# The Preparation of 4-Substituted Bicyclo[2.2.2]oct-2-ene-1-carboxylic Acids[1]

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*Received June 28, 1967*

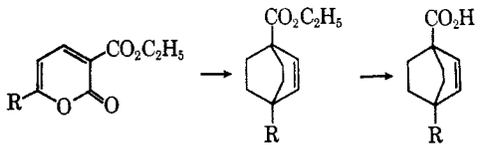
Several 4-substituted bicyclo[2.2.2]oct-2-ene-1-carboxylic acids have been prepared and characterized. The 4-methyl and 4-phenyl derivatives, as well as the unsubstituted acid, were prepared by the addition of ethylene to the corresponding 3,6-disubstituted 2-pyrones. The 4-chloro derivative was formed by the addition of ethylene to ethyl 4-chlorocyclohexa-1,3-diene-1-carboxylate. A detailed procedure for the preparation of 1,4-dicarbomethoxycyclohexa-1,3-diene is reported. The addition of ethylene to this compound[2] provided the 1,4 diester which was converted to several other derivatives including the 4-cyano-, 4-trifluoromethyl-, and 4-trimethylammonium compounds.

Many useful methods have been reported for the preparation of substituted derivatives of bicyclo[2.2.2]-octane.[2,3] Several of these methods were exploited for the syntheses of 4-substituted bicyclo[2.2.2]oct-2-ene-1-carboxylic acids.[4] The general synthetic approach used in this work centered on the intermediacy of an appropriately substituted 1,3-cyclohexadiene.

One route, Scheme I, involved the preparation of 2-pyrone-3-carboxylic acid derivatives[5,6] and their conversion to bicyclic compounds *via* an ethylene addition reaction.[7]

This approach proved successful for the preparation of bicyclo[2.2.2]oct-2-ene-1-carboxylic acid (**3**) and its 4-methyl (**6**) and 4-phenyl (**9**) derivatives. Acid **3** was also prepared from 2-pyrone-6-carboxylic acid[8] and from 1-carboethoxycyclohexa-1,3-diene by the Grob approach.[9] The products obtained by these

SCHEME I



**1**, R = H; **4**, R = $CH_3$; **7**, R = $C_6H_5$ — **2**, R = H; **5**, R = $CH_3$; **8**, R = $C_6H_5$ — **3**, R = H; **6**, R = $CH_3$; **9**, R = $C_6H_5$

(1) Chemistry of the Bicyclo[2.2.2]octanes. Part VI. This research was supported by Grant GP 4398 from the National Science Foundation.

(2) A succinct review of the work in this area is presented by J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, **30**, 1431 (1965). Morita and his associates have developed another important method in subsequent work.[3]

(3) Z. Suzuki and K. Morita, *ibid.*, **32**, 31 (1967), and previous papers in the series; J. Kopecký and J. Smejkal, *Tetrahedron Letters*, 1931 (1967).

(4) These acids were desired to assay the influence of unconjugated unsaturation on the efficiency of propagation of the polar effect: F. W. Baker, R. C. Parish, and L. M. Stock, *J. Am. Chem. Soc.*, **89**, 5677 (1967).

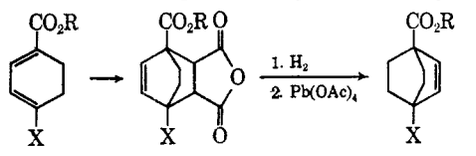
(5) N. K. Kochetkov and L. I. Kudriashov, *Zh. Obshch. Khim.*, **27**, 248 (1957). N. K. Kochetkov and L. I. Kudriashov, *J. Gen. Chem. USSR*, **28**, 1562 (1958).

(6) T. B. Windholz, L. H. Peterson, and G. J. Kent, *J. Org. Chem.*, **28**, 1443 (1963).

(7) A pertinent example is the addition of ethylene to 3,4,5,6-tetrachloro-2-pyrone to yield 1,2,3,4-tetrachlorobicyclo[2.2.2]oct-2-ene: E. Leon, Canadian Patent 623,289 (1961); J. C. Kauer, French Patent 1,345,138 (1963). J. C. Kauer (Netherlands Patent Appl. 6,507,979 (1966)) has also used the method described here to prepare 1-carboxy-4-alkylbicyclo[2.2.2]-oct-2-enes.

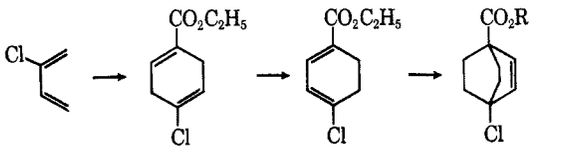
(8) R. H. Wiley and A. J. Hart, *J. Am. Chem. Soc.*, **76**, 1942 (1954).

(9) C. A. Grob, M. Ohta, E. Renk, and A. Weiss (*Helv. Chim. Acta*, **41**, 1191 (1958)) used the following reaction sequence for the synthesis of 1-



carbomethoxybicyclo[2.2.2]oct-2-ene (X = H; R = $CH_3$). The method is generally useful.

