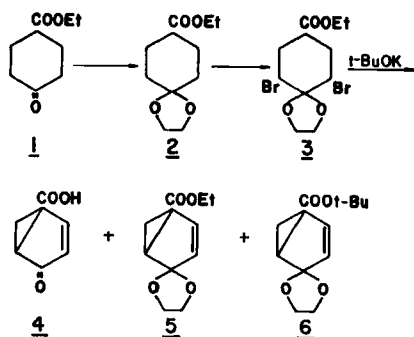


Novel Preparation of Bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylic Acid and Related Compounds

By EDWARD E. SMISSMAN, THOMAS L. LEMKE, and MARY WEIR CREESE

An attempt to dehydrohalogenate 4-carbethoxy-2,6-dibromocyclohexanone ethylene ketal afforded bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylic acid, ethyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate ethylene ketal, and *t*-butyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate ethylene ketal. Under milder conditions it was possible to secure 3-bromo-bicyclo[3.1.0]hexane-4-one-1-carboxylic acid ethylene ketal.

AN ATTEMPT was made to dehydrobrominate 4-carbethoxy-2,6-dibromocyclohexanone ethylene ketal (3) in order to prepare ethyl cyclohexa-2,4-dienone-4-carboxylate as a starting material in a synthesis of prephenic acid. Collidine proved unsuccessful in this dehydrohalogenation reaction and therefore potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) was utilized (1) (Scheme I).

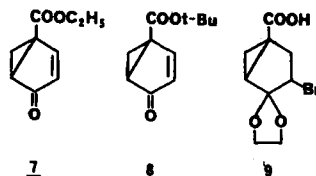


Scheme I

The dibromide, 3, was prepared by first converting 4-carbethoxycyclohexanone (1) to the ethylene ketal 2, which was then brominated by the procedure of Garbisch (1). The dibromide, 3, appeared to be the *cis* diequatorial dibromide since the NMR spectrum showed a singlet for the methylene protons of the ketal, suggesting that they were located in a symmetrical environment. This would not be the situation if the halogens were *trans*. This assignment is consistent with the findings of Garbisch. A second component was isolated in 8% yield and proved to be 4-carbethoxy-*trans*-2,6-dibromocyclohexanone

ethylene ketal. This material exhibited a multiplet for the methylene protons of the ketal, indicating that the methylenes are no longer in a symmetrical environment. A monobromide was isolated in 15% yield.

The 4-carbethoxy-*cis*-2,6-dibromocyclohexanone ethylene ketal (3) was dissolved in DMSO and added to a suspension of potassium *tert*-butoxide in DMSO. Acidic and neutral frac-



tions were recovered from the reaction mixture. The acidic material, a low melting solid, proved to be bicyclo [3.1.0]hex-2-ene-4-one-1-carboxylic acid (4). The neutral fraction contained two compounds which were identified as ethyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate ethylene ketal (5) and *t*-butyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate ethylene ketal (6).

DISCUSSION

Assignment of these structures was based on spectral evidence obtained from the acid, 4, the ketones, 7 and 8, which were prepared either by chromatography of the ketals on silica gel or by treatment with hydrochloric acid, and from the ketals, 5 and 6. The NMR spectrum of ethyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate (7) exhibited a doublet at 7.80 δ ($J = 6.0$ c.p.s.) and a slightly split doublet at 5.60 δ ($J = 5.5$ and 0.5 c.p.s.), both of which integrated for single protons. These absorptions are similar to those found by Dutler and co-workers (2) for the α and β protons of the steroid systems 10 (partial structure), in which case the α proton appeared at 5.82 δ as a doublet of doublets with $J = 5.5$ and 0.5-1.0 c.p.s., while the β proton was found as a doublet at 7.20 δ with $J = 5.5$ c.p.s. The methylene of the ester 7 was found at 4.20 and the methyl at 1.28 δ . The tertiary proton on the cyclopropane ring was found as a doublet of doublets at 2.58 δ with $J = 5$

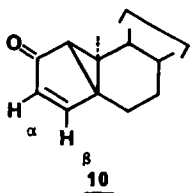
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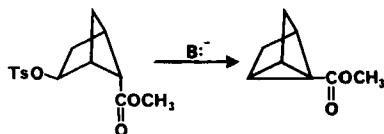
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and 8 c.p.s., while the methylene protons on the cyclopropane ring appeared as multiplets centered



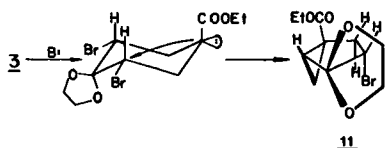
at 2.15 and 1.82 δ . A similar system has recently been reported by Meinwald (Scheme II) (3). A



Scheme II

more detailed analysis of the NMR spectra of these systems is the subject of a subsequent paper (4).

