Tetrahedron Letters No. 5, pp 401 - 404, 1976. Pergamon Press. Printed in Great Britain.

A NOVEL EPOXIDE REARRANGEMENT: THE CONVERSION OF OXIRANES INTO TETRAHYDROFURANS

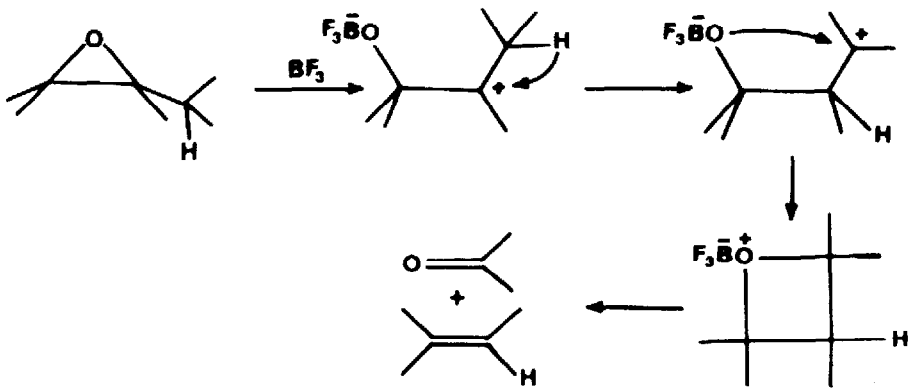
Giancarlo Berti, Serena Catalano, Antonio Marsili, Ivano Morelli* and Valerio Scartoni

Istituto di Chimica Organica della Facoltà di Farmacia
Via Bonanno, 6 - 56100 Pisa, Italy

(Received in UK 26 November 1975; accepted for publication 22 December 1975)

THE action of acids on 1,2-epoxides can produce a wide range of ring-opening and rearrangement reactions; the recently reported cleavage to alkenes and oxo derivatives (Scheme)[1], involving the intermediate formation of an oxetane,[1,2] takes a particular position in this picture and is of some interest, since it appears to be mechanistically related to the biosynthetic conversion of phytosterols into cholesterol in insects.[3]

SCHEME



With the purpose of investigating the scope and mechanism of this reaction and of finding new routes for the controlled degradation of the

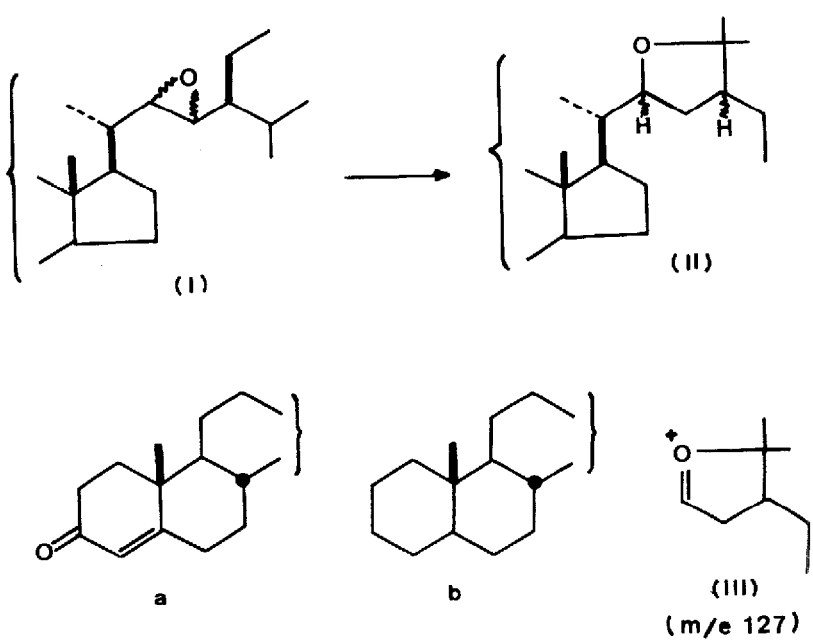
steroid side chain, we reacted 22,23-epoxystigmast-4-en-3-one (Ia) and 22,23-epoxy-5α-stigmastane (Ib) with BF_3-ether complex, in the hope that the presence of a bisecondary epoxy function flanked by two tertiary carbons could make them good candidates for a cleavage of this type. No fragmentation took place however in either case and the main products (ca. 70% yields), m.p. 113-115° from (Ia) and m.p.104-107° from (Ib), were isomeric with the starting epoxides. The absence of OH or C=O stretching bands in the i.r. (except for the 3-oxo group in the product from Ib), the disappearance of the two epoxide α proton signals at δ 2.52 and 2.76 ppm, and the appearance of a one-proton multiplet at δ 4.05 ppm pointed to the conversion of the oxirane into a cyclic ether with a larger ring in which oxygen is bound to a tertiary and a secondary carbon. The possibility that this was an oxetane ring, formed by the first three steps in the Scheme, was unlikely because of the ease with which heavily substituted compounds of this type undergo cleavage under the reaction conditions (fourth step in the Scheme). A tetrahydropyran ring was also ruled out both on mechanistic and on structural grounds, since it should have more than one proton α to oxygen. On the other hand the tetrahydrofuran structures (IIa) and (IIb) were fully consistent with the experimental data. The involvement of C(25) in the oxygen bridging is indicated by a strong downfield shift in the spectra of the new ethers of the signals corresponding to two methyl groups, which appear as a single singlet at δ 1,22 ppm, in agreement with the deshielding effect of the nearby oxygen atom and with the disappearance of the coupling with the proton at C(25). Shidasterone, a steroid with a 22,25-epoxide bridge,[4] shows the signals for the protons at C(22) and at C(26) and C(27) respectively at δ 4.06 and 1.22 ppm, in perfect agreement with the data for (II). Furthermore the mass spectrum of (IIa) and (IIb) show a molecular peak of very low abundance, but a very strong base peak, at m/e 127, containing oxygen (loss of water to give m/e 109, with corresponding metastable peak). Of the several possible cyclic ethers deriving from (I) only those of type (II) could give such a fragmentation, producing ion (III). The same type of fragmentation has been reported for shidasterone, except for the fact that since this compound lacks the ethyl group at C(24), the strong base peak is found at m/e 99.[4]

