dl-Desmethyldihydrocorynantheine (XVIII, R = CH_3). To an ice-cold, stirred solution of 503.4 mg (1.54 mmoles) of XVII (R = CH_3) in 5 ml of dry ether, under pure nitrogen, was added 25 ml of a 0.165 *N* ethereal solution of triphenylmethylsodium. As the rapid addition proceeded the solution became cloudy and finally red as the last of the reagent was added. After 0.5 min 2 ml of methyl formate (freshly distilled from phosphorus pentoxide) was added to the reaction mixture and the resulting solution was allowed to stand in the ice bath for 3 hr. A small amount of glacial acetic acid was then added to the cloudy solution, and the resulting acetic acid salt was extracted with water. Acidification of the ether solution with concentrated hydrochloric acid yielded a crystalline hydrochloride of trityl ketone (XIX·HCl) which was collected by filtration and dried to yield 276.7 mg, mp 295.8–299.8°. An analytical sample, mp 304.5–305.2°, was prepared by crystallizing XIX (HCl) from ethanol–chloroform and drying the pure, finely ground crystals at 100° (0.01 mm) for 24 hr.

Anal. Calcd for $C_{38}H_{39}ON_2Cl$: C, 79.35; H, 6.83. Calcd for $C_{38}H_{39}ON_2Cl \cdot 0.5H_2O$: C, 78.12; H, 6.90. Calcd for $C_{38}H_{39}ON_2Cl \cdot 1H_2O$: C, 76.94; H, 6.97. Found: C, 77.79, 77.85; H, 7.04, 7.01.

The infrared spectrum of XIX has maxima at 2.86, 3.55, 3.61, 5.86, 6.24, and 6.66 μ. In the ultraviolet XIX absorbs at λ_{max} 290 mμ (ϵ 5780), 283 (6870), and 224 (43,900).

The aqueous solution, which contained the acetic acid salts of the formyl derivative and of the unreacted starting material, was made ammoniacal and extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 410.3 mg of the crude free base which was purified by silicic acid chromatography. Unreacted starting material was eluted from the column with chloroform and was isolated as its hydrochloride to yield 184.2 mg (33.0%), mp 272.6–274.2°. The formyl derivative (XVIII, R = CH_3), which had infrared bands at 5.80 and 6.05 μ, was eluted with 0.5% ethanol–chloroform and was crystallized from ethyl acetate to yield 100.6 mg (18.5%), mp 185.2–187.0°. An analytical sample of XVIII [R = CH_3], mp 185.0–186.2° dec (sealed tube), was prepared by rapidly chromatographing a sample of the crystalline formyl derivative on silicic acid and crystallizing the resulting material from ethyl acetate–petroleum ether. It had infrared bands 2.87, 3.55, 3.61, and 6.05 μ.

Anal. Calcd for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.40. Found: C, 70.68; H, 7.47.

The hydrochloride of XVIII (R = CH_3) crystallized from ethanol–ethyl acetate, mp 236.2–238.0° dec (sealed tube).

dl-Dihydrocorynantheine. An ice-cold solution of XVIII (R = CH_3) (88.3 mg, 0.248 mmole) in 15–20 ml of ethyl acetate was treated with 4 ml of a cold 0.49 *M* ethereal solution of diazomethane. Within a short time the reaction mixture became cloudy and a white solid began to form. After this mixture had been kept at 0° for 6 hr the solvent was removed under a stream of nitrogen; the residue was dissolved in chloroform and chromatographed on silicic acid. With 0.25% ethanol–chloroform 24.8 mg (27.2%) of the O-methylated product was obtained. *dl*-Dihydrocorynantheine was characterized as its hydrochloride, mp 242.2–243.3° dec (sealed tube), which crystallized from 95% ethanol–ethyl acetate.

Anal. Calcd for $C_{22}H_{28}O_3N_2 \cdot HCl$: C, 65.25; H, 7.22. Found: C, 64.90; H, 7.17.

The infrared spectrum of a solution of pure *dl*-dihydrocorynantheine in chloroform was identical in every respect with that of a solution of the natural product[29] in the same solvent.

Further elution of the silicic acid column with 0.5% ethanol–chloroform yielded 11.6 mg of the starting material. With methanol 30.0 mg of a compound was eluted which was crystallized from ethanol–ethyl acetate, mp 228.3–238.0° dec (sealed tube). Crystallization of the hydrochloride of this compound, mp 254.8–257.2° dec (sealed tube), from ethanol–ethyl acetate resulted in considerable decomposition.

Anal. Calcd for $C_{22}H_{29}O_3N_2Cl$: C, 65.25; H, 7.22. Found: C, 64.64; H, 7.06.

Although a satisfactory analysis was not obtained, this compound was considered to be i.

Acknowledgments. This work was supported by a grant from the Research Committee of the University of Wisconsin, with funds supplied by the Wisconsin Alumni Research Foundation.

(29) A mixture of *d*-corynantheine and *d*-dihydrocorynantheine was obtained by the method of Janot and Goutarel[30] from a crude alkaloidal extract. An ethanolic solution of this mixture was hydrogenated at atmospheric pressure over a 10% palladium-on-carbon catalyst, and the resulting alkaloid was crystallized several times from methanol–water and dried in a vacuum desiccator over anhydrous calcium chloride to yield pure *d*-dihydrocorynantheine, mp 103–106° after softening at 88°, $[\alpha]^{24.5}D$ +31.2 ± 1.4° (*c* 1.04, methanol) [lit. softens at 70°, resolidifies at 95°, mp 103–104°; $[\alpha]^{18}D$ +30° (*c* 0.93, methanol)].

(30) M. M. Janot and R. Goutarel, *Bull. Soc. Chim. France*, **18**, 588 (1951).

Total Synthesis of *dl*-Corynantheine

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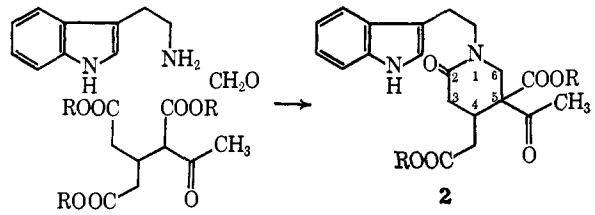
Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received January 30, 1969*

Abstract: By utilizing a key tetracyclic intermediate in the ajmalicine synthesis,[2] the first total synthesis of corynantheine (**3**) (racemic form) was achieved, along with a related base in the geissoschizine family. The corynantheine synthesis proceeds through the following sequence of intermediates: **5**, **25b**, **26**, and **31**.

In the biogenesis of indole alkaloids of the yohimbine family, appearance of many structural variants seems to depend on various oxidation, reduction, and cyclization options open to certain key biological intermediates. For example, it seems certain that such diverse structures as the corynantheine, ring-E heterocycle, ajmaline/sarpagine, and other types derive from a common—as yet unknown—elementary precursor. As one facet in our program of biogenetic-type synthesis, we have attempted to simulate this over-all behavior by carrying out a biogenetically patterned synthesis of a polycyclic indole derivative, which by suitably different chemical operations could be transformed to one or another alkaloidal type. As an example of this approach, we cite the simple, Mannich type condensation of tryptamine, formaldehyde, and keto triester **1** to the lactam **2**, which can be converted to ajmalicine,[2] or in-

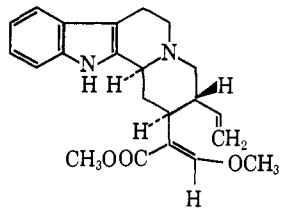
(1) To whom all correspondence should be addressed: Stanford University, Stanford, Calif. 94305.

(2) E. E. van Tamelen and C. Placeway, *J. Am. Chem. Soc.*, **83**, 2594 (1961); E. E. van Tamelen, C. Placeway, I. G. Wright, and G. P. Schiemenz, *ibid.*, **91**, 7359 (1961).



1 2

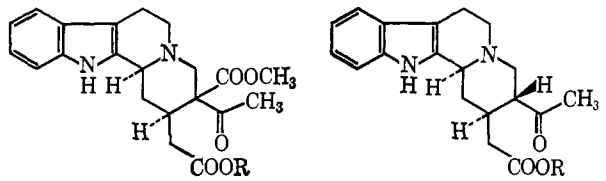
stead diverted to other natural product systems. One of these is corynantheine (**3**).[3]



3

A member, along with dihydrocorynantheine, corynantheidine, and others, of the important tetracyclic, ring-E *seco* family of indole alkaloids, corynantheine itself is the best known[4,5] and up until the time of our work had not been secured by total synthesis. In our eyes, the synthetic problem reduced to a search for means of transforming lactam **2**, or some other intermediate in the ajmalicine synthesis, to corynantheine. At the same time, the possibility of securing another indole alkaloidal type from such an intermediate was also open.

In the project planned, the most obvious task was modification of the acetyl side chain to the vinyl substituent characteristic of the target alkaloid. Three possible substances, **2**, **4**, and **5**, suitable for such structural change, were available,[2] and attempts along these lines were made on all three.



