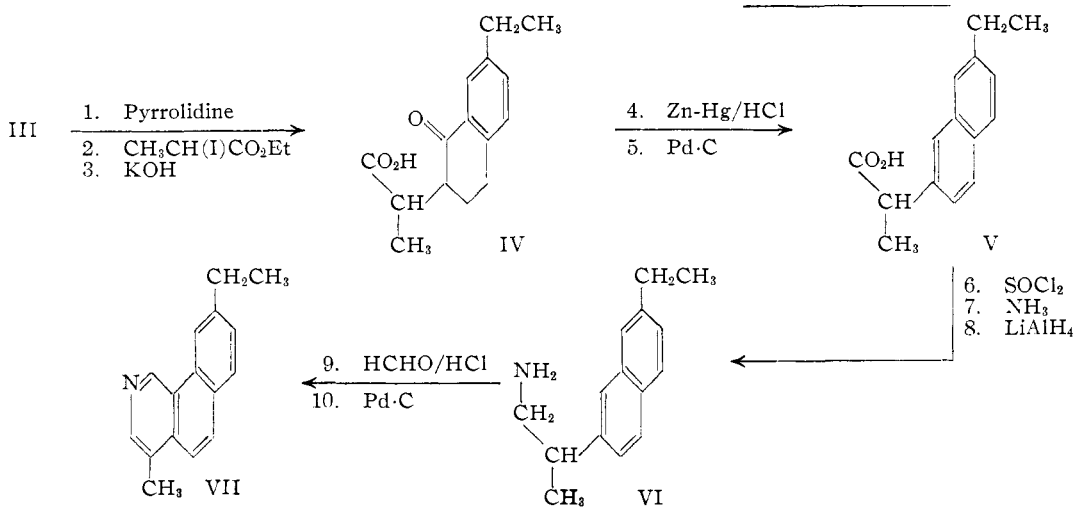
basic hydrolysis a crystalline mixture of acids (IV),[18] various fractions of which showed melting points between 103 and 129°, $\nu_{max}$ 1707 cm.$^{-1}$, 1680 cm.$^{-1}$ (Nujol). This material was reduced




by the Clemmensen method to a resinous product,[18] $\nu_{max}$ 1712 cm.$^{-1}$ (film) which on dehydrogenation with 10% palladium on carbon[16] at 240–250° furnished the crystalline α-methyl-7-ethyl-2-naphthaleneacetic acid (V),[18] m.p. 109–110°. Treatment of this acid with thionyl chloride followed by anhydrous ammonia in benzene gave the amide,[18] m.p. 105–107°, $\nu_{max}$ 1651 (Nujol). This amide was reduced by lithium aluminum hydride to the amine (VI) which was isolated as the hydrochloride,[18] m.p. 208–209°; picrate,[18] m.p. 215–218°. Reaction of the hydrochloride with formalin in 20% aqueous ethanolic hydrochloric acid[19] furnished the cyclization product (tetrahydro VII), also isolated as the crystalline hydrochloride,[18] m.p. 217–221°. Dehydrogenation of the free base was accomplished with 10% palladium on carbon at 225–235° to give 1-methyl-6-ethyl-3-azaphenanthrene (VII)[18] m.p. and mixture m.p. with material[20] from dehydrogenation of atisine, 83.5–85°; picrate,[18] m.p. and mixture m.p., 220–221°; trinitrobenzene adduct,[18] m.p. and mixture m.p. 122.5–123.5°. Infrared and ultraviolet absorption spectra of the two samples of the azaphenanthrene were identical.

(18) Analyses for carbon and hydrogen were satisfactory.

(19) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6** 151 (1951).

(20) We wish to express our gratitude to Drs. Jacobs and Craig for providing us with a sample of the $C_{16}H_{15}N$ dehydrogenation product from atisine.

THE ROCKEFELLER INSTITUTE DAVID M. LOCKE
NEW YORK 21, NEW YORK S. W. PELLETIER

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## 1,2-METHYL SHIFTS IN THE CYCLIZATION OF SQUALENE TO LANOSTEROL[1]

*Sir:*

For the rearrangement of the carbon skeleton in the cyclization of squalene to lanosterol the alternatives of a single 1,3-methyl shift and two 1,2-methyl shifts have been considered.[2,3] The two mechanisms can be distinguished as follows. All-*trans* squalene composed of the labeled species AA, BB, AB and BA (Fig. 1) was synthesized[4,5] from a mixture of 3-$C^{13}$, and 4-$C^{13}$ ethyl acetoacetate (65 at. % excess $C^{13}$ in the labeled carbons) and converted enzymatically to lanosterol.[6] The purified lanosterol was oxidized to acetic acid[7] which was converted to ethylene.[8] The relative amounts of $CH_2{=}CH_2$, $C^{13}H_2{=}CH_2$ and $C^{13}H_2{=}C^{13}H_2$ were determined in the mass spectrometer. $C^{13}$-labeled acetic acid (and hence ethylene) will be derived from $C_{13} + C_{18}$ and $C_{14} + C_{30}$ and diluted by normal acetic acid from other branched portions of lanosterol. Had the labeled carbons initially been 100% $C^{13}$, the relative amounts of masses 30, 29 and 28 would be 1:4:19 for 1,2-methyl shifts[9] and 0:6:18 for a 1,3-methyl shift. With 65% $C^{13}$ in the labeled position the excess of the labeled ethylenes above normal abundance should be those shown:

