685. *The Constituents of* Ecballium elaterium L. *Part XIX.*[1] *Elateric Acid.*

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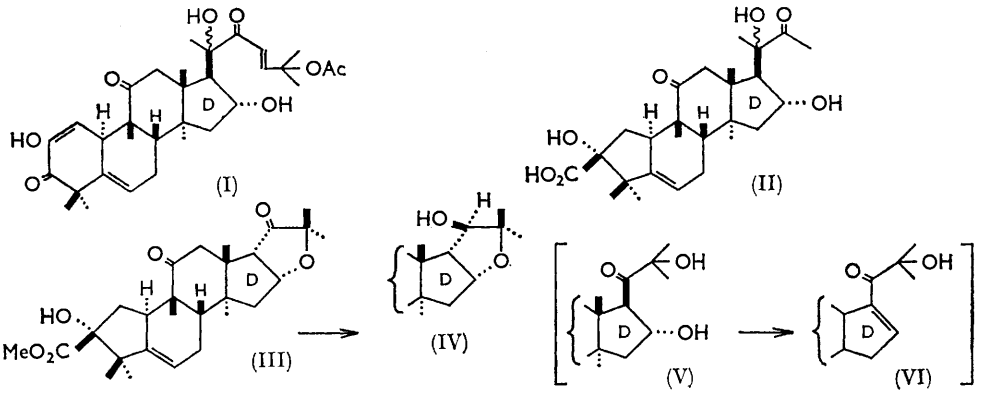
The alkaline degradation of elaterin has been studied. Two new compounds have been isolated and identified as methyl elaterate (III) and methyl isoelaterate (IX). The rearrangements leading to these compounds and their complete stereochemistry are described and discussed.

The alkaline treatment of elaterin (cucurbitacin E) (I) has been the subject of several publications.[2] A series of rather complicated reactions takes place when elaterin and a few other cucurbitacins are treated with aqueous alkali. Ring A, which contains a diosphenol system, undergoes a benzilic acid rearrangement to give an α-hydroxy-acid. At the same time a hydrolytic splitting takes place in the side-chain whereby the double bond conjugated to the carbonyl group is hydrated and subsequently cleaved. The resulting

[1] Part XVIII, Lavie, Shvo, Gottlieb, and Glotter, *Tetrahedron Letters*, 1961, No. 18, 615. However, chronologically, the preceding part is Part XVI, Lavie, Shvo, Gottlieb, and Glotter, *J. Org. Chem.*, 1963, **28**, 1790.

[2] Lavie and Willner, *J. Amer. Chem. Soc.*, 1960, **82**, 1668, and references therein.

product, ecballic acid,[3] has in its shortened side-chain an α-hydroxy-ketone system, as shown in (II). It is interesting to note that, under these alkaline conditions, the severed portion of the side-chain, α-hydroxyisobutyraldehyde, also underwent an acyloin rearrangement yielding acetoin as the final product.[4] The major product, ecballic acid, representing the main portion of the molecule, was obtained in varying and unexpectedly low yields. On subjecting elaterin to alkaline treatment, Borsche and Diacont obtained ecballic acid [5a] in addition to what had previously been referred to as " acide élatérique." *



In our experiments, the product of the alkaline treatment of elaterin was converted into a methyl ester with diazomethane before purification. Careful column chromatography of the crude ester yielded a crystalline substance in addition to methyl ecballate.[3] A distinct relationship was established between the relative yields of these two substances and the duration of the alkaline treatment. Prolonged treatment gave a higher yield of the new product, methyl elaterate. Moreover, treatment of pure methyl ecballate under the above conditions for a long time (47 hours) resulted in its complete conversion into methyl elaterate. Similarly, methyl elaterate was obtained to the complete exclusion of methyl ecballate on treatment of elaterin with alkali for a comparable time.

