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The Conformation and Rearrangement Reactions of Derivatives of 10,11-Dihydrodibenzoxepin [1]

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The conformational behaviour of 10-substituted 10,11-dihydrodibenz[*b,f*]oxepins (V—XVI) has been investigated by n.m.r. spectroscopy. The favoured conformation is shown to be that in which the 10-substituent has the quasi-equatorial conformation with respect to the seven-membered ring. The stereo-electronic requirements for the observed rearrangement reactions of 10-chloro-10,11-dihydrodibenz[*b,f*]oxepins to give 9-chloromethyldibenzoxanthens are considered in relation to this favoured conformation.

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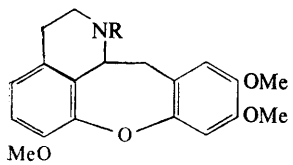
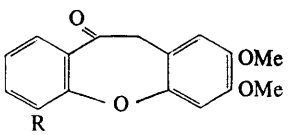
THE cularine alkaloids [2] (I) and (II), which are phytochemically characteristic of the *Dicentra* and *Corydalis* genera, are of interest in that they are biosynthetically modified benzylisoquinoline alkaloids containing a diphenyl ether grouping accommodated within the seven-membered oxepin ring system. Total syntheses of cularine (I) and cularimine (II) have been reported.[3-6] The configuration and conformation of the cularine alkaloids have also been investigated [7] and, in continuation of these studies, we have now examined the conformational behaviour by n.m.r. spectroscopy † of various 10-substituted 10,11-dihydrodibenz[*b,f*]oxepins (V—XVI). These derivatives contain three of the four rings present in the tetracyclic cularine alkaloid structures (I) and (II). During these studies various rearrangements and elimination reactions of derivatives of 10,11-dihydrodibenz[*b,f*]oxepin were encountered.



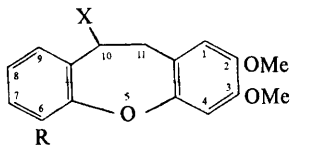
(I) R = Me, cularine
(II) R = H, cularimine



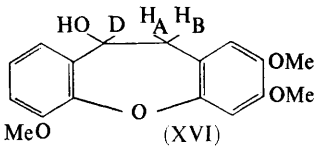
(III) R = H
(IV) R = OMe

The trimethoxy-compounds (XI—XIV) and the tetramethoxy-compound (XV) may be regarded as structural analogues of the cularine alkaloids (I) and (II). The compounds (XI—XV) were obtained by the following reactions. The alcohol (XI) was prepared either by Meerwein-Ponndorf reduction of the ketone (IV) [8,9] or by nitrous acid deamination of the amine (XIV).[10] This alcohol (XI) gave the chloride (XIII) by reaction with thionyl chloride in benzene. However, when the alcohol (XI) was treated with acetyl chloride and pyridine in glacial acetic acid a rearrangement occurred to give the isomeric chloride (XIX). Similarly, treatment of the acetate (XII) [10] with acetyl chloride in acetic acid gave the chloride (XIX) the formation of which also involved rearrangement. The direct transformation (XIII) ⟶ (XIX) was achieved by dissolving the chloride (XIII) in acetic acid, whereas the chloride (XIII) when dissolved in methanol gave the ether (XV) without rearrangement.

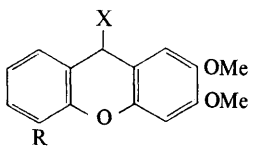
Exactly analogous reactions were obtained with the 2,3-dimethoxy-10,11-dihydrodibenzoxepins (V), (VI), and (VII). The alcohol (V) [10] gave the chloride (VII) by reaction with thionyl chloride. However, the isomeric chloride (XVII) was formed either when the alcohol



	R	X
(V)	H	OH
(VI)	H	OAc
(VII)	H	Cl
(VIII)	H	OMe
(IX)	H	NH_2
(X)	H	NH·CHO
(XI)	OMe	OH
(XII)	OMe	OAc
(XIII)	OMe	Cl
(XIV)	OMe	NH_2
(XV)	OMe	OMe



(XVI)



	R	X
(XVII)	H	CH_2Cl
(XVIII)	H	Me
(XIX)	OMe	CH_2Cl
(XX)	OMe	Me

† N.m.r. spectra were determined ($CDCl_3$ and CCl_4 solutions) with a Varian A-60 spectrometer. Chemical shifts (δ) are given in p.p.m. downfield from tetramethylsilane as the internal standard.

[1] Studies on the Syntheses of Heterocyclic Compounds, Part CCLVII; Part CCLVI, *J. Chem. Soc.* (*C*), 1968, 1798.
[2] R. H. F. Manske and H. L. Holmes, 'The Alkaloids—Chemistry and Physiology,' Academic Press, New York, 1954, vol. 4, p. 249.
[3] T. Kametani and K. Fukumoto, *Chem. and Ind.*, 1963, 291; *J. Chem. Soc.*, 1963, 4289.
[4] T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *Tetrahedron Letters*, 1964, 25; *J. Chem. Soc.*, 1964, 4146.
[5] T. Kametani and S. Shibuya, *Tetrahedron Letters*, 1965, 1897; *J. Chem. Soc.*, 1965, 5565.
[6] T. Kametani and K. Ogasawara, *J. Chem. Soc.*, 1964, 4142.
[7] N. S. Bhacca, J. Cymerman Craig, R. H. F. Manske, S. K. Roy, M. Shamma, and W. A. Slusarchyk, *Tetrahedron*, 1966, **22**, 1467.
[8] M. Kulka and R. H. F. Manske, *J. Amer. Chem. Soc.*, 1955, **75**, 1322.
[9] T. Kametani, K. Fukumoto, and T. Nakano, *J. Pharm. Soc. Japan*, 1962, **82**, 1548.
[10] T. Kametani and C. Kibayashi, *J. Pharm. Soc. Japan*, 1961, **84**, 642.

