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CATION RADICALS IN THE BROMINATION OF BENZODIPYRAN DERIVATIVES

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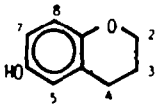
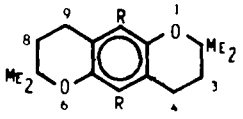
Abstract - Bromine attacks the free aromatic sites in 2,3,4,7,8,9-hexahydro-2,2,7,7-tetramethylbenzo[1,2-b:4,5-b']dipyran and its angular isomer 1,2,3,8,9,10-hexahydro-3,3,8,8-tetramethylbenzo[1,2-b:4,3-b']dipyran without clear evidence for the intermediacy of cation radicals. When the nuclear sites are methylated [as in (2)] bromine affords a cation radical tribromide (8) and then monohalogenates each aromatic methyl group giving 5,10-bis-(bromomethyl)- 2,3,4,7,8,9-hexahydro-2,2,7,7-tetramethylbenzo[1,2-b:4,5-b']-dipyran (10). In contrast, N-bromosuccinimide dehydrogenates and brominates the two pyran rings giving 3,8-dibromo-2,7-dihydrobenzo-2,2,5,7,7,10-hexamethyl[1,2-b:4,5-b']dipyran (14). The angular isomer reacts with either bromine or N-bromosuccinimide at the pyran rings only, giving (21). The part played by cation radicals in these reactions is discussed, related to the ^{1}H nmr line broadening phenomena observed earlier, and explained in terms of a slight preferential concentration of unpaired spin at position 5 of a cation-radical derived from 6-hydroxychroman.

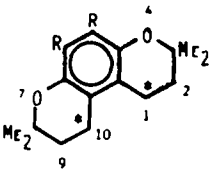
Studies[1] on the ^{1}H nmr line broadening in spectra of 6-hydroxychroman (1) and its derivatives indicated that in the derived cation radicals there was some concentration of spin at position 5. However, the method is open to the objection that the effect of spin at any aromatic site and the consequent broadening in the signal from an attached methyl or methylene group are connected by a transmission factor that is different for methyl groups and methylene groups, but is generally not known and might change if the type of compound is altered substantially.[2] To reduce this problem we have examined the benzodipyran derivatives (2) and (5) which have relatively simple spectra because of symmetry and where the starred groups (methyl in one and methylene in the other) can be considered as attached to the 5-position in a benzopyran (chroman) nucleus. For the linear isomer (2) the broadening of the aromatic methyl groups is



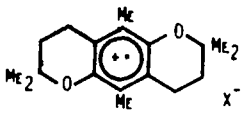
(1)



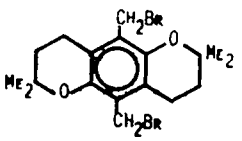
(2) R = Me*
(3) R = H
(4) R = Br



(5) R = Me
(6) R = H
(7) R = Br



(8) X = Br_3^-
(9) X = IBr_2^-



(10)

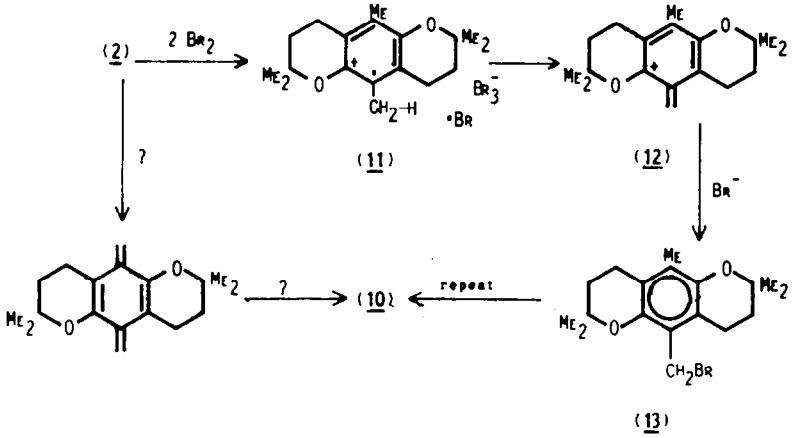
17.8 Hz under specified conditions,[1] and this has to be modified by a transmission factor T_{Me}. Similarly, the methylene groups are broadened by 7.2 Hz which has to be modified by a transmission factor T_{CH_2}. For the angular isomer (5) the broadenings are 3.6 Hz for the methyl groups and 2.9 Hz for the methylene groups. If it is assumed that the transmission factors will be much the same for the two structures, then they cancel out when the effects at position 5 of the chroman nucleus (1) are compared with those at position 7 by combining the expressions for linear and angular isomers thus:

