The Molecular Rearrangements of Cyclopropyl Epoxides generated from Various Flavonoid Systems

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The fused three-ring systems, naphtho[1,2-*c*]pyran and 1*H*-pyrano[4,3-*b*]benzofuran, were obtained by the reaction of αβ-unsaturated ketones and cyclopropyl ketones with DMOSM and DMSM, presumably *via* cyclopropyl epoxides. An attempt to prepare a pyranobenzopyran by reaction of a 3-bromo-2,3-dihydrochromenone with DMOSM gave 1a,7a-dihydro-1a-phenylcyclopropa[*b*]chromen-7(1*H*)-one and a ring-contracted product, a spiro[benzofuran-2,1'-cyclopropan]-3(2*H*)-one; methylenation of both products gave benzofurans. The αβ-unsaturated carbonyl group of 2-phenylchromen-4-one reacted with DMOSM to give, as well as 1a,7a-dihydro-1a-phenylcyclopropa[*b*]-chromen-7(1*H*)-one, diastereoisomeric 2-(methylphenylmethylene)benzofuran-3(2*H*)-ones, a thiin oxide, and a 2,3-dihydro-3-methylenebenzofuran.

CYCLOPROPYL EPOXIDES, whether contiguous (1), fused (2), or spiro (3), rearrange [1] spontaneously or under mildly acidic conditions to a wide variety of products. As they are generally easy to prepare and react cleanly,

(1) (2) (3)

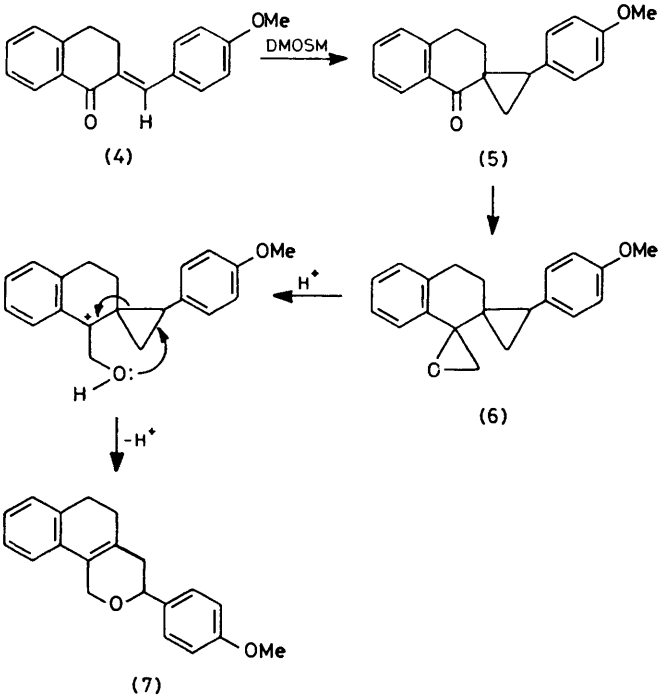
they are useful synthetic intermediates. Contiguous cyclopropyl epoxides are readily available [1] from the reactions of α,β-unsaturated ketones with dimethyloxosulphonium methylide (DMOSM) and from the reactions of the cyclopropyl ketone intermediates of this reaction with dimethylsulphonium methylide (DMSM). The present work describes the use of these cyclopropyl epoxides in the synthesis of more complicated ring systems.

RESULTS AND DISCUSSION

(*E*)-3,4-Dihydro-2-[(4-methoxyphenyl)methylene]-naphthalen-1(2*H*)-one (4) reacted with DMOSM and gave the spirocyclopropyl ketone (5) and the tetrahydro-1*H*-naphtho[1,2-*c*]pyran (7). This 1*H*-naphtho[1,2-*c*]-pyran (7) was also obtained from the reaction of the spirocyclopropyl ketone (5) with DMSM. With neither ylide reagent was the cyclopropyl epoxide intermediate (6) observed.

