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# Bicyclic analogues of cyclohexane-1,4-dione. I. Bicyclo[3·2·2]nonan-6,8-dione[1]

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Bicyclo[3·2·2]nonan-6,8-dione has been synthesized as an example of a molecule in which the cyclohexane-1,4-dione ring is constrained to non-chair forms. The synthesis includes the double decarboxylation of the corresponding bridgehead diacid. This reaction is consistent with a new formulation of Bredt's Rule. Conformational studies suggest that the title compound exists in solution as an equilibrium mixture of two twist forms.

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## Introduction

It is well known that cyclohexane and its derivatives exist predominantly in the chair form in which all the adjacent C—H and C—C bonds are staggered. The flexible (twist-boat) form is 5.3 kcal higher in energy, mainly as a result of the partial eclipse of four pairs of adjacent C—H bonds (two ethane units).

In cyclohexanone certain flexible forms with only one eclipsed ethane unit are possible (1, 2). The net effect of the carbonyl, then, is to reduce the energy difference between the flexible and the chair forms. Cyclohexane-1,4-dione, with two carbonyl groups, would be expected to have certain flexible forms of even lower energy. The energies (relative to the chair forms) of the flexible forms of cyclohexanone and cyclohexane-1,4-dione have been calculated by Allinger (2). The values calculated for cyclohexanone agree well with experimental data (2–4). The minimum values calculated for cyclohexane-1,4-dione are 1.8 kcal. Assuming reasonable values for the entropy difference between the chair and the flexible form it was concluded that the flexible form should be an important contributor, but that an unreasonably high entropy difference favoring the flexible form would be required for this latter to be the exclusive conformation (2). However, evidence from X-ray crystallography (5), Kerr constant measurement (6), and infrared and Raman spectroscopy (7) all support the exclusive preference for the flexible form.

In an attempt to clarify the conformational situation in cyclohexane-1,4-dione we have synthesized certain bicyclic analogues in which the additional bridge provides some constraint on the conformation of the dione ring. This paper describes the synthesis and some conformational studies of bicyclo[3·2·2]nonan-6,8-dione. This molecule lends itself to dipole moment studies since the two possible twist-boat forms have very different calculated moments. It may also prove useful as a precursor in the preparation of other disubstituted cyclohexanes locked in the twist conformation.

Mass spectra were obtained on several of the compounds prepared. Some evidence for a new fragmentation of diketals will be presented in a separate publication.

## Results and Discussion

### *Synthesis of Bicyclo[3·2·2]nonan-6,8-dione*

We chose alkylation of diethyl succinylsuccinate with 1,3-dibromopropane as entry to the bicyclo[3·2·2]nonane system (Scheme 1). The established procedure (8) for the synthesis of diethyl succinylsuccinate by condensation of two moles of diethyl succinate requires 3 to 4 days of reflux. We found that with sodium hydride in monoglyme the reaction time was shortened to 12 h with improved yield (75%). Heating the disodium salt of diethyl succinylsuccinate with 1,3-dibromopropane gave 50–55% yield of 1,5-dicarbethoxybicyclo[3·2·2]nonane-6,8-dione **2**, a substantial increase from the 30% yield reported by Guha (9). Acid hydrolysis of **2** afforded the corresponding diacid **3**.

When the diacid **3** was heated to a temperature slightly above its melting point (ca. 245°) for a

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[2] Holder of a Province of Ontario Fellowship 1965–1968.

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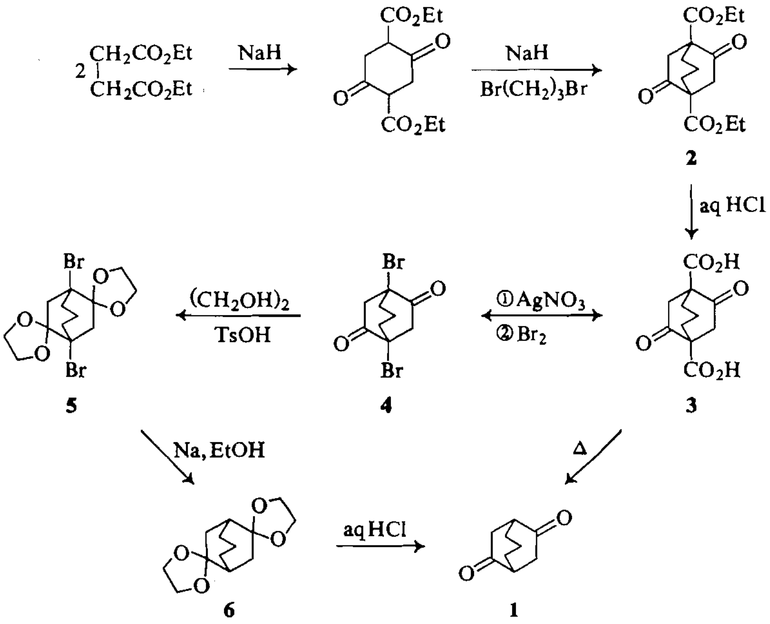
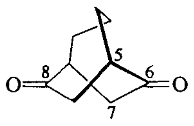