The analysis of the new compound, methyl elaterate, to which structure (III) is assigned, indicated an empirical formula $C_{27}H_{38}O_6$, which differed from that of methyl ecballate by the elements of one molecule of water. The two compounds had markedly different spectral properties. The ultraviolet spectrum of the new compound showed the end-absorption of the C-5 double bond, whereas the infrared spectrum displayed, in addition to the expected bands at 1698 and 1733 cm.$^{-1}$ for the C-11 carbonyl and the ester grouping, respectively, strong new bands at 1751 and 1156 cm.$^{-1}$. The former indicates a five-membered-ring ketone and the latter a cyclic ether. Moreover, the hydroxyl region of the spectrum of methyl elaterate showed a much weaker band than that of methyl ecballate. The nuclear magnetic resonance (n.m.r.) spectra of the two substances, which were similar in several aspects, differed noticeably in the low region of the methyl-group signals. In methyl ecballate, in addition to the six methyl-group signals, one at τ 7·70 was observed for the methyl ketone group. In methyl elaterate, however, this signal was lacking. Instead, the spectrum showed a cluster of peaks which accounted for seven methyl groups. Furthermore, the C-16 proton vicinal to the ether linkage was observed as a multiplet centred at

* The name " acide élatérique " or " Elaterinsaüre " was first given to a crude, amorphous mixture of substances.[5b] This mixture must have contained, in addition to ecballic acid, the products described in this Paper, elateric and isoelateric acid.

[3] Lavie and Szinai, *J. Amer. Chem. Soc.*, 1958, **80**, 707; Lavie, Shvo, Gottlieb, and Glotter, *J. Org. Chem.*, 1962, **27**, 4546.

[4] Lavie, Shvo, and Willner, *J. Amer. Chem. Soc.*, 1959, **81**, 3062.

[5] (*a*) Borsche and Diacont, *Annalen*, 1937, **528**, 39; (*b*) Berg, *Bull. Soc. chim. France*, 1906, **35**, 435; *Compt. rend.*, 1909, **148**, 1679; Hemmelmayr, *Ber.*, 1906, **39**, 3652; Moore, *J.*, 1910, **97**, 1797.

τ 4·95. These observations strongly suggest a conversion from structure (II) into (III). The change involves the disappearance of the COMe group, consistent with the earlier observation that methyl elaterate (III) gives a negative iodoform test.

The above spectroscopic evidence can best be explained with structural formula (III), which is also supported by chemical data. Methyl ecballate consumed one mole of periodic acid with cleavage of the α-hydroxy-ketone of its side-chain,[2] whereas methyl elaterate (III) was recovered unchanged. Furthermore, acetylation of methyl elaterate did not produce an acetate, which would have been indicative of the 16-hydroxy-group originally present in methyl ecballate.[6] Reduction of methyl elaterate with aluminium amalgam gave the alcohol (IV) in which the 17-carbonyl group was reduced, as shown by the infrared spectrum, the band at 1751 cm.$^{-1}$ due to the five-membered ring ketone being absent. The n.m.r. spectra of the alcohol and of methyl elaterate distinctly show that only in the case of the alcohol is there a doublet at τ 6·74 (J = 5·9 c./sec.) due to the proton at C-20 which is split by its neighbouring C-17 β-proton (as discussed later). By comparing the coupling constant displayed by the C-20 proton with the data obtained by Anet,[7] we could not reach an unequivocal decision as to the magnitude of the dihedral angle formed by the system involving the protons in question. However, the coupling constant (J = 5·9 c./sec.) corresponds to a favoured dihedral angle of 140° and the hydroxyl group in the alcohol should therefore be β-oriented.

The alcohol (IV) was easily acetylated; its infrared spectrum displayed a broad ester band at 1736 cm.$^{-1}$, and oxidation with chromium trioxide gave back methyl elaterate.

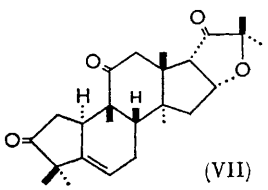
The formation of ring E in methyl elaterate, as shown in (III), can be explained by the following sequence. In the course of the alkaline treatment of elaterin (I), the α-hydroxy-ketone present in the side-chain of ecballic acid undergoes an acyloin rearrangement whereby the 20-methyl group shifts to position 22, thus resulting in structure (V). At this stage the 16-hydroxy-group readily undergoes elimination, yielding an αβ-unsaturated ketone (VI). Furthermore, under the conditions of the reaction an electron deficiency is induced at C-16, which brings about a nucleophilic attack from the 22-hydroxy-group, thus resulting in the formation of an ether linkage and in the completion of the five-membered ring E.

