envelope; τ 8.22 (three-proton doublet, J = 6.5 Hz), ethylidene group methyl protons.

The nuclear magnetic resonance spectrum of the synthetic ethylidene α-hydroxymethylene ester **30** was considerably more complex than that of geissoschizine, apparently due to the presence of a mixture of two isomers in not quite equal amounts. The spectra of the unresolved free base and of the bases regenerated from the crystalline and amorphous dibenzoyltartrate salts were essentially identical. Only the spectrum of the free base regenerated from the crystalline dibenzoyltartrate salt will be described, since presumably this material represented the purest available. Signals due to the major and minor components are indicated where possible. The spectrum was as follows: τ 1.86 (broad singlet), indole NH; τ 2.02 (minor) and 2.25 (major), hydroxymethylene group vinyl hydrogens; τ 2.5–3.1 (multiplet), aromatic hydrogens; τ 4.4–5.1 (multiplet), best interpreted as two overlapping sets of quartets (at τ 4.63 and 4.88, J = 6.5 Hz) due to the ethylidene group vinyl hydrogens; τ 6.27 (major) and 6.38 (minor), sharp singlets due to the ester methyl groups; τ 5.9–8.3, methylene envelope; τ 8.3–8.6 (triplet), best interpreted as two overlapping sets of doublets (at τ 8.38 (major) and 8.49 (minor), J = 6.5 Hz) due to the ethylidene group methyl protons.

Formylation of 3-vinyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (the *trans*-vinyl ester 26) was carried out in the same manner as described above for the ethylidene ester **27**.

In a 25-ml reaction vessel, the vinyl ester **26** (221.7 mg, 0.684 mmole, regenerated from the crystalline hydrochloride salt as described before) was suspended in anhydrous ether (10 ml) and the triphenylmethylsodium solution added (15 ml, 0.10 *N*, 1.5 mmoles), immediately followed by freshly distilled methyl formate (4 ml). After 6 hr stirring at room temperature, the reaction mixture was worked up as described before and the products were chromatographed on silicic acid (40 g). The column fractions were analyzed by infrared spectroscopy and thin layer chromatography. Fraction numbers 3–8 (0.75% methanol in chloroform, 600 ml; 1% methanol in chloroform, 1200 ml; and 1.5% methanol in chloroform, 300 ml) consisted of recovered vinyl compound **26** (79.7 mg, 36% recovery). Fraction numbers 10–20 (1.5% methanol in chloroform, 600 ml; 2% methanol in chloroform, 1200 ml; 3% methanol in chloroform, 1200 ml) contained the formylated product **31** (29.6 mg, 0.084 mmole, 19% yield based on unrecovered vinyl ester **26**). The vinyl α-hydroxymethylene ester **31** was rechromatographed on silicic acid after attempts to induce crystallization failed. The infrared spectrum showed bands at 5.81 and 6.02 μ, characteristic of the α-hydroxymethylene ester system.

Since attempts to prepare crystalline hydrochloride and tartrate salts failed, the free base was regenerated by shaking with chloroform and dilute ammonia and treated with diazomethane as described below.

***dl*-Corynantheine (3).** The method of Hester[12] was employed in the methylation of the vinyl α-hydroxymethylene ester **31** (*dl*-desmethylcorynantheine).

The vinyl α-hydroxymethylene ester (27.3 mg) was dissolved in methyl acetate, cooled in ice, and treated with a large excess of diazomethane (prepared from nitrosomethylurea). After standing for 7 hr at 0°, the reaction mixture was concentrated on the steam bath under nitrogen. The residue was dissolved in chloroform and washed five times with 15–20-ml portions of 2 *N* hydrochloric acid to remove unreacted starting material (corynantheine hydrochloride is soluble in chloroform). A further wash with dilute ammonia regenerated the free base, and the chloroform solution was worked up as usual to yield crude *dl*-corynantheine. Further purification by preparative thin layer chromatography yielded *dl*-corynantheine (3.9 mg) contaminated only by solvent residue (as indicated by the infrared spectrum and thin layer chromatography). This material was combined with a further 3.0 mg prepared separately in a similar manner, converted to the hydrochloride salt, and chromatographed on silicic acid (1 g). Fraction numbers 5–7 (3, 4, and 6% methanol in chloroform, 25 ml each) contained 5.6 mg of *dl*-corynantheine hydrochloride which, when combined in chloroform and treated with solid sodium carbonate regenerated *dl*-corynantheine which had an infrared spectrum identical in every respect with that of a sample of *d*-corynantheine.

Dissolution of the *dl*-corynantheine in acetonitrile, addition of 1 drop of methanolic hydrogen chloride, and concentration yielded crystalline *dl*-corynantheine hydrochloride, mp 177–181° (hs). Three crystallizations gave 0.9 mg, mp 176–179° (hs).

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Total Syntheses of *dl*-Ajmalicine and Emetine

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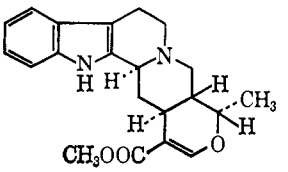
Contribution from the Department of Chemistry, The University of Wisconsin, Madison, Wisconsin. *Received January 30, 1969*

Abstract: The first total synthesis of a ring-E heterocyclic indole alkaloid, ajmalicine (**1**, racemic form), was accomplished by means of an initial, biogenetically patterned condensation of tryptamine, formaldehyde, and keto triester **4** and succeeding steps proceeding through the intermediates **16, 19, 20, 22, 23, 25,** and **26**. The stereochemistry of synthetic intermediates, and therefore of ajmalicine itself, was established by chemical correlations with reference compounds of known structure. Adaptation of the ajmalicine synthesis to the emetine case is also described.

Among the important and interesting variants in the yohimbine family of indole alkaloids is the ring-E heterocyclic type, a large and well-established class which includes ajmalicine (**1**).[2] This natural product, known also as tetrahydroserpentine and δ-yohimbine,



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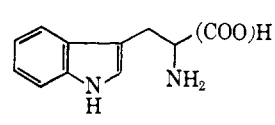
was early described by plant component investigators, and its gross structure was established during the early

(1) Address correspondence to this author at Stanford University, Department of Chemistry, Stanford, Calif. 94305.

(2) For a review, see R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia," Little, Brown and Co., Boston, Mass., 1957, Chapter 3.

1950's through the efforts of several groups.[3] During the same decade, partial tentative stereochemical assignments were made,[4] but these were revised on the basis of later observations, made in this and other laboratories. Interest in ajmalicine was sharpened when it became recognized as a peripheral vasodilator effective in treatment of angina and Raynaud's disease.

Biosynthetic investigations in this natural product area proceed still. However, despite earlier speculations,[5] it is now known that the D/E moiety does not arise from a phenylalanine precursor, but finds its origin in the terpene biochemical pool.[6] According to the latest views, the ring-E heterocyclic type derives from tryptamine (or tryptophan) (**2**) and loganin (**3**), although



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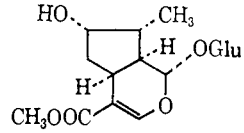

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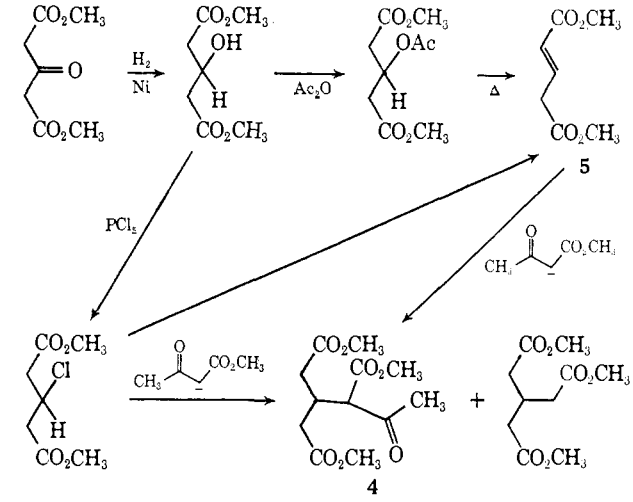
the nature of the biochemical component which actually reacts with the amine remains obscure.

On the basis of early conjecture in this laboratory that the D/E moiety found its origins in a nonaromatic precursor, a "biogenetic-type" laboratory synthesis was projected during the mid-1950's and pursued with increasing intensity until completion of a short, efficient synthesis of *dl*-ajmalicine in 1961. At the time of conception, the biosynthesis route was obscure and uninvestigated; chemical precedent for certain key synthetic operations was lacking; and stereochemical assignment to possible target natural products was insecure. However, as the synthetic work unfolded, progress was made along biogenesis lines, complementing the biogenetic-type approach being followed; simpler models of certain steps planned emerged from our own and other laboratories; and crucial stereochemical aspects came to light essentially concurrently with our synthesis endeavors. Although the particular ring-E heterocycle destined to mark the termination of our synthetic work could not have been singled out, it was, as it turned out, ajmalicine.

The first objective in the synthesis program was preparation of an acyclic component corresponding to the nontryptophan-derived portion of the indole alkaloids. This acyclic intermediate would be condensed with formaldehyde and tryptamine in a biogenetically patterned key step, which would assemble at the outset the essential skeletal features of the alkaloid molecule. The chosen compound, methyl 5-keto-4-carbomethoxy-3-carbomethoxymethylhexanoate[7] (hereafter called the "keto triester," **4**), was prepared from dimethyl acetonedicarboxylate and methyl acetoacetate by the conventional methods outlined in Chart I. High-pressure cat-

Chart I



alytic hydrogenation of dimethyl acetonedicarboxylate yielded dimethyl β-hydroxyglutarate, which was converted to the keto triester **4** in two ways. Pyrolysis of the acetate gave dimethyl glutaconate (**5**), which condensed with excess methyl acetoacetate in the Michael fashion under the influence of sodium methoxide in methanol, giving the desired keto triester **4**. The same product (**4**) was obtained more conveniently and in better yield by treatment of the sodium salt of methyl acetoacetate with dimethyl β-chloroglutarate prepared from dimethyl β-hydroxyglutarate and phosphorus pentachloride.[7] By-products of this sequence were dimethyl glutaconate (**5**) and trimethyl methanetriacetate. The structure of the keto triester (**4**) was confirmed by elemental analysis, and infrared and nmr spectra.

At this point there were several possible ways to proceed. For example, it seemed reasonable to build up ring C of the alkaloid before attempting to close ring D by means of the Mannich condensation (Chart II). To this end, the keto triester (**4**) was converted to the ethylene ketal anhydride (**6**) by the following sequence of reactions: hydrolysis, decarboxylation, reesterification, ketalization, saponification, and anhydride formation. Condensation of the ethylene ketal anhydride with tryptamine (**7**) gave the amide (**8**), which was subjected to the conditions of the Bischler–Napieralski reaction in order to form the desired product (**9**). However, the only identifiable product from this reaction was compound **10**, formed by cyclization involving the ketal moiety instead of the amide function. Evidently the ethylene ketal unit provides insufficient protection for the keto group.[8]

After some study it was found that condensation of the desired type could be effected by interaction of tryptamine and the keto anhydride (**11**) during a very short reaction time at room temperature. The crude product was immediately reduced with sodium borohydride, and treatment with diazomethane followed by chromatography on silicic acid yielded the required lactone amide (**12**). A small quantity of glutarimide (**13**) was also

(3) (a) R. Goutarel and A. LeHir, *Bull. Soc. Chim. France*, **18**, 909 (1951); (b) M. W. Klohs, M. D. Draper, F. Keller, W. Malesh, and F. J. Petracek, *J. Am. Chem. Soc.*, 76, 1332 (1954).

(4) E. Wenkert and D. K. Roychaudhuri, *ibid.*, 79, 1519 (1957); 80, 1613 (1958); N. Neuss and H. E. Boaz, *J. Org. Chem.*, 22, 1001 (1957).