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(V) was treated with acetyl chloride and pyridine in acetic acid, or when the acetate (VI) was treated with acetyl chloride alone in acetic acid. The rearrangement of the chloride (VII) into its isomer (XVII) occurred when the former was dissolved in acetic acid.

Table). On the other hand, the n.m.r. spectra of the chlorides (XVII) (see Figure 2) and (XIX) demanded that their formation was associated with rearrangement; they showed signals characteristic of the A_2X system expected for the partial structure $Ar^1Ar^2CH_X{-}C(H_A)_2Cl$.

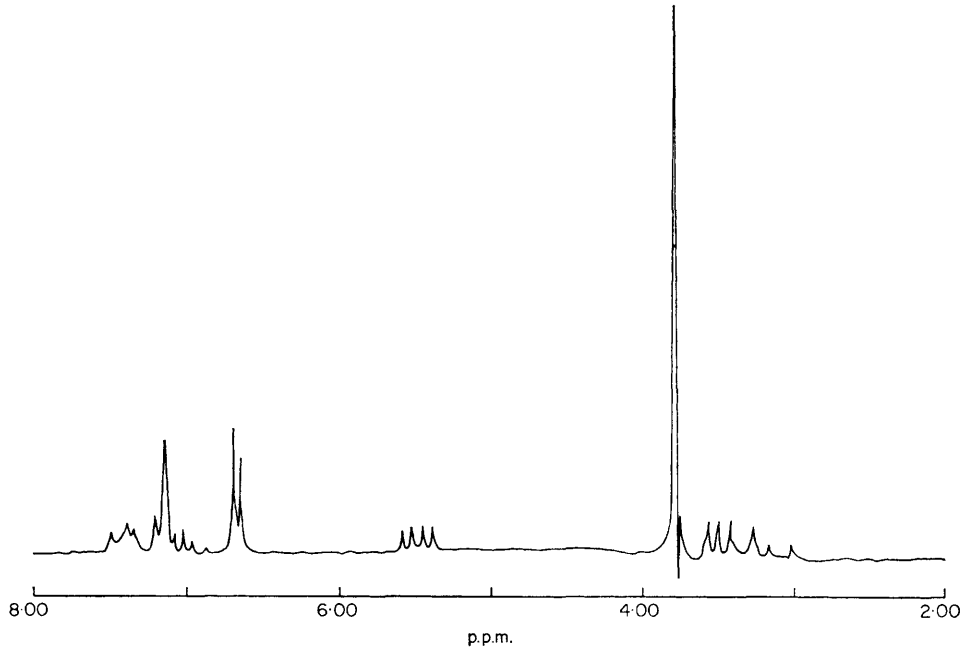

FIGURE 1 The n.m.r. spectrum of 10-chloro-10,11-dihydrodibenz[*b*,*f*]oxepin (VII); solvent CCl_4

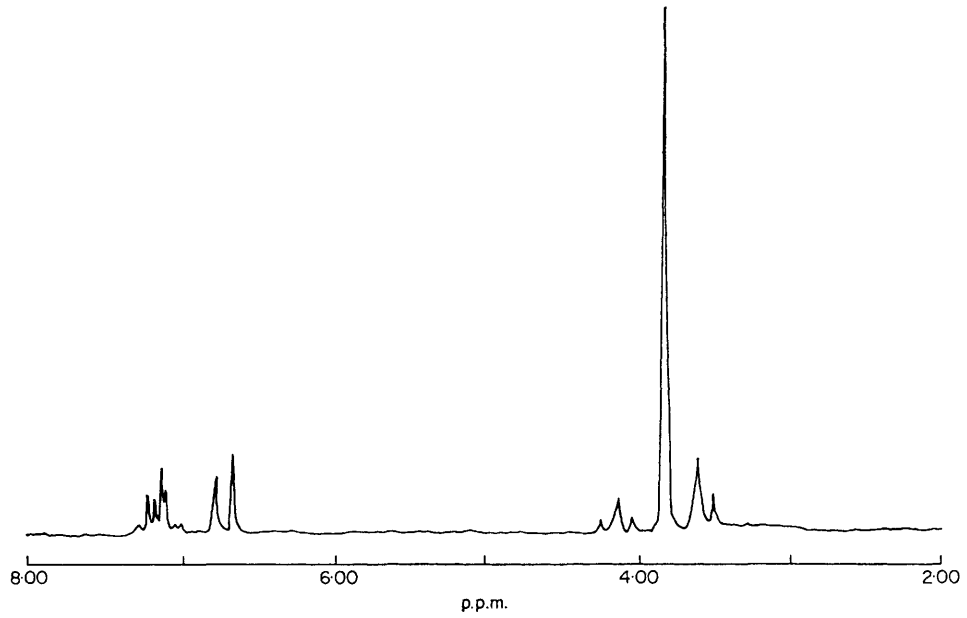

FIGURE 2 The n.m.r. spectrum of 9-chloromethyl-2,3-dimethoxyxanthen (XVII); solvent $CDCl_3$

The constitution of the chlorides (VII) and (XIII) was verified by their n.m.r. spectra, which clearly showed signals characteristic of an ABX system which could be associated with the indicated protons of the grouping $Ar^1{-}CH_XCl{-}CH_AH_B{-}Ar^2$ (see Figure 1 and

Thus the chloride (XIX) showed a triplet due to H_X (δ 4·14, J 5·2 c./sec.) and a doublet due to $(H_A)_2$ (δ 3·6, J 5·2 c./sec.). The constitutions of the chlorides (XVII) and (XIX) were confirmed by catalytic hydrogenation to give the 9-methylxanthens (XVIII) and (XX)

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respectively, the n.m.r. spectra of which clearly showed a doublet (δ 1·45, J 7·0 c./sec.) assignable to the methyl of the Me–CHAr^{1}Ar^2 grouping.

