Flavothebaone. Part VIII.[1] Hofmann Degradation of Flavothebaone Trimethyl Ether ψ-Methine Methiodide

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The Hofmann degradation of flavothebaone trimethyl ether ψ-methine has been re-examined and shown to give, as major product, 2-[3,6-dimethoxy-2-(2-oxopropyl)phenyl]-7,8-dimethoxy-1-vinylnaphthalene (6). A minor product, previously considered to be the ketone (9), has been identified as the cyclic enol ether (11) derived from (6).

THE quaternary salt (1) has been shown previously to be degraded at room temperature to the phenylnaphthalene (2; R = H), the essential feature of the reaction being cleavage of the 5,13-bond following attack by a carbanion at C-13, the carbonyl group at C-6 being the electron sink.[2] Flavothebaone trimethyl ether methine (3) contains a similar bridged-ring system which could be cleaved in the same way, but the subsequent rearrangement of bonds whereby the phenol (2) is generated could not follow in this case. The ψ-methine salt (4), into which (3) is readily converted in alkali, should, however, be convertible into the phenylnaphthalene (6), through the intermediate (5), by the simple sequence shown. This salt (4) has been previously degraded to 1,2,7,10-tetra-methoxybenzo[a]fluorene and ' Compound E ' together with much non-crystalline material.[3] Compound E was tentatively formulated as the ketone (9), though the mechanism advanced for its formation, involving a base-catalysed ring opening initiated by attack at an un-activiated position, was unconvincing. This ketone (9) could, however, be generated via the βγ-unsaturated ketone (8) from the ylide (7), which is a likely inter-mediate under the prevailing conditions. A re-examina-tion of the products of this degradation, using tech-niques not available to the earlier workers, has accord-ingly been made.

Degradation of the ψ-methine methiodide with potas-sium hydroxide in refluxing cyclohexanol afforded 1,2,7,10-tetramethoxybenzo[a]fluorene (4%) ' Compound E ' (13%), and a new substance (70%), which could not be crystallised even when chromatographically pure, and which is isomeric with Compound E ($C_{25}H_{26}O_5$). Its u.v. spectrum is similar to that of the hindered phenyl-naphthalene (2; R = H) and its i.r. spectrum shows bands characteristic of a saturated carbonyl group (1720 cm^{-1}) and a vinyl group (910 and 990 cm^{-1}). It has been assigned the structure (6) on the basis of its ^{1}H and ^{13}C n.m.r. spectra.

The high-field region of the ^{1}H n.m.r. spectrum showed four methoxy-singlets (δ 3·63—3·87), a benzylic methyl-ene AB quartet (δ 3·40, J 17 Hz), and an acetyl singlet (δ 1·95). The ^{13}C spectrum confirmed the presence of these six sp^3-hybridized carbon atoms, its high-field region comprising four signals (resolved on scale expan-sion) at δ 55·96—60·63 (4 × OCH$_2$), one at δ 43·22

$(ArCH_2CO)$, and one at δ 29·44 $(COCH_3)$. Each reson-ance showed the expected multiplicity in the off-reson-

(1)   (2)   (3)

(4)   (5)

(6)   (7)