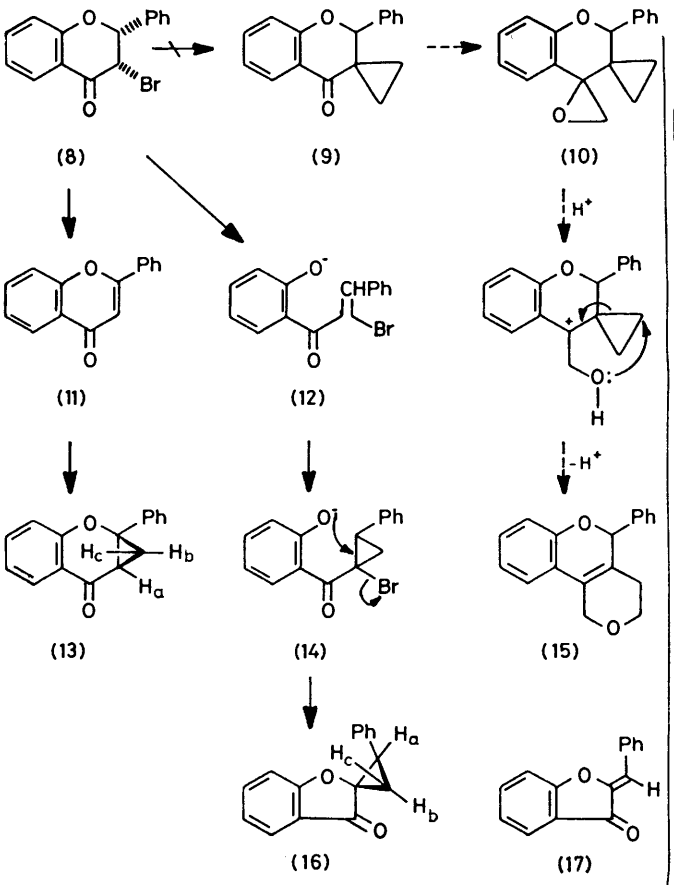
Bravo *et al.*[2] have shown that α-halogeno-ketones react with DMOSM to form cyclopropyl ketones. However, an attempt to synthesise [3] the pyranochromene system (15) from a 2,3-dihydro-3-bromo-2-phenylchromen-4-one (8) *via* the cyclopropyl ketone (9) and the cyclopropyl epoxide (10) failed at the initial step. *cis*-3-Bromo-2,3-dihydro-2-phenylchromen-4-one (8) reacted with DMOSM but gave 1a,7a-dihydro-1a-phenylcyclopropa[*b*]chromen-7(1*H*)-one (13), 2'-phenylspiro-[benzofuran-2,1'-cyclopropan]-3(2*H*)-one (16), and the 2-phenyl-2,3-dihydrochromenone (11). The interesting ring-contraction of a chromenone (8) to a benzofuranone (16) possibly occurs by initial ring-opening of the 3-bromo-2,3-dihydrochromenone (8) to an α-bromochalcone (12) prior to cyclopropane (14) formation and phenoxide-substitution of the bromine. This benzofuranone (16) was also prepared by the reaction of (*Z*)-2-(phenylmethylene)benzofuran-3(2*H*)-one (17) with DMOSM; on hydrolysis with aqueous hydrochloric acid in dioxan, it gave 2-(2-chloro-2-phenylethyl)benzofuran-3(2*H*)-one (18).

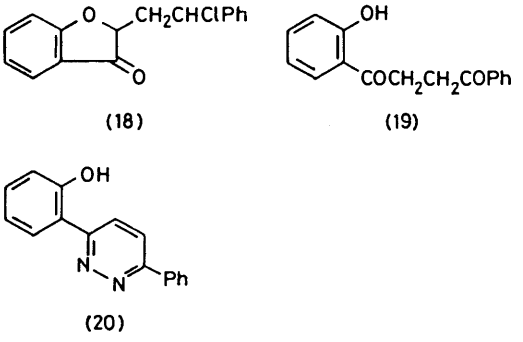
1a,7a-Dihydro-1a-phenylcyclopropa[*b*]chromen-7(1*H*)-one (13) undoubtedly arises by dehydrobromination of 2,3-dihydro-*cis*-3-bromo-2-phenylchromen-4-one (8) to the chromenone (11), followed by reaction of the latter with DMOSM. On hydrolysis with aqueous hydrochloric acid in dioxan it gave 1-(2-hydroxyphenyl)-4-phenylbutane-1,4-dione (19) which formed a pyridazine (20) with hydrazine. Methylenation of the