The n.m.r. spectrum (see Figure 3) of the alcohol (XI) shows an ABX system [δ 3·03 (A), 3·33 (B), and 5·15 (X); J_{AX} 8·0, J_{BX} 4·0, J_{AB} 15 c./sec.] assignable to the indicated protons of the Ar^1–CH$_X$(OH)–CH$_A$H$_B$–Ar^2 grouping. This first-order analysis was supported by the n.m.r. spectrum of the deuterio-derivative (XVI) prepared by reduction of the ketone (IV) with lithium aluminium deuteride. This spectrum clearly shows the expected simplification and the non-equivalent protons H$_A$ and H$_B$ (see XVI) are associated with the pair of doublets [δ 2·98 (A) and 3·47 (B); J_{AB} 15·0 c./sec.] observed (see Figure 4).

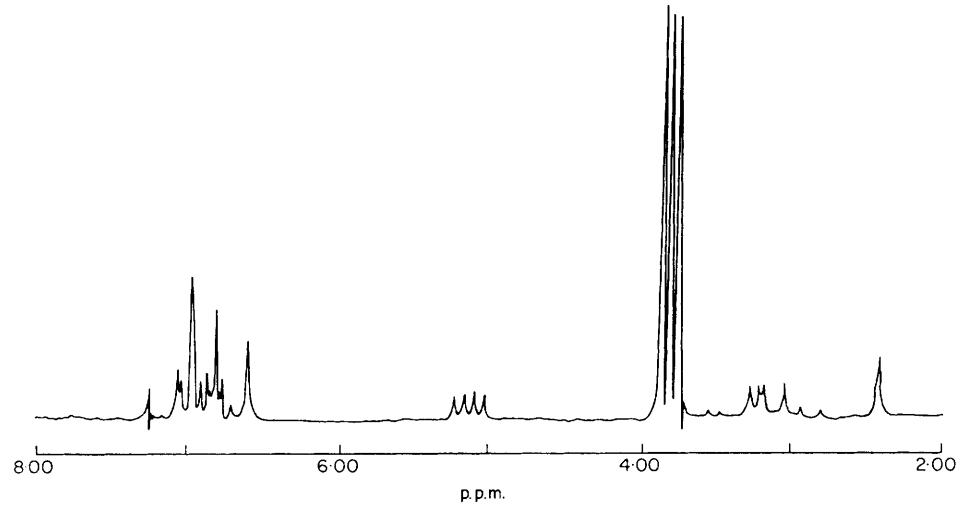

FIGURE 3 The n.m.r. spectrum of 10,11-dihydro-2,3,6-trimethoxydibenz[*b*,*f*]oxepin-10-ol (XI); solvent $CDCl_3$

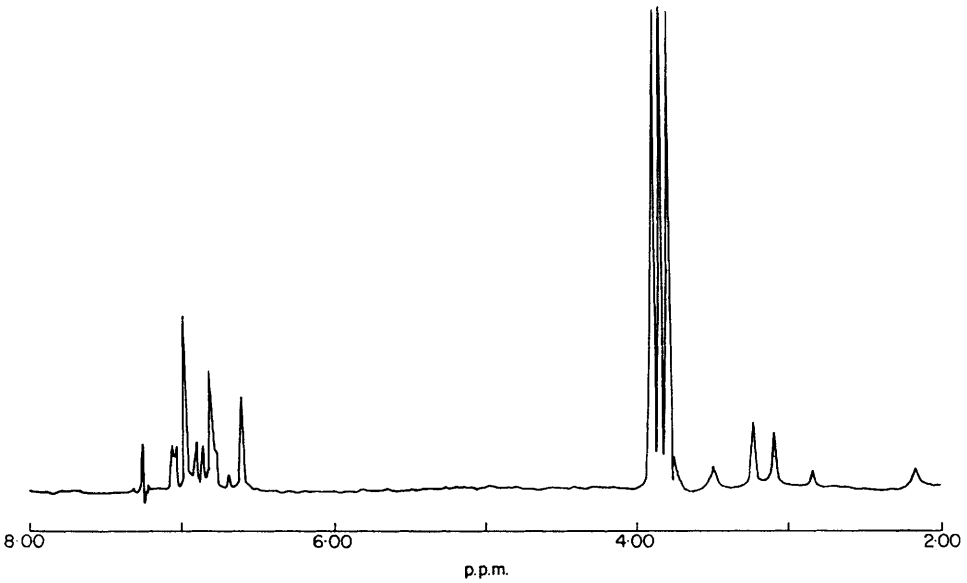

FIGURE 4 The n.m.r. spectrum of 10,11-dihydro-2,3,6-trimethoxy[10-^{2}H]dibenz[*b*,*f*]oxepin-10-ol (XVI); solvent $CDCl_3$

With reference to the stereochemical implications of the coupling constant information summarised in the Table, the diagrams A, B, C, and D in Figure 5 represent four particular conformations related to the configurational formula (XXI). In two conformations (A and C) the molecule is folded with the diphenyl ether oxygen *down* and the other two folded conformations (B and D) have the diphenyl ether oxygen *up*. The difference between conformations A and C is in the conformational arrangement adopted by the C_{11a}–C_{11}–C_{10}–C_{10a} unit; interconversion involves rotation only about the bond C_{11}–C_{10} without alteration of the folded conformation. A similar relationship exists between B and D. The conformational relationships between the hydrogens H$_A$, H$_B$, and H$_X$, and the substituent X are shown in the

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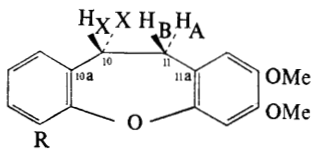
Newman projections (i) and (ii) obtained by projection along the C_{11}–C_{10} bond. Conformations A and B in which X is quasi-axial (*qax*) give the Newman projection (i) and conformations C and D in which X is quasi-equatorial (*qeq*) give the Newman projection (ii).