(8)   (9)
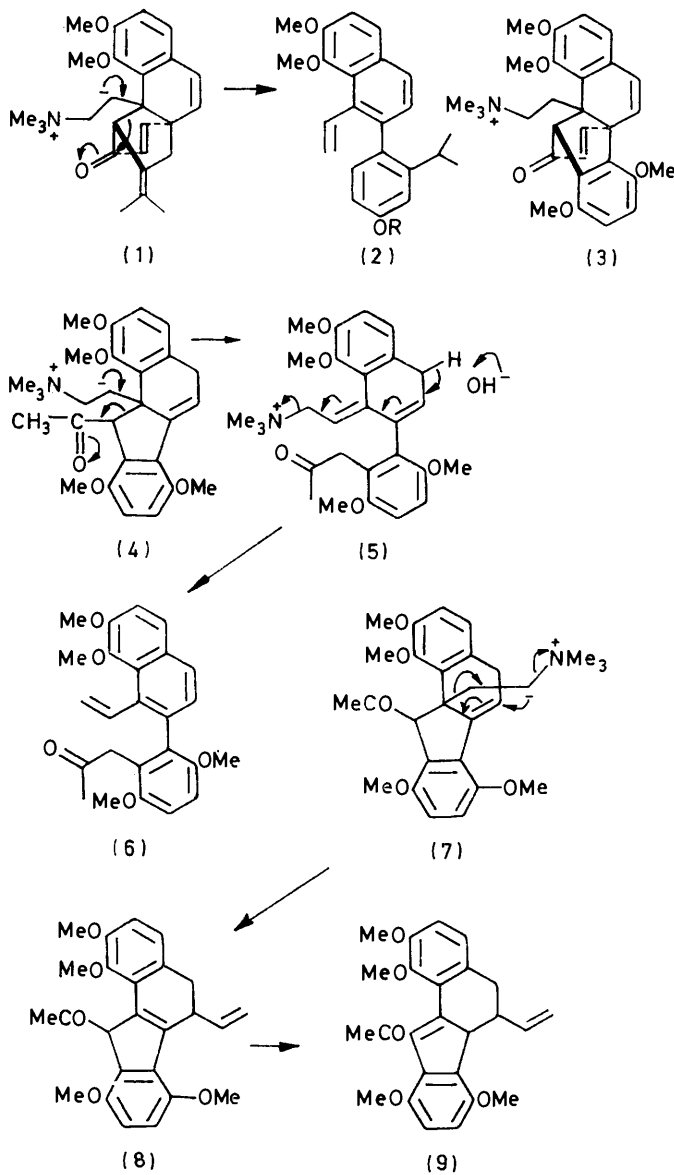
ance continuous wave (ORCW) proton-decoupled spec-trum: five quartets for the five methyl carbons, and a triplet for the methylene carbon.

[1] Part VII, K. W. Bentley, S. F. Dyke, and A. R. Marshall, *J. Chem. Soc.*, 1963, 4055.

[2] K. W. Bentley, H. P. Crocker, R. Walser, W. Fulmor, and G. O. Morton, *J. Chem. Soc.* (C), 1969, 2225.

[3] K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, 1957, 22, 409.

The low-field region of the ^{13}C spectrum showed nineteen lines due to sp^2-hybridized carbon atoms and ORCW proton decoupling showed that these were due to eleven quaternary carbons, seven carbons bearing one hydrogen atom and one carbon bearing two hydrogen atoms. Since the molecule contains only hydrogen atoms bound to carbon (D_2O has no effect on the ^{1}H spectrum) the partial formula $C_{25}H_{26}$ can be deduced by inspection of the proton-decoupled and ORCW proton-decoupled spectra. The sp^2-hybridized carbon bearing two hydrogen atoms resonates at δ 114·58 and this and another carbon resonance at δ 137·19 agree well in chemical shift with the olefinic resonances of styrene itself [4] (δ 113·2 and 136·7). The acetonyl carbonyl resonance at δ 206·21 agrees well with that of acetone [5] (δ 204·1).

The arrangement of the hydrogen-bearing sp^2-hybridized carbon atoms was confirmed by the low-field region of the ^{1}H spectrum. This showed olefinic signals at δ 4·79 (1H, dd, J 17 and 2 Hz), 4·95 (1H, dd, J 12 and 2 Hz), and 7·25 (1H, dd, J 17 and 12 Hz) and aromatic resonances at δ 6·7—7·8 (7H). The olefinic signals are consistent with the presence of a vinyl system and agree closely with the corresponding signals in the spectrum of (2; R = Me).[2] The aromatic pattern simplified in the presence of 1 molar proportion of tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium to three simple AB quartets, each with J 9 Hz, and this is consistent with the presence of the three isolated pairs of ortho-protons. All these facts constituted strong evidence for structure (6). The presence of an AB quartet for the benzylic methylene protons may be due to the generation of enantiomers by hindrance to rotation of the 7- and 8-substituents.[2] The appearance of the AB quartet was unaltered when the spectrum of the compound in tetrachloroethylene was recorded at 92°, but coalescence temperatures of 150—200° are not uncommon for this type of hindered rotation.[6]

A similar examination of Compound E immediately showed that the structure (9) is incorrect, since the n.m.r. spectrum shows no signals attributable to a vinyl group, and the spectrum of its dihydro-derivative lacks signals attributable to an ethyl group. Re-examination of the u.v. and i.r. spectra of Compound E showed that the former is compatible with a styrenoid but not with a stilbenoid structure and led to the recognition of absorption band at 1670 cm^{-1} in the latter, originally attributed to an $\alpha\beta$-unsaturated carbonyl group, as due to an enol ether system. These studies led to the assignment of structure (11) to Compound E, which is supported by ^{1}H and [13]C n.m.r. data for the compound and its dihydro-derivative.