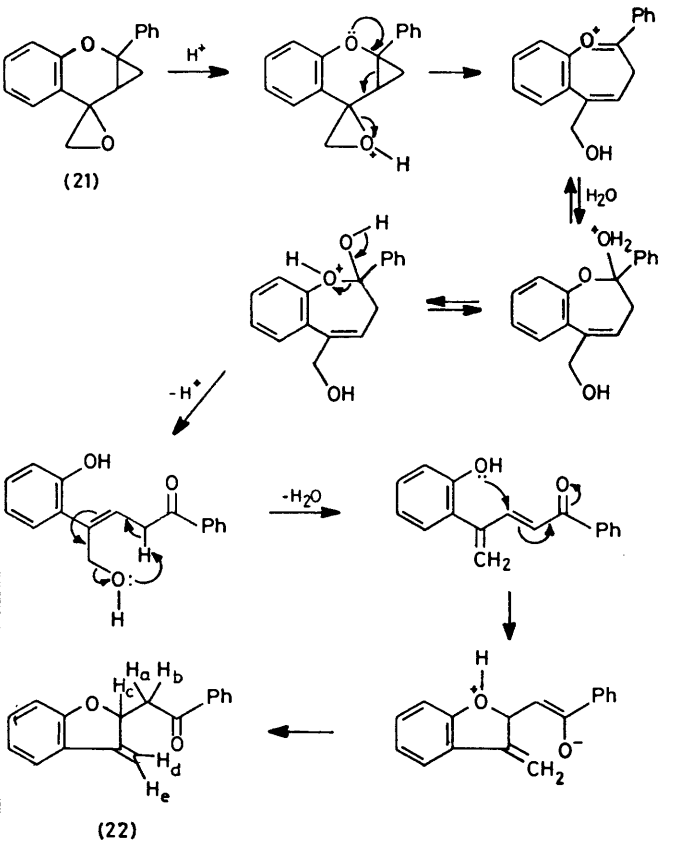
cyclopropachromenone (13) with DMSM gave 2,3-dihydro-3-methylene-2-phenacylbenzofuran (22) which is possibly formed from the epoxide (21) as shown in Scheme 1. The 2-methylenebenzofuran (22), on ozonolysis, formed formaldehyde. Caplin *et al.*[4] obtained

the above mentioned 1,4-diketone (19) from the reaction of chromenone (11) with DMOSM, correctly assuming that it was produced by the hydrolysis of the intermediate cyclopropachromenone (13). It has now been found that the cyclopropyl ketone (13) can be obtained from this reaction of chromenone (11) with DMOSM, together with several other products.