Formation of these bicyclic compounds, 4-6, probably occurs by base abstraction of the proton α to the carboxy group followed by internal nucleophilic displacement of the halogen as shown in Scheme III. A facile dehydrobromination may



Scheme III

occur in intermediate 11 due to the nearly axial conformation of the bromine. Since an excess of potassium *t*-butoxide was present, a considerable amount of ester exchange occurred leading to 6. In addition, it appears that some water was present in either the DMSO or *tert*-butanol causing ester hydrolysis. Under milder conditions it was possible to obtain the bicyclobromo acid, 9.

EXPERIMENTAL¹

4-Carboethoxycyclohexanone (1)—This material was prepared by two different methods. *Method A*—A mixture of 12.5 g. (0.149 mole) of 2-methoxybutadiene, 11.2 g. (0.112 mole) of ethyl acrylate, and 70 ml. of benzene was placed in an autoclave and heated to 160°. A total time of 1.5 hr. was required to reach this temperature which was maintained for 0.5 hr. The system was then cooled to 25°. Removal of the solvent resulted in recovery of 16.5 g. (80%) of 1-carboethoxy-4-methoxy-3-

cyclohexene; IR: 5.78 (*s*) and 6.0 μ (*m*); NMR: 4.50 (1 H, multiplet), 4.07 (2 H, quartet, $J = 7$ c.p.s.), 3.41 (3 H singlet), 2.00 (7 H, multiplet), and 1.22 (3 H, triplet, $J = 7$ c.p.s.). Upon treatment with 2,4-dinitrophenylhydrazine a solid formed, which after recrystallization from EtOH had m.p. 115–118°.

To 15 ml. of 1% H₂SO₄ was added 1.70 g. (0.0092 mole) of the enol ether obtained above. The mixture was shaken for 5 min. and then thoroughly extracted with ether. The combined ether layers were dried (MgSO₄). Removal of the solvent left a residue of 1.22 g. (84%) of 4-carboethoxycyclohexanone; IR: 5.80 (*s*); NMR: 4.16 (2 H, quartet, $J = 7.0$ c.p.s.), 2.71 (1 H, multiplet); 2.20 (8 H, multiplet), 1.28 (3 H, triplet, $J = 7.0$ c.p.s.). Reaction with 2,4-dinitrophenylhydrazine gave a solid which after recrystallization from 95% ethanol melted at 119–120° [lit. (5, 6) m.p. 125–126°].

Method B—Ethyl *p*-hydroxybenzoate (30 g., 0.18 mole) in 75 ml. of 95% EtOH was hydrogenated in the presence of 3 g. of rhodium-on-alumina catalyst (5%) in a Parr apparatus. The solvent was removed and the remaining oil was distilled under reduced pressure. The product, b.p. 80°/0.1 mm., was obtained in 75% yield. The resulting alcohol, 4-carboethoxycyclohexanol (37 g., 0.22 mole), was dissolved in 200 ml. of acetone and was treated with 27 ml. of Jones reagent. The temperature was maintained at 30–35° throughout the addition. An 89% yield of the desired product was obtained.

