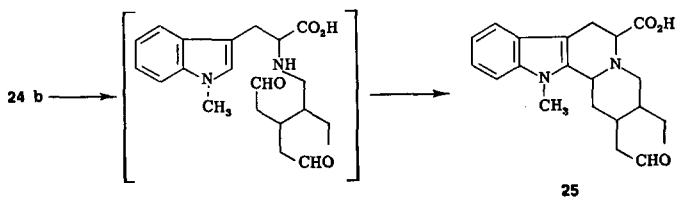
23 a, X = CH_2OH
b, X = CHO

Reductive alkylation of *N*-methyltryptophan with aldehyde **23b**, carried out in ethanol with the H_2/Pd-on-C provided in 51% yield the N_b-substituted amino acid **24a**, which without purification was saponified to the required diol **24b**. After the incorporation of the tryptophan unit, elementary analyses of intermediates in the synthesis were generally unsatisfactory, presumably because of the presence of varying amounts of water or solvent. However, spectral properties were found to be in accord with assigned structures.



24 a, R, R = CO
b, R = H

As with similar cases, it was anticipated that, under propitious conditions, the dialdehyde resulting from cleavage of the cyclopentandiol ring would cyclize under the conditions of the oxidation, yielding tetracyclic aldehydoacid **25**. In the event, the



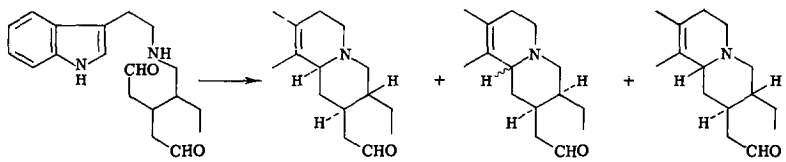
25

dialdehyde was formed and subsequently cyclized when a suspension of glycol **24b** was stirred for 24 hr. at room temperature with a dilute aqueous solution of metaperiodate in sodium acetate buffer. The product, obtained in 53% yield, displayed

[2] Each of the intermediates **21**–**24b** was a noncrystalline mixture of diastereomers, which, because of the impermanence of the asymmetric relationships present, we did not attempt to separate into pure components.

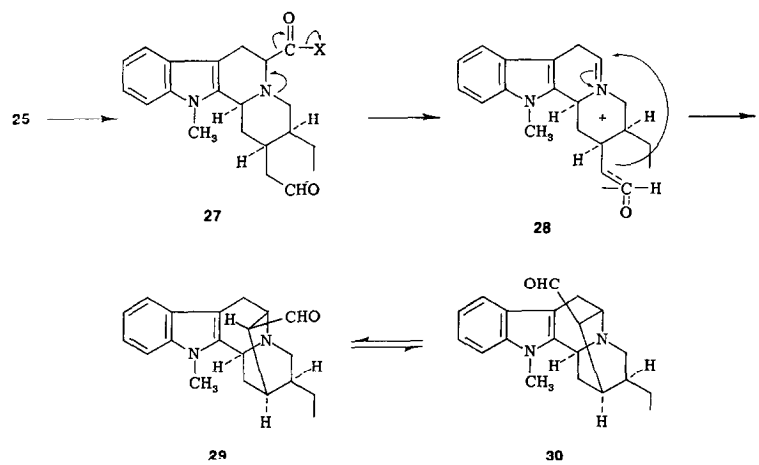
ir spectral peaks ascribable to aldehyde and carboxylate anion functions; gave no response to the Ehrlich test for indoles with an unsubstituted α-position; and, although unstable, analyzed correctly for the assigned structure **25**.

With the formation of intermediate **25**, two new chiral centres are added to the pair already present in precursor **24b**. Of the four, three (C-3, -15, and -20) correspond to asymmetric carbons in ajmaline and, for the purposes of the synthesis, must be all *cis*. Although the C-3, C-15, C-20 *cis,trans* arrangement in **25** is presumably the most stable, there was good reason to expect, on the basis of model studies (*22*), that product of thermodynamic control would not necessarily be formed in the conversion of **24b** to **25**. Thus, the simpler dialdehyde **26** was converted under conditions similar to those employed herein to a mixture of three racemates in the yields indicated. With these findings



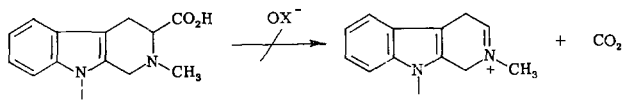
in hand, generation of some C-3, -15, -20 all *cis* isomer was anticipated in the present, more complicated case. The stereochemical arrangement of carboxyl would not appear to be crucial, in that the C-5 center will be destroyed in a later stage of the synthesis. Although in this study the tedious separation of stereoisomers corresponding to **25** was not attempted, such a program was carried out in the adirubine synthesis (**23**), which features identical structures except for the presence of hydrogen instead of methyl at N_a. In keeping with the results of the parallel cases, a goodly amount of the ring D all *cis* isomer was formed from **24b**, as the findings below demand.

