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Structure of pithecolobine. III. The synthesis of the 1,5- and 1,3-desoxypithecolobines

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The second communication of this series has shown that "pithecolobine" is a family of closely related analogues represented by the general formula **1**. In the present paper a crude semiquantitative estimate of the individual components is achieved by a combination of vapor-phase chromatography and chemical degradation.

The synthesis of the desoxypithecolobines **3***a* and **3***b* and their tetratosylates **11***a* and **11***b* is described. A comparison of these compounds with the corresponding "natural" mixtures by thin-layer chromatography in several systems, infrared, nuclear magnetic resonance, and mass spectrometry was found to support strongly the conclusions reached by the previous degradative work.

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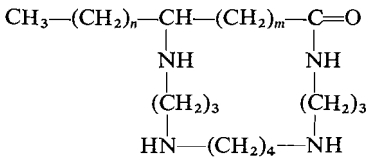
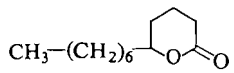
In the second communication (1) of this series we have shown that the "alkaloid pithecolobine" is in fact a mixture of homologues and analogues represented by the general formula **1**.



1 ($m + n = 9, 10, 11$)
1*a* ($m = 3, n = 6$)
1*b* ($m = 1, n = 8$)
1*c* ($m = 1, n = 10$)

In this mixture we have rigorously demonstrated the presence of **1***a* and we have shown that a significant proportion of compounds with $m = 1$ is present.

As a necessary prerequisite of the synthetic studies to be described in the sequel, we wished to have at least a semiquantitative estimate of the main components in the pithecolobine mixture.[1] It was possible to achieve such a crude analysis by vapor-phase chromatography (v.p.c.) of straight chain acids (in the form of their methyl esters) obtained from the Hofmann degradation of pithecolobine. We have shown in our second communication (1) that the Hofmann degradation of pithecolobine yields besides a mixture of neutral unsaturated amides, the lactone **2** by internal displacement. Hydrogenation and hydrolysis of the unsaturated amides gave *n*-dodecanoic acid contaminated by some *n*-tridecanoic and *n*-tetradecanoic acid. We have now determined quantitatively the proportions of these three acids in the mixture by v.p.c. of the methyl esters. The result was as follows: C-12 acid, 65%; C-13 acid, 4%; C-14 acid, 30%. The quantities of lactone **2** and unsaturated amides obtained in the experiment were 122 mg and 391 mg, respectively.



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From these results it is clear that a minimum of 24% of the pithecolobines is compound **1***a* ($m = 3$, $n = 6$), a further 49% are other C-22 ($m + n = 9$) pithecolobines (including possibly some more **1***a* which did not yield the lactone **2**, but gave a normal Hofmann degradation); 3% are C-23 pithecolobines ($m + n = 10$), and

[1]Vapor-phase chromatography and other methods of separation on the alkaloids and their derivatives were repeatedly tried and failed.

23% are C-24 pithecolobines ($m + n = 11$). To get a further breakdown of the individual pithecolobine components, the neutral unsaturated amides were oxidized by permanganate–periodate in tertiary butanol. The fatty acids thus obtained were converted to methyl esters and analyzed by v.p.c. The result of this analysis is given in Table I.

TABLE I

Yield of straight chain acid from oxidation of unsaturated amides

Acid	Yield (%)
C_5	0
C_6	8
C_7	1
C_8	5
C_9	25
C_{10}	40
C_{11}	10
C_{12}	12

These results may now be simply interpreted as follows:

(a) There is only 6% of C-7 + C-8 acids. Consequently, most of the pithecolobine **1***a* degrades to lactone **2** rather than to the unsaturated amides.

(b) There is 22% of C-11 + C-12 acids. Most of these must be derived from the C-24 pithecolobine **1***c*.

(c) Finally, there is 65% of C-9 + C-10 acids.

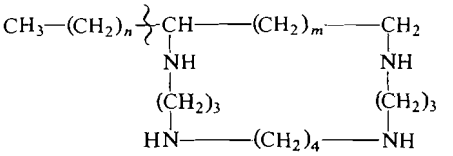
Since the C-24 pithecolobines are mostly accounted for by the C-11 + C-12 acids and the amount of the C-23 pithecolobines is small, most of the C-9 + C-10 acids must be derived from the C-22 pithecolobine **1***b* ($m = 1, n = 8$).

If we neglect the possibility of yield differences in the various degradation pathways and take our data at face value, we may estimate the percentages of the three main pithecolobine components as follows: **1***a*, ($m = 3, n = 6$), 24–30%; **1***b*, ($m = 1$, $n = 8$), 40–49%; **1***c*, ($m = 1$, $n = 10$), 13.5–16.5%.