$$\frac{17.8 \times T_{Me} \quad 2.9 \times T_{CH_2}}{7.2 \times T_{CH_2} \quad 3.6 \times T_{Me}} = 1.99$$

From this it appears that there is more broadening (i.e. more unpaired spin) at position 5 than elsewhere in the 6-hydroxychroman nuclei but in view of the fact that broadenings in this series may vary over several orders of magnitude the effect is a minor one.

In order to determine whether this bias in spin distribution would affect the chemistry of such compounds we have examined some halogenations. Iodine induces the line broadening of benzodipyrans characteristic of cation radical formation but there seems to be no further reaction and removal of solvent also removes the iodine and leaves the substrate intact. With bromine in tetrachloromethane the benzodipyran derivatives (3) and (6) with free nuclear positions are immediately brominated giving the dibromo derivatives (4) and (7), respectively. No intermediate stage was noted, and the reactions might be simple electrophilic substitutions although this is unlikely in view of other results and of the recent recognition that many reactions believed to be purely ionic actually have radical ion intermediates.[3]

With bromine the fully methylated dipyran (2) at once gave a brown solid too unstable for detailed study but must be the cation radical tribromide (8) because if reduced immediately by ascorbic acid it mainly regenerates the original benzodipyran and because iodine bromide produces a similar brown solid readily characterisable as the dibromiodate (9). Further reaction with bromine affords a mixture that has not been analysed fully but which contains as the main constituent the bisbromomethyl benzodipyran derivative (10). Light and benzoyl peroxide have little effect.



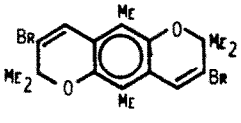
Scheme 1

The structure of the bisbromomethyl product (10) is clearly defined by analysis and nmr spectrum (Table). Scheme 1 outlines the steps that we consider to underlie this result; the species depicted are of course delocalised systems in reality, but with a bias in charge and spin distribution in (11) in accordance with our argument. The intermediate is (12), which accepts bromide ion and aromatises. Two separate brominations are required according to this Scheme. It is less easy to formulate a credible route through a quinone bismethide although

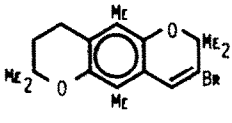
this, once produced, would give the correct product. In our preferred route the selective monobromination of each methyl group follows from the fact that removal of a hydrogen atom can occur only when the CH bond is perpendicular to the aromatic plane; after the replacement it is the relatively bulky bromine atom that will take up the out-of-plane site leaving the remaining two hydrogen atoms more or less in-plane and relatively unreactive.

The yield of bisbromomethyl compound (10) is about 36% by isolation (45% by ^{1}H nmr analysis); on the assumption that the two brominations are very similar, the yield of each is therefore between 60% and 67% indicating a moderate degree of selectivity.