The [1]H n.m.r. spectrum showed the presence of six low-field (δ 6·30—6·80) and twenty high-field protons,

the latter appearing in two groups. One group (δ 1·83—2·23; 5H) included a three-proton singlet at δ 2·04. The other (δ 3·40—4·66; 15H) included four methoxy-singlets (δ 3·36—3·73) and a one-proton triplet (J 2·6 Hz) at δ 3·47.

The δ 2·04 singlet cannot be due to an acetyl methyl group since the ^{13}C spectrum contains no signals in the carbonyl region (δ ca. 200) or in the acetyl methyl region (δ ca. 30). However, the ^{13}C spectrum does show a total of five sp^2-hybridized carbon atoms singly bonded to oxygen (δ 147·30—153·37) and this is consistent with the presence of the four aromatic C–OCH_3 systems implied by the ^{1}H spectrum, together with one enol ether carbon [$CH_3C(O)=$]. The observed shifts agree reasonably well with those calculated [7] for the 3- and 4-carbons of 2-methyl-3,4-dimethoxystyrene (δ 145·6 and 143·1) and for the 1-carbon of p-dimethoxybenzene (δ 152·2); the enol ether carbon of 2-methylfuran resonates at δ 151·8,[8] and the 6-carbon of 2,3-dihydropyran at δ 143·2.[9] The other olefinic carbon of the enol ether system would be expected to resonate at δ 109·6—114·1 (the chemical shifts of the β-carbons of furan [8] and anisole [7]); this quaternary carbon signal is in fact found at δ 112·12.

The high-field part of the ^{13}C spectrum of Compound E (δ 19—63) shows there are nine sp^3-hybridized carbon atoms, and the proton-coupled spectrum indicates further that these consist of five methyl and two methylene groups, one methine carbon and one quaternary carbon. This last (δ 49·50) gives a low amplitude signal on account of the lack of Overhauser enhancement and the long relaxation time (T_1) characteristic of this type of carbon atom. Four of the methyl carbon resonances occur at shifts (δ 53·39—56·30) characteristic of aromatic methoxy carbons ($PhOCH_3$, δ 54·8 [6]), but the fifth occurs at higher field (δ 19·89), consistent with a C-methyl group. The methylene resonance at δ 62·49 is very close to the value of δ 64·2 reported for the 2-carbon of 2,3-dihydropyran.[9] The allylic methine carbon resonance at δ 60·42 is in reasonable agreement with those of other allylic methine carbons in ring systems (a similar carbon in prostaglandin $F_{2\alpha}$ resonates at δ 55·0 [10]).

The low-field region of the ^{13}C spectrum shows sixteen sp^2-hybridized carbon atoms, ten of these being quaternary and six bearing one hydrogen atom. The latter correspond to the six low-field protons of the ^{1}H spectrum. Irradiation of the δ 3·49 triplet (1H) caused a multiplet at δ 6·35 (2H) to collapse to a broad singlet, and expansion showed that the multiplet was in fact two superimposed doublets with J 3·2 and 2·0 Hz due to CH=CH and the δ 3·49 triplet was an unresolved double doublet due to the allylic methine proton. These signals are therefore ascribed to the allyl system $>$CH–CH=CH–, the observed splittings being due to vicinal and allylic coupling. The near chemical shift equivalence of the

[4] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley-Interscience, New York, 1972, p. 65.
[5] Ref. 4. p. 111.
[6] R. M. Acheson and I. A. Selby, *J. Chem. Soc. (C)*, 1971, 691.
[7] Ref. 2, pp. 65, 81.
[8] Ref. 2, p. 97.

[9] T. Pehk and E. Lippmaa, *Eesti N.S.V. Tead. Akad. Toim. Keem. Geol.*, 1968, **17**, 291; δ with respect to Me_4Si determined from $\delta(Me_4Si) = 192 - \delta(CS_2)$.
[10] G. Lucas, F. Piriou, S. D. Gero, D. A. Van Dorp, E. W. Hagaman, and E. Wenkert, *Tetrahedron Letters*, 1973, 515.

two olefinic protons results in no measurable coupling between them.