In anticipation of more facile isolation of the desired stereomer at the later, pentacyclic stage, the next step in the synthesis was carried out on a presumed stereochemical mixture of aldehydoacids (**25**). The carboxyl in **25** is properly positioned for directing iminium ion formation specifically at $\Delta^{4(5)}$, a decarbonylation process (**27**→**28**) which



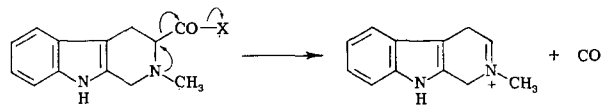
in turn would permit requisite bond formation between C-5 and C-16, thus giving the deoxyajmalal system (**29**/**30**). Biosynthesis of this pentacyclic type also could proceed along the same, or a similar, line; and it was hoped that conditions could be found which would permit realization of the entire sequence **25**→**27**→**28**→**29** or **30** in one reaction vessel. Ultimately this plan was brought to fruition; but only after establishment of a precedent, viz, the decarbonylation of tetrahydro-β-carboline acid **33a** to dihydro-β-carboline **34**, a heretofore unknown variant of the general reaction type (*24*). In fact, development of conditions for this case was completed before the ajmaline synthesis proper was initiated.

In view of the general requirements for the overall conversion **25** to **29**/**30**, we originally considered the hypohalite-induced *decarboxylation* of *N*,*N*-dialkyl aminoacids, as in the model **31**→**32**. However, attempts along such lines resulted in formation of more



31 **32**

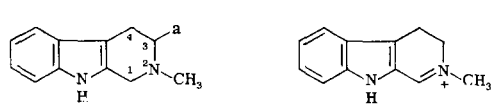
highly dehydrogenated or rearranged products, with no isolation of dihydro-β-carboline **32** (*25*). Attention was therefore redirected to dihydro-β-carboline synthesis through decarbonylation, a reaction not requiring an overt oxidizing agent and therefore having the potential for avoiding undesired modification of **32**, once formed. Following this approach, we attempted first the action of thionyl chloride on acid **33a**, prepared by



33 a: X = OH
b: X = Cl
c: X = OCOR
d: X = $OSO_2C_6H_4p-CH_3$
e: X = $O-C=NC_6H_{11}(NHC_6H_{11})$

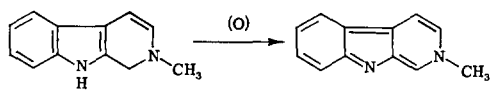
34

treatment of N_b-methyltryptophan (*26*) with formaldehyde (*27*). Perhaps surprisingly, the acyl chloride **33b** was found to show no great tendency to decompose; hydrolysis returned the starting amino acid in good yield. Furthermore, mixed anhydrides (**33c**) derived from **33a** and other carboxylic acids were not subject to heat- or acid-induced fragmentation. Even the *p*-toluenesulfonic anhydride (**33d**) was found to be stable under conditions which might have been expected to provoke decarbonylation. However, dicyclohexylcarbodiimide was found to bring about the desired change. On addition of *p*-toluenesulfonic acid to a suspension of amino acid **33a** and the diimide in dry dioxane, carbon monoxide was immediately evolved. After addition of sodium borohydride, N_b-methyl-tetrahydro-β-carboline (**35**, a = H) was formed, a result consistent



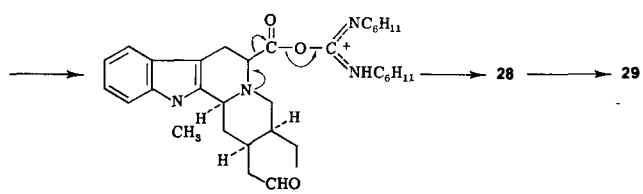
35 **36**

with the appearance of **34**. However, the initially formed dihydrocarboline readily isomerized, especially in the presence of methanol, to iminium salt **36**, as evidenced by the concurrent appearances of a peak at 308 nm and disappearance of the typical simple indole spectrum anticipated for the initially formed cation **34**. In light of the uncertainties surrounding the generation and behavior of the new species **34**, it was necessary to prove the presence of the latter; and this was done by trapping by such means that a telling label would be introduced. Sodium borodeuteride reduction gave rise to a deuterated product which possesses structure **35** (a = D), since the substance possessed nmr peaks at *inter alia* τ 6.39 (1H, doublet, 16 Hz), 5.82 (1H, doublet, 16 Hz) (C-1 hydrogens) and at 7.00–7.30 (3H, multiplet) (C-3 and C-4 hydrogens). In the fragmentation reaction, dicyclohexylurea is formed in nearly quantitative yield, demonstrating the nature of the leaving group in **33e**. Attempts to isolate the iminium salt **34** resulted only in its decomposition. Treatment of the cation in solution with bases such as triethylamine was followed by facile air oxidation, presumably of enamine **37**, to the β-carboline **38**.



37 **38**

On application of the fragmentation reaction conditions to the tetracyclic amino acid **25**, there was formed crystalline DL-deoxyajmalal-B, isolated in 18% yield after tlc on silica gel and compared (tlc, ir, uv, nmr, ms) with deoxyajmalal-B derived from ajmaline (*28*). First, acid **25** is converted by dicyclohexylcarbodiimide to the "activated" acid **39**, which collapses as shown. As hoped, the resulting dihydro-β-carboline **28**, under the conditions of the decarbonylation, engages in a biogenetic-type cyclization



39

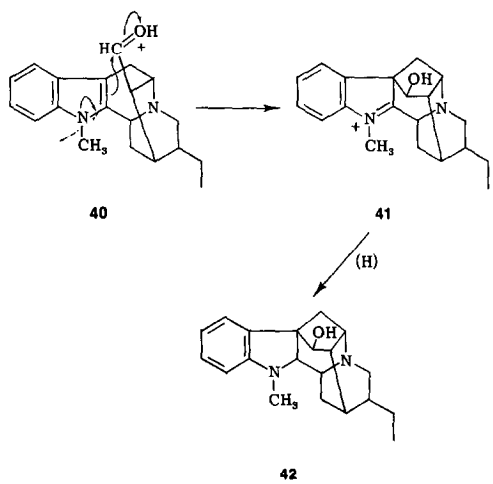
(**18**→**29**), giving the deoxyajmalal. No deoxyajmalal-A (**30**) could be isolated as a product of this reaction sequence. Although starting material with alternate ring-D stereochemistry must have been present and also undergone the fragmentation, no effort was made to identify either a deoxyajmalal with the opposite relative stereochemistry of the ethyl group or tetracyclic material with the C-3, C-15 *trans* arrangement and therefore not subject to cyclization of the type **28**→**29**. The yield of DL-deoxyajmalal observed, which reflects the minimum amount of all *cis*-tetrahydro-β-carboline formed in the original cyclization, corresponds well with those of all *cis* tetracycle found in related studies (*22*, *23*).

