Stereochemistry of the Electrophilic Addition of Bromine to Dibenzo-[*b,f*]thiepin and its 5,5-Dioxide

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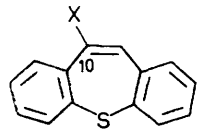
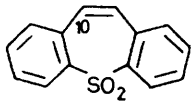
The dibromide formed by kinetically controlled bromine addition to dibenzo[*b,f*]thiepin (3) is the *trans*-isomer (5). Treatment of this product with methanolic sodium methoxide gives the bromo-ene (1) together with products resulting from substitution and rearrangement reactions, but the reaction with potassium t-butoxide in t-butyl alcohol gives only the bromo-ene (1). Bromine addition to the sulphone (2) in carbon tetrachloride gives the *cis*-dibromide whereas in acetic acid the *trans*-dibromide is obtained. The acid-catalysed dehydration and rearrangement of 9-hydroxymethylthioxanthen (18) proceeds abnormally under anhydrous conditions in toluene giving 10,11-dihydro-10-*p*-tolyldibenzo[*b,f*]thiepin (19).

We required 10-bromodibenzo[*b,f*]thiepin (1) as an intermediate in the synthesis of compounds for conformational studies.[1] Since it had been reported [2] that the sulphone analogue (2) could be converted into the 10-bromo-derivative by bromine addition followed by dehydrobromination we investigated the use of a similar reaction sequence with dibenzo[*b,f*]thiepin (3).



(1) X = Br
(3) X = H



(2)

The reaction of the thiepin derivative (3) with bromine in dichloromethane at room temperature was complete in a few minutes and gave both the *cis*- and the *trans*-dibromide [(4) and (5)], which could be separated by fractional crystallisation. The molecular formulae of these products (elemental analysis and mass spectrum) were consistent with these structures but stereochemical assignments could not be made directly: the isomers are designated A (m.p. 145°) and B (m.p. 139°) in the discussion that follows. Bromine addition in dichloromethane at −70° gave a product ratio (A : B) of 93 : 7; *cf.* 2 : 1 at room temperature. The use of acetic acid as the solvent at room temperature gave the dibromide A exclusively. The n.m.r. spectrum of the mixed products shows two singlet signals assignable to the C-10 and C-11 protons (isomer A, τ 4·12; isomer B, τ 3·55). The temperature and solvent dependence of the product ratio and the observation that either of the pure isomers reverts to the equilibrium mixture when kept in solution in the presence of hydrogen bromide † indicate that the dibromide A is the kinetically favoured product.

† Owing to some aromatic bromination, hydrogen bromide is always present when the solvent is CH_2Cl_2. In acetic acid the product crystallises almost immediately and is therefore not subject to subsequent equilibration.

‡ The fact that the *cis*-dibromide (4) is achiral and the *trans*-compound (5) a racemic mixture has no direct relevance to the present discussion. Differentiation between the chiral and achiral species by partial dehydrobromination with a chiral base (*e.g.* brucine, ref. 5) failed with compounds (4) and (5). The argument used also assumes rapid interconversion, on the n.m.r. time scale, of equivalent twist-boat conformations [see (10)]. This is justified on the basis of the observed n.m.r. spectra.

The *cis*- rather than *trans*-addition of halogen has frequently been demonstrated in cyclic systems, and mechanistic interest in the stereochemical aspects of such electrophilic additions continues.[3,4] It was therefore of interest to determine the configuration of the dibromides A and B, since the results could be related to the dibromo-derivatives of analogous compounds. This stereochemical assignment could be made with certainty in the case of the thiepin derivatives by the examination of the n.m.r. spectra of the corresponding sulphones and sulphoxides as described below.

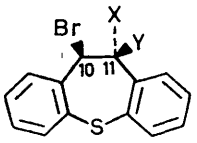
The *cis*-10,11-dibromo-10,11-dihydrodibenzothiepin (4) can give rise to a pair of epimeric sulphoxides (6a) and (6b) which differ in the relative dispositions of the bromine atoms and the oxygen atom. The compounds (4), (6a), and (6b) all have a plane of symmetry rendering the C-10 and C-11 protons enantiotopic and hence magnetically equivalent. The n.m.r. spectrum of the mixture of sulphoxides derived from the *cis*-dibromide (4) should therefore show singlets of unequal intensity in the region of benzylic proton resonance. Further oxidation of this mixture of sulphoxides (6a and b) would give a single sulphone (8).

