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THE ETHOXYETHYNYL CARBINOL–$\alpha\beta$-UNSATURATED ESTER CONVERSION: STEREOMUTATION ACCOMPANYING A SELENIUM DIOXIDE OXIDATION

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Abstract—Benzsuberone reacts with ethoxyethynyl magnesium bromide to give 1-ethoxyethynyl-1-hydroxy-2,3-benzocycloheptene, which on rearrangement with mild acid (carbon dioxide) yields ethyl *cis*-1,2-benzo-3-cycloheptenylidene acetate (4, $R^1 = CO_2Et$, $R^2 = H$) and the corresponding *trans*-compound. With selenium dioxide, both esters yield the same γ-lactone.

In a previous communication[1] we reported that the ethoxyethynyl carbinols **2** derived from the ketones **1**, Ar = aromatic ring, gave, on mild acid treatment, a mixture of esters in which the *cis*- *Z* forms **3** predominated. We have now extended this study to the system **4**. The alicyclic ring in **4** can adopt a flexible boat-like form and a chair-like form. The flexible form has numerous possible conformations; the group R^1 can be above, in (if R^1 is small, i.e. H), and below the plane defined by the aromatic ring (likewise R^2) and for each conformation with R^1 above this plane there exists a corresponding (and enantiomeric) conformation with R^1 the same perpendicular distance below the plane. Unlike the chair form of cycloheptane which is flexible,[2] the chair form of **4** exists as two (enantiomeric) rigid conformations, R^1 being at a maximum distance above (and below) the plane of the aromatic ring. The chair form should be energetically the most favoured;[2] in this form the plane of the exocyclic double bond is dihedrally oriented at approximately 65° to that of the aromatic ring† and it is not obvious from an inspection of models that the *cis Z*-form **4**, $R^1 = CO_2Et$, $R^2 = H$ is more sterically compressed than the corresponding *trans E* isomer. In the previous cases examined[1] in which the alicyclic rings were five and six membered the group R^1 was always close to the aromatic ring and this was reflected in the properties of the compounds, in particular their stability relations and their NMR spectra. The degree of twist in the system **4** leads to the interesting conclusion that if values for the anisotropic effect of the aromatic ring are obtained using the accepted ring current model,[4] the ethylenic proton of the *trans*- ester **4**, $R^1 = H$, $R^2 = CO_2Et$ should be less deshielded (by *ca* τ 0·04) than that of the *cis*- ester. An empirical rule is available[5] for the calculation of the chemical shifts of ethylenic protons but its application in the present instance does not constitute a fair test as the aromatic ring is not coplanar with the conjugated double bond.

Benzsuberone **4**, =O in place of $=CR^1R^2$, when treated with ethoxyethynyl magnesium bromide gave the corresponding ethoxyethynyl carbinol. The latter with ethanol containing carbon dioxide formed a readily separabale (1:1) mixture of two esters (A and B). The Reformatskii reaction on benzsuberone yielded initially a moderately stable hydroxyester **6**, R = Et which on dehydration yielded a third ester C (major product) along with some ester B. Ester C was clearly the $\beta\gamma$- unsaturated compound **7**, R = Et (IR, ν_{max} 1740 cm^{-1}; NMR, τ, 3·92, triplet, J 7 Hz, $C{=}C\underline{H}$, τ, 6·57, singlet, $C\underline{H}_2CO_2Et$). Esters A (IR, ν_{max} 1728 cm^{-1} and 1710 cm^{-1}) and B (ν_{max} 1715 cm^{-1}) were obviously $\alpha\beta$-unsaturated and, as expected, their NMR olefin proton signals were close together (τ, 4·04 and 4·12 respectively). The ethoxyl group of compound A gave NMR signals centred at τ 8·98 ($C\underline{H}_3$) and 6·04 ($C\underline{H}_2$), the corresponding signals for compound B being at τ 8·70 and 5·79. The higher values are evidently due to shielding by the aromatic ring and models reveal that only in the *cis*- form **4**, $R^1 = CO_2Et$, $R^2 = H$ is it possible for the ethoxyl group to reach the shielding zone of the ring.

