Preparation and Ring Fission of Some Benzocyclobuten-1(2H)-one Derivatives

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2,5-Dihydroanisole and its 3-methyl homologue react with dibromocarbene to give 1 : 2 adducts (I; R = H or Me) which, when boiled with pyridine, give pyridinium salts (II). These are converted by the Kröhnke reaction into the corresponding 3-bromo-6-methoxybenzocyclobutenones (III). The structure of the ketone (III; R = H) is proved by its fission under alkaline conditions and by oxidation of its pyridinium salt precursor, to give known compounds. Alkaline fission products of two isomeric bromomethoxybenzocyclobutenones are compared and the results are rationalised in terms of the −I and +E effects of the methoxy-group.

THE preparation of benzocyclobuten-1(2H)-one was first reported [1] in 1960. Relatively simple syntheses of some substituted derivatives were later described,[2,3] involving the action of silver salts on the 1 : 2 adduct formed from the Birch reduction product of 1,4-dimethoxybenzene and dibromocarbene.

We now report that the similar adduct (I; R = H) from 2,5-dihydroanisole, when boiled with pyridine, gives in 63% yield the pyridinium salt (II; R = H) which, by a Kröhnke reaction with p-nitrosodimethylaniline, affords the corresponding benzocyclobutenone (III; R = H). Homologous products (II) and (III; R = Me) are obtained from the adduct (I; R = Me) derived from 3-methylanisole.

The substitution pattern of the ketone (III; R = H) was proved by its ready fission under alkaline conditions to give 2-bromo-5-methoxyphenylacetic acid (IV), distinguished from its isomers by its n.m.r. spectrum. Moreover, oxidation by alkaline permanganate of the pyridinium salt (II; R = H) gave 3-bromo-6-methoxyphthalic acid (V), characterised as its anhydride, together with some 2,4-dibromo-5-methoxybenzoic acid (VI).

The formation of the acid (VI) may be rationalised in terms of oxidation of the pyridinium salt to the ketone, followed by alkaline fission to give the phenylacetic acid, further oxidation to the benzoic acid, and bromination, perhaps during acidification of the mixture, by the bromide ion in the presence of the oxidising agent. In agreement with this sequence, when the pyridinium salt (II; R = Me) was oxidised with permanganate under the same conditions, a crystalline steam-volatile substance, shown to be the benzocyclobutenone (III; R = Me), at first collected in the reflux condenser and was later consumed. Furthermore, the presence of bromine vapour was noted during final acidification of a similar permanganate oxidation mixture, and the

dibromo-acid (VI) is known [4] to be formed from 3-methoxybenzoic acid with bromine in water.
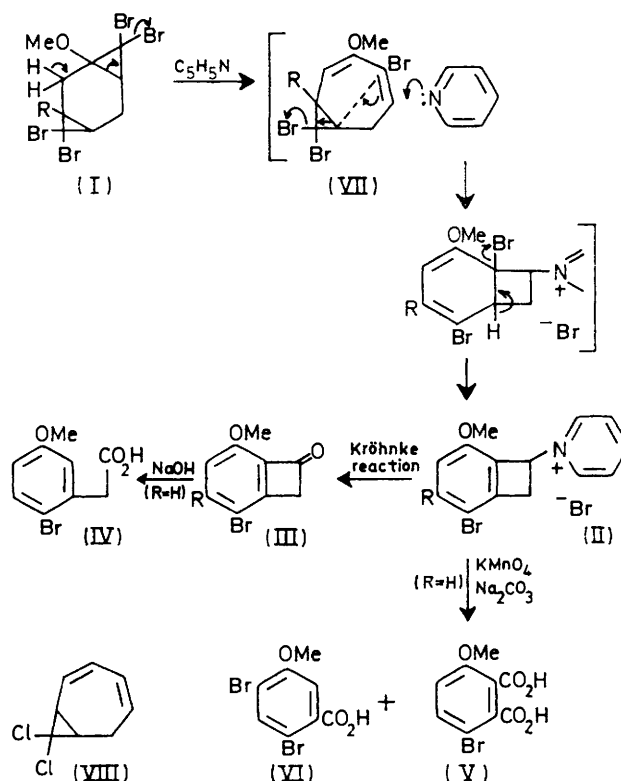
The mechanism of formation of the pyridinium salts (II) is uncertain, but probably involves initial formation of the cycloheptadiene intermediate (VII) by opening of the dibromomethoxycyclopropane ring, since the unmethoxylated bis-adduct from cyclohexa-1,4-diene is not attacked by boiling pyridine. Moreover, the analogous cycloheptatriene adduct (VIII), on heating in an