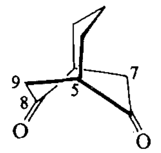
SCHEME 1

few minutes, a ketone was obtained. The same compound was obtained in 60–65% yield by refluxing **3** in triglyme for 3–5 h.[3] It was identified as **1** by the following data. It gives a disemicarbazone and has infrared (i.r.) absorption at 1725 $cm^{-1}$ (C=O). Its nuclear magnetic resonance (n.m.r.) spectrum shows multiplets at 7.20 (2H), 7.37 (4H), and 8.20 (6H), which are assigned to the bridgehead protons, methylene protons *alpha* to carbonyl groups, and the six protons of the trimethylene bridge, respectively. Further proof of structure was accomplished by the synthesis of **1** through another pathway (Scheme 1). The diacid **3** was decarboxylated by the Hunsdiecker reaction to **4**. Conversion of **4** to the diketal **5** and subsequent hydrogenation afforded **6**. Acid hydrolysis of **6** gave a diketone identical to that obtained from thermal decarboxylation.

### *Conformations of Bicyclo[3·2·2]nonan-6,8-dione*



**1***a*



**1***b*

Study of Drieding models suggests that there are two conformations of **1** which are free of angle strain (**1***a* and **1***b*). In both these forms the cyclohexane-1,4-dione ring is in a twisted boat. In one of these the carbonyl carbons lie in the same plane with the two carbons (C-5 and C-7) flanking one of them (**1***a*); in the other, one of the carbonyl carbons (C-8) lies on a plane with three (C-5, C-7, C-9) of the saturated carbons (**1***b*). Between these forms lies a form in which the cyclohexane-1,4-dione ring is in a stretched boat form and the cycloheptanone rings are pure boat and pure chair forms. This form has some angle strain (models) so that it will be populated only if the non-bonded interactions are considerably less than in the twist forms. Our qualitative estimation suggests that the non-bonded interactions are at least as bad in the chair–boat form and therefore we shall neglect this latter form. It should be noted that the trimethylene bridge is capable of a flipping motion, but this does not result in any additional conformations because of the symmetry of the molecule.

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[3] The ease of decarboxylation of 3 is not predicted by the S number formulation of Bredt's Rule. However, Wiseman (10) has proposed that S number is not as important as the ring size of *trans*-olefin formed. Our compound behaves in the manner predicted by this criterion.

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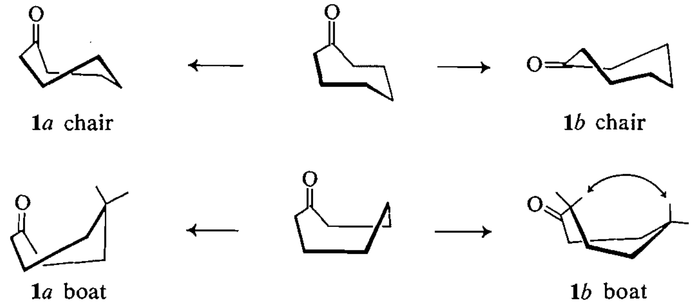

FIG. 1. The chair and boat rings of the cycloheptanone moieties of 1*a* and 1*b*.

Some indication that **1** may exist in solution as a mixture of 1*a* and 1*b* is derived from the i.r. spectra. There are a number of bands between 1100 and 1400 cm$^{-1}$ which are characteristic of ketones. We have compared spectra obtained in the solid phase (KBr pellet) with those obtained in solution ($CCl_4$). In both spectra we find six major bands in this region (1095, 1120, 1210, 1250, 1300, and 1335 cm$^{-1}$), but the relative intensities are very different. The simplest interpretation of these results is that there is only one conformation present in the solid, but a mixture of conformations in solution.