In an attempt to confirm that the esters A and B were respectively the *cis*- and *trans*- compounds, both were separately treated with selenium dioxide. Selenium dioxide oxidation of some steroid esters of type **8** gave the hydroxy compounds **9** and **10**.[6] In the present case both the *cis*- and the *trans*- esters gave, apparently with equal ease, the same lactone

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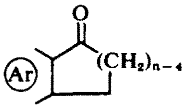
†The degree of twist possible in a cycloheptane ring is demonstrated by the very large Cotton effect found for (+) **5**; K. Mislow, M. A. W. Glass, A. Moscowitz and C. Djerassi, *J. Am. Chem. Soc.* **83**, 2771 (1961); **84**, 2823 (1962).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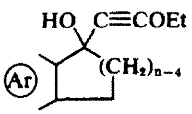
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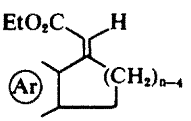
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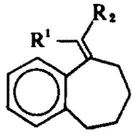
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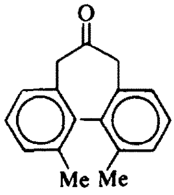
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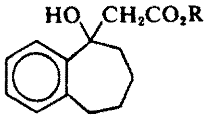
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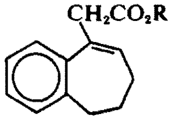
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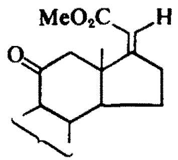
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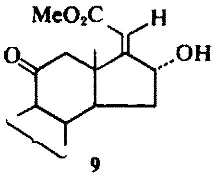
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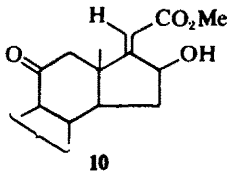
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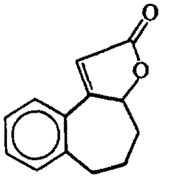
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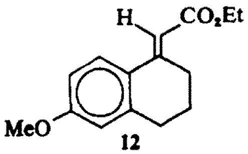
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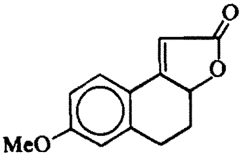
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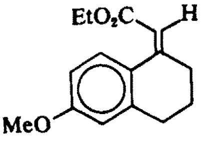
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11 (NMR, τ 3·88, C=C$\underline{H}$). However, the UV absorption of this (λ_{max} 268 nm,ϵ 11600) was similar to that of ester B (λ_{max} 264 nm, ϵ 9950) and markedly different from that of A (λ broad shoulder 250 nm, ϵ 4300), hence ester B should have the same (*trans*-) configuration as that of the lactone.

Unlike the NMR evidence that of UV absorption is based on an analogy which should apply to other systems. Compound **12** of secure configuration[1] on oxidation with selenium dioxide gave the lactone **13** (NMR, τ, 4·05, C=C$\underline{H}$), the UV absorption spectrum of which (λ_{max} 310 nm, ϵ 21080) proved to be strikingly similar to that of the parent ester **12** (λ_{max} 315 nm, ϵ 18500; shoulder 301 nm, ϵ 16400) and different from that of the *cis*-isomer **14** (λ_{max} 304 nm, ϵ 10300). The IR carbonyl absorptions of the lactones **11** and **13**, though composite, exhibited single maxima unlike the absorptions of some less conjugated analogues.[7]

EXPERIMENTAL

General procedures are given in Ref 1. NMR spectra refer to deuteriochloroform solutions, UV spectra to ethanol solutions. All evaporations were performed at reduced pressure.

Ethyl cis-1, 2 - *benzo* - 3 - *cycloheptylidene acetate* **4**, $R^1 = CO_2Et$, $R^2 = H$ and *ethyl* trans - 1, 2 - *benzo* - 3 - *cycloheptylidene acetate* **4**, $R^1 = H$, $R^2 = CO_2Et$. Benzsuberone (8 g) and ethoxyacetylene were reacted as for 6-methoxy-1-tetralone.[1] The crude ethoxyethynyl carbinol (*ca* 11 g) was dissolved in 95% ethanol (100 cm³) and treated with solid carbon dioxide (*ca* 0·05 g). After 12 h the solution was evaporated and the product chromatographed by PLC.[1] The band nearest the origin gave the *cis-ester* as a colourless oil; τ, 4·04 (1H, S, C=C$\underline{H}$), 6·04 (2H, q, J 7 Hz, C$\underline{H}_2$CH$_3$), 8·98 (3H, t, J 7 Hz, CH$_2$C$\underline{H}_3$); ν_{max} (film) 1728, 1710 cm^{-1} (CHCl$_3$, 1734, 1714 cm^{-1}); λ_{max} 214 nm (ϵ 16700), 250 nm (broad shoulder, ϵ 4300) (Found: C, 78·02; H, 7·74. $C_{15}H_{18}O_2$ requires C, 78·23; H, 7·88%). The furthermost band gave the *trans-ester* also as a colourless oil; τ, 4·12 (1H, s, C=C$\underline{H}$), 5·79 (2H, q, J 7

