through which nitrogen was passed. The flask containing the solution, covered by an atmosphere of nitrogen, was tightly stoppered and allowed to stand at room temperature for 2 days.

The brown liquid was then distilled under nitrogen giving a clear liquid (4.35 g., 0.022 mole, 38%), b.p. 54° (1 mm.). The distillate showed only ester absorption in the infrared.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.10; H, 6.21.

Bis-2,3,5,6-(N-phenyl-*vic*-triazolino)bicyclo[2.2.1]heptane (Phenyl Azide–Norbornadiene Adduct).—A 76-ml. carbon tetrachloride solution containing 12.0 g. (0.10 mole) of phenyl azide was added to 4.6 g. (0.05 mole) of bicyclo[2.2.1]heptadiene. The pale green precipitate which first appeared after 12 hr. at room temperature was collected after 48 hr. A yield of 9.1 g. (55%), m.p. 229° dec., was obtained. This material proved insoluble in the usual solvents. Recrystallization was effected, however, in nitrobenzene (7.3 g., m.p. 229° dec.). The once recrystallized material was boiled with absolute ethanol and chloroform, to give analytically pure material (6.7 g., 41%), m.p. 229° dec.

Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49. Found: C, 69.07; H, 5.64.

This compound reacts to form a bright blue solution on treatment with glacial acetic acid.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid[1]

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Bicyclo[2.2.2]octane-1,2-dicarboxylic acid has been synthesized *via* the reaction of dimethyl 1,3-cyclohexadiene-1,6-dicarboxylate with maleic anhydride (Chart I) and *via* the reaction of ethyl 1,3-cyclohexadiene-1-carboxylate with ethyl acrylate (Chart II). The latter reaction affords the four possible Diels–Alder adducts in the ratio of 30 (head-to-head *endo*): 8 (head-to-tail *endo*): 5 (head-to-head *exo*): 1 (head-to-tail *exo*). Stereochemical and structural assignments for the intermediates in the syntheses are described.

As part of a program for the investigation of the behavior of cyclic diacyl peroxides,[2] an aliphatic six-membered cyclic diacyl peroxide was desired. Since peroxides prepared from the cyclohexane-1,2-dicarboxylic acids have been reported to be unstable,[3] a requirement placed on the system at the outset was a structure in which bisdecarboxylation would be difficult. The system selected was bicyclo[2.2.2]octane-1,2-dicarboxylic acid (**9**). The preparation and proof of structure of compounds in this series are reported in this paper.

Bicyclo[2.2.2]octane-1,2-dicarboxylic acid (**9**) was prepared by two routes. The chemical evidence for the structural assignments is summarized in Charts I, II, and III. A higher over-all yield of **9** was obtained from the (less direct) route shown in Chart I, patterned after a synthesis reported by Grob, Ohta, Renk, and Weiss.[4] However, the Diels–Alder reaction between ethyl 1,3-cyclohexadiene-1-carboxylate and ethyl acrylate (Chart II) shows a fourfold preference for the formation of head-to-head adducts over the head-to-tail adducts; and this preference for head-to-head reaction, coupled with the ease of separation of 1,2-diacid **9** from 1,3-diacid **17** by means of the cyclic anhydride **10**, renders route II a reasonable one for compound **9**.

A few aspects of structure require amplification: (a) the structure of the product **3** of the base-catalyzed isomerization of dimethyl 1,4-cyclohexadiene-1,2-dicarboxylate (**2**); and (b) the stereochemistry of **7**, **19**, and **4**.

Isomerization of 2.—Structure **2**, expected by the method of synthesis, is supported by the ultraviolet ($\lambda_{\max}^{\text{MeOH}}$ 239, ϵ 2259)[5] and n.m.r. data. The n.m.r. spectrum exhibits three regions of absorption of area ratio 2:4:6 at 4.21 τ [one band weakly split into a triplet (vinyl H)]; 7.06 τ [one band weakly split into a doublet (methylene)]; and 6.30 τ [singlet (methyl)]. Compound **2** is readily isomerized by base. Of the six possible diene diesters, the new isomer is assigned structure **3** on the basis of the n.m.r. spectrum (five regions of absorption of area ratio 1:2:6:1:2 at 3.02 τ [broadened triplet (1 vinyl H)]; 3.96 τ [multiplet (2 vinyl H's)]; 6.27 and 6.38 τ [two sharp singlets (6 methyl H's)]; 6.5 τ [multiplet, partly obscured by the methyl peaks (1 tertiary H)]; 6.83–7.98 τ [complex multiplet (2 methylene H's)]. Further support for this assignment is found in the infrared absorption at 1710 and 1735 cm.$^{-1}$ (both conjugated and unconjugated esters) and the ultraviolet absorption at $\lambda_{\max}$ 288 (ϵ 8120) [compare with ethyl 1,3-cyclohexadiene-1-carboxylate **14**, $\lambda_{\max}$ 292 (ϵ 8260)]. That no further isomerization of **3** occurs during the Diels–Alder reaction with maleic anhydride may be concluded from an examination of Charts I and III and the spectral data cited in the Experimental section.