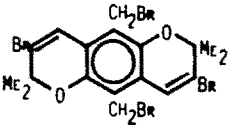
We next examined bromination by N-bromosuccinimide by the usual method in tetrachloromethane with heating. Again a complex mixture resulted, but it contained none of the bisbromomethyl compound (10). The first of two main constituents was assigned the doubly brominated and dehydrogenated structure (14) with intact aromatic methyl groups; bromine was located by means of the ^{1}H nmr spectrum (Table) with reference to a published and closely similar system.[4] The other main constituent was found to be the singly brominated and dehydrogenated product (15), further treatment of which converted it into the first component (14). If the two dehydrogenation-brominative sequences have the same efficiency, then the yield for each is about 69%. At first the result appeared to contradict our view that uncoupled spin would be in some excess at the points with the attached aromatic methyl groups but no other explanation occurred to us so we have assumed that, despite appearances, the initial attack is still at the methyl



(14)



(15)

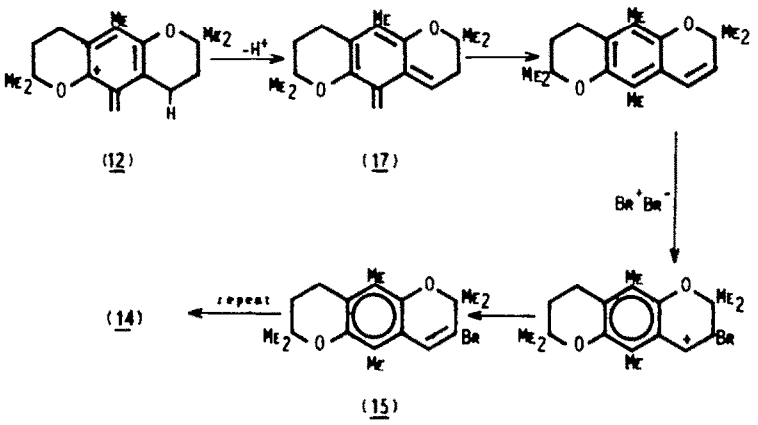


(16)

groups with either bromine atoms or imidoyl radicals abstracting hydrogen in the first stage. When bromine itself is the reagent the mixture is rich in bromide ion as already explained, but this is not the case for the N-bromosuccinimide reaction where bromine/bromide concentrations remain low in solution[5]. Scheme 2 shows the reaction beginning with the same key intermediate (12) as in the bromine reaction, but in the absence of much bromide ion there can be time for this intermediate to change, the Scheme showing first a loss of a proton giving a quinone methide and then a prototropic shift that regenerates the methyl group and the aromaticity. The sequence provides one chromane nucleus in which the double bond can be brominated giving (15) either through an electrophilic substitution reaction or, more probably, through another cation-radical sequence. Similar operations at the other side of the molecule give the other product (14).

Table. ^{1}H NMR Spectra (220 MHz; $CDCl_3$/TMS) of Benzodipyran Derivatives

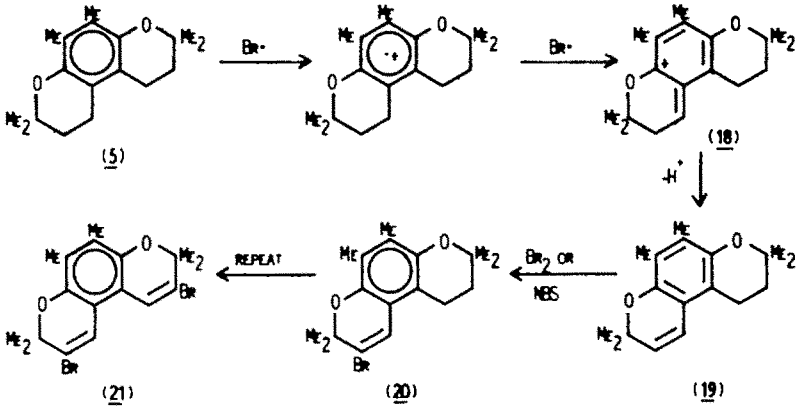
Structure	ArH	$ArCH_3$	$ArCH_2CH_2$	$ArCH_2CH_2$	gem-Me	BrC:CH	CH_2Br
(3)	6.48		2.67	1.72	1.28		
(6)	6.58		2.55	1.78	1.28		
(4)			2.76	1.80	1.31		
(7)			2.54	1.80	1.31		
(2)		2.06	2.61	1.77	1.27		
(5)		2.08	2.54	1.76	1.28		
(10)			2.81	1.87	1.35		4.61
(15)		2.05	2.59	1.78	1.27	6.91	
		2.09			1.50		
(14)		2.12			1.51	6.94	
(20)		2.07	2.66	1.76	1.28	6.87	
					1.50		
(21)		2.08			1.50	6.87	
(16)					1.56	6.95	4.52