Synthetic DL-deoxyajmalal-B was resolved successfully by means of D-camphor-10-sulfonic acid, after assay of various other, less promising optically active acids. As

obtained from the racemic material, the D-camphor-10-sulfonate salt of optically active base melted at 238–251°C, undepressed after admixture with authentic salt, mp 237–240°C. Recovered resolved base melted at 212–213.5°C, not lowered in a mixture mp determination with authentic deoxyajmalal-B, mp 212–213°C (*28*). Circular dichroism determinations on the salts confirmed the identification.

Completion of the synthesis depends on certain relay operations. In order that the hexacyclic, ajmaline skeleton be produced from the deoxyajmalal type, the stereochemistry of the aldehyde function must be fixed as in the A isomer (**30**); the B case is sterically prohibited from entering into any cyclization which would lead to the natural framework. Thus an indispensable requirement for completion of the synthesis was conversion of deoxyajmalal-B to a related substance with the opposite chirality of the carbon to which the formyl group is attached. The claim (*28*) that under basic conditions isomer A is transformed quantitatively to B was not encouraging. In the hope that some B might be converted under cyclization conditions to A_1 which then would react *in situ* and thus overcome an unfavorable A/B equilibrium, B was subjected to the action of zinc and acid. However, no useful product resulted from such attempts. Despite these forebodings, it was found that, under appropriate conditions, there exists an A/B equilibrium mixture from which the A isomer can in fact be isolated. In experiments with either deoxyajmalal-A or -B in room temperature acetic acid–sodium acetate or in refluxing benzene over alumina, equilibrium characterized by 14–16% A and 84–86% B was demonstrated (nmr). Analysis, also by nmr methods, of an 11-year-old sample of A (provided by M. F. Bartlett) revealed that this isomer had been converted to the same extent to B. Isomer B can be removed from an A/B mixture by direct crystallization from ethyl acetate. In order to isolate A from an equilibrium mixture, rapid preparative tlc over silica gel GF sufficed, material of satisfactory purity (mp 179–180°C) being obtained directly.

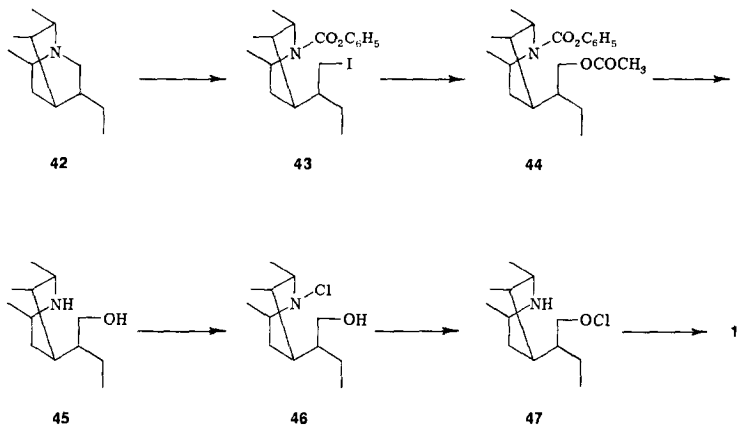
Through use of the elegant reductive alkylation method of Bartlett, Taylor and co-workers (*28*), deoxyajmalal-A can be converted directly to deoxyajmaline (**42**). Strong acid and zinc dust induce a bioorganic process undoubtedly initiated by an aldol reaction (**40**) involving nucleophilic attack of the β-position of the indole ring



40 41 42

on the carbonyl group, followed by reduction of the resulting indolinenium ion in intermediate **41**.

The only structural feature of ajmaline missing in hexacycle **42** is the C-21 hydroxyl, a substituent which stamps the alkaloid as an alkanolamine. Fortunately, for the purpose of this synthesis, the introduction of this function into deoxyajmaline can be accomplished by a ring opening–oxidative ring closure sequence due to Hobson and McCloskey (*29*). According to this methodology, ring D is opened when the base **42** is treated with phenyl chloroformate in the presence of lithium iodide, giving urethane **43**. Displacement of halogen by acetate ion affords the C-21 acetoxy compound (**44**) which can be saponified to the parent aminoalcohol (**45**). *N*-chlorosuccinimide oxida-



42 43 44

45 46 47

tion then gives the *N*-chloroamine (**47**). Further treatment with strong base effects conversion to ajmaline, presumably via transfer of halonium ion to C-21 oxygen, followed by collapse of the resulting hypohalite (**47**) to aldehyde, the open chain tantomer of the alkanolamine **1**. Through inclusion of this relay, the total biogenetic-type synthesis of ajmaline is complete.

EXPERIMENTAL

All melting points were determined using a Reichert hot stage microscope and are uncorrected. All boiling points are uncorrected.