4-Carboethoxycyclohexanone Ethylene Ketal (2)—To a solution of 1.61 g. (0.0094 mole) of 4-carboethoxycyclohexanone (1), 0.73 g. (0.012 mole) of ethylene glycol and 30 ml. of dry benzene was added 53 mg. of *p*-toluenesulfonic acid. The solution was heated under reflux for 4.5 hr., the evolved water being collected in a Dean-Stark trap. The solvent was distilled and the oil, which remained, was taken up in ether and washed with 10 ml. of 10% NaOH. The ether solution was dried (MgSO₄). Removal of the solvent left a residue of 1.80 g. (89%) of ethylene ketal, b.p. 85°/0.6 mm.; IR: 5.80 (*s*), 8.25 (*s*), 8.50 (*s*) μ ; NMR: 1.22 (3 H, triplet, $J = 7.0$ c.p.s.), 1.40 to 2.50 (9 H, broad band), 3.87 (4 H, singlet), and 4.10 (2 H, quartet, $J = 7.0$ c.p.s.). A sample was treated with 2,4-dinitrophenylhydrazine, and in a short time a precipitate resulted. After recrystallization from 95% ethanol the solid melted at 119–121°. The mixed melting point with the phenylhydrazone of 4-carboethoxycyclohexanone showed no depression.

4-Carboethoxy-2,6-cis-dibromocyclohexanone Ethylene Ketal (3)—To a solution of 4.76 g. (0.022 mole) of 4-carboethoxycyclohexanone ethylene ketal (2) in 50 ml. of diethyl ether was added 7.20 g. (0.045 mole) of Br₂, while stirring. The addition was at such a rate as to cause gentle reflux. Near the end of addition of the bromine a two-phase system developed. A solution containing 1.11 g. (0.048 g. atoms) of sodium in 20 ml. of ethylene glycol was added. Water was added to the reaction mixture and the ether layer was removed. The aqueous layer was extracted with ether and the combined ether layers were dried (MgSO₄). Removal of the solvent left a residue of 7.00 g. (85%) of a mixture of products. A portion of the oil,

¹ Melting points were obtained on a Thomas-Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR-5, IR-8, and IR-10 spectrophotometers, and the ultraviolet data were recorded on a Cary-14 spectrophotometer. NMR data were obtained from a Varian Associates model A-60 spectrometer utilizing CCl₄ as a solvent, unless otherwise stated, with tetramethylsilane as an internal standard, and reported in p.p.m. as δ values. Elemental analyses were performed by Hoffman Micro-analytical Laboratories, Wheatridge, Colo., and by Drs. G. Weiler and F. B. Strauss, Oxford, England.

2.14 g., was chromatographed on 50 g. of silica gel (Brinkmann) using benzene as the eluting solvent. The first few fractions, 783 mg., contained the desired dibromide, 3. The compound was further purified by rechromatographing on silica gel (Brinkmann); IR: 5.78 (s) μ ; NMR: 1.32 (3 H, triplet, $J = 7.5$ c.p.s.) 2.2 to 2.9 (5 H, multiplet), 4.35 (4 H, singlet), 4.25 (4 H, multiplet).

Anal.—Calcd. for $C_{11}H_{16}Br_2O_4$: C, 35.51; H, 4.34. Found: C, 35.59; H, 4.22.

The next oil removed from the column, 460 mg., was 4-carbethoxy-2-bromocyclohexanone ethylene ketal; IR: 5.78 (s) μ ; NMR: 1.27 (3 H, triplet, $J = 7.5$ c.p.s.), 1.5 to 2.9 (7 H, broad multiplet), 4.15 (2 H, quartet, $J = 7.5$ c.p.s.), 4.08 (5 H, multiplets).

Anal.—Calcd. for $C_{11}H_{17}BrO_4$: C, 45.06; H, 4.84. Found: C, 45.07; H, 5.62.

In a later experiment another oil was isolated during chromatography of the reaction mixture on a silica gel (Brinkmann) column. This material was eluted from the column after the *cis*-dibromide and before the monobromide. It appeared to be 4-carbethoxy-*trans*-2,6-dibromocyclohexanone ethylene ketal; IR: 5.79 (s) μ ; NMR: 1.25 (3 H, triplet, $J = 7.0$ c.p.s.), 2.0-3.1 (5 H, broad multiplet), 4.11 (7 H, multiplet), 4.68 (1 H, doublet of doublets, $J = 5.0$ and 12.0 c.p.s.); n_D^{25} 1.5221.