Scheme 2

In theory, therefore, bromine should halogenate the aromatic methyl groups of (14) giving a product (16) containing four bromine atoms but, in practice, additions competed and the product was unmanageable. However, we could also expect N-bromsuccinimide to introduce halogen at these methyl groups now that prototropic shifts etc. are no longer possible, and we were able in fact to obtain the product (16) with four bromine atoms in this way. Contrariwise, N-bromosuccinimide should not dehydrogenate the bisbromomethyl compound (10) readily because the bromomethyl groups bar the chief mode of attack; in fact, there is some reaction but it is complex and the mixture produced appears not to contain the tetrabromo compound (16).

The angular benzodipyran (5) reacted (badly) with bromine and (well) with succinimide to give dehydrogenated products (19) and (20), the aromatic methyl groups surviving in agreement with the view that sensitivity to radical attack will now be at the ring methylene groups. Scheme 3 continues the previous arguments and also discloses that the angular arrangement



Scheme 3

of the intermediate cation (18) permits full aromatisation to (19) by a single proton shift, which will therefore be energetically more favourable than the aromatisation in Scheme 2 in which a quinone methide intervenes. We can therefore view the outcome as kinetically controlled. Consequently, all our results can be explained by (i) initial cation radical formation, (ii) a modest preference for hydrogen abstraction from groups (methyl or methylene) at position 5 of a 6-hydroxychroman cation- radical, and (iii) kinetic control of the fate of the cationic intermediates mainly by the ease of transformation into fully aromatic species.

EXPERIMENTAL

5,10-Dibromo-2,3,4,7,8,9-hexahydro-2,2,7,7-tetramethylbenzo[1,2-b:4,5-b']dipyran (4). Bromine (0.2 ml) in tetrachloromethane (20 ml) was added to 2,3,4,7,8-hexahydro-2,2,7,7-tetramethylbenzo[1,2-b:4,5-b']dipyran (254 mg) also in tetrachloromethane (50 ml) during 10 min. There was an immediate darkening of colour but no precipitate. After 4.5 h, air was blown through the solution until all free bromine had been removed; the solution was then washed with aqueous sodium hydrogen sulphite, then sodium hydrogen carbonate solution, and finally with water. The dried solution was concentrated under vacuum leaving a clear gum that was subjected to purification on silica with hexane-toluene (3:1) as eluant. Three fractions were obtained, the first and third consisted of mixtures and were not examined further; the second (R_f 0.28) supplied the dibromohexahydrobenzodipyran as rectangular plates (233 mg; 56%), m.p. 160 - 164°C (from methanol), $\nu_{max.}$ 2 959, 2 918, 1 432, 1 409, 1 365, 1 312, 1 179, 1 155, 960, 900, and 828 cm^{-1} (Found: C, 47.6; H, 5.0%. M, 401.983 00, 403.981 03, 405.978 91 0. $C_{16}H_{20}Br_2O_2$ requires C, 47.55; 5.0%); M, 401.983 00, 403.981 03, 405.979 06.