Coupling constants determined by first-order analysis of the n.m.r. spectra of the 10,11-dihydrodibenz[*b*,*f*]-oxepins (XXI)



(XXI)

	J_{AX} (c./sec.)	J_{BX} (c./sec.)
(V) [a]	7·8	3·8
(VI) [b]	7·8	4·0
(VII) [b]	7·0	5·0
(IX) [a]	7·5	4·0
(X) [a]	6·0	3·0
(XI) [a]	8·0	4·0
(XII) [a]	8·0	4·7
(XIII) [b]	8·5	4·5

[a] Ref. 10. [b] This paper.

The observed coupling constants J_{AX} *ca.* 8 and J_{BX} *ca.* 5 c./sec. for the 10-substituted-10,11-dihydrodibenz-[*b*,*f*]oxepins (XXI) (see Table) are characteristic of an ABX system with the geometry associated with Newman projection (ii).[11] On the assumption that the qualitative application of the Karplus relation [12] is justified in this case, the preferred conformation of 10-substituted-10,11-dihydrodibenz[*b*,*f*]oxepins is either C or D. Both C and D are, as expected, preferred conformations because the substituent X is quasi-equatorial with respect to the seven-membered ring in each. The difference in chemical shift between protons H_A and H_B (see XXI) is small, which suggests that neither H_A nor H_B is appreciably influenced by the diamagnetic anisotropy of the diphenyl ether grouping.[13] As the diphenyl ether oxygen atom could influence H_A in the conformation C, this evidence, although not compelling, favours conformation D for the configuration (XXI).

The formation of the chloride (XVII) either from the alcohol (V) or by rearrangement of the chloride (VII), and the corresponding reactions leading to the chloride (XIX), are unusual in that the rearrangements formally involve a secondary ⟶ primary carbonium ion transformation or an equivalent mechanistic process. Detailed consideration of this on the basis of the evidence available is not justified, but it may be mentioned that if the rearrangements (VII) ⟶ (XVII) and (XIII) ⟶ (XIX) are taking place under equilibration conditions, then the products may well be less strained than the precursors. Also conformation D, with its anti-peri-planar arrangement of X and the 3,4-dimethoxyphenyl group [Figure 5, projection (ii)] has the best geometry to meet the stereo-electronic requirements of the rearrangement reactions which have been observed in the compounds (VII and XIII; X = Cl).

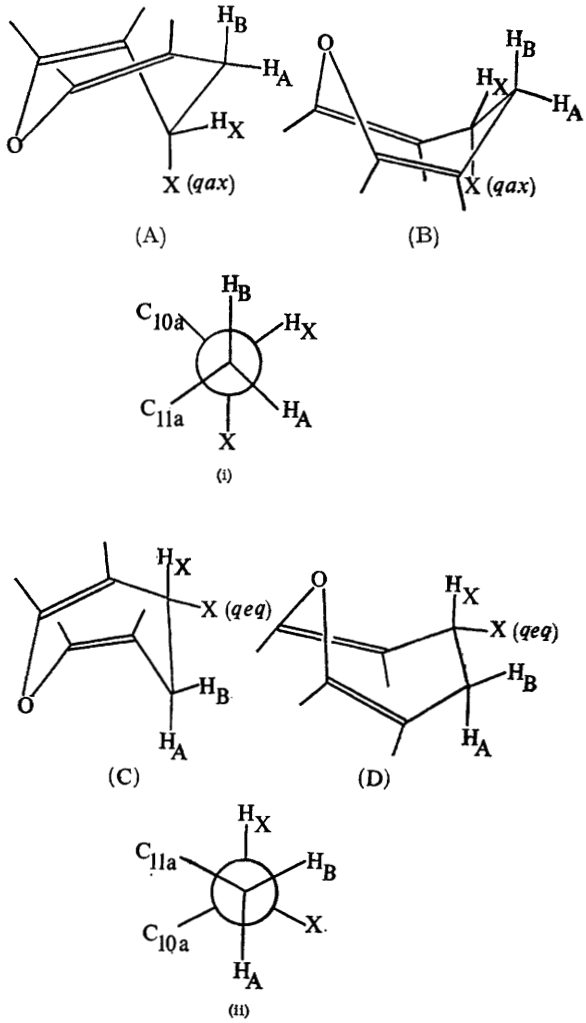


FIGURE 5 Four conformations (A, B, C, and D) related to the 10-substituted 10,11-dihydrodibenz[*b*,*f*]oxepin (XXI). The Newman projection associated with A and B is projection (i) and that associated with C and D is projection (ii).

For clarity the complete benzene rings are not indicated in the conformational diagrams

In connection with these rearrangements, stabilisation of the reaction intermediates by the 3,4-dimethoxyphenyl group is likely to be important. The synthesis of the alcohol (XXVIII) and the chloride (XXX) which are isomers of the alcohol (V) and the chloride (VII) was therefore undertaken. This involved the preparation of the diphenyl ether (XXII) from salicylaldehyde and 4-bromoveratrole, the homologation

[11] N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, California, 1964, p. 51 and references there cited.

[12] M. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.

[13] L. M. Jackman, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 1959, pp. 115—119.

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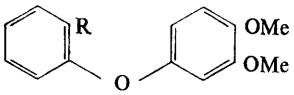
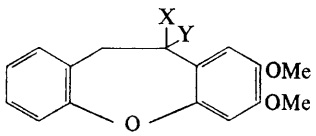
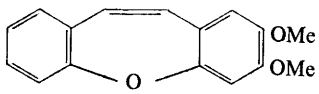
of the aldehyde (XXII) by the sequence (XXII) ⟶ (XXIII) ⟶ (XXIV) ⟶ (XXV) ⟶ (XXVI), cyclisation of the acid (XXVI) to give the ketone (XXVII), and reduction to the alcohol (XXVIII).