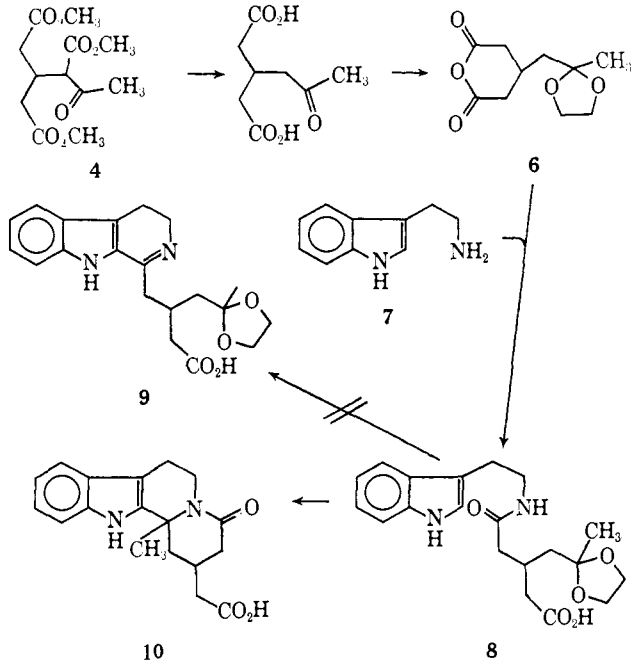
(5) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, 81, 1474 (1959); see also (a) G. Barger and C. Scholz, *Helv. Chim. Acta*, 16, 1343 (1933); (b) G. Hahn and H. Werner, *Ann.*, 520, 123 (1935); (c) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955; (d) R. B. Woodward, *Nature*, 162, 155 (1948).

(6) (a) T. Money, I. G. Wright, F. McCapra, and A. I. Scott, *Proc. Natl. Acad. Sci. U.S.*, 53, 901 (1965); (b) F. McCapra, T. Money, A. I. Scott, and I. G. Wright, *Chem. Commun.*, 537 (1965); (c) A. R. Battersby, R. T. Brown, R. S. Kapil, A. O. Plunkett, and J. B. Taylor, *ibid.*, 46 (1966); (d) H. Goeggel and D. Arigoni, *ibid.*, 538 (1965); (e) A. R. Battersby, R. T. Brown, R. S. Kapil, J. A. Martin, and A. O. Plunkett, *ibid.*, 890 (1966).

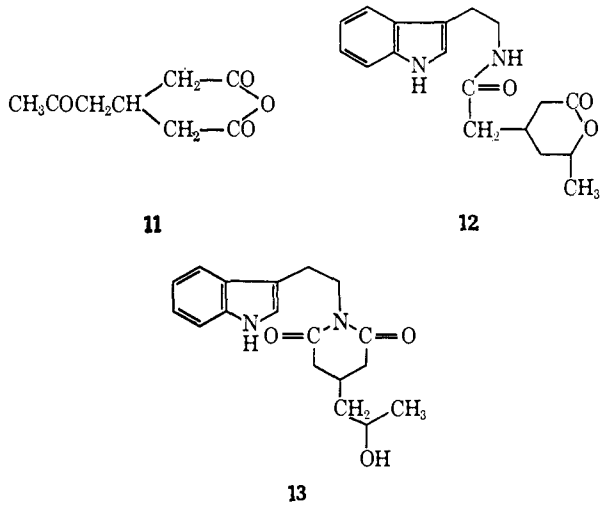
(7) M. H. Dreifuss and C. K. Ingold, *J. Chem. Soc.*, 123, 2964 (1932), first prepared the triethyl ester of the same acid.

(8) The reactions leading to compounds 10 and 12 were carried out by Dr. J. E. Davies.

Chart II



isolated. In spite of many attempts to carry out a Bischler–Napieralski ring closure on **12**, a crystalline tetracyclic compound could not be isolated.

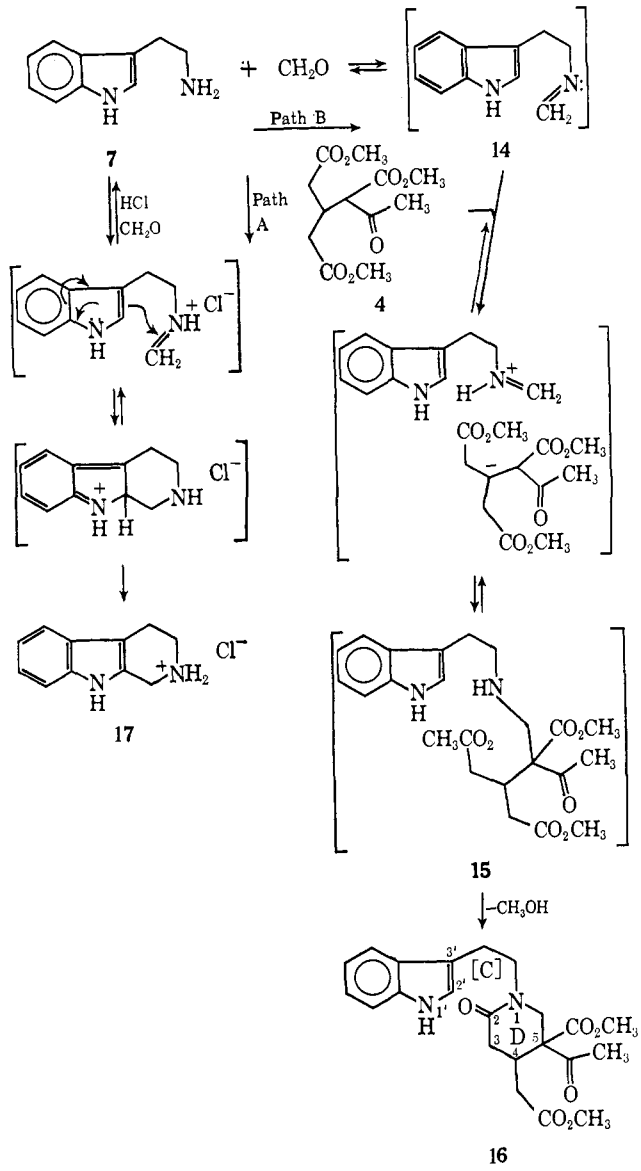


With this effort frustrated, attention was concentrated on an alternative route (Chart III). The plan required the initial Mannich condensation of the acyclic intermediate **4** with formaldehyde and tryptamine (**7**) in the biogenetically patterned key step. The intermediate Mannich base (**15**) was expected to stabilize itself by cyclization to the lactam **16**, thus forming ring D. It seemed unlikely that the keto group of **16** would interfere in the Bischler–Napieralski closure of ring C.

Before committing valuable keto triester (**4**) a model study was made. Equivalent quantities of tryptamine hydrochloride, paraformaldehyde, and ethyl α-ethylacetoacetate in refluxing ethanol (the conditions usually employed to effect the Mannich condensation) led only to 1,2,3,4-tetrahydro-β-carboline (**17**) (86% yield) (path A, Chart III). There was no evidence for the formation of the desired Mannich base.

The desired condensation was achieved, however, under mild conditions analogous to those used by Gott-

Chart III



stein, *et al.*[9] When a solution of equivalent quantities of tryptamine (**7**), aqueous formaldehyde, and the keto triester (**4**) in *t*-butyl alcohol was allowed to stand overnight and then heated to reflux for 1 hr, the desired product 5-acetyl-5-carbomethoxy-4-carbomethoxymethyl-1-[β-(3′-indolyl)ethyl]-2-piperidone (the lactam **16**) was obtained, after chromatography, in about 50% yield (path B, Chart III). The 50% unchanged keto triester (**4**) which was recovered could be recycled. Little tryptamine could be recovered unchanged, and it is evidently consumed by competing reactions. The structure of the lactam (**16**) was assigned on the basis of spectral data. The infrared spectrum showed bands due to indole N–H (2.85 μ), aliphatic ester (5.75 μ), aliphatic ketone (5.80 μ), and six-membered ring lactam (6.09 μ). The ultraviolet spectrum was characteristic of a simple indole [λ_{max} 221 mμ (ϵ 33,700), 276 (5100), 284 (5000), 292 (4900)]. The nmr spectrum supported the structural assignment, showing, among other signals, the indole α-proton (broad, one-proton signal at τ 3.05), the two methyl ester groups (tertiary at τ 6.32, primary at

(9) W. J. Gottstein, W. F. Minor, and L. C. Cheney, *J. Am. Chem. Soc.*, **81**, 1198 (1959).

τ 6.35, both three-proton singlets), and the ketone methyl group (three-proton singlet at τ 7.89).

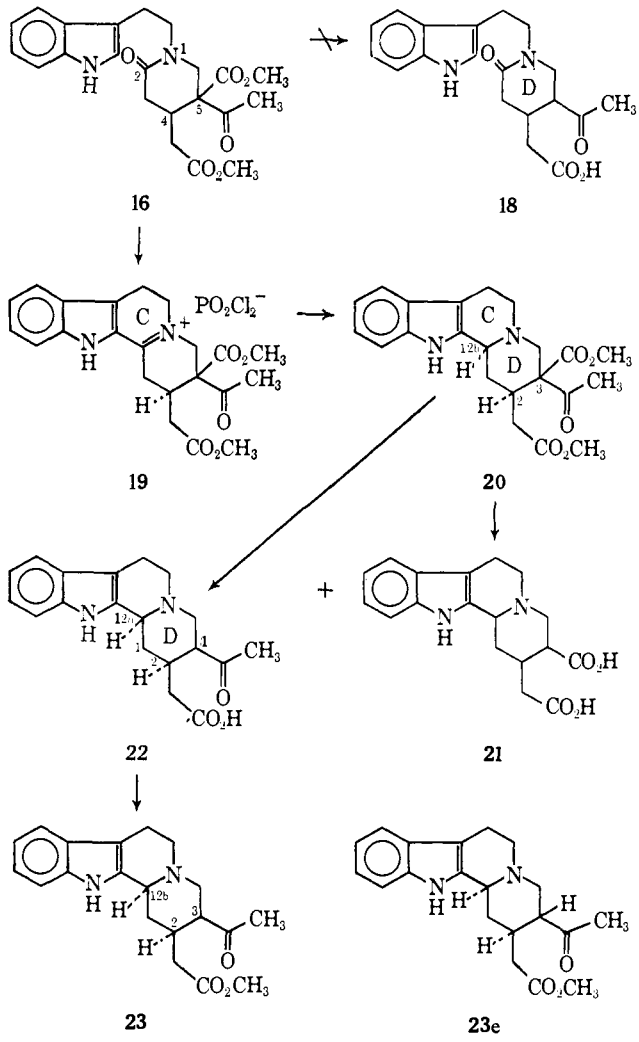
It is pertiment at this point to discuss the dramatic difference in the results of acidic and basic Mannich reaction conditions. The mechanism of the reaction between tryptamine hydrochloride and formaldehyde to form 1,2,3,4-tetrahydro-β-carboline (**17**) can be envisioned as shown in Chart III (path A). The presence of strong acid suppresses removal of the weakly acidic proton of the β-keto ester and prevents its participation in the desired intermolecular Mannich condensation. In the absence of strong acid, one of the basic components [*e.g.*, tryptamine (**7**) or the tryptamine–formaldehyde Schiff base (**14**)] can abstract the acidic proton from the β-keto ester portion of the keto triester (**4**), allowing the desired Mannich reaction to take place. Cyclization of the intermediate Mannich base (**15**) to the stable lactam (**16**) prevents retrogression or further condensation (Chart III, path B).

The lactam (**16**) was ordinarily obtained as a viscous yellow oil and was utilized as such in subsequent reactions. It could, however, be obtained in crystalline form by sharply cooling a concentrated methanol solution in acetone–Dry Ice and allowing the mixture to stand at -20 to $-30°$ overnight. In this way approximately 70% of the amorphous material could be obtained in crystalline form, mp 53–60°. No attempt was made to separate the individual isomers in this material (the lactam **16** contains two asymmetric centers) since subsequent reactions were expected to cause equilibration to the more stable *trans* configuration.

Two alternate schemes for subsequent utilization of the lactam **16** were envisioned (Chart IV). The ultimately successful sequence involved closure of the C ring by means of the Bischler–Napieralski reaction and subsequent modification of the ring D substituents. The unsuccessful route involved modification of the D ring substituents before closure of the C ring, and it was investigated because of the advantage of working with compounds having the sensitive, basic nitrogen atom neutralized as the amide. The tertiary carbomethoxy group at position 5 of the lactam **16**, originally included in the keto triester **4** as an extra activating group to direct the Mannich reaction in the desired sense, proved to be very resistant to removal under ordinary aqueous hydrolytic conditions sufficiently mild to leave the lactam ring unaffected. It was expected, however, that the anhydrous ester cleavage conditions described by Eschenmoser[10] would be ideally suited to this situation. Boiling the lactam **16** with anhydrous lithium iodide in pyridine was expected to bring about both cleavage of the ester groups and decarboxylation of the resulting β-keto acid, yielding the lactam keto acid (**18**) directly. In fact, these conditions did result in evolution of about one-half of the theoretical quantity of carbon dioxide, but the product was a complex mixture containing at most only small amounts of the desired substance (**18**), which was never isolated in pure form.

