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BREDT'S RULE—III[a]
AN ANOMALOUS DECARBOXYLATION

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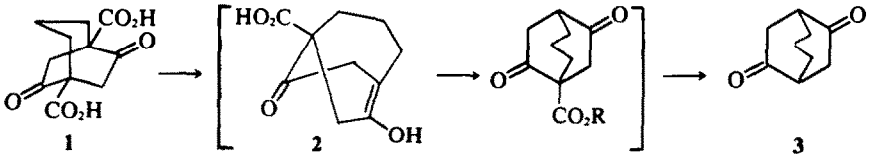
Abstract—The thermal mono-decarboxylation of (+)-bicyclo(2,2,2)octan-2,5-dione-1,4-dicarboxylic acid has been shown to proceed with racemisation. Accordingly, the decarboxylation does not infringe Bredt's Rule and a mechanism is postulated. The term *Bredt's Strain* is introduced, and defined.

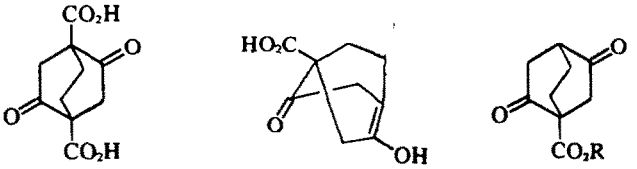
As an expression of Bredt's Rule, the ease of decarboxylation of bridgehead β-keto-acids (e.g. **1**) should be related to the strain in the intermediate enol (**2**); and indeed, a rough correlation exists[1] between the decaboxylation temperature and the size of the ring which incorporates the *trans*-double bond. Of all the recorded decarboxylations of β-keto-acids, only one (**4**→**6a**) described by Guha,[2] appears to involve a *trans*-cyclohexenol intermediate (**5**).† It is therefore of exceptional interest since no bridgehead alkenes incorporating a *trans*-cyclohexene have ever been isolated. Their transient existence has been inferred only from the isolation of dimers or adducts. Supporting evidence, e.g. from a decarboxylation, would be welcome, and this paper describes a reinvestigation of the decarboxylation of **4**.

Under Guha's conditions, (285°C *in vacuo*), the diacid (**4**) affords a product in up to 50% yield, having all the characteristics he described, but in view of the possibility of skeletal rearrangement it was first of all necessary to establish the structure of the product. This was achieved by an unambiguous degradation of **4** to **6a** in the following way. The diketo–diester (**7a**) was ketalised,[5] the product (**8a**) was half-hydrolysed to **9a** and thereafter transformed via the bromo–ester (**10a**) into **11a** by hydrogenolysis. Hydrolysis afforded (**6a**), identical in all respects with the decarboxylation product. Guha's structure assignment was thus correct.

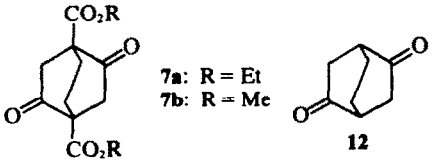
[a] Part II, G. L. Buchanan and G. Jamieson, *Tetrahedron* **28**, 1129 (1972).

†Other known examples[3] are not simple decarboxylations, but involve skeletal rearrangement, for which a mechanism has been suggested.[4]