Of the several attempts to cleave the ether linkage in ring E of methyl elaterate (III) using such systems as benzoyl chloride–zinc chloride, methylene dichloride–boron tribromide, lithium bromide–boron trifluoride–acetic anhydride, only boiling in lithium aluminium hydride proved satisfactory. This reagent also reduced all the carbonyl groups, producing a mixture which was oxidized with periodic acid in order to bring about the cleavage of the newly formed glycol in ring A which might otherwise have interfered in the subsequent reactions. The mixture was treated with chromium trioxide in cold acetone to oxidize the carbinol groups. Column chromatography yielded two crystalline substances. Whilst one of these appeared to be the cleaved-ring compound (VIII), the other major product was identified chemically and spectroscopically as the trione, elatericone, (VII) derived from methyl elaterate. Compound (VIII), which was obtained in minute quantity, showed a strong ultraviolet band at 242 mμ (ε 11,460) and its infrared spectrum displayed three sharp bands in the carbonyl region: 1751 (ring A five-membered-ring ketone), 1704 (11-carbonyl group), and 1670 cm.$^{-1}$ (Δ^{16}-20-ketone). From the above spectroscopic evidence the structure of (VIII) was derived; it could be formed by cleavage of the ether linkage in (IV) resulting in the formation of a 16-hydroxy-group which is readily eliminated under the experimental conditions.

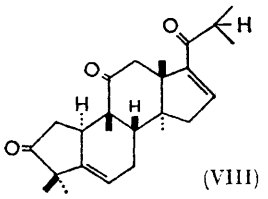
During the careful purification of methyl elaterate, a crystalline isomer, methyl isoelaterate (IX), was isolated in somewhat smaller amount. The n.m.r. measurements of the two isomers showed a set of doublets for methyl elaterate centred at τ 6·51 and 7·48 (J = 16 c./sec.) whilst the doublets for methyl isoelaterate were centred at τ 6·90 and 7·41 (J = 16 c./sec.). These signals were assigned to the two non-equivalent C-12 protons in

[6] Gilbert and Mathieson, *Tetrahedron*, 1958, **4**, 302.
[7] Anet, *Canad. J. Chem.*, 1961, **39**, 789.

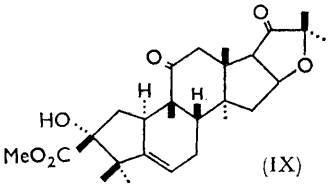
each of the two compounds. A comparison of the models of these two isomers reveals that, when ring E is α-oriented with respect to the plane of ring D, the α-hydrogen at C-12 assumes a position equidistant from the deshielding cones of the carbonyl groups [8] at the neighbouring C-11 and the non-neighbouring C-20; this proton should therefore display a signal at lower field. Since in the spectrum of methyl elaterate a low-field signal was recorded at



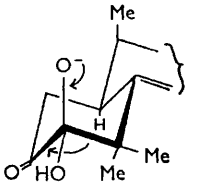
(VII)



(VIII)



(IX)



(X)

τ 6·51, structure (III) assigned to this compound has an α-oriented ring E, whilst in methyl isoelaterate this ring is β-oriented.

The peaks for the C-17 proton, which couples its spin with that of C-16, appeared in each isomer as a doublet centred at τ 7·25 and 6·97 (J = 7 c./sec.) for methyl elaterate and methyl isoelaterate, respectively. The observed coupling constant for both doublets is in good agreement with that for *cis*-fused five-membered-ring systems.[7]

Additional support for these conclusions was secured from the optical rotatory dispersion curves of methyl elaterate and isoelaterate. Their respective amplitudes [9] were $a = +360$ and $a = +217$. In order to eliminate the contribution of the 11-carbonyl group the curve of the alcohol (IV), $a = +238$, was subtracted from that of each of the two isomers. The contributions of the 17-keto-group, assuming no vicinal action, are, therefore, for methyl elaterate $\Delta a = +122$ and for methyl isoelaterate, $\Delta a = -21$. Octant diagrams drawn for ring E indicate that for methyl elaterate the molecule falls almost entirely into a positive octant, whilst for methyl isoelaterate it falls into a negative octant. These observations reaffirm the α- and β-orientation of ring E in methyl elaterate and isoelaterate, respectively.

