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THE REACTION OF SOME DIBROMOCYCLOHEXANEDIONES WITH BASES

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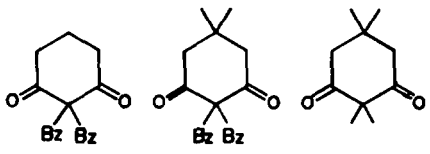
Abstract—The reaction of some dibromocyclohexanediones with bases is reported. Elimination of HBr, believed to proceed via cyclopropane intermediates, yields ultimately cyclopentenediones. A possible mechanism is described.

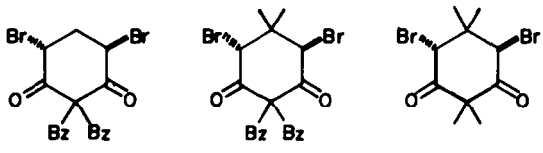
The reaction of cyclic α-bromoketones with bases has been extensively investigated. Dehydrobromination sometimes produces $\alpha\beta$-unsaturated ketones and sometimes accompanying acidic products by a ring contraction known as the Favorski reaction.[1] This paper reports a novel Favorski reaction of some cyclic α-dibromodiketones with various bases, during which cyclopropane intermediates are probably involved. In one case such a cyclopropane was isolated. Some of the compounds formed (11 and 12) might be useful in prostaglandin synthesis.[2]

The solid diketones 1, 2 and 3 were prepared by direct alkylation of either dihydroresorcinol or dimedone in the standard way.[2]



1 2 3

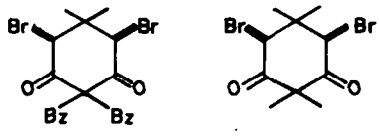
The bromination of these ketones was achieved using bromine in acetic acid catalysed by hydrogen bromide and the products were the crystalline *trans*-dibromides 4, 5 and 6.



4 5 6

Attempts to prepare the monobromides by using 1 mol bromine under various conditions always gave dibromide and starting material. Possible reasons for this will be discussed at the end of the paper. No bromination occurred using bromine in acetic acid containing potassium acetate.

When the dibromides 5 and 6 were heated in pyridine they were partly (10–15%) converted into the crystalline *cis*-isomers 7 and 8. Molecular weight measurements by mass spectrometry, and microanalytical data clearly indicate that 7 and 8 are isomers of 5 and 6. The stereochemistry is based upon evidence from NMR and IR. The NMR spectra of 7 and 8 are more complex than those of 5 and 6 indicating less molecular symmetry. Thus in that of 8, the four Me groups each has a different

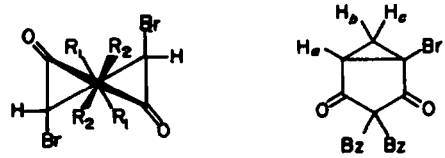


7 8

chemical shift whereas in 6 this is not so. In that of 2 the two Me groups have different chemical shifts as do the benzylic protons whereas in 5 this is not so. The resonance of the CHBr protons showed a downfield shift when 6→8, but an upfield shift when 5→7. However as is known, no firm stereochemical conclusions can always be drawn from such movements.[5]

Both 5 and 6 showed lower carbonyl frequencies than 7 and 8. It is therefore likely that 5 and 6 are the *trans*- and 7 and 8 the *cis*-isomers. Models show that a symmetrical conformation 9 is available to the *trans*-isomers in which all the dipole interactions between C=O and C-Br and all steric interactions are minimal. Isomerisation to a *cis*-isomer would result in a less symmetrical arrangement, in which one of the C=O groups is always eclipsed by a C-Br, thereby raising the mean value of $\nu_{C=O}$.

On the other hand when the dibromide 4 was heated in pyridine, no isomer was isolated, but only the cyclopropane 10 in low yield. The failure to isolate an isomer of 4 means that the assignment of a *trans*-configuration to 4 is conjectural and based upon an analogy with 5 and 6.

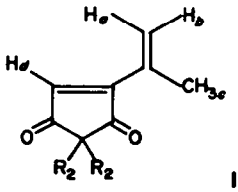


9 10

The evidence for the structure 10 rests upon analytical data and the NMR spectrum. The protons H_b and H_c both show as quartets of lines, while the details of the resonance of H_a are lost beneath the resonance of the 4 benzylic protons.[4] The carbonyl absorption in the IR indicates that there is no olefinic conjugation, thereby ruling out any possibility of a straightforward elimination of HBr.

