diluted to 100 ml. with water and extracted with ether (3 × 30 ml.) to give 240 mg. of (+)-α-**isobalfourodine** (**VI**) which, after recrystallization from acetone–hexane and sublimation at 150° (30 μ) melted at 198–201°, $[\alpha]_D$ + 30°; ultraviolet absorption: λ_{max} 217 mμ (ε 27,500), 234 (31,000), 246 (26,200), 252 (26,700), 268 (7,700), 279 (8,000), 289 (8,000), 321 (3,200); in methanol, 0.2 *M* in HCl: λ_{max} 216 mμ (ε 27,200), 234 (30,000), 246 (28,500), 251 (29,000), 267 (7,200), 278 (7,700), 288 (7,700), 320 (3,200); in hexane: λ_{max} 214 mμ (ε 16,200), 237 (37,000), 248 (22,000), 263 (6,250), 274 (6,000), 285 (6,500), 322 (3,250).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.4; H, 6.6. Found: C, 66.2; H, 6.6.

Reaction of Balfourodine (I) with Alkali.—To a solution of 500 mg. (1.73 mmoles) of balfourodine (I) in 10 ml. of ethanol was added 10 ml. of 30% aqueous sodium hydroxide. After being boiled in a nitrogen atmosphere for 4 hours, the solution was diluted to 100 ml. with water and extracted with chloroform (3 × 30 ml.) to give 500 mg. of material. Chromatography on 15 g. of alumina gave, on elution with benzene and benzene–chloroform (3:1), (+)-ψ-**balfourodine** (**V**), which, on recrystallization from acetone–hexane followed by sublimation at 160° (5 μ) and a second recrystallization from the same solvent, melted at 142–143°, mixed with (−)-ψ-balfourodine (m.p. 144–145°) m.p. 165–168°, $[\alpha]_D$ + 52°. The ultraviolet and infrared spectra of (+)- and (−)-ω-balfourodine were identical. Elution with benzene–chloroform (1:1) gave (−)-ψ-**isobalfourodine** (**VI**), which after two recrystallizations from acetone–hexane melted at 204–205°, mixed with (+)-ψ-isobalfourodine (m.p. 198–201°) m.p. 190–191°, $[\alpha]_D$ −31°. The ultraviolet and infrared spectra of (+)- and (−)-ψ-isobalfourodine were identical.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Alkaloids of Geissospermum vellosii. Further Studies on Geissospermine and the Structures of the Indolic Cleavage Products, Geissoschizine[1] and Apogeissoschizine

BY HENRY RAPOPORT, RICHARD J. WINDGASSEN, JR.,[2] NEIL A. HUGHES AND THOMAS P. ONAK

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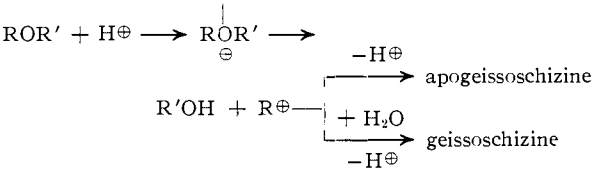
The nature of the ester function in geissospermine is discussed together with supporting evidence for the postulate that the indole and indoline moieties of geissospermine are joined through an ether bridge. The structures of the indolic cleavage products, geissoschizine and apogeissoschizine, have been established by degradative and spectral studies, and by the fact that apogeissoschizine can be converted to geissoschizine. From this evidence a partial structure for geissospermine itself is proposed.

In a previous communication[3] on the alkaloids of *Geissospermum vellosii* we reported that treatment of the main alkaloid, geissospermine, $C_{40}H_{48}N_4O_3$, with hydrochloric acid gives geissoschizoline, $C_{19}H_{26}N_2O$, an indoline alkaloid also present in the bark as such, and two indolic products, geissoschizine, $C_{21}H_{24}N_2O_3$, and apogeissoschizine, $C_{21}H_{22}N_2O_2$. In this paper we report further observations on the functional groups of geissospermine and the determination of the structures of geissoschizine and apogeissoschizine.

Functional Groups of Geissopermine.—The functional groups of geissospermine with which we are concerned at the moment are (1) the linkage between the indolic and indolinic portions of the molecule and (2) the nature of the carbonyl group. Both of these are pertinent to the structure determination of geissoschizine and apogeissoschizine.

The cleavage of geissospermine can be effected by concentrated acid,[3] in which the products are geissoschizine and apogeissoschizine; by 2 *N* acid[4,5] in which the products are geissoschizoline and geissoschizine; and by fuming acid[5] in which apogeissoschizine replaces most of the geissoschizine. Geissoschizine, as ultraviolet absorption spectra clearly suggest (see below), contains two essentially independent chromophores, one indolic and one sensitive to *p*H. In apogeissoschizine these isolated systems apparently have been joined through loss of a molecule of water. The fact that geissoschizine and apogeissoschizine are not interconverted to an appreciable extent under the cleavage conditions used[3] led to the hypothesis that the indole and indoline moieties of geissospermine are joined by a labile ether bridge. When this bridge is cleaved, an intermediate carbonium ion arises which can react by two different pathways to give either geissoschizine or apogeissoschizine.



Here geissospermine is designated ROR′ and geissoschizoline R′OH. In accord with the evidence, the ether postulate suggests that geissoschizine formation is favored in dilute acids were the concentration of "free" water is highest.

Since geissospermine does not form carbonyl derivatives but does contain a methoxyl group, the presence of a methyl ester is indicated. However, the carbonyl band in the infrared at 5.82 μ is sufficiently far removed from that of a normal saturated ester, 5.71–5.76 μ, that conjugation or other effects must be present. On the other hand, the fact that the ultraviolet spectrum of geissospermine is obtained by simple addition of the spectra of an indole and indoline[6,7] essentially rules out any conjugation between the ester function and one of these chromophores. With the further structural evi-

(1) See H. Rapoport, R. J. Windgassen, N. A. Hughes and T. P. Onak, THIS JOURNAL, **81**, 3166 (1959), for a preliminary communication on this subject.

(2) National Science Foundation Postdoctoral Fellow, 1958–1959.

(3) H. Rapoport, T. P. Onak, N. A. Hughes and M. G. Reincke, THIS JOURNAL, **80**, 1601 (1958).

(4) A. Bertho, M. Koll and M. I. Ferosie, *Ber.*, **91**, 2581 (1958).

(5) M. M. Janot, R. Goutarel, A. LeHir and F. Puisieux, *Compt. rend.*, **248**, 108 (1959).

(6) Recently M. Gorman, N. Neuss and G. H. Svoboda [THIS JOURNAL, **81**, 4745 (1959)] claimed to have discovered in leurosine and vincaleukoblastine representatives of a new class of dimeric alkaloids containing both indole and indoline moieties. However, this overlooked the fact that such a combination also exists in geissospermine, as has been pointed out previously (ref. 3, 4, 5, 7).

(7) K. Weisner, W. Rideout and J. A. Manson, *Experientia*, **9**, 369 (1953).

dence reported herein, it is difficult to write an alternate structure with a conjugated ester.

When geissospermine was treated with sodium in liquid ammonia, reduction occurred as expected to give dihydrodemethoxygeissospermine, $C_{39}H_{48}N_4O_2$, and this product exhibited an ultraviolet spectrum almost identical to that of geissospermine.

The reduction of geissospermine by lithium aluminum hydride gave an isomeric alcohol, dihydrodemethoxyisogeissospermine.[8] Not only was its ultraviolet spectrum quite different from that of geissospermine, but the spectrum was unchanged by acid or alkali. Since the acid shifts observed with geissospermine reflect protonation of the indoline nitrogen, the lithium aluminum hydride reaction must have a profound effect on the environment of this nitrogen atom. Actually the effect (Fig. 1) also produces a bathochromic shift in the indoline absorption.[9] That the presence of the ester group in geissospermine was not necessary for this effect was shown when dihydrodemethoxygeissospermine underwent isomerization readily to dihydrodemethoxyisogeissospermine in the presence of lithium aluminum hydride. However, such bases as lithium hydride, sodium hydride, sodamide or potassium hydroxide produced no change in the dihydrodemethoxygeissospermine, nor was dihydrodemethoxyisogeissospermine affected by sodium in liquid ammonia.

When geissospermine was boiled with potassium hydroxide (2 *N*) in ethanol and this solution was diluted with water, all the alkaloidal material could be extracted into chloroform. This clearly demonstrated that more than simple ester-hydrolysis was taking place. Decarboxylation must be occurring since the product was extractable from an alkaline solution and no longer showed carbonyl absorption. Experiments in which alkaloidal material was isolated and carbon dioxide was liberated from parallel aliquots clearly demonstrated that loss of carbonyl absorption was concurrent with liberation of carbon dioxide. Since loss of the carbonyl function from geissospermine takes place before acidification, it must be lost by a reverse Claisen type of reaction, *e.g.*

$$R-\overset{O}{\overset{\|}{C}}-OCH_3 + OH^{\ominus} \longrightarrow$$

$$CH_3OH + R-\overset{O}{\overset{\|}{C}}-O^{\ominus} \longrightarrow CO_2 + R^{\ominus}$$

where the anion, $R^{\ominus}$, is resonance stabilized.

It is difficult at this time to postulate a suitable structure which would account for this decarbomethoxylation since, as already mentioned, the carbomethoxy group of geissospermine cannot be conjugated with the indole or indoline chromophores. However, both this ready decarboxylation and the ester absorption at 5.82 μ undoubtedly have their origin in the same structural features.

(8) A similar reaction has been reported in ref. 5 and 7. In the latter case, a dihydrogeissospermine which still showed carbonyl absorption was reported. Repetition of this work has led us to the conclusion that this carbonyl absorption was due to ethyl acetate of crystallization. When the ethyl acetate was removed, material identical to our dihydrodemethoxyisogeissospermine was obtained (see Experimental).

(9) A similar effect has been demonstrated in studies on geissoschizoline itself and will be dealt with in a forthcoming paper.