TABLE I

Dipole moments of **1**

| Solvent | μ (D) | Conformation (1*a*:1*b*) | Δ*G*° (1*a*–1*b*) |
|---|---|---|---|
| Benzene | 1.39 | 89:11 | 1.2 kcal |
| Dioxan | 1.81 | 82:18 | 0.9 kcal |

Stronger evidence for the presence of more than one conformation in solution comes from dipole moment studies. We have determined the dipole moment of **1** in benzene and in dioxan solution at 20°. The moment of cyclohexane-1,4-dione was determined to be 1.25 D (benzene) by our method. This value agrees well with Allinger's result of 1.26 D at 18° (2). Our dipole moment results for **1** are presented in Table I. It will be noted that in both solvents the measured moment indicates significant amounts of each conformer[4] and further the proportion of the more polar 1*b* is greater in dioxan.[5] The 1 kcal free energy difference between 1*a* and 1*b* may be the result of an H–H non-bonded interaction in 1*b* (Fig. 1). Attempts to gain conformational evidence from variable temperature n.m.r. studies were unsuccessful. The spectrum of the diketone is constant over the temperature range studied (−99° to +164°).

## Experimental

Mass spectral analyses were performed by Morgan and Schaffer Corporation, Montreal. Dipole moments were calculated according to the method of Moll and Lippert (12) from the dielectric constants determined with a Wissenschaftlich–Technische Werkstätten (Germany) Dipolemeter DM01. Atom polarization was neglected throughout. Preparative gas–liquid chromatography (g.l.c.) columns were all of the same dimensions (8 ft × 0.5 in.) and packed with 10% silicone gum rubber SE-30 or LAC-728, on Diatoport W, 80–100 mesh. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

The structures of all compounds reported are in accord with their infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectra.

### *Diethyl Succinylsuccinate*

Sodium hydride (0.2 mole, 9.6 g of 50% dispersion in mineral oil) was stirred in 80 ml of monoglyme (dried over sodium wire). *t*-Butyl alcohol (0.5 g) was added and the solution was heated at 60° until gas evolution ceased. Ethyl succinate (0.2 mole, 34.9 g) was added dropwise over a period of 0.5 h. After addition was complete, the viscous slurry was stirred and heated at 60–65° for 12 h. Sufficient cold 6 *N* sulfuric acid was added to acidify the solution. The solid material was filtered and washed with petroleum ether and water. Upon recrystallization from ethanol, 37 g (75%) yield of light-yellow solid was obtained, m.p. 125.5–126.5° (lit. (8) m.p. 126–127°).

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[4] Calculated values of dipole moments for 1*a* and 1*b* were obtained by measurements of the carbonyl–carbonyl angle (ten measurements on two different models). The angles obtained (175° and 90°) and the carbonyl group moment (3.00 D) leads to values of 0 D and 4.2 D for 1*a* and 1*b*.

[5] In spite of its low bulk dielectric constant, dioxan behaves as a fairly polar solvent in the presence of polar solutes (11).

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### *1,5-Dicarbethoxybicyclo[3·2·2]nonan-6,8-dione (2)*

Sodium hydride (0.555 mole, 25 g of 53.5% dispersion) and diethyl succinylsuccinate (0.25 mole, 64 g) were added alternately in small portions to 500 ml of dry monoglyme. After all the reagents had been added, the slurry was heated at 100–110° for 3 h. Monoglyme was removed *in vacuo* and 710 ml of 1,3-dibromopropane (freshly distilled) and 90 ml of monoglyme were added. Heating was continued for 22 h. The mixture was filtered and the filtrate was steam distilled. The residue was allowed to cool with occasional shaking and crystallized from ethanol. The product was washed with 1% sodium hydroxide solution until the washing was no longer yellow. Subsequent washing with water, cold ethanol and petroleum ether, and recrystallization from ethanol gave 38.5 g (52%) of **2**, m.p. 130–132.5° (lit. (9) m.p. 132°).

### *1,5-Dicarboxybicyclo[3·2·2]nonan-6,8-dione (3)*

The diester **2** was hydrolyzed by refluxing with 6 *N* hydrochloric acid for 8 h. Two recrystallizations from water gave an analytical sample, m.p. (decomp.) 245–247° (lit. (9) m.p. 238°).

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.88; H, 5.08.

### *1,5-Dibromobicyclo[3·2·2]nonan-6,8-dione (4)*

A solution of the diacid **3** (5 mmoles, 1.2 g) in 20 ml of warm water was titrated to the end-point of phenolphthalein with 0.5 *N* sodium hydroxide, and treated with 20% silver nitrate solution. The precipitate was filtered and repeatedly washed with water, methanol, and ether. After drying in a vacuum desiccator for 24 h, the disilver salt was mixed with 35 ml of carbon tetrachloride (dried over $P_2O_5$). Bromine (0.011 mole, 1.76 g, distilled from $P_2O_5$) was added dropwise with vigorous stirring. The solution was slowly heated to boiling and refluxed for 8 h in the dark. The mixture was filtered and the filtrate distilled to give a residue which upon crystallization from a methanol–chloroform mixture gave 270 mg of **4**, m.p. 181–184°, 19% yield. An analytical sample was obtained by recrystallization from a chloroform – carbon tetrachloride mixture, m.p. 184.5–185.5°.