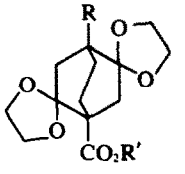


6a: R = H
6b: R = Me



7a: R = Et
7b: R = Me

12



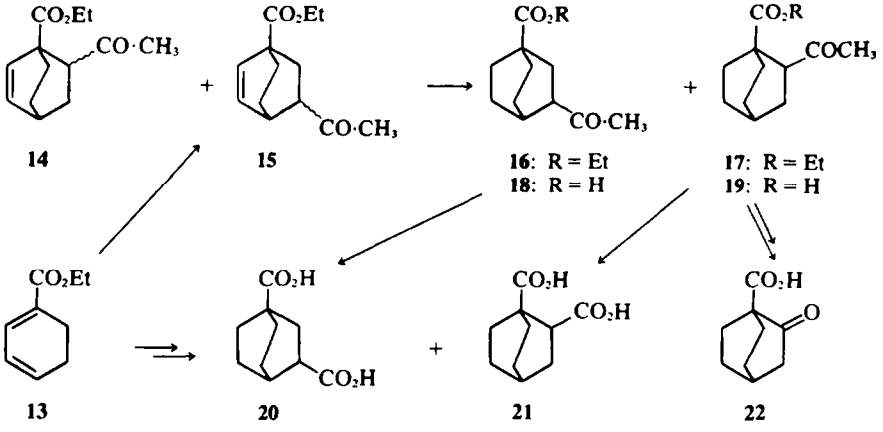
8a: R = CO_2Et; R' = Et
9a: R = CO_2H; R' = Et
10a: R = Br; R' = Et
11a: R = H; R' = Et
8b: R = CO_2Me; R' = Me
9b: R = CO_2H; R' = Me
10b: R = Br; R' = Me
11b: R = H; R' = Me

An intriguing feature of Guha's work is his failure to effect further decarboxylation to **12**, although the homologous di-acid (**1**) has been decarboxylated[6] to **3**, at 240°. This might imply that he had failed to detect the dione **12** or that so volatile a product had been lost under his (vacuum) conditions. It was important to establish this fact and so the decarboxylation was repeated in a sealed tube and by dropping a solution of the acid rapidly through a hot tube, in a N_2 atmosphere, and trapping the effluent in a cold trap. In both cases a thorough search (GLC) for **12**, using a synthetic sample,[7] for reference failed to find any trace of the diketone. Pyrolysis of the monocarboxylic acid (**6a**) in a sealed tube led to its recovery in 37% yield. The residue was a tar, but again a search for **12** by GLC showed that none had been formed. It thus appeared that the monodecarboxylation achieved by Guha had been abnormal, and in order to explore this process further, the model compound **22** was synthesised as shown below. Methyl vinyl ketone was condensed with **13**, to give two pairs of diastereomers, **14** and **15**, as an inseparable mixture in which one predominated. This mixture was hydrogenated yielding an equally intractible 4:1 mixture of isomeric esters (**16** and **17**) but after hydrolysis, the major keto–carboxylic acid (56% yield) could be crystallised out in >95% purity. That this was the 1,2-disubstituted isomer (**19**) was proved by the following correlation. It is known[8] that the reaction of ethyl acrylate with **13** yields a 1:4 mixture of the diacids **20** and **21**, in which the latter predominates. When the major crystalline keto-acid was oxidised (NaOI) it afforded **21**, whilst similar treatment of the (non-crystalline) mixture obtained from the mother liquors gave both **20** and **21**.

The desired keto–acid **22** was obtained from **19** via its methyl ester by Baeyer–Villiger oxidation followed by hydrolysis and Jones oxidation. It was now subjected to decarboxylation conditions. Under Guha's conditions, **22** merely sublimed; under the hot tube conditions, it was recovered, albeit in low yield; under sealed tube conditions it was recovered (crude) in 98% yield and after esterification, the methyl ester was isolated by preparative TLC in 84% yield. No neutral products could be detected by GLC.