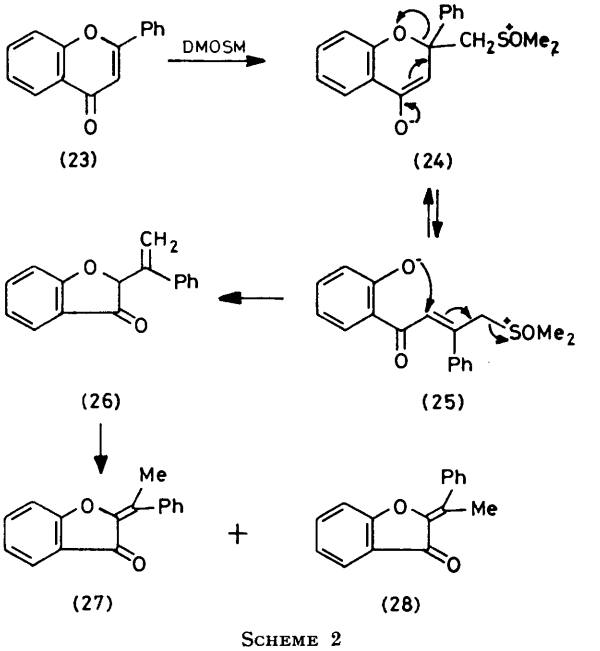




Among these were the (*E*) and (*Z*) isomers of 2-(methylphenylmethylene)benzofuran-3(2*H*)-one (27), (28) which are believed to arise (Scheme 2) from the addition of the ylide to the double bond, followed by ring-opening of the resulting zwitterion (24) to a chalcone (25) and recyclization to the α-position [5] of the unsaturated ketone with elimination of dimethyl sulphoxide; allylic rearrangement of the ethylenic benzofuranone (26) then gives the observed isomers (27) and (28). Also isolated was a thiin oxide (30) which is possibly formed (Scheme 3) *via* a secondary ylide (29) which adds to the carbonyl group. Subsequent dehydration yields the thiin oxide (30). Harris *et al.*[6] have also isolated a thiin oxide from the reaction of a β-oxyenone with DMOSM. Finally,

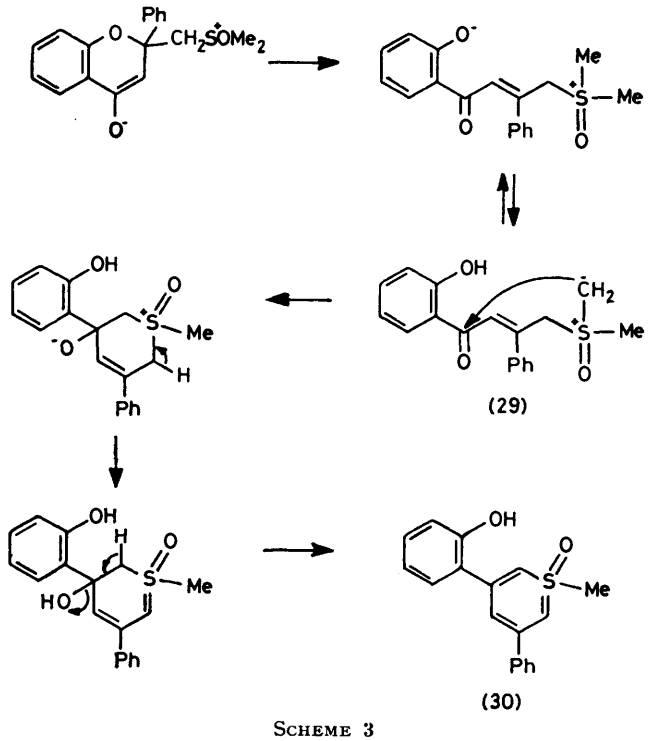


SCHEME 1



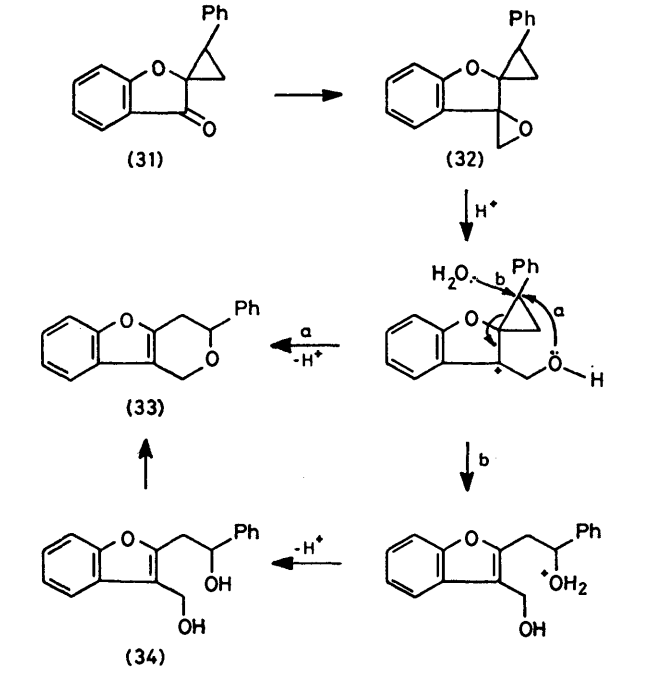
SCHEME 2

there was isolated a trace of the previously mentioned 2,3-dihydro-3-methylene-2-phenacylbenzofuran (22).