	R
(XXII)	CHO
(XXIII)	CH_2OH
(XXIV)	CH_2Cl
(XXV)	$CH_2{\cdot}CN$
(XXVI)	$CH_2{\cdot}CO_2H$



(XXVII) X,Y = O
(XXVIII) X = H, Y = OH
(XXIX) X = H, Y = OAc
(XXX) X = H, Y = Cl



(XXXI)

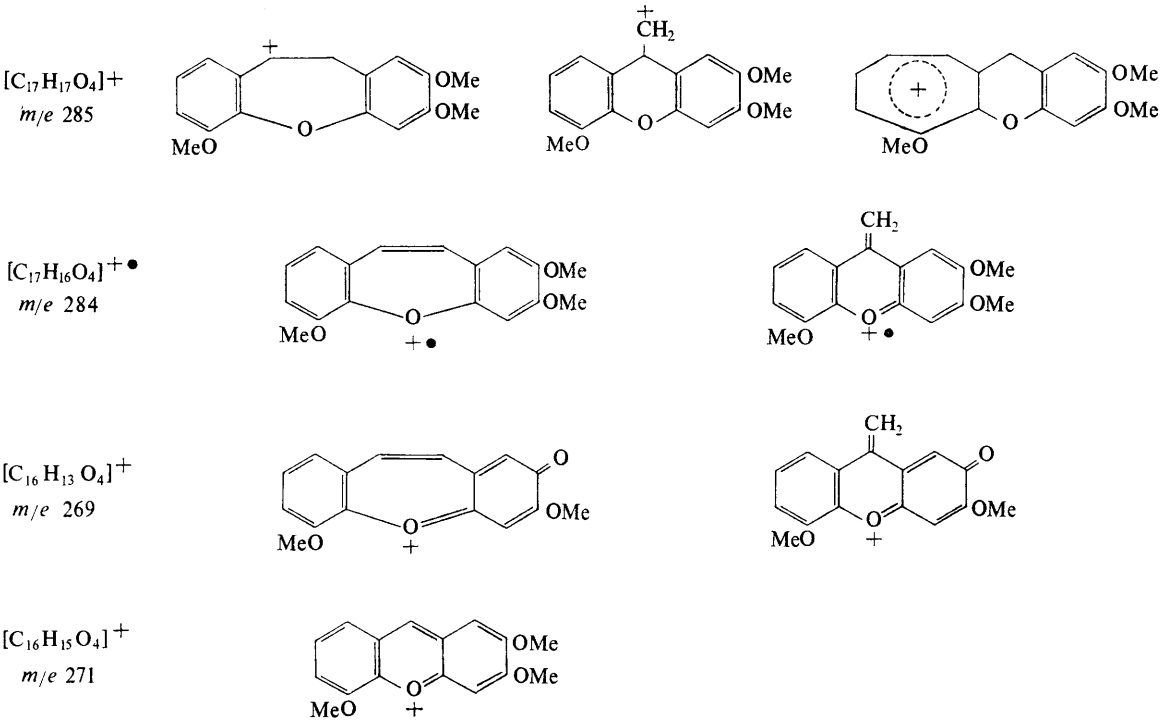
Attempts to prepare the chloride (XXX) either by reaction of the alcohol (XXVIII) with thionyl chloride or by reaction of the acetate (XXIX) took a different course. Thus, neither substitution nor rearrangement to a dibenzoxanthen was observed and in this case the product was the dibenzoxepin (XXXI). The formation of this elimination product (XXXI) rather than the chloride (XXX) is easily interpreted in terms of the expected stability of the intermediate carbonium ion related to the chloride (XXX). This easily generated carbonium ion would give the oxepin (XXXI) by deprotonation.

Ready rearrangement reactions may also be responsible for the virtual identity of the mass spectra of the chlorides (XIII) and (XIX), which show parent peaks at *m/e* 320 and fragment ions at *m/e* 285, 284, 271, and 269; the ion *m/e* 271 is the base peak in both spectra. The striking similarity between these two mass spectra may well be an indication that the same ions are involved in the fragmentation of both chlorides (XIII) and (XIX), but it is not possible from the mass spectrometric evidence to distinguish between the alternatives indicated in the Scheme. Reasonable routes to these or equivalent structures may be devised.

EXPERIMENTAL

Infrared spectra were determined with a Hitachi EPI-3 spectrometer. Mass spectra were determined with a Hitachi RMU-6D spectrometer with a direct inlet system (accelerating voltage 1200v, chamber voltage 70v, total emission 80 μA, target current 60 μA, evaporation temp. 200°, ion-chamber temp. 250°).

10,11-*Dihydro*-2,3,6,-*trimethoxydibenz*[b,f]*oxepin*-10-*ol* (XI).—(a) *Meerwein-Ponndorf reduction of the ketone* (IV). A mixture of 10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]-oxepin-10-one [8,9] (IV) (1 g.), propan-2-ol (50 ml.), and aluminium isopropoxide (1 g.) was heated under reflux for 10 hr., then volatile material was removed under diminished pressure. Addition of hydrochloric acid (5%;



SCHEME
Possible formulations for the fragment ions in the mass spectra of the chlorides (XIII) and (XIX)

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50 ml.) to the residue and extraction with chloroform gave 10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]oxepin-10-ol (0·6 g.) as needles, m.p. 169—170° (from methanol), identical (m.p. and i.r. spectrum) with an authentic sample.[10]

(b) *Deamination of the amine* (XIV). Sodium nitrite (100 mg.) in water (1 ml.) was added to a stirred solution prepared by the addition of 10-amino-10,11-dihydro-2,3-dimethoxydibenz[*b,f*]oxepin [10] (XIV) (300 mg.) in water (10 ml.) to a solution of sodium acetate (100 mg.) in aqueous acetic acid (55%; 2·4 ml.). The temperature was maintained at −5° during the dropwise addition of the sodium nitrite solution and for a further 2 hr. Then the mixture was kept at 0—2° for an additional 1 hr. An excess of saturated aqueous potassium carbonate solution was then added and chloroform extraction yielded 10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]oxepin-10-ol (250 mg.), identical with the product from method (a), δ ($CDCl_3$) 3·79, 3·82, and 3·88 (three OCH_3), 3·03 (A), 3·33 (B), and 5·15 (X) (ABX system, J_{AB} 15·0, J_{AX} 8·0, J_{BX} 4·0 c./sec.), and 6·56—7·15 (m, 5 aromatic H) (see Figure 3).

