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THE STRUCTURE OF PITHECOLOBINE

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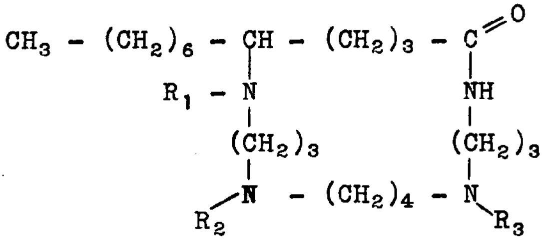
SOME time ago we have isolated[1] from the bark of the tree Pithecolobium saman Benth. the alkaloid pithecolobine, $C_{22}H_{46}N_4O_2$. Subsequently, we have shown[2,3] that this compound must be represented by the structures I or II.



(I)

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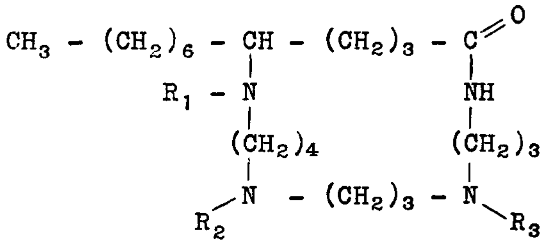
[1] K. Wiesner, D. M. MacDonald, Z. Valenta and R. Armstrong, Can. J. Chem. 30, 761 (1952).

[2] K. Wiesner, D. M. MacDonald and C. Bankiewicz, J. Am. Chem. Soc. 75, 6348 (1953).

[3] D. E. Orr and K. Wiesner, Chem. and Ind. 672 (1959).



(II)

one of R_1, R_2 or R_3 = OH
remaining two = H

We have now corroborated the formula I by a synthesis of racemic desoxypithecolobine tetratosylate (V). Desoxypithecolobine is a tetrasecondary base[2], $C_{22}H_{48}N_4$ obtainable from pithecolobine by lithium aluminum hydride reduction[1]. The synthesis was performed in analogy to the elegant syntheses of nitrogen containing macrocycles by Stetter[4].

Our starting material was 1,5-dibromododecane[5] which was converted into 1,5-diazidododecane by treatment with sodium azide in diethyleneglycol monomethyl ether as solvent at 95° for 30 hours. The diazide was not characterized but immediately converted into the hygroscopic oily 1,5-diaminododecane by hydrogenation in methanol with platinum oxide (b.p. 95°/0.04 mm outside temperature).

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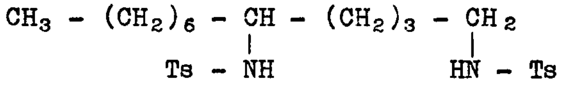
[4] H. Stetter and E. E. Roos, Chem. Ber. 87, 566 (1954).

[5] A. Franke and A. Kroupa, Monatsh. 56, 347 (1930).

The ditosylate of this compound (III) was a thick syrup which sublimed without decomposition in high vacuo. Found: C, 61.53; H, 7.93; N, 4.96; O, 13.14; S, 11.69. Calc. for $C_{26}H_{40}N_2O_4S_2$: C, 61.39; H, 7.93; N, 5.50; O, 12.58; S, 12.61%.

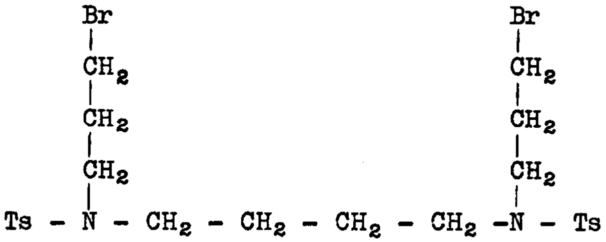
1,4-Diaminobutane was converted into the ditosylate (m.p. 140°) in the usual manner. Found: C, 54.34; H, 6.04; O, 15.82; N, 7.70; S, 15.89. Calc. for $C_{18}H_{24}N_2S_2O_4$: C, 54.52; H, 6.10; O, 16.14; N, 7.06; S, 16.17%.