SCHEME 3

(Z)-2-(Phenylmethylene)benzofuran-3(2*H*)-one (17), as well as giving 2'-phenylspiro[benzofuran-2,1'-cyclopropan]-3-one (31) on reaction with DMOSM, gave 3,4-dihydro-3-phenyl-1*H*-pyrano[4,3-*b*]benzofuran (33) which undoubtedly arises (Scheme 4) from the molecular rearrangement [7] of a cyclopropyl epoxide (32) derived from the initially formed cyclopropyl ketone (31). This is evidenced by the formation of the benzofuran (33) by reaction of the cyclopropyl ketone (31) with DMSM. The latter reaction also yielded 3-hydroxymethyl-2-(2-hydroxy-2-phenylethyl)benzofuran (34), the product of the hydration of the putative cyclopropyl epoxide (32). The 1,5-diol (34) was dehydrated to the pyranobenzofuran (33) by toluene-*p*-sulphonic acid in benzene.

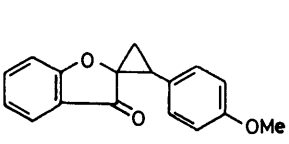


SCHEME 4

(Z)-4'-Methoxy-2-(phenylmethylene)benzofuran-3(2*H*)-one reacted similarly and formed 2'-(4-methoxyphenyl)spiro[benzofuran-2,1'-cyclopropan]-3-one (35) and 3,4-dihydro-3-(4-methoxyphenyl)-1*H*-pyrano[4,3-*b*]-benzofuran (36). The spirocyclopropyl ketone (35) reacted with DMSM to form the pyranobenzofuran (36) and 3-hydroxymethyl-2-(4-methoxystyryl)benzofuran (37), the dehydration product of a 1,5-diol analogue of diol (34).

EXPERIMENTAL

M.p.s were taken on a hot stage apparatus. ^{1}H N.m.r. spectra in deuteriated chloroform with tetramethylsilane as internal standard were obtained for all products. Chemical shifts are given in p.p.m. (δ). The usual reaction work-up consisted of diluting with water, extracting with diethyl ether, washing the ether extract with water and saturated



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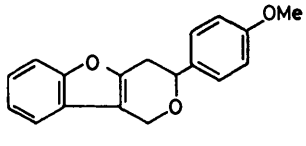

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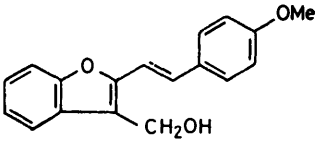

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aqueous sodium chloride solution, drying the extract over anhydrous sodium sulphate, removing the solvent by distillation, and fractionating the residue by thin layer chromatography (t.l.c.) on silica gel.

3,4,5,6-*Tetrahydro*-3-(4-*methoxyphenyl*)-1H-*naphtho*-[1,2-c]*pyran* (7).—A solution in dimethyl sulphoxide (DMSO) (50 ml) of (*E*)-3,4-dihydro-2-[(4-methoxyphenyl)-methylene]naphthalen-1(2*H*)-one (4) (7.82 g) was added to a DMSO solution of DMOSM [8] (4.09 g). After 2 h, the mixture was heated at 50 °C for 1 h. The usual work-up, but using crystallization in place of chromatography, gave 3,4-*dihydro*-2'-(4-*methoxyphenyl*)*spiro*[*naphthalene*-2,1'-*cyclopropan*]-1(2H)-*one* (5) (7.65 g), m.p. 69—70 °C (Found: C, 81.9; H, 6.4. $C_{19}H_{18}O_2$ requires C, 82.0; H, 6.5%); n.m.r.: δ 1.32 (q, 3'-H, *cis* to Ar; *J* 4 and 8 Hz), 1.63—2.06 (m, 3'-H, 3-CH_2), 2.60—3.15 (m, 2'-H, 4-CH_2), 3.85 (s, OMe), 6.84—7.59 (m, Ar), and 8.13 (q, 8-H).