In order to present the complete stereochemistry of elateric acid, a more detailed study of the benzilic acid rearrangement of ring A is necessary. It has been observed [2] that the α-diketone in ring A occurs primarily as a diosphenol system having the carbonyl group at C-3 (I). Since, logically, the diosphenol is largely, if not entirely, present as a C–O^- anion in alkaline solution, it is reasonable to assume that the C-3 atom of the carbonyl group offers the better acceptor site for the hydroxyl-ion attack. Once C-3 is attacked, the enolising potential of the diosphenol system in ring A is greatly relieved, thus making it possible to revert from the enol to the keto-form.[10] This in turn is followed by a typical benzilic acid rearrangement which, in this case, is unidirectional, resulting in a new bond between C-4 and C-2. As shown in (X), C-2, which becomes a carboxyl group, remains above the plane of the ring, *i.e.*, assuming a β-orientation. That only one site (C-3) is preferred for the hydroxyl-ion attack is supported by the fact that repeated preparations of methyl elaterate by the alkaline treatment of elaterin or of ecballic acid consistently produced only one isomer with respect to ring A. This was verified by thin-layer chromatography.

[8] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London and New York, 1959, p. 122.
[9] Djerassi and Klyne, *J.*, 1962, 4929.
[10] Wendler, Taub, and Graber, *Tetrahedron*, 1959, **7**, 173.

The above evidence made the completion of the stereochemistry of elateric and ecballic acid possible. The configuration at C-2 conforms with previous observations of the benzilic acid-rearrangement product of 2-hydroxy-4,4-dimethylcholest-1-en-3-one, in which the carboxylic acid is α-oriented.[11] In the latter compound, the C-10 substituent is β-oriented, whereas in the cucurbitane series it is α-oriented. The conclusion (ref. 11) that attack by hydroxyl ion at position 2 or 3 of the diketone form would lead only to a β-oriented hydroxy-group in the hydroxy-acid is not acceptable. Such an attack should lead to the formation of two different isomers, depending on the acceptor site.[12]

Experimental

Melting points were taken on a Kofler hot-stage apparatus and are corrected. Optical rotations refer to chloroform solutions. Ultraviolet spectra were determined in 95% ethanol with a Cary 14 Spectrophotomoter. Infrared spectra were recorded on a Perkin-Elmer Infracord model 137 spectrophotometer equipped with a sodium chloride prism and were for potassium bromide discs. N.m.r. spectra were recorded on a Varian A-60 Spectrometer for 5—10% solutions in $CDCl_3$ containing tetramethylsilane as internal standard. Thin-layer chromatography was done on chromatoplates of silica gel G (Merck) and spots were developed with 0·5% potassium permanganate in saturated cupric acetate solution.

Methyl Elaterate (III).—Elaterin (5 g.) was refluxed with 4% aqueous sodium hydroxide (300 ml.) for 47 hr., with stirring, under nitrogen, filtered, and the filtrate was acidified with dilute hydrochloric acid. The crude elateric acid (4·0 g.) was extracted with ether (3 × 100 ml.) and the extract treated with 10% aqueous sodium hydrogen carbonate. Acidification of the aqueous portion gave a precipitate which was taken up in chloroform. The solution was washed with water, dried (Na_2SO_4), and evaporated, and the residue treated with diazomethane. The crude methyl elaterate (1·7 g.) was purified by chromatography on Florisil (100—200 mesh) in benzene then ether–benzene. The main fraction containing the product (1·4 g.) was eluted with ether–benzene (1 : 9). *Methyl elaterate* had m. p. 192—194° (from light petroleum), $[\alpha]_D$ +185° (*c* 1·0), single spot on chromatoplate, $\nu_{max.}$ 1751, 1733, 1698, and 1156 cm.$^{-1}$, τ 4·48, 4·97, doublets at 6·51 and 7·48 (J = 17 c./sec.), doublet at 7·25 (J = 7 c./sec.), and 6·21 (OMe), $[\phi]_{312·5}$ +13,200 and $[\phi]_{272·5}$ −22,800 (Found: C, 70·95; H, 8·15. $C_{27}H_{38}O_6$ requires C, 70·7; H, 8·35%).