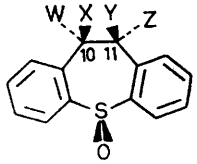
The *trans*-10,11-dibromo-10,11-dihydrodibenzothiepin (5) has C_2 symmetry and the protons at C-10 and C-11 would therefore be equivalent (homotopic).‡ Since the two faces of the molecule are also equivalent, only one sulphoxide (7) can be produced on oxidation. In this sulphoxide (7) the axis of symmetry, present in (5), is absent in (7) so that its benzylic protons are rendered diastereotopic and are expected to be associated with an

[1] M. Nógrádi, W. D. Ollis, and I. O. Sutherland, *Chem. Comm.*, 1970, 158.
[2] W. Tochtermann, K. Oppenlander, and M. N. D. Hoang, *Annalen*, 1967, **701**, 117.
[3] For reviews see R. C. Fahey, *Topics Stereochem.*, 1968, **3**, 237; T. G. Traylor, *Accounts Chem. Res.*, 1969, **2**, 152.
[4] J. A. Berson and R. Swidler, *J. Amer. Chem. Soc.*, 1954, **76**, 4060; V. Georgian, L. Georgian, and A. V. Robertson, *Tetrahedron*, 1963, **19**, 1219; R. Huisgen and G. Boche, *Tetrahedron Letters*, 1965, 1769; R. Huisgen, G. Boche, W. Hechtl, and H. Huber, *Angew. Chem. Internat. Edn.*, 1966, **5**, 585; R. C. Fahey and C. Schubert, *J. Amer. Chem. Soc.*, 1965, **87**, 5172; M. C. Cabaleiro and M. D. Johnson, *J. Chem. Soc.* (*B*), 1967, 565; R. Huisgen, G. Boche, and H. Huber, *J. Amer. Chem. Soc.*, 1967, **89**, 3345; R. Huisgen, *Atti Accad. naz. Lincei*, 1968, 281; R. E. Singler and D. J. Cram, *J. Amer. Chem. Soc.*, 1972, **94**, 3512; R. Huisgen and J. Gasteiger, *Angew. Chem. Internat. Edn.*, 1972, **11**, 1104.
[5] S. J. Cristol, F. R. Stermitz, and P. S. Ramey, *J. Amer. Chem. Soc.*, 1956, **78**, 4939.

AB system in its n.m.r. spectrum. Further oxidation of (7) to the sulphone (9) restores the C_2 symmetry and the equivalence of the benzylic protons would again be expected to give a singlet n.m.r. signal.

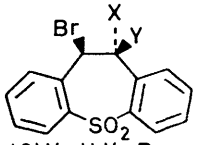
The n.m.r. spectra (see Experimental section) of the sulphoxides (6a), (6b), and (7) and the sulphones (8) and (9) derived from the individual 10,11-dibromodibenzothiepins (4) and (5) showed all the features described above and permitted the assignment of the *trans*-configuration (5) to the kinetically favoured product (A).



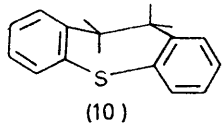


(4) X = H, Y = Br (Isomer B)
(5) X = Br, Y = H (Isomer A)

(6a) W = Z = H, X = Y = Br
(6b) W = Z = Br, X = Y = H
(7) W = Y = Br, X = Z = H

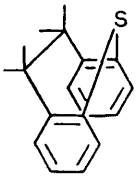


(8) X = H, Y = Br
(9) X = Br, Y = H



(10)

The reactivity of the 10,11-dibromides (4) and (5) is in accord with the above conclusions. From the examination of models, an antiperiplanar relation between a pair of hydrogen and bromine substituents is realised only in each of the twist-boat conformations [*e.g.* (10)] of the *cis*-compound, but no such arrangement is possible with any conformer in the *trans*-series. The boat conformation (11) is related to the transition state for synperiplanar elimination from the *trans*-compound, but this is expected to be a higher energy pathway for elimination owing to torsional strain and angle strain in this conformation (11). It is therefore not surprising that the



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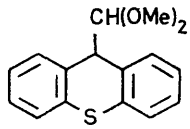

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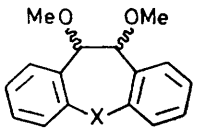
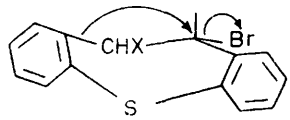