A solution of the naphthalenone (4) (1 g) in DMSO (5 ml) was added to a solution of DMOSM (1.05 g). After 3 d, and the usual work-up, the *naphtho*[1,2-c]*pyran* (7) (0.043 g) was obtained, m.p. 130—131 °C (methanol) (Found: C,

82.3; H, 7.1. $C_{20}H_{20}O_2$ requires C, 82.2; H, 7.0%); n.m.r.: δ 2.08—3.05 (m, 4-CH_2, 5-CH_2, 6-CH_2), 3.83 (s, OMe), 4.52—4.85 (m, 1-CH_2, 3-CH), and 6.90—7.52 (m, Ar). A solution of the spirocyclopropyl ketone (5) (1 g) in DMSO (4 ml) was added to a DMSO solution of DMSM [8] (0.34 g). After 3 h and the usual work-up, the following were isolated in order of decreasing R_F values; the naphtho-[1,2-*c*]pyran (7) (0.186 g) and starting material (5) (0.225 g).

1a,7a-*Dihydro*-1a-*phenylcyclopropa*[b]*chromen*-7(1H)-*one* (13).—A solution of 2,3-dihydro-*cis*-3-bromo-2-phenylchromen-4-one (5 g) in DMSO was added to a similar solution of DMOSM (6.1 g). After 10 min and the usual work-up, the following were isolated in order of decreasing R_F values: 2′-*phenyl*[*spirobenzofuran*-2,1′-*cyclopropan*]-3(2H)-*one* (16) (0.44 g), m.p. 103—104 °C (light petroleum, b.p. 60—80 °C) (Found: C, 81.7; H, 5.2. $C_{16}H_{12}O_2$ requires C, 81.3; H, 5.1%); n.m.r.: δ 2.11 (q, H_b), 2.14 (q, H_c), 3.03 (q, H_a), and 7.76 (q, 4-H), J_{ab} 9.7, J_{ac} 9.5, and J_{bc} 5.9 Hz: the *cyclopropachromenone* (13) (1.24 g), m.p. 64—65 °C (light petroleum, b.p. 60—80 °C) (Found: C, 81.7; H, 5.3. $C_{16}H_{12}O_2$ requires C, 81.3; H, 5.1%); n.m.r.: 1.70 (q, H_c), 2.01 (q, H_b), and 2.56 (q, H_a), J_{ab} 11.1, J_{ac} 6.6, and J_{bc} 6.5 Hz: and the chromenone (11) (0.10 g), m.p. 95—97°C (lit.,[9] m.p. 96—97 °C).

A solution of (*Z*)-2-(methylphenylmethylene)benzofuran-3(2*H*)-one (1.0 g) in DMSO was added to a similar solution of DMOSM (0.78 g). After 3 min and the usual work-up, the spirocyclopropanebenzofuranone (16) (0.88 g), m.p. 103—104 °C, was obtained.

Hydrochloric acid (6 drops) was added to a solution of the spirocyclopropanebenzofuranone (16) (0.147 g) in aqueous dioxan (25%; 25 ml). After 18 h, the usual work-up (but replacing ether by chloroform and chromatography by crystallization) gave 2-(2-*chloro*-2-*phenylethyl*)*benzofuran*-3(2H)-*one* (18) (0.150 g), m.p. 115—116 °C (light petroleum, b.p. 60—80 °C) (Found: C, 70.9; H, 5.1; Cl, 13.1. $C_{16}H_{13}ClO_2$ requires C, 70.5; H, 4.8; Cl, 13.0%); n.m.r.: δ 1.84—2.98 (m, CH_2), 4.90 (q, OCH; *J* 3 and 9 Hz), and 5.26 (q, CHCl; *J* 4 and 11 Hz).

Hydrochloric acid (6 drops) was added to a solution of the cyclopropachromenone (13) (0.3 g) in aqueous dioxan (25%; 20 ml). It was heated on a steam-bath for 15 min and then worked up as in the previous reaction. The product crystallized from ethanol to give 1-(2-hydroxyphenyl)-4-phenylbutane-1,4-dione (19) (0.31 g), m.p. 107—108 °C (lit.,[4] m.p. 107 °C). Hydrazine hydrate (4 drops) was added to a solution of the 1,4-dione (19) (0.32 g) in ethanol (100 ml). After 6 h, a stream of air was passed through the solution for 6 h. Concentration of the solution gave needles (0.325 g) of 3-(2-*hydroxyphenyl*)-6-*phenylpyridazine*, m.p. 170—171 °C (Found: C, 77.3; H, 4.9. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9%).

