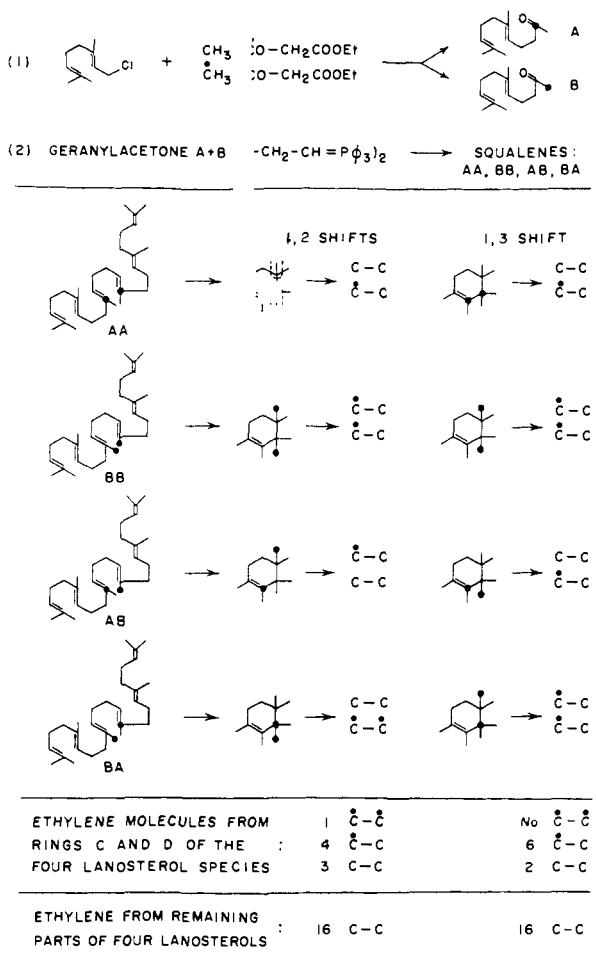

Fig. 1.—Since squalene is a symmetrical molecule, the species BA and AB are identical in the free state. However, the two are distinct in the form of a complex with the enzyme which may be assumed to have asymmetry.

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.

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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.

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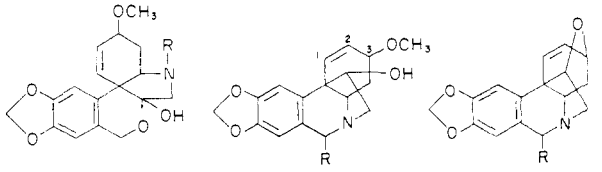
OXOHAEMANTHIDINE: A BICYCLIC LACTAM POSSESSING A BRIDGEHEAD NITROGEN

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 μ), 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), λ_{sh}^{EtOH} 240 mμ (3700) and λ_{max}^{EtOH} 294 mμ (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), λ_{max}^{EtOH} 241 (3700) and 293 mμ (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°, λ_{max}^{Nujol} 3.16 (OH), 5.90 (C=O) and 6.20 (Ar) μ, λ_{max}^{EtOH} 232 (20,000), 275 (6300) and 326 mμ (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 μ). 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).

(II, R = O=, no 1,2-unsaturation), m.p. 254–255°, $[\alpha]^{23}D$ +36°, $\lambda_{max}^{CHCl_3}$ 2.75, 5.90 and 6.18 μ, λ_{max}^{EtOH} 234 (22,900), 274 (6500) and 325 mμ (5300), (found for $C_{17}H_{19}NO_5$: C, 64.42; H, 5.96), and oxoapohaemanthidine, (III, R = O=), m.p. 142–145°, $[\alpha]^{24}D$ +230°, $\lambda_{max}^{CHCl_3}$ 5.88 and 6.20 μ, λ_{max}^{EtOH} 236 (24,200), 276 (6000) and 322 mμ (5000), (found for $C_{16}H_{13}NO_4$: C, 67.89; H, 4.53), respectively. These oxidation products represent three compounds of proven structure which, for theoretical reasons, should possess the properties of amino ketones rather than lactams.[8] Preliminary evidence supporting this view includes the positions of the infrared carbonyl maxima, the ultraviolet spectra and the facile reduction in methanol of each oxo compound to the respective starting alcohol by sodium borohydride.

(8) *Cf.* the reported synthesis of 2-quinuclidone, L. N. Yakhontov and M. V. Rubtsov, *Zhur. Obshchei Khim.*, **27**, 72 (1957); *C.A.*, **51**, 12085b (1957).