Even if we assume that the lowest numbers are correct, we see that compounds **1***a*, **1***b*, and **1***c* account for more than three-quarters of the pithecolobine mixture.

Since **1***a* and **1***b* are by far the most abundant components, we wished to synthesize the corresponding desoxypithecolobines and compare them with the "natural" desoxypithecolobine mixture.

We decided to synthesize first the desoxypithecolobine **3***a* which corresponds to the pithecolobine **1***a*.[2]

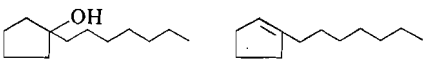


3*a* ($m = 3, n = 6$)
3*b* ($m = 1, n = 8$)
3*c* ($m = 1, n = 10$)

In this first approach, we have largely followed the work of Stetter and Roos (2) and our initial aim was thus the synthesis of the tetratosylate **11***a*. This work was reported in a preliminary paper (3) and it was accomplished as follows. Our starting material was 1,5-dibromododecane, previously described by Franke and Kroupa (4). We have, however, prepared this compound by a different and more convenient route.

Treatment of cyclopentanone with the Grignard reagent from 1-bromoheptane yielded the tertiary alcohol **4**. Dehydration of **4** with phosphorus pentoxide in benzene gave the olefin **5**, which was converted to the acid **6** by ozonolysis, followed by hydrogen peroxide oxidation. The acid was esterified with methanol and the methyl ester **7** was reduced with lithium aluminium hydride to 1,5-dihydroxydodecane. This last compound on treatment with fuming hydrobromic acid finally yielded the desired 1,5-dibromododecane **8**. The dibromide **8** was converted into 1,5-diazidododecane by treatment with sodium azide in diethylene glycol monomethyl ether. The diazide was not characterized, but immediately hydrogenated to the hygroscopic oily 1,5-diaminododecane. This material was finally tosylated to the ditosylate **9**. The dibromide **10** which was required as the second component of the synthesis was constructed as follows. The ditosylate of 1,4-diaminobutane was prepared in the usual manner and converted to (**10**) by treatment with 1,3-dibromopropane under the conditions recommended by Stetter and Roos (2)

[2]The reason for this was our initial belief that **1***a* is the major component of the pithecolobine mixture. This in turn was due to the comparatively good yield of lactone **2**, and the absence of the quantitative data reported in the present communication.



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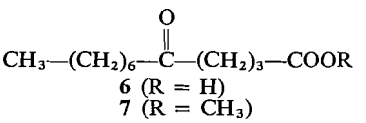
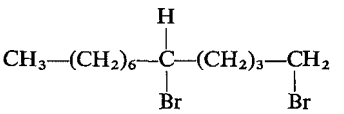


6 (R = H)
7 (R = CH_3)



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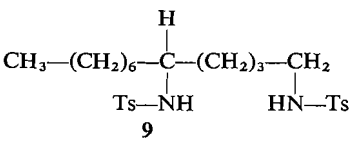

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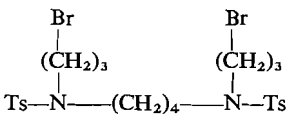

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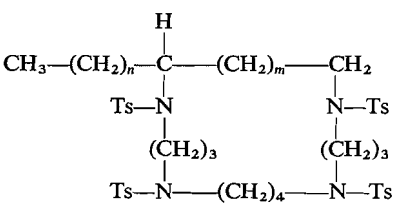
(see Experimental). The coupling of the disodium salt of **9** with compound **10** was performed in dimethyl formamide under high dilution. The product **11***a* was isolated in pure form by chromatography on alumina. It was a colorless



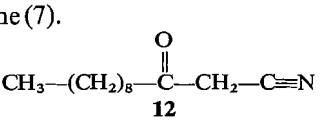
11*a* (m = 3, n = 6)
11*b* (m = 1, n = 8)

glass and the peak fraction showed a constant infrared (i.r.) spectrum on repeated chromatography and was homogeneous in thin-layer chromatography (t.l.c.).

Since the synthetic compound **11***a* resisted all detosylation attempts, we have prepared the tetratosylate of the "natural" desoxypithecolobine mixture and were able to show that both synthetic and "natural" material gave superimposable i.r. spectra in potassium bromide and chloroform. This finding certainly corroborates the structure of the pithecolobines in principle. However, at the same time it is clear that since the individual desoxypithecolobine components show insufficient differences in i.r. spectroscopy, this method of comparison has to be supplemented by others (*vide infra*).