2,3-*Dihydro*-3-*methylene*-2-*phenacylbenzofuran* (22).—A solution of the cyclopropachromenone (13) (2.4 g) in DMSO (30 ml) was added to a solution of DMSM (1.2 g) in DMSO (60 ml) and tetrahydrofuran (20 ml). After 1.5 h and the usual work-up, the *phenacylbenzofuran* (22) (0.8 g) was obtained, m.p. 95—96 °C (aqueous ethanol) (Found: C, 81.8; H, 5.6. $C_{17}H_{14}O_2$ requires C, 81.6; H, 5.6%). N.m.r.: δ 3.27 (q, H_a; *J* 17 and 5 Hz), 3.60 (q, H_b; *J* 17 and 7 Hz), 5.05 (d, H_d; *J* 2.5 Hz), 5.52 (d, H_e; *J* 2.5 Hz), 5.91 (m, H_c), and 6.80—8.28 (m, Ar).

Excess of ozone was passed through a solution of the phenacylbenzofuran (22) (1 g) in acetic acid (50 ml). Water (150 ml) and zinc dust (2 g) were added before the mixture was steam-distilled. The distillate (250 ml) was neutralized by aqueous sodium hydroxide and a solution of dimedone (3 g) in aqueous ethanol (50%; 50 ml) was added. The white precipitate of dimedone–formaldehyde (0.3 g) crystallized from aqueous ethanol, m.p. 189 °C (lit.,[10] m.p. 186—188 °C).

2-(*Methylphenylmethylene*)*benzofuran*-3(2H)-*ones*.—DMOSM (2.02 g) in DMSO (60 ml) was added to a solution of 2-phenylchromen-4-one (4.4 g) in DMSO (100 ml). After 3 h and the usual work-up, the following products were isolated in order of decreasing R_F values. 2,3-Dihydro-3-methylene-2-phenacylbenzofuran (22) (0.14 g), m.p. 95—96 °C. (Z)-2-(*Methylphenylmethylene*)*benzofuran*-3(2H)-*one* (28), an oil (0.66 g) (Found: C, 80.9; H, 5.1. $C_{16}H_{12}O_2$ requires C, 81.3; H, 5.1%); n.m.r.: δ 2.88 (s, Me) and 7.05—8.00 (m, Ar). (E)-2-(*Methylphenylmethylene*)*benzofuran*-3(2H)-*one* (27), an oil (0.33 g) (Found: C, 81.7; H, 4.9. $C_{16}H_{12}O_2$ requires C, 81.3; H, 5.1%); n.m.r.: δ 2.60 (s, Me) and 7.00—8.00 (m, Ar). The cyclopropachromenone (13) (2.11 g), m.p. 63—64 °C. 2-Phenylchromen-4-one (11) (0.32 g), m.p. 96—97 °C. 3-(2-*Hydroxyphenyl*)-1-*methyl*-5-*phenylthiin* 1-*oxide* (30) (0.61 g), m.p. 173—175 °C (aqueous ethanol) (Found: C, 73.4; H, 5.4; S, 10.5. $C_{18}H_{16}O_2S$ requires C, 72.9; H, 5.4; S, 10.8%); n.m.r. [$(CD_3)_2SO$]: δ 3.57 (s, SMe), 5.96 (s, 2- and 6-H), 6.05 (s, 4-H), 6.70—7.70 (m, Ar), and 9.45 (s, OH).