The epoxides (Ia), m.p.114-116°,[5] and (Ib), m.p.92-94°, were prepared by protracted treatment of the corresponding olefins with m-chloroperoxybenzoic acid. In both cases mixtures of two diastereoisomeric epoxides were

obtained, from which the major components (80% by g.l.c.)[6] were isolated and purified by fractional crystallisation. The unknown 5α-stigmast-22-ene, m.p.123-125°, was obtained from stigmasta-5,22-diene,[7] by a route which will be described in the full paper.

The fact that the epoxides (I) do not behave according to the sequence shown in the Scheme, but that the initially formed carbonium ion rather undergoes a 1,3- or two consecutive 1,2-hydride shifts before ring closure must in some way be related to the very crowded surroundings of the oxirane ring, imposing a conformational situation not favourable for the cyclisation at the 24-carbonium ion stage, or particularly favourable for the 1,3-hydride shift at the 23-carbonium ion stage. The problem will be analysed in a more detailed way when the relative configuration of (II) at C(22) and C(25) will be known.

A number of steroids with an oxygen bridge between positions 22 and 25 have been isolated from natural sources:[4,8] the easy formation of (II) from (I) may suggest that 22,23-epoxides could play some role in their biogenesis. This reaction could also find some use as an easy way for introducing an oxygenated function at C(25), such as is found in many ecdysones.



Acknowledgements Thanks are due to Dr.V.Nuti for the elemental analyses and Prof.A.Selva (Milan) for the mass spectra. This work was supported by a grant from Consiglio Nazionale delle Ricerche (C.N.R.)

References and footnotes

[1] I.Morelli, S.Catalano, G.Moretto and A.Marsili, Tetrahedron Letters, 717(1972).

[2] I.G.Guest and B.A.Marples, J.Chem.Soc.(C), 1626(1970).

[3] M.Morisaki, H.Ohtaka, M.Okubayashi, N.Ikekawa, Y.Horie and S.Nakasone, Chem.Commun., 1275(1972).

[4] H.Hikino, J.Okuyama, S.Arihara, Y.Hikino, T.Takamoto, H.Mori and K.Shibata, Chem.Pharm.Bull.(Jap.), 23, 1458(1975).

[5] J.B.Jones and N.Baskevitch, Steroids, 22, 525(1973).

[6] The degree of stereoselectivity of these epoxidation reactions is higher than in ergost-22-ene derivatives [see D.H.R.Barton, J.P.Poyser and P.G.Sammes, J.C.S. Perkin I, 53, (1972)]. The preferential formation of the (22R, 23R) isomer found for the latter derivatives cannot be safely assumed to apply also to the stigmast-22-ene derivatives, since the opposite chirality and different substituents at C(24) could produce different preferential conformations of the side chain. However, if the bulky steroid ring system is the determinant factor for the stereoselectivity, it could be likely that also in the case of the stigmastene derivatives the main epoxide has the (22R, 23R) configuration. We are at present trying to clarify this point.

[7] D.H.R.Barton and A.J.Head, J.Chem.Soc., 932(1956).

[8] J.S.Grossert, Chem.Soc.Rev., 1, 1(1972).