Our next synthetic objective was the tetratosylate **11***b*, which we hoped to reach by methods completely analogous to those used for the tetratosylate **11***a*.

For this end, it was first necessary to synthesize 1,3-diaminododecane. After some difficulties experienced with more conventional approaches, the following route was found to be effective.[3] The ketonitrile **12** (5) was converted (6) by the action of hydroxylamine into the crystalline aminoisoxazole **13**. Catalytic hydrogenation of this last compound gave the amide **14** in quantitative yield. The reduction of **14** to the desired 1,3-diaminododecane **15** could not be accomplished by lithium aluminium hydride but it was achieved with an excellent result by the use of diborane (7).



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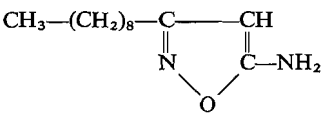

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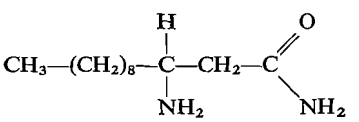

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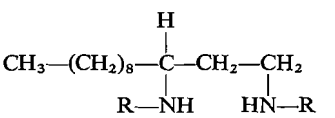


15 (R = H)
16 (R = Ts)

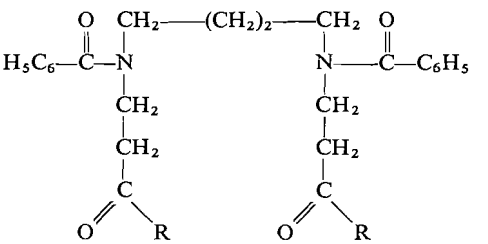
The tosylation of **15** to **16** and the subsequent synthesis of the tetratosylate **11***b* were uneventful and proceeded exactly as in the case of the tetratosylate **11***a*. The details may be found in the Experimental.

The i.r. spectrum of the synthetic tetratosylate

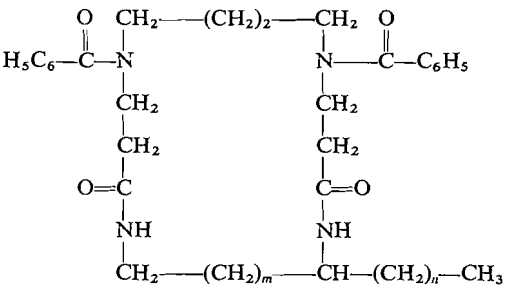
[3]This method is an application of a general procedure for the preparation of 1,3-diamines which has been worked out by two of the present authors (Z. V. and G. K.) and will be published in due course. To our surprise, no really acceptable and convenient route to these compounds was found in the literature.

11*b* was superimposable on the spectrum of the tosylated "natural" desoxypithecolobine mixture and of course also on the spectrum of the synthetic tetratosylate **11***a*. This was a clear proof that i.r. spectroscopy is not capable of distinguishing the fine details of ring size in the pithecolobine series.

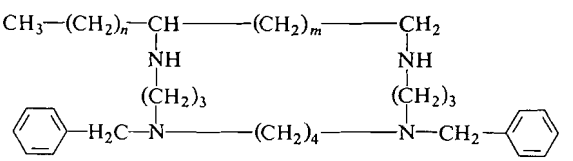
Since all detosylation experiments on **11***a* and **11***b* resulted in complete failure, it was decided to design a new synthetic method which would yield directly the free desoxypithecolobines.



17 (R = —O—CH_2—CH_3)
18 (R = —OH)
19 (R = —Cl)



20 (*m* = 3, *n* = 6)
21 (*m* = 1, *n* = 8)



22 (*m* = 3, *n* = 6)
23 (*m* = 1, *n* = 8)

The basic idea of the new synthetic scheme was to synthesize the dichloride **19** and couple it under high dilution with 1,5- and 1,3-diaminododecane to the compounds **20** and **21**, respectively. These materials could be expected to yield the desoxypithecolobines **3***a* and **3***b* by reduction and hydrogenolysis.

The reaction of 1,4-diaminobutane with ethyl acrylate, followed by benzoylation of the product yielded the diester **17**, which was hydrolyzed to the crystalline diacid **18**. This last compound was then converted to the dichloride **19** by the action of thionyl chloride. The reaction of **19** with the two diamines (1,3- and 1,5-diaminododecanes) was performed under high dilution in carbon tetrachloride. The two tetramides **20** and **21**, thus obtained, were reduced to the dibenzyl desoxypithecolobines **22** and **23** by diborane and these last compounds were hydrogenolyzed to the desoxypithecolobines **3***a* and **3***b*. The two synthetic desoxypithecolobines were finally converted into the tetratosylates **11***a* and **11***b* and thus it was possible to interrelate the two synthetic series.