Dehydrobromination of 4-Carbethoxy-2,6-*cis*-dibromocyclohexanone Ethylene Ketal—To a suspension of potassium *tert*-butoxide (prepared by addition of 2.03 g., 0.052 g. atom, of potassium to an excess of dry *tert*-butanol followed by removal of most of the excess alcohol) in 40 ml. of DMSO was added 4.08 g. (0.011 mole) of 4-carbethoxy-*cis*-2,6-dibromocyclohexanone ethylene ketal (3) in 10 ml. of DMSO. The reaction mixture was cooled during the addition. After the addition was complete the mixture was stirred at 25° for 3 hr. To the reaction mixture was added 1.80 g. (0.03 mole) of acetic acid in 25 ml. of H₂O. The reaction was made alkaline with NaHCO₃ and extracted with ether. The ether extract was dried (MgSO₄) (ether extract I). The aqueous layer was acidified with 10% HCl and then extracted with ether. The ether extract was dried (MgSO₄) (ether extract II).

Removal of the solvent from ether extract II resulted in recovery of a thick oil, 437 mg., which solidified on standing. The material was bicyclo-[3.1.0]hex-2-ene-4-one-1-carboxylic acid (4); IR (CHCl₃): 1700 to 1745 (s), 1580 (w) cm.⁻¹; near IR (CHCl₃): 1626 (s), 2217 (m) μ m; NMR (CDCl₃): 7.89 (1 H, doublet, $J = 6.0$ c.p.s.), 5.77 (1 H, broad doublet, $J = 5.5$ c.p.s.), 11.10 (1 H, singlet), 2.90 (1 H, doublet of doublets, $J = 5.0$ and 9.0 c.p.s.), 1.8 to 2.4 (2 H, multiplets); λ_{max}^{EtOH} 205 and 249 μ m.

Treatment of 4 with 2,4-dinitrophenylhydrazine resulted in recovery of a dark-red phenylhydrazone which was recrystallized from 95% EtOH, m.p. 202° dec.

Anal.—Calcd. for $C_{13}H_{10}N_4O_6$: C, 49.06; H, 3.18; N, 17.61. Found: C, 49.35; H, 3.32; N, 17.55.

Removal of the solvent from ether extract I resulted in recovery of 2.20 g. of an oil which contained acetic acid, DMSO, and two unknowns as shown by GLC. An NMR spectrum of the crude reaction mixture showed the presence of vinyl and

alkoxy protons suggesting that the mixture contained 5 and 6.

A second sample of the crude oil was chromatographed on silica gel (Brinkmann) using CHCl₃ as the eluting solvent. The first few fractions contained a mixture of products. Later fractions contained two oils which were different from those placed on the column. These two oils possessed similar infrared spectra. One of the oils was identified as ethyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate (7) by its IR and NMR spectra; infrared: 1720 (s), 1580 (s) cm.⁻¹; NMR: 7.80 (1 H, doublet, $J = 6.0$ c.p.s.), 5.60 (1 H, broad doublet, $J = 5.5$ and 0.5 c.p.s.), 4.20 (2 H, quartet, $J = 7.0$ c.p.s.), 1.47 to 2.73 (3 H, multiplets), 1.28 (3 H, triplet, $J = 6.5$ c.p.s.); λ_{max}^{EtOH} 199 and 250 μ m. It would appear that the ketal group was removed on the column. To verify this a sample of starting oil was shaken with 10% HCl. The aqueous layer was extracted with ether. GLC analysis showed that the material had undergone conversion to the same mixture as was formed during chromatography. The second unknown was identified as *tert*-butyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate (8); the NMR was essentially the same as that of 7 with the exception of a singlet at 1.46 and the loss of peaks at 4.20 and 1.28; near IR (CHCl₃): 1628 and 2219 μ m with peak height ratio of 4.16 (2219:1628).

Another sample of the crude oil, 652 mg., was heated under reflux for 2 hr. with 25 ml. of 10% NaOH. After cooling the aqueous layer was extracted with ether and the ether was discarded. The aqueous phase was acidified with 10% HCl and extracted with ether. The combined ether extracts were dried (MgSO₄). Removal of the solvent resulted in recovery of 200 mg. of a thick oil which solidified on standing and which by spectral data was shown to be the carboxylic acid (4).