The base-catalyzed isomerization of **2** to **3** rather than to either of the two conjugated isomers (1,2-dicarbomethoxy-1,3-cyclohexadiene or 2,3-dicarbomethoxy-1,3-cyclohexadiene) is probably associated with the unfavorable steric situation between the adjacent ester groups in the latter two cases. The ester groups in **3** may be staggered, permitting full conjugation of one of the groups with the diene system.[6a]

Stereochemistry of 7 and 19.—Compound **7** may be isomerized by sodium methoxide in methanol, affording a mixture in which the *endo* isomer **19** predominates over the *exo* isomer **7** by a ratio of 3.5 to 1.[6b] The assignment of the *exo* structure to **7** and the *endo* to **19** is based on the inability of the former, and the ability of the latter, to afford a bromo lactone (Chart III). In addition, examination of the n.m.r. and

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(1) Supported in part by the research program of the Atomic Energy Commission under Contract No. AT(30-1)-905. Reproduction is permitted for any purpose of the U. S. Government.

(2) See F. D. Greene and W. W. Rees, *J. Am. Chem. Soc.*, **80**, 3432 (1958).

(3) W. von E. Doering, M. Farber, and A. Sayigh, *ibid.*, **74**, 4370 (1952).

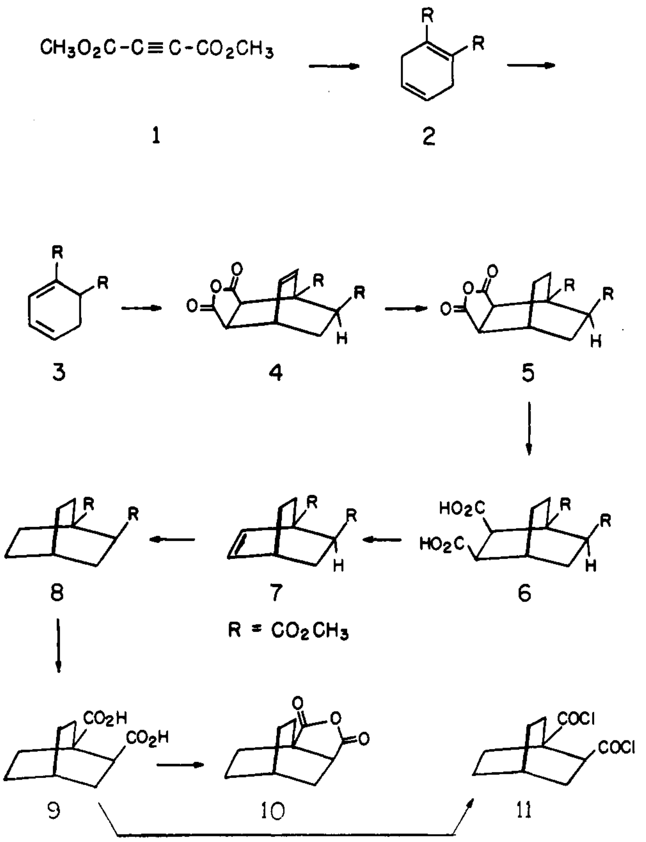
(4) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).

(5) For related cases, see A. T. Nielson, *J. Org. Chem.*, **22**, 1539 (1957).

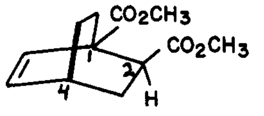
(6) (a) The positions of equilibria in cyclohexadienes present a number of points of special interest. W. von E. Doering, Abstracts, Carbanion Symposium, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963. (b) In methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate the *endo–exo* ratio is 51.5:48.5 [A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959)].