Infrared comparison of the desoxypithecolobines **3***a* and **3***b* in chloroform and carbon tetrachloride showed, as in the case of the tetratosylates **11***a* and **11***b*, complete superimposability of the spectra. It is thus not surprising that the i.r. spectra of both synthetic desoxypithecolobines were also superimposable on the corresponding spectrum of the "natural" desoxypithecolobine mixture. If the two main components of a mixture have identical spectra, then also the spectrum of the mixture itself must be identical with the spectra of the pure components. Next we have studied the synthetic and "natural" desoxypithecolobines and their tosylates by t.l.c. in several systems. The situation here is the same as in i.r. spectroscopy. Both in the case of the free desoxypithecolobines and their tosylates the two synthetic materials do not show significant differences from each other and from the "natural" mixture, which behaves as a single compound.

These studies, while clearly not possessing the rigorous validity of a confrontation between a pure synthetic and natural compound, nevertheless show that the "natural" desoxypithecolobine mixture possesses many physical characteristics which are identical with those of the pure synthetic components of known structure. Thus the conclusions drawn from our degradative work receive considerable synthetic support.

It now seemed desirable to find physical methods which would reveal some significant difference between the two synthetic compounds and the "natural" mixture. The first such method which revealed minor differences was nuclear magnetic resonance (n.m.r.) spectroscopy of the tetratosylates. The two synthetic tetratosylates differ by ring-size, i.e. by the number of hydrogens

situated inside the macrocycle. These hydrogens are subject (to put it in most general terms) to special shielding and deshielding influences which are quite different from those affecting the hydrogens of the side-chain. Thus, n.m.r. spectroscopy was expected to show some differences between **11***a* and **11***b*. The n.m.r. spectra revealed the following groups of hydrogens.

(a) A quadruplet (16 H) at τ 2.29, 2.43, 2.68, and 2.82 p.p.m. (aromatic hydrogens);

(b) A broad unresolved multiplet (15 H) centered at τ 7.00 p.p.m. (hydrogen unshielded by the four nitrogens);

(c) A singlet (1 2H) τ 7.6 p.p.m. (four aromatic methyl groups);

(d) A multiplet between τ 8.78 and 9.26 p.p.m. This group contains most of the aliphatic hydrogen including the *C*-methyl group and cannot be quantitatively separated from group *(e)*;

(e) A multiplet around τ 8.3–8.5 p.p.m. This group cannot be quantitatively separated from the preceding group *(d)* and contains a smaller part of the aliphatic hydrogens, subject to special unshielding influence, presumably inside the macrocycle.

It is only the precise shape of this last multiplet in which the two synthetic tosylates **11***a* and **11***b* differ. The shape of this group in the "natural" mixture lies in between, much closer to compound **11***b*. The remaining features of the spectra in all compounds are the same.

The closer resemblance of the "natural" tetratosylate to **11***b* is due not only to the greater concentration of this component in the "natural" mixture, but presumably also to the fact that the third most abundant component of the "natural" mixture (derived from the desoxypithecolobine **3***c*) contains the same macrocycle as compound **11***b*.

The second method which should reveal differences between the desoxypithecolobines **3***a* and **3***b* is mass spectrometry. The breaking of the side-chain on electron impact (indicated by the wavy line in **3**) should be important and it might differentiate between **3***a* and **3***b*. Again, the "natural" desoxypithecolobine mixture should resemble closely the synthetic desoxypithecolobine **3***b*, since the desoxypithecolobines **3***b* and **3***c* yield the same fragment by this type of fragmentation.

The mass spectra of the two synthetic samples **3***a* and **3***b* and "natural" desoxypithecolobine do not show a molecular ion, are extremely complicated and difficult to interpret. All three samples are very similar but *non-identical.* As expected, the spectrum of "natural" desoxypithecolobine is "almost identical" with the synthetic compound **3***b*.

Experimental

Vapor-phase Chromatography of Saturated Esters

The ether solutions of the saturated methyl esters were chromatographed on an SE30 column (25%) at 250 °C. The peaks of the individual components were identified by the addition of authentic samples. The percentage composition of the mixture was obtained by determining the area under each peak. (For tabulation of results see theoretical part.)

