Stereospecific Cyclisation of Agerol to an Isovetivane Carbon Framework

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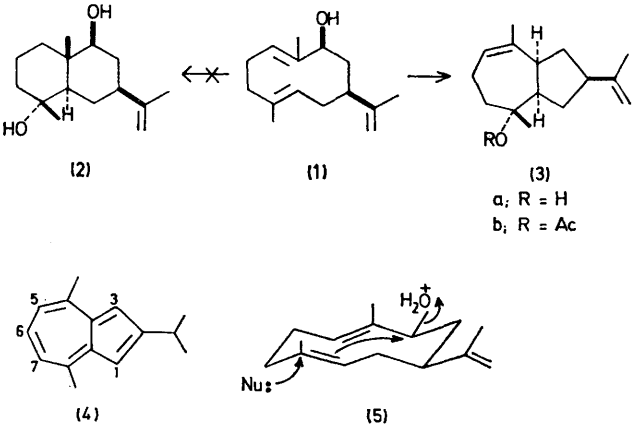
Summary Acid-catalysed conversion of a germacrane sesquiterpene into compounds with the unknown isovetivane framework was carried out by using aqueous acetic acid.

DURING our investigation of biogenetic type synthesis[1] of natural products, the hypothesis was put forward that a structure like (**2**) (selinane structure), relating, for example, to the still controversial structure of canarone,[2] may be obtained by acid cyclisation[3a] of agerol[4] (**1**).

After several unsuccessful attempts, which led mainly to tars, we succeeded in converting (88%) agerol (**1**) into two bicyclic compounds. The spectral properties of neither of these compounds were consistent with a structure like (**2**). Treatment of (**1**) with 80% aqueous AcOH afforded a mixture (2:1) of two compounds recognised as the alcohol (**3a**) [b.p. 110—112 °C at 0·1 mmHg, $[\alpha]_D^{20}$ — 6·8° (*c* 3 MeOH); δ (CCl_4) 1·12 (3H, s), 1·7 (6H, br s), 4·68 (2H, br s), and 5·45 (1H, m); *m/e* 202 ($M^+ - H_2O$)] and its acetate (**3b**) [b.p. 115—117 °C at 0·5 mmHg, δ (CCl_4) 1·46 (3H, s) and 1·9 (3H, s)]. When treated with NaOH or $LiAlH_4$, (**3b**) was converted into (**3a**).

The isovetivane framework was assigned on the basis of dehydrogenation (Se, 280 °C) of (**3a**) to give a homogeneous



(g.l.c.) purple oil (**4**), 90%, b.p. 120—122 °C at 1 mmHg; λ_{max} (hexane) 350 (log ε 3·56), 336 (3·48), 310 (3·62), 291

(4·63), 283 (4·58), and 248 (4·36) nm; δ (CCl_4, 100 MHz) 1·40 (6H, d), 2·85 (6H, s), 3·24 (1H, m), 7·10 (2H, s, H-1 and H-3), 7·25 (1H, H-6), and 6·96 (2H, H-5 and H-7, AB_2, J 10·4 Hz); m/e 198 (M^+). The number and the type of signals in the ^1H n.m.r. spectrum of (**4**) indicate a degree of symmetry which, among all the skeletons which can be suggested from the cyclisation of (**1**), is appropriate only to isovetivazulene, a hydrocarbon which, as far as we know, is hitherto unknown.

The stereochemistry indicated in (**3a**) and (**3b**) was proposed on the basis of a stereospecific electrophile-induced cyclisation.[3a] Certain assumptions are made in this cyclisation. Firstly, it is assumed that the same conformation of agerol involved in the cyclisation to β-elemen-9β-ol[4] is involved in this acid-catalysed rearrangement. Secondly, the formation of the bicyclic products involves the conversion of a *trans* double bond into *cis*. This, we believe occurs by isomerisation of the *trans* to the *cis* cyclic allylic cation.[3b] In order to get the *cis* A/B ring fusion in the products, the formation of the cation must not affect the conformation of the rest of the molecule before ring closure takes place. Further, successive treatments of (**3a**) with H_2–PtO_2, mesyl chloride–pyridine, and $NaBH_4$–Me_2SO[5] afforded a mixture (6:1·2:1) of three isomeric saturated hydrocarbons. The most abundant of these, separated by preparative g.l.c., was optically inactive.

The formation of (**3a**) and (**3b**), which is unexpected according to the normal cyclisation to selinane systems, can be considered as an allylic cation-promoted olefinic cyclisation,[6] which is usually highly stereospecific and takes place with high yields.

Considering the absence of stereoisomers even under different experimental conditions (*e.g.*, H_2O–$MeC_6H_4SO_3H$-*p*) and the conformation[4] of the agerol molecule, the most likely mechanism is a concerted one and the formation of the allylic cation is immediately followed by cyclisation and preferential equatorial attack by nucleophile at C-4 (**5**).

As far as we know, compounds (**3a**) and (**3b**) are the only examples of isovetivane structures, since the natural products previously reported as derived from isovetivane, were later shown to have spiranic structure.[7] Thus isovetivazulene (**4**) is the new aromatic hydrocarbon which characterises the skeleton of this class of compounds.

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