A final sample was treated with ozone in methylene chloride. The methylene chloride was then replaced by H₂O and hydrogen peroxide, and the mixture was digested on a steam bath. Removal of the solvent left a thick oil which was taken up in ether and dried. After filtration, diazomethane was added and the resulting ester was examined; NMR (CDCl₃): 3.80 (6 H, singlet), 3.73 (3 H, singlet), 1.0 to 2.0 (broad bands); near IR (CHCl₃): 1622 (w), 2209 (m) μ m, indicating this material to be methyl 1,1,2-cyclopropane tricarboxylate.

When the above reaction was performed in a similar manner but the stirring was discontinued after 1 hr., a product containing bromine was obtained. On work-up the acidic material recovered was recrystallized from CHCl₃, m.p. 141.5-142.5°.

Anal.—Calcd. for $C_9H_{11}BrO_4$: C, 41.06; H, 4.18. Found: C, 40.99; H, 4.28.*

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* A detailed discussion of the structure proof of this compound (9) by NMR is to be found in Reference 4.



Bicyclo [3.1.0]hex-2-ene-4-one-1-carboxylic acid, related compounds—syntheses
Column chromatography—separation

GLC—analysis
NMR spectroscopy—structure
IR spectrophotometry—structure

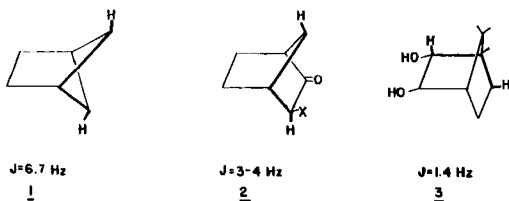
Long-Range Spin-Spin Coupling in Bicyclo[3.1.0]hexane Systems

By ROGER C. BRIDEN, EDWARD E. SMISSMAN*, and MARY WEIR CREESE

The NMR parameters of 3-bromo-bicyclo[3.1.0]hexan-4-one-1-carboxylic acid ethylene ketal and ethyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate have been recorded and the chemical shifts of all protons assigned. Both of these compounds show interesting cases of long-range spin-spin coupling.

LONG-RANGE ^1H - ^1H spin-spin coupling in general (1, 2), and coupling through $4-\sigma$ bonds in particular (3-6), are receiving increasing attention. Two features are apparent in compounds exhibiting $4-\sigma$ bond coupling: first, the compounds have well-defined stereochemistry resulting from the rigidity of the molecule due to a fixed or preferred conformation; second, the $\text{H}-\text{C}-\text{C}-\text{C}-\text{H}$ skeleton through which the protons are coupled exists in a configuration.

The magnitudes of the coupling constants reported for $4-\sigma$ bond coupling range from less than 1 to about 7 c.p.s., with values of 1-2 c.p.s. being most common. Some examples of compounds in which long-range $4-\sigma$ bond coupling has been observed are shown by 1, 2, and 3 (4-6).



The authors have observed long-range $4-\sigma$ bond

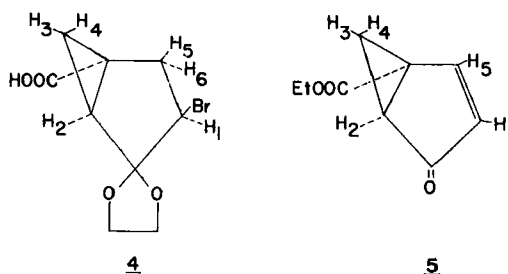
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* To whom inquiries concerning this paper should be addressed.

coupling in 3-bromo-bicyclo[3.1.0]hexan-4-one-1-carboxylic acid ethylene ketal (4) and in ethyl bicyclo[3.1.0]hex-2-ene-4-one-1-carboxylate (5).



The 100-Mc.p.s. spectrum of 4 is shown in Fig. 1. The coupling constants and chemical shift values determined from this spectrum are listed in Table I.

RESULTS AND DISCUSSION

The ethylene ketal resonance is assigned to the 3.88- δ absorption on the basis of its four-proton

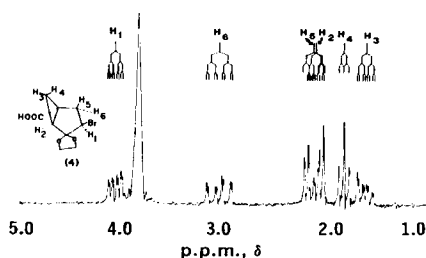


Fig. 1—100-Mc.p.s. spectrum of 4.