Permanganate–Periodate Oxidation of the Unsaturated Amides

One millimole of the unsaturated secondary amide mixture from the Hofmann degradation of pithecolobine **1** was dissolved in 6 ml of *t*-butyl alcohol and a few drops of water were added. Sodium metaperiodate (8 mmoles) was added in a 10% aqueous solution which has been adjusted by sodium carbonate to a pH of 7.5–7.8. Potassium permanganate (0.134 mmole) was then added in a 1% aqueous solution. Finally, approximately 2 ml of *t*-butyl alcohol were added and the mixture stirred for 5 h. After this time, 5 ml of water were added and the solution was made alkaline and exhaustively extracted, first with chloroform and then with ether. The aqueous alkaline layer was acidified with sulfuric acid and extracted with ether. The ether solution was concentrated to a small volume, esterified with diazomethane, dried, and further concentrated to a volume of 0.5 ml. This solution was analyzed by vapor-phase chromatography (v.p.c.) (*vide supra*).

Preparation of Compound ***4***

Normal heptyl bromide (268 g), dissolved in 600 ml of absolute ether, was added under nitrogen to 36 g of magnesium turnings. After 4 h of gentle reflux, the magnesium had dissolved and a slow addition of cyclopentanone (127 g) in 150 ml of absolute ether was started. The addition took 2 h and the solution was then heated under reflux for an additional 2 h. The reaction mixture was decomposed by pouring into an excess of aqueous ammonium chloride and exhaustively extracted with ether. The pure product was isolated by fractional distillation *in vacuo*. It was obtained in a yield of 161 g (67%) and it boiled at 114–115 °C (11 mm Hg).

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.20; H, 13.13; O, 8.68. Found: C, 78.41; H, 12.69; O, 8.82.

Dehydration of ***4*** *to* ***5***

Compound (**4**) (160 g) was dissolved in 2 l of dry benzene and 500 g of phosphorus pentoxide were gradually added with stirring at room temperature. After 1 h ice water was added and the organic layer was washed with water and dried. The benzene was distilled off *in vacuo* and the residue was dissolved in petroleum ether

and filtered through 800 g of basic alumina. The petroleum ether was then distilled off and the product fractionated *in vacuo*. The olefin (**5**) was obtained in a yield of 139 g (95%) and it distilled at 132–133 °C (50 mm Hg).

Anal. Calcd. for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 87.38; H, 13.63.

Preparation of 5-Ketododecanoic Acid (6)

Distilled 1-*n*-heptyl cyclopentene **5** (120 g) was dissolved in 1600 ml of ethyl acetate and the solution cooled to −70 °C. Ozone (6%) was bubbled through until the solution turned blue and ozone was no longer absorbed. After this most of the ethyl acetate was distilled off *in vacuo* at room temperature. The oily ozonide was dissolved in a mixture of the following composition: 750 ml glacial acetic acid, 500 ml water, 2 ml concentrated hydrochloric acid, and 360 ml 30% hydrogen peroxide. The resulting solution was stirred for 24 h after which the acidic material produced in the reaction was isolated in the usual manner. After recrystallization from ether, 94 g (61%) of the acid **6** were obtained. After several more crystallizations it melted at 69 °C.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.34; O, 22.40. Found: C, 67.46; H, 9.93; O, 22.18.

Preparation of 1,5-Dodecane Diol

The acid **6** (94 g) was dissolved in 950 ml of absolute methanol containing 52 g of dry hydrogen chloride. The solution was refluxed for 1 h and the methyl ester **7** isolated in the usual manner and distilled. The middle fraction (62 g) boiled constantly at 114–118 °C (0.5 mm Hg). This material was reduced in dry ether with an excess (40 g) of lithium aluminium hydride. The product 1,5-dodecane diol was isolated in the usual manner and melted after crystallization at 45 °C. The yield of recrystallized material was 39 g (71%).

Anal. Calcd. for $C_{12}H_{26}O_2$: C, 71.24; H, 12.95; O, 15.82. Found: C, 71.08; H, 12.88; O, 16.24.

Preparation of 1,5-Dibromododecane (8)

Hydrobromic acid (48%, 100 ml) was saturated with hydrobromic acid gas and 20 g of 1,5-dodecane diol were added with stirring to this solution. The mixture was heated under reflux for 1 h after which it was diluted with water and extracted with ether. The dibromide **8** was isolated by distillation. The yield of constantly boiling material was 24.7 g (74%). The boiling point was 121–123 °C (0.7 mm Hg).

Anal. Calcd. for $C_{12}H_{24}Br_2$: C, 43.93; H, 7.38; Br, 48.71. Found: C, 45.69; H, 7.66; Br, 46.84.