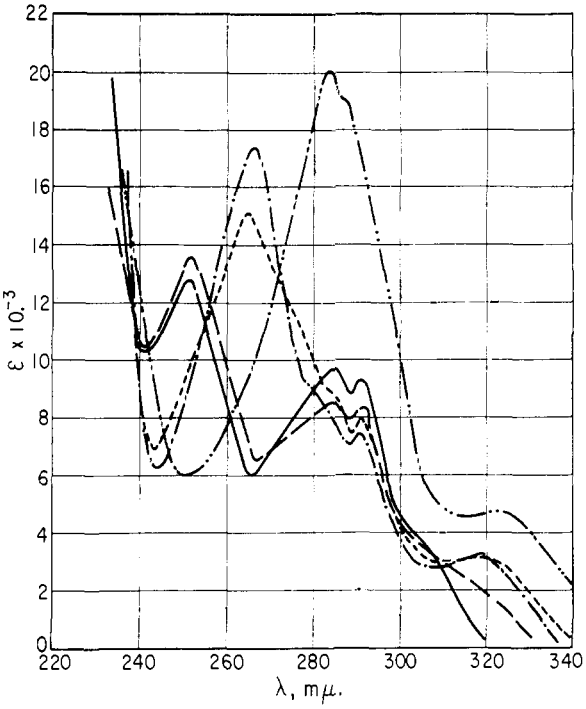


Fig. 1.—Ultraviolet absorption spectra in ethanol of geissospermine (———), dihydrodemethoxygeissospermine (— —), dihydrodemethoxyisogeissospermine (— · —), decarbomethoxyisogeissospermine (– – –), and decarbomethoxyneogeissospermine (—··—) The spectrum of decarbomethoxygeissospermine is very similar to that of dihydrodemethoxygeissospermine.

Although the ultraviolet spectrum of the alkaline ethanol solution before addition of water was similar to that of geissospermine, the precipitated alkaloidal material had a different spectrum. This material, named decarbomethoxyneogeissospermine, unfortunately was too labile to purify; on treatment with dilute acid, elution from an alumina column or even standing in neutral solution it was converted to an isomer, decarbomethoxygeissospermine, $C_{38}H_{46}N_4O$.

Since decarbomethoxygeissospermine exhibits a geissospermine type of spectrum, one is tempted to think of it as the "normal" product. However, transformations in the ester-reduced or decarbomethoxylated geissospermines are probably complex, but may be closely related, for decarbomethoxygeissospermine is converted to the isomeric decarbomethoxyisogeissospermine on treatment with lithium aluminum hydride. The ultraviolet spectral relationship of the isomers described is illustrated in Fig. 1.

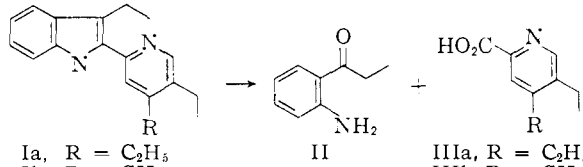
Of the various geissospermine derivatives, dihydrodemethoxyisogeissospermine and decarbomethoxygeissospermine proved particularly useful in establishing the structure of geissoschizine (see below).

Structure of Geissoschizine.—The first phase of the geissoschizine structure determination focused on getting information on the skeleton of the molecule through dehydrogenation studies. Both palladium-on-charcoal and selenium procedures were applied directly to geissochizine, and only from the

latter were useful products obtained. These were alstyrines; however, the yield was very poor and a number of closely related alstyrines appeared to have been formed. After preliminary studies indicated that dehydrogenation of readily accessible geissospermine derivatives gave much better yields, experiments were devised to ascertain whether the indoline moiety of the geissospermine derivatives might also lead to alstyrines. In common with other indoline alkaloids, no alstyrines were formed from geissoschizoline; the only products appeared to be indolic. Therefore, the alstyrines must arise from the indolic portion of the molecule, and these reactions and their products are pertinent to the structure of geissoschizine.

When dihydrodemethoxygeissospermine, or the more readily available dihydrodemethoxyisogeissospermine, was heated with selenium, in addition to alstyrines, compounds containing the indolo[2,3-a]quinolizine chromophore were formed. However, by conducting the dehydrogenation in tetrahydroquinoline, the indolo[2,3-a]quinolizines are converted to alstyrines,[10] and in this way an alstyrine, $C_{19}H_{22}N_2$, was isolated in 27% yield from dihydrodemethoxyisogeissospermine.

Although this alstyrine melted at 92–94° as compared to 106–108° reported[11] for alstyrine [3-ethyl-2-(4,5-diethyl-2-pyridyl)-indole] (Ia), its ultraviolet and infrared absorptions were practically identical with those of alstyrine, and when mixed with an authentic sample[12] there was no depression in the melting point. Since a variety of further purification steps failed to raise its melting point, this material was oxidized to the picolinoylaminophenone, which was hydrolyzed to the corresponding aminophenone and picolinic acid. The aminophenone was identified as 2-aminopropiophenone (II). The picolinic acid was shown to be 4,5-diethylpicolinic acid (IIIa) by comparison with



Ia, R = C_2H_5
Ib, R = CH_3

II

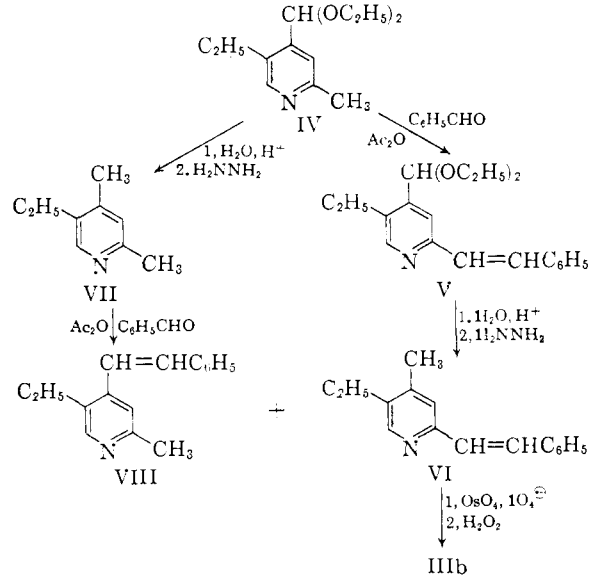
IIIa, R = C_2H_5
IIIb, R = CH_3

an authentic sample.[12] Therefore, the alstyrine obtained from dihydrodemethoxyisogeissospermine is Ia.

When decarbomethoxygeissospermine similarly was dehydrogenated, an alstyrine was isolated with the composition $C_{18}H_{20}N_2$ and an infrared spectrum very similar to that of Ia. This was oxidized and a picolinoylaminophenone, $C_{18}H_{20}N_2O_2$, was formed. Hydrolysis of this oxidation product gave 2-aminopropiophenone (II) and a new picolinic acid, $C_9H_{11}NO_2$. It was suspected that this was 4-methyl-5-ethylpicolinic acid rather than the isomeric 4-ethyl-5-methylpicolinic acid. By analogy to other indole alkaloids it was assumed that the C_{15}- rather than C_{16}-position would carry the oxygen-bearing substituents; differences in oxidation level of the C_{15}-substituent would thus account for the fact that the alstyrine produced from dihydrodemethoxyisogeissospermine bears one more carbon atom than the alstyrine produced from decarbomethoxygeissospermine.

To identify the picolinic acid, $C_9H_{11}NO_2$, positively as IIIb, 4-methyl-5-ethylpicolinic acid was synthesized from the known 2-methyl-4-diethoxymethyl-5-ethylpyridine (IV).[13] When IV was boiled with benzaldehyde and acetic anhydride, the styryl derivative V was obtained, and this was converted to 2-styryl-4-methyl-5-ethylpyridine (VI) by hydrolysis followed by reduction. However, the over-all yields were poor.

In another approach to VI, Wolff–Kishner reduction of the aldehyde obtained on hydrolysis of IV gave 2,4-dimethyl-5-ethylpyridine (VII). Treatment of VII with benzaldehyde and acetic anhydride gave VI, along with the isomeric 2-methyl-4-styryl-5-ethylpyridine (VIII). This route was found to be preferable for preparing VI, which was then oxidized with the osmium tetroxide–periodate reagent[14] followed by further oxidation with hydrogen peroxide to give IIIb.



The synthetic 4-methyl-5-ethylpicolinic acid was shown to be identical to the picolinic acid IIIb obtained from degradation of decarbomethoxygeissospermine by m.p., mixed m.p., and comparison of the infrared absorption and X-ray diffraction patterns.

The implication of the alstyrine dehydrogenation product obtained from decarbomethoxygeissospermine is that the partial skeletal structure of the indolic portion of geissospermine as well as that of the indolic cleavage products, geissoschizine and apogeissoschizine, can be represented by IX. Isolation of alstyrine itself from dihydrodemethoxyisogeissospermine permits extension of IX to X, leaving only one carbon atom unaccounted for.

We next turned to geissoschizine itself and to some of its derivatives for details of the peripheral

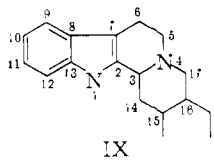
(10) N. A. Hughes and H. Rapoport, THIS JOURNAL, **80**, 1604 (1958).

(11) P. Karrer and P. Enslin, *Helv. Chim. Acta*, **32**, 1390 (1949).

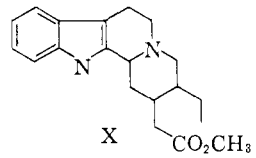
(12) Synthetic sample supplied by Dr. G. A. Swan, King's College, Newcastle upon Tyne, England, to whom we are very grateful.

(13) F. D. Popp and W. E. McEwen, THIS JOURNAL, **80**, 1181 (1958).

(14) R. Pappo, D. S. Allen, Jr., R. U. Lemieux and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).



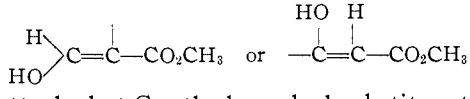
IX



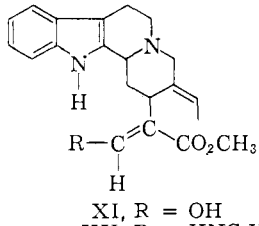
X

groups. Missing from structure X is a carbon atom, an oxygen atom and two degrees of unsaturation, probably double bonds.