Methyl Isoelaterate (IX).—Elution of the above column with ether yielded the *ester* (420 mg.), long needles, m. p. 263—264° (from ether), $[\alpha]_D$ −119° (*c* 1·0), single spot on chromatoplate, $\nu_{max.}$ 1751, 1736, 1698, and 1170 cm.$^{-1}$, τ 4·47, 4·97, doublets at 6·90 and 7·41 (J = 17 c./sec.), doublet at 6·97 (J = 7 c./sec.), and 6·17 (OMe), $[\phi]_{312·5}$ +5590 and $[\phi]_{272·5}$ −16,100 (Found: C, 70·7; H, 8·25. $C_{27}H_{38}O_6$ requires C, 70·7; H, 8·35%).

Reduction of Methyl Elaterate.—Methyl elaterate (III) (1·3 g.) was dissolved in ether and the solution treated with freshly prepared aluminium amalgam. A few drops of water were added periodically to ensure steady evolution of hydrogen. The reaction was allowed to proceed for 1 week, the mixture was filtered, and the solid continuously extracted (24 hr.) with chloroform. The chloroform extract and the above ethereal filtrate were combined and evaporated to dryness. The residue (545 mg.) was purified by chromatography on acid-washed alumina (Merck) in benzene then ethyl acetate–benzene. The *alcohol* (IV) (249 mg.), eluted in ethyl acetate–benzene (1 : 1), had m. p. 207—212° (from ether), $\nu_{max.}$ 1736, 1692, and 1153 cm.$^{-1}$, doublets at τ 7·45 and 7·77 (J = 11 c./sec.), doublet at 6·74 (J = 5·9 c./sec.), $[\phi]_{312·5}$ +7720 and $[\phi]_{272·5}$ −16,100 (Found: C, 70·45; H, 8·7. $C_{27}H_{40}O_6$ requires C, 70·4; H, 8·75%).

Elatericone (VII).—To a suspension of lithium aluminium hydride (2 g.) in tetrahydrofuran (80 ml.) a solution of methyl elaterate (800 mg.) in tetrahydrofuran (60 ml.) was added dropwise. The mixture was heated under reflux for 3·5 hr., decomposed by addition of ethyl acetate and saturated sodium sulphate solution, filtered, dried (Na_2SO_4), and evaporated to dryness, leaving a residue (840 mg.), $\nu_{max.}$ 1727, 1686, and 1145 cm.$^{-1}$.

A solution of periodic acid (5·5 g.) in water (40 ml.) was added to a solution of the above reduced product (840 mg.) in dioxan (30 ml.) and set aside for 24 hr. at room temperature. Ethylene glycol (4 ml.) was added to destroy any unreacted periodic acid, and, after a further

[11] Chaudhry, Halsall, and Jones, *J.*, 1961, 2725.
[12] Biellmann and Rajic, *Bull. Soc. chim. France*, 1962, 441; Georgian and Kundu, *Tetrahedron*, 1963, **19**, 1037.

½ hr., the mixture was diluted with water (50 ml.) and the crude product extracted with chloroform and dried (Na_2SO_4). Evaporation of the chloroform solution yielded a residue (650 mg.), $\nu_{max.}$ 1742, 1704, and 1151 cm.$^{-1}$.

To an ice-cooled solution of this residue (650 mg.) in purified acetone (30 ml.), 0·5 ml. of a chromium trioxide solution (68 g. of chromium trioxide and 57 ml. of concentrated sulphuric acid diluted to 250 ml. with water) was added dropwise with constant stirring. The excess of oxidant was destroyed with methanol and the mixture diluted with water. The product (600 mg.) was extracted with chloroform and dried (Na_2SO_4). Evaporation of the solvent left a residue which was purified by chromatography on Florisil (100—200). Elution with benzene then ether–benzene (3 : 7) gave the main *product*, platelets, m. p. 235—238° (from methanol), $[\alpha]_D$ +87° (*c* 1·0), single spot on chromatoplate, $\nu_{max.}$ 1745, 1698, and 1159 cm.$^{-1}$, τ 4·35, 4·92, doublets at 6·56 and 7·44 (J = 17 c./sec.), doublet at 7·24 (J = 7 c./sec.) (Found: C, 75·45; H, 8·55. $C_{25}H_{34}O_4$ requires C, 75·35; H, 8·6%).

Compound (VIII).—This substance was obtained in minute quantity from the above column chromatography in the final fractions which were eluted with ether–benzene (3 : 7). It formed needles, m. p. 256—260° (from methanol), $\nu_{max.}$ 1751, 1704, and 1670 cm.$^{-1}$, $\lambda_{max.}$ 242 mμ (ε 11,460).

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