4 5

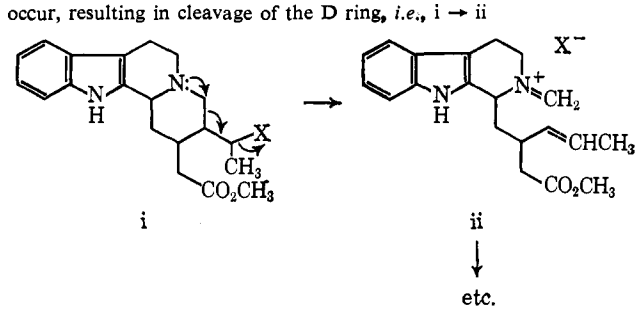
Since the lactam **2** was the most readily accessible intermediate in the ajmalicine synthesis, several attempts were made to modify the substitution at position 5 before going on to close the C ring. The use of compounds in which the nitrogen was incorporated into an amide linkage would allow utilization of carbonium ion type olefin-forming reactions without fear of detrimental participation of the nitrogen, resulting in cleavage of the D ring.[6]

(3) For a preliminary description of this synthesis, see E. E. van Tamelen and I. G. Wright, *Tetrahedron Letters*, 295 (1964).

(4) See reviews by (a) L. Marion in "The Alkaloids," R. H. F. Manske and H. L. Holmes, Ed., Vol. II, Academic Press, New York, N. Y., 1952, p 420; (b) J. E. Saxton in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p 37.

(5) For stereochemistry of corynantheine, see E. E. van Tamelen, P. E. Aldrich, and T. J. Katz, *Chem. Ind.* (London), 793 (1956).

(6) Specifically, there was considered to be a reasonable probability that a 1,3-elimination reaction involving the tertiary nitrogen would occur, resulting in cleavage of the D ring, *i.e.*, i → ii



i ii

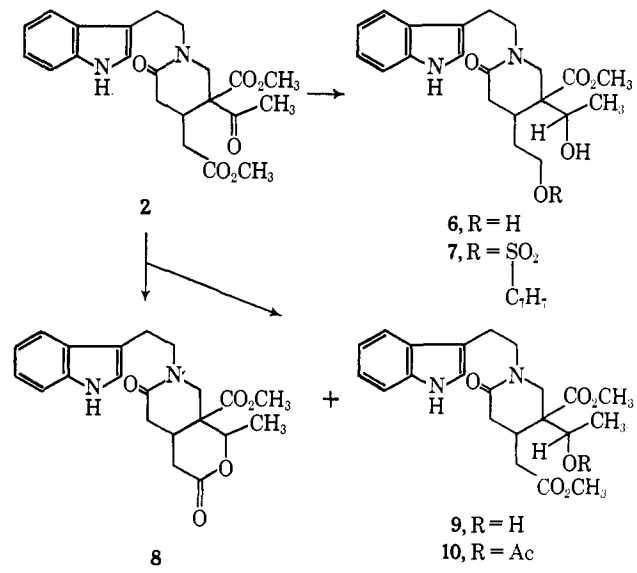
etc.

As mentioned elsewhere,[2] the tertiary carbomethoxy group at position 5 proved to be very resistant to hydrolysis by aqueous acid or base—conditions could not be found which left the lactam ring of **2** intact. Also the anhydrous conditions using lithium iodide for cleavage of methyl esters,[7] although apparently ideally suited to this situation, failed.

Reduction of the keto group of the lactam **2** was also investigated. With excess sodium borohydride in methanol, reduction of both the ketone and one of the ester groups occurred at temperatures above 0°. The infrared spectrum of the product (**6**) showed a large band at 2.9–3.0 μ due to hydroxyl, and the combined ester–ketone band at 5.75–5.80 μ was much reduced in intensity. In addition, the product **6** reacted with *p*-toluenesulfonyl chloride in pyridine to give a derivative **7** which still contained a hydroxyl group, according to the infrared spectrum.

Treatment of the lactam **2** with excess sodium borohydride in methanol solution at Dry Ice temperatures for a shorter time (24 min) resulted in more selective reduction. Although small amounts of the dihydroxy compound **6** were still found, the two main products were the lactone lactam **8** and the hydroxy lactam **9**, formed in approximately equal amounts and separated by chromatography on silicic acid.

The nuclear magnetic resonance spectrum of the first, homogeneous column fraction showed the following changes from that of the lactam **2**: the ketone methyl group signal at τ 7.89 was shifted to τ 8.92 and split into a doublet (J = 6.4 Hz); a new, one-proton quartet (J = 6.4 Hz) appeared at τ 5.96, and was assigned to the



2 6, R = H 7, R = $SO_2C_7H_7$

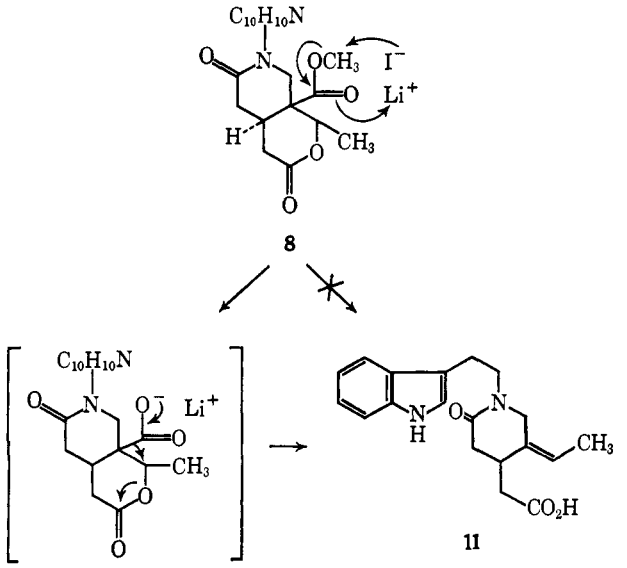
8 9, R = H 10, R = Ac

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

proton attached to the same carbon as the alcohol oxygen; a broad peak which appeared at about τ 5.4 was assinged to the proton of the hydroxyl group. Treatment of the hydroxy lactam **9** with acetic anhydride in pyridine gave the acetoxy derivative **10** as shown by the presence of a new methyl group signal at τ 7.99 in the nuclear magnetic resonance spectrum. In addition, the quartet due to the hydrogen on the same carbon as the oxygen had shifted from its former position at τ 5.96 downfield to τ 4.96. All the changes described were consistent with structure **9**.

The second major fraction from the column crystallized readily from methanol to give two crude fractions, mp 208–212 and 201–205° (further purification by this means was not attempted). The nuclear magnetic resonance spectrum, although quite weak due to the low solubility of the material in deuteriochloroform, showed a single ester methyl group signal at τ 6.30 (the tertiary ester methyl group in lactam **2** comes at τ 6.32) and a doublet methyl group signal at τ 8.80 (J = 6.5 Hz). The mixture was unaffected by treatment with acetic hydride in pyridine. The data, although not as complete as in the former case, support the structure **8**.

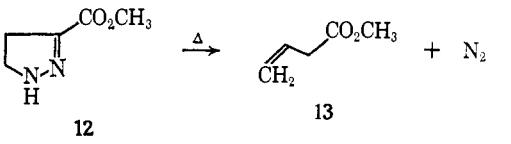
Reduction of the keto group of the lactam **2** by means of catalytic hydrogenation was complicated by simultaneous slow reduction of the indole nucleus. Otherwise the products appeared to be the same as those obtained by reduction with sodium borohydride.



The lactone lactam **8** and the acetoxy lactam **10** were both heated with lithium iodide in lutidine[7] in the hope that they might undergo ester cleavage and decarboxylative elimination to give products of structure **11** (the mechanism is indicated above for **8**). No gas was evolved, however, and the tarry products were not investigated.

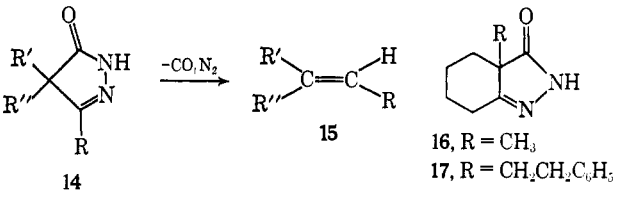
One final attempt to modify the lactam **2** was based on the known tendency of simple pyrazolines to decompose thermally (150–200°) with evolution of nitrogen to give olefinic products,[8] for example, **12** → **13**.

(8) For examples, see (a) C. G. Overberger and J.-P. Anselme, *J. Am. Chem. Soc.*, 86, 658 (1964); (b) T. V. Van Auken and K. L. Rinehart, Jr., *ibid.*, 84, 3736 (1962); (c) T. L. Jacobs in "Heterocyclic Compounds," Vol. 5, R. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 76.



12 13

It seemed possible that a thermal decomposition might also be induced in 5-pyrazolones (**14**) with formation of carbon monoxide, nitrogen, and an olefin (**15**).



14 15

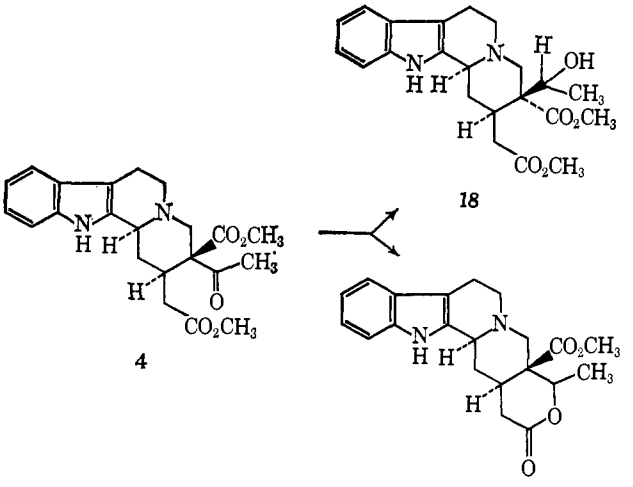
Since 5-pyrazolones are generally synthesized by reaction of β-keto esters with hydrazine,[8c] such a reaction could be ideal for carrying out the desired conversion of the lactam **2** to a member of the unsaturated series, for example, **11**. However, since no examples of such a reaction could be found in the literature, a brief preliminary study with some simple model compounds was undertaken in order to test the feasibility of the idea.