It can be concluded from these experiments that the decarboxylation of **4** to **6a** is abnormal with respect to the bicyclo[2.2.2]octane skeleton and must be a special consequence of the bis-β-keto-acid system. An indication of the nature of the special mechanism was obtained by studying the decarboxylation of the resolved diketo–diacid (+)**4**. The acid (**6a**), obtained by decarboxylation of (+)**4** showed no measurable rotation and its methyl ester (**6b**) showed no significant CD. An optically active sample of the same ester, prepared for comparison from (+)**4** by the route **4**→**7b**→**10b**→**6b** shows sizeable absorption ($\Delta\epsilon$ +0·62 at 289 nm; −0·58 at 214 nm). Thus the pyrolytic decarboxylation of **4** to **6a** proceeds with racemisation and this fact eliminates any mechanism in which the bridged ring system remains intact, e.g. **4**→**5**→**6a**. The reaction must involve bond rupture to a monocyclic intermediate β-keto-acid followed by loss of CO_2 and ring-closure. Our experiments do not disclose the nature of the bond fission process, but one possible mechanism is illustrated below (see Scheme 1). Such a mechanism explains the mono–decarboxylation of **4** and the thermal stability of **6a** and **22**, for only bis-β-keto-acids can both ring open and decarboxylate. That β-keto-acids *can* reversibly open under thermal conditions is supported by the observation that when a sample of (+)**6a** was heated briefly at 280° under low vacuum, it underwent about 28% racemisation. This will arise via slow enolisation of the monocyclic intermediate **23**.

The conclusion to be drawn from these experiments is that the enol intermediate (**5**) has not been formed and so it could be claimed that Bredt's rule has not been broken. Indeed it has not been broken under these reaction conditions, but bicyclo[2.2.2]oct-1-ene (**24**) has been formed under different reaction conditions.[9] In these circumstances it becomes meaningless to use the term "rule" to describe a stricture which may be flaunted at will. It would be more accurate to speak of Bredt Strain which arises from that combination of in-plane and out-of-plane deformations incurred in placing a double bond at a bridgehead,[4] and which may be overcome only under suitable reaction conditions.

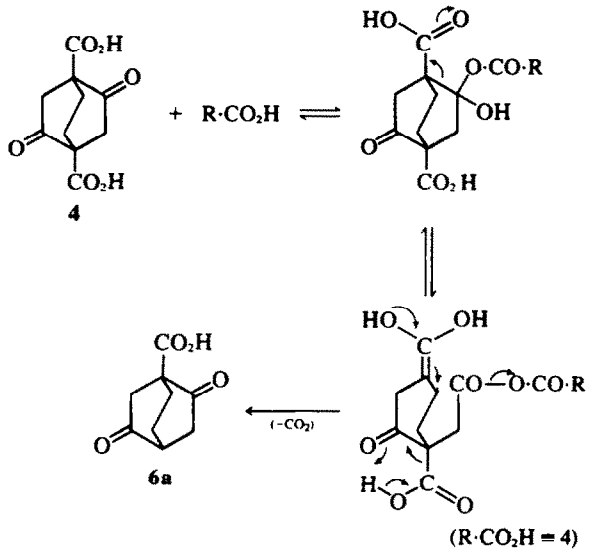


EXPERIMENTAL

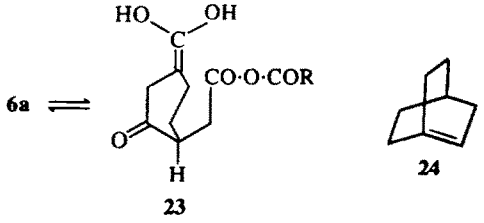
2,5-bis(Ethylene acetal) of 1-ethoxycarbonylbicyclo-[2.2.2]-octan-2,5-dione-4-carboxylic acid (**9a**). A soln of **8a** (1 g) and KOH (0·154 g) in abs EtOH (3·7 ml) was refluxed for 16 hr, then poured into water and the aqueous soln washed with EtOAc.

The aqueous soln was then acidified to pH 5 with 1N H_2SO_4 extracted with chloroform (3 × 20 ml) and the chloroform extracts dried and evaporated to yield **9a** (385 mg, 43%) m.p. 142° (benzene/light petroleum). (Found: C, 55·92; H, 6·55. $C_{16}H_{22}O_8$ requires: C, 56·14; H, 6·48%); ν(CCl_4) 1770, 1728, 1700 cm^{-1}; *m/e* 342.