SCHEME II



**10** — **11** — **12**, R = $C_2H_5$; **13**, R = H

three methods were identical. Attempts to extend the attractive pyrone approach for the preparation of other compounds, *e.g.*, 4-bromobicyclo[2.2.2]oct-2-ene-1-carboxylic acid, were frustrated by difficulties in the synthesis of appropriately substituted pyrones (see Experimental Section).

In a second approach (Scheme II), 4-chlorobicyclo-[2.2.2]oct-2-ene-1-carboxylic acid (**13**) was prepared from chloroprene *via* the conjugated diene (**11**). The addition of ethyl propiolate to chloroprene provided a mixture of 85% **10** and 15% **11**. The mixture was treated with sodium ethoxide to yield an equilibrium mixture of dienes containing about 85% **11**. The addition of ethylene at high pressure[10] (about 1000 atm) provided **12** which was hydrolyzed to **13**. Small amounts of substituted ethyl benzoates are formed under the conditions of the addition reaction. However, these contaminants may be conveniently removed from the bicyclic compounds by chromatography on charcoal. The chloro acid was also prepared by the Grob procedure.[9]

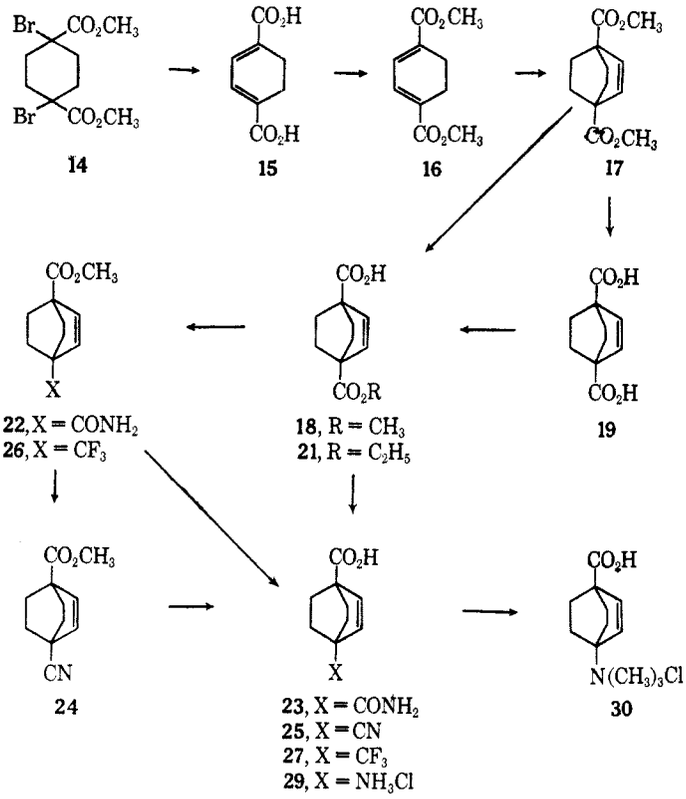
Roberts and his associates converted ethyl 4-bromobicyclo-[2.2.2]octane-1-carboxylate into 4-hydroxybicyclo[2.2.2]octane-1-carboxylic acid in aqueous base.[11] Unfortunately, neither **12** nor the sodium salt of **13** could be hydrolyzed to 4-hydroxybicyclo-[2.2.2]oct-2-ene-1-carboxylic acid under much more severe conditions. Presumably, the greater restraint imposed on the bridgehead carbon atom by the incorporation of a double bond in the octane nucleus is primarily responsible for the failure of the reaction.

1,4-Dicarbomethoxycyclohexa-1,3-diene (**16**) provided the third entry into the bicyclo[2.2.2]oct-2-ene series. Kauer and his associates have reported a method for the preparation of this ester.[2] An alternate, somewhat more convenient method is presented in the Experimental Section. The addition of ethylene at high pressure provided the bicyclic diester (**17**).[2,10] Many desired derivatives were prepared from this intermediate as outlined in Scheme III. Diester **17**

(10) We are indebted to Dr. Kauer for advising us of the utility of the high-pressure addition reaction prior to publication.[2]

(11) J. D. Roberts, W. T. Moreland, and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953).

SCHEME III




was selectively hydrolyzed to the half-ester (**18**). This compound was readily converted into the amide (**22**), the trifluoromethyl derivative (**26**), and the amino acid (**29**). Amide **23** was converted to the 4-cyano derivative (**25**) and amino acid **29** was methylated to yield the trimethylammonium compound (**30**). The conversions were accomplished by conventional procedures that had proved useful in prior syntheses of bicyclo[2.2.2]octane derivatives.[11-13]

## Experimental Section[14-16]

Nmr spectra are given in Tables I and II.