Compound 10 was also obtained when the dibromoketone 4 was heated with LiBr and Li_2CO_3 un-

der N_2 in DMF at 100° for 4 hr. However the dibromoketones **5** and **6** with this reagent, lost two molecules of HBr to give the cyclopentenediones **11** and **12** respectively (15–25%). Small quantities of the isomeric *cis*-dibromides **7** and **8** were also isolated.



11 R_2 = Bz
12 R_2 = Me

The UV spectra of the molecules **11** and **12** show an intense maximum at 288 and 284 nm respectively, indicating extensive conjugation corresponding to the elimination of two molecules of HBr. The $\nu_{C=O}$ in the IR spectra at 1740, 1705 cm^{-1} are too high for a cyclohexenone, and certainly for a cyclohexadienone, but are compatible with the cyclopentenedione structures **11** and **12** proposed. The NMR spectrum reveals a proton pattern completely in accord with these structures, the CH_{3c} appearing as a narrow quartet of lines, H_a and H_b as narrow multiplets (it is not possible to distinguish unequivocally between H_a and H_b in the spectrum) and H_d as a low field singlet.

A possible mechanism for this elimination reaction involving a cyclopropane intermediate is outlined below (Scheme 1), though this intermediate has as yet not been isolated from the reaction mixture.

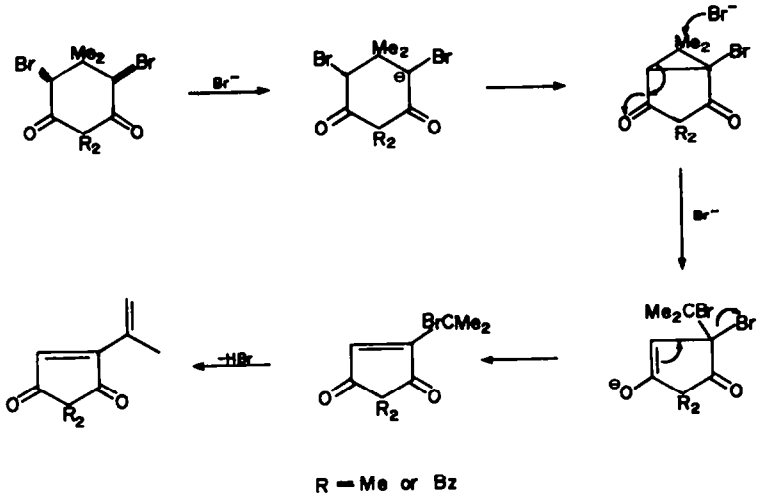
It might be added that the attack of Br^- on the other sites of the cyclopropane ring would regenerate either the dibromide starting material or a geminal dibromide, both of which could reform the cyclopropane and so ultimately **11** or **12**. These then represent the ultimate products of elimination.

It is interesting to note that the intermediacy of a cyclopropane could also account for the formation of the *trans*-dibromides **4**, **5** and **6** during the bromination of the diones **1**, **2** and **3** mentioned at the beginning of this paper, *and* the failure to isolate any monobromides (Scheme 2).

EXPERIMENTAL

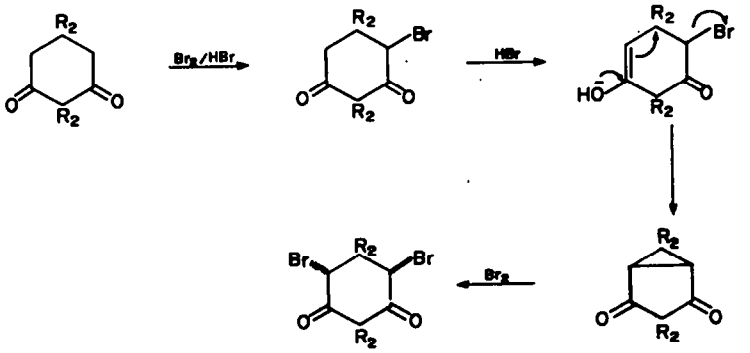
M.ps are uncorrected. NMR spectra PE-R20—Hitachi and Varian HA 100. UV spectra—Cary 118X. IR spectra-PE 257 and Infracord 137. Al_2O_3 for chromatography—Peter Spence's Grade H, deactivated with 5% of 10% HOAc.