CHART I

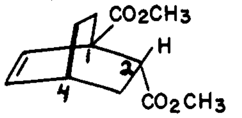
SYNTHESIS OF BICYCLO[2.2.2]OCTANE-1,2-DICARBOXYLIC ACID AND ITS DERIVATIVES *via* MALEIC ANHYDRIDE ROUTE



mass spectra[7] of these isomers indicates that the stereochemistry also may be assigned by either of these physical methods.



7



19

(superimposed) 7.2–7.6 τ	H at C-2	6.8–7.1 τ quartet (four roughly equal peaks)
	H at C-4	7.2–7.6 τ (broad)
(singlet) 6.32 τ	H's of 1-COOCH$_3$. .	6.31 τ (singlet)
(singlet) 6.40 τ	H's of 2-COOCH$_3$. .	6.46 τ (singlet)
(two unequal peaks) 3.65–3.8 τ	vinyl H's	3.34–4.0 τ (five major peaks)

The principal n.m.r. distinction between the *exo* and the *endo* isomers arises from the magnetic shielding effect of the 5,6-double bond at the region of C-2 that is *endo* to the double bond.[8] The methyl peak of the C-2 carbomethoxy group may be expected to appear at higher field in **19** than in **7** and the C-2 hydrogen may be expected to appear at higher field in **7** than in **19**. Such differences are seen in the n.m.r. spectra of the *endo* and *exo* isomers, and this assignment of configuration is in accord with the conclusion from the chemical data (Chart III). A further difference in the n.m.r. spectrum is seen in the vinyl region. This region is more complex and broad in **19** than in **7**, ascribed to the magnetic shielding effect of the carbon–oxygen double bond of the *endo*-carbomethoxy group on the C-6 hydrogen.

The mass spectrometric distinction between the two isomers is associated with the proximity in **7** of the 2-

CHART II

SYNTHESIS OF BICYCLO[2.2.2]OCTANE-1,2-DICARBOXYLIC ACID *via* ETHYL ACRYLATE

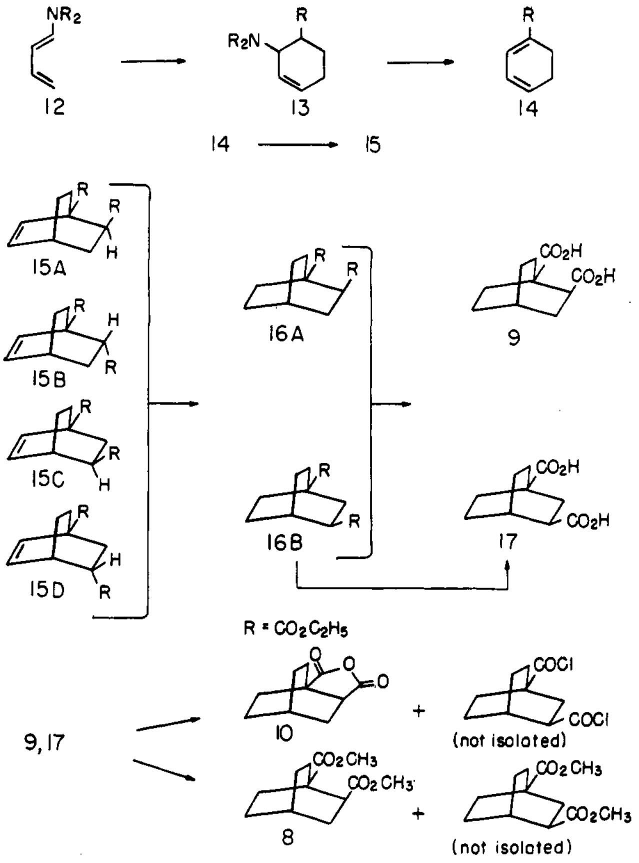
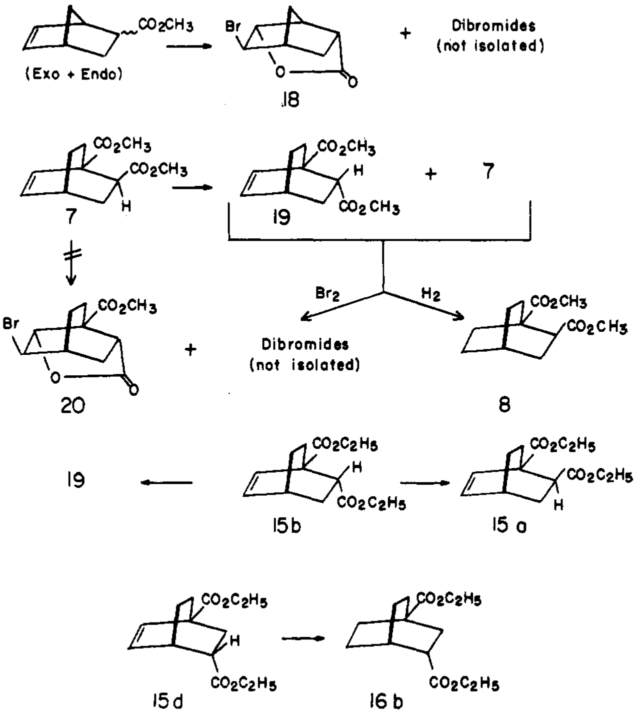