Besides the carbonyl band at 5.95 μ, the infrared spectrum of geissoschizine exhibits two sharp bands at 3.03[15] and 2.90 μ which are shifted to 4.00 and 3.83 μ, respectively, after deuteration in deuterium methoxide. The band at 2.90 μ is indicative of an indole NH, whereas the band at 3.03 μ, because of the acidic properties of geissoschizine, was assumed to be due to an enolic OH. From the rather unusual ester carbonyl absorption, it would appear likely that a substituent of the type



was attached at C_{15}, the branched substituent being preferred since it would account for the almost completely enolic character of geissoschizine. Thus XI was selected as the most probable structure, the ethylidene group at C_{16} having been established by isolation of acetaldehyde after ozonolysis. Confirmation for the ethylidene group was provided by C-methyl determinations on geissoschizine before and after hydrogenation. In both cases, one such group was found, consisting only of acetic acid from the former and of a mixture of acetic and propionic acids from the latter.



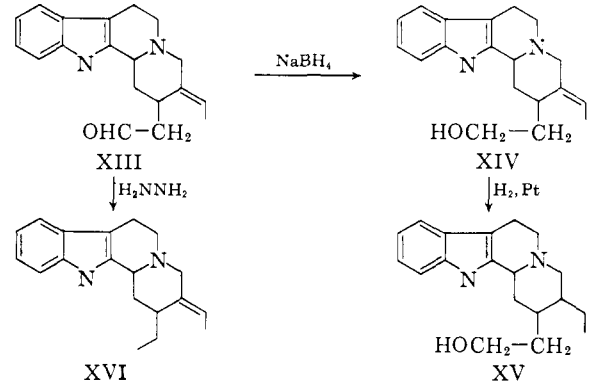
XI, R = OH
XII, R = HNC_6H_5

In XI two isolated chromophores are present; one of these, the indole chromophore, exhibits only minor changes on addition of acid or base, whereas the enol ester, capable of forming an anion in base, should exhibit large spectral changes. If this postulate were true then the spectrum of geissoschizine should be approximated by adding the spectrum of an indole to that of ethyl acetoacetate. This was indeed the case. In 0.1 *N* ethanolic alkali, geissoschizine had a λ_{max} at 277 mμ (ϵ 24,200), ethyl acetoacetate at 273 mμ (ϵ 24,300), and ethyl acetoacetate plus alloyohimbine (calcd. value) at 274 mμ (ϵ 30,000). In ethanol alone, geissoschizine still showed a very strong contribution from the enolate ion.

Although the C_{15}-substituent in geissoschizine appears to be almost completely enolic, it does give carbonyl derivatives. On heating with aniline, the anilinoacrylic ester XII was obtained; it exhibited a carbonyl band at 6.11 μ in the infrared and had an ultraviolet spectrum in agreement with XII.

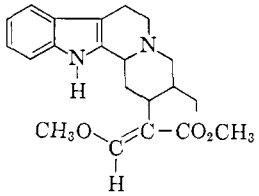
(15) Incorrectly reported as 3.30 μ, ref. 1.

When geissoschizine was boiled in dilute acid, carbon dioxide was evolved and an amorphous aldehyde (XIII) was obtained. Reduction of the aldehyde with sodium borohydride gave the carbinol XIV in good yield. The C-methyl data for XIV, in agreement with one such group, eliminate the possibility of the substituent at C_{15} being straight chain, *i.e.*, β-ketoester instead of β-aldehydoester, since this would require the presence of two C-methyl groups in XIV. Wolff–Kishner reduction of XIII



proceeded as expected to give a product, XVI, which contained two C-methyl groups. When XVI was dehydrogenated with palladium-on-carbon, one mole of hydrogen was evolved and alstyrine Ia was formed.

These reactions clearly and uniquely establish the structure of geissoschizine as XI, and attention then was turned to the stereochemistry of the molecule. From XI it can readily be seen that only two optically active centers are present; one of these, at C_{15}, is presumably the same in all known indole alkaloids.[16] Since it has been shown[17] that dihydrocorynantheine (XVIIa) has the stereochemical relationship 3:15:16, *cis-trans-*, and corynantheidine (XVIIb) the relationship 3:15:16, *cis-cis-*, it should be possible to convert geissoschizine to one of these naturally occurring alkaloids if the stereochemistry of geissochizine were C_3:C_{15}, *cis-*. Hydrogenation of the ethylidene group in geissoschizine would then generate a new optical center at C_{16}, and this center would be related to the C_3- and C_{15}-centers as the C_{16}-center in XVIIa or XVIIb. Since, however, the ethylidene double bond in geissoschizine itself cannot be selectively hydrogenated, this would have to be done on some derivative.



XVIIa, C_3:C_{15}:C_{16}, *cis-trans-*
XVIIb, C_3:C_{15}:C_{16}, *cis-cis-*

The carbinol XV was considered for stereochemical comparison purposes since the corresponding carbinols, corynantheidol and dihydro-

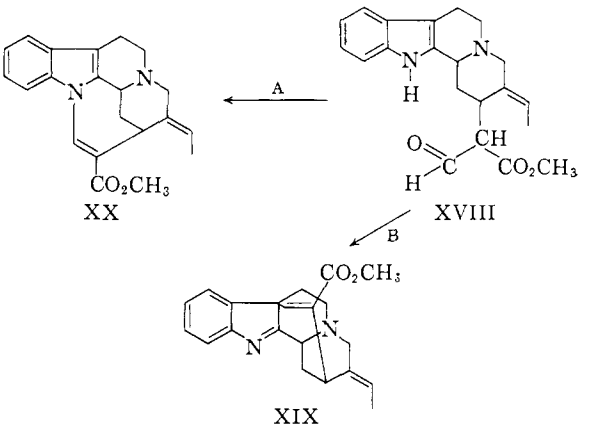
(16) E. Wenkert and N. V. Bringi, THIS JOURNAL, **80**, 3484 (1958)
(17) E. E. van Tamelen, P. E. Aldrich and T. J. Katz, *Chemistry & Industry*, 793 (1956).

corynantheol, were already known.[18] Samples of dihydrocorynantheol and corynantheidol were obtained,[19] and the specific rotations of XV in ethanol and in pyridine suggest that it is identical to corynantheidol.[19,20] However, there were sufficient differences in the specific rotations of XV and corynantheidol to cause some doubt. Although the infrared spectra differ slightly, the differences suggest that one or both compounds have retained traces of impurities. The mixed melting point of XV and corynantheidol shows no depression, but this may be unreliable since the mixed melting point of corynantheidol and dihydrocorynantheol shows only a small depression. Further efforts to make the comparison were hampered since no corynantheidine was available for preparation of a highly purified sample of corynantheidol.

Structure of Apogeissoschizine.—In writing plausible structures for apogeissoschizine, the possibilities were greatly narrowed by the elucidation of the structure of geissoschizine and by the close interrelationships between the two compounds. When apogeissoschizine was dissolved in concentrated hydrochloric acid, a significant conversion to geissoschizine was observed; at the same time the rate of conversion was far too slow to cause any doubts about geissoschizine and apogeissoschizine being simultaneously formed during the acid cleavage of geissospermine.[3] When the reverse reaction was attempted, no conversion of geissoschizine to apogeissoschizine was noted.[21] This facile conversion of apogeissoschizine to geissoschizine by addition of a molecule of water indicated the compounds must have very similar structures. However, the great difference in ultraviolet absorption and specific rotation (377°) suggested that this relationship has some unique features.

Apogeissoschizine still retains the ethylidene group at C_{16} since on ozonolysis acetaldehyde is formed. However, it is free of active hydrogen since no exchange was noted in deuterium methoxide. Therefore, we considered apogeissoschizine as arising from the β-formyl ester tautomer of geissoschizine (XVIII) by condensation of the aldehydro-carbon at either the 1- or 3-position of the indole nucleus followed by loss of one mole of water.

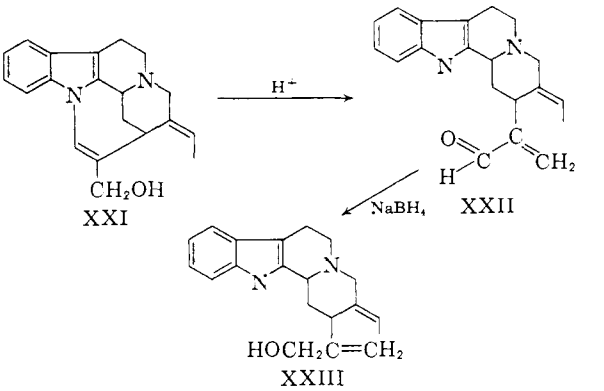
Path B is ruled out by spectral evidence; XIX would possess an indolenine ultraviolet spectrum and exhibit a shift in acid since both nitrogens would be basic. These are properties not associated with apogeissoschizine, which possesses only one basic nitrogen (*pK* 7.7 in 50% aq. ethanol; *cf.* geissoschizine, *pK* 7.4) and has a unique ultraviolet spectrum only slightly affected by acid. There is,



however, no evidence against XX and, as will be shown, XX is the structure of apogeissoschizine.

Lithium aluminum hydride reduction of apogeissoschizine gave the carbinol XXI whose ultraviolet spectrum is somewhat similar to that of apogeissoschizine. When XXI was dissolved in acid, a change in the ultraviolet absorption from that of XXI to an indole was noted; the change was irreversible. On repeating the reaction on a preparative scale an amorphous aldehyde, XXII, with carbonyl absorption at 5.93 μ, was isolated but this could not be purified and the usual carbonyl derivatives were not crystalline.

Reduction of the aldehyde XXII with sodium borohydride led to the crystalline carbinol XXIII. In the series of compounds XXI, XXII, XXIII, the positions of the double bonds are strongly indicated as shown by the following evidence: in XXI the double bonds are essentially limited to the structure shown by spectral and steric considerations. In XXII and XXIII the presence of only one C-methyl group eliminates the possibility of the methylene double bond having migrated into conjugation with the ethylidene double bond. The ultraviolet absorption of XXIII rules out a butadiene type chromophore, which would result from migration of the ethylidene double bond, since the expected strong maximum at 230–240 mμ is completely absent. Both XXII and XXIII exhibit an indole NH band in the infrared.