| For 1,2-Methyl shifts | | For 1,3-Methyl shift | |
|---|---|---|---|
| Before dilution | After dilution[10] | Before dilution | After dilution[10] |
| Excess $C^{13}H_2{=}C^{13}H_2$ | | | |
| $\frac{0.65 \times 0.65}{24} = 1.76$ | 0.117% | 0 | 0 |
| Excess $C^{13}H_2{=}CH_2$ | | | |
| $\frac{(2 \times 0.65 \times 0.35 + 4 \times 0.65)^{11}}{24} = 12.7\%$ | 0.84% | $\frac{6 \times 0.65}{24} = 16.2\%$ | 1.08% |

(1) This work was supported by grants-in-aid from the National Science Foundation, the U. S. Public Health Service, the Life Insurance Medical Research Fund and the Eugene Higgins Trust Fund of Harvard University.

(2) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(3) T. T. Tchen and K. Bloch, *J. Biol. Chem.*, **226**, 931 (1957).

(4) S. Trippett, *Chem. and Ind.*, 80 (1956).

(5) D. W. Dicker and M. C. Whiting, *ibid.*, 351 (1956). The authors wish to thank Dr. Whiting for making available the full details for the synthesis of all-*trans* squalene, prior to publication.

(6) T. T. Tchen and K. Bloch, *J. Biol. Chem.*, **226**, 921 (1957).

(7) R. Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).

(8) H. G. Wood, *J. Biol. Chem.*, **194**, 905 (1952).

(9) Since lanosterol has six branched methyl groups which can give rise to acetic acid and since the squalene contained four isotopic species, only one out of twenty-four acetic acid molecules can be doubly labeled.

(10) Non-isotopic acetic acid was added to the acetic acid derived from lanosterol.

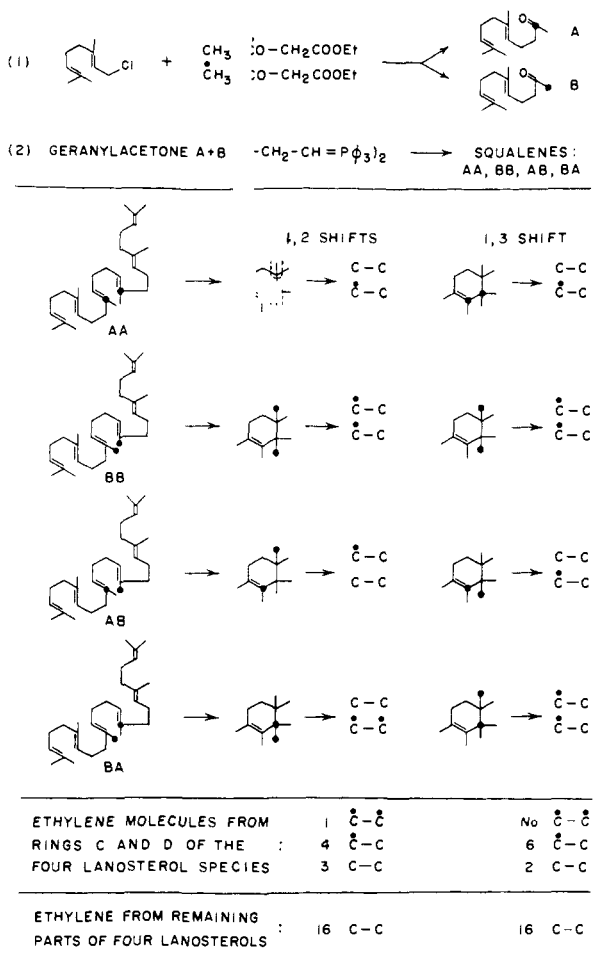


Fig. 1.—Since squalene is a symmetrical molecule, the species BA and AB are identical in the free state. However, the two are distinct in the form of a complex with the enzyme which may be assumed to have asymmetry.

Experimentally 0.181% excess $C^{13}H_2{=}C^{13}H_2$ and 1.652% $C^{13}H_2{=}CH_2$ were found.[12] The acetic acid from lanosterol thus contained doubly labeled molecules, proving methyl migration from $C_8$ to $C_{14}$, *i.e.*, two 1,2-methyl shifts in the course of cyclization.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
DEPARTMENT OF CHEMISTRY
12 OXFORD STREET
CAMBRIDGE, MASSACHUSETTS

R. K. MAUDGAL
T. T. TCHEN[13]
KONRAD BLOCH

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(11) The second term in the numerator represents the amount of singly labeled ethylene as indicated in Fig. 1. The first term arises from the fact that the starting material contained only 65% $C^{13}$; therefore, the "doubly labeled" acetic acid or ethylene actually contains singly labeled molecules to the extent of $2 \times 0.65 \times 0.35$. It is true that the "singly" labeled acetic acid also makes a contribution to doubly labeled species because of the normal abundance of $C^{13}$ but this will be less than 1% of the amount of singly labeled acetic acid and can therefore be neglected.