2,2-Dibenzyl-5,5-dimethylcyclohexan-1,3-dione(2). Benzyl chloride (10.4 g, redist) was added to dimedone (5.6 g) in a soln of NaOEt (from 1.84 g Na) in EtOH (50 ml) at 20°, and the mixture refluxed for 3 hr. After dilution with water, the product was recovered in ether. Extraction with dil Na_2CO_3 aq followed by addition of HOAc gave 2-benzyl-5,5-dimethylcyclohexan-1,3-dione (2.5 g) as needles, m.p. 157° (from MeOH). (Stetter[3] gives m.p. 155°.) The ether extract on evaporation gave *2,2-dibenzyl-5,5-dimethylcyclohexan-1,3-dione*(2) (600 mg) as prisms, m.p.



R = Me or Bz

Scheme 1.



Scheme 2.

140–1° (from MeOH); IR (Nujol) ν_{max} 1705, 1740, 1610, 1500, 1345, 1325 cm^{-1}; NMR ($CDCl_3$) δ, 0.30(s, 6H), 2.00(s, 4H), 3.20(s, 4H) 7.20(m, 10H) (Found: C, 82.7; H, 7.5. $C_{22}H_{26}O_2$ requires; C, 82.5; H, 7.5%), and an oil which was distilled to give *3,3-dimethyl-5-benzyloxycyclohex-5-enone* (1.8 g), b.p. 230–5°/20 mm, n_D^{25} 1.5482; IR (film) ν_{max} 3100, 1650, 1595, 1500, 1230, 1210, 1155, 1140 cm^{-1}; UV (EtOH) λ_{max} 250.5 nm (log ϵ 4.30); NMR (CCl_4) δ 1.0(s, 6H), 2.05(s, 2H), 2.22(s, 2H), 4.80(s, 2H), 5.35(s, 1H), 7.30(s, 5H) (Found: C, 78.6; H, 7.9. $C_{15}H_{18}O_2$ requires; C, 78.3; H, 7.8%).

2,2-Dibenzylcyclohexan-1,3-dione(1). Benzyl chloride (20 g, redist) was added to a cool soln of dihydroresorcinol (18 g) in EtOH (96 ml) containing NaOEt (from 3.6 g Na). The mixture was refluxed for 3 hr, cooled, and diluted with ether and dil Na_2CO_3 aq. The aqueous phase on acidification gave 2-benzylcyclohexan-1,3-dione (8 g) as needles m.p. 190° (from MeOH aq). Stetter[3] gives m.p. 184–5°. The ethereal phase on evaporation gave an oil from which 1 (4 g) separated as needles, m.p. 135° (from MeOH aq); IR (Nujol) ν_{max} 1705, 1730, 1605, 1500 cm^{-1}; NMR (CCl_4) δ0.75(m, 2H), 1.70(m, 4H), 3.10(m, 4H), 7.10(m, 10H). (Stetter[3] gives m.p. 137°). The oily material was fractionated to remove unchanged benzyl chloride and the residue crystallised to give *3-benzyloxycyclohex-2-enone* as prisms, m.p. 67° (from pet ether 40°–60°); IR (Nujol) ν_{max} 1645, 1600, 1500 cm^{-1}; NMR (CCl_4) δ 2.10(m, 6H), 4.75(s, 2H), 5.30(s, 1H), 7.25(s, 5H); UV (EtOH) λ_{max} 249 nm (log ϵ 4.32) (Found: C, 77.2, H, 7.0. $C_{13}H_{14}O_2$ requires: C, 77.2, H, 6.9%).

2,2,5,5-Tetramethylcyclohexan-1,3-dione(3). MeI (15.5 g) was added at 20° to a soln of dimedone (10 g) in MeOH (30 ml) containing NaOMe (from 1.66 g Na), and the mixture refluxed 4 hr. The mixture was diluted with water and ether and washed with dil Na_2CO_3 aq. Acidification of the aqueous phase gave 2,5,5-trimethylcyclohexane-1,3-dione (3 g) m.p. 165° (from EtOAc) Halsall and Thomas[4] give m.p. 158–9°, while the ether on evaporation gave 3 (2 g) as plates, m.p. 96–97° (from pet ether 60°–80°); IR (Nujol) ν_{max} 1730, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.00(s, 6H), 1.30(S, 6H), 2.65(s, 4H) Halsall and Thomas[4] give m.p. 98°.