2-Methyl-2-carboethoxycyclohexanone and 2-β-phenethyl-2-carboethoxycyclohexanone both formed crystalline pyrazolones (**16**, mp 118–121°, and **17**, mp 115–120°, repectively) upon treatment with hydrazine hydrate in methanol solution. Distillation of **16** could be carried out under atmospheric pressure without extensive decomposition at approximately 295°. A sample heated to 360° in a sealed, evacuated capillary tube crystallized upon cooling, and the melting point of starting material was only depressed a few degrees (mp 112–114°). The pyrazolone **17** distilled at about 340°, with only a little more decomposition than in the previous case.

As in the case of the lactam **2**, several attempts were made to modify the β-keto ester system present in the tetracyclic keto diester **4**. Sodium borohydride reduction of keto diester **4** (mmp 194–197°) proceeded smoothly at −10° in aqueous tetrahydrofuran. One of the two products formed was isolated in pure crystalline form (flat plates, mp 223–225°) by recrystallization from methanol. On the basis of elemental analysis, and infrared and nuclear magnetic resonance spectra, this product was assigned the structure of the hydroxy diester **18**. This infrared spectrum (in Nujol mull) showed a new hydroxyl band at 2.84 μ in addition to the indole N–H band at 2.94 μ. The carbonyl region showed two peaks at 5.79 and 5.85 μ in contrast to that of the starting material which shows three bands at 5.75, 5.80, and 5.90 μ.

The other product from the sodium borohydride reduction of the keto diester **4** was not isolated in pure form, but from the infrared spectrum of a sample (mp 210–211°) and by analogy with the case of the lactam **2** (see above) it can be assigned the lactone ester structure **19**. The infrared spectrum of an impure sample showed only small absorption at 2.84 μ, which could be due to contamination by the hydroxy diester **18**; the carbonyl region showed only a single band at 5.83 μ in contrast to the two observed in the spectrum of the hydroxy diester **18** and the three in that of the keto diester

4. The stereochemistry of the two compounds **18** and **19** is probably the same as that of the corresponding



18

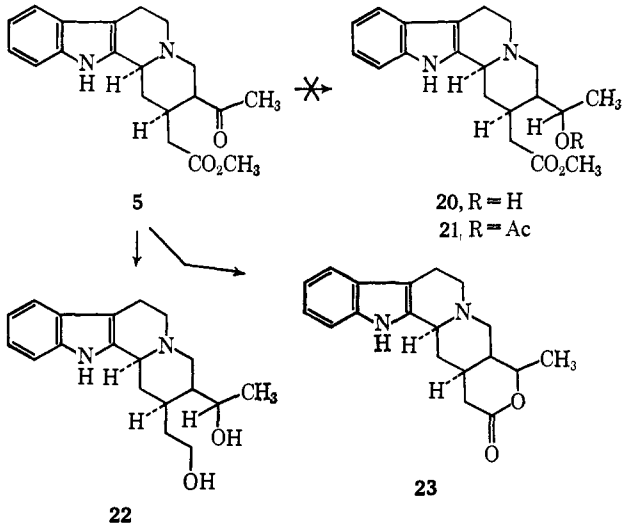
4

19

compounds in the lactam series, as indicated in the structural formulae.

The hydroxy diester **18** also proved to be very resistant to complete hydrolysis. Even vigorous acid hydrolysis (5 days in refluxing 18% hydrochloric acid) failed to affect the tertiary carbomethoxy group, and thus the hydroxy diester **18** is even more resistant to hydrolysis than the keto diester **4**. Treatment of the hydroxy diester **18** with lithium iodide in lutidine resulted in no evolution of carbon dioxide.

Having failed in our endeavors to modify usefully the acetyl side chain in keto polyester cases, we turned our attention to the keto monoester (**5**). One approach in this series was reduction of this keto to the corresponding hydroxy ester **20**, formation of the acetoxy compound **21**, and pyrolysis.[9] This route was expected to result in formation of a mixture of the desired olefins without the complications which could arise during ordinary elimination reactions involving carbonium ion intermediates.[6] Reduction of the keto ester **5** with excess sodium borohydride in methanol at ordinary temperatures resulted in complete reduction of both the ketone and the ester, with formation of the diol **22**. As



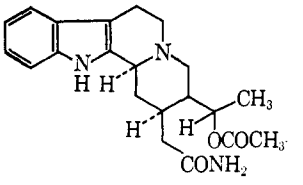
5

20, R = H
21, R = Ac

22

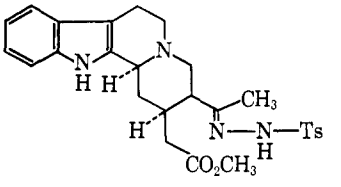
23

in the cases discussed previously, lowering the temperature and shortening the reaction time resulted in selective reduction of the ketone, but the lactone **23** was the only product isolated. The product **23** was recovered unchanged from treatment with acetic anhydride in pyridine. Catalytic hydrogenation of the keto ester **5** also gave the lactone **23**.[2] The stereoisomeric composition of the lactone was not investigated, but it probably consisted chiefly of the 15,20-*trans* compound. Sublimation of the acetoxy amide **24** at atmospheric pressure and 400° resulted in little or no loss of the acetoxy group as determined from the infrared spectrum of the crude product.



24

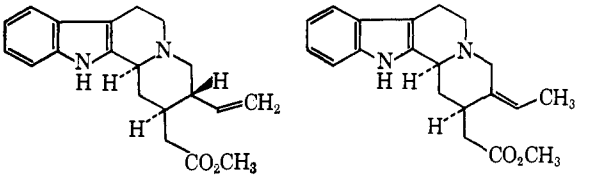
The thermal decomposition of sulfonylhydrazone salts is known to produce olefinic compounds *via* a carbenoid mechanism, especially when carried out in an aprotic medium.[10] Use of this reaction for carrying out the conversion of keto ester **5** to unsaturated compounds appeared to be worth investigating, since carbonium ion intermediates would be avoided. The mixture of *cis*- and *trans*-keto esters **5** was readily converted to a mixture of the corresponding toluenesulfonylhydrazones **25**



25

in excellent yield by treatment with toluenesulfonylhydrazine in a mixture of glacial acetic acid and methanol at room temperature. The mixture of tosylhydrazones could be separated partially by chromatography, and recrystallization from methanol yielded pure samples of the *cis* and *trans* compounds, **25a** and **25b**, mp 202 and 227–228°, respectively.

Decomposition of the *trans*-tosylhydrazone **25b** was carried out by heating it to reflux in diglyme (diethylene glycol dimethyl ether) with sodium methoxide for approximately 20 min, during which time the evolution of nitrogen was rapid and nearly quantitative. Analysis of the reaction mixture by thin layer chromatography revealed the presence of two major products (and a minor component which was not characterized), olefins **26** and **27**, which were partially separated by chromatography of the hydrochlorides on silicic acid and purified by repeated crystallization.



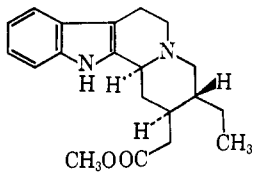
26

27

(9) C. H. DePuy and R. W. King, *Chem. Rev.*, 60, 431 (1960).

(10) J. W. Powell and M. C. Whiting, *Tetrahedron*, 12, 168 (1961).

3-Vinyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine hydrochloride (**26** hydrochloride salt), eluted first from the column, was the isomer formed in lesser quantity, the hydrochloride salt melting at 276–278° with decomposition. The structure **26** was assigned on the basis of the elemental analysis and the infrared and the nuclear magnetic resonance spectra. The infrared spectrum showed a weak band at 6.10 μ due to the C=C stretching, bands at 10.0 and 10.8 μ due to out-of-plane =CH deformations, and a band at 7.10 μ due to the $=CH_2$ in-plane deformation. These bands are all characteristic of a vinyl group,[11] and were absent from the spectrum of the saturated compound **28**. The evidence from the nuclear magnetic resonance spectrum was especially convincing; a complex, three-proton signal at τ 4.3–5.1 could be assigned to the three vinyl hydrogens, and there was no absorption above τ 8.0 which could be assigned to a methyl group. The ester methyl group signal came at τ 6.13.



28

Catalytic hydrogenation of the vinyl compound **26** over 10% palladium on carbon resulted in very rapid uptake of the theoretical quantity of hydrogen. The product was identified as the *trans*-ethyl compound **28** by comparison with an authentic sample.[12]

3-Ethylidene-2-carbomethoxymethyl-1,2,3,4,6,7,12-12b-octahydroindolo2,3-*a*]quinolizine hydrochloride melted at 264–265° with decomposition. The structure **27** was assigned on the basis of the elemental analysis and the infrared and the nuclear magnetic resonance spectra. The infrared spectrum showed a weak band at 6.16 μ due to C=C stretching, and a band at 12.0 μ which might be due to CH out-of-plane deformation.[11] The 12.0-μ band occurred also, however, in the spectra of the saturated compound **28** and the vinyl compound **26**, although it was much weaker in the spectra of these two compounds. The nuclear magnetic resonance spectrum, however, left little doubt that the ethylidene structure **27** was correctly assigned. A one-proton quartet at τ 4.83 (J = 7 Hz) and a three-proton doublet at τ 8.33 (J = 7 Hz) were due to the vinyl hydrogen and the allylic methyl group, respectively. The ester methyl group signal came at τ 6.29. The geometry of the ethylidene group in the compound **27** was tentatively assigned as being *anti* (as written) on the basis of the mechanistic arguments given later.