To return to the successful sequence, closure of the C ring was effected smoothly and in good yield by boiling the lactam **16** with 10% phosphorus oxychloride in benzene. When the reaction and work-up were carried out

Chart IV



with rigorous exclusion of air and moisture, the product 3-acetyl-3-carbomethoxy-2-carbomethoxymethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-*a*]quinolizinium dichlorophosphate (**19**), could be isolated in crystalline form directly from the reaction mixture in 87% yield. This iminium salt (mp 154–157° after recrystallization from chloroform–ethyl acetate) gave correct elemental analyses and had an ultraviolet spectrum consistent with the assigned structure [λ_{max} 247 mμ (ϵ 11,900), 307 (7500), 314 (9900), 358 (23,500)].

Catalytic hydrogenation of the Bischler–Napieralsky product **19** over platinum or palladium proceeded smoothly to give 3-acetyl-3-carbomethoxy-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]quinolizine (hereafter called the keto diester **20**), which crystallized readily from methanol in 88% yield as a mixture of isomers, mp 180–190°. From the ketone and ester methyl group peak intensities in the nmr spectrum of the crude mixture it was apparent that the isomers were present in about equal amounts. Repeated recrystallization of a sample from methanol concentrated one isomer, mp 197–199° (probably the isomer with the acetyl group at position 3 axial, judging from behavior of other derivatives[11]). Since catalytic hydrogenation of iminium salts such as **19** is known[12]

(10) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 43, 113 (1960).

(11) See accompanying paper: E. E. van Tamelen and I. G. Wright, *J. Am. Chem. Soc.*, 91, 7349 (1969).

(12) E. E. van Tamelen, P. E. Aldrich, and T. J. Katz, *ibid.*, 79, 6426 (1957); E. Wenkert and D. K. Roychaudhuri, *ibid.*, 79, 1519 (1957);

to occur preferentially from the less hindered side of the molecule to produce the 2,12b-*cis* stereochemistry, the observed isomerism is undoubtedly due to the substituents at position 3. Because the asymmetry at this position was to be destroyed in subsequent reactions, no special attempt was made to separate the isomers of **20**.

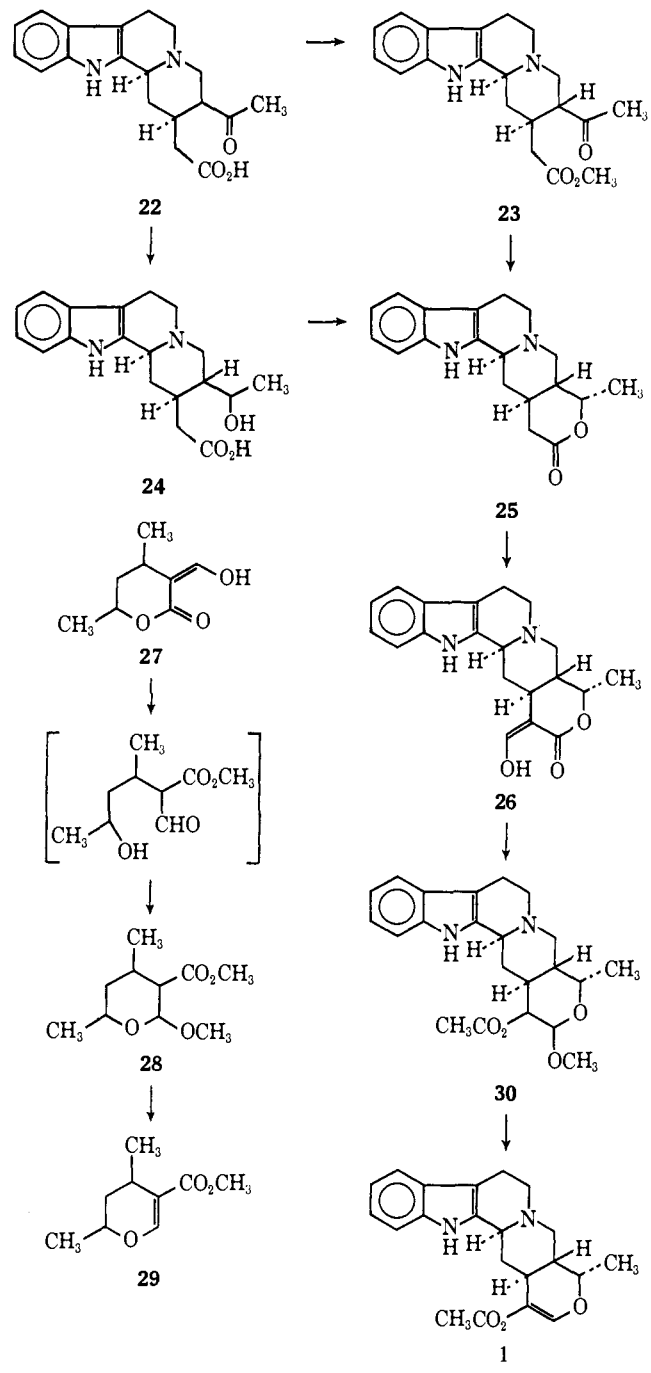
In the keto diester **20** we again faced the problem of removing the extra carbomethoxy group at position 3. The first attempt to accomplish this hydrolysis and decarboxylation involved heating the substance at reflux for 20 hr in constant boiling hydrochloric acid. The predominant product, which crystallized out of the reaction mixture as the hydrochloride salt (mp 268.8–269.4° dec) in 51% yield, proved to be the diacid **21**. This unwanted product of acid-catalyzed deacetylation was characterized by elemental and C-methyl analysis, neutralization equivalent, and the infrared spectrum of the sodium salt. The desired product, the keto acid **22**, was obtained as the hydrochloride salt (mp 236.5–238.0° dec) in 12% yield by silicic acid chromatography of the remaining portion of the hydrolysis product. The structural assignment was based again on elemental and C-methyl analysis, neutralization equivalent, and the infrared spectrum.[13]

Considerable study of the conditions for hydrolysis and decarboxylation of **20** led to a greatly improved yield of the desired product, the keto ester **23**. Refluxing the keto diester **20** for 2 weeks in 2% hydrochloric acid with careful exclusion of light and air resulted in predominant decarboxylation. The product was most conveniently worked up by direct esterification of the hydrochloride salt of the keto acid **22** with methanol and chromatography on silicic acid. In this way there could be obtained a 63% yield of 3-acetyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine hydrochloride (keto ester **23** hydrochloride) in crystalline form (mp 245–250° dec).

The nmr spectrum of the keto ester **23** supported the assignment of structure of the keto acid **22** and revealed the originally unsuspected presence of two isomers in a ratio of approximately 3:2. On the basis of the expected order of stability the major isomer was tentatively assigned the more stable 2,3-*trans* configuration (**23e**) with both ring D substituents occupying equatorial positions. This assignment was later confirmed by chemical correlation with known compounds available by reason of previous work in this laboratory.[12] The details of the correlation, along with its implications for the stereochemistry of ajmalicine and related alkaloids, are discussed later.

For the further elaboration of the ajmalicine (**1**) skeleton (Chart V) it was necessary to convert the δ-keto acid (or ester) system of **22** (or **23**) to the δ-lactone. The most direct method was tried first. Reduction of the keto acid **22** with sodium borohydride in basic aqueous solution gave the δ-hydroxy acid (**24**) in yields ranging from 50 to 80%. The hydroxy acid **24** was isolated as the zwitterion by precipitation from aqueous solution and was characterized only by its infrared spectrum. Treatment of the crude δ-hydroxy acid with dicyclohexylcarbodiimide (DCC) in pyridine gave the δ-lactone

Chart V



25 in 43% yield (hydrochloride mp 240–241° dec). A better method for the preparation of the lactone **25** was the reduction of the keto ester **23** with sodium borohydride at −10°, which gave the lactone directly in nearly quantitative yield. The isomeric composition of the lactone from either procedure was not determined, but the *trans* isomer was expected to be predominant.

The method envisioned for the construction of ring E of ajmalicine (**1**) required the conversion of the lactone **25** to the α-hydroxymethylene lactone **26**. Prededent for this reaction was afforded by the synthesis of *dl*-dihydrocorynantheine.[14] It had been found that bases weaker than triphenylmethylsodium would not effect the desired condensation of methyl formate with the active methylene group next to the ester carbonyl, and it

80, 1613 (1958); E. E. van Tamelen, M. Shamma, and P. Aldrich, *J. Am. Chem. Soc.*, **78**, 4678 (1956).

(13) The studies of the hydrolysis products of 20 were carried out in collaboration with Dr. Thomas A. Spencer, Jr., who characterized 21 and first isolated and characterized 22.

(14) E. E. van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 3805 (1959).

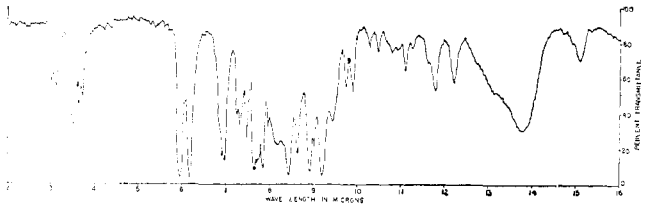


Figure 1. Ir spectrum of tetrahydroalstonine.

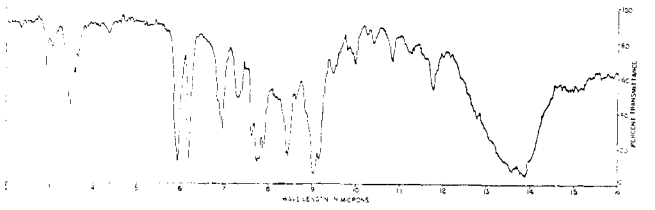


Figure 2. Ir spectrum of *dl*-ajmalicine.

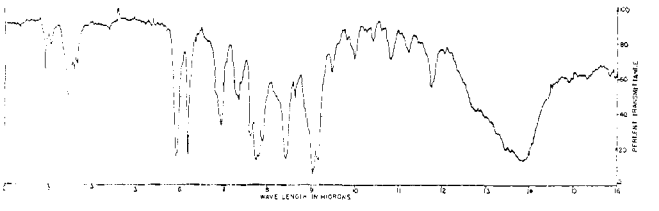


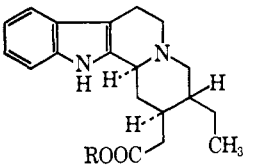
Figure 3. Ir spectrum of natural ajmalicine.

would be expected that initial formation of the anion of the acidic indole might interfere with the subsequent abstraction of a proton from the carbon atom α to the carbonyl group except with very strong bases. In the event, treatment of a suspension of the hydrochloride of the lactone **25** in dioxane with 5 molar equiv of ethereal triphenylmethylsodium, followed by a large excess of methyl formate, gave the α-hydroxymethylene-lactone **26** in 74% crude yield. The infrared spectrum of **26** exhibits bands at 3.0 and 6.05 μ characteristic of the α-hydroxymethylene lactone system.[14] The presence of the enol group was confirmed by a positive ferric chloride test. The crude α-hydroxymethylene lactone (**26**) was converted directly to *dl*-ajmalicine without further purification.

From the outset the plan for the completion of the synthesis involved the application of a reaction subsequently described as the "acyl lactone rearrangement."[15] Korte and his coworkers have studied this reaction in detail, determining that the conversion of an α-acyl-δ-lactone (*e.g.*, **27**[16]) to the corresponding dihydropyran-carboxylic ester (**29**) is convenient and facile. The reaction is carried out by treatment with dilute methanolic hydrogen chloride at room temperature, followed by heating with polyphosphoric acid to bring about elimination of methanol from the cyclic acetal **28**.

Somewhat more vigorous conditions for the rearrangement were applied in our case because of possible hindrance of the reaction through protonation of the basic nitrogen at the C/D ring junction, and because it seemed possible to effect the elimination of methanol from the acetal without resorting to treatment with polyphosphoric acid. Heating a solution of the α-hydroxymethylene lactone **26** in 10% methanolic hydrogen chloride at reflux for 27 hr produced *dl*-ajmalicine (**1**), mp 222–225°, in 37% yield, along with a small amount of the intermediate acetal **30** and a high-melting compound which was not identified. The infrared spectrum of the synthetic *dl*-ajmalicine was identical with that of natural *d*-ajmalicine.