**Ethyl Bicyclo[2.2.2]oct-2-ene-1-carboxylate** (**2**).—Compound **1**, ethyl 2-pyrone-3-carboxylate[6] (3 g, 0.018 mole), benzene (100 ml), and ethylene[17] were heated at 120° for 2 days. Benzene was removed *in vacuo*. The residue was chromatographed on neutral alumina (eluent, benzene) to provide **2** (1.8 g, 0.010 mole, bp 95–97° at 10 mm, lit.[9] bp 95–96° at 10 mm) identical with the material prepared by the Grob procedure.[9,18]

**Bicyclo[2.2.2]oct-2-ene-1-carboxylic Acid** (**3**).—Ester **2** (2 g, 0.020 mole), potassium hydroxide (1.1 g), and ethanol (90%, 10 ml) were refluxed for 10 hr. The solution was concentrated, extracted with three 10-ml portions ether, and acidified with hydrochloric acid (12 *M*). The product was dried *in vacuo* and sublimed[19] to yield **3** (1.3 g, 0.09 mole, mp 120–121°; nmr, Table II).

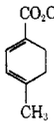
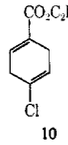
Acid **3** was also prepared in 46% yield by the reaction of ethylene[17] with 2-pyrone-6-carboxylic acid[8] in pyridine for 2 days at 120°. The product was isolated by the procedure used for dibenzobicyclo[2.2.2]octa-2,5-diene-1-carboxylic acid.[4]

*Anal.* Calcd for $C_9H_{12}O_2$: C, 71.00; H, 7.95. Found: C, 71.07; H, 8.18.

**Ethyl 4-Methylbicyclo[2.2.2]oct-2-ene-1-carboxylate** (**5**).—Ethyl 6-methyl-2-pyrone-3-carboxylate (**4**) (mp 85–86°, lit.[5] mp 86°) was prepared from 1-chlorobuten-3-one[20] and the magnesium salt of ethyl malonate followed by acetyl chloride catalyzed cyclization.[5] Pyrone **4** (10 g, 0.055 mole), benzene (100 ml), and ethylene[17] were heated at 165° for 4 days. The solution was fractionated to yield a mixture of **5** and ethyl 4-methylcyclohexa-1,3-diene-1-carboxylate ($\nu_{CO}^{CCl_4}$ 1733 cm$^{-1}$; nmr, Table I). Ester

TABLE I

NMR SPECTRA OF SUBSTITUTED CYCLOHEXADIENES

| Compound | Observations (δ) and assignments[a,b] Vinyl | Allyl | -C2H5 | 4-X |
|---|---|---|---|---|
|  | 6.85 bd[c]<br>5.75 m | 1.8–2.7 m | 1.25 tr<br>4.15 qt | 1.8 bs[c] |
|  10 | 6.85 m<br>5.86 m | 3.05 m | 1.25 tr<br>4.15 qt | ... |
|  11 | 6.5 qt<br>$J$ = 6.5<br>$\Delta\nu$ 44[d] | 2.60 m | 1.25 tr<br>4.15 qt | ... |

[a] In carbon tetrachloride solution. [b] In ppm from tetramethylsilane. [c] Broadened doublet and broadened singlet (width at half-height is 3 cps at 60 Mc). [d] $\Delta\nu$ $(Q^2 - J^2)^{1/2}$: K. B. Wiberg and B. J. Nist, "Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962.

(12) H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.*, **86**, 5183 (1964).

(13) C. F. Wilcox and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965).

(14) Melting points and boiling points are uncorrected except as noted. Beckman IR-7,[15] Cary Model 14, and Varian A-60[16] spectrometers were used to record the spectroscopic properties. Microanalyses were performed by Mr. William Saschek and Microtech Laboratories, Skokie, Ill.

(15) Grants from the National Science Foundation enabled the acquisition of these instruments.

(16) Detailed procedures for all preparations are presented in the dissertation by Dr. F. W. Baker, University of Chicago Library, 1966.

(17) Ethylene was used at cylinder pressure, about 1000 psi at 25° and about 3000 psi at the reaction temperature. Hydroquinone or *t*-butylcatechol (0.5 g) was added to the reaction mixture.

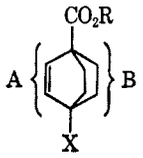
(18) H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.*, **87**, 2404 (1965).

(19) The octene acids sublime at about 100° at 0.1–1.0 mm.

(20) F. Asinger, L. Schröder, and S. Hoffmann, *Ann.*, **648**, 83 (1961).