Catalytic hydrogenation of the ethylidene compound **27** was much more sluggish than hydrogenation of the vinyl compound **26**, even when platinum catalyst was used instead of palladium. The product with either catalyst was a mixture of the *trans*-ethyl compound **28** and its 15,20-*cis* isomer, as shown by comparison with authentic samples using thin layer chromatography.

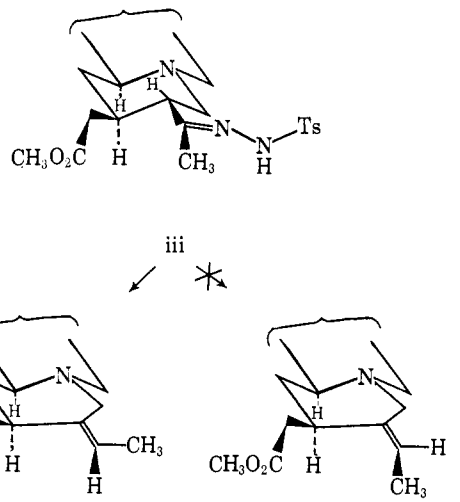
(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1960.

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

Decomposition of the *cis*-tosylhydrazone **25a** was only investigated in a preliminary way, but some observations are worth mentioning. Whereas only three primary products could be detected from the decomposition of the *trans*-tosylhydrazone **25b**, decomposition of the *cis* isomer produced a mixture of five primary products, as shown by thin layer chromatographic analysis. One of the extra products can be accounted for as the second possible geometric isomer of the ethylidene structure, a surmise supported by nmr spectral data.[13]

The formylation of compounds such as **26** and **27** on the activated methylene adjacent to the ester carbonyl function is well precedented in the total syntheses of *dl*-dihydrocorynantheine and *dl*-ajmalicine, previously accomplished in these laboratories.[2,12] The formylation of the ethylidene compound **27** (or the geometric isomer presumably available from decomposition of the *cis*-tosylhydrazone **25a**; see above) should yield *dl*-geisso-

(13) The difference in behavior of the two isomeric tosylhydrazones **25** upon decomposition was interesting and must have originated in steric factors, but it could not be experimentally investigated further. It is interesting, however, to speculate on the geometry of the two ethylidene isomers, especially since the geometry of the final target compound, geissoschizine, has not been determined. Why should the *trans*-tosylhydrazone (**25b**) decompose to give a single ethylidene isomer while the *cis* (**25a**) gives both? Inspection of models of the isomeric tosylhydrazones shows that there is considerable steric interaction between the two equatorial side chains on the D ring of the *trans* isomer. The "methyl tosylhydrazone" side chain must lie on or near a plane perpendicular to that of the ring (see perspective drawing iii, below) or be subject to severe hindrance. This means that during the formation of the olefin the side chain must twist through an angle of 90° into the plane of the ring before the π bond can form. This is true no matter what the detailed mechanism of the olefin-forming reaction may be. This rotation of the side chain could conceivably occur in either direction, but one would expect it to occur predominantly in the less hindered direction to give the olefin with the methyl group directed away from the adjacent carbomethoxymethyl side chain (*anti* geometry). Thus one would predict the *anti* isomer to predominate in the ethylidene product from the *trans* tosylhydrazone. In fact, only one ethylidene isomer was detected, so it must be the *anti* isomer. (This argument assumes that the hindered rotation of the side chain is slow compared to the rate of reaction of the intermediate carbene with the adjacent protons.)



27 (*anti*) **27** (*syn*)

In contrast, inspection of models of the *cis*-tosylhydrazone shows no overriding steric interactions between the axial "methyltosylhydrazone" side chain and the equatorial carbomethoxymethyl side chain. In this case the serious steric interactions of the tosylhydrazone side chain are due to its axial orientation and are greatly relieved by rotation in either direction during formation of the olefin (see drawing iv below). Decomposition of the *cis*-tosylhydrazone, then, would be expected to produce both *syn*- and *anti*-ethylidene isomers, as was apparently observed. In this case one might also expect a greater variety of products

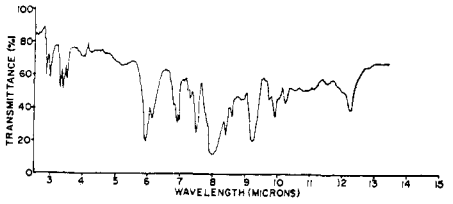
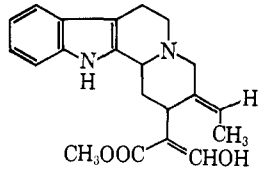


Figure 1. Ir spectrum of geissoschizine.

schizine **29**[14] or double bond isomer. Because the ethylidene compound **27** was available in larger quan-



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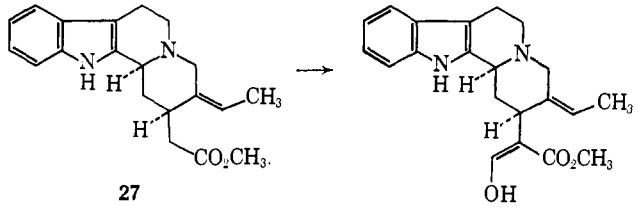
tity than the vinyl case **26**, its formylation was investigated first.

The enolate anion of the ethylidene ester **27** was generated by reaction with excess triphenylmethylsodium and immediately condensed with methyl formate. The mixture of unchanged ethylidene ester and the formylated product **30** obtained after work-up could be separated inefficiently into its components by repeated chromatography on silicic acid. Although successful chromatography of geissoschizine **29** on alumina has been reported,[15] no synthetic formylated product could be eluted from alumina columns, indicating that the synthetic ethylidene α-hydroxymethylene ester (**30**) was not *dl*-geissoschizine (**29**).



27 **30**

The spectral properties of the synthetic ethylidene α-hydroxymethylene ester **30** indicated that the desired gross structure had been obtained, but also proved finally that the synthetic material was not *dl*-geissoschizine (**29**). The ultraviolet spectrum of geissoschizine in neutral solution is essentially indolic (λ_{max} 268 mμ (ϵ 14,600), 290 (7800), in ethanol),[14] but in the presence of base the absorption of the enolate anion of the α-hydroxymethylene ester system becomes predominant (λ_{max} 277 mμ (ϵ 24,200), in 0.1 *N* ethanolic alkali).[16] The spectrum of the synthetic ethylidene α-hydroxymethylene ester exhibited closely similar behavior, indicating that the same type of chromophore was present.

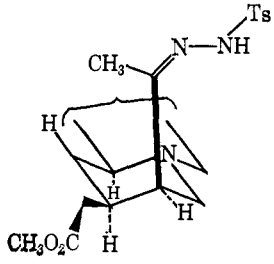
The infrared spectrum of geissoschizine shows bands attributed to an α-hydroxymethylene ester system at 3.03 μ (enolic hydroxyl) and 5.96 μ (ester carbonyl).[16] The infrared spectrum of the synthetic ethylidene α-hydroxymethylene ester showed corresponding bands at 3.03 μ (enolic hydroxyl) and 6.03 μ (ester carbonyl). The differences in position and appearance of the ester carbonyl bands in the spectra of the natural and synthetic compounds could not be considered as evidence against the α-hydroxymethylene ester structure for the synthetic compound, since similar systems prepared previously had spectra in agreement with that of the synthetic compound. During the course of the synthesis of *dl*-dihydrocorynantheine,[12] there was found a marked difference in the infrared spectra of a similar α-hydroxymethylene ester system before and after crystallization, ascribed to the selective crystallization of one or another of the geometric forms of the α-hydroxymethylene ester unit.

Of nine optically active acids assayed, geissoschizine itself formed a crystalline salt, mp 180–182° dec, with only one, dibenzoyl-D-tartaric acid. The amorphous synthetic ethylidene α-hydroxymethylene ester also formed a crystalline dibenzoyltartrate salt (mp 173–176° dec), different in all respects from the authentic specimen.

Finally, nuclear magnetic resonance spectrometry supplied supporting evidence against the identity of the synthetic ethylidene α-hydroxymethylene ester (**30**) and geissoschizine (**29**). Prominent features in the spectrum of geissoschizine could not be detected in the spectrum of the synthetic compound. Especially convincing was the clear absence from the spectrum of the synthetic material of the geissoschizine single proton doublet at τ 5.52, and the position of the ethylidene methyl group doublet at τ 8.38–8.49 instead of at τ 8.22, as in the spectrum of geissoschizine.

Since there is little doubt that the structure and C-3:C-15 stereochemistry of geissoschizine are correct,[14] the only point of difference between the natural and synthetic compounds can be the geometry of the ethylidene double bond. The double bond assignment in geissoschizine has been made; however, if the arguments given previously are correct, the relationship in the synthetic compound **27** is probably *anti* and that in geissoschizine, then, is *syn*.[17]

because of the proximity of the intermediate carbene to axial protons on the ring. Again, experiment agrees with expectation.



iv

↓

transannular

insertion products

(14) M.-M. Janot, *Tetrahedron*, **14**, 113 (1961).

(15) H. Rapoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Am. Chem. Soc.*, 80, 1601 (1958).

(16) H. Rapoport, R. J. Windgassen, Jr., N. A. Hughes, and T. P. Onak, *ibid.*, 82, 4404 (1960).