Stereochemistry of Synthetic Intermediates and Ring-E Heterocyclic Indole Alkaloids. At the keto acid (**22**) stage of the synthesis, stereostructure became a crucial matter since at this point the determining factors for the ultimate D/E ring fusion stereochemistry first appeared. Efforts were therefore made to assign unambiguously the nature of the asymmetric centers present in this intermediate, and this goal was accomplished by reference to the tetracycle (**31**) of known structure. An



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additional issue of this program was reassignment of stereochemistry of the alkaloids in the ring-E heterocyclic class, a matter also pursued successfully in other laboratories.[17]

The nuclear magnetic resonance spectrum of the crude keto ester (**23**) revealed the presence of a mixture of isomers in approximately a 3:2 ratio. The ester and ketone methyl group signals due to the *trans* isomer appeared at τ 6.36 and 7.38, respectively; signals due to the other isomer (assumed to be the all-*cis* compound) appeared at τ 6.31 and 7.87, respectively.

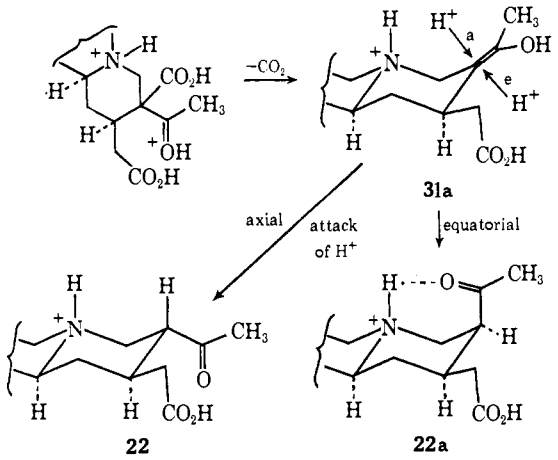
Although it is at first sight perhaps surprising that the *cis* keto acid (**22a**) isomer occurs in such high proportion relative to the more stable *trans* isomer, upon more careful examination this fact would appear reasonable. Resistance to isomerization is undoubtedly caused by the close proximity of the ketone to the basic nitrogen atom, which would be fully protonated under the acidic conditions employed. Protonation of the enol resulting from β-keto acid decarboxylation (**31a**), from the axial direction (to give the thermodynamically more stable compound with the acetyl group equatorial, **22**), would be expected to be highly inhibited by the proximity of the positively charged nitrogen. Protonation from the equatorial side of the enol **32** (to give the less stable axial acetyl isomer **22a**) thus would be particularly favorable, encouraging the initial formation of the axial isomer **22a**.

Reprotonation of the ketones **22**–**22a** once formed would be expected to be difficult, but not impossible, since protonation in the same position was required for the preceeding hydrolysis and decarboxylation reactions. It may be that protonation and enolization of the axial isomer **22a** is hindered more than that of the equatorial isomer **22** due to the closer proximity of the carbonyl oxygen to the full positive charge on the nitrogen, again favoring the survival of the axial isomer **22a**. Also, the stability of the axial isomer may be increased

(15) For a review, see F. Korte and K. H. Büchel, *Angew. Chem.*, 71, 709 (1959).

(16) F. Korte and H. Machleidt, *Ber.*, 88, 136 (1955).

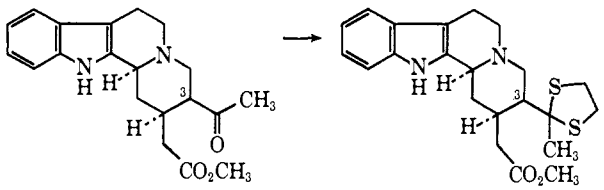
(17) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Am. Chem. Soc.*, 83, 5037 (1961); M. Shamma and J. B. Moss, *ibid.*, 83, 5038 (1961); 84, 1739 (1962).



by formation of an internal hydrogen bond between the carbonyl group and the tertiary ammonium hydrogen, all in a pseudo-six-membered ring. Equilibration of the mixture of keto ester **23** isomers under basic conditions was attempted, but led to decomposition.

The mixture of keto ester isomers was converted to a mixture of the corresponding thioketals (**32** and **32a**) by treatment with ethanedithiol and boron trifluoride ether complex. Integration of the "ketone" methyl group signals in the nuclear magnetic resonance spectrum indicated that the mixture contained 62% *trans*- and 38% *cis*-thioketals (signals at τ 8.28 and 8.22, respectively); thus little or no isomerization had occurred during the thioketalization reaction, as expected.[18] The mixture of thioketals was partially separated by chromatography on silicic acid, the *trans* isomer (**32**) being eluted first. The *cis* isomer (**32a**) crystallized readily from methanol as a solvate and could be purified by repeated crystallization from methanol. Both thioketals formed crystalline hydrochloride salts, the *trans*-thioketal hydrochloride, mp 259.5–260° dec, and the *cis*-thioketal hydrochloride, mp 295–298° dec.

The structures of the two thioketals were established by the elemental analyses of the hydrochloride salts and by the nuclear magnetic resonance spectra. The spectrum of the *trans* isomer (**32**) showed an ester methyl group signal at τ 6.30, a new, four-proton signal at τ 6.78 due to the protons of the ethylene thioketal, and the "ketone" methyl group signal at τ 8.32. The spectrum

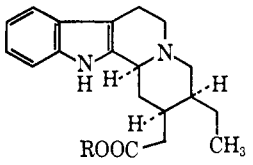


23, C-3 H axial
23a, C-3 H equatorial

32, C-3 H axial
32a, C-3 H equatorial

of the *cis* isomer **32a** showed the ester methyl group signal at τ 6.27, the ethylene thioketal protons at τ 6.75, and the "ketone" methyl group signal at τ 8.21. In addition, the spectrum of the crystalline *cis*-thioketal showed a methyl group signal at τ 6.63 due to the methanol of crystallization.

Desulfurization of the *trans*-thioketal **32** with Raney nickel yielded the *trans*-ethyl compound, *trans*-3-ethyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**31**), identical with the van Tamelen and Hester compound **31** as indicated by thin layer chromatography, infrared spectra, and melting point of hydrochloride salt (mp 275–276.2° dec) (lit.[14] mp 275–276.8° dec). Similarly, desulfurization of the *cis*-thioketal gave a substance assigned the all-*cis* structure (**33**).



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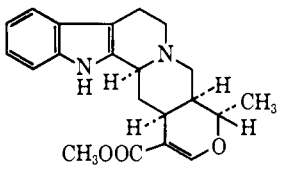
Up until the time of completion of this synthesis, the stereochemistry of ajmalicine was thought by some to possess the D/E *cis* ring juncture.[4] The obtention of ajmalicine from our synthetic sequence cast grave doubt as to the correctness of this stereochemical assignment, since the more stable D/E *trans* isomer, supposedly tetrahydroalstonine, was expected as the end product of the synthetic sequence. These suspicions, allusion to which was made in our original communication,[19] were supported by the stereochemical correlation described in this section, and were also confirmed by the essentially simultaneous structure work of Wenkert, Wickberg, and Leicht as well as Shamma and Moss.[17]

Thus, it is now established that ajmalicine possesses the stereostructure **1**, and that tetrahydroalstonine should be portrayed as **34**. Stereochemical revision



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of other ring-E heterocycles follows from these considerations and reassignments.

Synthesis of Emetine. Because of the structural and biosynthetic parallelism between the *Ipecac* and ring-E heterocyclic indole alkaloid categories, it appeared to us that the biogenetically patterned total synthesis route developed in the latter area could be applied to the emetine system (**35**).[20–22] Outlined below is such an adaptation.[23]

By means of a Mannich reaction involving 3,4-dimethoxyphenethylamine, formaldehyde, and the keto triester (**4**) and carried out in *t*-butyl alcohol, the integral part of the emetine molecule can be constructed

(18) R. K. Hill and J. G. Martin, *Proc. Chem. Soc.*, 390 (1959).

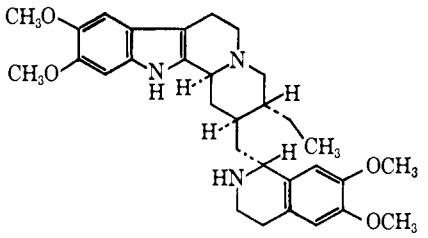
(19) The synthesis of ajmalicine was first disclosed and discussed at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 28, 1961, and was published as a Communication to the Editor, *J. Am. Chem. Soc.*, **83**, 2594 (1961).

(20) For a review, see M. M. Janot, *Alkaloids*, 3, 363 (1959).

(21) For stereochemical assignments, see (a) E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, Jr., *J. Am. Chem. Soc.*, 79, 4817 (1957); (b) E. E. van Tamelen and J. B. Hester, Jr., *ibid.*, **81**, 507, 6214 (1959); (c) A. R. Battersby and S. Garratt, *Chem. Ind.* (London), 86 (1959), and earlier references cited therein; (d) Y. Ban, M. Terashima, and O. Yonemitsu, *ibid.*, 568, 569 (1959).

(22) For earlier syntheses, see (a) R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova, and N. A. Preobrazhenskii, *Dokl. Acad. Nauk SSSR*, 75, 539 (1950); (b) A. Brossi, M. Baumann, and O. Schnider, *Helv. Chim. Acta*, 42, 1515 (1959); (c) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 717 (1960); (d) D. E. Clark, R. F. K. Meredith, A. C. Ritchie, and T. Walker, *ibid.*, 2490 (1962).

(23) A preliminary account of this work has been published: E. E. van Tamelen, G. P. Schiemenz, and H. L. Arons, *Tetrahedron Letters*, **No. 16**, 1005 (1963).



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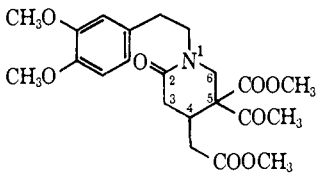
in a single operation. Spontaneous lactamization of the initially produced Mannich base is involved in the over-all, high-yield conversion to isolated product (**36**),



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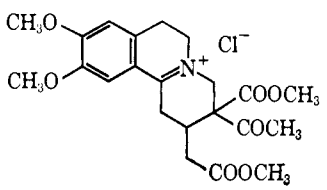
an oil distillable under high vacuum. The condensation product exhibited infrared absorption bands, *inter alia*, at 5.75 (ester), shoulder 5.8 (ketone), and 6.10 μ (lactam), and maxima in the ultraviolet (methanol solvent) at 230 mμ (log ϵ 3.93) and 280 (3.47). A small amount of 6,7-dimethoxytetrahydroisoquinoline, formed by simple interaction of the starting amine with formaldehyde, was also isolated from this reaction.

Although toluene could serve as solvent for the Bischler–Napieralski reaction on **36**, troublesome decomposition of product occurred at the boiling point of this solvent; refluxing benzene proved ideal, permitting phosphorus oxychloride promoted conversion to iminium chloride **37**, which crystallized out directly from the reaction medium in approximately 80% yield.



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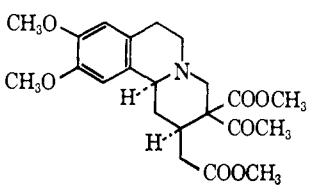
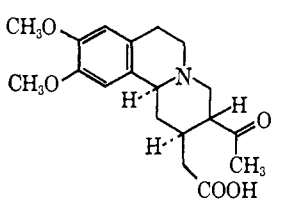


38

Recrystallized from nitrobenzene–petroleum ether (bp 30–60°), the salt so produced melted at 148.5–150° and exhibited uv maxima (methanol solvent) at 246 mμ (log ϵ 4.12), 307 (3.91), and 359 (3.94). Despite the fact that "crude" material resulting directly from the cyclization could be used as such for the next chemical step, and despite purification by chromatography and recrystallization to material of relatively sharp melting point, the tricyclic iminium salt gave carbon analyses which were 1.5–2.0% off—a difficulty encountered with no other intermediate in the synthesis.

Platinum-catalyzed reduction of iminium salt **37** in methanol proceded reliably, even with crude substrate, giving dihydro product without difficulty. Since there was no evidence at this point or later for diastereoisomerism developing at the new center of asymmetry, we believe the catalytic reduction to be highly stereoselective, as would be anticipated on the basis of less steric hindrance to approach of catalyst from the side opposite the acetic ester side chain. The hydrochloride of product **38** crystallized with difficulty, and was best converted to the corresponding free base, which appeared as needles, mp 119–120°, out of ether. In the hydrogenated material, the longer wavelength absorption had disappeared and was replaced by absorption characteristic of the simple 1,2-dimethoxybenzene chromophore, λ_{max} 232 mμ (log ϵ 3.71) and 283 (3.38).