Addition of tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-octane-4,6-dionato)praseodymium caused the ^{1}H methoxy-resonances to shift upfield according to the following gradients: 16·9, 7·3, 3·3, and 0·6 p.p.m. per mole of shift reagent. The markedly stronger co-ordination at one of these methoxy-groups is probably due to steric crowding of the other three, and this is corroborated in an interesting way by the ^{13}C methoxy resonances (observed in the absence of shift reagent). One of these has a much lower amplitude signal than the other three and the relatively longer relaxation time (T_1) causing this may be due to the fact that the other methoxy-groups are sterically hindered and relatively immobilized.[11] Inspection of a Dreiding model of structure (11) suggests that the 2-methoxy-group is the most mobile and nucleophilic of the four.

The [1]H n.m.r. spectrum of the dihydro-derivative of Compound E shows signals for 28 protons, and shows four more high-field and two less low-field protons than E itself. There are three methoxy-singlets (δ 3·48—3·73; 12H), a vinyl methyl singlet (δ 2·02; 3H) at almost the same shift as that of Compound E, and a triplet (J 6 Hz; 1H) at δ 3·27, ascribed to the methine proton formerly α to the styrenoid double bond of Compound E, which can be decoupled from the signal at δ 2·33 ($-CH_2-CH$). All these features support the view that the styrenoid double bond has been hydrogenated. Further structural evidence was provided by the addition of 0·07 molar proportions of tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium, which caused the three methoxy-resonances to be resolved into four; further additions separated the aromatic proton signals into two distinct AB quartets (J 8 Hz).

Further support for structure (11) for Compound E was obtained from the results of solvolysis of the enol ether system: treatment with dilute sulphuric acid in aqueous acetic acid gave the acetoxy-ketone (12; R = OAc), and treatment with concentrated hydrochloric acid in boiling 2-ethoxyethanol gave the chloro-ketone (12; R = Cl). The spectral properties of these ketones were in accord with the assigned structures; in particular the [1]H n.m.r. spectra showed signals at δ 5·10 also present in the spectrum of the ψ-methine (4) at δ 4·66 but absent from the spectra of Compound E and its dihydro-derivative, and attributed to the $-CH-$ system situated between the carbonyl group and the quinol methyl ether system.

Since Compound E is not an $\alpha\beta$-unsaturated ketone, epoxidation of its dihydro-derivative should not give a saturated ketone and ' dihydro-E$_1$ ' prepared in this way was re-examined. This product is indeed a saturated ketone and must be generated by some hydrolytic process, though not by simple hydrolysis since its [1]H n.m.r. spectrum lacks the characteristic signal at δ 4·66—5·10, attributable in the spectra of the ψ-methine and the ketones (12; R = OAc or Cl) to the proton in the

[11] Ref. 2, p. 180.

–CO–CHAr system, and also lacks a signal attributable to a hydroxy-group. An entirely satisfactory structure (15) may be deduced on the basis that epoxidation of the enol ether is followed by acid-catalysed hydrolysis [(13) ⟶ (14)], which would be expected under the conditions of formation of this compound in the presence
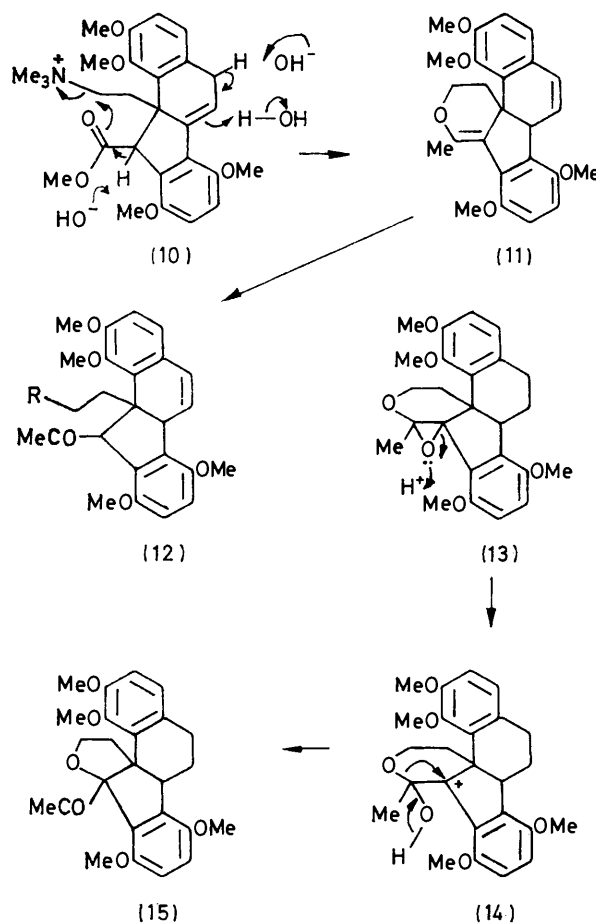
of trifluoroacetic acid resulting from the action of 87% hydrogen peroxide on trifluoroacetic anhydride. The spectra of ' dihydro-E$_1$ ' and its known stability to hydrolysis are simply explicable on the basis of structure (15).