10-*Chloro*-10,11-*dihydro*-2,3,6-*trimethoxydibenz*[b,f]*oxepin* (XIII).—A mixture of the alcohol (XI) (800 mg.), ether (20 ml.), benzene (20 ml.), and thionyl chloride (2·5 g.) was heated under reflux (1 hr.), then volatile material was removed by warming under diminished pressure. The residue gave 10-*chloro*-10,11-*dihydro*-2,3,6-*trimethoxydibenz*[b,f]*oxepin* (450 mg.) as needles, m.p. 116—117° (from ether–chloroform) (Found: C, 63·7; H, 5·6. $C_{17}H_{17}ClO_4$ requires C, 63·65; H, 5·3%), δ ($CDCl_3$) 3·79, 3·83, and 3·88 (three OCH_3), 3·29 (A), 3·36 (B), and 5·51 (X) (ABX system; J_{AB} 13·0, J_{AX} 8·5, J_{BX} 4·5 c./sec.), and 6·56—7·10 (5 aromatic H).

9-*Chloromethyl*-2,3,5-*trimethoxyxanthen* (XIX).—(*a*) Acetyl chloride (200 mg.) in pyridine (200 mg.) was added to a solution of the alcohol (XI) (300 mg.) in glacial acetic acid (20 ml.) and the mixture was kept overnight at room temperature. It was then diluted with water (20 ml.) and basified with an excess of saturated aqueous sodium carbonate solution. Chloroform extraction followed by washing of the extract with hydrochloric acid (10%) and with water gave after removal of the chloroform 9-*chloromethyl*-2,3,5-*trimethoxyxanthen* (200 mg.) as needles, m.p. 134—135° (from methanol) (Found: C, 63·7; H, 5·6. $C_{17}H_{17}O_4Cl$ requires C, 63·65; H, 5·3%).

(*b*) Acetyl chloride (300 mg.) was added to a solution of 10-acetoxy-10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]-oxepin (XII) [10] (350 mg.) in acetic acid (22 ml.) and the mixture was set aside at room temperature for 18 hr. Work-up as in method (*a*) gave 9-chloromethyl-2,3,5-trimethoxyxanthen (200 mg.), identical with the product from method (*a*).

(*c*) 10-Chloro-10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]-oxepin (XIII) (100 mg.) dissolved in hot glacial acetic acid (20 ml.) was set aside at room temperature. After 18 hr., work-up as in experiments (*a*) and (*b*) gave 9-chloromethyl-2,3,5-trimethoxyxanthen (50 mg.).

2,3,5-*Trimethoxy*-9-*methylxanthen* (XX).—Catalytic hydrogenation (48 hr.; room temperature; 1 atmos.) of 9-chloromethyl-2,3,5-trimethoxyxanthen (100 mg.) in ethanol (70 ml.) with palladised charcoal catalyst (5%; 50 mg.) gave, after removal of the catalyst, evaporation of the solvent, and crystallisation of the residue from n-hexane–benzene, 2,3,5-*trimethoxy*-9-*methylxanthen* (40 mg.) as needles, m.p. 116—117° (Found: C, 67·65; H, 6·1. $C_{17}H_{18}O_4$,0·75H_2O requires C, 68·1; H, 6·55%), δ ($CDCl_3$) 1·45 (d, A) and 3·75 (q, X) (A_3X system; J_{AX} 7·0 c./sec., CH_3–CH), 3·88, 3·88, and 3·93 (three OCH_3), and 6·66—6·97 (5 aromatic H).

10,11-*Dihydro*-2,3,6,10-*tetramethoxydibenz*[b,f]*oxepin* (XV).—A solution of 10-chloro-10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]oxepin in anhydrous methanol (10 ml.) was heated under reflux for 5 min., then the solvent was removed under diminished pressure. Crystallisation from methanol gave 10,11-*dihydro*-2,3,6,10-*tetramethoxydibenz*-[b,f]*oxepin* as needles, m.p. 135—136° (Found: C, 68·5; H, 6·6. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%), δ ($CDCl_3$) 3·48, 3·80, 3·87, and 3·89 (four OCH_3), 3·10 (A), 3·20 (B), and 4·95 (X) (ABX system; J_{AB} 15·0, J_{AX} 9·5, J_{BX} 4·5 c./sec.), and 6·55—7·15 (m, 5 aromatic H).

10-*Chloro*-10,11-*dihydro*-2,3-*dimethoxydibenz*[b,f]*oxepin* (VII).— 10,11-Dihydro-2,3-dimethoxydibenz[*b,f*]oxepin-10-ol [10] (V) in ether (20 ml.) was added to a solution of thionyl chloride (2 g.) in benzene (20 ml.) and the mixture was heated under reflux for 1 hr. Removal of volatile material under diminished pressure gave a residue which gave 10-*chloro*-10,11-*dihydro*-2,3-*dimethoxydibenz*[b,f]*oxepin* (200 mg.) as needles, m.p. 126—127° (from ether–chloroform) (Found: C, 65·6; H, 5·4. $C_{16}H_{15}ClO_3$ requires C, 66·0; H, 5·2%), δ ($CDCl_3$) 3·76 (two OCH_3), 3·20 (A), 3·41 (B), and 5·45 (X) (ABX system; J_{AB} 14·0, J_{AX} 7·0, J_{BX} 5·0 c./sec.), and 6·58—7·55 (6 aromatic H) (see Figure 1).