The elemental analyses were performed at the Stanford Microanalytical Laboratory by Mr. E. Meier and Mr. J. Consul.

All infrared spectra were recorded on a Perkin–Elmer Model 421 grating spectrometer. The ultraviolet spectra were recorded on a Cary Model 14 recording spectrometer or a Bausch and Lomb Spectronic 505. The proton magnetic resonance (pmr) spectra were recorded on Variant instruments, Model A-60, T-60, or HR-100. The internal reference for aqueous solutions was sodium 2,2-dimethyl-2-silapentane-5-sulfonate and, for other solvents, tetramethyl silane.

The substrates for column chromatography were silica gel (100–200 mesh, Davidson Chemical), and alumina (Merck A.G.). All preparative thin-layer chromatographies (tlc) were carried out on Merck silica fel GF_{254}, 1 mm thick.

Acid chloride of 3-methyl-2,3,4,5-tetrahydro-β-carboline-4-carboxylic acid (**33a**) *and its reconversion to* **33a**. Amino acid **33a** (25 mg, 0.11 m*M*) was suspended in a chloroform or benzene solution of triethylamine (20 mg, 0.20 m*M*), and thionyl chloride (ca. 20 mg, 0.17 m*M*) was added. The suspension cleared up immediately, and the infrared spectrum of the resulting solution showed carbonyl absorption at 1795 cm^{-1} (acid halide). No decomposition occurred on standing or on heating of the solution to reflux temperatures. Shaking of the organic solution with water led to separation of the amino acid **33a** which collected at the interface between the layers.

Mixed anhydride of amino acid **33a** *and toluenesulfonic acid.* Amino acid **33a** (40 mg, 1.75 m*M*) was dissolved in 1 ml of dry pyridine, and tosyl chloride (40 mg, 2.1 m*M*) was added. The solution was stirred for 2 h, after which time tlc showed that both tosyl chloride and **33a** were gone. Addition of hexane to the solution gave a black oily lower layer. Removal of pyridine and hexane on the rotary evaporator gave a black oil that exhibited infrared absorption at 1750 cm^{-1} (RCO_2R) and 1200 cm^{-1} (RSO_3R). Heating this oil neat or with ammonium chloride in tetrahydrofuran gave no recognizable products (by tlc analysis) but led to some decomposition of the anhydride. This reaction was not investigated further.

Decarbonylation of amino acid **33a**. Amino acid **33a** (100 mg, 0.435 m*M*) was added to a suspension of dicyclohexylcarbodiimide (100 mg, 0.485 m*M*) in 10 ml of spectroquality dioxane at 80°C. The mixture was stirred magnetically for ½ hr under a nitrogen atmosphere, and then toluenesulfonic acid monohydrate (83 mg, 0.435 m*M*) was added. Bubbling commenced immediately and continued for about 1 min. Addition of sodium borohydride (25 mg, 0.66 m*M*) to the suspension resulted in a clear solution Removal of the solvent on a rotary evaporator gave a solid which was taken up in minimal 2*N* hydrochloric acid, and the resulting solution was then made basic with 2*N* sodium hydroxide. Extraction of this basic solution with chloroform gave solid β-carboline **35** which, after recrystallization from benzene/methanol and drying under a vacuum, melted at 208–210°C; mixture mp with authentic material was undepressed.

The β-carboline resulting from reduction with sodium borodeuteride gave the following pmr spectrum (ppm in $CDCl_3$): 2.36 singlet, 3H (*N*-methyl); 2.70–3.00 multiplet, 3H (C-3 and C-4 hydrogens); 3.61 doublet ($J = 16$ Hz), 1H (C-1); 4.18 doublet ($J =$ 16 Hz), 1H (C-1); 7.25 multiplet, 4H (aromatic).

When the reaction was performed in methanol and the suspension of iminium salt treated with 1 equiv of triethylamine in the presence of air, a slow color change occurred, giving an orange solution. The ultraviolet spectrum of this solution had absorptions at 275 and 325 nm, with a minimum at 390 nm. Acidification of the solution with 1 *N* hydrochloric acid gave a solution that exhibited ultraviolet absorptions at 255, 305, and 375 nm, typical of the N_b-alkyl-β-carboline anhydro bases (*30*).

Test for carbon monoxide evolution in decarbonylation of amino acid **33a**. Amino acid **33a** (83 mg, 0.36 m*M*) was added to 10 ml of methanol in which dicyclohexylcarbodiimide (100 mg, 0.485 m*M*) had been suspended. The mixture was stirred magnetically for ½ hr under nitrogen. Then toluenesulfonic acid monohydrate (ca. 100 mg) was mixed in with vigorous stirring. The solution was kept cool in an ice bath to reduce vaporization of methanol. The gases were blown into a suspension of palladium (II) chloride (50 mg, 0.28 m*M*) in 19 ml of water. The brown color of the palladium suspension slowly darkened, indicative of reduction of palladium (II) (*31*).

1-Methyl tryptophan (**2a**). This compound was prepared by the method of Yamada (**32**). The yield was 95% and the material melted at 265–267°C with decomposition (lit. mp 269°C).

1-Methyl-tryptophan methyl ester. This substance was also prepared by the method of Yamada (*32*). The yield was 90% and the infrared spectrum of the oil showed absorptions at $\nu_{max}^{film}(cm^{-1})$: 3390, 3310 ($-NH_2$), 1730 ($-CO_2CH_3$).