As in the ajmalicine synthesis, hydrolysis and decarboxylation of the β-keto ester function was managed by heating of the tricyclic keto diester **38** in refluxing 2% hydrochloric acid for several days. After chromatography on silicic acid, the product keto acid (**39**) hydrochloride (mp 196–198°; mol wt by titration, 393) was recrystallizable from chloroform–carbon tetrachloride. The over-all yield of keto acid from Bischler–Napieralski product was 50%. Consistent with structure **39**, the new acid exhibited ir carbonyl absorption at 5.76



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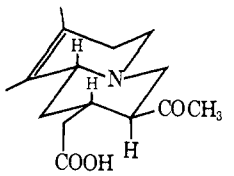
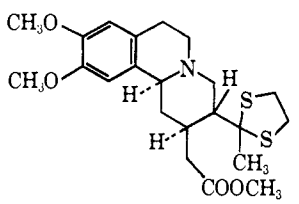


40

and 5.80 μ. Conversion to methyl ester was readily carried out by treatment with cold methanolic hydrogen chloride. Because (1) keto acid **39** was the sole decarboxylation product isolated (and in good yield) and (2) because the conditions used might well be, at least in part, equilibrating, there seemed to be little reason to doubt that the new asymmetric center formed would appear in the more stable configuration, *viz.*, equatorial and *trans* to the other two points of asymmetry (**40**). Successful completion of the synthesis confirmed this view.

Conversion of the acetyl to ethyl group was accomplished by preparation from keto ester of the ethylene dithioketal ester (**41**), which was then reductively desulfurized with Raney nickel. Since the hydrogen chloride–acetic acid method gave rise to dithioketal which caused trouble in the succeeding, desulfurization step, the dithioketalization was carried out using a boron trifluoride etherate catalyst. The dithioketal **41** itself was found to be a well-defined crystalline material of mp 126–127.5°, forming a hydrochloride, mp 207.5–209°. The intermediate dithioketal was not ordinarily purified, but reductively desulfurated in boiling methanol directly to tricyclic ester **42**.



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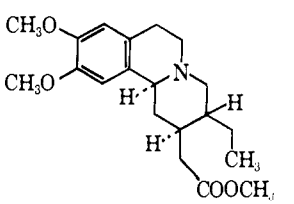
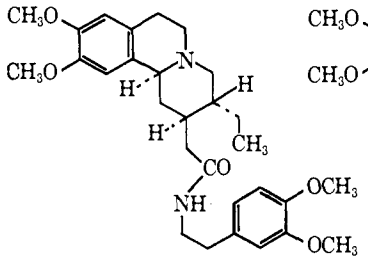


42

Since this intermediate had already been transformed, *via* amide **43** and imine **44**, to emetine,[24] obtention of that substance by the route outlined constitutes a new total synthesis of the alkaloid. Identification of the key intermediate **42** was made by comparison of the hydro-

(24) N. A. Preobrazhenskii, R. P. Evistigneeva, T. S. Levchenko, and K. M. Fedyshkina, *Dokl. Acad. Nauk SSSR*, **81**, 421 (1951).

chloride (mp 199–199.5°) with equivalent *dl* material (mp 198.5–199°) produced by an alternative route (mp 199–199.3°). Similarly, melting point and mixture melting point comparison of the amide **43** (mp 148–150°), prepared from ester secured as described herein,



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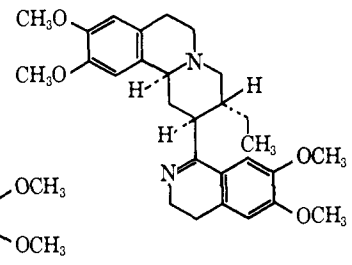

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with authentic amide (melting point as observed in parallel determination, 151.5–153°) were satisfactory, as were infrared spectral comparisons made on free base **42**, amide **43**, and corresponding authentic specimens.

Experimental Section

All melting points are corrected unless otherwise specified and were taken in capillary tubes in a Hershberg apparatus using Anschutz total-immersion thermometers unless otherwise specified (HS meaning Koefler hot stage). All boiling points are uncorrected.

Analyses were performed by the Microanalytical Laboratory of the University of Wisconsin, the Huffman Microanalytical Laboratories, Wheatridge, Colo., or the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Ultraviolet spectra were measured on substances in ethanol or methanol with a Cary recording spectrophotometer (Model 11MS). Infrared spectra were taken on either a Baird double-beam self-recording spectrophotometer (Model B or Model 4-55), a Perkin-Elmer Infracord spectrophotometer (Model 137), or a Beckman double-beam recording spectrophotometer (Model IR-5).

The silicic acid used for chromatography was obtained from the Mallinckrodt Chemical Works and was washed with acetone and dried at 100° before use.

Nuclear magnetic resonance spectra were determined on a Varian A-60 nmr spectrometer. Unless otherwise noted, deuteriochloroform (Merck Sharp and Dohme of Canada Ltd., Montreal, Canada) was employed as solvent and hexamethyldisiloxane (K & K Laboratories Inc., Jamaica, N. Y.) as internal standard. Chemical shifts are reported in τ units; the position of hexamethyldisiloxane being taken as τ 9.94 in deuteriochloroform solution and τ 9.88 in pyridine solution (calibrated with respect to tetramethylsilane).

Dimethyl β-Hydroxyglutarate.[25] Hydrogenation of dimethylacetone dicarboxylate (Aldrich Chemical Co., Inc., Milwaukee, Wisc.), bp 138–140° (18 mm) (527.5 g, 3.03 moles) in a steel bomb over Raney Nickel W-2 catalyst (40 g) at a temperature of 100° and a pressure of 1600 psi resulted in absorption of 125% of the theoretical quantity of hydrogen within 2 hr. The catalyst was separated by filtration through Celite and washed with methanol. Distillation of the product yielded dimethyl β-hydroxyglutarate (**27**) (507.1 g, 2.88 moles, 95.1%), bp 130–139° (18 mm).

Dimethyl β-Chloroglutarate. This was prepared by a large-scale modification of the procedure of Dreifuss and Ingold,[7] who prepared the corresponding diethyl ester. Dimethyl β-hydroxyglutarate (477 g, 2.72 moles) was dissolved in anhydrous ether (2.5 l.) in a 5-l. three-necked flask immersed in an ice bath and equipped with a mechanical stirrer and Dry Ice cold finger condenser. Phosphorus pentachloride (565 g, 2.72 moles) was weighed into a 500-ml erlenmeyer flask which was then attached to the remaining neck of the reaction vessel with a short length of Gooch tubing. The phosphorus pentachloride was added to the stirred ether solution, slowly at first until refluxing commenced, then at a rate sufficient to maintain a vigorous but not excessive rate of reflux and gas evolution. When the evolution of hydrogen chloride ceased and all the phosphorus pentachloride had been added, the erlenmeyer flask and tubing were removed and replaced with a dropping funnel. Ice water (2 l.) was added through the funnel, dropwise until vigorous reaction ceased, then rapidly. The mixture was then transferred to a 12-l. separatory funnel and the aqueous layer discarded. The ether solution was washed with sodium carbonate solution until neutral and worked up as usual. In contrast to the reported behavior of the diethyl ester,[7] the crude chloro compound (406.5 g, 2.09 moles, 76.8%) distilled without decomposition, bp 104–110° (4 mm) (378.6 g, 1.95 moles, 71.6%). The infrared spectrum of product showed negligible hydroxyl absorption.

Dimethyl Glutaconate (5).[26] A mixture of 800 g (4.54 moles) of dimethyl acetonedicarboxylate and 80 g of W-2 Raney nickel was hydrogenated at an initial pressure of 1645 psi at 100°. After being filtered through Filtercel the crude product was refluxed with 560 g (5.49 moles) of acetic anhydride for 30 min. The acetic acid and excess acetic anhydride were removed by distillation. The residue was transferred to a 1000-ml three-necked flask equipped with a Hershberg stirrer, a thermometer, a 35-cm Vigreux column, and a heating mantle. The pot temperature was raised to 240–260° with stirring, and a mixture of dimethyl glutaconate and acetic acid was slowly distilled out at a head temperature of 165–195°. Redistillation of the product gave 361 g (50.0%) of dimethyl glutaconate, bp 124–128° (25 mm).

Methyl 3-Carbomethoxymethyl-4-carbomethoxy-5-ketohexanoate (4). A. The following procedure is based on that of Preobrazhenskii, *et al.*, for the preparation of diethyl 2-cyano-3-carbethoxymethylglutarate.[27]

To a solution of 180 g (1.14 moles) of dimethyl glutaconate (**5**) and 400 g (3.42 moles) of methyl acetoacetate in 400 ml of absolute methanol (dried by distillation from magnesium methoxide) was added 75 ml of 0.57 *M* methanolic sodium methoxide, and the solution was heated to reflux with stirring. After 20 hr of refluxing, 60 ml of the sodium methoxide solution was added dropwise over a period of 9 hr; and after 44 hr, 65 ml of the sodium methoxide solution was added dropwise over a period of 12 hr. Heating was discontinued after 94 hr, and 8.0 ml of glacial acetic acid was added to the cooled reaction mixture. The solvent was removed by distillation at reduced pressure, ether was added to the residue, and the solution was washed twice with 5% sodium bicarbonate solution and twice with saturated sodium chloride solution. The ethereal solution was dried over anhydrous magnesium sulfate and the ether and excess methyl acetoacetate were removed by distillation at reduced pressure. The residue was fractionated through a 20-cm Vigreux column. The first fraction consisted of 29 g of dimethyl glutaconate, bp 125–138° (15 mm). Fractions, bp 176–210° (10 mm), were refractionated yielding 133 g (50.8% based on unrecovered starting material) of the keto triester (**4**), bp 127–129° (0.6 mm). An analytical sample of **4**, bp 125° (0.1 mm), $n^{25}D$ 1.4534, was prepared by one further fractionation.

Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.38; H, 6.49.

B. Sodium hydride (Metal Hydrides Inc., Beverly, Mass.) (28.8 g, 1.20 moles) was suspended in freshly dried (distillation from lithium aluminum hydride) tetrahydrofuran (700 ml) in a dry 2-l. flask equipped with stirrer, reflux condenser, and dropping funnel under an atmosphere of dry nitrogen. Methyl acetoacetate (145 g, 1.25 moles) was added slowly, and the reaction mixture was stirred until the sodium hydride had completely dissolved and evolution of hydrogen had become slow. Dimethyl β-chloroglutarate (232 g, 1.20 moles) was added rapidly, and the mixture was heated gently at reflux for 4 hr (a preliminary experiment in which the reaction was followed by titration showed that consumption of base was slow at room temperature but had essentially ceased after 3 hr reflux). Most of the solvent was removed under reduced pressure, and the residual slurry was poured into dilute hydrochloric acid and extracted with ether. The ether extract was washed with sodium carbonate solution and worked up as usual. The residue was fractionated through a spinning band column: fraction 1, bp 25–65° (2 mm), methyl acetoacetate (29.0 g); fraction 2, bp 65–120° (0.4 mm), dimethyl glutaconate (51.2 g, 0.324 mole, 27.0%); fraction 3, bp 120–145° (0.4 mm), keto triester **4** (160.5 g, 0.585 mole, 48.8%); fraction 4, bp 160° (0.4 mm), trimethyl methanetriacetate (37.5 g, 0.162 mole, 13.5%). Refractionation of combined suitable fractions from several runs yielded the pure compounds. Dimethyl glutaconate, bp 109–114° (11 mm) [lit.[21] bp 94–95° (2 mm)], was

(25) R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. I. Zakharkin, and N. A. Preobrazhenskii, *J. Gen. Chem. USSR*, **22**, 1467 (1952).

(26) M. E. E. Blaise, *Bull. Soc. Chim. France*, [3] **29**, 1028 (1903).

(27) For a revised procedure and early references, see E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 6214 (1959).

identified by infrared spectral comparison with an authentic sample. The keto triester **4** possessed bp 130–135° (0.5 mm). Trimethyl methanetriacetate, bp 140–154° (0.2 mm), was characterized only by its infrared spectrum and the structure was assigned on the basis of earlier work on the triethyl ester.[7]

The nuclear magnetic resonance spectrum of the keto triester **4** showed signals as follows: τ 6.10 (one-proton doublet, J = 6.5 cps), methine hydrogen of the β-keto ester moiety; τ 6.29 (three-proton singlet), tertiary ester methyl group; τ 6.36 (six-proton singlet), primary ester methyl groups; τ 7.05 (one-proton multiplet, J = 6.5 cps approximately), methine hydrogen of the glutarate portion; τ 7.49 (four proton doublet, J = 6.0 cps), methylene hydrogens of the glutarate portion; τ 7.78 (three-proton singlet), ketone methyl group.