3,4-*Dihydro*-3-*phenyl*-1*H*-*pyrano*[4,3-b]*benzofuran* (33).—A solution of (*Z*)-2-(methylphenylmethylene)benzofuran-3(2*H*)-one (4 g) in DMSO (40 ml) was added to a solution of DMOSM (1.01 g) in DMSO (25 ml). After 0.5 h and the usual work-up, the following were isolated in order of decreasing R_F values: the *pyranobenzofuran* (33) (0.12 g), m.p. 89—90 °C (aqueous ethanol) (Found: C, 81.6; H, 5.9. $C_{17}H_{14}O_2$ requires C, 81.6; H, 5.6%). N.m.r.: δ 3.11 (br d, 4-CH_2), 4.87 (t, 3-CH), 5.05 (br s, 1-CH_2), and 7.05—7.90 (m, Ar), J_{34} 7 Hz: and 2-′phenylspiro[benzofuran-2,1′-cyclopropan]-3(2*H*)-one (16) (2.8 g), m.p. 103—104 °C.

A solution of the spirocyclopropylbenzofuranone (16) (0.73 g) in DMSO (10 ml) was added to a solution of DMSM (0.28 g) in DMSO (10 ml) and tetrahydrofuran (15 ml). After 18 h and the usual work-up, the following were obtained in order of decreasing R_F value: the pyranobenzofuran (33) (0.05 g), m.p. 88—89 °C: and 3-*hydroxymethyl*-2-(2-*hydroxy*-2-*phenylethyl*)*benzofuran* (34) (0.55 g), m.p. 93—94 °C (aqueous ethanol) (Found: C, 76.0; H, 5.9. $C_{17}H_{16}O_3$ requires C, 76.1; H, 6.0%). N.m.r.: δ 3.12 (d, CH_2), 3.18 (s, OH), 3.45 (s, OH), 4.57 (s, OCH_2), 5.00 (t, OCHPh), and 6.97—7.85 (m, Ar), $J_{1'2'}$ 7 Hz. A solution of this 1,5-diol (34) (0.7 g) in benzene (50 ml) was refluxed with a crystal of toluene-*p*-sulphonic acid for 6 h. Removal of the solvent and fractionation of the residue by t.l.c. on silica gel gave the pyranobenzofuran (33) (0.05 g), m.p. 89—90 °C.

3,4-*Dihydro*-3-(4-*methoxyphenyl*)-1H-*pyrano*[4,3-b]*benzofuran* (36).—A solution of (Z)-2-(methyl-*p*-methoxyphenylmethylene)benzofuran-3(2*H*)-one (1.3 g) in DMSO (15 ml) was added to a DMSO (25 ml) solution of DMOSM (0.58 g). After 0.5 h and the usual work-up, the following were isolated in order of decreasing R_F values: the *pyranobenzofuran* (36) (0.08 g), m.p. 127 °C (aqueous ethanol) (Found: C, 77.1; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.7%). N.m.r.: δ 3.11 (br d, 4-CH_2), 3.87 (s, OMe), 4.86 (t, 3-CH), 5.04 (br s, 1-CH_2), and 6.90—7.60 (m, Ar), J_{34} 7 Hz: and 2′-(4-*methoxyphenyl*)*spiro*[*benzofuran*-2,1′-*cyclopropan*-3(2H)-*one* (35) (0.87 g), m.p. 87—90 °C (light petrol-

eum, b.p. 60—80 °C) (Found: C, 77.1; H, 5.1. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%); n.m.r.: δ 2.00—2.40 (m, CH_2), 3.04 (q, 2′-H; *J* 8 and 10 Hz), 3.81 (s, OMe), and 6.75—7.85 (m, Ar).

A solution of the spirocyclopropanebenzofuranone (35) (0.8 g) in DMSO (10 ml) was added to a solution of DMSM (0.27 g) in dimethyl sulphoxide (10 ml) and tetrahydrofuran (15 ml). After 18 h, the usual work-up (but without chromatography) gave a solid residue which crystallized from aqueous ethanol to give 3-*hydroxymethyl*-2-(4-*methoxystyryl*)*benzofuran* (37) (0.29 g), m.p. 163—165 °C (Found: C, 77.2; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.8%). N.m.r.: δ 1.60 (br s, OH), 3.91 (s, OMe), 5.00 (d, CH_2; *J* 4 Hz), 6.92—7.86 (m, ArCH=CH). Purification of the mother-liquor by t.l.c. on silica gel gave the pyranobenzofuran (36) (0.075 g), m.p. 127 °C.

[8/1755 *Received*, 9*th October*, 1978]

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