CHART III

STRUCTURAL CONFIRMATION AND CORRELATION OF THE INTERMEDIATES OF THE TWO SYNTHESES



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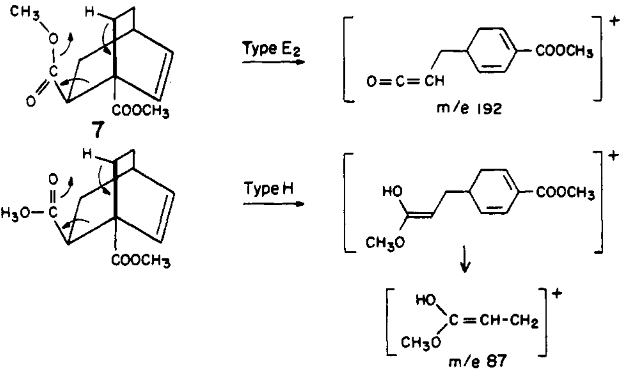
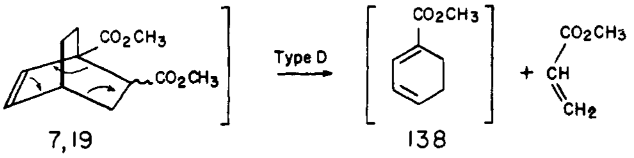
[7] The mass spectral distinction was suggested and elucidated by Dr. Klaus Biemann of this department.

[8] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 129.

carbomethoxy group to a hydrogen atom of the saturated bridge. The spectrum of **7** shows intense peaks *m/e* 192 (associated with type E_2 fragmentation leading to the M − 32 ion) and *m/e* 87 (associated with type H fragmentation). Both peaks are also present in **19** but at approximately one-fifth the intensity. These cases and others are discussed in more detail elsewhere.[9]



Both **7** and **19** exhibit strong peaks at *m/e* 138, associated with cleavage of type D, a process not appreciably influenced by the stereochemistry of the carbomethoxy group.



Stereochemistry of 4.—The orientation of the 2-carbomethoxy group *endo* to the double bond in compound **4** is derived from the assignment of the *exo* structure to **7** and is supported by n.m.r. analysis in two ways: (a) the methyl band for the 2-carbomethoxy group appears at higher field (6.38 τ) in the spectrum of compound **4** than in the spectrum of its hydrogenation product **5** in which it is found at 6.33 τ; (b) the vinyl region of **4** bears a strong resemblance to the vinyl region of compound **19** (*cf.* discussion of stereochemistry of **7** and **19**). The orientation of the anhydride group *endo* to the double bond in **4** is based on the Alder rule analogies.[10]

Stereochemistry of 15A–D.—The Diels–Alder reaction of ethyl 1,3-cyclohexadiene-1-carboxylate and ethyl acrylate (Chart II) affords all four possible isomers. The expected, and observed, major product is the 2-*endo* isomer **15B**, which constitutes 68% of the diester mixture. Diesters **15D, A,** and **C** constitute 18, 11, and 2.3% of the mixture. The basis for the assignment of structure and stereochemistry of the major product **15B** is shown in Charts II and III. The structural assignments of **15A, B,** and **D** rest on the chemical relations shown. The *endo* and *exo* distinction between **15D** and **C** is based on the Alder rule analogies.[10]

Experimental

The order of description of experiments parallels the order of presentation in Charts I, II, and III. All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird Model B, Perkin-Elmer Model 21, or Perkin-Elmer Infracord spectrophotometer; ultraviolet spectra were determined with a Cary recording spectrophotometer; n.m.r. spectra were determined on a Varian A-60 with internal reference by tetramethylsilane. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

Dimethyl acetylenedicarboxylate (1) was prepared[11] in 75% yield, b.p. 97–99° (23 mm.) [lit.[11] b.p. 95–98° (19 mm.)].