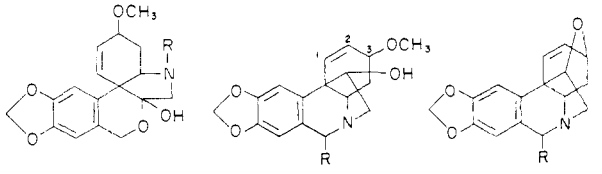
(12) The experimental values for ethylene of both mass 29 and 30 are higher than those calculated. This may be attributed to the unequal yield of acetic acid from different parts of the lanosterol molecule. This result does not affect our arguments which are based on the qualitative presence of doubly labeled ethylene rather than on the absolute amounts of this species.

(13) Scholar in Cancer Research of the American Cancer Society.

## OXOHAEMANTHIDINE: A BICYCLIC LACTAM POSSESSING A BRIDGEHEAD NITROGEN

*Sir:*

Haemanthidine,[1] $C_{17}H_{19}NO_5$, has been considered to be N-demethyltazettine (I, R = H) since methylation of the base with either methyl iodide[2] or formaldehyde and formic acid[3] affords tazettine (I, R = $CH_3$).[4] Data obtained recently in this Laboratory show this assignment to be incorrect.



I II III

The revised structure (II, R = OH) for haemanthidine is supported by these data. Haemanthidine has been found to form an O,O-diacetate ($\lambda_{max}^{CHCl_3}$ 5.73 $\mu$), not an O,N-diacetate as previously reported.[1] 6 *N* Hydrochloric acid at 90° converted haemanthidine to apohaemanthidine (III, R = OH), m.p. 195–196° dec., $[\alpha]^{23}D$ + 123°[5], (found for $C_{16}H_{15}NO_4$: C, 67.34; H, 5.27; N, 4.95; $OCH_3$, 0.00), $\lambda_{sh}^{EtOH}$ 240 m$\mu$ (3700) and $\lambda_{max}^{EtOH}$ 294 m$\mu$ (5050). Catalytic hydrogenation of III (R = OH) afforded a dihydro derivative, m.p. 258–260°, $[\alpha]^{24}D$ + 20.7°, (found for $C_{16}H_{17}NO_4$: C, 66.63; H, 5.90; N, 4.84), $\lambda_{max}^{EtOH}$ 241 (3700) and 293 m$\mu$ (4580), which was treated with thionyl chloride and then reduced directly with lithium aluminum hydride in tetrahydrofuran.[6] The product (III, R = H, no unsaturation 1, 2), m.p. 159–160°, $[\alpha]^{24}D$ + 108° (EtOH), was identical in all respects (infrared, ultraviolet spectra; rotation; m.p. and m.m.p. determinations) with dihydroapohaemanthamine[7] obtained by the action of 6 *N* hydrochloric acid on haemanthamine (II, R = H)[7] and then catalytic reduction.

Although the conversion of haemanthidine to haemanthamine has not been achieved by this route, the positions of the functional groups of haemanthidine must be as in II (R = OH) to account for its unusual conversion to tazettine (I, R = $CH_3$). In agreement with this structure, a chloroform solution of haemanthidine was oxidized by manganese dioxide to oxohaemanthidine, (II, R = O=), m.p. 194–196°, $[\alpha]^{23}D$ −41.4°, $\lambda_{max}^{Nujol}$ 3.16 (OH), 5.90 (C=O) and 6.20 (Ar) $\mu$, $\lambda_{max}^{EtOH}$ 232 (20,000), 275 (6300) and 326 m$\mu$ (5100), (found for $C_{17}H_{17}NO_5$: C, 64.94; H, 5.64; N, 4.33). Oxohaemanthidine formed a non-crystalline O-acetyl derivative ($\lambda_{max}^{CHCl_3}$ 5.75, 5.88 $\mu$). Under similar conditions dihydrohaemanthidine and apohaemanthidine afforded oxodihydrohaemanthidine

(1) H. G. Boit, *Chem. Ber.*, **87**, 1339 (1954).

(2) H. G. Boit and W. Stender, *ibid.*, **89**, 161 (1956).

(3) W. C. Wildman, *Chemistry and Industry*, 123 (1956).

(4) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 4749 (1956).

(5) Rotations obsd. in chloroform solution unless otherwise noted.

(6) In one attempt to isolate the intermediate chloroamine, only dihydroapohaemanthidine was recovered, presumably through the facile hydrolysis of the benzylic chloride.

(7) H. M. Fales and W. C. Wildman, *Chemistry and Industry*, 561 (1958).