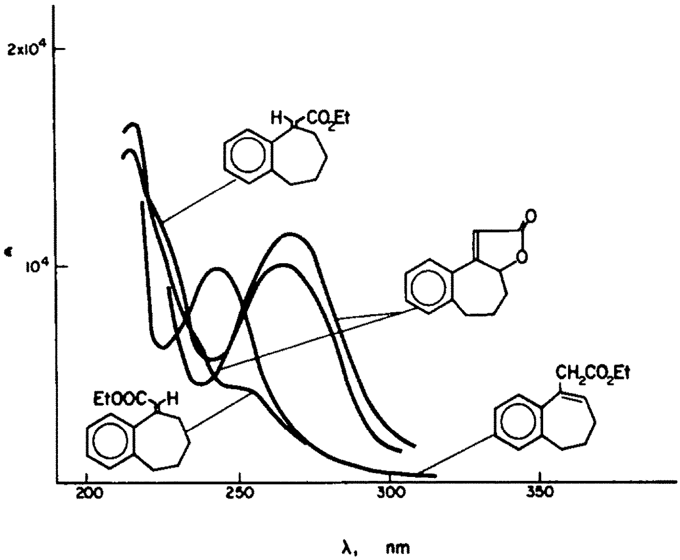

Fig 1. UV spectra of the benzsuberone derivatives.

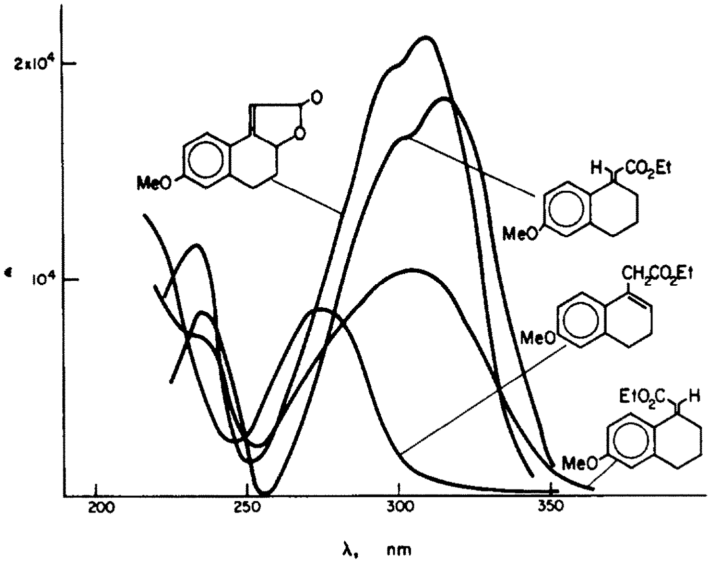

Fig 2. UV spectra of the corresponding 6-methoxy-1-tetralone derivatives.

Hz, $C\underline{H}_2CH_3$), 8·70 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$); ν_{max} (film) 1715 cm^{-1} ($CHCl_3$, 1722 cm^{-1}); λ_{max} 264 nm (ϵ 9950) (Found: C, 78·40; H, 8·08. $C_{15}H_{18}O_2$ requires C, 78·23; H, 7·88%). No change in configuration was observed when the above esters were refluxed separately with hydrogen chloride in anhydrous ethanol.

Hydrolysis of the above esters with 5% aqueous alcoholic potassium hydroxide under nitrogen gave the free acids. The *cis-acid* formed colourless plates (from benzene–light petroleum), m.p. 150°; τ, −0·84 (1H, s, $CO_2\underline{H}$), 4·09 (1H, s, $C{=}C\underline{H}$); ν_{max} (KBr) 1692, 1670 cm^{-1}; λ_{max} 250 nm (broad shoulder, ϵ 4590), pK_a 6·60 (Found: C, 77·60; H, 7·30. $C_{13}H_{14}O_2$ requires C, 77·20; H, 7·00%). The *trans-acid* formed colourless needles, m.p. 100° (from light petroleum); τ, −1·73 (1H, broad singlet, $CO_2\underline{H}$), 4·08 (1H, s, $C{=}C\underline{H}$); ν_{max} (KBr) 1690 cm^{-1}; λ_{max} 260 nm (ϵ 10050), pK_a 6·74 (Found: C, 76·90; H, 6·82. $C_{13}H_{14}O_2$ requires C, 77·20; H, 6·98%).