As was mentioned earlier, the great differences in the specific rotations of apogeissoschizine and geissoschizine, −262° and +115°, respectively, caused some concern. The fact that the specific rotations of XXI and XXIII were both positive

(18) C. Vamvacas, W. v. Phillipsborn, E. Schlittler, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **40**, 1793 (1957).

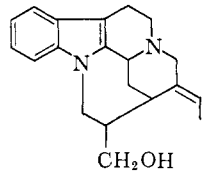
(19) The sample of dihydrocorynantheol was supplied by Dr. E. Wenkert, Iowa State College, Ames, Iowa, and the sample of corynantheidol by Dr. P. Karrer, University of Zurich, Zurich, Switzerland.

(20) In a recent communication [F. Puisieux, R. Goutarel, M. M. Janot and A. LeHir, *Compt. rend.*, **249**, 1369 (1959)] it was reported that XV and cornantheidol are identical but no details were presented.

(21) In one experiment a small amount of material possessing an ultraviolet absorption similar to that of apogeissoschizine was obtained. The results were not reproducible. Further, there was no trace of apogeissoschizine formed when geissoschizine was dissolved in liquid hydrogen fluoride or in warm polyphosphoric acid.

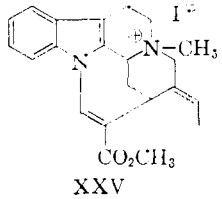
indicates that the large difference was caused by the presence of the polar carbomethoxyvinyl function of apogeissoschizine near the optical centers rather than a difference in configuration at C_3 or C_{15}.

When apogeissoschizine was reduced with sodium in ethanol, a crystalline carbinol, $C_{20}H_{24}N_2O$, was isolated which had the properties expected for XXIV. In the infrared there was hydroxyl absorption at 2.77 μ but no indole NH band; the ultraviolet spectrum was indolic.

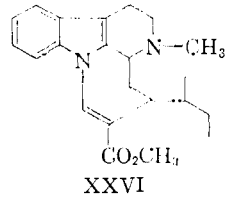


XXIV

These studies of apogeissoschizine were completely consistent with structure XX, and all that remained was positive identification of its unique ultraviolet chromophore. Therefore, attention was turned to the synthesis of model compounds which possessed the chromophores present in apogeissoschizine and its derivatives. Since the apogeissoschizine molecule is strained, it seemed worthwhile to relieve the strain and observe the resulting effects on the spectrum. Complete relief of the strain could not be achieved since no convenient method of breaking the bond of the seven-membered ring at C_{15} was available. However, cleavage of the N_4–C_{17} bond should partially relieve the strain in the apogeissoschizine system. This was achieved by converting apogeissoschizine to the methiodide XXV, and reducing this with platinum as catalyst in ethanol. There was a rapid two-mole hydrogen pickup to give the Emde product XXVI whose ultraviolet spectrum differed only slightly from that of apogeissoschizine. It was not possible to obtain XXVI in crystalline form or to prepare crystalline derivatives, possibly due to nonstereoselective hydrogenation. It might be further mentioned that the acrylic double bond of apogeissoschizine or the corresponding double bond in XXVI cannot be catalytically reduced without concurrent reduction of the indole moiety.



XXV



XXVI

The chromophore of XXI is considerably simpler than that of apogeissoschizine and should be similar to that of the known N-vinyltetrahydrocarbazole.[22] Comparison of the two spectra (Fig. 2) shows that this conclusion is correct.

The first attempts to prepare a model of the apogeissoschizine chromophore itself involved addition of appropriate unsaturated compounds to tetrahydrocarbazole and other indoles. All of these

(22) G. R. Clemo and W. H. Perkin, *J. Chem. Soc.*, **125**, 1804 (1924).

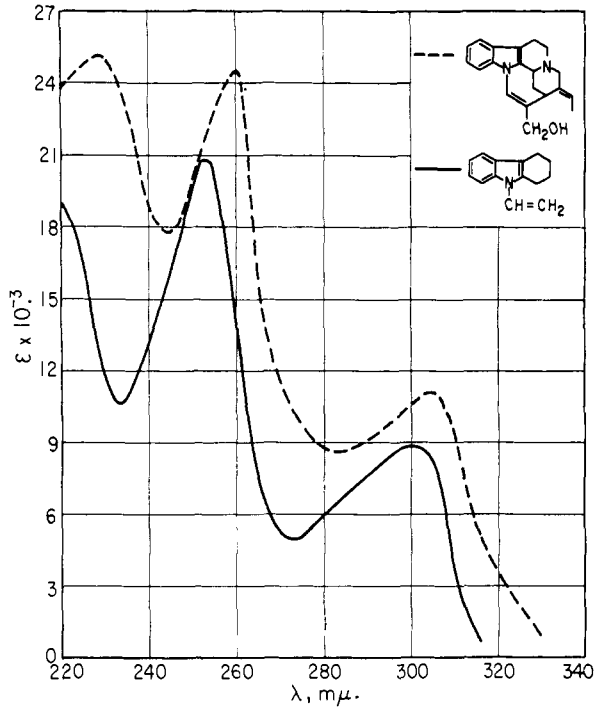
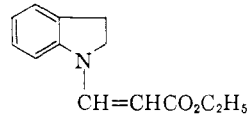
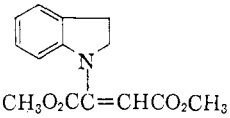


Fig. 2.—Ultraviolet absorption spectra in ethanol of dihydrodemethoxyapogeissoschizine (XXI) (– – –) and N-vinyltetrahydrocarbazole (———).

were unsuccessful under a large variety of conditions. However, indoline reacted readily with ethyl propiolate and dimethyl acetylenedicarboxylate to give XXVII and XXVIII, respec-



XXVII



XXVIII

tively. But neither compound could be dehydrogenated to the corresponding indole derivative.

Although unsuccessful, these experiments defined what was needed to prepare the desired chromophore. An indoline was sought which contained a substituent in the 3-position that could be eliminated, along with a hydrogen atom from the 2-position, after addition of ethyl propiolate to the nitrogen atom. Such a compound, 4a-hydroxy-1,2,3,4,-4a,9a-hexahydrocarbazole (XXIX), seemed to be ideal since it is readily dehydrated to tetrahydrocarbazole on boiling with picric acid in ethanol.[23]

A series of compounds (XXXa, b, c) was prepared by addition of ethyl propiolate, dimethyl acetylenedicarboxylate and diethyl ethoxymethylenemalonate to the hexahydrocarbazole XXIX. These were dehydrated to the corresponding indoles XXXIa, b, c, whose ultraviolet spectra are shown in Fig. 3. Both XXXIb and XXXIc differ somewhat from apogeissoschizine. In both, the effect of the second carboalkoxy group would be expected to be weak and cause only a slight bathochromic shift, since conjugation is inhibited on steric grounds. Although the expected bathochromic shift appears, the lowered extinction coef-

(23) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 2188 (1951).

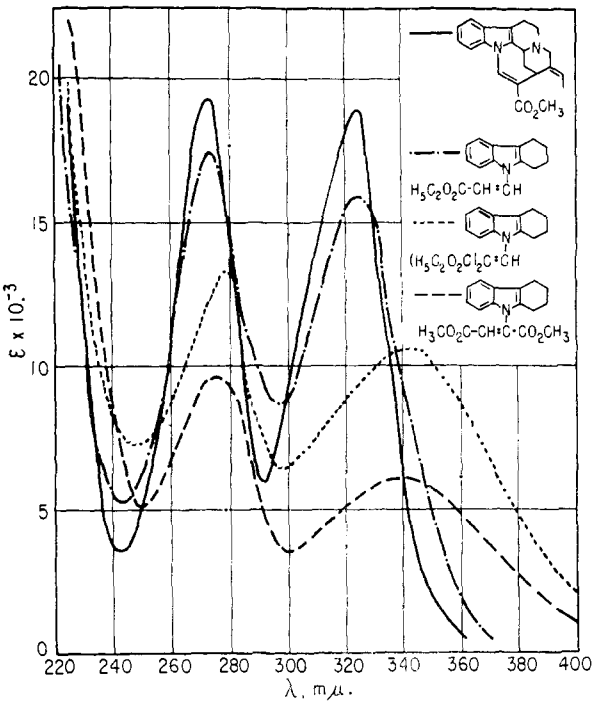
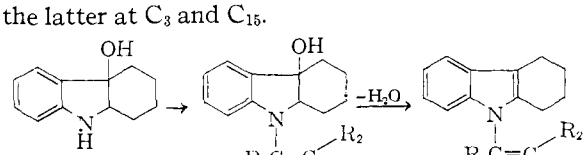


Fig. 3.—Ultraviolet absorption spectra in ethanol of apogeissoschizine (XX) (———), N-(2-carbethoxyvinyl)-tetrahydrocarbazole (XXXa) (— · —), N-(2,2-dicarbethoxyvinyl)-tetrahydrocarbazole (XXXc) (.....) and N-(1,2-dicarbomethoxyvinyl)-tetrahydrocarbazole (XXXb) (– – –).

ficients would suggest that conjugation of the nitrogen substituent in these compounds with the indole ring is strongly hindered. The infrared spectra support this conclusion for in XXXIb the carbonyl band occurs at 5.85 μ and in XXXIc carbonyl absorption occurs at 5.83 μ.

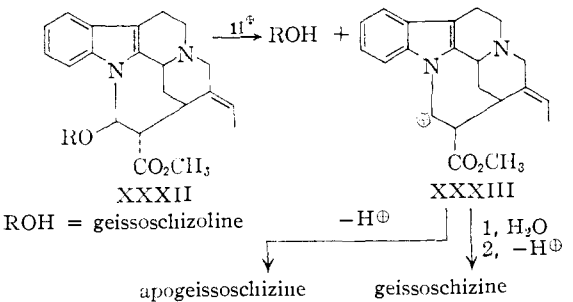
However, XXXIa, which is the nearest analog of apogeissoschizine (XX), has a very similar ultraviolet spectrum. Also, the carbonyl absorption of XXXIa, at 5.94 μ, is the same as that of apogeissoschizine.