(17) Theoretically a hydroxymethylene system can exist in two forms, two geometric isomers which should be readily interconvertible through the common *aldehydo* tautomer. In the case of the synthetic compound **30**, both of these forms apparently occur in approximately equal amounts, resulting in the observation of a mixture in the nuclear magnetic resonance spectrum; in the case of geissoschizine one form predominates to the exclusion of the other. The cause of the difference in behavior must be the steric influence of the ethylidene methyl group.

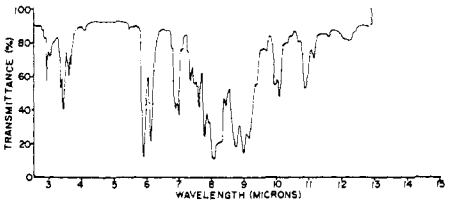


Figure 2. Ir spectrum of natural corynantheine.

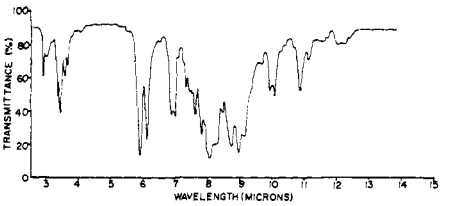
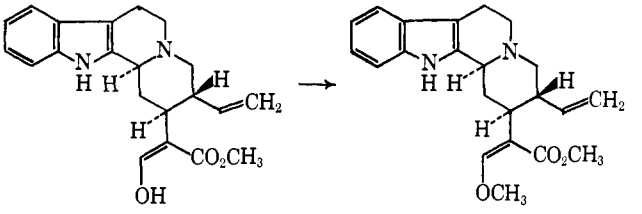


Figure 3. Ir spectrum of *dl*-corynantheine.

Formylation of the *trans* vinyl ester **26** was carried out in the same way as described for the ethylidene ester **27**. The intermediate vinyl α-hydroxymethylene ester **31** was purified by chromatography on silicic acid but could not be obtained crystalline. Treatment of a solution of crude **31** in methyl acetate with a large excess of ethereal diazomethane gave *dl*-corynantheine (**3**), which was separated from starting materials **26** and **31** by taking advantage of the well-known solubility of the hydrochloride salt in chloroform, and by preparative thin layer chromatography. Final purification by chromatography of the hydrochloride salt on silicic acid and regeneration of the free base with anhydrous sodium carbonate gave an amorphous compound with an infrared spectrum (Figure 3) identical in every respect with that of an authentic sample of *d*-corynantheine (Figure 2). Treatment of a methanol solution of *dl*-corynantheine (**3**) with methanolic hydrogen chloride and replacement of methanol by acetonitrile yielded a crystalline hydrochloride salt, mp 177–181°. Thus the synthesis of *dl*-corynantheine was complete.



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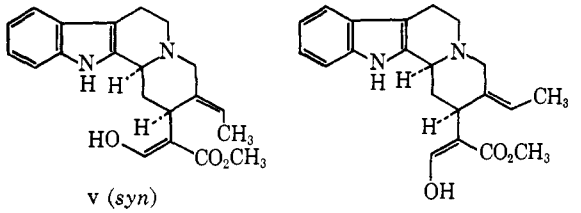
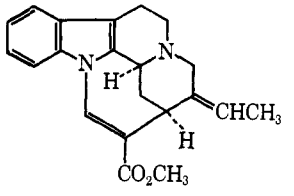
Inspection of models makes it clear that the isomer with the ethylidene methyl group *syn* to the adjacent α-hydroxymethylene ester side chain (structure v, below) experiences much more severe steric interaction than does the isomeric *anti* compound (structure vi, below), at least when the D rings maintain chair forms. That at least one isomer can react in a nonchair form is shown by the dehydration of geissoschizine to apogeissoschizine (vii) under the influence of strong acid.[14] A factor tending to make nonchair conformations less unfavorable than usual is the absence of atoms in two of the axial positions of the D ring. If, due to severe steric interactions present in the chair form, the D ring of the *syn* isomer v does exist in a boat or twist form, the relative stability of this conformer might be further enhanced by hydrogen bonding of the acidic enol hydroxyl to the basic tertiary nitrogen. If these hydrogen bonding and steric effects in the *syn* isomer v are such that only the normally less favorable *anti* isomer of the α-hydroxymethylene ester system is present in solution, structure v would represent geissoschizine and vi the synthetic series. In this case, the mixture of isomers observed in the synthetic series is simply due to the presence in solution of both geometric forms of the α-hydroxymethylene ester system, one stabilized by internal hydrogen bonding to the ester carbonyl oxygen, the other by hydrogen bonding to the amino nitrogen.



v (*syn*)

vi (*anti*)



vii

Physical data which might have a bearing on the problem must also be considered. For example, the ultraviolet spectrum of geissoschizine in neutral solution shows a stronger contribution from the enolate anion form than does the spectrum of the synthetic material, while the spectra of the dibenzoyltartrate salts are more nearly identical. This suggests a strong contribution to the spectrum of geissoschizine from a zwitterionic species and supports a structure v for geissoschizine in which the D ring is "twisted" and hydrogen bonding of the acidic enol to the basic nitrogen predominates. The solution infrared spectrum of geissoschizine has the ester carbonyl band at 5.95 μ, at somewhat shorter wavelength than that of any of the synthetic examples from this work (ethylidene α-hydroxymethylene ester vi, 6.03 μ, vinyl α-hydroxymethylene ester **31**, 6.01 μ) and the work of Placeway ("α-hydroxymethylene lactone," 6.05 μ)[2] and Hester (desmethyl *dl*-dihydrocorynantheine, 6.05 μ).[12] This might suggest again that the enolic hydroxyl is not strongly hydrogen bonded to the ester carbonyl in geissoschizine (because the geometry is *anti*), as was also suggested by the ultraviolet data.

Finally, the nuclear magnetic resonance spectrum of geissoschizine contained a broad doublet centered at τ 5.52 (J = 12 Hz). No similar signals occur in the spectra of any of the synthetic compounds, but such low-field signals do occur in the spectra of certain indole alkaloids which have an equatorial proton at C-3 (alkaloid numbering system), or equatorial protons attached to oxygen-bearing carbon atoms.[18] There should be no such protons in geissoschizine unless the D ring assumes a boat form, whereupon the diallylic tertiary hydrogen at C-15 (alkaloid numbering) becomes quasi-equatorial and could conceivably come at such low field. Alternatively, the axial proton at C-3 might be abnormally deshielded by the transannular ethylidene double bond when the D ring is in a boat form. This effect should not be possible when the D ring has the chair form. In either case the absence of such a signal from the spectrum of the synthetic material argues that the D ring maintains a chair form in the predominant conformer. Thus the spectral evidence supports the earlier conclusion that geissoschizine has the structure v and the synthetic ethylidene α-hydroxymethylene ester has structure vi.

Experimental Section

Melting points, unless otherwise specified (hs indicating Kofler micro hot stage apparatus), were determined in evacuated sealed capillary tubes in a Hershberg melting point apparatus with total immersion thermometers and are therefore corrected. Boiling points are uncorrected.

Infrared spectra were recorded on Perkin-Elmer Infracord spectrophotometers, Model No. 137 and 137b. Unless otherwise specified, 10% solutions in chloroform were used in 0.1 mm sodium chloride cells. Ultraviolet spectra were recorded on a Cary spectrophotometer, Model No. 11 MS, in methanol solutions. 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 9.88 in pyridine solution (calibrated with respect to tetramethylsilane).

The phrase "worked up as usual" signifies that the solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure on a rotary evaporator.

(18) (a) W. F. Rosen and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 4816 (1961); (b) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961).

Silicic acid used for chromatography was Mallinckrodt Analytical Reagent mesh powder from which the fine particles had been removed by repeated suspension in acetone and decantation of the solvent after 2 min of settling. The residual acetone was removed by oven drying at 60–100° for several days. Chloroform used for chromatography was dried prior to use by distillation from phosphorus pentoxide.

Thin layer chromatography was carried out on silica gel G (E. Merck Ag., Darmstadt, Germany; Brinkmann Instruments Inc., Great Neck, L. I., N. Y.) using 5–10% methanol in chloroform as the solvent. The positions of spots were determined by fluorescence under ultraviolet light and by staining with iodine vapor. All compounds are racemic unless otherwise indicated.

Elemental analyses were performed by the following: Huffman Microanalytical Laboratories, Wheatridge, Colo., Spang Microanalytical Laboratory, Ann Arbor, Mich., and Alfred Bernhardt Mikroanalytisches Laboratorium in Max-Planck-Institut für Kohlenforschung, 433 Müllheim (Ruhr).

Experiments on the Reduction of the Lactam 2. A. The Dihydroxy Lactam 6. Sodium borohydride (252 mg, 6.6 mmoles) (Metal Hydrides, Inc., Beverly, Mass.) was added to methanol (10 ml) cooled to −15°. A cold solution of lactam **2** (238 mg, 0.58 mmole) was added, and the mixture was stirred for 2.5 hr at −15 to −5°. The reaction mixture was then poured into saturated sodium chloride solution and extracted with chloroform. The chloroform solution was worked up as usual and the crude product (207 mg, 88%) chromatographed on silicic acid. The major product (105 mg, 0.28 mmole, 48%), eluted with 3% methanol in chloroform, was assigned the dihydroxy lactam structure **6** on the basis of the following evidence. The infrared spectrum showed strong hydroxyl absorption at 2.8–3.0 μ and a single sharp ester carbonyl band at 5.75 μ. Treatment of the diol **34** (160 mg, 0.41 mmole) with *p*-toluenesulfonyl chloride (221 mg, 1.15 mmoles) in anhydrous pyridine (3 ml) for 2 days at room temperature gave a product **7** (198 mg, 0.37 mmole, 90%) the infrared spectrum of which still showed hydroxyl absorption at 2.9–3.1 μ and also showed new bands at 8.5 and 8.9 μ characteristic of *p*-toluenesulfonyl esters.