2-Δ^3-Cyclopentenyl-butyric acid (**14**). 2-Δ^3-Cyclopentenylnitrile (*19*) (10.0 g, 74.1 m*M*) was added to 15 g of potassium hydroxide in 60 ml of ethylene glycol, and the mixture was stirred magnetically. The solution was heated to reflux and kept at that temperature for 25 days. The resulting brown solution was cooled and diluted with 100 ml of water and 40 ml of 2 *N* hydrochloric acid. The cloudy solution was extracted with ether four times. The combined extracts were washed successively with 2 *N* hydrochloric acid, water, and saturated aqueous sodium chloride. After drying of the solution over magnesium sulfate, concentration on a rotary evaporator gave a clear oil (78–85%) which later crystallized (mp 40–41°C). The acid showed infrared absorption at $\nu_{max}^{film}(cm^{-1})$: 3400–2500 broad (–OH) of acid); 1700 (carboxyl); 1600 (olefin).

2-Δ^3-Cyclopentenyl-butanol (**15**). To a suspension of lithium aluminium hydride (2.02 g, 53.1 m*M*) in 250 ml of dry tetrahydrofuran, there was added dropwise and with stirring a solution of the above acid (8.9 g, 57.8 m*M*) in dry tetrahydrofuran. The resulting mixture was heated to reflux temperature and held at that temperature overnight. The excess lithium aluminum hydride was destroyed by slowly adding wet tetrahydrofuran to the cooled solution. Filtration of the mixture through Celite gave a yellow solution which was diluted with 200 ml of water and then extracted three times with ether. The crude extracts were concentrated on a rotary evaporator and then distilled at aspirator pressure. The alcohol, bp (25 mm) 112–115°C, showed a small amount of impurity by tlc. The yield was 94–97%. The infrared spectrum showed $\nu_{max}^{film}(cm^{-1})$: 3380 (–OH), 3024 (vinyl CH); 1612 (olefin); other absorptions at 1460, 1379, 1345, 1030, and 695. The pmr spectrum (ppm in $CDCl_3$): 5.7 singlet for two hydrogens (vinyl CH); 3.65 doublet ($J = 4$ Hz) for two hydrogens (CH_2–O); an envelope between 2.6 and 0.9 ppm.

2-Δ^3-Cyclopentenyl-butyraldehyde (**11**). The solid complex of chromium tioxide and pyridine (*21*) (10.0 g, 38.8 m*M*) was added to freshly distilled methylene chloride. Alcohol **15** (0.897 g, 6.40 m*M*) in methylene chloride was added quickly, and the resulting mixture was stirred at room temperature for 15 min. The entire reaction mixture was filtered through a 2-in. column of alumina–9% water. The resulting pale brown organic solution was extracted once with cold 2 *N* hydrochloric acid to give a clear organic layer. Concentration of this organic layer gave a golden oil which decomposed on attempted distillation. The yield of the oil was 100%. The infrared spectrum confirmed the structural assignment: $\nu_{max}^{CH_2Cl_2}(cm^{-1})$: 3050 (vinyl CH); 2710 (aldehyde CH); 1720 (aldehyde carbonyl); 1617 (olefin); other absorptions at 1458, 1382, 1345.

2-(3,4-Dihydroxycyclopentyl)-butyraldehyde (**18**). To a flask containing 50 ml of dry tetrahydrofuran and a stirring bar, unsaturated aldehyde **11** (492 mg, 3.66 m*M*) was added, followed by osmium tetroxide (1 g, 3.94 m*M*) in 10 ml of tetrahydrofuran. The resulting mixture was stirred for 24 hr at room temperature, and then gaeous hydrogen sulfide was bubbled through for 10 min. After 3 hr, the mixture was filtered through Celite; subsequent chromatography of the filtrate on silica gel–10% water, with ether

elution, gave two pure compounds. The less polar one was the acetal **19**, while the other was the desired aldehyde-diol **18**. The acetal could not be opened readily when treated with refluxing 2 *N* hydrochloric acid.

The infrared spectrum of the acetal was as follows: $\nu_{max}^{film}(cm^{-1})$: 2970, 3860, 1456, 1440, 1381, 1364, 1348, 1338, 1182, 1114, 1070, and 946. The pmr spectrum showed (ppm in $CDCl_3$): 5.50 broad singlet for one hydrogen [$-CH(OR)_2$]; 3.88 crude triplet ($J = 6$ Hz) for two hydrogens (CH_2–C*H*–O–); 0.95 triplet ($J = 5$ Hz) for three hydrogens (CH_2–C*H*$_3$); methylene envelope between 1.4 and 2.0 ppm.

Benzylether of 2-Δ^3-cyclopentenyl-butanol (*20*). The alcohol **15** (3.105 g, 22.2 m*M*) was added to approximately 10 ml of benzyl chloride containing powdered potassium hydroxide (1.40 g, 25 m*M*). The resulting solution was heated to 100°C and kept at that temperature for 22 hr. After this time, tlc showed that all of the alcohol was gone. Workup consisted of dilution of the reaction mixture with water, extraction with chloroform and distillation of the extracts. The nondistillable portion was a misture of dibenzyl ether and benzyl ether of the unsaturated alcohol **15**. This mixture was used directly in the next reaction without further purification. Analysis by pmr indicated 83% of the mixture was the desired unsaturated ether, **20** (99%). A sample was chromatographed on silica gel–15% water, and the purified benzyl ether was analyzed.

Anal. Calcd. for $C_{16}H_{22}O$: C, 82.99; H, 9.63. Found: C, 83.10; H, 9.68.