When considered together with the degradative evidence presented previously, these spectral data establish XX as the structure of apogeissoschizine beyond any doubt. Its conversion to geissoschizine also indicates the same stereochemistry as for the latter at C_3 and C_{15}.



a: R_1, R_2 = H; R_3 = $CO_2C_2H_5$
b: R_1, R_2 = CO_2CH_3; R_3 = H
c: R_1 = H; R_2, R_3 = $CO_2C_2H_5$

Implications on the Structure of Geissospermine.—From work previously published on geissoschizoline,[3] it is known that this alkaloid contains both an indoline NH and an OH. Assuming the indoline and indole moieties of geissospermine are indeed linked *via* an ether bridge, as seems most likely, then XXXII would be in agreement with most of the known properties of geissospermine. The ether bridge would be labile and the carbonium ion XXXIII formed in acid could readily lead to both geissoschizine and apogeissoschizine. Several questions remain to be answered, however, such as the various isomerizations in the ester-reduced and



decarbomethoxylated derivatives of geissospermine. These are undoubtedly primarily concerned with the geissoschizoline portion of the molecule and should become clear as studies on the structure of geissoschizoline are completed.

Experimental[24]

Dihydrodemethoxygeissospermine.—A 1.40-g. sample of anhydrous geissospermine was suspended in 30 ml. of liquid ammonia without any special precautions being taken to exclude atmospheric moisture. With stirring, 230 mg. of sodium, in small portions, was added and after 45 minutes methanol was added to decompose the excess sodium. After the solvent had evaporated to about 10 ml., 100 ml. of water was cautiously added and this mixture was extracted with four 100-ml. portions of benzene. From the benzene extracts on concentration was obtained 1.38 g. of a residue which no longer exhibited carbonyl absorption in the infrared. This material was crystallized several times from ethyl acetate and then from ethanol–water (3:2) to give dihydrodemethoxygeissospermine in 56% yield, m.p. 182–184°, $[\alpha]_D$ −107°; ultraviolet absorption: λ_{max} 252 (ϵ 13,500), 285 (8,500), 292 (8300).

Anal. Calcd. for $C_{39}H_{48}N_4O_2 \cdot {}^1/_2H_2O$: C, 76.3; H, 8.0; N, 9.1; O, 6.5; (2) CCH_3, 4.9; equiv. wt., 307. Found: C, 76.0; H, 7.9; N, 9.4; O, 6.7; CCH_3, 4.3; equiv. wt., 308.

Dihydrodemethoxyisogeissospermine. A. From Geissospermine.—To a stirred solution of 60 ml. of 0.85 *M* lithium aluminum hydride in tetrahydrofuran under a nitrogen atmosphere was added, over a period of 10 minutes, a solution of 2.50 g. of anhydrous geissospermine in 100 ml. of tetrahydrofuran. This mixture was subsequently boiled for 10 hours and then cooled in an ice-bath and treated cautiously with 200 ml. of water to decompose the excess hydride. After 200 ml. of chloroform was added, the mixture was filtered, the filtered solids were washed well with chloroform, and the chloroform extracts were concentrated to dryness on the steam-bath to give 2.44 g. of residue. A hot solution of this residue in 70 ml. of isopropyl alcohol was filtered, diluted with 200 ml. of acetone and set aside to crystallize in the cold. The resulting crystals of dihydrodemethoxyisogeissospermine were washed with acetone and dried; yield 2.30 g. (90%), m.p. 182–184, mixed m.p with dihydrodemethoxygeissospermine (m.p. 182–184°) 166–180°, $[\alpha]_D$ −86° (reported[5] for the hemi-ethanolate, m.p. 180–182°, $[\alpha]_D$ −82°); ultraviolet absorption: λ_{max} 266 (ϵ 17,400), 291 (7,450), 319 (3,300).

Anal. Calcd. for $C_{39}H_{48}N_4O_2$: C, 77.5; H, 8.0; N, 9.3; O, 5.3; (2)CCH_3, 5.0; equiv. wt., 302. Found: C, 77.5; H, 8.5; N, 9.3; O, 6.0; CCH_3, 4.1; equiv. wt., 301.

B. **From Dihydrodemethoxygeissospermine.**—To 25 ml. of 0.15 *M* lithium aluminum hydride solution in tetrahydro-

(24) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Optical rotations were measured on 1% solutions in ethanol in one decimeter tubes at 25°, infrared spectra were taken in chloroform, and ultraviolet spectra were taken in ethanol, unless otherwise specified.

furan was added 50 mg. of dihydrodemethoxygeissospermine and this was boiled for 20 hours under a nitrogen atmosphere. The resulting solution then was cooled, treated with methanol to decompose the excess hydride, and extracted with four 75-ml. portions of chloroform. Concentration of the filtered chloroform extracts gave 48 mg. of a residue which, after crystallization from acetone–isopropyl alcohol, melted at 182–184°. It was identical with dihydrodemethoxyisogeissospermine in the ultraviolet, in the infrared, and by mixed m.p.

A sample of dihydrodemethoxyisogeissospermine, after crystallization from ethyl acetate, melted at 177–180° (reported[7] m.p. for "dihydrogeissospermine," 178–180°) and exhibited a strong carbonyl band at 5.76 μ. This material is the hemi-ethyl acetate solvate (Calcd. for $C_{39}H_{48}N_4O_2 \cdot {}^1/_2EtOAc$: C, 75.8; H, 8.1. Found: C, 75.3; H, 8.4). By dissolving this solvate in chloroform, evaporating the solution to dryness, and crystallizing the residue from acetone–isopropyl alcohol (4:1), solvent-free and carbonyl-free dihydrodemethoxyisogeissospermine resulted, m.p. 182–184°.

Decarbomethoxygeissospermine.—A 2 *N* solution of potassium hydroxide in ethanol (250 ml.), through which nitrogen had been bubbled for several hours, was boiled with 1.0 g. of geissospermine in a nitrogen atmosphere for 4 hours. At this point the solution had an ultraviolet absorption very similar to that of geissospermine. The cooled mixture was diluted with 700 ml. of 10% aqueous potassium carbonate and then was extracted with chloroform. Evaporation of the chloroform left 890 mg. of a solid, characterized as **decarbomethoxyneogeissospermine** by its ultraviolet spectrum: λ_{max} 284 (ϵ 20,100), 323 (4,800). This residue then was dissolved in a small amount of benzene and adsorbed on an alumina column after which one liter of benzene was passed through, followed by elution with 20:1 benzene–chloroform. The resulting eluate was evaporated and the residue was dissolved in the minimum amount of chloroform, followed by dilution with 150 ml. of ether. Slow concentration induced crystallization, and after two further crystallizations there was isolated 750 mg. (78% yield) of decarbomethoxygeissospermine, m.p. 254–255°; ultraviolet absorption: λ_{max} 253 (ϵ 13,500), 285 (8,700), 291 (8,400).

Anal. Calcd. for $C_{38}H_{46}N_4O$: C, 79.4; H, 8.1; N, 9.7; equiv. wt., 287. Found: C, 79.1; H, 8.1; N, 9.8; equiv. wt., 286.

By determining the amount of carbonate formed and the rate at which infrared carbonyl absorption in alkaloidal material disappeared, it was shown that decarbomethoxylation was essentially complete under the above conditions. Addition of phosphoric acid to a parallel reaction mixture which had been boiled for 4 hours resulted in the liberation of 98 mole % of carbon dioxide.

Decarbomethoxyisogeissospermine.—To a solution of 500 mg. of decarbomethoxygeissospermine in 60 ml. of purified tetrahydrofuran was cautiously added 1.0 g. of powdered lithium aluminum hydride and this was then boiled for 18 hours. After the hydride was carefully decomposed with methanol, 200 ml. of water and 200 ml. of chloroform were added, the mixture was filtered, and the precipitate was digested with chloroform. The chloroform phases were combined and concentrated and the residue was crystallized three times from benzene–chloroform. Decarbomethoxyisogeissospermine thus was obtained in 60% yield (300 mg.), m.p. 240–241°; ultraviolet absorption: λ_{max} 265 (ϵ 15,100), 291 (8,000), 318 (3,200).

Anal. Calcd. for $C_{38}H_{46}N_4O$: C, 79.4; H, 8.1; N, 9.7; equiv. wt., 287. Found: C, 79.1; H, 8.0; N, 9.9; equiv. wt., 282.

Selenium Dehydrogenation of Dihydrodemethoxyisogeissospermine.—A mixture of 2 g. of dihydrodemethoxyisogeissospermine, 4 g. of selenium and 2 ml. of tetrahydroquinoline was placed in a dehydrogenation apparatus equipped with condenser and gas inlet and outlet. The lower part of the apparatus was placed in a salt-bath maintained at 270°, and the mixture was heated for 40 minutes as a slow steam of nitrogen was passed over it. The mixture was then cooled and extracted thoroughly with chloroform, the combined chloroform extracts were filtered and evaporated, and the residue was dissolved in 150 ml. of ether. After the ether phase was washed with two 150-ml. portions of 0.2 *M* phosphoric acid, the ether was evaporated, and the residue, dissolved in 15 ml. of absolute ethanol, was treated with a satd. ethanolic solution of picric acid until precipitation of the picrate ceased. The free base was regenerated by passing the picrate through an alumina (Merck) column with 1:1 chloroform–benzene. Evaporation of the chloroform–benzene left 440 mg. of a residue which was chromatographed on alumina. Elution with hexane removed a small amount of indolic material, and benzene then removed the alstyrine. Several crystallizations from hexane followed by sublimation at 90° (10 μ) gave **alstyrine** [3-ethyl-2(4,5-diethyl-2-pyridyl)-indole] (Ia), m.p. 92–94°, yield 250 mg., 27%. The m.p. of this material was unchanged by further chromatography and crystallizations from hexane.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 82.0; H, 8.0. Found: C, 81.7; H, 7.7.