2,5-bis(Ethylene acetal) of 1-ethoxycarbonyl-4-bromobicyclo-[2.2.2]octan-2,5-dione (**10a**). A stirred mixture of **9a** (2·22 g),



Scheme 1.



red mercuric oxide (1·00 g) and 1,2-dibromoethane (22 ml) was heated to 75°, and Br_2 (1·04 g) in 1,2-dibromoethane (9 ml) was added over 15 min. The mixture was stirred and heated at 75° for 12 hr, then cooled and filtered, and the solids were washed with ether and benzene. The filtrate was washed with dil $NaHSO_3$ aq, dil NaOH aq, and brine, and finally dried and evaporated to a colourless oil (1·83 g). Chromatography on alumina (Spence grade "H") gave the white crystalline **10a** (1·09 g, 45%), m.p. 62° (sublimed 120–130/0·05 mm). (Found: C, 47·70; H, 5·57. $C_{15}H_{21}O_6Br$ requires: C, 47·74; H, 5·57%); $\nu(CCl_4)$ 1728 cm^{-1}; *m/e* 376/378.

Bicyclo[2.2.2]*octan*-2,5-*dione*-1-*carboxylic acid* (**6a**). To a soln of **10a** (200 mg) and Na (100 mg) in abs EtOH (10 ml) was added Raney Ni (*ca.* 3 g). The mixture was stirred in an H_2 atmosphere till absorption ceased (3 hr) and TLC indicated complete conversion to a more polar product. The catalyst was then filtered off and washed with H_2O and EtOH. The combined filtrate was poured into water and extracted with ether (2 × 10 ml). The ether extracts were dried and evaporated to yield **11a** as a colourless oil (148 mg, 98%), pure by TLC; ν(CO) 1720 cm^{-1}. This product (140 mg) in EtOH (5 ml) and 5N HCl (25 ml) was refluxed for 14 hr, cooled and extracted with EtOAc (2 × 25 ml). The extract was washed with brine, dried and evaporated to yield **6a** (70 mg, 75%), m.p. 214–216° (dec) (H_2O). (Found: C, 59·27; H, 5·74. $C_9H_{10}O_4$ requires: C, 59·34; H, 5·53%); *m/e* 182, identical (m. m.p.) with a specimen prepared by pyrolysis of **4**.

Treatment of the acid with diazomethane gave **6b**, which was purified by sublimation m.p. 119–121°, $\nu(CCl_4)$ 1751, 1735 cm^{-1}; *m/e* 196, R_t 5·6 min (1% APL, 150°).

Decarboxylations (Three sets of conditions were employed)

(A) Guha's conditions were optimised as follows: the acid in a specimen tube loosely plugged with glass-wool, was heated in a sublimation tube at a pressure of 200 mm.

(B) A pyrex tube (70 × 1 cm), heated electrically over 60 cm, and containing a 20 cm packing of glass-wool, was mounted vertically and a stream of dry N_2 was passed continuously down the tube. A U-tube immersed in acetone–Drikold was attached to the outlet. The acid dissolved in dry THF was dropped through the tube, over 15 min. All solns were saturated with dry N_2 prior to use. In a blank run, it was established that THF itself gave rise to none of the observed products.

(C) The acid, dissolved in anhyd THF (*ca.* 2 ml) was placed in a Carius tube, flushed with dry N_2, sealed and heated in an oven.

In each experiment the pyrolysis products were taken up in EtOAc and separated into acidic and neutral fractions. The former were esterified (CH_2N_2) and both were thereafter examined by GLC.