(13) X = S
(14) X = S=O

cis-dibromide (4) gives exclusively the elimination product (1) on treatment with methanolic sodium methoxide, whereas the *trans*-dibromide (5) yields, in addition to the olefin (1), products (12) and (13) that appear to result from either rearrangement of an intermediate carbonium ion or competing nucleophilic displacement reactions. The formation of thioxanthen-9-carbaldehyde dimethyl acetal (12) can be rationalised on this basis, and it appears reasonable that the ring contraction reaction (15) → (16) involves the carbonium ion derived from the methoxy-bromide (15; X = OMe) obtained after initial displacement of one of the bromine atoms by methoxide. The methoxy-bromide (15) could also reasonably give rise to the mixture of diastereomers (13) * by simple nucleophilic attack without rearrangement. The ring contraction reaction of 5,6-dibromo-5,6-dihydrodibenzo[*a*,*d*]cyclo-octene under similar conditions has previously been reported.[6] With potassium t-butoxide in t-butyl alcohol the initial nucleophilic displacement is prevented and only the elimination product (1) is formed. The rearrangement of (5) has also been observed under other conditions: on one occasion thioxanthen-9-carbaldehyde (17) [*M* 226; $\nu_{C=O}$ 1720 cm^{-1}, τ 0·60 (d, *J* 2 Hz, CH–C*H*O)] was formed from the *trans*-dibromide (5) during chromatography on silica gel.



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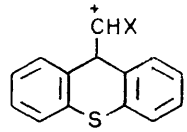

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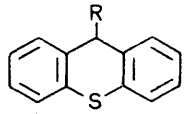
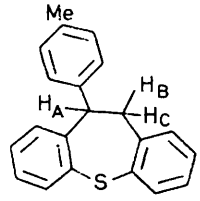


(17) R = CHO
(18) R = CH_2·OH



(19)

The addition of bromine to dibenzo[*b*,*f*]thiepin 5,5-dioxide (2) also takes a solvent-dependent course. Thus the reaction of the sulphone (2) with bromine in boiling carbon tetrachloride gives a *cis*-dibromide,[2] m.p. 206—208°, identical with a sample of the sulphone (8) prepared by the oxidation of the *cis*-dibromodibenzothiepin (4). On the other hand the sulphone (2) with bromine in acetic acid at room temperature gives the *trans*-dibromide (9), m.p. 170—172°, identified by comparison with a sample prepared from the *trans*-dibromodibenzothiepin (5).

Related studies on the electrophilic addition reactions of dibenz[*b*,*f*]oxepin (3; O for S) have been reported.[7] This heterocycle with bromine in chloroform–ether gave one isolable 10,11-dibromide but its configuration was not determined.[7]

Dibenzo[*b*,*f*]thiepin (3) was prepared (with slight

* This compound was shown to be a mixture of *cis*- and *trans*-isomers by examination of the n.m.r. spectrum of the corresponding sulphoxides.

[6] M. P. Cava, R. Pohlke, B. W. Erickson, and G. Fraenkel, *Tetrahedron*, 1962, **18**, 1005; M. Avram, I. G. Dinulescu, D. Dinu, G. Mateescu, and C. D. Nenitzescu, *Tetrahedron*, 1963, **19**, 309.

[7] P. M. G. Bavin, K. D. Bartle, and D. W. Jones, *J. Heterocyclic Chem.*, 1968, **5**, 327.

modification of the published procedure [8]) by treatment of 9-hydroxymethylthioxanthen (18) with toluene-*p*-sulphonic acid hydrate in boiling toluene. When this reaction was carried out under anhydrous conditions (Dean–Stark apparatus) then a major product was obtained in addition to the expected dibenzo[*b*,*f*]thiepin (3). This was identified as the *p*-tolyl derivative (19) [*M* 302, ABC system in the n.m.r. spectrum, τ_A 5·31, τ_B 5·75, τ_C 6·32 (J_{AB} 10, J_{BC} 14, J_{AC} 4 Hz, $CH_A{\cdot}CH_BH_C$)]. The formation of this product (19) is apparently a result of the electrophilic activity of the intermediate carbonium ion under anhydrous reaction conditions.

EXPERIMENTAL

cis-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* (4).—Bromine (3·81 g) was added to a solution of the dibenzothiepin (3) [8] (5·0 g) in dichloromethane (50 ml), and after 15 min the solution was evaporated. The residue crystallised on treatment with light petroleum giving a mixture of the dibromides (4) and (5) (7·9 g, 91%) shown by n.m.r. analysis to contain about 65% of the dibromide (5). The mixture was allowed to crystallise by slow evaporation of a solution in benzene to give pure *trans*-dibromide (5) as plates, m.p. 145°. The addition of light petroleum to the mother liquors resulted in the slow crystallisation of the cis-*dibromide* (4) (0·6 g), m.p. 139°, from benzene (Found: C, 45·2; H, 2·8; S, 8·5%; *M*, 370. $C_{14}H_{10}Br_2S$ requires C, 45·4; H, 2·7; S, 8·7%; *M*, 370); τ 2·50—2·90 (m, 8 aromatic H) and 3·55 (s, CHBr·CHBr).