5-Acetyl-5-carbomethoxy-4-carbomethoxymethyl-1-[β-(3′-indolyl)-ethyl]-2-piperidone (16). Tryptamine (48.04 g, 0.30 mole), keto triester **4** (82.23 g, 0.30 mole), and formaldehyde (22.5 ml of 40% solution, 0.30 mole) were mixed in *t*-butyl alcohol (1.4 l.) and stirred under solution was complete, then allowed to stand at room temperature for 14 hr. The mixture was then heated on the steam bath for 1 hr and concentrated under reduced pressure. The residual heavy orange syrup was taken up in chloroform and chromatographed on silicic acid (2.5 kg). Chloroform (30 l.), 0.5% methanol in chloroform (25 l.), and 0.75% methanol in chloroform (18 l.) eluted unchanged keto triester **4** (39 g, 0.14 mole, 47% recovery). The lactam **16** [70 g, 0.17 mole, 56% yield (maximum value as chloroform was retained tenaciously)] was eluted immediately afterward by 0.75% methanol in chloroform (43.1 l.), 1% methanol in chloroform (28 l.), and 2% methanol in chloroform (15 l.). In carrying out the chromatographic separation it was found that it was desirable to increase the solvent polarity slowly, otherwise the sharpness of the separation suffered considerably. Usually the lactam **16** was used directly in the crude form, but crystallization could be induced by sharply cooling a concentrated methanol solution in Dry Ice and allowing the solution to stand in the freezing compartment of the refrigerator (−20 to −30°) overnight. Filtration was carried out in a cold jacketed sintered glass funnel, and the material was dried *in vacuo* over phosphorus pentoxide to constant weight. In this way there was obtained from various fractions a total of 51.53 g of crystalline material, with melting points ranging from 46 to 54 and 62 to 70°. One recrystallization of the combined crystalline material gave 46.1 g (0.11 mole, 37.1%), mp 53–60°.

The nuclear magnetic resonance spectrum of the lactam **16** showed signals as follows: τ 2.3–3.0 (four-proton multiplet), aromatic protons; τ 3.05 (one-proton broad singlet), indole α-hydrogen; τ 6.32 (three-proton singlet), tertiary ester methyl group; τ 6.35 (three-proton singlet), primary ester methyl group; approximately τ 6.35 (two-proton diffuse multiplet?), isolated methylene group?; τ 6.83–7.83 (nine protons), methylene envelope; τ 7.89 (three-proton singlet), ketone methyl group. The infrared spectrum of **16** exhibited bands at 2.85, 3.33, 3.38, 5.75, 5.80, and 6.09 μ. The ultraviolet spectrum revealed λ_{max} 221 mμ (ϵ 33,700), 276 (5100), 284 (5600), and 292 (4900).

Attempted Model Mannich Reaction. 1,2,3,4-Tetrahydro-β-carboline (17). A solution of 1.000 g (5.09 mmoles) of tryptamine hydrochloride, 807 mg (5.11 mmoles) of ethyl α-ethylacetoacetate, and 153 mg (5.09 mequiv) of paraformaldehyde in 30 ml of 95% ethanol was refluxed for 23 hr. The solution, after being concentrated and cooled, deposited 916 mg (86%) of crystalline material, mp 284–288° dec (hs) (hs indicates Koffler micro hot stage apparatus). The free base (**17**), mp 207–210° dec (hs) (lit. mp 207–208°), was generated by treating the hydrochloride with aqueous potassium hydroxide and was crystallized from ethanol. An authentic sample of **17**, mp 208–211° dec (hs), was prepared by repetition of the above procedure without the ethyl α-ethylacetoacetate. A mixture of the two samples gave a mp of 207–211° dec (hs).

3-Acetyl-3-carbomethoxy-2-carbomethoxymethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-*a*]quinolizinium dichlorophosphate (19) was prepared by means of the Bishler–Napieralski reaction.

The lactam **16** (42.4 g, 0.10 mole) was dissolved in benzene (1800 ml) in a 2-l. flask equipped with a mechanical stirrer, reflux condenser, and pressure-compensated addition funnel. Provision was made for maintaining an atmosphere of dry nitrogen throughout the reaction and subsequent operations. Approximately 300 ml of benzene was distilled out of the apparatus to remove traces of water. Freshly distilled phosphorus oxychloride (93 ml, approximately 1 mole) was placed in the dropping funnel, and the whole apparatus was alternately evacuated and filled with nitrogen several times to remove traces of oxygen. The phosphorus oxychloride was then added to the solution, and the mixture was heated at reflux and stirred for 2–6 hr. During this time the product (**19**) separated from the reaction mixture as a yellow precipitate or as a red oil which crystallized on cooling. The apparatus was allowed to cool to room temperature (with continual stirring), and the dropping funnel replaced with a side arm attached to the top of a large sintered glass funnel through a short length of wide bore flexible plastic tubing and a large rubber stopper (both previously extracted with benzene). The precipitate was then separated from the solution (while maintaining an atmosphere of dry nitrogen) by decanting the reaction mixture through the tubing into the funnel. Both vacuum and nitrogen pressure were used to speed filtration.

The precipitate was washed twice by suspension in ethyl acetate and filtration through sintered glass, then dried *in vacuo* over phosphorus pentoxide and potassium hydroxide. The Bishler–Napieralski product **19** (47.4 g, 0.894 mole, 87%) had mp 143–146° dec at this stage of purification. For analysis, several recrystallizations from chloroform–ethyl acetate raised the melting point to 154–157° dec.

Anal. Calcd for $C_{22}H_{25}N_2O_7PCl_2$: C, 49.73; H, 4.75; N, 5.28; P, 5.83; Cl, 13.34 Found: C, 50.07; H, 4 65; N, 5.40; P, 5.70; Cl, 13.16.

3-Acetyl-3-carbomethoxy-2-carbomethoxymethyl-1,2,3,4,6,7,12-12b-octahydroindolo[2,3-*a*]quinolizine (20) was prepared by catalytic hydrogenation of the Bishler–Napieralski product **19**. The reaction (on 47.4 g, 0.089 mole of **46**) was carried out at room temperature and atmospheric pressure in methanol solution (approximately 500 ml) over prereduced platinum oxide catalyst (2.1 g). It was found to be unnecessary to dissolve completely the starting material; use of a thick slurry was satisfactory since solution occurred as the reduction proceeded. The total uptake of hydrogen was 113% of the theoretical amount in 20 hr. The product was separated from catalyst by filtration through Celite and the solution concentrated under reduced pressure. The residue was shaken between chloroform and 5% sodium carbonate solution and the organic phase worked up as usual. The residue crystallized readily from methanol to give a total of 31.3 g (0.087 mole, 88%) of crystalline keto diester **20**, mp 180–190°. From the mixture of isomers one pure isomer (mp 196.8–199.0°) was isolated by repeated crystallization from methanol.

Anal. Calcd for $C_{22}H_{26}O_5N_2$: C, 66.32; H, 6.58; O, 20.08; N, 7.03. Found: C, 66.25; m, 6.54; O, 19.89; N, 6.97

The nuclear magnetic resonance spectrum of the pure isomer of the keto diester **20** exhibited the following signals: τ 2.02 (one-proton, broad singlet), indole NH; τ 2.4–3.1 (four-proton multiplet), aromatic hydrogens; τ 6.31 (three-proton singlet), tertiary ester methyl group; τ 6.35 (three-proton singlet), primary ester methyl group; τ 6.58 (two protons?), isolated methylene group?; τ 6.7–7.7 methylene envolope; τ 7.80 (three-proton singlet), ketone methyl group. The nuclear magnetic resonance spectrum of the mixture of isomers of the keto diester **20** (mp 180–190°) showed additional signals as follows: τ 1.92, indole NH; τ 6.28, tertiary ester methyl group; τ 6.31, primary ester methyl group; τ 6.64, isolated methylene group (?).

Acid Hydrolysis of the β-Keto Diester 20. A. A solution of *ca.* 5.8 g (0.013 mole) of **20** (carried on from hydrogenation without purification) in 200 ml of 18% hydrochloric acid was refluxed with stirring in an atmosphere of nitrogen for 20 hr. The crystalline precipitate (**21**) which formed in the reaction mixture was isolated by filtration and dried *in vacuo*, wt 2.39 g (51%). The infrared spectrum (KBr disk) exhibits bands at 2.98, 3.42, 3.71, 3.74, and 5.84 μ.

An analytical sample of **21**, mp 268.8–269.4° dec (cor), was prepared by crystallization from methanol–ethyl acetate.

Anal. Calcd for $C_{15}H_{21}N_2O_4Cl$: C, 59.26; H, 5.80; C-methyl, 0.00; neut equiv, 182. Found: C, 59.53; 59.64; H, 5.76, 5.91; C-methyl, 0.40; neut equiv, 145.

The mother liquor after removal of **21** was evaporated to dryness at reduced pressure in an atmosphere of nitrogen. The residue was dissolved in methanol, and 10 g of silicic acid was added to the solution. The resulting slurry was evaporated to dryness in a stream of nitrogen and placed on the top of a 100-g column of silicic acid. Elution with 5% methanol in chloroform gave 1.32 g of material from which 570 mg (12.3%) of crystalline keto acid hydrochloride (**22**), mp 224–237° dec (hs), was obtained by recrystallization from methanol–acetonitrile. The infrared spectrum (KBr disk) of **22** exhibits bands at 3.21, 3.29, 4.00, 5.80, and 5.85 μ. An analytical sample, mp 236.5–238° dec (sealed, evacuated capillary), was prepared by several recrystallizations from methanol–acetonitrile.

Anal. Calcd for $C_{19}H_{23}N_2O_3Cl$: C, 62.89; H, 6.39; N, 7.72; C-Methyl, 4.14; N.E., 363. Found: C, 63.18; H, 6.50; N, 7.60; C-Methyl, 3.75; N.E. 178.

B. To a mixture of concentrated hydrochloric acid (27 ml) and water (359 ml) saturated with nitrogen in a 500-ml flask was added the crystalline keto diester **20** (36.3 g, 0.091 mole). The flask was equipped with a heating mantle, a magnetic stirrer, and a reflux condenser which was also attached to a 2-l. gas measuring buret. The system was flushed thoroughly with nitrogen to remove traces of oxygen and the flask and condenser were wrapped with aluminum foil to exclude light. The reaction mixture was heated at reflux until evolution of gas ceased, approximately 10 days. The total volume of gas collected amounted to 53.4% of the theoretical amount. The reaction mixture was taken to dryness on a rotary evaporator; and the residue was esterified by boiling with benzene and methanol, while repeatedly allowing the boiling point to rise to 80°, then adding more methanol and benzene as required. The crude material was then mixed with silicic acid (100 g), dried *in vacuo*, placed on top of a column of approximately 3 lb of silicic acid, and chromatographed. The keto ester **23** hydrochloride was eluted with 3% methanol in chloroform, and the crude material was crystallized from methanol. The yield of crystalline keto ester **49** hydrochloride, mp 245–250° dec, was 21.8 g (0.058 mole, 63.5%).

The presence of two sets of signals due to ester and ketone methyl groups in the nuclear magnetic resonance spectrum first revealed that the material was a mixture of isomers. These proved impossible to separate efficiently; and generally the mixture of isomers was used in subsequent reactions, since derivatives were found to be more easily separated. Very careful recrystallization of the hydrochlorides resulted in concentration of the minor isomer in the less soluble fraction, but samples of pure isomers were never isolated. The nuclear magnetic resonance spectrum of the major isomer tentatively assigned the more stable 2,3-*trans* structure) follows: τ 1.81 (single-proton, broad singlet), indole NH; τ 2.5–3.1 (four-proton multiplet), aromatic protons; τ 6.36 (three-proton singlet), ester methyl group; τ 6.65–7.90 (approximately 13 protons), methylene envelope; τ 7.83 (three-proton singlet), ketone methyl group. The spectrum of the minor isomer (assigned the 2,3-*cis* structure) differed from that of the major isomer in the positions of the ester and ketone methyl group signals (τ 6.31 and 7.87, respectively) and in the shape of the methylene envelope.

A sample containing mostly the *cis* isomer **49a** possessed, as the hydrochloride salt, mp 254–256° dec.

Anal. Calcd for $C_{20}H_{23}O_3N_2Cl$: C, 63.73; H, 6.68; O, 12.73; N, 7.43; Cl, 9.41. Found: C, 64.13; H, 6.74; O, 12.74; N, 7.23; Cl, 9.06.