TABLE II

NMR SPECTRA OF SUBSTITUTED BICYCLO[2.2.2]OCT-2-ENES




| Compd | X | R | Observations (δ) and assignments[a,b] A, δ | A, J[c] | A, Δν[d] | B, δ | R, δ | X, δ |
|---|---|---|---|---|---|---|---|---|
| 3 | H | H | 6.3 m | | | 1.1–2.1 m | | 2.57 m |
| 5 | $CH_3$ | $C_2H_5$ | 6.2 qt | 8.5 | 25 | 1.0–2.05 m | 1.25 tr<br>4.15 qt | 1.15 s |
| 12 | Cl | $C_2H_5$ | 6.3 qt | 9 | 6 | 1.30–2.20 m | 1.25 tr<br>4.15 qt | |
| 17 | $CO_2CH_3$ | $CH_3$ | 6.4 s | | | 1.25–2.10 m | 3.7 s | 3.7 s |
| 18 | $CO_2CH_3$ | H | 6.45 s | | | 1.25–2.0 m | | 3.7 s |
| 22 | $CONH_2$ | $CH_3$ | 6.5 qt | 8 | 6 | 1.25–2.10 m | 3.7 s | |
| 24 | CN | $CH_3$ | 6.45 qt | 9 | 16 | 1.35–2.10 m | 3.7 s | |
| 26 | $CF_3$ | $CH_3$ | 6.4 qt | 9 | 21 | 1.20–2.0 m | 3.7 s | |
| 29a | $CON_3$ | $CH_3$ | 6.4 s | | | 1.25–2.0 m | 3.7 s | |
| 29b | NCO | $CH_3$ | 6.3 qt | 8.5 | 15 | 1.35–2.10 m | 3.7 s | |
| 30a[e] | $N(CH_3)_3$ | $CH_3$ | 6.65 qt | 9.5 | 6 | 1.6–2.35 m | 3.75 s | 3.2 s |

[a] In carbon tetrachloride solution. [b] In ppm from tetramethylsilane. [c] In cps. [d] $\Delta\nu\ (Q^2 - J^2)^{1/2}$: K. B. Wiberg and B. J. Nist, "Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962. [e] In deuterium oxide, chemical shifts are reported relative to external tetramethylsilane.

**5** (4.3 g, 0.022 mole, bp 40.5–41.5° at 0.1 mm) was isolated in 40% yield by preparative vpc (RCA Polyadipate on firebrick, 8.5 ft × 3/8 in.).

**4-Methylbicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (6).**—Ester **5** was hydrolyzed by the procedure used for **2**. Acid **6** (mp 144–145.5°) was purified by sublimation.

*Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.35; H, 8.40.

**Ethyl 4-Phenylbicyclo[2.2.2]oct-2-ene-1-carboxylate (8).**—Ethyl 6-phenyl-2-pyrone-3-carboxylate (**7**) (mp 103.5–104.5°, lit.[5] 105°) was prepared from 1-chloro-2-phenylprop-1-en-3-one[20] as outlined for **4**.[5] Pyrone **7** (12 g, 0.049 mole), benzene (100 ml), and ethylene[17] were heated at 150° for 3 days. Ester **8** (1.4 g, 0.005 mole, mp 125–126.5°) was isolated by the procedure used for **5**.

**4-Phenylbicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (9).**—Ester **8** was hydrolyzed by the procedure used for **2**. Sublimation yielded acid **9** (mp 291–292.5°).

*Anal.* Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.80; H, 7.00.

**Electrophilic Substitution of Pyrone Acids.**—Coumalic acid brominates[21] and chlorinates[22] under relatively mild conditions to yield 3-halo derivatives. Other 2-pyrones also substitute in the 3 position.[23] We examined the bromination, chlorination, and nitration of 2-pyrone-6-carboxylic acid as a route to pyrones useful for the preparation of 1,4-disubstituted bicyclic compounds. Bromination in acetic acid at 75° failed; the starting material was recovered. This substitution reaction also failed under more severe conditions, *e.g.*, bromine, aluminum bromide at 60°. Chlorination and nitration were similarly unsuccessful under mild and forcing conditions.

**Ethyl 4-Chlorocyclohexa-1,4-diene-1-carboxylate (10) and Ethyl 4-Chlorocyclohexa-1,3-diene-1-carboxylate (11).**—Chloroprene (30 g, 0.34 mole), ethyl propiolate (31 g, 0.32 mole), toluene (125 ml), and hydroquinone (2 g) were heated at 130° for 20 hr. Distillation provided three product fractions—bp 55–59° (8.5 g), 59–62° (10.0 g), and 62–62.5° (23.0 g) at 0.1 mm, respectively. The first fraction (vpc analysis) contained 45% **10**, 10% **11**, and 45% ethyl 4-chlorobenzoate. The other fractions contained about 85% **10** and 15% **11** with a trace of ethyl 4-chlorobenzoate. Compounds **10** and **11** were identified by nmr spectroscopy (Table I).

Several base–solvent pairs were examined to determine the most satisfactory conditions for the isomerization of **10** to **11**. The method reported below was preferable to potassium *t*-butylate in *t*-butyl alcohol or dimethyl sulfoxide, and potassium *t*-amylate in *t*-amyl alcohol. In dimethyl sulfoxide, the major product of the reaction was ethyl 4-chlorobenzoate.