trans-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* (5).—Bromine (2·08 g) was added to a solution of the dibenzothiepin (3) (2·6 g) in acetic acid (26 ml) at room temperature. The crystalline product that separated from the solution (3·2 g, 73%) was recrystallised from t-butyl alcohol giving the trans-*dibromide* (5) as plates, m.p. 145° (Found: C, 45·3; H, 2·6; Br, 44·0; S, 9·0%; *M*, 370. $C_{14}H_{10}Br_2S$ requires C, 45·4; H, 2·7; Br, 43·2; S, 8·7%; *M*, 370); τ 2·44—2·90 (m, 8 aromatic H) and 4·12 (s, CHBr·CHBr).

cis-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* 5-*Oxide* (6).—Peroxylauric acid [9] (160 mg) was added at 0° to a solution of the *cis*-dibromide (4) (200 mg) in benzene (2·5 ml) and the solution was kept overnight at room temperature. Evaporation and treatment of the residue with light petroleum gave a crystalline mixture of the sulphoxides (6a and b) shown by n.m.r. analysis to contain *ca.* 85% of the major isomer. Recrystallisation from benzene gave the *major isomer* (6) as prisms (100 mg), m.p. 146—148° (Found: C, 43·6; H, 2·7; S, 8·4. $C_{14}H_{10}Br_2OS$ requires C, 43·45; H, 2·6; S, 8·3%); τ [$(CD_3)_2SO$] 2·15—2·60 (m, 8 aromatic H) and 3·16 (s, CHBr·CHBr). The mixture also showed n.m.r. absorption (*ca.* 15%) assignable to the minor isomer (6) τ 3·20 (s, CHBr·CHBr) but this was not isolated.

trans-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* 5-*Oxide* (7).—This was prepared in a similar manner to the *cis*-dibromide (6) from the *trans*-dibromothiepin derivative (5) (200 mg), giving the *sulphoxide* (7) as prisms, m.p. 141—143° (Found: C, 43·65; H, 2·9; S, 8·1. $C_{14}H_{10}Br_2OS$ requires C, 43·45; H, 2·6; S, 8·3%); τ 1·95—2·78 (m, 8 aromatic H), and τ_A 3·94, τ_B 4·49 (AB system, J_{AB} 9·5 Hz, $CH_ABr{\cdot}CH_BBr$).

cis-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* 5,5-*Dioxide* (8).—Peroxylauric acid [9] (216 mg) was added to a solution of the *cis*-dibromide (4) (125 mg) in dichloromethane (5 ml) and the solution was left overnight. Recrystallisation of the product from ethanol–chloroform gave the sulphone (8), m.p. 206—208°, identical (m.p., i.r. spectrum) with a sample prepared [2] from the sulphone (2) and bromine in carbon tetrachloride; τ 1·81 (q, *J* 1·5, 8 Hz, 4-H and 6-H), 2·10—3·10 (m, 6 aromatic H), and 3·24 (s, CHBr·CHBr).

trans-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* 5,5-*Dioxide* (9).—Similarly, oxidation of the *trans*-dibromodibenzothiepin (5) with an excess of peroxylauric acid [9] gave the corresponding *sulphone* (9) as prisms, m.p. 170—172° (from ethanol) (Found: C, 42·0; H, 2·65; S, 7·8. $C_{14}H_{10}Br_2O_2S$ requires C, 41·8; H, 2·5; S, 8·0%); τ 1·99 (q, *J* 7·5, 2·0 Hz, 4-H and 6-H), 2·23 (q, *J* 7·0 and 1·5 Hz, 1-H and 9-H), 2·35—2·60 (m, 4 aromatic H), and 3·52 (s, CHBr·CHBr).

10-*Bromodibenzo*[b,f]*thiepin* (1).—A solution of the *trans*-dibromide (5) (1·5 g) in t-butyl alcohol (30 ml) containing potassium t-butoxide (0·72 g) was heated (1 h) under reflux. The mixture was poured into water and the product extracted into chloroform. Chromatography on silica followed by crystallisation from hexane gave the *bromothiepin* (1) (0·8 g, 68%) as plates, m.p. 94—96° (Found: C, 58·3; H, 3·25; Br, 26·7; S, 10·4%; *M*, 288·290. $C_{14}H_9BrS$ requires C, 58·2; H, 3·1; Br, 27·65; S, 11·1%; *M*, 288·290); τ 2·05—2·30 (m, 8 aromatic H) and 2·20 (s, =CH–).