Sodium Borohydride Reduction of the Keto Acid (22). A solution prepared by heating 136 mg (0.375 mmole) of **22** and 8 ml of 5% sodium hydroxide solution on a steam bath was cooled in an ice bath, and a solution of 50 mg (1.32 mmoles) of sodium borohydride in 5 ml of water was added dropwise with stirring over a period of 15 min. The ice bath was removed and the solution was stirred at room temperature for 3.5 hr. The solution was cooled in an ice bath and neutralized by dropwise addition of concentrated hydrochloric acid. The resulting precipitate (**24**), 99 mg (80.5%), mp 248–251° dec (hs), was separated by filtration and dried *in vacuo*. The infrared spectrum (KBr disk) of **24** exhibited bands at 2.90, 3.13, 3.21, 4.04, and 6.35 μ.

Cyclization of the δ-Hydroxy Acid to the δ-Lactone (25). A 1.681-g sample (5.12 mmoles) of **25** mp 240–245° dec (hs), was dissolved in 100 ml of hot pyridine. The solution was filtered and cooled to room temperature. To the solution was added 1.089 g (5.28 mmoles) of N,N′-dicyclohexylcarbodiimide, and the mixture was allowed to stand at room temperature in an atmosphere of nitrogen for 91 hr. The crystalline precipitate of N,N′-dicyclohexylurea, 614 mg, mp 236–238°, was collected by filtration. The solvent was removed by distillation at reduced pressure in an atmosphere of nitrogen. The residue was dissolved in methanol and made acidic to Congo red with concentrated hydrochloric acid. The solution was evaporated with 3.0 g of silicic acid and placed on the top of a 60-g column of silicic acid. Elution with 2% methanol in chloroform gave 535 mg of N,N′-dicyclohexylurea (total yield 99%). Elution with 3–5% methanol in chloroform gave 1.236 g of amorphous material, from which was isolated by crystallization from methanol–acetonitrile 758 mg (42.6% **25**, mp 235–240° dec. The infrared spectrum of **25** (as the free base in $CHCl_3$) exhibited bands at 2.90, 3.45, 3.52, 3.57, and 5.78 μ. An analytical sample, mp 240–241° dec, was prepared by several recrystallizations from methanol–acetonitrile. The sample was dried at 65° and 0.01 mm for 60 hr.

Anal. Calcd for $C_{19}H_{23}N_2O_2Cl$: C, 65.79; H, 6.88; N, 8.08. Calcd for $C_{19}H_{23}N_2O_2Cl \cdot CH_3OH$: C, 63.30; H, 7.17; N, 7.39. Found: C, 63.16, 63.21; H, 6.87, 6.87; N, 7.56, 7.62.

Treatment of the keto ester **23** hydrochloride (248 mg, 0.658 mmole) with sodium borohydride (294 mg, 7.75 mmoles) in methanol solution (20 ml) at −10 to 0° for 20 min gave the lactone **25** (204 mg, 0.655 mmole, 99%). The infrared spectrum showed no hydroxyl absorption and a single sharp band at 5.80 μ in the carbonyl region. The lactone **25** (123.5 mg) was recovered unchanged from treatment with acetic anhydride (1 ml) in pyridine (10 ml) overnight at room temperature. A sample of the lactone **25** was converted to the hydrochloride salt with methanolic hydrogen chloride and crystallized from methanol–acetonitrile. The first crop melted at 241° dec.

Catalytic reduction of the keto ester **23** hydrochloride (108 mg, 0.286 mmole) over platinum in methanol solution resulted in absorption of about 75% of the theoretical amount of hydrogen in 2 hr. The product (88 mg, 0.282 mmole, 97%) had the same infrared spectrum as the lactone **25** obtained from the sodium borohydride reduction, and gave a hydrochloride salt, mp 242° dec.

The α-Hydroxymethylene Lactone (26). A 100-ml, three-necked flask was equipped with a magnetic stirrer, a reflux condenser, a buret connnected to the flask by a three-way stopcock, and an inlet for dry nitrogen. Provision was made for keeping a nitrogen atmosphere in the top of the buret when the buret contained solution by connecting the top of the condenser to the top of the buret before the nitrogen outlet. The system was thoroughly flushed with nitrogen and flame dried. A 0.284 *N* ethereal solution of triphenylmethylsodium was prepared in a Pyrex bottle. Nitrogen pressure was used to force the triphenylmethylsodium up into the buret through a delivery tube connected to the third arm of the stopcock. The reaction flask was charged with 300 mg (0.865 mmole) of **25** and 30 ml of dioxane (freshly distilled from sodium after being passed through a column of alumina). The suspension was stirred while 15.2 ml (4.32 mmoles) of the triphenylmethylsodium solution was added rapidly from the buret. After stirring for 10 min, 2.0 ml of methyl formate (freshly distilled from phosphorus pentoxide) was added. The suspension immediately turned light yellow. Stirring was continued at room temperature for 21 hr. The reaction flask was cooled in an ice bath, and 15 ml of ice–water and 25 ml of ether were added. The ethereal phase was separated, and the aqueous solution was extracted with five 15-ml portions of ether. The aqueous solution was acidified with glacial acetic acid and then neutralized with saturated sodium bicarbonate solution. The neutral solution was saturated with sodium chloride and extracted five times with 25-ml portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, and concentrated by distillation at reduced pressure in an atmosphere of nitrogen. The residue (**26**) was dried at 0.01 mm overnight (yield 216 mg, 74%). The hydroxymethylene lactone gave a dark purple color with ferric chloride. The infrared spectrum exhibited bands at 2.90, 3.00, and 6.05 μ.

***dl*-Ajmalicine (1).** A solution of 162 mg (0.479 mmole) of **26** in 25 ml of 10% methanolic hydrogen chloride was refluxed in an atmosphere of nitrogen for 27 hr. The solution was concentrated by distillation in an atmosphere of nitrogen, and the resulting crystalline precipitate (**1**·HCl) weighing 52 mg was isolated by filtration. The mother liquor was concentrated, and acetonitrile was added. Further concentration gave two crops of crystalline material, 33 mg, mp >300°. The mother liquor was evaporated to dryness and treated with saturated sodium bicarbonate solution and chloroform. The chloroform solution was separated, dried over anhydrous sodium sulfate, and concentrated in a stream of nitrogen. The residue was chromatographed on 5.0 g of silic acid. Elution with pure chloroform gave 30 mg of material, which on crystallization from methanol–water gave 16 mg of **1**. Elution with 0.5% methanol in chloroform gave 35 mg of material, presumably the acetal **30**. The infrared spectrum of **30** exhibited a band at 5.80 μ. The free base (**1**) was converted to the hydrochloride by treatment with concentrated hydrochloric acid in methanol followed by recrystallization from methanol–acetonitrile. The total yield of *dl*-ajmalicine hydrochloride (**1**·HCl), mp 285–286° dec, was 69 mg (37%). The free base, mp 222–225°, was generated by treatment of the hydrochloride with saturated sodium bicarbonate solution and chloroform, and was recrystallized from methanol–water.

The infrared spectrum of **1** is identical with that of natural *l*-ajmalicine (see Figure 3).

An analytical sample of **1**·HCl was prepared by several recrystallizations from methanol–acetonitrile, followed by drying for 60 hr at 65° and 0.01 mm.

Anal. Calcd for $C_{21}H_{24}N_2O_3 \cdot HCl$: C, 64.85; H, 6.48; N, 7.21. Found: C, 64.44; H, 6.77; N, 7.42.

Stereochemical Studies on Keto Ester 23. A sample of the keto ester **23** hydrochloride (mp 248–252° dec, 113.8 mg, 0.302 mmole) was shaken with chloroform and sodium carbonate solution. The chloroform layer was worked up as usual to yield the free base keto ester **23** (102.1 mg, 0.300 mmole, 99.5%). The nuclear magnetic resonance spectrum was obtained and the ester and ketone methyl group signals were integrated on an expanded scale so the relative proportions of the two isomers could be determined. From the integral spectrum of the ester methyl group signals (τ 6.31 and 6.36) the proportions were found to be 38.2% *cis* isomer and 61.8% *trans* isomer. From the integral spectrum of the ketone methyl group signals (τ 7.87 and 7.83) the proportions were 39% *cis* and 61% *trans*.

The Ethylene Thioketals of the Keto Esters 23. These were prepared under the conditions described by Fieser.[28] Ketones with epimerizable centers in the α position have been found to be unaffected by these conditions.[18]

A sample (607 mg, 1.61 mmoles) of the keto ester **23** hydrochloride containing 61% *trans* isomer and 39% *cis* isomer (determined from the nuclear magnetic resonance spectrum as described above) was suspended in glacial acetic acid (8 ml) by stirring magnetically. Excess ethanedithiol (4 ml) and boron trifluoride ether complex (1 ml) were added, and the reaction mixture was protected with a Drierite drying tube. The mixture was stirred at room temperature overnight (10.5 hr), during which time the original solid dissolved, and a fine, white precipitate formed. The mixture was diluted with a large volume of anhydrous ether and the solid separated by filtration through sintered glass. The precipitate was washed well with anhydrous ether to remove excess ethanedithiol and dried briefly *in vacuo*. The boron trifluoride complex of the thioketal **32** (773 mg, 1.60 mmoles, 99%) was then dissolved in the minimum volume of hot methanol and shaken between chloroform and 1% sodium carbonate solution. The organic layer was worked up as usual to yield the free base thioketals **32** (670 mg, 1.61 mmoles, 100%). The nuclear magnetic resonance spectrum of the mixture revealed that it contained approximately 62% *trans* isomer and 38% *cis* isomer, indicating that little or no isomerization had occurred under the conditions of the reaction, as had been expected.

Chromatography of the mixture of thioketals on silicic acid (40 g) (0.75% ethanol in chloroform) resulted in partial separation of the two isomers. The *trans* isomer, eluted first from the column, could not be induced to crystallize. The *cis* isomer was obtained from the trailing fractions by crystallization of the methanol complex and could be obtained pure by repeated crystallization from methanol (mp 198.5° after loss of solvent at 120° and sintering at 184 and 188°).

Anal. Calcd for $C_{22}H_{28}O_2N_2S_2 \cdot OH$: C, 61.57; H, 7.19; O, 10.70; N, 6.24; S, 14.29. Found: C, 61.77; H, 7.42; O, 10.72; N, 7.07; S, 13.85.

The amorphous *trans*-thioketal formed a rystalline hydrochloride salt, mp 259.5–260.0° dec, after several recrystallizations from methanol–methyl acetate.

Anal. Calcd for $C_{22}H_{29}O_2N_2S_2Cl$: C, 58.33; H, 6.45; N, 6.18; S, 14.16; Cl, 7.83. Found: C, 57.95; H, 6.25; N, 5.71; S, 14.38; Cl, 8.39, 8.27.

The nuclear magnetic resonance spectrum of the *trans*-thioketal showed signals as follows: τ 1.83 (one-proton, broad singlet), indole NH; τ 2.45–3.11 (four-proton multiplet), aromatic hydrogens; τ 6.30 (three-proton singlet), ester methyl group; τ 6.78 (four-proton multiplet), thioketal methylene protons; τ 6.4–8.1, methylene envelope; τ 8.32 (three-proton singlet), "ketone" methyl group.

The *cis*-thioketal also formed a crystalline hydrochloride salt, mp 295–298° dec, after several recrystallizations from methanol–methyl acetate.

Anal. Calcd for $C_{22}H_{29}O_2N_2S_2Cl$: C, 58.33; H, 6.45; N, 6.18; S, 14.16; Cl, 7.83. Found: C, 58.13; H, 6.35; N, 6.06; S, 14.05; Cl, 7.90, 8.04.

The nuclear magnetic resonance spectrum of the crystalline *cis*-thioketal methanolate showed signals as follows: τ 1.74 (one-proton, broad singlet), indole NH; τ 2.5–3.11 (four-proton multiplet), aromatic hydrogens; τ 6.27 (three-proton singlet), ester methyl group; τ 6.63 (three-proton singlet), methanol methyl group; τ 6.75 (four-proton multiplet), thioketal methylene protons; τ, 6.4–8.1, methylene envelope; τ 8.21 (three-proton singlet), "ketone" methyl group.