A solution of sodium (3.3 g, 0.14 mole) in ethanol (100 ml) was cooled to 0° under nitrogen. The fractions containing 85% **10** and 15% **11** (33 g, 0.17 mole) in ethanol (60 ml) were added slowly to keep the temperature below 5°. The solution was stirred for 5 hr at ambient temperature. Water was added and the product was extracted into five 100-ml portions of methylene chloride. The extract was dried and distilled to yield three product fractions—bp 53–58° (6.6 g), 58–59.5° (7.4 g), and 59.5–61.0° (15.6 g) at 0.1 mm, respectively. The first fraction containing ethyl benzoate and ethyl 4-chlorobenzoate was discarded. The other fractions containing 5% ethyl 4-chlorobenzoate, 85% **11**, and 10% **10** were used without further purification.

**Ethyl 4-Chlorobicyclo[2.2.2]oct-2-ene-1-carboxylate (12).**—Mixed **10** and **11** (23 g, 0.12 mole, 85% **11**), *t*-butyl catechol (0.5 g), toluene (125 ml), and ethylene[24] (95%, initial pressure 12,250 psi) were heated at 150° for 3 days. The toluene solution was concentrated *in vacuo* and **12** (5.7 g, 0.027 mole, bp 64–65° at 0.1 mm, nmr, Table II) was isolated by preparative vpc (SF 96 on firebrick, biwall column (6 ft × 1 in.), Nester-Faust Prepkro II). This ester was also prepared by the Grob procedure as described elsewhere.[15]

**4-Chlorobicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (13).**—Ester **12** (1.3 g, 6.1 mmoles) and concentrated hydrochloric acid (25 ml) were refluxed for 6 hr. The mixture was poured into water and the product was extracted into five 20-ml portions of methylene chloride. After drying, the solvent was removed *in vacuo* and the residue sublimed to yield **13** (1.0 g, 5.4 mmoles), mp (cor) 198.5–199°.

*Anal.* Calcd for $C_9H_{11}ClO_2$: C, 57.90; H, 5.94; Cl, 19.01. Found: C, 57.85; H, 5.99; Cl, 19.05.

**Dimethyl 1,4-Dibromocyclohexane-1,4-dicarboxylate (14).**—A synthesis of **16** from cyclohexane-1,4-dicarboxylic acid was recently described.[2] Somewhat better yields are obtained in the procedures presented here. Thionyl chloride (264 g, 2.22 moles, purified[25]) was added to cyclohexane-1,4-dicarboxylic acid (156 g, 0.91 mole) over a 3-hr interval. The solution was refluxed for 1.5 hr. Excess thionyl chloride was removed *in vacuo* as the mixture was heated to 150°. Bromine (360 g, 2.0 moles) was added dropwise in 2 hr at this temperature which was maintained for an additional 2 hr. Unreacted bromine was then removed *in vacuo*. The solution was cooled to −10°. Methanol (500 ml)

(21) H. von Pechmann, *Ber.*, **17**, 2396 (1884); **37**, 3830 (1904).
(22) F. Feist, *ibid.*, **26**, 747 (1893); **34**, 1992 (1901).
(23) L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947).
(24) We are grateful to the American Oil Co. for the use of their high-pressure equipment.
(25) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass. (1955), p 345.

was added cautiously and the solution was allowed to stand overnight and then refluxed for 6 hr. The solution was cooled to precipitate **14**. Recrystallization from methanol provided *trans* **14** (150 g, 0.4 mole): mp 150–150.5° (lit.[26] 150°); nmr, singlets at $\delta$ 2.3 (8 H) and 3.82 (6 H). A mixture of *cis* and *trans* **14** (50.5 g, 0.14 mole) was collected from the mother liquors. Further concentration of the recrystallization solvent yielded a third batch (48.5 g, a mixture of *cis* and *trans* **14** and about 15% dimethyl terephthalate).

**1,3-Cyclohexadiene-1,4-dicarboxylic Acid (15).**—*trans* **14** (33.5 g, 0.10 mole) was added to potassium hydroxide (85 g) in methanol (85 g) at −15°. The solution was refluxed for 5 hr. The solution was cooled to −10° and acidified with hydrochloric acid (6 *N*). Water (200 ml) was added to dissolve potassium bromide. The residual solid was collected and dried to give **15** (18.0 g, 0.10 mole), mp 349–351° (lit.[2] 350° dec).

**Dimethyl 1,3-Cyclohexadiene-1,4-carboxylate (16).**—Thionyl chloride (50 g, 0.42 mole) and dry **15** (18 g, 0.10 mole) were refluxed for 6 hr. Excess thionyl chloride was removed *in vacuo*. The solid residue was cooled to −10° prior to the addition of methanol (150 ml). The mixture was allowed to stand overnight and then refluxed for 5 hr. After cooling, crystalline **16** was collected. Additional material was obtained by the addition of water to the mother liquors. The solids were combined and dried *in vacuo* prior to recrystallization from aqueous methanol (90%) to give **16** (19.0 g, 0.10 mole), mp 85–85.5° (lit.[2,26] mp 85°, 83.1–84.6°).