10-*Acetoxy*-10,11-*dihydro*-2,3-*dimethoxydibenz*[b,f]*oxepin* (VI).—Acetyl chloride (300 mg.) was added dropwise to a cooled solution of 10,11-dihydro-2,3-dimethoxydibenz[*b,f*]-oxepin-10-ol [10] (V) and after 7 hr. at room temperature the mixture was diluted with water, acidified (10% sulphuric acid) and extracted with chloroform. This extract yielded 10-*acetoxy*-10,11-*dihydro*-2,3-*dimethoxydibenz*[b,f]*oxepin* (500 mg.) as prisms, m.p. 104—105° (from ethanol) (Found: C, 68·8; H, 6·0. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%), δ ($CDCl_3$) 2·06 ($O{\cdot}CO{\cdot}CH_3$), 3·83, and 3·84 (two OCH_3), 3·22 (A), 3·56 (B), and 6·23 (X) (ABX system; J_{AB} 15·0, J_{AX} 7·8, J_{BX} 4·0 c./sec.), and 6·7—7·3 (6 aromatic H).

9-*Chloromethyl*-2,3-*dimethoxyxanthen* (XVII).—(*a*) Acetyl chloride (1·2 g.) was added dropwise to a solution of 10,11-dihydro-2,3-dimethoxydibenz[*b,f*]oxepin-10-ol [10] (V) (2·5 g.) in acetic acid (160 ml.) and pyridine (1·2 g.). After 12 hr. at room temperature, the mixture was diluted with water and extracted with chloroform. This extract was shaken with 10% aqueous sodium carbonate solution and with water, and yielded 9-chloromethyl-2,3-dimethoxyxanthen (2·1 g.) as needles, m.p. 116—117° (from ethanol) (Found: C, 66·3; H, 5·5. $C_{16}H_{15}ClO_3$ requires C, 66·0; H, 5·2%), δ ($CDCl_3$) 3·83 (two OCH_3), 3·60 (A) and 4·14 (X) (A_2X system; J_{AX} 6·5 c./sec.), and 6·64—7·40 (6 aromatic H) (see Figure 2), $\nu_{max.}$ ($CHCl_3$) 1630, 1584, 1481, 1465, and 1440 $cm.^{-1}$.

(*b*) A mixture of 10-acetoxy-10,11-dihydro-2,3-dimethoxydibenz[*b,f*]oxepin (VI) (300 mg.) and acetyl chloride (200 mg.) in acetic acid (20 ml.) was kept at room temperature for 16 hr., then worked up as in method (*a*). This gave 9-chloromethyl-2,3-dimethoxyxanthen (200 mg.), m.p. 116—117°.

(*c*) A solution of 10-chloro-10,11-dihydro-2,3-dimethoxydibenz[*b,f*]oxepin (VII) (200 mg.) in acetic acid (40 ml.) was set aside at room temperature overnight then volatile material was removed by warming under diminished pressure. Work-up as in methods (*a*) and (*b*) gave 9-chloromethyl-2,3-dimethoxyxanthen (180 mg.).

2,3-*Dimethoxy*-9-*methylxanthen* (XVIII).—Catalytic

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hydrogenation (70 hr.; room temp.; 1 atmos.) of 9-chloromethyl-2,3-dimethoxyxanthen (60 mg.) in ethanol (70 ml.) with palladised charcoal catalyst (5%; 40 mg.) gave *9-methyl-2,3-dimethoxyxanthen* (45 mg.) as needles, m.p. 95—96° (from n-hexane) (Found: C, 75·0; H, 6·25. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%), δ ($CDCl_3$) 1·45 (d, A) and 4·0 (q, X) (A_3X system; J_{AX} 7·0 c./sec., CH_3–CH), 3·81 and 3·84 (two OCH_3), and 6·60—7·35 (m, 6 aromatic H).

10,11-*Dihydro*-2,3,10-*trimethoxydibenz*[b,f]*oxepin* (VIII).—10-Chloro-10,11-dihydro-2,3-dimethoxydibenz[*b,f*]oxepin (VII) (200 mg.) in anhydrous methanol (10 ml.) was heated under reflux for 5 min. Removal of methanol under diminished pressure left 10,11-*dihydro*-2,3,10-*trimethoxydibenz*[b,f]*oxepin* (200 mg.) as needles, m.p. 101—102° (from methanol).

10,11-*Dihydro*-2,3,6-*trimethoxy*[10-^{2}H]*dibenz*[b,f]*oxepin*-10-*ol* (XVI).—10,11-Dihydro-2,3-trimethoxydibenz[*b,f*]-oxepin-10-one [8,9] (IV) (1 g.) was gradually added to a suspension of lithium aluminium deuteride (500 mg.) in tetrahydrofuran (45 ml.) at room temperature. The mixture was then heated under reflux for 7 hr., and cooled, and the excess of reagent was decomposed with tetrahydrofuran containing deuterium oxide. The solution was dried (Na_2SO_4) and yielded the *monodeuteriated alcohol* (XVI) (0·6 g.) as needles, m.p. 169—170° (from methanol) [Found: C, 67·5; H(D), 6·0. $C_{17}H_{17}DO_5$ requires C, 67·3; H(D), 6·3%], δ ($CDCl_3$) 3·79, 3·83, and 3·88 (three OCH_3), and 2·98 (d, A) and 3·47 (d, B) [AB system; J_{AB} 15 c./sec., $-CH_AH_B-CD(OH)-$] (see Figure 4).

2-(3,4-*Dimethoxyphenoxy*)*benzaldehyde* (XXII).—A mixture of salicylaldehyde (75 g.), 4-bromoveratrole (75 g.), copper powder (7 g.), anhydrous potassium carbonate (24 g.), and pyridine (1 ml.) was heated at 160—165° (bath) for 1 hr., cooled, and triturated with hot benzene. The benzene extract was filtered, shaken with aqueous sodium hydroxide (10%) and with water, dried (Na_2SO_4), and evaporated. Unchanged 4-bromoveratrole was removed by heating under diminished pressure and the residue was then chromatographed (alumina). Elution with benzene gave 2-(3,4-dimethoxyphenoxy)benzaldehyde as needles (12 g.), m.p. 94—95° (from n-hexane–benzene) (Found: C, 69·5; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·75; H, 5·5%), $\nu_{max.}$ ($CHCl_3$) 1690 cm.$^{-1}$, δ ($CDCl_3$) 3·84 and 3·81 (two OCH_3), 7·05—6·45 (m, 7 aromatic H), and 10·36 (CHO).