Preparation of the Ditosylate 9

The dibromide **8** (24 g) was added to a solution of 1.368 g of sodium azide in water (34 ml) and diethylene glycol monomethyl ether (225 ml). The mixture was heated with stirring to 95 °C for 30 h. After this time it was diluted with water and the yellow diazide was extracted with ether. This material was hydrogenated in 700 ml of methanol with 700 mg of prehydrogenated platinum oxide. As no uptake of hydrogen is observable in this reaction the hydrogen was simply bubbled through the mixture for 24 h. The hygroscopic oily 1,5-diaminododecane was distilled and the fraction (9.24 g) boiling at 102–104 °C (10 mm Hg) was collected. It was immediately converted into the ditosylate **9**. For the tosylation the diamine (6.68 g) was suspended in 150 ml of water containing 2.68 g of sodium hydroxide. The suspension was vigorously stirred and 12.78 g of *p*-toluenesulfonyl chloride in 50 ml of ether were gradually added to it. The stirring was continued for 3 h. After this time the tosylate **9** was extracted with ether and purified by chromatography on alumina. The glassy ditosylate was obtained in a 94% yield. It was homogeneous in thin-layer chromatography (t.l.c.) and was sublimed for analysis in high vacuum at 200 °C.

Anal. Calcd. for $C_{26}H_{40}O_4N_2S_2$: C, 61.39; H, 7.93; O, 12.58; N, 5.50; S, 12.61. Found: C, 61.53; H, 7.93; O, 13.14; N, 4.96; S, 11.69.

Ditosyl-1,4-diaminobutane

The tosylation of 1,4-diaminobutane was performed exactly as described in the previous case. The yield of the product was 90%. It was recrystallized from methanol to a melting point 139–140 °C.

Anal. Calcd. for $C_{18}H_{24}O_4N_2S_2$: C, 54.52; H, 6.10; O, 16.14; N, 7.06; S, 16.17. Found: C, 54.35; H, 6.04; O, 15.82; N, 7.70; S, 15.89.

Preparation of the Dibromide 10

Ditosyl-1,4-diaminobutane (19.86 g) was added to a solution of 2.3 g of sodium in 75 ml of absolute methanol. The solution was refluxed for 30 min during which time the disodium salt precipitated. The methanol was removed *in vacuo* and the salt pulverized and dried *in vacuo* at 100 °C for 15 min. The salt was then suspended in dry dimethyl formamide and heated to 100 °C. At this point 30.3 g of 1,3-dibromopropane were added and the heating with vigorous stirring continued for 10 min. The reaction mixture was filtered, poured into water, and extracted with ether. The extract (41 g of yellow oil) was purified by chromatography on 800 g of neutral alumina. Benzene eluted crystalline material which after several crystallizations from chloroform–ether melted at 105 °C. The yield was 3.79 g of pure recrystallized compound **10**.

Anal. Calcd. for $C_{24}H_{34}O_4N_2S_2Br_2$: C, 45.15; H, 5.36; O, 10.02; N, 4.39; S, 10.04; Br, 25.03. Found: C, 44.63; H, 5.28; O, 10.42; N, 4.26; S, 9.98; Br, 25.32.

Preparation of the Tetratosyl Desoxypithecolobine 11a

The cyclization reaction was performed in a large round bottom flask containing 1000 ml of refluxing dimethyl formamide. To this flask were added at a very slow and equal rate the solutions *a* and *b* over a period of 30 h. Composition of solution *a*: 1.432 g of compound **10** in 160 ml of dimethyl formamide. Composition of solution *b*: 24 ml of absolute methanol, 100 mg of sodium, 1.136 g of compound **9**, 136 ml of dimethyl formamide. After the completion of the addition the reflux was continued for 3 h and then the reaction mixture was evaporated almost to dryness *in vacuo*. The residue was taken up in chloroform, washed with water, dried, and again evaporated to dryness. The yield was 2.65 g of brown oil. After chromatography on 80 g of neutral alumina 484 mg of a clear glass were obtained which was homogeneous in t.l.c. and had an infrared (i.r.) spectrum identical with "natural" desoxypithecolobine tetratosylate. This material was rechromatographed and the peak fraction of this new chromatogram did not show any difference either in i.r. or t.l.c. from either the bulk of

the material or from the "natural" tetratosylate. The material was a glass and could not be sublimed. It was consequently dried as a film deposited from carbon tetrachloride. The analysis for all the elements shows significant agreement. It shows that all of the oxygen, nitrogen, and sulfur, is in the form of sulfamido groups and that the ratio of these groups to carbon and hydrogen is the expected one. Since the compound is synthetic and from known elements, this ratio is sufficiently accurate to insure the correct molecular formula. A multiple of this formula is excluded by the approximate agreement of the molecular weight determination. Nuclear magnetic resonance (n.m.r.) spectroscopy (see theoretical part) corroborates quite accurately the correct ratios for various kinds of hydrogens. It is, in fact, in this case the most significant of all the analytical methods and has been used extensively besides i.r. spectroscopy and t.l.c. in the compounds prepared subsequently.