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INTRAMOLECULAR BIFUNCTIONAL CATALYSIS OF ESTER HYDROLYSIS

Sir:

It has been demonstrated previously that the solvolysis of phenyl esters is powerfully catalyzed by suitably spaced neighboring ionized carboxyl groups.[1,2,3] Such reactions should be further accelerated, if the ester carries a second substituent which will stabilize the transition state, *e.g.*, by hydrogen bonding or by ion pair formation. The principle is similar to the "bifunctional catalysis" of Swain and Brown[4] except that all three functional groups form part of a single molecule.

We have tested this assumption by comparing the *p*H dependence of the solvolysis rate of compounds I, II, and III. The results obtained in aqueous solution at 25° are plotted in Fig. 1 and show that I and II hydrolyze in the *p*H range 3–9

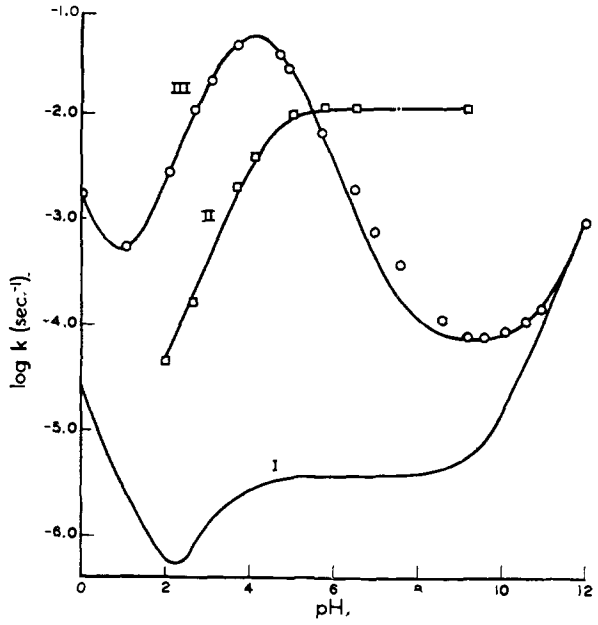
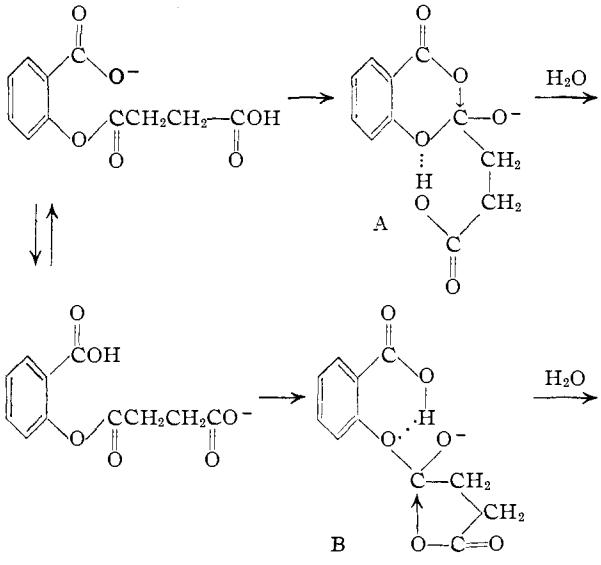


Fig. 1.—Hydrolysis rate constants at 25°; data for compound I from reference 3.

at rates proportional to their carboxyl ionization, while III hydrolyzes at a rate corresponding to the concentration of the singly ionized species, assuming pK = 3.62 and 4.5 for the salicylic and succinic carboxyls, respectively. Two pathways are possible and no distinction may be made between them from kinetic data. If the reaction proceeds exclusively through A, this intermediate would decompose 24,000 times as fast as ionized I which has the carboxylate in the same position but lacks the second, un-ionized, carboxyl. Conversely, if the reaction proceeds through B, this intermediate is 66 times as reactive as ionized II.



Intramolecular catalysis by neighboring functional groups, such as observed with compound

(1) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).

(2) (a) H. Morawetz and P. E. Zimmering, *J. Phys. Chem.*, **58**, 753 (1954). (b) P. E. Zimmering, E. W. Westhead, Jr., and H. Morawetz, *Biochim. Biophys. Acta*, **25**, 376 (1957).

(3) E. R. Garrett, THIS JOURNAL, **79**, 3401 (1957).

(4) C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2538 (1952).