Anal. Calcd. for $C_9H_{10}O_2Br_2$: C, 34.88; H, 3.25; Br, 51.59. Found: C, 34.88; H, 3.45; Br, 51.61.

### *Diketal of 1,5-Dibromobicyclo[3·2·2]nonan-6,8-dione (5)*

The diketal **5** was prepared by refluxing **4** (3.6 g, 11.6 mmoles) with 0.5 g of *p*-toluenesulfonic acid and 5 ml of ethylene glycol in 20 ml of benzene for 4 days. The benzene solution was washed with 5% sodium hydroxide and water. After removal of the solvent, the residue was crystallized from a hexane–ethanol mixture to give 3.47 g (75%) of **5**, m.p. 127–130°. Two more recrystallizations gave an analytical sample, m.p. 128.5–130°.

Anal. Calcd. for $C_{13}H_{18}O_4Br_2$: C, 39.22; H, 4.56; Br, 40.15. Found: C, 39.43; H, 4.54; Br, 39.96.

### *Diketal of Bicyclo[3·2·2]nonan-6,8-dione (6)*

Sodium (6.8 g) was added in small pieces over a period of 2 h to a well-stirred solution of **5** (3.27 g, 8.2 mmoles) in 110 ml of absolute ethanol. Precipitation of sodium bromide was observed when about one-quarter of the sodium had been added. The solution was cooled and poured into 600 ml of water and was extracted with five 100-ml portions of 1:1 mixture of petroleum ether and ether. The solvents were removed after drying to give a yellow oil which solidified on standing. Preparative g.l.c. (silicone gum rubber) gave **6** in 53% yield, m.p. 63–64.2°.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.17; H, 8.31.

### *Hydrolysis of* **6**

The diketal **6** (430 mg, 1.8 mmoles) and 6 ml of 1.2 *N* hydrochloric acid was refluxed for 7 h. The solution was poured onto 15 g of ice and extracted with methylene chloride. After washing with a 10% sodium bicarbonate solution and drying, the solvent was evaporated to give 290 mg (79%) of bicyclo[3·2·2]nonan-6,8-dione, **1**. The crude product was purified by sublimation (85°/5 mm) to give 215 mg of pure material, m.p. (sealed tube) 218–223°. This sample was shown to be pure by g.l.c. and thin-layer chromatography (t.l.c.) (silica gel). Multiple recrystallizations from various solvents and sublimations did not narrow its broad melting range.[6]

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.10; H, 7.95. Found: C, 70.85; H, 7.86.

The disemicarbazone of **1** melts at 277.5–279°.

Anal. Calcd. for $C_{11}H_{18}O_2N_6$: C, 49.61; H, 6.81; N, 31.56. Found: C, 49.66; H, 7.00; N, 31.86.

### *Decarboxylation of 1,5-Dicarboxybicyclo[3·2·2]nonan-6,8-dione*

(*a*) The diacid **3** (0.5 g) was placed in a sublimator which was quickly heated to 240–245° in an oil bath. The solid melted with evolution of gas and a light-yellow solid began to collect on the cold-finger. Reaction was complete after 15 min. Recrystallization from ether afforded 61 mg of impure **1**, m.p. (sealed tube) 194–212°. Purification was achieved by conversion of **1** to its diketal, **6**. A sample obtained this way is identical in every respect (i.r., n.m.r., g.l.c., and m.p.) to that obtained previously.

(*b*) A solution of **3** (24 g, 0.1 mole) and 300 ml of triglyme was refluxed for 5 h (temperature of the solution was 210–218°). Evolution of carbon dioxide was followed by the weight increase of the Ascarite tube. The reaction became very slow after 3 h of heating. At the end of 5 h, the weight of carbon dioxide generated indicated a conversion of 80% of diacid to **1**, while g.l.c. showed 81.5% yield. The triglyme solution was poured into 2.5 l of benzene and extracted with five 1-l portions of water. Benzene was removed after drying to give a heavy oil which upon treatment with pentane gave a crystalline solid and a gummy material. The solid was dissolved in methanol and filtered to remove the gummy material. Evaporation of methanol and recrystallization from a hexane–benzene mixture afforded 16.1 g of **1**. One sublimation gave 13.9 g (62%) of pure material.

## Acknowledgments

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[6] Similar melting behavior was observed in tricyclo-[4·4·0·0$^{4,9}$] decan-3-one (13).

chase of a nuclear magnetic resonance spectrometer. We also thank Mr. David Hill for determining the infrared spectra and Mr. Maurice Miskow for assistance in measuring the dipole moments.

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