The above compound was converted into the dibromide IV (m.p. 109°) by treatment with 1,3-dibromopropane under the conditions recommended by Stetter[4].



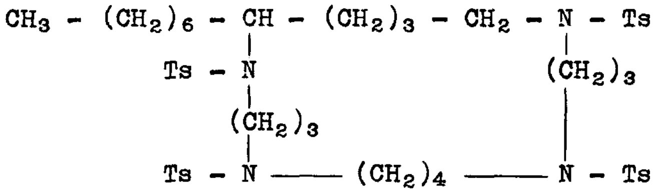
$CH_3-(CH_2)_6-CH(NH-Ts)-(CH_2)_3-CH_2-NH-Ts$

(III)



$Ts-N(CH_2-CH_2-CH_2-Br)-CH_2-CH_2-CH_2-CH_2-N(CH_2-CH_2-CH_2-Br)-Ts$

(IV)



(V)

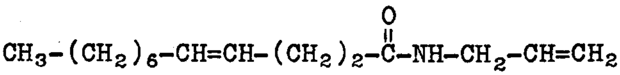
Found: C, 44.63; H, 5.28; O, 10.42; N, 4.26; S, 9.98; Br, 25.32. Calc. for $C_{24}H_{34}N_2S_2O_4Br_2$: C, 45.14; H, 5.36; O, 10.02; N, 4.39; S, 10.04; Br, 25.03%.

The coupling of the disodium salt of III with the dibromide IV was performed under high dilution in dimethyl formamide according to the directions of Stetter[4]. Compound V was separated from polymeric products by chromatography on alumina. It was eluted as a colorless glass by benzene-ether (1:1). It was rechromatographed and the peak fraction, which showed a constant infrared spectrum on repeated chromatography, was analysed after drying in high vacuo at 95°. Found: C, 61.93; H, 8.11; N, 5.61; O, 12.46; S, 12.13. Calc. for $C_{50}H_{72}N_4O_8S_4$: C, 60.94; H, 7.37; N, 5.69; O, 13.00; S, 13.03%.

The synthetic racemic compound V had an infrared spectrum superimposable on the spectrum of 'natural' desoxypithecolobine tetratosylate both in potassium bromide and in CCl_4 and $CHCl_3$ solution. Also, the NMR spectra of both materials were identical and fully compatible with structure V.

The NMR spectrum of pithecolobine is fully compatible with the formula I. It shows a peak (area 1H) at 1.50 ppm assigned to the hydroxylamine hydroxyl, and a multiplet (area 1H) at 4.68 ppm assigned to the amidic hydrogen. A multiplet centered at 6.65 ppm (area 2H) was assigned to the two hydrogens unshielded by the amidic nitrogen. A multiplet centered at 7.28 ppm (area 11H) was assigned to hydrogens unshielded by the three basic nitrogens. A triplet centered at 7.72 ppm (area 2H) was assigned to the two hydrogens unshielded by the amide carbonyl. A large unresolved peak between 8.43 and 8.57 ppm contained all the remaining hydrogens of I except the $C-CH_3$ group which appeared as a peak between 9 and 9.07 ppm (area 3H).

We have now ascertained by model experiments that diakyl hydroxylamines of the type I remained largely unchanged in the reduction with formic acid-formaldehyde and yield tertiary amine N-oxides by methylation with methyl iodide. Consequently, these two processes would be expected to convert I into a bis quaternary salt N-oxide. The fact that pyrolytic decomposition of this material yields tetramethyltrimethylene diamine and compound VI[2] is very



$$CH_3-(CH_2)_6-CH=CH-(CH_2)_2-\overset{O}{\overset{\|}{C}}-NH-CH_2-CH=CH_2$$

(VI)

easily rationalized if R_3 in formula I is a hydroxyl and R_1 and R_2 are hydrogens.

We wish to thank the Schering Corporation, New Jersey, and Hoffmann-LaRoche Inc., New Jersey for grants which enabled us to carry out this investigation. D.E.O. thanks the National Research Council, Ottawa, for a studentship.