The picrate was prepared with ethanolic picric acid and was recrystallized from acetone–ethanol; m.p. 212–214°, undepressed by admixture with authentic alstyrine picrate,[25] m.p. 214–217°.

***o*-(4,5-Diethylpicolinoylamino)-propiophenone** was formed when a solution of 225 mg. of alstyrine in 2.5 ml. of acetic acid and 1.5 ml. of 30% hydrogen peroxide was allowed to stand overnight. The resulting crystals, on recrystallization from methanol–water, melted at 88–89° (reported[26] m.p. 82–83°).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.5; H, 7.2. Found: C, 73.6; H, 7.1.

Hydrolysis of *o*-(4,5-Diethylpicolinoylamino)-propiophenone.—After a solution of 195 mg. of the picolinoylaminophenone in 7 ml. of 10 *N* sulfuric acid had been boiled for 4 hours, it was cooled and the *p*H was raised to 9.5 by addition of sodium carbonate. Extraction with three 40-ml. portions of ether removed 75 mg. of an oil (II) which was benzoylated with benzoyl chloride in pyridine. **The 2-benzoylaminopropiophenone** formed (67 mg.) melted at 126–128° and did not depress the m.p. of an authentic sample[10] (m.p. 128–129°).

The aqueous phase was adjusted to *p*H 4 with sulfuric acid and was extracted continuously for 18 hours with ether. Evaporation of the ether, sublimation of the residue (80° (80 μ)), and crystallization of the sublimate from benzene–hexane (5:1) gave 31 mg. of **4,5-diethylpicolinic acid (IIIa)**, m.p. 142–145°. This material was identical in m.p. (unchanged on mixing), ultraviolet and infrared absorption, and X-ray diffraction pattern to an authentic sample.[12]

Selenium Dehydrogenation of Decarbomethoxygeissospermine.—This reaction was carried out exactly as described for dihydrodemethoxyisogeissospermine above. From 2 g. of starting material there resulted 310 mg. (30%) of **demethylalstyrine** [3-ethyl-2-(4-methyl-5-ethylpyridyl)-indole] (Ib), m.p. 109–110°.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.8; H, 7.6. Found: C, 81.5; H, 7.7.

Oxidation of demethylalstyrine (Ib) was performed exactly as described above for alstyrine. The ***o*-(4-methyl-5-ethylpicolinoylamine)-propiophenone** was crystallized from methanol–water and melted at 103–105°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 73.0; H, 6.8. Found: C, 73.0; H, 6.6.

Hydrolysis of *o*-(4-methyl-5-ethylpicolinoylamine)-propiophenone paralleled the procedure used for the diethyl compound above. The basic portion was converted to **2-benzoylaminopropiophenone**, m.p. 127–129°, identical with the previous sample.

The picolinic acid was identical with a synthetic sample of **4-methyl-5-ethylpicolinic acid (IIIb)** prepared below; m.p. 146–154°.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.4; H, 6.7. Found: C, 65.8; H, 6.8.

2-Styryl-4-diethoxymethyl-5-ethylpyridine (V).—A mixture of 2.2 g. of 2-methyl-4-diethoxymethyl-5-ethylpyridine (IV),[13] 2.2 g. of benzaldehyde and 2.2 ml. of acetic anhydride was boiled for 40 hours under a nitrogen atmosphere. After the mixture had been cooled, the acid was neutralized with satd. aqueous sodium carbonate and this was then extracted with ether. Extraction of the ether phase with 30 ml. of 1

(25) Prepared from a sample of alstyrene, m.p. 103–105°, very kindly supplied by Dr. H. B. MacPhillamy, Ciba Pharmaceutical Products, Inc., Summit, N. J.

(26) P. Karrer, R. Schwyzer and A. Flam, *Helv. Chim. Acta*, **35**, 851 (1952).

N sulfuric acid removed the organic bases which were liberated by treating the acid solution with sodium hydroxide. The bases were taken up in ether; concentration gave 1.73 g. of a brown liquid. This was chromatographed on alumina (100 g.) using hexane and later benzene–chloroform as eluents. The main fraction was dissolved in 30 ml. of hot ethanol to which an excess of picric acid was added. After crystallization was complete, the picrate was collected and was recrystallized from ethanol, giving 1.02 g., melting at 179–225°.

Anal. Calcd. for $C_{20}H_{25}O_2N$: C, 57.8; H, 5.2; N, 10.4. Found: C, 58.1; H, 5.0; N, 10.1.

2-Styryl-5-ethylpyridine-4-carboxaldehyde.—A solution of 500 mg. of 2-styryl-4-diethoxymethyl-5-ethylpyridine (V) in 15 ml. of 10% hydrochloric acid was boiled for 3 hours, cooled, diluted with water, neutralized with excess sodium carbonate and extracted with chloroform. Concentration of the extract gave 430 mg. of crude aldehyde; λ_{CO} 5.89 μ; λ_{max} 313 mμ. This aldehyde was not further purified. It formed a 2,4-dinitrophenylhydrazone which melted at 248–249° after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{19}N_5O_4$: C, 63.3; H, 4.6; N, 16.8. Found: C, 63.5; H, 4.7; N, 16.6.

2,4-Dimethyl-5-ethylpyridine (VII).—A solution of 4.33 g. of 2-methyl-4-diethoxymethyl-5-ethylpyridine (IV) was boiled in 50 ml. of 10% hydrochloric acid for 3 hours under nitrogen and then cooled and swirled into excess aqueous sodium carbonate with 50 ml. of chloroform. Concentration of the chloroform layer (combined with subsequent chloroform extracts) gave an oil which was reduced by the modified Wolff–Kishner procedure.[27] The reduction mixture was then cooled, combined with the material distilled from the diethylene glycol solution, diluted with 100 ml. of water and extracted with ether. The ether extract was washed with dilute sodium carbonate solution, dried over anhydrous potassium carbonate and concentrated. Distillation of the concentrate gave 2.03 g. of 2,4-dimethyl-5-ethylpyridine, b.p. 66–68° (12.5 mm.). The base formed a picrate, m.p. 155–157° after recrystallization from ethanol.

Anal. Calcd. for $C_9H_{13}N \cdot C_6H_3N_3O_7$: C, 49.5; H, 4.4; N, 15.0. Found: C, 49.6; H, 4.4; N, 15.0.

2-Styryl-4-methyl-5-ethylpyridine (VI) and 2-Methyl-4-styryl-5-ethylpyridine (VIII).—A solution of 2.03 g. of 2,4-dimethyl-5-ethylpyridine, 4 ml. of acetic anhydride and 4 ml. of benzaldehyde was boiled for 4 days under a nitrogen atmosphere. This was cooled, diluted with 50 ml. of ether, and extracted twice with 100-ml. portions of 1 *N* sulfuric acid. The acidic extract was washed once with ether and mixed with excess 1 *N* sodium hydroxide, and the liberated base was taken up in chloroform. Concentration of this chloroform solution gave 1.46 g. of a brown gum. When this gum was chromatographed on 100 g. of alumina using hexane–benzene as eluent, there were obtained three fractions: (1) 768 mg., (2) 178 mg. of an intermediate fraction, (3) 236 mg. The first fraction was mostly **2-styryl-4-methyl-5-ethylpyridine** (λ_{max} 311 mμ) and formed a **picrate**, m.p. 267–269° after crystallization from methanol. It was identical with the picrate of an authentic sample prepared by Wolff–Kishner reduction[21] of 2-styryl-5-ethylpyridine-4-carboxaldehyde.

Anal. Calcd. for $C_{16}H_{17}N_3O_7$: C, 58.4; H, 4.4; N, 12.4. Found: C, 58.7; H, 4.5; N, 12.5.

The third fraction was mostly **2-methyl-4-styryl-5-ethylpyridine** (λ_{max} 302 mμ) and formed a **picrate**, m.p. 259–260° after crystallization from ethanol.

Anal. Found: C, 58.5; H, 4.6; N, 12.3.

4-Methyl-5-ethylpicolinic Acid (IIIb).—To a flask containing 231 mg. of 2-styryl-4-methyl-5-ethylpyridine in 10 ml. of ether and 10 ml. of 0.25 *M* aqueous sodium periodate solution was added 12 mg. of osmium tetroxide dissolved in 2 ml. of ether. This mixture was stirred for 10 hours after which an additional 10 mg. of tetroxide was added; after a further 12-hour stirring, the ultraviolet spectrum indicated that starting material had been completely consumed. The ether layer was combined with subsequent ether extracts of the aqueous phase and these were in turn extracted with 1 *N* sulfuric acid. After it has been extracted with ether, the acid solution was mixed with excess sodium carbonate solution and the resulting oil taken up in ether. Concentration of this ether solution gave 121 mg. of crude 4-methyl-5-ethylpyridine-2-carboxaldehyde which was immediately dissolved in a mixture of 1.4 ml. of acetic acid and 0.8 ml. of 30% hydrogen peroxide. After standing for 15 hours, this solution was diluted with 20 ml. of water. Extraction of this with ether gave 5 mg. of a gum which was discarded. The acidity of the aqueous solution was now raised to *p*H *ca.* 1 by adding sulfuric acid. Continuous extraction with ether for 12 hours not only removed the acetic acid, but unexpectedly most of the picolinic acid as well. The picolinic acid was freed of acetic acid by evaporation *in vacuo*. This residue (124 mg.) was sublimed (70° (50 μ)) and the sublimate was crystallized from 1:4 benzene–hexane to give 77 mg. of 4-methyl-5-ethylpicolinic acid, melting at 156–158°.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.1; H, 6.5; N, 8.3.

Ozonolysis of Geissoschizine (XI) and Apogeissoschizine (XX).—Over a period of 0.5 hour, 7 liters of oxygen containing 1% ozone was passed into an ice-cooled solution of 100 mg. of geissoschizine in 20 ml. of purified 2% acetic acid. Excess ozone was then removed by bubbling in a stream of nitrogen. Finally the solution was heated on the steam-bath and the nitrogen stream was bubbled into a filtered solution of 15 ml. of 5% *p*-nitrophenylhydrazine hydrochloride solution until precipitation stopped. The precipitate was collected, dried and sublimed three times *in vacuo* and finally recrystallized from ethanol–water to give acetaldehyde *p*-nitrophenylhydrazone, m.p. 123–126°. This material showed no melting point depression on admixture with authentic material.