Under conditions A, at 280–290° the diacid **4** (65 mg) afforded a semicrystalline oil (33 mg), condensed on the upper parts of the tube. After esterification it comprised **7b** (35%), **6b** (50%) and neutrals, none of which corresponded to the dione **12** on GLC. The dimethyl ester **7b** m.p. 148–150° (EtOH) was identical with the product obtained directly from **4** by CH_2N_2. (Found: C, 56·67; H, 5·52. $C_{12}H_{14}O_6$ requires: C, 56·69; H, 5·55%); *m/e* 254. The mono-ester (**6b**) was identical (m. m.p., IR and GLC) with the product described above and afforded **6a** on hydrolysis.

Under identical conditions, **6a** and **22** sublimed at *ca.* 200°.

Under conditions B at 285°, **4** (200 mg) in 10 ml dry THF afforded 105 mg, acidic product and a trace (1 – 2 mg) of neutrals. After esterification of the acid fraction the main component of the resulting mixture was **6b**. The neutral fraction comprised four components of R_t 4·0, 4·9, 7·7 and 8·8 min, on 1% APL at 100°. On the same column under identical conditions, **12** had R_t 6·4 min.

Under conditions C at 315° for 15 min, **4** (50 mg) gave 35 mg, of crude product. After esterification, the acid fraction yielded **6b**. No neutral component corresponding to **12** was found.

Similar pyrolysis of **6a** (50 mg) followed by esterification afforded **6b** (25 mg) isolated by preparative TLC. The neutral fraction contained none of the dione (**12**) as monitored by GLC.

Under identical conditions 51 mg, of **22** afforded 50 mg, of crude product. This contained no component with $R_f > 0$, on TLC. It was esterified (CH_2N_2) and furnished 42 mg of a crystalline methyl ester, identical in IR, GLC and NMR with that derived from **22** directly (*vide infra*).

2-*Acetylbicyclo*[2.2.2]*octan*-1-*carboxylic acid* (**19**). The ester[10] **13** (10 g) methyl vinyl ketone (9 g) and hydroquinone (5 mg) were placed in a Carius tube which was flushed with N_2, sealed and heated in an oven at 140° for 18 hr. Thereafter, fractional distillation gave the mixture of **14** and **15** (13 g, 89%) b.p. 150–152/15 mm, $\nu(CCl_4)$ 1730, 1716 cm^{-1}, GLC (5% QF-1, 130°)—four peaks, retention times 2·5, 3·3, 4·6 and 5·7 min, ratio 1:10:1:2. The mixture of keto esters (12·6 g) in THF (30 ml) and 10% Pd/c (200 mg) was shaken in an H_2 atmosphere until uptake ceased, then filtered and the solvent was removed *in vacuo*,

affording a mixture of **16** and **17** as a clear colourless liquid (12·5 g, 95%). $\nu(CCl_4)$ 1735, 1715 cm^{-1}; GLC (5% QF-1, 100°)—two peaks, of R_t 3·3 and 5·8 min (ratio 4:1).

A soln of the saturated keto–esters (12·0 g) and KOH (10 g) in aqueous EtOH was refluxed for 2 hr, then cooled, acidified and extracted with ether (3 × 50 ml). The combined ether extracts were dried and evaporated, yielding **19** as prisms (5·7 g, 55%) m.p. 164–167° (EtOH). (Found: C, 67·25; H, 8·24. $C_{11}H_{16}O_3$ requires: C, 67·32; H, 8·22%); $\nu(CCl_4)$ 1758, 1745, 1717 and 1705 cm^{-1}. Esterification (CH_2N_2) gave the methyl ester of **19** R_t 2·6 min on 5% QF-1 at 130°. The mother liquor from the crystallisation was similarly esterified and gave a mixture of the methyl esters of **18** and **19** R_t (respectively) 4·7 and 2·6 min (5% QF-1 at 130° in the ratio 2:3.

Bicyclo[2.2.2]octan-1,2-dicarboxylic acid (**21**) *and its* 1,3-*isomer* (**20**)

(a) The (4:1) mixture of **21** and **20** prepared as described[8] was esterified (CH_2N_2) giving the related methyl esters[8] as a 4:1 mixture. R_t (respectively) 2·4 and 3·6 min on 5% QF-1 at 130°.