Dimethyl 1,4-cyclohexadiene-1,2-dicarboxylate (2) was prepared by the method of Sopov and Miklashevskaya[12] in 94% yield, b.p. 92–93° (0.3 mm.), $n^{25}\mathrm{D}$ 1.4918, $n^{19}\mathrm{D}$ 1.4941 [lit.[12] b.p. 138.5–139.5° (10 mm.), $n^{20}\mathrm{D}$ 1.4950].

The ultraviolet spectrum of the product in methanol has a peak at 239 mμ (ε 2259); the infrared spectrum (CCl_4) exhibits bands at 1710 and 1660 cm.$^{-1}$.

Dimethyl 1,3-Cyclohexadiene-1,6-dicarboxylate (3).—To 100 ml. of absolute methanol–sodium methoxide [prepared from 0.87 g. (0.0307 g.-atom) of sodium] was added 30 g. (1.53 moles) of **2** under a nitrogen atmosphere. After 30 min. 2.53 g. (0.0422 mole) of glacial acetic acid was added to neutralize the base. The bulk of the methanol was removed under reduced pressure and the residue was extracted with 500 ml. of ether. The ethereal solution was washed with 275 ml. of water in two portions, and 75 ml. of saturated sodium bicarbonate, and then dried over anhydrous magnesium sulfate. The ether solution was separated from the drying agent, and the ether was removed by distillation. Fractionation of the residue gave 27.4 g. (91.5%) of dimethyl 1,3-cyclohexadiene-1,6-dicarboxylate (**3**) boiling at 85–93° (0 055 mm.); the refractive index of the fraction boiling at 90–93° (0.055 mm.) was $n^{25}\mathrm{D}$ 1.5039. Gas–liquid phase chromatography (g.l.p.c.) indicated that the material was 92% **3**, 8% **2**. A sample of **3** was collected by g.l.p.c. for analytical and spectral data.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.19; H, 6.17. Found: C, 61.30; H, 5.96.

The ultraviolet spectrum of the product in methanol has a peak at 288 mμ (ε 8120); the infrared spectrum (CCl_4) exhibits bands at 1710, 1735 and 1650 cm.$^{-1}$ attributed to a conjugated ester group, unconjugated ester group, and carbon–carbon double bonds.

1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]oct-5-ene-7,8-*endo*-dicarboxylic Anhydride (4).—To 6.38 g. (0.033 mole) of **3** was added 3.21 g. (0.033 mole) of maleic anhydride (crystallized from chloroform). The mixture was heated on a steam bath for 2 hr. The resulting yellow solution when cooled to room temperature solidified to a viscous semisolid material. An equal volume of ether was added, and the mixture was stirred and scratched, whereupon the substance crystallized to a white solid. Filtration gave 7.82 g. of crude material. Recrystallization from chloroform–hexane gave 7.21 g. (75%) of **4** in the form of colorless prisms, m.p. 125.5–127.5°. A portion of the material recrystallized three times from the same solvent mixture, melted at 126.5–127.5°.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.12; H, 4.80. Found: C, 57.09; H, 4.64.

The ultraviolet spectrum of the compound in methanol does not show a maximum above 210 mμ; the infrared spectrum ($CHCl_3$) exhibits bands at 1780 and 1860 cm.$^{-1}$ attributed to the anhydride group, and a band at 1740 cm.$^{-1}$ attributed to unconjugated ester groups.

1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Anhydride[13] (5).—A sample of **4**, 27.5 g. (0.094 mole), was dissolved in 100 ml. of tetrahydrofuran (distilled from lithium aluminum hydride, b.p. 66°). The solution was added to a suspension of 2.8 g. of reduced platinum oxide in 50 ml. of tetrahydrofuran and the mixture was hydrogenated under atmospheric pressure. Hydrogen uptake amounted to 0.095 mole. Following the removal of the catalyst the solution was concentrated until crystallization occurred. Three crops of crystals were obtained, the last upon addition of hexane,

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[9] K. Biemann, "Applications of Mass Spectroscopy to Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, p. 148-151.