B. The Lactone Lactam 8 and Hydroxy Lactam 9. Sodium borohydride (1.14 g, 30 mmoles) was added to methanol (20 ml) cooled in a Dry Ice bath. The mixture was magnetically stirred, and a precooled solution of the lactam 2 (2.16 g, 5.2 mmoles) was added. After 25 min of stirring, methanolic hydrogen chloride was added to destroy excess hydride; and the reaction mixture was worked up as in the previous section. The crude product (2.13 g, 98%) was chromatographed on silicic acid. With 2–3% methanol in chloroform, a mixture of lactone lactam **8** and hydroxy lactam **9** (1.91 g) was eluted in a single peak. Analysis by thin layer chromatography indicated the presence of a mixture. Crystallization of one of the fractions on the trailing end of the peak occurred from the methanol solution used in spotting the thin layer chromatogram. From this fraction was isolated 170 mg of lactone lactam **8**, mp 204–207° (see below). Crystallization of the other fractions could not be induced.

Very careful rechromatography of a sample of the mixture (977 mg) on silicic acid resulted in better separation. The hydroxy lactam **9** (504 mg) was eluted first with 2% methanol in chloroform. The nuclear magnetic resonance spectrum of **9** showed signals as follows: τ 5.4 (one-proton, broad singlet), hydroxyl hydrogen; τ 5.96 (one-proton quartet, J = 6.4 Hz), proton on the carbon bearing the alcoholic oxygen; τ 6.35 (three-proton singlet), tertiary ester methyl group; τ 6.38 (three-proton singlet), primary ester methyl group; τ 8.92 (three-proton doublet, J = 6.4 Hz), methyl group attached to the carbon bearing the alcoholic oxygen (in addition to the usual indole and methylene proton signals). Treatment of the hydroxy lactam **9** (453 mg) with acetic anhydride in pyridine for 5 hr at room temperature gave the acetoxy lactam **10**. The nuclear magnetic resonance spectrum of **10** showed signals as follows: τ 4.69 (one-proton quartet, J = 6.5 Hz), proton on the carbon bearing the alcoholic oxygen; τ 6.32 (three-proton singlet), tertiary ester methyl group; τ 6.34 (three-proton singlet), primary ester methyl group; τ 7.99 (three-proton singlet), acetoxy group methyl protons; τ 8.85 (three-proton doublet, J = 6.5 Hz), methyl group attached to the carbon bearing the alcoholic oxygen (in addition to the usual indole and methylene signals).

The second major fraction was the lactone lactam **8** (484 mg), eluted with 3% methanol in chloroform. The nuclear magnetic resonance spectrum of **8** showed signals at τ 6.30 (tertiary ester methyl group) and 8.80 (doublet, J = 6.5 Hz) in a spectrum which was weak due to the low solubility of **8** in deuteriochloroform. This material was identical in infrared spectrum with the material of mp 204–207° obtained as described above. Combined (654 mg), and crystallized from methanol, these fractions yielded 98.0 mg, mp 208–212°, and 281 mg, mp 201–205°. Treatment of the sample, mp 201–205°, with acetic anhydride in pyridine for 5 hr at room temperature resulted only in recovery of starting material.

The reaction of the lactone lactam and the acetoxy lactam with lithium iodide in 2,6-lutidine resulted in no evolution of gas after several hours at reflux, and the dark colored products were not investigated further.

Preparation and Pyrolysis of the Model Pyrazolones 16 and 17. The β-keto ester (2-methyl-2-carbethoxycyclohexanone or 2-β-phenylethyl-2-carbethoxycyclohexanone) was allowed to stand in methanol solution with a slight molar excess of 100% hydrazine hydrate for several days at room temperature. Solvent was then removed on the steam bath and the residue was crystallized from benzene–ethyl acetate. Heating pyrazolone 16 (mp 118–121°) to 360° in a sealed tube resulted in little decomposition (the material melted at 112–114° after solidifying on cooling). Pyrazolone **17** had melting point 115–120°. The infrared spectra of both pyrazolones showed bands at 2.90 μ (N–H), 5.8–6.0 μ (several carbonyl bands), and 6.2 μ (C=N?).

The pyrazolones **16** and **17** were distilled at atmospheric pressure using a free flame. The distillate (bp 295°) from 16 crystallized upon cooling (mp 118–121°), the infrared spectrum indicating only starting material. The pyrazolone **17** distilled at 340° with a little more decomposition than in the previous case, but the infrared spectrum of the distillate indicated that it was largely unchanged starting material.

Sodium Borohydride Reduction of the Keto Diester 4. Formation of the Hydroxy Diester 18. A solution of the keto diester **4** (1.05 g, 2.64 mmoles) in tetrahydrofuran (30 ml) was cooled to about −10°, and a solution of sodium borohydride (211 mg, 5.55 mmoles) in cold water (3 ml) was added. The mixture was stirred magnetically for 2 hr at temperatures from −10 to 0°. (A preliminary experiment which was followed by thin layer chromatography indicated that reduction was essentially complete within this time.) The reaction mixture was poured into saturated sodium chloride solution (100 ml) and extracted with chloroform. The chloroform solution was worked up as usual and the product crystallized from methanol: first crop 660 mg (62.5%), mp 222–223° after softening at 220°; second crop, 100 mg (9.5%), mp 209–212° after softening at 195°.

Recrystallization of the higher melting first crop yielded pure hydroxy diester **18** in the form of flat plates, mp 223–225°. The infrared spectrum showed bands at 2.84 μ (hydroxyl group), 2.94 (indole N–H), and at 5.79 and 5.85 μ (ester carbonyl). The nuclear magnetic resonance spectrum, although weak due to the low solubility of the compound in deuteriochloroform, showed signals at τ 6.28 and 6.36 (ester methyl groups) and τ 8.72 (doublet, J = 7 cps), "ketone" methyl group.

Anal. Calcd for $C_{22}H_{28}O_5N_2$: C, 65.99; H, 7.05; O, 19.98; N, 7.00. Found: C, 66.24; H, 7.16; O, 19.94; N, 6.91.

From the lower melting point second crop was obtained an impure sample of a second compound, mp 210–211°, which was tentatively assigned the lactone ester structure **19** by analogy with the corresponding product (the lactone lactam **8**) obtained from the reduction of the lactam **2**. The infrared spectrum of the impure lactone ester **19** had no hydroxyl absorption except that attributable to contamination by the hydroxy diester **18**, and there was only a single carbonyl band at 5.83 μ. The nuclear magnetic resonance spectrum showed only one ester methyl group signal (τ 6.28).

Hydrolysis of the Hydroxy Diester 18. The hydroxy ester **18** (308 mg) was heated under reflux with 18% hydrochloric acid (20 ml) under a nitrogen atmosphere for 5 days. An aliquot (2 ml) was removed and evaporated to dryness in a tared flask *in vacuo* over sodium hydroxide. The 44.7-mg sample was titrated over 0.0264 *N* sodium hydroxide (8.00 ml required), the equivalent weight (212) indicating that hydrolysis of only one of the ester groups had occurred.

Reduction of the Keto Ester 5. A. Sodium Borohydride Reduction. Reduction of the keto ester **5** hydrochloride (110 mg, 0.290 mmole) with sodium borohydride (203 mg, 5.35 mmoles) in methanol (15 ml) containing sodium methoxide (58 mg, 1.07 mmoles) for 1.5 hr at room temperature yielded only the diol **22** (92 mg, 0.291 mmole, 100%). The infrared spectrum showed a large hydroxyl band at 2.90 μ, indole NH at 2.7 μ, and no peak in the carbonyl region.

The *p*-Toluenesulfonylhydrazones (25) of the Keto Esters 5. The mixture of isomeric keto ester **5** hydrochlorides (2.29 g, 6.08 mmoles) was stirred with *p*-toluenesulfonylhydraine (Aldrich Chemical Co.,

Inc., Milwaukee, Wis.; 2.27 g, 12.2 mmoles) in a solution of methanol (60 ml) and acetic acid (20 ml) at room temperature overnight. The solvent was then removed using a rotary evaporator, and the residue was taken up in a minimum of methanol and shaken between chloroform and 5% sodium carbonate solution. The organic layer was worked up as usual and the products were chromatographed on silicic acid (200 g). Unreacted *p*-toluenesulfonylhydrazine (1.13 g) was eluted with 1% methanol in chloroform (24 l.), while the isomeric tosylhydrazones **25** (2.88 g, 93% yield of crude crystalline material) were eluted in a broad single peak with 2% methanol in chloroform (27 l.).

The first fractions consisted of the *trans* isomer **25b**, mp 227–228° dec, after several recrystallizations from methanol.

Anal. Calcd for $C_{27}H_{32}O_4N_4S$: C, 63.76; H, 6.34; O, 12.58; N, 11.02; S, 6.30. Found: C, 64.29; H, 6.52; O, 12.66; N, 10.60, S, 6.31.

The infrared spectrum (Nujol mull) of the *trans*-tosylhydrazone showed bands at 2.92 (indole NH), 3.09 (tosylhydrazone NH), 5.77 (ester carbonyl), and 7.53 and 8.59 μ ($-SO_2-$). The nuclear magnetic resonance spectrum (in pyridine solution) showed the ester methyl group signal at τ 6.58, the toluene methyl group signal at 7.82, and the ketonic methyl group signal at 8.00.