Anal. Calcd. for $C_{50}H_{72}O_8N_4S_4$ (mol. wt., 985): C, 60.94; H, 7.37; O, 12.99; N, 5.69; S, 13.03. Found (mol. wt. (osmometry in benzene) synthetic, 1032; "natural", 1045): C, 61.93; H, 8.11; O, 12.46; N, 5.61; S, 12.13.

Preparation of 2-Nonyl-4-amino-isoxazole (13)

The ketonitrile **12** (5) (20 g) was heated with hydroxylamine hydrochloride (21 g) and sodium acetate (41 g) in 450 ml of ethanol and 150 ml of water to 60 °C for 35 min. After this time the reaction mixture was poured into 2 l of water, extracted exhaustively with ether, and the isoxazole **13** recrystallized from petroleum ether to a melting point of 56 °C. The yield was 19.5 g (92.7%).

Anal. Calcd. for $C_{12}H_{22}N_2O$ (mol. wt., 210): C, 68.60; H, 10.50; N, 13.05; O, 7.57. Found (mol. wt., osmometry, 209): C, 68.60; H, 10.41; N, 13.31; O, 7.51.

Ultraviolet spectrum: λ_{max} 242 mμ (log ε 4.0).

Hydrogenation of the Isoxazole 13

Compound **13** (15 g) was hydrogenated in 100 ml of ethanol with 800 mg of prehydrogenated platinum oxide. Two moles of hydrogen were taken up overnight and the product **14** was recrystallized from chloroform–carbon tetrachloride to a melting point 124–128 °C; yield of recrystallized product 13.5 g (90%).

Anal. Calcd. for $C_{12}H_{26}N_2O$: C, 67.20; H, 12.10; N, 13.08. Found: C, 66.15; H, 11.62; N, 13.65.

Preparation of 1,3-Diaminododecane (15)

A solution of the amide **14** (10.5 g) in 150 ml of tetrahydrofuran was added dropwise with stirring to 200 ml of a 1 *M* solution of diborane in the same solvent. The whole operation was performed in a dry nitrogen atmosphere. When the addition was complete, the solution was refluxed for 3 h. After this time, the reaction mixture was evaporated to a small volume, an excess of absolute methanolic hydrochloric acid was added, and the precipitate which appeared was removed by filtration. The solution was then evaporated to dryness. The residue was dissolved in methanol and filtered through a column of Amberlite IR 400 in the OH^- form. The evaporation of the filtrate gave 7.6 g of 1,3-diaminododecane which was homogeneous in v.p.c. For characterization, it was converted into the crystalline diacetate by acetylation with acetic anhydride in pyridine. This derivative was recrystallized from carbon tetrachloride and melted at 128 °C.

Anal. Calcd. for $C_{16}H_{30}N_2O_2$ (mol. wt., 282): C, 68.04; H, 10.71; N, 9.92; O, 11.33. Found (mol. wt., osmometry, 280): C, 67.53; H, 11.55; N, 9.66; O, 11.51.

Preparation of the Ditosyl Derivative 16

The tosylation of **15** to **16** was performed in the same manner as the preparation of the ditosylate **9**. Compound **16** was obtained in a yield of 62%. It was a neutral glass homogeneous in several t.l.c. systems. The n.m.r. spectrum of this material was in quantitative agreement with the structure **16**.

Preparation of the Compound 11b

The coupling of **16** and **10** under high dilution to yield the tetratosyl desoxypithecolobine **11***b* was performed precisely as described above for the compound **11***a*. The quantities used were 420 mg of **16** and 540 mg of **10**. Extensive chromatography on two alumina columns followed by preparative t.l.c. on silica gel yielded 115 mg of glassy material, which was homogeneous in several t.l.c. systems and indistinguishable by t.l.c. from "natural" desoxypithecolobine tetratosylate. It had an i.r. spectrum identical both with the compound **11***a* and the "natural" tetratosylate. The n.m.r. spectrum of the product **11***b* was in quantitative agreement with the spectrum of the compound **11***a* (see theoretical part).