Repetition of the preceding experiment with 90 mg. of apogeissoschizine gave acetaldehyde *p*-nitrophenylhydrazone, m.p. 123–135°.

Detection of C-Ethyl Groups in Hydrogenated Geissoschizine and Apogeissoschizine.—Using paper chromatography to detect the acids[28] formed on Kuhn–Roth oxidation and using a 30-minute digestion period to maximize the amount of propionic acid, geissoschizine and apogeissoschizine both gave only acetic acid in 59 and 87% yield, respectively.

In a subsequent set of experiments geissoschizine and apogeissoschizine were hydrogenated in ethanol using platinum oxide catalyst at atmospheric pressure until pickup of hydrogen ceased. The crude products were then carried through the same procedure as before. Both hydrogenated products gave propionic as well as acetic acid, 75 mole % from the hydrogenated geissoschizine and 136 mole % from the hydrogenated apogeissoschizine.

Condensation of Aniline with Geissoschizine.—A solution of 100 mg. of geissoschizine and 50 mg. of aniline hydrochloride in 2 ml. of isopropyl alcohol was boiled to dryness and then heated for 2 hours at 100° under a nitrogen atmosphere. The resulting solid was shaken with chloroform and aqueous sodium carbonate solution; concentration of the chloroform layer gave a residue which was crystallized from benzene to give colorless crystals, m.p. 114–116°, with gas evolution. This material was dried at 110° (0.1 mm.) for 21 hours to give the **anilinoacrylic ester (XII)**, m.p. 170–171°; ultraviolet absorption: λ_{max} 315 mμ (ϵ 26,200), 289 (21,500).

Anal. Calcd. for $C_{27}H_{29}N_3O_2$: C, 75.8; H, 6.8; OCH_3, 7.3. Found: C, 76.1; H, 6.7; OCH_3, 7.7.

Decarbomethoxygeissoschizine (XIII).—A solution of 1.45 g. of geissoschizine in 240 ml. of 1 *N* hydrochloric acid was boiled for 1.25 hours, after which the ultraviolet spectrum of the solution was indolic and no longer exhibited shifts on addition of base. From the boiling solution there was evolved 78 mole % of carbon dioxide. The hot solution was cooled to 0° and a small amount of insoluble material was collected and discarded. The clear solution was made basic with aq. ammonia and the precipitated base was taken up in methylene chloride. Concentration of the methylene chloride solution *in vacuo* gave 1.1 g. of a yellow gum which was further dried at 25° (0.4 mm.) for 8 hr.

Anal. Calcd. for $C_{19}H_{22}N_2O$: (1)CCH_3, 5.8. Found: CCH_3, 3.9.

Dihydrodecarbomethoxygeissoschizine (XIV).—A solution of 100 mg. of decarbomethoxygeissoschizine (XIII) in

(27) A. G. Anderson and R. H. Wade, THIS JOURNAL, **74**, 2274 (1952).

(28) H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955).

10 ml. of methanol was mixed with a solution of 70 mg. of sodium borohydride in 15 ml. of methanol. After this had stood overnight it was acidified with hydrochloric acid to *p*H 2 and then boiled to dryness. The residue was shaken with aqueous sodium carbonate and chloroform; concentration of the chloroform layer gave a crystalline residue. This residue was boiled with 5 ml. of benzene, then cooled and the dark benzene solution decanted from the crystals. Recrystallization from isopropyl alcohol and drying at 80° (0.2 mm.) for 36 hr. gave a product which melted at 210–215°; the melted material then soon polymerized and did not become fluid at 300°; ultraviolet absorption: λ_{max} 282 mμ (ε 7,470), 288 (6,330).

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.2; (1) CCH_3, 5.3. Found: C, 76.9; H, 8.1; CCH_3, 4.9.

Tetrahydrodecarbomethoxygeissoschizine (XV).—A solution of 60 mg. of dihydrodecarbomethoxygeissoschizine (XIV) was catalytically hydrogenated at atmospheric pressure in 20 ml. of ethanol using 20 mg. of platinum oxide catalyst. After 0.5 hour, a net pickup of 100 mole % was absorbed and no further pickup occurred. The solution was filtered and concentrated and the resulting crystalline residue was twice recrystallized from chloroform and sublimed at 170° (0.1 mm.) to give white crystals, m.p. 192–195°; ultraviolet absorption: λ_{max} 282 mμ (ε 7,310), 288 (6,210).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.5; H, 8.8. Found: C, 76.1; H, 8.7.

A series of melting points was determined under nitrogen atmosphere: XV, 193–200°; authentic corynantheidol,[19] 188°; mixed melting point 193–195°.

The reported specific rotation of corynantheidol is $[\alpha]_D$ −99.1° (*c* 0.464, pyridine).[18] For XV the values $[\alpha]_D$ −95° (*c* 0.29, 95% ethanol) and $[\alpha]_D$ −130° (*c* 0.51, pyridine) were found whereas corynantheidol[19] gave $[\alpha]_D$ −90° (*c* 0.50, 95% ethanol) and $[\alpha]_D$ −109° (*c* 0.20, pyridine).

Desoxydihydrodecarbomethoxygeissoschizine (XVI).—To a solution of 450 mg. of crude decarbomethoxygeissoschizine in 3 ml. of 95% hydrazine was added 40 ml. of ethylene glycol containing 3.0 g. of dissolved sodium. This mixture was boiled for 7.5 hours under a nitrogen atmosphere, cooled, diluted with water, and extracted with benzene. Concentration of the benzene extracts gave a gummy residue. When this gum was dissolved in ethanol–water, crystals were obtained; these were recrystallized three more times and air-dried; m.p. 85–95° followed by gas evolution at 105°.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot {}^1/_3C_2H_5OH \cdot {}^1/_2H_2O$: C, 77.4; H, 8.9; OC_2H_5, 5.3; (2.33)CCH_3, 11.5. Found: C, 77.5; H, 9.2; OC_2H_5, 5.7; CCH_3, 11.7.

When the above crystalline material was dried at 60° (0.1 mm.) for 24 hr., a light yellow glass was obtained; ultraviolet absorption: λ_{max} 282 mμ (ε 7,440), 289 (6,320); $[\alpha]_D$ + 42.1°.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.4; H, 8.6; (2) CCH_3, 10.7. Found: C, 81.0; H, 8.5; CCH_3, 8.2.

Dehydrogenation of Dihydrodesoxydecarbomethoxygeissoschizine (XVI)I.—When a mixture of 100 mg. of crystalline XVI and 300 mg. of 10% palladium-on-carbon was placed in a dehydrogenation apparatus and this placed in a bath at 200–215°, there was evolved in 15 minutes 8.5 ml. of hydrogen (calcd. for 100 mole %, 7.5 ml.). Short heating at 250° did not evolve any additional hydrogen. The dehydrogenation residue was boiled with 20 ml. of methanol for 10 minutes; this was filtered and the filtrate concentrated to give 40 mg. of semi-crystalline material. The catalyst was boiled for several hours with chloroform and again filtered; in this case 20 mg. of material was obtained from the filtrate. The filtrate residues were combined and sublimed and the sublimate was crystallized from hexane to give alstyrine melting at 83–93°, raised to 86–103° on resublimation.

The alstyrine was degraded to 4,5-diethylpicolinic acid (IIIa) and 2-aminopropiophenone (II). The latter was identified as the benzoyl derivative. On heating the picolinic acid, a pyridine was obtained which had a retention time identical to authentic 4,5-diethylpyridine on gas phase chromatography.[29]

Conversion of Apogeissoschizine to Geissoschizine.—A solution of 69 mg. of apogeissoschizine in 1 ml. of concd. hydrochloric acid was allowed to stand for 20 minutes and then stirred with ice and excess aq. ammonia. The resulting mixture was extracted with chloroform and the residues from the extracts were chromatographed on 5 g. of alumina. There was eluted with benzene 38 mg. of apogeissoschizine, identified as the picrate, and further elution with chloroform–methanol gave 10 mg. of geissoschizine, identified by melting point and mixed melting point.

Dihydrodemethoxyapogeissoschizine (XXI).—To a solution of 1.5 g. of apogeissoschizine in 125 ml. of tetrahydrofuran there was added 10 ml. of 2.7 *M* lithium aluminum hydride in tetrahydrofuran. This was boiled 3 hours, allowed to stand overnight and then treated with ethyl acetate to destroy unreacted hydride. Saturated sodium sulfate solution was added and the resulting solid was collected and washed with 1:1 chloroform–methanol. The residue obtained by concentrating the filtrate and washings was boiled in 200 ml. of ethanol until complete solution was attained. After concentration of the ethanol solution to 50 ml., it was cooled overnight to give 955 mg., 70% yield, of dihydrodemethoxyapogeissoschizine, m.p. 248–251° (reported[5] m.p. 245°), $[\alpha]^{21}_D$ +57.1° (*c* 0.6), *pK* 8.4 (50% aq. ethanol); ultraviolet absorption: λ_{max} 260 (ε 24,500), 305 (11,100).

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.4; H, 7.3. Found: C, 78.5; H, 7.2.

Dihydrodemethoxydesoxygeissoschizine (XXIII).—To a solution of 161 mg. of dihydrodemethoxyapogeissoschizine (XXI) in 15 ml. of 95% ethanol was added 1.5 ml. of concentrated hydrochloric acid. After this solution had stood for 10 minutes, 10% sodium hydroxide was added to *p*H 8 (extraction at this point with chloroform gives the amorphous aldehyde XXII, demethoxydesoxygeissoschizine). There was then added a solution of 50 mg. of sodium borohydride in 3 ml. of ethanol. After 1.5 hours the solution was made acidic and then diluted with chloroform and water. The residue (125 mg.) obtained on concentration of the chloroform layer was dissolved in ethanol, and cooling gave crystalline carbinol XXIII which was sublimed at 170° (0.1 mm.); m.p. 233–235° dec., $[\alpha]_D$ + 25° (*c* 0.5)[30]; ultraviolet absorption: λ_{max} 280 mμ (ε 7,420), 289 (6,120).