The *cis* tosylhydrazone **25a**, mp 202° dec after loss of solvent at about 150°, was obtained from trailing fractions of the column and purified by repeated recrystallization from methanol.

Anal. Calcd for $C_{27}H_{32}O_4N_4S\cdot CH_3OH$: C, 62.19; H, 6.71; O, 14.80; N, 10.37; S, 5.93. Found: C, 62.20; H, 6.71; O, 15.00; N, 10.44; S, 5.66.

The infrared spectrum (Nujol) mull) of the *cis*-tosylhydrazone showed characteristic bands at 2.92 (indole NH), 3.22 (hydrogen bonded tosylhydrazone NH), 5.82 (ester carbonyl), and 7.50 and 8.60 μ ($-SO_2-$). The nuclear magnetic resonance spectrum was obtained in both pyridine and deuteriochloroform solution, the signal positions in the latter solvent are given in parentheses. The ester methyl group signal came at τ 6.59 (6.35), the toluene methyl group signal at τ 7.75 (7.57), the ketonic methyl group at τ 8.06 (8.24) and a methyl group signal due to solvent of crystallization at τ 6.43 (6.54 τ).

Middle fractions from the column consisting of mixtures of tosylhydrazone isomers could be separated into the two components by fractional crystallization from methanol, the *cis* isomer being the less soluble.

The tosylhydrazone of acetone was prepared in the same manner as described above, for the purpose of spectral comparison. The infrared spectrum showed characteristic bands at 3.11 (NH), 7.50 and 8.60 μ ($-SO_2-$). The nuclear magnetic resonance spectrum showed the toluene methyl group signal at τ 7.61 and the ketone methyl groups at τ 8.17 and 8.25. The spectral properties thus agreed with those of the tosylhydrazones **25**.

Decomposition of the *trans*-Tosylhydrazone 25b. The *trans*-tosylhydrazone (2.00 g, 3.93 mmoles) was weighed into a 100-ml flask containing a magnetic stirring bar and equipped with a Drierite drying tube. The flask was then evacuated through the drying tube, heated in the steam bath for 30 min, and allowed to cool to room temperature, still under vacuum. Sodium methoxide (Mathieson Alkali Works Inc., Niagara Falls, N. Y.; 536 mg, 9.93 mmoles) was weighed into the flask as rapidly as possible, and diglyme (diethylene glycol dimethyl ether) (dried by refluxing over lithium aluminum hydride) was allowed to distill directly into the reaction vessel. The flask was then attached to a reflux condenser and gas-measuring buret, and the system flushed rapidly with dry nitrogen. Heating and stirring were begun immediately and reflux temperature was reached in about 5 min. By this time most of the gas had been evolved, but the heating was continued for another 20 min until gas evolution had ceased entirely. The apparatus was then cooled to room temperature in a strong steam of air and the final gas volume measured (85.3 ml, 3.81 mmoles, 97%).

The reaction mixture was rinsed with methyl acetate into a large volume of anhydrous ether containing solid sodium bicarbonate. After about 15 min of stirring, the solid material was separated by filtration and discarded. When analyzed by thin layer chromatography at this point, the solution revealed only three detectable products. In order to separate the desired products from diglyme, the ether solution was acidified with methanolic hydrogen chloride and allowed to stand under nitrogen in the refrigerator overnight; the amorphous precipitate of hydrochloride salts was separated by filtration and washed well with anhydrous ether. The precipitate was dissolved in methanol, transferred to a tared flask, and evaporated to dryness *in vacuo*, and under nitrogen (1.52 g, 107%). Careful chromatography of the hydrochloride salts on silicic acid (150 g, paste load technique) resulted in partial separation of the products. The fractions were crystallized from methanol–acetonitrile, and the crystalline materials were analyzed by thin layer chromatography. (Since the products were in the form of the hydrochloride salts which streaked badly upon thin layer chromatography, the thin layer plates were also spotted with a solution of sodium methoxide in methanol in such a manner that the solvent carried the base into the spot of compound thus generating the free base *in situ*). Thin layer analysis of the column fractions indicated the presence of two major products corresponding to two of the three products detected previously and also indicated that extensive decomposition had occurred during the latter part of the work-up. Of 1.52 g of crude mixed products placed on the column, approximately 900 mg was recovered undecomposed, the remaining 600 mg have suffered decomposition to hydroxyl containing products which were not further investigated.

The first identifiable material eluted from the column (with 3.5% methanol in chloroform) was *trans*-3-vinyl-2-carbomethoxymethyl-1,2,3,4,6,7-12,12b-octahydroindolo[2,3-*a*]quinolizine (**26**) hydrochloride (approximately 80 mg of crystalline material), mp 276–278° dec after several recrystallizations from methanol–acetonitrile. (The progress of purification *via* recrystallization was most conveniently followed by thin layer chromatography.)

Anal. Calcd for $C_{20}H_{25}O_2N_2Cl$: C, 66.56; H, 6.98; O, 8.86; N, 7.76; Cl, 9.82. Found: C, 66.74; H, 6.87; O, 9.57; N, 8.56; Cl, 8.33.

The nuclear magnetic resonance spectrum of the vinyl compound **26** showed signals as follows: τ 1.93 (one proton, broad singlet), indole NH; τ 2.4–3.1 (four-proton multiplet), aromatic protons; τ 4.3–5.1 (three proton multiplet), vinyl hydrogens; τ 6.13 (three proton singlet), ester methyl group; τ 6.6–8.2 methylene envelope.

Next eluted from the silicic acid column was a mixture of the vinyl compound **26** hydrochloride and the ethylidene compound **27** hydrochloride (323 mg). The mixed hydrochlorides could be separated by repeated recrystallization from methanol–acetonitrile by following the course of the separation with thin layer chromatography.

Further elution with 3.5–5% methanol in chloroform gave 3-ethylidene - 2 - carbomethoxymethyl - 1,2,3,4,6,7,12,12b - octahydroindolo [2,3-*a*]quinolizine (**27**) hydrochloride (204 mg of crystalline material), mp 264–265° dec after several recrystallizations from methanol–acetonitrile.

Anal. Calcd for $C_{20}H_{25}O_2N_2Cl$: C, 66.56; H, 6.98; O, 8.86; N, 7.76; Cl, 9.82. Found: C, 66.46; H, 6.79; O, 9.78; N, 8.53; Cl, 8.50.

The nuclear magnetic resonance spectrum of the ethylidene compound **27** showed signals as follows: τ 1.95 (one-proton, broad singlet), indole NH; τ 2.5–3.1 (four-proton multiplet), aromatic hydrogens; τ 4.83 (one-proton quartet, J = 7 Hz), vinyl hydrogen; τ 6.29 (three-proton singlet), ester methyl group; τ 6.0–8.1, methylene envelope; τ 8.33 (three-proton doublet, J = 7 Hz), vinyl methyl group.

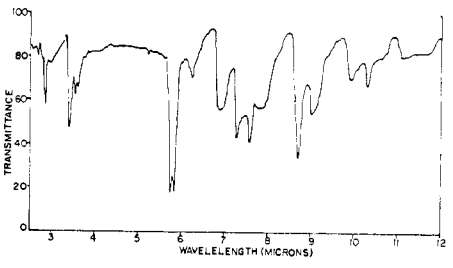


Figure 4. Ir spectrum of **27**.

Eluted from the silicic acid column with 5–10% methanol in chloroform was a further 650 mg of material which was not investigated further after it was shown by thin layer chromatography to be a mixture of compounds not originally present in the tosylhydrazone decomposition mixture. The infrared spectra of some samples of this material obtained previously by preparative scale thin layer chromatography showed large hydroxyl bands at 3.0–3.2 μ.

Catalytic Hydrogenation of 3-Vinyl-2-carbomethoxymethyl-1,2,3,-4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (26) Hydrochloride. The vinyl compound **26** (37.6 mg, 0.104 mmole) in methanol solution over 10% palladium on carbon (100 mg) within 10 min absorbed the theoretical amount of hydrogen. The catalyst was

removed by filtration and washed well with methanol. The solution was concentrated and the product crystallized from methanol–methyl acetate (17.7 mg, 0.049 mmole, 47%), mp 273–274° dec (lit.[12] mp of *trans*-ethyl compound **28** hydrochloride 274.6–275.2°). The infrared spectra (Nujol mull) of the hydrogenation product and the authentic *trans*-ethyl compound **28** hydrochloride were identical. The compounds from the two sources also exhibited identical thin layer chromatography mobility.

Catalytic Hydrogenation of 3-Ethylidene-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (27) Hydrochloride. The ethylidene compound **27** (39.2 mg, 0.109 mmole) in methanol solution over platinum oxide (100 mg, prereduced) absorbed hydrogen more slowly than did the vinyl compound **26**; the reaction was stopped after 30 min, at which point 107% of the theoretical amount of hydrogen had been absorbed. The crystalline product (17.1 mg, mp 247–250°) was shown by thin layer chromatography to be a mixture of the hydrochlorides of the *cis*- and *trans*-ethyl compounds.[2,12]

Repeating the reaction using 10% palladium on carbon (100 ml of catalyst; 28.0 mg, 0.078 mmole of ethylidene compound **61** hydrochloride) resulted in much slower uptake of hydrogen (108% of the theoretical quantity in 7 hr). Although, as indicated by tlc, both *cis* and *trans* isomers were again formed, the product in this case was chiefly the *trans*-ethyl compound **28** (5.5 mg of hydrochloride, mp 271–272° dec, identified by comparison of the infrared spectrum (Nujol mull) of the hydrochloride salt with that of an authentic sample.[12] Thin layer chromatographic comparison also indicated that the two compounds were the same.