Selenium dioxide oxidation. Each of the foregoing esters (1 g) in acetic acid (15 cm^3) was treated with selenium dioxide (0·5 g; prepared by combustion of selenium in oxygen containing nitrogen dioxide) in water (6 cm^3) and then heated on a steam bath for ½ h. After removal of solvent the crude product (0·75 g) was chromatographed (PLC). The top band contained unchanged ester; the bottom band furnished *lactone* **11** (0·27 g) which crystallised from aqueous methanol, m.p. 74°; τ, 3·88 (1H, s, $C{=}C\underline{H}$), 4·8–5·15 (1H, m, $C\underline{H}{\cdot}O{\cdot}CO$); u.v., λ_{max} 268 nm (ε 11600); ν_{max} (KBr) 1767 cm^{-1} ($CHCl_3$, 1752 cm^{-1}) (Found: C, 78·10; H, 6·20. $C_{13}H_{12}O_2$ requires C, 78·00; H, 6·04%). Oxidation in aqueous dioxane gave the same result.

Ethyl 1, 2 - *benzocyclohepta* - 1, 3 - *dienyl* - 3 - *acetate*. The Reformatskii reaction on benzsuberone has been previously reported by Sukh Dev,[8] and also by Anderson and Wang[9] as a means to the unsaturated ester which was formulated correctly[9] but on incomplete evidence. The intermediary hydroxyester has not so far been described. Benzsuberone (11 g) was treated with activated zinc wool (7 g) and ethyl bromoacetate (13 g) in benzene (50 cm^3) containing ether (10 cm^3). The reaction mixture was worked up with aqueous ammonium chloride and the organic material extracted into ether. Evaporation of solvent left the crude hydroxyester **6**, R = Et which crystallised. *Ethyl* 1, 2 - *benzo* - 3 - *hydroxy* - 3 - *cycloheptenyl acetate* formed colourless prisms, m.p. 66° (from light petroleum); τ, 5·6 (1H, s, $O\underline{H}$), 7·11 (2H, s, $C\underline{H}_2CO_2Et$); ν_{max}(KBr) 1703, 1203 cm^{-1}; λ_{max} 260 nm (ε 245) (Found: C, 72·72; H, 8·16; $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·12%). Hydrolysis with 5% aqueous alcoholic potassium hydroxide under nitrogen (24 h at 15°) gave the *acid* **6**, R = H, colourless rosettes, m.p. 118° (from benzene–light petroleum); τ, 1·7–3·0 (2H, broad, $O\underline{H}$ and $CO_2\underline{H}$); ν_{max}(KBr) 1680 cm^{-1}; λ_{max} 260 nm (ε 263) (Found: C, 70·80; H, 7·47. $C_{13}H_{16}O_3$ requires C, 70·89; H, 7·32%).

The hydroxyester (2 g) was dehydrated by heating it with 98% formic acid (6 g) on a water bath at 85° for 2 h. The crude product was purified by PLC and yielded the *trans*-ester **4**, R^1 = H, R^2 = CO_2Et (0·18 g) (top band) and ethyl 1, 2 - benzocyclohepta - 1, 3 - dienyl - 3 - acetate **7**, R = Et (1·05 g) (bottom band) (Found: C, 78·44; H, 7·97. Calc for $C_{15}H_{18}O_2$: C, 78·23; H, 7·88%); ν_{max} (film) 1740 cm^{-1}; τ, 3·92 (1H, t, J 7 Hz, $C{=}C\underline{H}$), 6·57 (2H, s, $C\underline{H}_2CO_2Et$). Hydrolysis gave the acid **7**, R = H, colourless needles and plates, m.p. 94° (Found: C, 77·33; H, 7·07. Calc for $C_{13}H_{14}O_2$: C, 77·20; H, 6·98%); τ, 3·89 (1H, t, J 7 Hz, $C{=}C\underline{H}$), 6·55 (2H, s, $C\underline{H}_2CO_2H$); ν_{max} (KBr) 1698 cm^{-1}.

Selenium dioxide oxidation of ethyl *trans* - 1, 2, 3, 4 - tetrahydro - 6 - methoxy - 1 - naphthylideneacetate **12**. The ester (1 g) was oxidised as for the esters **4**, R^1,R^2 = H, CO_2Et (see earlier). The product was isolated by crystallisation from methanol; it formed colourless plates, m.p. 144°; τ, 4·05 (1H, s, $C{=}C\underline{H}$); ν_{max} (KBr) 1753 cm^{-1} ($CHCl_3$, 1735 cm^{-1}); λ_{max} 310 nm (ε 21080) (Found: C, 72·60; H, 5·75. $C_{13}H_{12}O_3$ requires C, 72·22; H, 5·59%).

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