(28) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

Desulfurization of the Thioketals. The *trans*-thioketal (435 mg, 1.042 mmoles) was suspended in methanol (about 20 ml), and 5-day old Raney nickel W-2 catalyst (about 8 ml of a suspension in methanol) was added. The mixture was mechanically stirred and heated at reflux under a nitrogen atmosphere for 12 hr. The mixture was then cooled; the catalyst was separated by filtration and washed thoroughly with methanol; and the solution was concentrated to a small volume *in vacuo*. The concentrate was shaken between chloroform and 5% sodium carbonate solution and the chloroform solution was worked up as usual. The crude product, *trans*-3-ethyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**31**) (278.6 mg, 0.855 mmole, 82%) had the same mobility on thin layer chromatography and the same infrared spectrum as the authentic sample.[14] The *trans* ester **31** was converted to the hydrochloride salt (270 mg, 0.744 mmole, 71%) with methanolic hydrogen chloride and recrystallized from methanol–methyl acetate, mp 275.0–276.2° dec (lit.[14] mp for authentic **31** hydrochloride salt), 275.0–276.8° dec.

Anal. Calcd for $C_{20}H_{27}O_2N_2Cl$: C, 66.19; H, 7.50; N, 7.72; Cl, 9.77. Found: C, 66.15; H, 7.05; N, 7.71; Cl, 9.91.

The infrared spectra (Nujol mulls) of the two samples of hydrochloride salts of **31** from the different sources were completely identical.

The nuclear magnetic resonance spectrum of **31** was as follows: τ 1.86 (one-proton, broad singlet), indole NH; τ 2.5–3.1 (four-proton multiplet), aromatic protons; τ 6.31 (three-proton singlet), ester methyl group; τ 6.7–8.9, complex methylene multiplets; τ 8.95–9.25 (three-proton lopsided diffuse doublet), methyl protons of the ethyl group.

The *cis*-thioketal (230 mg, 0.551 mmole) was desulfurized in exactly the same way as described above for the *trans* isomer. The *cis*-3-ethyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**33**) hydrochloride salt (136 mg, 0.375 mmole, 68%) had mp 277.0–278.6° dec after several recrystallizations from methanol–methyl acetate. The new compound **33** had a mobility on thin layer chromatography slightly slower than that of the *trans*-ethyl compound **31**. The infrared spectrum of the *cis*-ethyl compound **33** hydrochloride salt (in Nujol mull) was different from that of the *trans*-ethyl compound **31**.

Anal. Calcd for $C_{20}H_{27}O_2N_2Cl$: C, 6.619; H, 7.50; N, 7.72; Cl, 9.77. Found: C, 66.28; H, 7.22; N, 7.74; Cl, 9.76.

Synthesis of Emetine. Melting points, unless otherwise stated, were measured on an electrically heated Kofler block equipped with a microscope and standardized thermometer. Unless otherwise stated, infrared spectra were measured on chloroform solutions with an Infracord, and ultraviolet spectral determinations were carried out on methanol solutions with a Cary instrument. Elemental analyses were executed by Spang and by Huffman analytical laboratories. Silicic acid used for chromatography (100 mesh Mallinckrodt) was washed 15 times with acetone; after decantation of solvent, the solid was dried in an oven at about 75°.

Mannich Reaction of Keto Triester 4, Formaldehyde, and 3,4-Dimethoxyphenethylamine. Formaldehyde solution (2.40 ml) was added to the solution of 5.72 g (31.7 mmoles) of homoveratrylamine in 80 ml of *t*-butyl alcohol. After 18 hr standing at 8°, 8.6 g (31.4 mmoles) of the ketotrimethyl ester **4** was added. The mixture (which, during 8 hr at room temperature, had turned slightly yellow) was then refluxed for 1 hr, allowed to stand for 2 more days, then evaporated under vacuum. A chloroform solution of the residue was extracted with two 25-ml portions of 3.5% aqueous hydrochloric acid, then with water, dried over sodium carbonate, and evaporated to give 13.208 g of oily, crude lactam **6**. The combined acid extracts were made basic with sodium carbonate and then extracted with chloroform. Evaporation yielded 1.279 g of a slightly yellow viscous oil. On addition of hydrogen chloride gas, there precipitated from solution of the oil in THF 0.893 g (yield 12%) of a crystalline, nonhygroscopic hydrochloride which, after recrystallization from ethanol, formed leaflets of mp 261.5–262.5°. By means of comparison with authentic material, the salt was identified as 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride.

Bischler–Napieralski Cyclization of Lactam 36. To a stirred, boiling solution of 11.576 g (26.6 mmoles) of crude lactam **36** in 300 ml of benzene, which was kept under N_2 in a three-necked flask fitted with mechanical stirrer, reflux condenser, and N_2-inlet tube, 32 ml (305 mmoles) of phosphorus oxychloride was added. Reflux was maintained for 3.5 hr, during which time a dark oil precipitated. Then, with continued stirring, the mixture was allowed to cool down slowly. The oil solidified, and more crystals separated directly from the solution. The slightly yellow crystals (**37**) were filtered,

washed three times with benzene, and dried under vacuum (yield (8.849 g, *ca.* 80% from **36**, of material which could be used for the subsequent step without further purification).

The yield was lower and the product less pure when the reaction was not carried out under N_2 or when the mixture was cooled down too rapidly. In such cases, the crystalline product contained red, gummy particles which should be removed to ensure success of the hydrogenation step. The iminium salt **37** decomposed slightly in boiling benzene, much faster in boiling toluene, but not at room temperature in the solid state. The salt could be recrystallized from acetone–ethyl acetate as fine crystals, mp 148.5–150°.

Anal. Calcd for $C_{22}H_{28}ClNO_7$: C, 58.21; H, 6.22; Cl, 7.81. Found: C, 56.40; 56.71; H, 6.36, 6.47; Cl, 8.09.

Hydrogenation of Bischler–Napieralski Product (37). Crystalline **37** (6.433 g) as obtained directly from the Bischler–Napieralski reaction mixture (see above) was dissolved without further purification in 100 ml of methanol. This solution was added to a suspension of Pt catalyst in 50 ml of methanol obtained by hydrogenation of 2 g of PtO_2. During 100 min 287 ml (82%) of hydrogen was absorbed, mostly during the first 60 min. During 3 more hr, only 5 ml of H_2 were absorbed. The solution was filtered and evaporated, 7.12 g of noncrystalline product being obtained. The hydrogenation failed when iminium salt of lower purity was used. The reduced hydrochloride could be crystallized from a concentrated solution in THF/acetone, but the crystals could not be completely purified. The free base (**38**), however, prepared from an aqueous solution of the hydrochloride with ammonia, and extracted into ether, crystallized rather easily. After two recrystallizations from ether the base exhibited mp 119–120°.

Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.96; H, 6.98; N, 3.29.

Hydrolysis and Decarboxylation of Keto Diester 38. The total amount of crude **38** obtained as described above (7.12 g) was refluxed in 86 ml of water and 5.0 ml of concentrated hydrochloric acid for 90 hr. The solution was then evaporated and the oily residue chromatographed on 100 g of silicic acid using chloroform–methanol. With 98:2 ratio of solvent a zone was eluted which, after evaporation, consisted of a gum. On treatment with a little acetone, the material crystallized to give 2.723 g of hydrochloride of keto acid **39**. The over-all yield of the salt from **37** is thus 50% of the theoretical. The crystals obtained from the original gum with acetone were rather pure (mp 196–198°), but no completely satisfactory solvent for recrystallization was found. Material recrystallized from chloroform–carbon tetrachloride had an unsharp melting point from about 130° upward. Drying the recrystallized sample at room temperature *in vacuo* brought the melting point up remarkably and indicated that the reason for the melting point behavior was solvent which had not been removed completely, equivalent weight 393.

Anal. Calcd for $C_{19}H_{26}ClNO_5$: C, 59.45; H, 6.83; Cl, 9.24. Found: C, 59.28; H, 6.86; Cl, 9.15.

Conversion of Keto Acid 39 to Ester 42. Hydrogen chloride gas was passed into an ice cold solution of 584 mg (1.43 mmoles) of **39** in 20 ml of methanol. After 22.5 hr standing at room temperature the solution was evaporated under N_2. The crude methyl ester hydrochloride weighed 631 mg. This product was dissolved in a mixture of 2.5 ml of ethanedithiol and 2.5 ml of BF_3 etherate, and the clear solution stirred for 7 hr at room temperature. Ether and 2 *N* aqueous HCl were added; the aqueous layer was separated and extracted with ether once more; both ether extracts were discarded; the aqueous layer was made basic with sodium carbonate, and the mixture was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ solution yielded 714 mg of gummy material. The total product was heated in refluxing methanol (65 ml) with 3.8 g (ethanol, wet) of Raney Ni for 24 hr. After filtration, HCl gas was passed into the green solution, which was then evaporated. The residue was chromatographed on 10 g of silic acid, the desired product (304 mg) being eluted with $CHCl_3$–1% CH_3OH. (A second compound was eluted with $CHCl_3$–2% CH_3OH, which showed a multiple carbonyl band in the 5.8–5.9-μ region and therefore probably still contained a keto group. It was not further investigated.) When treated with acetone, the crude ester **42** hydrochloride crystallized (304 mg, 56%). The tetracyclic ester **42** hydrochloride, recrystallized from a mixture of methanol, methyl acetate, benzene, and high boiling petroleum ether, melted at 199.2–199.4°, mmp (undepressed) with an authentic sample[21a] 199.0–199.3°.

Preparation of the Free Base 42. When an aqueous solution of crude keto ester **42** hydrochloride was basified with dilute ammonia, extracted with ether, and the ether evaporated, the free base **42** was obtained as an oil. When this oil was dissolved in an amount of petroleum ether (bp 60–68°) sufficient to prevent immediate precipitation after cooling down to room temperature, and this solution then allowed to crystallize slowly at room temperature, crystals of mp 100–107° were obtained. When, however, the petroleum ether solution was concentrated so much that it was still clear at boiling temperature but became cloudy as soon as cooled down, crystals of mp 83–92° were obtained. This result is in agreement with the reported melting point behavior of the tricyclic ester **13** free base.[21b]

Preparation of Amide 43. A mixture of 121 mg (0.35 mmole) of crystalline keto ester **42** and 241 mg (1.33 mmoles) of homoveratrylamine was heated under N_2 to 185° for 280 min. After being cooled, the mixture was dissolved in 5 ml of chloroform, to which 1 ml of acetic anhydride was added. After 10 hr the solution was evaporated to give 357 mg of an oily residue which was chromatographed on 9 g of silicic acid. Pure $CHCl_3$ eluted 201 mg of N-acetylhomoveratrylamine, while $CHCl_3$ containing 1% CH_3OH provided 91 mg of crude amide **43**. More **43** was eluted as hydrochloride (136 mg) with $CHCl_3$–5% CH_3OH into which dry HCl gas had been passed. The crude material was dissolved in dilute aqueous hydrochloric acid, and this solution extracted with ether, basified with dilute ammonia, and again extracted with ether. This ether extract, after evaporation, yielded 116 mg of crystalline **43**. After recrystallization from benzene, the amide melted (evacuated, sealed capillary) at 148.0–150.0°; mmp 148.0–150.0° was observed with an authentic sample, mp 151.4–153.2°.[21b]

Isolation of Dithioketal 41 and Its Hydrochloride. Dry hydrogen chloride gas was passed into a solution of 448 mg (1.17 mmoles) of keto acid **40** in 15 ml of methanol. After 23 hr at room temperature, the solution was evaporated, leaving 486 mg of crude methyl ester. This product was dissolved in 20 ml of glacial acetic acid; excess ethandithiol was added; and, with external cooling in an ice bath, dry hydrogen chloride gas was passed in for 0.75 hr. After evaporation, 775 mg of viscous oil remained which was chromatographed on silicic acid (8 g) with chloroform–methanol. Material eluted with chloroform containing 1% methanol crystallized instantly when treated with a small amount of acetone. Two successive recrystallizations yielded 321 mg (58%) of the ethylene dithioketal **41** hydrochloride, mp 207.5–208.5°.

Anal. Calcd for $C_{22}H_{32}ClNO_4S_2$: C, 55.73; H, 6.80; Cl, 7.48. Found: C, 55.74; H, 6.42; Cl, 6.79.

From 367 mg of crude **41** hydrochloride, by treatment with an aqueous solution of dilute ammonia, 238 mg of crystalline free base was obtained (mp of the crude product 111–123°). Recrystallization from petroleum ether (boiling range 60–68°) afforded colorless needles of mp 126–127.5°.

Anal. Calcd for $C_{22}H_{31}NO_4S_2$: C, 60.38; H, 7.14. Found: C, 60.23; H, 6.92.

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