Formylation of 3-Ethylidene-2-carbomethoxymethyl-1,2,3,4,6,7,-12,12b-octahydroindolo[2,3-*a*]quinolizine (27). A 50-ml three-necked flask was equipped with a magnetic stirrer, a reflux condenser, and nitrogen inlet, and was attached to a 50-ml buret through a three-way stopcock. The third neck of the flask was closed with a rubber serum cap. Triphenylmethylsodium was prepared in a glass-stoppered bottle, and the bottle was attached to the third arm of the three-way stopcock already attached to the buret and the reaction vessel. Provision was made for maintaining an atmosphere of dry nitrogen over the triphenylmethylsodium solution at all times. Nitrogen pressure was used to force the triphenylmethylsodium solution through a sintered glass filter disk up into the buret. The ethylidene ester **27** (459.9 mg, 1.42 mmoles) was regenerated from the crystalline hydrochloride salt by shaking it with chloroform and 5% sodium carbonate solution. The chloroform solution was worked up as usual, final evaporation being carried out in the reaction vessel under nitrogen and *in vacuo*. The reaction system was then flushed thoroughly with nitrogen. The ethylidene ester **27** was dissolved in anhydrous ether (10 ml) injected through the serum cap by means of a hypodermic syringe, and a slight excess of triphenylmethylsodium (30 ml, 0.13 *N*, 3.9 mmoles) was added rapidly from the buret. Freshly distilled methyl formate (4 ml) was then immediately injected into the red solution through the serum cap, whereupon the red color was discharged. The cloudy solution was stirred for 8 hr at room temperature, then acetic acid (5 ml) was added and the ether solution was extracted several times with water (in the smallest convenient quantities). The aqueous extract containing the acetate salts of the formylated product and of the unreacted starting material was made slightly alkaline with aqueous ammonia, saturated with sodium chloride (optional) and extracted with chloroform. The chloroform solution (worked up as usual) contained 422 mg of material, the infrared spectrum of which showed a new carbonyl band at 6.01 μ characteristic of α-hydroxymethylene esters of the desired type.

Chromatography on silicic acid yielded, in order of elution, unchanged ethylidene ester **27** (113 mg, 0.348 mmole, 25% recovery), mixtures of ethylidene ester and the formylated product (83 mg), and finally the formyl derivative **30** (148 mg, 0.348 mmole, 39% yield based on unrecovered starting material) which resisted all efforts at crystallization. Column fractions were analyzed by thin layer chromatography and infrared spectroscopy. The infrared spectrum of the synthetic ethylidene α-hydroxymethylene ester **30** was consistent with the desired gross formulation, showing a weak hydroxyl band at 3.02 μ and a carbonyl band at 6.02 μ with shoulders at 5.82 and 6.22 μ. The spectrum was, however, clearly different from that of geissoschizine **29** (Figure 1).

The ultraviolet spectrum of the synthetic ethylidene α-hydroxymethylene ester **30** showed λ_{max} 225, 274, and 290 mμ in methanol solution. In the presence of base, the 225-mμ band was only slightly affected (shift to 226 mμ), while the 274-mμ band was greatly intensified and shifted slightly to 275 mμ, completely masking the 290-mμ band. The ultraviolet spectrum of geissoschizine had λ_{max} 223, 271, and 290 mμ. In basic solution the 223-mμ band was shifted to 226 mμ while the 271-mμ band was greatly intensified and shifted to 276 mμ (lit. for geissoschizine λ_{max} 268 mμ (ϵ 14,600), 290 (7800) in ethanol[15]; λ_{max} 277 mμ (ϵ 24,200) in 0.1 *N* ethanolic alkali[16]). The ultraviolet spectra of the two compounds were clearly very similar and showed the same behavior upon basification, indicating that the same chromophore was present in both compounds (the α-hydroxymethylene ester chromophore).

The spectral differences between the natural and synthetic compounds were considered to be due to isomerism centered in the α-hydroxymethylene ester system and the following experiments were designed to produce the correct isomer, both geometric and optical.

Preparation of Geissoschizine Dibenzoyltartrate. A small sample of geissoschizine (2–6 mg) was mixed with 1 molar equiv of dibenzoyl-D-tartaric acid and dissolved in a small quantity of methanol by warming on the steam bath. A cosolvent was then added to reduce the solubility of the salt, and the mixture allowed to cool. Geissoschizine dibenzoyl tartrate crystallized from methanol–ethyl acetate or methanol–acetone and had mp 180–182° dec (hs), the same as geissoschizine itself. However, the analysis, the infrared spectrum, and depression of the mixture melting point (171–178°) with geissoschizine proved the nature of the product. Recrystallization of geissoschizine dibenzoyl tartrate resulted in no change in the melting point or the infrared spectrum. The infrared spectrum showed a strong ester carbonyl band at 5.80 μ. The ultraviolet spectrum (in methanol) had λ_{max} 223 mμ (ϵ 59,700), 268 (10,500) (shoulder), 273 (10,700), 282 (9700) (shoulder), and 290 (6400). In alkaline solution (sodium methoxide in methanol) the spectrum was as follows: λ_{max} 227 mμ (ϵ 63,200) and 276 (24,700).

Preparation of the Dibenzoyl-D-tartrate of the Synthetic Ethylidene α-Hydroxymethylene Ester 30. Chromatographically purified amorphous synthetic ethylidene α-hydroxymethylene ester **30** (90.2 mg, 0.253 mmole) was mixed with dibenzoyl-D-tartaric acid (90.6 mg, 0.253 mmole), and the mixture was dissolved in a little hot methanol. The methanol was diluted with acetone, added at the boiling point, concentrated slightly, and allowed to cool for crystallization. The yellow salt (71.8 mg, 0.101 mmole, 40.0%) obtained in this way exhibited peculiar melting point behavior. Fast heating of the hot stage resulted in melting at about 175–180°; whereas, if a normal, slow rate of heating was used, only a slight, subtle change in the appearance of the crystals occurred at about 175°. The crystals did not lose form even up to 360°, although they gradually turned black as heating was continued past 200°. For analysis, the salt was recrystallized several times from ethanol and dried *in vacuo* over phosphorus pentoxide. The melting point was 174–181° dec (hs, fast heating).

Anal. Calcd for $C_{39}H_{38}O_{11}N_2$: C, 65.89; H, 5.39; O, 24.76; N, 3.94. Found: C, 65.52; H, 5.54; O, 25.01; N, 3.83.

The infrared spectrum of the synthetic salt was very similar to that of the salt of geissoschizine but there were small, definite differences. The ultraviolet spectrum (in methanol) had λ_{max} 223 mμ (ϵ 63,400), 268 (10,100) (shoulder), 273 (10,400), 282 (9600) (shoulder), and 290 (6800). In alkaline solution (sodium methoxide in methanol) the spectrum showed λ_{max} 227 mμ (ϵ 64,900), 274 (27,400). The spectra were very similar to those of the geissoschizine dibenzoyl tartrate salt (see above) but not identical.

Several recrystallizations of the synthetic salt from ethanol did not change the melting point or spectral properties, nor did seeding solutions of the synthetic salt with authentic geissoschizine dibenzoyl tartrate crystals. Similarly, recycling of the amorphous salt fraction (the noncrystallizable mother liquors from the first preparation of the salt, containing approximately one-half of the total amount of material used initially) through the free base and reformation of the salt with fresh dibenzoyltartaric acid gave back only noncrystallizable salt. The infrared spectra of the free bases regenerated from crystalline and amorphous dibenzoyl tartrate salts were virtually indistinguishable. These observations were taken to indicate that resolution of the synthetic material had been accomplished, although the optical rotation of the free bases was not obtained.

The nuclear magnetic resonance spectrum of geissoschizine (**29**) exhibited the following signals: τ 1.6 (single-proton, broad singlet), indole NH; τ 2.14 (single-proton, sharp singlet), hydroxymethylene group vinyl hydrogen; τ 2.3–3.1 (four-proton multiplet), aromatic hydrogens; τ 4.62 (one-proton quartet, J = 6.5 Hz), ethylidene group vinyl hydrogen; τ 5.52 (one-proton, broad doublet, J = 12 Hz), proton at C-3 or C-15 (see Discussion); τ 5.8–~6.3 (two-proton multiplet), not assigned; τ 6.30 (three-proton singlet), ester methyl group; τ 6.5–~8.1 (about eight protons), methylene

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).

Acknowledgment. The authors are appreciative of financial support from the National Institutes of Health (RG 3892) and the National Science Foundation (Grant 19519). Thanks are also due to Dr. N. Neuss (Eli Lilly and Co.) for a sample of corynantheine, and to Professor H. Rapoport (University of California, Berkeley) for a gift of geissoschizine.

Total Syntheses of *dl*-Ajmalicine and Emetine

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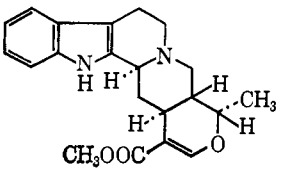
Abstract: The first total synthesis of a ring-E heterocyclic indole alkaloid, ajmalicine (**1**, racemic form), was accomplished by means of an initial, biogenetically patterned condensation of tryptamine, formaldehyde, and keto triester **4** and succeeding steps proceeding through the intermediates **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

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(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.