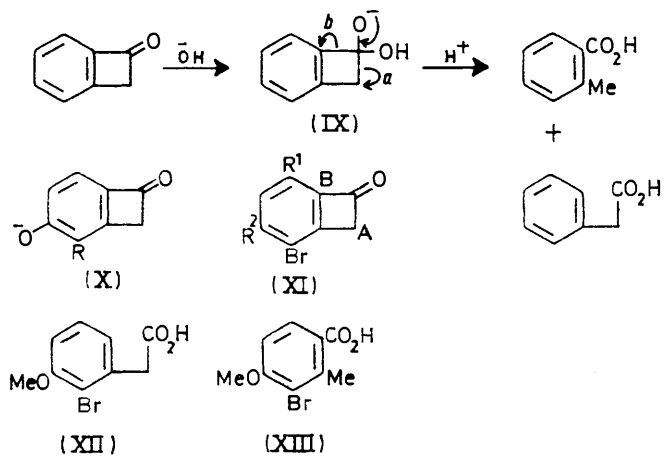[1] M. P. Cava and K. Muth, *J. Amer. Chem. Soc.*, 1960, **82**, 652.
[2] A. J. Birch, J. M. Brown, and F. Stansfield, *J. Chem. Soc.*, 1964, 5343.
[3] G. M. Iskander and F. Stansfield, *J. Chem. Soc.*, 1965, 1390.
[4] H. Bauer and P. Vogel, *J. prakt. Chem.*, 1913, **88** [2], 330.

inert solvent, has been reported [5] to give mainly 1-chloro-1,2-dihydrobenzocyclobutene. However, the substitution pattern of the pyridinium salts shows that the pyridine does not directly displace a bromo-substituent on the same carbon atom, and an indirect displacement such as that shown must occur.

Alkaline fission of unsubstituted benzocyclobutenone was reported [1] to give approximately equal amounts of o-toluic and phenylacetic acids, formed by the two possible cleavage modes (IX; a and b), whereas the 4-hydroxy- and 3-bromo-4-hydroxy-derivatives gave only the corresponding o-toluic acids,[3] because the high electron density at the para-carbon atoms of the phen-

oxide ions present (X; R = H or Br) inhibits fission by mode (b). Since the two isomeric bromo-methoxy-ketones (XI; R^1 = OMe, R^2 = H) and (XI; R^1 = H, R^2 = OMe) [2] were available, it was of interest to find out whether their alkaline fission products could also be explained in terms of electron density at the methylene carbon atom (A) and at the bridgehead carbon atom (B) adjacent to the carbonyl group.

As already stated, the ketone (XI; R^1 = OMe, R^2 = H) gives, in high yield, only the phenylacetic acid (IV), probably owing to low electron-density at atom B where the $-I$ effect of the o-methoxy-group is comparable with its $+E$ effect. However, with the isomer (XI; R^1 = H; R^2 = OMe), where the methoxy-group is para to position B, the $+E$ effect predominates, and the phenylacetic and o-toluic acids (XII) and (XIII) are obtained in the ratio ca. 2 : 1, respectively. It is well known that metallation of anisole derivatives occurs mainly in the ortho-positions owing to the greater $-I$ effect there.[6]

EXPERIMENTAL

I.r. and u.v. spectra were determined with Unicam SP 1200 and SP 800 spectrometers, respectively; n.m.r. spectra (solvent deuteriochloroform except where otherwise stated) were obtained with Varian T60 and HA-100 instruments.

4,4,8,8-Tetrabromo-1-methoxy-3-methyltricyclo[5.1.0.0^{3,5}]-octane (I; R = Me).—The adduct was prepared from dihydro-m-cresol methyl ether in the same way as its lower

[5] A. P. ter Borg and A. F. Bickel, Rec. Trav. chim., 1961, 80, 1217.

homologue (I; R = H) [2] and formed cubes from ethanol; m.p. 123—125° (Found: C, 25·8; H, 2·6; Br, 67·8. $C_{10}H_{12}Br_4O$ requires C, 25·6; H, 2·6; Br, 68·4%), $\nu_{max.}$ (Nujol) 1440s and 1340w cm^{-1}.