(b) The keto–acid **19** (40 mg) in dioxan (2 ml) and 4N NaOH (2 ml) was treated with a soln of I_2 (0·8 g) and KI (1·5 g) in 6 ml H_2O, warmed and set aside for 15 min. Then the yellow ppt was removed by filtration and to the filtrate was added $Na_2S_2O_3$ (1 g), 5 N HCl (3 ml) and 50 ml water. The mixture was extracted with ether and the extract re-extracted with 4N NaOH. The alkaline extract was acidified, yielding 26·6 mg (68%) of solid acid. It was esterified (CH_2N_2) giving the methyl ester of **21**, a single peak. R_t 2·4 min on 5% QF-1 at 130° which was identical on co-injection with the ester of **21** in (a) above.

(c) The mixture of keto–acids (**18** and **19**) obtained from the crystallisation mother liquor, was similarly oxidised, as in (b) to a mixture of dicarboxylic acids (**20** and **21**) which were esterified as before. GLC examination showed two peaks R_t 2·4 and 3·6 min (ratio 1:2) on QF-1 at 130°.

Methyl 2-acetoxybicyclo[2.2.2]octan-1-carboxylate. Trifluoroacetic anhydride (10·2 ml) was added over 30 min to a stirred mixture of methylene chloride (10 ml) and 90% hydrogen peroxide (1·6 ml) at 0°.

Anhyd sodium dihydrogen phosphate (16 g) was added to a soln of the methyl ester of **19** (5·6 g) in dry methylene chloride (48 ml). To this mixture at 0° was added with stirring over 1 hr the soln of trifluoroperacetic acid prepared as above. The mixture was stirred at 0° for a further 2 hr and was then allowed to come to room temp. After 3 hr stirring at room temp., methylene chloride (100 ml) was added and the mixture washed ($NaHCO_3$) dried and evaporated, affording the acetate (6·0 g, 95%), b.p. 100°/0·1 mm. (Found: C, 63·53; H, 7·83. $C_{12}H_{18}O_4$ requires: C, 63·70; H, 8·02%); $\nu(CCl_4)$ 1740 and 1735 cm^{-1}. τ8·00 (3H, s), 6·38 (3H, s), 4·80 (1H, d.d., J = 11 and 3 Hz).

2-Hydroxybicyclo[2.2.2]octan-1-carboxylic acid. A soln of the above acetate (5·9 g) and KOH (6 g) in 10% aqueous EtOH (90 ml) was refluxed for 1·75 hr, cooled, poured into water and extracted with ether. The aqueous phase was acidified and extracted with EtOAc (3 × 30 ml). After washing with brine, drying and evaporation the EtOAc extracts afforded the hydroxy acid (4·0 g, 95%) m.p. 110–111·5° (sublimed). (Found: C, 63·56; H, 8·20. $C_9H_{14}O_3$ requires: C, 63·51; H, 8·29%); τ 5·82 (1H, d.d., J = 9 and 3 Hz). The derived methyl ester (CH_2N_2) showed $\nu(CCl_4)$ 3650–3350, 1735 and 1712 cm^{-1}; τ 5·95 (1H, d.d., J = 9 and 3 Hz).

Bicyclo[2.2.2]octan-2-one-1-carboxylic acid (**22**). The hydroxy acid (4·0 g) in acetone (100 ml) was cooled to 0°. Jones reagent (8N) was added dropwise until a permanent orange colour persisted. The soln was then concentrated *in vacuo* and poured into water. After extraction with ether (3 × 15 ml) the combined extracts were washed with brine and dried. On removal of half of the ether *in vacuo*, **21** crystallised as platelets, m.p. 146°. (Found: C, 63·40; H, 7·12. $C_9H_{12}O_3$ requires: C, 64·27; H, 7·19%); *m/e* 168 $\nu(CCl_4)$ 1760, 1730 and 1707 cm^{-1}.