Reaction of trans-10,11-*Dibromo*-10,11-*dihydrodibenzo*[b,f]*thiepin* (5) *with Sodium Methoxide*.—The *trans*-dibromide (5) (4·3 g) was heated (15 min) under reflux in methanolic sodium methoxide (1N; 50 ml). The solution was evaporated, inorganic salts were removed by washing with water, and the residue was then chromatographed on silica gel with benzene as eluant. After the *bromothiepin* (1) (1·6 g) had been collected, later fractions gave *thioxanthen*-10-*carbaldehyde dimethyl acetal* (12) (0·8 g), as prisms, m.p. 86—88° (from ether–hexane) (Found: *M*, 272·0868. $C_{16}H_{16}O_2S$ requires *M*, 272·0872); τ 2·32—2·91 (m, 8 aromatic H), 5·45 (d, *J* 8 Hz, 10-H), 5·79 (d, *J* 8 Hz, O·CH·O), and 6·87 (s, 2 × OMe). Further elution gave 10,11-*dihydro*-10,11-*dimethoxydibenzo*[b,f]*thiepin* (13) (120 mg), prisms, m.p. 88—90° (from n-hexane) (Found: *M*, 272·0868. $C_{16}H_{16}O_2S$ requires *M*, 272·0872); τ 2·4—3·00 (m, 8 aromatic H), 4·91 (s, 10-H and 11-H), and 6·51 (s, 2 × OMe). Oxidation of this product with peroxylauric acid gave a mixture of isomeric *sulphoxides* (14) as prisms, m.p. 143—150° [Found: *m/e* 287·0738. $C_{16}H_{15}O_3S$ (*M* − 1) requires *m/e* 287·0742];* τ 1·80—2·80 (m, 8 aromatic H), 4·53 [s, C*H*(OMe)·C*H*(OMe) of *cis*-isomer], τ_A 4·85 and τ_B 5·53 [d, J_{AB} 8 Hz, $CH_A(OMe){\cdot}CH_B(OMe)$ of *trans*-isomer], and 6·40, 6·48, and 6·57 (s, OMe).

Thioxanthen-9-*carbaldehyde* (17).—On one occasion, attempted purification of an impure sample of the *trans*-dibromide (5) by chromatography on silica gel resulted in isolation of the *aldehyde* (17), which crystallised from ether–hexane as needles, m.p. 97—100° (Found: C, 73·8; H, 4·2; S, 14·7%; *M*, 226. $C_{14}H_{10}OS$ requires C, 74·3; H, 4·45; S, 14·2%; *M*, 226); τ 0·60 (d, *J* 2 Hz, CHO), 2·40—2·90 (m, 8 aromatic H), and 5·31 (d, *J* 2 Hz, 10-H).

10,11-*Dihydro*-10-(4-*methylphenyl*)*dibenzo*[b,f]*thiepin* (19).

* This compound did not give a molecular ion in the mass spectrum.

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—9-Hydroxymethylthioxanthen [8] (18) (16·5 g) and toluene-*p*-sulphonic acid monohydrate (82·5 g) were heated under reflux in toluene for 16 h and water was continuously removed by a Dean–Stark trap. The solution was extracted with alkali, washed with water, and evaporated, giving a mixture (12·1 g) of the dihydrothiepin derivative (19) and dibenzo[*b,f*]thiepin (3). Treatment of the mixture with bromine in acetic acid gave a mixture of (19) and the *trans*-dibromide (5). Chromatography on silica gel (benzene–light petroleum as eluant) gave the *dihydrothiepin derivative* (19) as a pale yellow oil (6·6 g), b.p. 200—204° at 0·2 mmHg (Found: *M*, 302·1124. $C_{21}H_{18}S$ requires *M*, 302·1129); τ 2·45—3·25 (m, 12 aromatic H), 5·38 (q, *J* 5·5 and 8·5 Hz, H_X of $ArCH_AH_B{\cdot}CH_X$), and 7·75 (s, $ArCH_3$). Oxidation of this product with formic acid (25 ml) and hydrogen peroxide (3·1 ml; 30%) at 40° gave the corresponding *sulphone*, which crystallised from ethanol as prisms, m.p. 162—165° (Found: C, 75·7; H, 5·2%; *M*, 334. $C_{21}H_{18}SO_2$ requires C, 75·4; H, 5·4%; *M*, 334); τ 1·68—2·00 (m, 4-H and 6-H), τ_A 5·31, τ_B 5·75, τ_C 6·32 (ABC system, J_{AB} 10, J_{BC} 14, J_{AC} 4 Hz, $CH_CH_B{\cdot}CH_A$), and 7·70 (s, CH_3).

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