The pmr spectrum of the purified ether showed absorptions at: (ppm in $CDCl_3$): 7.26 singlet for five hydrogens (aromatics); 5.66 singlet for two hydrogens (vinyl C–H); 4.48 singlet for two hydrogens (benzyl CH); 3.42 doublet ($J = 6.0$ Hz) for two hydrogens (CH_2–O); envelope between 0.8 and 3.0 for the rest. The infrared spectrum showed absorptions at: $\nu_{max}^{CHCl_3}(cm^{-1})$: 3060 (aromatic CH); 1600 (olefin); other absorptions at 1494, 1452, 1206, 1080, and 922.

Benzyl ether of 2-(3,4-dihydroxycyclopentyl)-butanol (**21**). The mixture of dibenzyl ether and the benzyl ether **20** (2.28 g, 9.90 m*M*) was placed in a flask with 5 ml of tetrahydrofuran and 1.5 ml of dry pyridine. Osmium tetroxide (3.0 g, 11.8 m*M*) in tetrahydrofuran was added dropwise under a nitrogen atmosphere. Stirring was continued for 5 hr, and then gaseous hydrogen sulfide was bubbled through for 10 min. The solution was stirred for 5 h and then filtered through Celite. The resulting clear filtrate was chromatographed on silica gel–15% water to yield 2.05 g (79%) of diol **21**. This diol held water tenaciously and a satisfactory elemental analysis could not be obtained.

The infrared spectrum showed absorptions at: $\nu_{max}^{film}(cm^{-1})$: 3400 (broad –OH); 3080–3020 (aromatics CH); 2960–2860 (aliphatic CH); other absorptions at 1590, 1493, 1480, 1450, 1440, 1358, 1065–1110 (broad), 1024, 740, 733, and 695. The pmr spectrum showed absorptions at: (ppm in $CDCl_3$): 7.35 singlet for five hydrogens (aromatics); 4.5 singlet for two hydrogens (benzyl-CH_2–); 4.13 triplet ($J = 5.0$ Hz) for two hydrogens (–C*H*–OH); 3.42 doublet ($J = 5.0$ Hz) for two hydrogens (–CH_2O); envelope for the other protons at higher fields.

Cyclic carbonate (**22**) *of* **21**. Diol **21** (1.80 g, 6.8 m*M*) was dissolved in 25 ml of dimethyl carbonate, and sodium methoxide (0.810 g, 15 m*M*) was added. The mixture was stirred and refluxed under nitrogen for 4 hr, and then 15 ml of the solvent was distilled at atmospheric pressure. The suspension resulting from dilution of the reaction mixture

with water was extracted four times with ether. The combined ether extracts were washed with water, followed by saturated aqueous sodium chloride, then dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator to 1.715 g of the carbonate **22** (87%).

The infrared spectrum showed absorptions at: $\nu_{max}^{CCl_4}(cm^{-1})$: 3080–3075 (aromatic CH); 2970–2850 (aliphatic CH); 1815 (broad, carbonyl of carbonate); other absorptions at 1452, 1367, 1280, 1148, 1110, 1080, 1045, and 692. The pmr spectrum showed absorptions at: (ppm in CCl_4): 7.20 singlet for five hydrogens (aromatic CH); 4.90 broad singlet for two hydrogens (–CHO–CHO–); 4.36 singlet for two hydrogens (benzyl-CH_2–); 3.32 crude doublet ($J = 4.0$ Hz) for two hydrogens (–CH_2O); envelope for the rest at higher fields.

Carbonate alcohol **23a**. Benzyl ether **22** (1.12 g, 3.83 m*M*) was dissolved in 50 ml of absolute ethanol, and 300 mg of 10% Pd/C was added. The mixture was hydrogenated on a Parr apparatus until uptake leveled off at about 1.1 equiv (22 hr). Fltration of the mixture and concentration of the filtrate on a rotary evaporator gave 725 mg of alcohol **23a** (95%).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.02; H, 8.01.

The infrared spectrum showed absorptions at: $\nu_{max}^{CHCl_3}(cm^{-1})$: 3600 (sharp) and 3460 (broad, OH); 2960–2870 (aliphatic CH); 1800 (broad, carbonyl of carbonate); 1460, 1372, 1326, 1170, 718, and 640. The pmr spectrum showed absorptions at: (ppm in $CDCl_3$): 5.15 broad singlet for two hydrogens (CHO–CHO–); 3.62 broad singlet for two hydrogens (CH_2O–); envelope for the rest between 0.9 and 3.0.

Carbonate aldehyde **23b**. The chromium trioxide–pyridine complex (*21*) (5.66 g, 22 m*M*), was added to 40 ml of freshly distilled methylene chloride and the reagent stirred under a nitrogen atmosphere while the alcohol **23a** (725 mg, 3.62 m*M*) in methylene chloride solution was added. Stirring was continued for 15 min at room temperature. Filtration of the mixture through 20 cm of silica gel–15% water and brief extraction of the resulting filtrate with 2 *N* hydrochloric acid gave a clear organic layer. Concentration of this organic layer on a rotary evaporator yielded 714 mg (98.5%) of aldehyde **23b**. The aldehyde was slowly oxidized by air, and no analysis was possible.

The infrared spectrum showed absorptions at: $\nu_{max}^{CHCl_3}(cm^{-1})$: 3000–2850 (CH); 2705 (aldehyde CH); 1800 (broad, carbonyl of carbonate); 1718 (sharp, carbonyl of aldehyde); other absorptions at 1368, 1210, 1165, 1100, 1073, 1040, 900, 750 (broad), and 660. The pmr spectrum showed absorptions at (ppm in $CDCl_3$): 9.63 doublet ($J = 3.0$ Hz) for one hydrogen (aldehyde CH); 5.13 set of four peaks of equal intensity for two hydrogens (–CHO–CHO–); envelope between 0.9 and 2.4 for the rest.