N-(3-Bromo-1,2-dihydro-6-methoxybenzocyclobuten-1-yl)-pyridinium Bromide (II; R = H).—The tetrabromo-compound (I; R = H) [2] (14·3 g) was boiled under reflux with pyridine (AnalaR; dried over KOH; 60 ml) for 2·5 h and the solution was evaporated to dryness. The gummy residue was triturated with a mixture of 46% hydrobromic acid (6 ml) and water (6 ml) and kept at 0 °C overnight, and the solid was filtered off, washed with small amounts of ice–water, and dried (yield 7·7 g, 63%). It was crystallised from boiling water (50 ml) (charcoal) forming pale yellow needles (5·9 g). The monohydrate formed needles from 95% ethanol, darkening at ca. 200° with vapour (water?) evolution; m.p. 213—214° (decomp.) (Found: C, 43·3; H, 3·9; Br, 41·1; N, 3·5. $C_{14}H_{15}Br_2NO_2$ requires C, 43·2; H, 3·9; Br, 41·1; N, 3·6%), $\lambda_{max.}$ (EtOH) 262 (ε 4900) and 287sh nm (1900), $\nu_{max.}$ (Nujol) 3420, 3380, 1625, 1605, 1270, 1195, and 1065 cm^{-1}, τ [(CD$_3$)$_2$SO] 0·83 (2H, m, pyridine α-H), 1·32 (1H, m, pyridine γ-H), 1·70 (2H, m, pyridine β-H), 2·39 (1H, d, J 9 Hz, benzenoid), 3·03 (1H, d, J 9 Hz, benzenoid), 3·25 (1H, m, CH–$\overset{+}{N}$), 6·25 (2H, m, CH$_2$·CO), 6·30 (3H, s, OMe), and 6·69 (2H, s, H$_2$O, replaceable by D$_2$O).

The methyl homologue (II; R = Me) (anhydrous), prepared similarly from the adduct (I; R = Me), formed yellow needles from ethanol; m.p. 197—199° (decomp.) (Found: C, 46·6; H, 3·9; Br, 41·9; N, 3·6. $C_{15}H_{15}Br_2NO$ requires C, 46·8; H, 3·9; Br, 41·6; N, 3·6%), $\lambda_{max.}$ (EtOH) 260sh (ε 12,600), 288sh (5100), and 408 nm (3150). Its n.m.r. spectrum (solvent CDCl$_3$) closely resmbled that of the lower homologue, with additional absorption at τ 7·60 (3H, s, CMe), and only one benzenoid proton absorption, at 3·20 (1H, s). Spin-decoupling experiments showed that the methine proton (CH–$\overset{+}{N}$) absorbing at 3·09 (1H, q) was coupled with each of the adjacent methylene protons (J_{cis} 1, J_{trans} 5 Hz), which absorbed at 5·80 (1H, q, trans to methine H) and 6·65 (1H, q, cis to methine H), and that the methylene protons were mutually coupled (J_{gem} 15 Hz).

Permanganate Oxidation of the Pyridinium Salt (II; R = H).—The salt (1·5 g), anhydrous sodium carbonate (3·0 g), and potassium permanganate (11·0 g) in water (100 ml) were boiled under reflux, with stirring, for 2 h, cooled, and acidified with a mixture of sulphuric acid (10 ml) and water (10 ml). Sodium disulphite was added in portions, with swirling, to remove manganese dioxide. After cooling, the solid was filtered off, washed with water, and dried (0·08 g). It was purified by dissolving in potassium hydrogen carbonate solution, filtering, re-precipitation from the filtrate with acid, drying, and sublimation, giving needles of 2,4-dibromo-5-methoxy-benzoic acid (VI), m.p. and mixed m.p.[4] 200°, M^+ 309/311. The filtrate from the crude acid was saturated with ammonium sulphate and continuously extracted with ether for 6 h. The extract was evaporated, the residue sublimed at 130° and 1 mmHg, and the sublimate crystallised from benzene, giving 3-bromo-6-methoxyphthalic anhydride, m.p. 212—214° (lit.,[7] 211—212°), τ 2·1 (1H, d,

[6] J. D. Roberts and D. Y. Curtin, J. Amer. Chem. Soc., 1946, 68, 1658; R. A. Barnes and W. M. Bush, ibid., 1959, 81, 4705.
[7] R. A. Barnes and R. W. Faessinger, J. Org. Chem., 1961, 26, 4544.

aromatic, J 8 Hz), 2·8 (1H, d, aromatic), and 5·95 (3H, s, OMe).

3-Bromo-6-methoxybenzocyclobuten-1(2H)-*one* (III; R = H).—The pyridinium bromide (II; R = H) monohydrate (2·91 g) and recrystallised *p*-nitrosodimethylaniline hydrochloride (1·41 g) suspended in ethanol (15 ml) and cooled in ice were stirred while aqueous sodium hydroxide (1N; 16·5 ml) was added dropwise over 10 min. Stirring and cooling were continued for 1 h more, then the solid was filtered off (suction) and washed with a little cold water, which precipitated a further crop from the filtrate. The combined solids were added to warm aqueous sulphuric acid (6N; 60 ml) and the mixture was triturated for 10 min and cooled in ice. The solid was filtered off, washed with water, and dried (yield 0·96 g, 58%). The *ketone* formed plates from light petroleum (b.p. 60—80°); m.p. 75° (Found: C, 47·8; H, 3·4; Br, 35·3. $C_9H_7BrO_2$ requires C, 47·6; H, 3·1; Br, 35·25%), $\lambda_{max.}$ (EtOH) 228, 252, 259, and 317 nm (ε 24,700, 8100, 8500, and 3400), $\nu_{max.}$ (Nujol) 1760 cm^{-1} (CO), τ 2·59 (1H, d, aromatic, J 8 Hz), 3·30 (1H, d, aromatic, J 8 Hz), 5·95 (3H, s, OMe), and 6·17 (2H, s, CH$_2$).