**Dimethyl Bicyclo[2.2.2]oct-2-ene-1,4-dicarboxylate (17).**—Ester **16** was converted to **17** by the addition of ethylene at high pressure.[2,24] The isolated product contained 8–9% dimethyl terephthalate. Several recrystallizations from aqueous methanol (60%) reduced the concentration of the aromatic ester to about 1% (analysis by ultraviolet spectroscopy). Further purification of this intermediate was mandatory in view of the intended applications.[4] Chromatography on charcoal (Norit A, 10 g; Celite, 25 g) with acetone reduced the aromatic impurity to <0.01%. The properties of **17** (mp 73.5–74.5°; nmr, Table II) were in agreement with Kauer's observations.[2] This ester was also prepared by the Grob method.[2,9,15]

**4-Carbomethoxybicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (18).** — Diester **17** (5.70 g, 0.026 mole) was hydrolyzed by sodium hydroxide (1.0 g) in aqueous methanol (95%, 100 ml) at reflux for 36 hr. Water (100 ml) was added to the cooled solution. Extraction with three 75-ml portions of ether removed unreacted **17** (0.65 g, 2.9 mmoles). The aqueous layer was concentrated and acidified with hydrochloric acid to precipitate **18** and the by-product, bicyclo[2.2.2]oct-2-ene-1,4-dicarboxylic acid (**19**). The solid mixture was treated with hot benzene to extract soluble **18** from insoluble **19** (0.35 g, 1.9 mmoles). The product was crystallized from benzene and sublimed to yield **18** (3.96 g, 0.019 mole): mp (cor) 159–159.5°; nmr, Table II.

**Bicyclo[2.2.2]oct-2-ene-1,4-dicarboxylic Acid (19).**—Diester **17** was hydrolyzed to **19** in aqueous methanol (70%) by potassium hydroxide in 3 hr. The product was isolated in the usual way. Sublimation (140° at 0.2 mm) yielded **19** (mp >320°, sublimes).

*Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.19; H, 6.17. Found: C, 61.06; H, 6.28.

**4-Carboethoxybicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (21).**—Sulfuric acid catalyzed esterification of **19** in ethanol yielded diethyl bicyclo[2.2.2]oct-2-ene-1,4-dicarboxylate (**20**), an oil, which was not purified. Diester **20** was converted to **21** by the method used for the conversion of **17** to **18**. Sublimation provided **21** (mp 102–103°) in 87% yield.

*Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.09.

**Methyl 4-carboxamidobicyclo[2.2.2]oct-2-ene-1-carboxylate (22)** was prepared from **18** by the method used for the corresponding saturated compounds.[11] Sublimation gave **22** (mp 154–156°; $\nu^{KBr}$ 3445, 3190 (NH), 1731 ($CO_2R$), 1655, 1651 ($CONH_2$) $cm^{-1}$; nmr, Table II) in 80% yield.

**4-Carboxamidobicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (23).**—Ester **22** was hydrolyzed by sodium hydroxide in aqueous methanol (90%). The product was isolated in the usual way. Sublimation (160° at 0.1 mm) provided **23** (mp 318–321° dec).

*Anal.* Calcd for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.58; H, 6.72; N, 7.01.

**Methyl 4-Cyanobicyclo[2.2.2]oct-2-ene-1-carboxylate (24).**—Amide ester **22** was converted to **24** by the procedure of Roberts and his associates.[11] Sublimation (65° at 0.5 mm) provided **24**: mp 82.5–83.5°; $\nu^{KBr}$ 2240 (CN), 1740 $cm^{-1}$ (CO); nmr, Table II.

**4-Cyanobicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (25).**—Ester **24** was hydrolyzed by sodium hydroxide in aqueous methanol (95%). The product was isolated in the usual way. Sublimation gave **25** (mp 199.5–201°; $\nu^{KBr}$ 2235 (CN), 1705 $cm^{-1}$ (CO); nmr, Table II) in 82% yield.

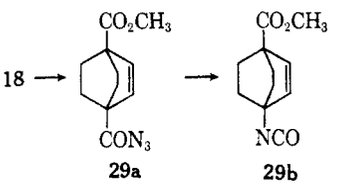
*Anal.* Calcd for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.60; H, 5.97; N, 7.93.

**4-Trifluoromethylbicyclo[2.2.2]oct-2-ene-1-carboxylic Acid (27).**—Ester acid **18** was converted to methyl 4-trifluoromethylbicyclo[2.2.2]oct-2-ene-1-carboxylate (**26**) with sulfur tetrafluoride[27a] by Dr. W. A. Sheppard.[27b] The crude ester[28] was hydrolyzed by sodium hydroxide in aqueous methanol (50%). Acid **27** was isolated in the usual way. Recrystallization from cyclohexane and sublimation provided **27**, mp (cor) 188–188.5°, in 58% yield based on **18**.