Bromination of the diketones 1, 2 *and* 3. The diketone (1 mmole) in HOAc (10–20 ml) containing Ac_2O (2–5 ml) and HBr (5 drops of a saturated solution in HOAc) was treated with Br_2 (2 mmoles). The mixture was set aside at 20° for 3–5 hr in the dark. The mixture was neutralised with $NaHCO_3$ and the solid dibromodiketone recovered in ether. Yields were generally 85–90% based upon the diketone.

Compound 2 gave *2,2-dibenzyl-5,5-dimethyl-trans-4,6-dibromocyclohexan-1,3-dione*(3), m.p. 154–6° (from acetone aq.); IR $\nu_{C=O}$(CS_2) 1740, 1705; IR (Nujol) ν_{max} 1735, 1705, 1610, 1590, 1500 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (s, 6H), 3.30 (s, 4H), 4.80 (s, 2H), 7.20 (m, 10H); (Found: C, 54.9; H, 4.8; Br, 35.6. $C_{22}H_{22}O_2Br_2$ req: C55.3; H, 4.6; Br 33.5%).

Compound 3 gave *2,2,5,5-tetramethyl-trans-4,6-dibromocyclohexan-1,3-dione* (6), m.p. 108–9° (from acetone aq.), IR $\nu_{C=O}$ (CS_2), 1740, 1705; IR (Nujol) $\nu_{C=O}$ 1730, 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.25(s, 6H), 1.55(s, 6H), 5.00(s, 2H); (Found: C, 37.1; H, 4.4; Br, 48.8. $C_{10}H_{14}O_2Br_2$ requires: C, 36.8; H, 4.3; Br, 49.0%).

Compound 1 gave *2,2-dibenzyl-trans-4,6-dibromocyclohexan-1,3-dione* (4), m.p. 149–50° (from acetone aq.); IR (Nujol) ν_{max} 1735, 1705, 1605, 1590, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.55(m, 2H), 3.30(s, 2H), 3.40(s, 2H), 4.10(m, 2H), 7.25(m, 10H); (Found: C, 54.0; H, 4.3; Br, 35.1. $C_{20}H_{18}O_2Br_2$ requires: C, 53.3; H, 4.0; Br, 35.5%).

3,3-Dibenzyl-1-bromobicyclo[3,1,0]*hexan-2,4-dione*(10). Compound 4, (250 mg) was refluxed in pyridine (10 ml) under N_2 for 3 hr. Recovery by dilution with ether and water gave on removal of the ether a dark red gum. This was adsorbed on Al_2O_3 (25 g). Elution with pentane:ether (10 : 1) gave *3,3-dibenzyl-1-bromobicyclo*[3,1,0]*-hexan-2,4-dione*(10; 25 mg) as prisms m.p. 128–9° (from pet ether 40–60°); IR (Nujol) $\nu_{C=O}$ 1745, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.20(q, 1H$_b$, J_{bc} 7.5 Hz, J_{ba} 5.0 Hz), 2.05(q, 1H$_c$, J_{cb} 7.5 Hz, J_{ca} 3.0 Hz), 3.05(m, 5H, benzylic + H$_a$), 7.20(m, 10H)[4] (Found: C, 65.4; H, 4.8; Br, 22.0. $C_{20}H_{17}O_2Br$ requires: C, 65.1; H, 4.6; Br, 21.7%).

The same product 10 was obtained by heating 4 with LiBr and Li_2CO_3 in DMF at 95° under N_2 for 4 hr.

Dehydrobromination of the dibromodiketone(5). A mixture of 5 (200 mg), LiBr (800 mg) and Li_2CO_3 (300 mg) was stirred under N_2 in DMF (15 ml) for 4 hr at 100°. The product was recovered by dilution with ether and water. Removal of the ether gave a yellow oily product. Addition of pentane caused the crystallisation of the *isomeric dibromodiketone*(7; 25 mg) m.p. 178°. The mother liquors on evaporation gave a yellow solid which was purified by elution from Al_2O_3 (20 g) with pentane/ether (10 : 1).