The *methyl homologue* (III; R = Me), prepared similarly, formed needles from light petroleum; m.p. 130—131° (Found: C, 49·8; H, 3·95; Br, 33·1. $C_{10}H_9BrO_2$ requires C, 49·8; H, 3·7; Br, 33·2%), $\lambda_{max.}$ (EtOH) 231, 259sh, 264, and 314 nm (ε 28,700, 9500, 11,100, and 3300), $\nu_{max.}$ (Nujol) 1760 (CO) and 1280 cm^{-1} (OMe), τ 3·33 (1H, s, aromatic), 5·95 (3H, s, OMe), 6·20 (2H, s, CH$_2$), and 7·60 (3H, s, CMe).

Fission of 3-*Bromo*-6-*methoxybenzocyclobuten*-1(2H)-*one*.— The ketone (0·17 g) was dissolved by warming in ethanol (0·8 ml), aqueous sodium hydroxide (10% w/v; 8 ml) was added, and the mixture was kept at *ca*. 50° for 10 min. The initial turbidity rapidly disappeared and the solution was diluted with water (16 ml) and acidified with conc. hydrochloric acid. The mixture was cooled in ice for 0·5 h and the crystals were filtered off, washed, and dried (0·17 g), giving 2-bromo-5-methoxyphenylacetic acid (IV), whose n.m.r. spectrum showed no impurity. It formed needles from water, m.p. 114—115° (lit.,[8] 114—115°)

(Found: C, 44·2; H, 3·7; Br, 32·4. Calc. for $C_9H_9BrO_3$: C, 44·1; H, 3·7; Br, 32·65%), τ −0·75br (1H, s, replaceable, CO$_2$H), 2·58 (1H, d, J 9 Hz, 3-H), 3·17 (1H, d, J 3 Hz, 6-H), 3·31 (1H, q, J 3 and 9 Hz, 4-H), 6·23 (2H, s, CH$_2$), and 6·26 (3H, s, OMe).

Fission of 3-*Bromo*-4-*methoxybenzocyclobuten*-1(2H)-*one*.— The ketone [2] (0·30 g) was dissolved by warming in ethanol (10 ml), aqueous sodium hydroxide (10% w/v; 5 ml) was added dropwise over 5 min, and the solution was kept at 50° for 10 min. Water (10 ml) was added and the solution was evaporated to *ca*. half its volume. Charcoal was added, the solution was filtered, and the filtrate was made up to 20 ml with water and acidified with conc. hydrochloric acid. The mixture was cooled in ice for 2 h and the solid was filtered off, washed, and dried (0·30 g). The n.m.r. spectrum showed that the phenylacetic and *o*-toluic acid derivatives were present in the ratio *ca*. 2 : 1, respectively. They were separated by fractional crystallisation from boiling water in which the toluic acid derivative is less soluble, as in the case of the unsubstituted acids.[1]

3-*Bromo*-4-*methoxy*-o-*toluic acid* (XIII) formed needles from water; m.p. 195—196° (Found: C, 44·4; H, 3·8; Br, 32·85. $C_9H_9BrO_3$ requires C, 44·1; H, 3·7; Br, 32·65%). Its n.m.r. spectrum showed the absence of the isomer: τ −0·33br (1H, s, replaceable, CO$_2$H), 1·95 (1H, d, J 9 Hz, 6-H), 3·21 (1H, d, J 9 Hz, 5-H), 6·02 (3H, s, OMe), and 7·20 (3H, s, CMe).

The isomeric 2-bromo-3-methoxyphenylacetic acid (XII), still containing a trace of the toluic acid derivative as shown by its n.m.r. spectrum, formed needles from water; m.p. 115—118° (Found: C, 44·2; H, 3·85; Br, 32·6%), τ −0·33br (1H, s, replaceable, CO$_2$H), 3·0 (3H, m, aromatic), 6·1 (5H, two s, only partially resolved, CH$_2$ and OMe).

[8] J. D. Berman and C. C. Price, *J. Amer. Chem. Soc.*, 1957, **79**, 5474.