Examination of models shows that the cyclic enol ether system of Compound E can be constructed without severe strain only if the second double bond (in ring B) is in the position shown.

EXPERIMENTAL

Hofmann Degradation of Flavothebaone Trimethyl Ether ψ-Methine Methiodide (4).—The salt (40 g) was degraded by heating with potassium hydroxide (23 g) in cyclohexanol (500 ml) and water (20 ml) under conditions previously described.[3] The nitrogen-free material (21 g) was dissolved in ethanol (100 ml) and cooled. The crystalline Compound E (13,14-*dihydro*-1,2,7,10-*tetramethoxy*-11-*methylbenzo*[1,2]*fluoreno*[9,9a-c]*pyran*), m.p. 190—192° (3·05 g) was collected. The mother liquors were concentrated to 70 ml and kept at 0° overnight; 1,2,7,10-tetramethoxybenzo[a]fluorene, m.p. 150—152° (0·85 g), separated and was removed. Evaporation of the mother liquors then afforded a brown oil that was shown by t.l.c. to be substantially one substance containing traces of the foregoing two products. A pure sample of this material {2-[3,6-*dimethoxy*-2-(2-*oxopropyl*)*phenyl*]-7,8-*dimethoxy*-1-*vinylnaphthalene*} (6) was obtained by preparative layer chromatography (alumina; chloroform) as an almost colourless gum from which it was found impossible to remove the final traces of chloroform so as to obtain a satisfactory analysis. Mass spectrometery showed a molecular ion peak at m/e 406 ($C_{25}H_{26}O_5$ requires M, 406).

Solvolysis of Compound E.—(a) Compound E (0·3 g) was boiled with 2-ethoxyethanol (10 ml) and concentrated hydrochloric acid (2 ml) for 10 min. The mixture was diluted with water and the precipitate was collected and crystallised from 90% ethanol to give 11-*acetyl*-11a-(2-*chloroethyl*)-11,11a-*dihydro*-1,2,7,10-*tetramethoxybenzo*[a]*fluorene* (12; R = Cl) as pale yellow prisms, m.p. 134° (0·26 g), raised to 136° on recrystallisation from 70% ethanol, $[\alpha]_D^{20} +28°$ (c 1·47 in $CHCl_3$) (Found: C, 67·85; H, 6·15; Cl, 8·45. $C_{25}ClH_{27}O_5$ requires C, 67·8; H, 6·1; Cl, 8·0%).

(b) Compound E (0·3 g) was dissolved in boiling glacial acetic acid (10 ml) and hot water was added until *ca.* 50% of the material was precipitated. 10N-Sulphuric acid (1 ml) was then added; the mixture was boiled until all Compound E had dissolved and then heated on a water-bath for 15 min. Water (50 ml) was added and the precipitated gummy material was collected and crystallised from aqueous methanol to give 11a-(2-*acetoxyethyl*)-11-*acetyl*-11,11a-*dihydro*-1,2,7,10-*tetramethoxybenzo*[a]*fluorene* (12; R = OAc) (0·25 g) as almost white prisms, m.p. 130° $[\alpha]_D^{20} +24°$ (c 1·97 in $CHCl_3$) (Found: C, 69·2; H, 6·5. $C_{27}H_{30}O_7$ requires C, 69·5; H, 6·5%).