5,6-Dibromo-1,2,3,8,9,10-hexahydro-3,3,8,8-tetramethylbenzo[1,2-b:4,3-b']dipyran (7). - 1,2,3,8,9-Hexahydro-3,3,8,8-tetramethylbenzo[1,2-b:4,3-b']dipyran (254 mg) was treated with bromine (0.2 ml) as in the foregoing experiment. Chromatography with hexane-toluene (1:1) as eluant furnished two fractions of which the first was a mixture and was discarded; the second (R_f 0.34) consisted of the dibromohexahydrobenzodipyran forming prisms (283 mg; 68%), m.p. 167 - 169°C (from methanol), $\nu_{max.}$ 2 965, 2 937, 2 920, 1 430, 1 410, 1 379, 1 365, 1 328, 1 238, 1 167, 1 120, 1 095, 962, 918, 899, 895, and 832 cm^{-1} (Found: C, 47.8; H, 5.1%; M, 401.983 022, 403.980 956, 405.979 810. $C_{16}H_{20}Br_2O_2$ requires C, 47.6; H, 5.0%; M, 401.983 00, 403.981 03, 405.979 06).

5,10-Bis(bromomethyl)-2,3,4,7,8,9-hexahydro-2,2,7,7-tetramethylbenzo[1,2-b:4,5-b']dipyran (10). - Bromine (0.8 ml) in tetrachloromethane (50 ml) was added to 2,3,4,7,8,9-hexahydro-2,2,5,7,7,10-hexamethylbenzo[1,2-b:4,5-b']dipyran (1.4 g) also in tetrachloromethane (150 ml). The colour darkened at once and a brown solid separated which decomposed with evolution of hydrogen bromide when attempts were made to isolate it. When left in situ with stirring for 4.5 h the solid redissolved and the reaction mixture was worked up in the manner described above except that, after removal of solvents, the residue was partly solid and, instead of immediate chromatography, was washed with hot hexane and then crystallised from trichloromethane giving the bisbromomethylhexahydrobenzodipyran as faintly yellow prisms (728 mg; 33%), m.p. 235 - 240°C, $\nu_{max.}$ 2 980, 2 920, 2 868, 1 466, 1 424, 1 418, 1 371, 1 362, 1 278, 1 263, 1 242, 1 220, 1 201, 1 160, 1 125, 1 110, 996, 974, 953, 887, 655, and 545 cm^{-1} (Found: C, 50.1; H, 5.6%; M, 430.014 024, 432.012 256, 434.010 210. $C_{18}H_{24}Br_2O_2$ requires C, 50.0; H, 5.6%; M, 430.014 28, 432.012 31; 434.010 34).

The same compound was obtained by using 2,4,4,6-tetrabromocyclohexa-2,5-dienone instead of bromine and with trichloromethane as solvent, and including an alkaline wash to remove phenolic products. However, it proved difficult to remove non-phenolic side products and the reaction was not studied further.

3,8-Dibromo-2,7-dihydro-2,2,5,7,7,10-hexamethylbenzo-[1,2-b:4,5-b']dipyran (14). - 2,3,4-7,8,9-Hexahydro-2,2,5,7,10-hexamethylbenzo[1,2-b:4,5-b']dipyran (1.4 g) and N-bromosuccinimide (2.7 g) were heated together in refluxing tetrachloromethane (150 ml) for 24 h. Air was blown through the solution for 20 min., and then the succinimide produced was filtered off and the filtrate washed, successively, with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and water. The residue left after drying and evaporation of the solvent was chromatographed on silica using hexane-toluna (4:1) as eluant. The first fraction contained a mixture not examined further. The second fraction (R_f 0.33) supplied 3,8-dibromo-2,7-dihydro-2,2,5,7,7,10-hexamethylbenzo[1,2-b:4,5-b']dipyran which separated from hexane as pale yellow, thick prisms (634 mg; 29%), m.p. 193 - 199°C, $\nu_{max.}$ 2 970, 2 950, 2 910, 1 449, 1 353, 1 267, 1 140, 1 007, 872, 855, and 817 cm^{-1} (Found: C, 50.6; H, 4.9%; M, 425.980 02, 427.980 95, 429.978 91. $C_{18}H_{20}Br_2O_2$ requires C, 50.5; 4.7%; M, 425.983 00, 427.981 03, 429.979 06).