*Anal.* Calcd for $C_{10}H_{11}O_2F_3$: C, 54.54; H, 5.04; F, 25.89. Found: C, 54.51; H, 5.19; F, 24.86.

**4-Trifluoromethylbicyclo[2.2.2]octene-1-carboxylic Acid (28).**—Acid **27** (0.25 g, 1.1 mmoles) was hydrogenated over platinum oxide in tetahydrofuran. The solvent was removed *in vacuo* and the residue was sublimed, recrystallized from cyclohexane, and resublimed to yield pure **28** (0.23 g, 1.0 mmole): mp (cor) 214–215.5°; $\nu_{CO}^{CCl_4}$ 1700 $cm^{-1}$; nmr, singlet at $\delta$ 1.8.

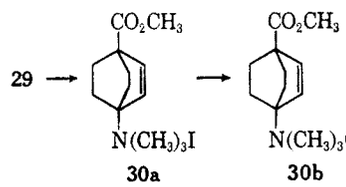
**4-Aminobicyclo[2.2.2]oct-2-ene-1-carboxylic Acid Hydrochloride (29).**—The amino acid was prepared from **18** by the sodium azide wet method.[29] Ester acid **18** (2.0 g, 9.5 mmoles) yielded **29a**: $\nu^{CCl_4}$ 2150 ($N_3$), 1735 ($CO_2R$), 1710 $cm^{-1}$ ($CON_3$); nmr, Table II). Compound **29a** was converted to **29b** ($\nu^{CCl_4}$ 2260 (NCO), 1740 $cm^{-1}$ ($CO_2R$); nmr, Table II) as described[29] (eq 1). Hydrochloride **29** was obtained by the acid hydrolysis of



(1)

**29b**. The infrared spectrum of the product indicated the presence of a small amount of the corresponding methyl ester. Since esterification was certain to occur in the next step of the sequence, the product was not purified.

**4-Carboxybicyclo[2.2.2]oct-2-ene-1-trimethylammonium Chloride (30).**—Compound **29** was converted to **30** by the sequence used by Wilcox and McIntyre[13] (eq 2). Compound **29** (1.50 g)



(2)

contaminated with its methyl ester was methylated.[14,30] All volatile materials were removed *in vacuo*. The residue was first extracted with six 50-ml portions of hot chloroform and then with chloroform in a Soxhlet apparatus for 72 hr. The solutions were combined and dried over magnesium sulfate. Chloroform was removed by distillation. The residue, crude **30a**, was dissolved in methanol, reprecipitated by ether, collected, and dried *in vacuo* to yield **30a** (1.58 g, 4.5 mmoles): mp >340°; nmr, Table II.

Exchange with freshly precipitated silver chloride was accomplished in the usual way. The product (**30b**) was obtained by the evaporation of the filtered aqueous solution. Compound **30b** was hydrolyzed in hydrochloric acid (1 *N*, 25 ml) for 24 hr.

(26) A. von Baeyer, *Ann.*, **245**, 175 (1888).

(27) (a) Upjohn Co., British Patent 930,888 (1964); (b) we are indebted to Dr. Sheppard of the DuPont Co. for his assistance in this preparation.

(28) The nmr spectrum of a pure sample is reported in Table II.

(29) P. A. S. Smith, *Org. Reactions*, **3**, 337 (1946).

(30) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1960).

The solution was evaporated to dryness *in vacuo*. The residue was recrystallized from acetone–ether to yield **30** (0.95 g, 3.9 mmoles), mp >340°.

*Anal.* Calcd for $C_{12}H_{20}O_2ClN$: C, 58.65; H, 8.20; Cl, 14.43. Found: C, 58.52; H, 8.25; Cl, 14.47.

**Registry No.**—**3**, 2534-80-7; **5**, 5549-04-2; ethyl 4-methylcyclohexa-1,3-diene-1-carboxylate, 14233-91-1; **6**, 14233-92-2; **8**, 5605-09-4; **9**, 14233-94-4; **10**, 14233-95-5; **11**, 14233-96-6; **12**, 14233-97-7; **13**, 14233-98-8; **16**, 1659-95-6; **17**, 1659-67-2; **18**, 14234-01-6; **19**, 1659-71-8; **21**, 14234-03-8; **22**, 14234-04-9; **23**, 14234-05-0; **24**, 14234-06-1; **25**, 14320-56-0; **26**, 14234-07-2; **27**, 14234-08-3; **28**, 14234-09-4; **29a**, 14234-10-7; **29b**, 14234-11-8; **30**, 14320-23-1; **30a**, 14234-12-9.