2-(3,4-*Dimethoxyphenoxy*)*benzyl Alcohol* (XXIII).—Sodium borohydride (5 g.) was gradually added to a stirred solution of the aldehyde (XXII) (10 g.) in methanol (60 ml.) and then the mixture was heated under reflux for 1 hr. Removal of the methanol by evaporation, addition of water, and extraction with benzene gave 2-(3,4-*dimethoxyphenoxy*)-*benzyl alcohol* (9·5 g.) as needles, m.p. 49—51° (from n-hexane–ether) (Found: C, 66·9; H, 6·35. $C_{15}H_{16}O_4$,0·5H_2O requires C, 66·9; H, 6·35%).

2-(3,4-*Dimethoxyphenoxy*)*benzyl Cyanide* (XXV).—Thionyl chloride (8 g.) was slowly added to a solution of the alcohol (XXIII) (8 g.) in dry benzene (80 ml.) and the mixture was heated under reflux for 30 min. Removal of benzene under diminished pressure gave the chloride (XXIV) which was dissolved directly in butan-2-one (100 ml.), and sodium cyanide (8 g.) and sodium iodide (8 g.) were added. The mixture was heated under reflux for 6 hr., water (120 ml.) was added, and ethyl acetate extraction yielded the *cyanide* (6·1 g.) as needles, m.p. 115—117° (from methanol) (Found: C, 70·9; H, 5·9; N, 5·15. $C_{16}H_{15}NO_3$ requires C, 71·4; H, 5·6; N, 5·2%).

2-(3,4-*Dimethoxyphenoxy*)*phenylacetic Acid* (XXVI).—Potassium hydroxide (9 g.) in water (9 ml.) was added to a solution of the cyanide (XXV) (4 g.) in dioxan (18 ml.) and methanol (27 ml.) and the mixture was heated under reflux for 30 min. The volatile material was then distilled off under diminished pressure, and acidification and extraction with ethyl acetate gave the *acid* (XXVI) (3 g.) as needles, m.p. 137—138·5° (from n-hexane–benzene) (Found: C, 66·85; H, 6·0. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%), $\nu_{max.}$ ($CHCl_3$) 1710 cm.$^{-1}$.

10,11-*Dihydro*-2,3-*dimethoxydibenz*[b,f]*oxepin*-11-*one* (XXVII).—The acid (XXVI) (4 g.) was added to polyphosphoric acid [prepared from phosphoric acid (85%; 24 ml.) and phosphoric anhydride (40 g.)] and the mixture was kept at 65—70° for 1 hr. It was then cooled and ice–water was added; extraction with benzene yielded the *ketone* (XXVII) (2·5 g.) as needles, m.p. 136° (from n-hexane–benzene or from methanol) (Found: C, 71·0; H, 5·25. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%), $\nu_{max.}$ ($CHCl_3$) 1665 cm.$^{-1}$, δ ($CDCl_3$) 3·82 (two OCH_3), 4·01 (s, CH_2–CO), 6·8 (s, 4-H), and 7·45—6·05 (m, 5 aromatic H).

10,11-*Dihydro*-2,3-*dimethoxydibenz*[b,f]*oxepin*-11-*ol* (XXVIII).—Sodium borohydride (2 g.) was added to a stirred solution of the ketone (XXVII) (2·3 g.) in methanol (50 ml.) and the mixture was heated under reflux for 30 min. Removal of the methanol under diminished pressure, addition of water, and extraction wich chloroform gave the *alcohol* (XXVIII) (1·8 g.) as needles, m.p. 147—148° (from n-hexane–benzene) (Found: C, 70·6; H, 5·8. $C_{16}H_{16}O_4$ requires C, 70·55; H, 5·9%), $\nu_{max.}$ ($CHCl_3$) 3495 cm.$^{-1}$, δ ($CDCl_3$) 3·07 (A), 3·46 (B), and 4·94 (X) (ABX system; J_{AB} 14, J_{AX} 7·5, J_{BX} 3·7 c./sec.), 3·78 and 3·83 (two OCH_3), δ 6·7 (s, 4-H) and 7·2—6·82 (5 aromatic H).

This alcohol (XXVIII) was characterised as its *acetate* (XXIX) (prepared with acetic anhydride–pyridine), colourless needles, m.p. 94—95° (from n-hexane–benzene) (Found: C, 69·0; H, 6·1. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%), $\nu_{max.}$ ($CHCl_3$) 1720 cm.$^{-1}$.

2,3-*Dimethoxydibenz*[b,f]*oxepin* (XXXI).—(*a*) The alcohol (XXVIII) (300 mg.), thionyl chloride (200 mg.), ether (10 ml.), and benzene (8 ml.) were heated under reflux for 1 hr., then volatile material was removed under diminished pressure. The residue was triturated with warm ether and the soluble fraction (120 mg.) gave 2,3-dimethoxydibenz[*b,f*]-oxepin (XXXI) as needles, m.p. 114—116° (from methanol) (Found: C, 75·55; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·55%), δ ($CDCl_3$) 3·80 and 3·83 (two OCH_3), 6·7 (s, 4-H), 6·57 (s, $-CH=CH-$), and 7·4—6·9 (m, 5 aromatic H).

(*b*) The alcohol (XXVIII), acetic acid (25 ml.), acetyl chloride (200 mg.), and pyridine (200 mg.) were set aside at room temperature overnight. After neutralisation with aqueous sodium carbonate solution, extraction with chloroform yielded the dibenzoxepin (XXXI) (150 mg.), m.p. 115—116°.

(*c*) The acetate (XXIX) (200 mg.) and acetyl chloride (300 mg.) in acetic acid (25 ml.) gave, as in method (*b*), the dibenzoxepin (XXXI) (150 mg.), m.p. 114—115°.

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