The next fraction contained this compound with another and later fractions contained only the other (R_f 0.21) which was obtained as a soft gum that crystallised from 2-propanol giving 3-bromo-2,7,8,9-tetrahydro-2,2,5,7,7,10-hexamethylbenzo[1,2-b:4,5-b']dipyran (15) as prisms (484 mg; 27%), m.p. 92 - 94°C, $\nu_{max.}$ 2 965, 2 938, 2 920, 1 367, 1 358, 1 275, 1 168, 1 147, and 970 cm^{-1} (Found: C, 61.7; H, 6.6%: M, 350.085 06, 352.086 75. $C_{18}H_{23}BrO_2$ requires C, 61.5; H, 6.6%; M, 350.088 07, 352.086 10).

2,9-Dibromo-3,8-dihydro-3,3,5,6,8,8-hexamethylbenzo[1,2-b:4,3-b']dipyran (21). - (i) Bromination by bromine. Bromine (0.2 ml) in tetrachloromethane (20 ml) was added to 1,2,3,8,9,10-hexahydro-3,3,5,6,8,8-hexamethylbenzo[1,2-b:4,3-b']dipyran (306 mg) also in tetrachloromethane (30 ml). As with the benzo[1,2-b:4,5-b']dipyran isomer above, a dark colour and brown precipitate were observed, and after 4.5 h at room temperature the mixture was worked-up in the same way. Recrystallisation of the crude product from trichloromethane failed to give pure material so it was chromatographed on silica gel using hexane-toluna (3:1) as eluant. After removal of an initial fraction containing a mixture (not analysed further) a main fraction was secured that contained a single substance (R_f 0.48) which separated from methanol to give the

dibromodihydrobenzodipyran as irregular prisms (62 mg; 13%), m.p. 137 - 140°C, $\nu_{max.}$ 2 965, 2 920, 1 373, 1 351, 1 275, 1 141, 1 333, 1 095, and 875 cm^{-1} (Found: C, 50.5; H, 5.0%; M, 425.983 02, 427.980 956, 429.987 910. $C_{18}H_{20}Br_2O_2$ requires C, 50.5; H, 4.7%; M, 425.983 00, 427.981 03, 429.979 06).

Subsequent fractions contained both (21) and another substance which later appeared alone and had R_f 0.33. This material crystallised from wet methanol giving 2-bromo-3,8,9,10-tetrahydro-3,3,5,6,8,8-hexamethylbenzo[1,2-b:4,3-b']dipyran (20) as plates (137 mg; 35%), m.p. 80 - 84°C, $\nu_{max.}$ 2 967, 2 930, 2 910, 2 890, 2 840, 1 441, 1 378, 1 355, 1 271, 1 164, 1 147, 1 118, 1 090, 968, and 870 cm^{-1} (Found: C, 61.5; H, 6.8%; M, 350.088 14, 352.086 10. $C_{18}H_{23}BrO_2$ requires C, 61.5; H, 6.6%; M, 350.088 07, 352.086 10). (ii) Bromination by N-bromosuccinimide. The requisite benzodipyran (6) (1.4 g) was heated with N-bromosuccinimide (2.7 g) in refluxing tetrachloromethane for 24 h and the products were isolated as in the previous reaction with this reagent. Chromatography supplied the dibromobenzodipyran (929 mg; 43%) and the monobromobenzodipyran (376 mg; 21%) identical with samples obtained by the use of bromine.