Reductive alkylation of amino acid **2a** *with aldehydes*. General procedure: Amino acid **2a** must be recrystallized from a basic solution, as excess acid tends to equilibrate catalyst poison. The amino acid is then suspended in absolute ethanol (95% ethanol is satisfactory but the reaction is slower); 10% palladium on carbon is added; and the mixture is allowed to equilibrate at room temperature overnight. Then more catalyst is added while keeping the suspension in an ice bath, and the flask is placed on the hydrogenation apparatus and equilibrated with hydrogen. Then 1 equiv of aldehyde in absolute ethanol is added, and hydrogenation is begun. Uptake of hydrogen levels off at 1 mole. Filtration of the reaction mixture and Soxhlet extraction of the catalyst–amino acid mixture with ethanol gives, after all the solvent is removed with a rotary

evaporator, an off-white solid which can be purified by recrystallization from methanol–ether or water.

It is essential to avoid heating the equilibrated catalyst–amino acid mixture, as this spreads the poison to the new catalyst. This procedure when applied to amino acid **2a** and isobutyraldehyde gave a product that had a pmr spectrum (ppm in D_2O): 3.52 doublet ($J = 7$ Hz) for two hydrogens (N–CH_2–CH); 0.91 doublet ($J = 6$ Hz) for six hydrogens [–CH(CH_3)$_2$].

Reductive alkylation of amino acid **2a** *to* **24a**. The procedure was exactly the same as given above, using the following amounts of starting material: amino acid **2a** (576 mg, 2.64 m*M*); aldehyde **23b** (524 mg, 2.64 m*M*). The crude yield was 592 mg (51%).

The infrared spectrum of the product showed absorptions at: ν_{max}^{KBr}(cm^{-1}):3400–2900 (broad absorption due to carboxyl); 1795 (carbonyl of carbonate); 1740 (carboxyl); other absorptions at 1470, 1375, 1328, 1170, 1045, and 740 (*ortho*-substituted benzene). The pmr spectrum showed absorptions at: (ppm in D_2O/NaOD): 7.34–7.67 multiplet for five hydrogens (aromatics and α-hydrogen of indole); 4.01 singlet for three hydrogens (*N*-methyl); multiplets between 4.1 and 3.2 for CH next to nitrogen. Aliphatic CH at higher field. The spectrum was generally poor due to slow decomposition in solution.

Amino acid-diol **24b**. Carbonate **24a** (64 mg, 0.16 m*M*) was suspended in 2 ml of methanol in a 4-ml flask. Upon addition of potassium hydroxide (100 mg) as a powder, the suspension cleared up immediately. Refluxing was begun and continued overnight. The solution was then cooled and neutralized by addition of 1 *N* hydrochloric acid, whereupon a solid separated that was collected by filtration. This solid was washed thoroughly with water to remove all inorganic salts. The infrared spectrum of this material was acceptable, but the analysis was consistently low and irreproducible, presumably because of water retention. Recrystallization from water gave 38 mg of **24b** (64%).

The infrared spectrum showed absorptions at: ν_{max}^{KBr}(cm^{-1}): intense hydroxyl absorption from acid and diol functions in the region between 3400 and 2800; 1660, 1600 (carboxylate); other absorptions at 1400, 1305, 1075, and 736 (*ortho*-substituted benzene). The pmr spectrum showed absorptions at: (ppm in D_2O/NaOD): 7.52–7.93 (aromatics); 4.20 singlet (*N*-methyl); the remainder of the spectrum was so complex that interpretation was not possible.

Amino acid aldehyde **25**. Diol **24b** (44 mg, 0.118 m*M*) was suspended in 5 ml of water, and sodium acetate (10.5 mg, 0.125 m*M*) was added. The suspension was treated with periodic acid (27 mg, 0.118 m*M*) dissolved in 1 ml of water, after which the cloudiness disappeared instantly. The flask was covered with aluminum foil, and the solution was stirred overnight at room temperature. Water was removed azeotropically with acetone, leaving a white solid which gave a negative Ehrlich test for α-unsubstituted indoles (*33*). Adjusting the pH of an aqueous solution of the solid to neutrality resulted in precipitation of an off-white solid (**25**) (21.3 mg, 53%). In solution this compound was unstable and decomposed quickly so no pmr analysis was possible.

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.40; N, 7.91. Found: C, 71.28; H, 7.33; N, 7.81.

The infrared spectrum showed absorptions at: ν_{max}^{KBr}(cm^{-1}): broad absorption centered at 3400 for the carboxyl OH; 2820 (aldehyde) CH; 1726 (aldehyde

carbonyl); other absorptions at 1465, 1380, 1280, 1120, 1070, and 740 (*ortho*-substituted benzene).