# The Preparation of Bicyclo[2.2.1]hepta-2,5-diene-7-spiro-1′-cyclopentane

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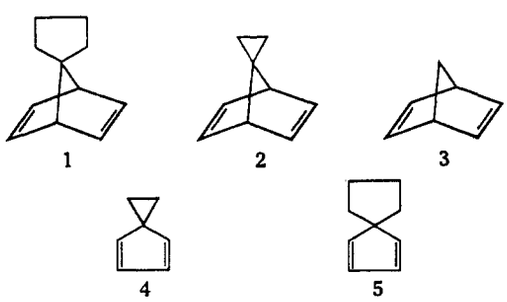
*Received March 8, 1967*

The preparation of bicyclo[2.2.1]hepta-2,5-diene-7-spiro-1′-cyclopentane by the Hofmann and amine oxide routes is described. Unlike the parent bicycloheptadiene, the N-oxide gave the better yield. The eliminations are compared with the earlier preparations of norbornadiene.

As part of a study of silver ion complexes of bicyclic olefins,[2] it became desirable to prepare the title compound **1** as an example of a diene in which the top sides of the $\pi$ bonds were effectively blocked. The only member of the 7-spiro-substituted bicyclo[2.2.1]heptadiene series that has been reported[3] is bicyclo[2.2.1]-hepta-2,5-diene-7-spiro-1′-cyclopropane (**2**). This diene presents complications for metal complex studies because the cyclopropyl group is itself potentially capable of complexing[4] and its unique geometry orients the hindering hydrogen atoms up and away from the center of the $\pi$ bond.




The route to the cyclopropyl diene **2** was by way of a Diels–Alder reaction between spiro[2,4]hepta-1,3-diene (**4**) and 1,2-dichloroethene.[3] Unfortunately, the precursor cyclopentadiene **5** for the preparation of **1** undergoes a preferential self Diels–Alder reaction at the high temperatures required for reaction with poor dienophiles like 1,2-dichloroethene. This limitation focused our attention on better dienophiles like acrylic acid derivatives and thence to the Cope[5] synthesis of the parent diene **3**. In that study, cyclopentadiene was adducted with methyl acrylate and the ester function then converted to both the amine oxide and a quaternary ammonium iodide group. Cope observed that the *exo*-amine oxide gave a 32% yield of diene **3** while the *endo* isomer gave only a 1.4% yield. Similarly the *exo*-ammonium iodide went in 58% yield while the *endo*-quaternary iodide gave only 3.1% of the diene. In the present case, the bulk of the spirocyclopentyl substituent promised to make the preparation of either *exo* isomer difficult with consequent low yields of **1**.

The Diels–Alder reaction of diene **5** with methyl acrylate went slowly at room temperature to give a mixture of *exo* and *endo* adducts in 77% yield.[3b] The *endo–exo* ratio was about 99:1 and an attempt to increase the amount of *exo* isomer by equilibration with sodium methoxide in methanol (17 hr under reflux) did not alter the ratio to any practical extent.[6] Because of the ready availability of the *endo* isomer, its chemistry was explored.[7]

The *endo* ester was readily converted to hydrazine **7** and thence by the Curtius reaction to carbamate **8**, which could be reduced in good yield to the secondary amine, **9**. This amine was methylated by the Clark–Eschweiler technique to give the tertiary amine **10** in an over-all yield from **5** of 35% (Scheme I). The methohydroxide **11** was prepared from the methiodide with silver oxide. Following the conditions employed by Cope, pyrolysis of **11** gave an isolated 10% yield of **1**.

Cram has reported[8] that the Cope elimination takes place at room temperature for many N-oxides when dry tetrahydrofuran is used as the solvent. In the present case these mild conditions failed for the N-oxide **12** and it was only by pyrolysis of the diene at 320° that elimination occurred. The diene was formed in surprisingly[9] high yield (53% by analytical glpc) and even after isolation in pure form by preparative glpc the yield was 22%.

(1) (a) Taken from the Ph.D. dissertation submitted by G. Whitney in partial fulfillment of the Cornell Graduate School requirements, 1966; (b) G. C. W. would like to acknowledge a predoctoral NIH fellowship for 1964–1966.

(2) C. F. Wilcox, M. F. Wilcox, G. Whitney, and R. Craig, unpublished results.

(3) (a) K. Alder, H. Ache, and F. H. Block, *Ber.*, **93**, 1988 (1960); (b) C. F. Wilcox, Jr., and R. R. Craig, *J. Am. Chem. Soc.*, **83**, 4258 (1961).

(4) Cyclopropane rings are widely noted for their ability to interact with protons and developing carbonium ions. The electron affinity of $Ag^+$ is close to that of $C^+$, thereby making it a potential contender for the electrons of the cyclopropane ring bonds.

(5) A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959).

(6) Whether this negative result reflects an extremely large *exo–endo* ratio or a slow equilibration was not determined. The question was not pursued because of the difficulty found in separating the mixture by distillation as well as the unexpectedly high yields obtained with the *endo* isomer.

(7) The interfering bulk of the spirocyclopentane ring might well have given poor yields in the pyrolysis of the *exo*-amine oxide. The expectation for the *exo*-ammonium salt is less clear.

(8) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 5450 (1960).

(9) In comparing the present results with those of Cope, *et al.*, it might be noted that their yields are based on analytical glpc before isolation.