3,8-Dibromo-5,10-bis(bromomethyl)-2,7-dihydro-2,2,7,7-tetramethylbenzo[1,2-b:4,5-b']dipyran (16). - The 3,8-dibromobenzo[1,2-b:4,5-b']dipyran (14) (1.8 g) was heated with N-bromosuccinimide (3.3 g) in tetrachloromethane for 24 h and the products isolated as in other such halogenations. The crude product was partly soluble in hexane-toluene (4:1); the insoluble part separated from hexane to give the 3,8-dibromo-5,10-bis(bromomethyl)benzodipyran as stout yellow prisms (932 mg; 35%), m.p. 197 - 199°C, $\nu_{max.}$ 2 970, 1 420, 1 280, 1 195, 1 133, 1 123, 989, 851, and 631 cm^{-1} (Found: C, 36.8; H, 3.2%; M, 581.804 02, 583.801 98, 585.799 93, 587.797 89, 589.795 84. $C_{18}H_{18}Br_4O_2$ requires C, 36.9; H, 3.1%; M, 581.804 14, 583.802 17, 585.800 20, 587.798 23, and 589.796 26).

Chromatography supplied a further quantity of this compound and also fractions containing mixtures that were not examined further.

2,3,4,7,8,9-Hexahydro-2,2,5,7,7,10-hexamethylbenzo[1,2-b:4,5-b']dipyran(1+) dibromoiodate (9). - The linear hexamethylbenzodipyran derivative (2) (2.9 g) in tetrachloromethane (200 ml) was treated with iodine(I) bromide (4.2 g) in the same solvent (200 ml). A precipitate formed rapidly and did not redissolve even on standing for some hours in diffuse daylight. Nitrogen was blown through the mixture to remove free halogens, then the solid was collected by filtration and washed with tetrachloromethane and dried in vacuo, leaving the dibromoiodate as a dark green-black microcrystalline powder (3.9 g, 65%), m.p. 190°C (decomp.), $\nu_{max.}$ 2 960, 2 915, 2 905, 2 840, 1 423, 1 399, 1 370, 1 340, 1 327, 1 293, 1 222, 1 151, 1 099, 1 079, 1 018, 918, and 888 cm^{-1} (Found: C, 39.0; H, 4.7. $C_{18}H_{26}Br_2IO_2$ requires C, 38.5; H, 4.7%). The mass spectrum exhibited a parent peak for the cation at m/e 274.193 28 ($C_{18}H_{26}O_2$ requires m/e 274.193 14). Attempted recrystallisation decomposed the compound.

The halogen could be removed and the cation radical reduced by aqueous sodium metabisulphite, ascorbic acid, of sodium thiosulphate; the last was the best. A solution of the cation radical salt (555 mg) in dichloromethane was shaken for 72 h with 2N-aqueous sodium thiosulphate until all the colour had disappeared. The organic layer was washed with water, dried, and concentrated until a solid residue remained. This was identified with the hexamethylbenzodipyran (2) (260 mg; 96%) by spectroscopic and other means.

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REFERENCES

1. I. Al-Khayat, F.M. Dean, S.N. France, D.A. Matkin, M.O.A. Orabi, M.L. Robinson, R.W. Turner, and R.S. Varma, J.Chem.Soc., Perkin Trans. 1, 1985, 1301.
2. G. Vincow, in "Radical Ions" ed. E.T. Kaiser and L. Kevan, Interscience, 151 (1968); J.K.M. Sanders, C.G. Newton and J.C. Waterton, J.Mag.Res., 1978, 31, 49.
3. J.F. Bunnett, J.Chem.Ed., 1974, 51, 312; N. Kornblum, Angew.Chem.Int.Ed., 1975, 14, 734; E.C. Ashby, A.B. Goel, and J.N. Argyropoulos, Tetrahedron Lett., 1982, 2273.
4. H. Hofmann and G. Salbeck, Chem.Ber., 1971, 104, 168.
5. P.S. Skell, J.C. Day, and M.J. Lindstrom, J.Am.Chem.Soc., 1974, 96, 5616.