The methyl ester (CH_2N_2) sublimed as needles, m.p. 62·5–64·5°. (Found: C, 65·56; H, 7·62. $C_{10}H_{14}O_3$ requires: C, 65·92; H, 7·74%); τ7·66 (2H, d, J = 3 Hz), 6·30 (3H, s), *m/e* 182, $\nu(CCl_4)$ 1757 and 1731 cm^{-1}.

Optically active series. Resolution of **4** by Guha's method[11] gave platelets m.p. 300° (EtOH) $[\alpha]_D^{25}$ +22·95° (H_2O, *c* = 0·13) (Lit.[2] +23·85°) which afforded (CH_2N_2) **7b** m.p. 143–144° $[\alpha]_D^{25}$ +17·7 (acetone, *c* = 0·3) indistinguishable (IR) from the ± product described above.

The conversion of **7b** to **6a**, via **8b**, **9b**, **10b**, and **11b** was carried out both on ± and on resolved material by the methods described above for the corresponding ethyl esters. In each case, the optically active product was spectroscopically identical with the ± analogue.

Bis(ethylene acetal) of dimethyl bicyclo[2.2.2]octan-2,5-dione-1,4-dicarboxylate (**8b**). Sublimed at 120°/1 mm, m.p. 100–102°. (Found: C, 56·26; H, 6·42. $C_{16}H_{22}O_8$ requires: C, 56·14; H, 6·48%); $\nu(CCl_4)$ 1734 cm^{-1}; τ6·36 (6H, s); *m/e* 342 optically active material showed m.p. 87–91°, $[\alpha]_D^{25}$ +40·0° (acetone).

Bis(ethylene acetal) of 1-methoxycarbonylbicyclo[2.2.2]octan-2,5-dione-4-carboxylic acid (**9b**). Sublimed at 180°/0·2 mm, m.p. 126–130°. (Found: C, 54·83; H, 6·33. $C_{15}H_{20}O_8$ requires: C, 54·88; H, 6·14%); *m/e* 328; τ 6·32 (3H, s) crude optically active material had m.p. 118–125°, $[\alpha]_D^{25}$ +38·7 (acetone, *c* = 0·06).

Bis(ethylene acetal) of methyl 4-bromobicyclo[2.2.2]octan-2,5-dione-1-carboxylate (**10b**). Sublimed at 130°/0·3 mm, m.p. 116–120°. (Found: C, 46·26; H, 5·31. $C_{14}H_{19}O_6Br$ requires: C, 46·3; H, 5·24%); *m/e* 364/362 crude optically active material had m.p. 95–100°, $[\alpha]_D^{25}$ +45·5° (acetone, *c* = 0·03).

(±)-*Methylbicyclo[2.2.2]octan-2,5-dione carboxylate* (**6b**). The optically active ester, purified by sublimation, had m.p. 70–72°. It showed no observable rotation at the sodium D line in benzene, chloroform or ethyl acetate but in methanol (0·0032 M) it showed CD, $\Delta\epsilon$ = +0·62 (289 nm), 0 (238 nm) and −0·58 (214 nm).

Decarboxylation of (+)-bicyclo[2.2.2]octan-2,5-dione-1,4-dicarboxylic acid (**4**). The diacid **4** (56·7 mg, $[\alpha]_D^{25}$ +23°) was pyrolysed under conditions A and treated with diazomethane, giving 34 mg of recovered material, from which the ester (**6b**) was isolated by preparative TLC (18·8 mg, 33%). This material was further purified by sublimation (110°/0·15 mm) to give 16·6 mg of TLC/GLC pure ester, m.p. 118–120° [m.p. of racemic (**6b**) 119–120°].

Solns of this material (0·15 M) in chloroform, ethyl acetate and benzene showed no observable net rotation. A soln in methanol (0·004 M) showed no observable CD.

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