Preparation of the Diester 17

Ethyl acrylate (200 g) was added dropwise to a solution of 54 g of 1,4-diaminobutane in 500 ml of ether. The mixture was stirred overnight at room temperature. After this time it was cooled to 5 °C and 150 g of trimethylamine were added to it. A slow addition of 70 g of benzoyl chloride over the period of 1 h was now started and the mixture was allowed to stand for an additional hour. After this time 500 ml of ice water were added and the neutral reaction product isolated in the usual manner. The yield was 120 g (40%) of neutral material which surprisingly was homogeneous in t.l.c. It was immediately, without further purification, converted into the crystalline acid **18**.

Preparation of the Diacid 18

Compound **17** (100 g) was hydrolyzed for 1 h at 70 °C in 400 ml of 10% aqueous methanolic potassium hydroxide. The hydrolysis mixture was poured into 2 l of water and acidified with 20% hydrochloric acid to pH 2. After a period of standing the product **18** crystallized; it was filtered off and washed with water and finally recrystallized from methanol. The yield was 65 g (60%) and the pure product melted at 181–182 °C.

Anal. Calcd. for $C_{24}H_{28}N_2O_6$ (neutralization equivalent, 440): C, 65.44; H, 6.41; N, 6.36; O, 21.80. Found (neutralization equivalent, 436): C, 64.86; H, 6.52; N, 6.39; O, 22.29.

Preparation of the Dichloride 19

The acid **18** (6 g) was dissolved in 25 ml of thionyl chloride and the solution was stirred at 50 °C for 5 h. After this period, the thionyl chloride was evaporated *in vacuo*, the residue dissolved in dry carbon tetrachloride, evaporated to dryness *in vacuo*, and dried in high vacuum for several hours. The chloride **19** prepared in this way was used for the next step.

Desoxypithecolobine 3a

A solution of 1,5-diaminododecane (3 g) in 450 ml of carbon tetrachloride and a solution of the dichloride **19** (4.7 g) in the same volume of the same solvent were added in the course of 5 h to a vigorously stirred reaction vessel containing 1500 ml of carbon tetrachloride at room temperature. When the addition was completed, the stirring was continued for 8 h. The carbon tetrachloride was then evaporated *in vacuo*, the products dissolved in methanol and passed through a column of (*a*) Amberlite IR 400 in the OH^- form; (*b*) Dowex 50X in the H^+ form. The methanol was then evaporated to dryness yielding 1.8 g of a neutral light-brownish foam. This material (1 g) was dissolved in 50 ml of 1 *M* diborane in tetrahydrofuran and the solution was heated under reflux for 3 h. The tetrahydrofuran was evaporated and the residue was dissolved in saturated methanolic hydrochloric acid. A solid which separated was filtered off, the solution was evaporated to dryness and the basic products isolated in the usual manner. The yield was 600 mg of crude basic material. The crude bases were reconverted into the hydrochlorides and debenzylated by hydrogenation in ethanol with 150 mg of 10% palladium on charcoal for 18 h. The basic products were isolated in the usual manner. The yield was 300 mg of crude basic material. Thin-layer chromatography showed several spots, one of which had the same R_f value in several systems as "natural" desoxypithecolobine. Column chromatography on alumina and preparative t.l.c. on silica gel led to the isolation of 60 mg of compound (**3***a*) which was homogeneous in several systems of t.l.c. and showed an i.r. spectrum superimposable on the spectrum of "natural" desoxypithecolobine. For characterization, it was tosylated in the usual manner (*vide supra*). The product obtained in quantitative yield was identical by t.l.c. in several systems, i.r. in chloroform and carbon tetrachloride, and n.m.r. in deuterated chloroform with the previously synthesized compound **11***a*.

Desoxypithecolobine (3b)

The starting materials were 1,3-diaminododecane **15** and the dichloride **19**. The quantities, volumes and the entire procedure were the same as described for the preparation of compound **3***a*. The yield of pure **3***b* was 55 mg. For characterization, it was converted in quantitative yield into the independently synthesized tetratosylate **11***b*. Identity of the two tetratosylates was proved by t.l.c. in several systems, i.r., and n.m.r. spectroscopy.

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1. K. Wiesner, D. M. MacDonald, C. Bankiewicz, and D. E. Orr. Can. J. Chem. **46**, 1881 (1968).
2. H. Stetter and E. E. Roos. Ber. **87**, 566 (1954).
3. K. Wiesner and D. E. Orr. Tetrahedron Letters, **16**, 11 (1960).
4. A. Franke and A. Kroupa. Monatsh. Chem. 347 (1930).
5. C. J. Eby and C. R. Hauser. J. Am. Chem. Soc. **79**, 723 (1957).
6. G. Shaw and G. Sugowdz. J. Chem. Soc. 665 (1954).
7. H. C. Brown and P. Heim. J. Am. Chem. Soc. **86**, 3566 (1964).