2,2-Dibenzyl-4-isopropenylcyclopent-4-en-1,3-dione(11; 30 mg) was obtained as yellow prisms, m.p. 113–4° (from pet ether 40–60°); IR (Nujol) ν_{max} 1740, 1705, 1615, 1570, 925 cm^{-1}; UV (EtOH) λ 390 nm (sh, log ϵ 1.96), 288 nm (max, log ϵ 3.97); NMR ($CDCl_3$) δ 1.60(q, 3H$_c$, J_{ca} 1.0 Hz, J_{cb} 2.0 Hz), 3.10(m, 4H), 5.35(m, 1H$_{a\,or\,b}$), 6.15(m, 1H$_{a\,or\,b}$), 6.40(s, 1H$_d$), 7.05(m, 10H) (Found: C, 83.0, H, 6.6. $C_{22}H_{20}O_2$ requires: C, 83.5; H, 6.3%).

Dehydrobromination of the dibromodiketone(6). A mixture of 6 (200 mg), LiBr (800 mg) and Li_2CO_3 (300 mg) was stirred under N_2 in DMF (15 ml) for 4 hr at 95°. The product was recovered as usual in ether. Evaporation of the ether gave a yellow oily product. Addition of pentane caused the crystallisation of the isomeric *dibromodiketone*(8; 15 mg), m.p. 146–7°. The mother liquors on evaporation gave a yellow oil which was purified by elution in pentane:ether (10 : 1) from Al_2O_3 (20 g). *2,2-Dimethyl-4-isopropenyl-cyclopent-4-en-1,3-dione*(12; 25 mg) was obtained as a yellow oil, m.p. 17–18°; IR (film) ν_{max} 1740, 1705, 1610, 1560, 930 cm^{-1}; UV (EtOH) λ 384 nm (sh, log ϵ 1.72), 284 nm (max, log ϵ 4.02); NMR ($CDCl_3$) δ 1.20(s, 6H), 2.05(q, 3H$_c$, J_{ca} 1.0 Hz, J_{cb} 2.0 Hz), 5.70(m, 1H$_{a\,or\,b}$), 6.55(m, 1H$_{a\,or\,b}$), 6.95(s, 1H$_d$) (This compound could not be obtained completely analytically pure).

The isomerisation of the trans-dibromodiketones 5 *and* 6 *to the cis-isomers* 7 *and* 8. The *trans*-isomers of the dibromodiketones (200 mg) as prepared by direct bromination of the corresponding diones were refluxed in pyridine (10 ml) for 3 hr. Recovery was by dilution with water and ether. Careful evaporation of the ether induced the crystallisation of the *cis*-isomers. The remaining *trans*-isomer was recovered by evaporation of the mother liquors. The *cis*-isomers were purified by further crystallisation. The eventual yield was 10–15%.

The *trans*-dibromide (5) gave *2,2-dibenzyl-5,5-dimethyl-cis-4,6-dibromocyclohexan-1,3-dione*(7) needles m.p. 178° (from EtOH); IR $\nu_{C=O}$ (CS_2) 1720, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.00(s, 3H), 1.55(s, 3H), 3.20(s, 2H) 3.35(s, 2H), 3.85(s, 2H), 7.10(m, 10H) (Found: C, 55.1; H, 4.7; Br, 33.5. $C_{22}H_{22}O_2Br_2$ requires: C, 55.3; H, 4.6; Br, 33.5%).

The *trans*-dibromide (6) gave *2,2,5,5-tetramethyl-cis-4,6-dibromocyclhexan-1,3-dione*(8) as prisms, m.p. 147° (from pet ether 60–80°); IR $\nu_{C=O}$ (CS_2) 1720, 1750 cm^{-1}; NMR ($CDCl_3$) δ 0.85(s, 3H), 1.40(s, 3H), 1.50(s, 3H), 1.58(s, 3H), 5.25(s, 2H) (Found: C, 37.9; H, 4.4; Br, 49.5. $C_{10}H_{14}O_2Br$ requires: C, 36.8; H, 4.3; Br, 49.0%).

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