Anal. Calcd. or $C_{20}H_{24}N_2O$: C, 77.9; H, 7.9; N, 9.1; CCH_3, 5.5. Found: C, 77.7; H, 7.6; N, 9.3; CCH_3, 4.7.

Tetrahydrodemethoxyapogeissoschizine (XXIV).—To a solution of 180 mg. of apogeissoschizine in 15 ml. of absolute ethanol was added 400 mg. of sodium; an additional 350 mg. was added as soon as the first portion had dissolved, and the mixture was heated to complete solution of the sodium. The mixture was cooled, diluted with 100 ml. of water, and then extracted with methylene chloride. Concentration of the methylene chloride extracts gave a residue which was crystallized three times from isopropyl alcohol and sublimed at 160° (0.1 mm.) to give material melting at 233–237°, $[\alpha]^{22}_D$ + 74.1° (*c* 0.52); ultraviolet absorption: λ_{max} 285 mμ (ε 6,670), 292 (6,280).

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.9; H, 7.9. Found: C, 77.8; H, 7.7.

Apogeissoschizine Methiodide (XXV).—When 120 mg. of apogeissoschizine was added to 3 ml. of methyl iodide, a precipitate of colorless crystals formed within a few seconds. The next day these were collected, recrystallized from methanol and dried at 180° (0.1 mm.) for 18 hr. to give a methiodide melting at 254–257°.

Anal. Calcd. for $C_{22}H_{25}N_2O_2I$: C, 55.4; H, 5.3; CCH_3, 3.2. Found: C, 55.1; H, 5.4; CCH_3, 2.20.

Hydrogenation of Apogeissoschizine Methiodide.—A solution of 175 mg. of apogeissoschizine methiodide (XXV) in 20 ml. of ethanol was catalytically hydrogenated at atmospheric pressure using 60 mg. of platinum oxide as catalyst and 60 mg. of sodium acetate. A pickup of 200 mole % of hydrogen was observed and hydrogenation then ceased. After removal of the catalyst, the solution was diluted with benzene and shaken with dilute sodium hydroxide. From the benzene phase on concentration, there was obtained a light yellow gum which was distilled onto a cold finger at 160° (0.1 mm.); ultraviolet absorption: λ_{max} 270 mμ (ε 18,000), 319 (20,400).

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.9; H, 8.0; (2) CCH_3, 8.5. Found: C, 75.6; H, 8.0; CCH_3, 7.0.

(29) This procedure for identifying micro-quantities of picolinic acids was developed in this Laboratory by M. G. Reinecke and will be presented in detail in a forthcoming publication.

(30) Since some material crystallized during this determination, the value given is a minimum.

N-Vinyltetrahydrocarbazole was prepared essentially by the method of Clemo and Perkin.[22] However, our attempts to fractionate the product under their conditions led to apparent polymerization and simultaneous formation of tetrahydrocarbazole. The N-(2-chloroethyl)-tetrahydrocarbazole was dehydrochlorinated with potassium *t*-butoxide and the product distilled in a short path still at 80° (0.2 mm.); ultraviolet absorption: λ_{max} 302 mμ (ε 8,800), 252 (20,800).

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.2; H, 7.7. Found: C, 84.8; H, 7.6.

N-(2-Carbethoxyvinyl)-indoline (XXVII).—A mixture of 1.96 g. of ethyl propiolate and 2.50 g. of indoline was cooled occasionally over a period of 10 minutes until spontaneous heating had subsided. The mixture was allowed to stand overnight, and the solid which resulted was crystallized from methanol and dried at 80° (0.3 mm.) For 12 hr. to give 3.65 g. (85%) of a product melting at 84–85°; ultraviolet absorption: λ_{max} 330 mμ (ε 34,700), 291 (19,800).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.9; H, 6.9. Found: C, 72.1; H, 6.9.

N-(1,2-Dicarbomethoxyvinyl)-indoline (XXVIII).—A solution of 1.1 g. of indoline in 50 ml. of methylene chloride was added to a solution of 1.30 g. of dimethyl acetylenedicarboxylate in 50 ml. of methylene chloride. As soon as spontaneous boiling had ceased, the solution was concentrated. The residue, after one recrystallization from methanol and sublimation at 120° (0.2 mm.), afforded 1.91 g. (79%) of white crystals, m.p. 130–131°; ultraviolet absorption: λ_{max} 330 mμ (ε 26,000), 293 (8,550).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8. Found: C, 64.7; H, 6.0.

9-(2-Carbethoxyvinyl)-4a-hydroxy-1,2,3,4,4a,9a-hexahydrocarbazole (XXXa).—To a solution of 1.0 ml. of ethyl propiolate and 0.3 ml. of methanol in 5 ml. of methylene chloride there was added one drop of triethylamine. As soon as spontaneous boiling of the solution ceased, a 1.0-ml. aliquot of this was added to 140 mg. of 4a-hydroxy-1,2,3,4,-4a,9a-hexahydrocarbazole,[23] and the mixture was shaken until a homogeneous solution was obtained. After standing overnight, the solvent had evaporated and a crystalline residue remained. This was recrystallized from ethanol and dried at 80° (0.2 mm.) for 12 hr. to give material melting at 133–134°; ultraviolet absorption: λ_{max} 323 mμ (ε 35,600), 294 (22,000).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4. Found: C, 70.9; H, 7.2.

9-(2,2-Dicarbethoxyvinyl)-4a-hydroxy-1,2,3,4,4a,9a-hexahydrocarbazole (XXXc).—A solution of 100 mg. of 4a-hydroxy-1,2,3,4,4a,9a-hexahydrocarbazole and 0.125 ml. of diethyl ethoxymethylenemalonate in 2 ml. of methylene chloride was allowed to stand for 18 hours and was then concentrated and heated at 100° for 20 minutes. The resulting residue solidified on standing; when this solid was recrystallized from methanol and dried at 80° (0.3 mm.) for 13 hr. there was obtained colorless needles, m.p. 135–136°; ultraviolet absorption: λ_{max} 328 mμ (ε 29,800), 295 (13,600); infrared absorption: λ_{max} 5.91, 5.98 μ.

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.8; H, 7.0. Found: C, 66.9; H, 7.1.

N-Vinyltetrahydrocarbazoles XXXIa, b, c.—The general procedure for dehydrating the 4a-hydroxyhexahydrocarbazoles was to boil the carbinol with an equal weight of picric acid in methanol for 15 minutes. The methanol then was evaporated, and the residue was dissolved in chloroform and poured through a short alumina column to remove the picric acid. Finally, the chloroform was evaporated and the residue was carefully chromatographed on alumina using benzene–chloroform as eluent.

N-(2-Carbethoxyvinyl)-tetrahydrocarbazole (XXXIa) was obtained as a viscous yellow oil by distillation onto a cold finger at 110° (50 μ); ultraviolet absorption: λ_{max} 324 mμ (ε 15,900), 274 (17,500).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1. Found: C, 75.8; H, 7.0.

N-(1,2-Dicarbomethoxy)-tetrahydrocarbazole (XXXIb) was prepared from the crude carbinol XXXb, itself prepared in the same manner as XXXc. The dehydration product crystallized from ethanol and sublimed at 100° (0.2 mm.). It melted at 107–108°; ultraviolet absorption: λ_{max} 340 mμ (ε 6,080), 277 (9,600).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1. Found: C, 68.9; H, 6.0.

N-(2,2-Dicarbethoxyvinyl)-tetrahydrocarbazole (XXXIc) was a yellow oil that was distilled onto a cold finger at 150° (0.1 mm.); ultraviolet absorption: λ_{max} 342 mμ (ε 10,600), 278 (13,300).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8. Found: C, 71.4; H, 6.7.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE REGA INSTITUTE, UNIVERSITY OF LOUVAIN]

The Structure of Factor S of Staphylomycin[1]

BY HUBERT VANDERHAEGHE AND GUIDO PARMENTIER

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Acid hydrolysis of Factor S of Staphylomycin has yielded the products: 3-hydroxypicolinic acid, L-threonine, D-α-aminobutyric acid, L-proline, N-methyl-L-phenylalanine, 4-oxo-L-pipecolic acid and L-phenylglycine. Further work has shown that the sequence of the (amino) acids is in the order given above and that a lactone linkage is present between phenylglycine and the hydroxy group of threonine.

Staphylomycin,[2] an antibiotic produced by a *Streptomyces* related to *S. virginiae*, is very active against Gram-positive bacteria.[3] Its clinical indications are mainly in the treatment of infections of staphylococcal origin.[4]

Paper chromatographic studies have shown the presence of two components active against micrococci.[3] These two components (Factors M I and M II) could be separated on a column of silica gel. Other fractions of the chromatogram, which were essentially inactive against micrococci, increased (up to 2.5 times) the *in vitro* antibacterial activity of Factor M I. From these fractions another product could be obtained in crystalline state. It was named Factor S, because it was more active against *B. subtilis* than Factor M.[5,6]

Factor S is a weak acid (pK'_a 7.7 in dimethylformamide–water, 1:2), soluble in organic solvents and nearly insoluble in water and petroleum ether.[5] The presence of a phenolic group was suggested by the brown-red color obtained with ferric chloride. The presence of this function was also supported

(1) Presented, in part, at the International Congress of Biochemistry, Vienna, September, 1958.

(2) Registered Trade Mark of S.A. R.I.T.

(3) P. De Somer and P. Van Dijck, *Antibiotics & Chemotherapy*, **5**, 632 (1955).

(4) P. De Somer and H. Van de Voorde, *Antibiotic Med. & Clin. Therapy*, **4**, 786 (1957).

(5) H. Vanderhaeghe, P. Van Dijck, G. Parmentier and P. De Somer, *Antibiotics & Chemotherapy*, **7**, 606 (1957).

(6) P. Van Dijck, H. Vanderhaeghe and P. De Somer, *ibid.*, **7**, 625 (1957).