Racemic deoxyajmalal-B: To a 5-ml round-bottomed single-neck flask equipped with a stirring bar and nitrogen inlet, and containing 3 ml of spectroquality dioxane at 80°C, was added dicyclohexylcarbodiimide (19.0 mg, 0.092 m*M*). Then aldehyde-acid **25** (17.1 mg, 0.048 m*M*) was dissolved in the carbodiimide solution. After 5 min, toluenesulfonic acid monohydrate (17.5 mg, 0.092 m*M*) was added. Bubbling occurred immediately, with a slight change in color and development of a suspended solid. The mixture was allowed to stir for ½ hr while being cooled to room temperature. Then the pale brown suspension was diluted with chloroform, and the mixture was filtered through a small plug of glass wool. Concentration of the filtrate on a rotary evaporator gave a brown solution which was filtered again to remove traces of dicyclohexylurea and possibly salts, and the solution was then applied to a preparative thin-layer plate of silica gel GF and eluted with 6% methanol in chloroform. The band at R_f 0.81–0.85, corresponding to authentic deoxyajmalal-B, was removed. There was much material at R_f 0.2–0.6 that was not investigated. Extraction of the silica gel with chloroform and concentration of the extracts under a stream of nitrogen gave 1.2 mg (8%) of an off-white solid. This was recrystallized once from ethyl acetate to a solid with mp 204–206°C (lit. mp for deoxyajmalal B, 212–213°C) (*28*). A mass spectrum was run, in parallel with authentic material. The spectra were identical, peak for peak, including metastables. The infrared and ultraviolet spectra were superimposable with those of authentic deoxyajmalal-B. The reaction was repeated using recrystallized starting material, giving a much improved yield (18%).

Resolution of racemic deoxyajmalal-B. Working with authentic (optically active) B, preparation of the following salts was attempted with optically active agents: D-tartaric acid, D-camphoric acid, D-camphor-10-sulfonic acid, di-*p*-toluoyl-D-tartaric acid, L-menthoxyacetic acid, L-malic acid, shikimic acid, L-2-pyrolidone-5-carboxyclic acid, *N*-carbobenzoxy-L-serine, *N*-carbobenzoxy-L-alanine. All preparations were carried out by mixing solutions of B dissolved in acetone and the acid dissolved in acetone, then dilution with two volumes of ether. Several preparations gave salts, but the D-camphor-10-sulfonate salt formed over a ½ hr period and gave flocculent plates which grew slowly. Separation and drying of these plates under high vacuum gave material which melted at 237–240°C and gave the expected infrared spectrum.

Resolution was accomplished by treatment of 4.2 mg of racemic B with D-camphor-10-sulfonic acid in acetone, dilution with two volumes of ether, and filtration of the resulting solid. Washing the solid with ether gave 2.8 mg of white solid, mp 236–240°C, mixture mp 236–240°C. The circular dichroism spectra of the salts were identical: authentic material; extrema at 250 nm (−1050), 288 (+3470), 297 (+3820), zero at 258 nm; resolved sample: extrema at 248 nm (−1365), 287 (+3150), 296 (+3780), zero at 258 nm.

Recovery of the free base by rapid extraction of a chloroform suspension of the salt with cold dilute aqueous ammonia gave 1.7 mg of optically active B from the chloroform layer, recrystallized from ethyl acetate to mp 212–213.5°C, mixture mp 212–213°C.

Attempted conversion of deoxyajmalal-B to deoxyajmaline. Into a 25-ml pear-shaped two-neck flask fitted with a serum cap and a condenser with an argon inlet was placed 6 ml of 70% perchloric acid, stirred magnetically. The B-aldehyde (89 mg, 0.29 m*M*)

was added, and the solution was stirred for ½ hr while slowly being heated to 90°C. Monitoring of the reaction by ultraviolet spectral means showed complete loss of the indole chromophore after 3 hr, but the new spectrum seemed to indicate a mixture of indolenium salt and some other, unknown, material, Reduction by addition of zinc dust changed the spectrum, but no recognizable dihydro-indole chromophore was present. Cooling and filtering of the aqueous solution gave a black liquid that was neutralized with ammonia. Repeated extraction with methylene chloride gave no basic material in the extracts. The reaction was repeated with 5 *N* hydrochloric acid instead of perchloric acid with similar results.

Equilibration of deoxyajmalal-B and deoxyajmalal-A. Deoxyajmalal-B (52.8 mg, 0.172 m*M*) was dissolved in glacial acetic acid, and sodium acetate (64.6 mg, 0.79 m*M*) was added. The solution was stirred for 5 days at room temperature under nitrogen atmosphere. High-vacuum freeze-drying of the acidic solution gave a solid that was taken up in chloroform, then extracted once with dilute aqueous sodium hydroxide. The organic layer was concentrated on a rotary evaporator to a solid exhibiting a pmr spectrum which revealed that 16% of the mixture was the A form of the aldehyde.

Basic equilibration of deoxyajmalal-B and deoxyajmalal-A. Deoxyajmalal-B (98.7 mg, 0.32 m*M*) (authentic material supplied by M. F. Bartlett, Ciba) was dissolved in 50 ml of dry benzene, and 1 g of alumina was added. The mixture was refluxed under dry nitrogen overnight. The pale yellow solution was then filtered and the filtrate concentrated on a rotary evaporator. The recovered solid (88 mg) was dissolved in chloroform-d_1 for pmr analysis, which showed 15–17% of the A-aldehyde was present. Preparative tlc of the solid on silica gel GF gave 2 mg of pure A (mp 179–180°C) and approximately 10 mg of an enriched mixture plus a quantity of pure B.

The pmr spectrum of pure A showed absorptions at: (ppm in $CDCl_3$): 9.25 broad singlet for one hydrogen (–CHO); 7.25 multiplet for four hydrogens (*N*-methyl); envelope between 0.9 and 3.4. The pmr spectrum of pure B showed absorptions at: (ppm at $CDCl_3$): 9.75 singlet for one hydrogen (–CHO); 7.25 multiplet for four hydrogens (aromatics); 2.76 singlet for three hydrogens (*N*-methyl); envelope between 0.9 and 3.4.

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