[10] M. C. Kloetzel, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 10; I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *J. Gen. Chem. USSR*, **25**, 75 (1955); J. C. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

[11] E. H. Huntress, T. E. Lesalie, and J. Bornstein, *Org. Syn.*, **32**, 55 (1952).

[12] W. P. Sopov and V. S. Miklashevskaya, *J. Gen. Chem. USSR*, **26**, 2133 (1956).

yielding 25.8 g. (93%) of **5** in the form of colorless plates, m.p. 156.5–157.5°. Sublimation and crystallization from tetrahydrofuran–hexane of a portion of the product gave a material melting at 157.7–158°.

Anal. Calcd. for $C_{14}H_{16}O_7$: C, 56.73; H, 5.45. Found: C, 56.73; H, 5.58.

The infrared spectrum ($CHCl_3$) of the product exhibits bands at 1790 and 1860 cm.$^{-1}$ attributable to the anhydride group and a band at 1740 cm.$^{-1}$ attributable to the presence of unconjugated ester groups.

1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Acid[13] (**6**).—To 96 ml. of 20% potassium carbonate was added 24 g. of **5**. The mixture was stirred and heated on a steam bath until a homogeneous solution was obtained. The solution was cooled to 0° and sufficient concentrated hydrochloric acid was added to make the mixture acidic. Filtration and crystallization of the material from water gave 23.1 g. (92%) of **6** in the form of colorless prisms, m.p. 150–152°. A sample of the material, heated and sublimed under reduced pressure, regenerated the anhydride **5** identical in infrared spectrum and showing no melting point depression. A sample of the material, recrystallized from chloroform–hexane, melted at 151–152°.

Anal. Calcd. for $C_{14}H_{18}O_8$: C, 53.48; H, 5.78; neut. equiv., 157. Found: C, 53.60; H, 5.81; neut. equiv., 154.

The infrared spectrum of the compound (KBr pellet) exhibits bands at 1700 (acid) and 1740 cm.$^{-1}$ (ester).

Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (**7**).—To 83 ml. of anhydrous benzene under a nitrogen atmosphere was added 14.79 g. (0.0471 mole) of **6**, 5.59 g. (0.0707 mole) of anhydrous pyridine, and 22 g. (0.0471 mole) of lead tetracetate (crystallized from glacial acetic acid). The mixture was heated to the reflux temperature with stirring. Before this point was reached the solid dissolved, and a vigorous evolution of carbon dioxide occurred. The solution was refluxed for 2 hr. during which time a white precipitate formed. The solution was separated from the solid and washed with 30 ml. of 2 *N* sodium carbonate, 40 ml. of 2 *N* hydrochloric acid, and 10 ml. of water. The solution was dried over magnesium sulfate and the bulk of the benzene was removed by fractional distillation. Addition of ether to the residue precipitated 1.9 g. of **5**. Fractionation of the residue under reduced pressure gave 5.21 g. (50%) of **7** boiling at 86–87° (0.26 mm.), $n^{25}D$ 1.4838.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.24; H, 7.20. Found: C, 63.98; H, 7.25.

The infrared spectrum of the product exhibits bands at 1740 and 1620 cm.$^{-1}$ attributable to unconjugated ester groups and a carbon–carbon double bond.

Dimethyl Bicyclo[2.2.2]octane-1,2-dicarboxylate (**8**).—To 5 ml. of absolute methanol was added 0.25 g. of platinum oxide. The catalyst was reduced and 2.49 g. of **7** dissolved in 6 ml. of methanol was added. Upon completion of the hydrogenation (uptake 95%) the solution was separated from the catalyst and the bulk of the methanol was removed by fractional distillation. Fractionation of the residue under reduced pressure gave 2.34 g. (93%) of **8**, b.p. 84–85° (0.35 mm.), $n^{25}D$ 1.4778.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.65; H, 8.34.

The infrared spectrum (CCl_4) exhibits a band at 1740 cm.$^{-1}$ attributable to the unconjugated ester groups.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid (**9**).—To 8 ml. of 75% methanol was added with stirring 1.49 g. (0.0265 mole) of potassium hydroxide. When the base had dissolved 2 g. (0.00885 mole) of **8** was added and the mixture was stirred and refluxed for 4 hr. After cooling the solution, the bulk of the methanol was removed under reduced pressure and the residue was diluted with 50 ml. of water. The resulting solution was cooled to ice-bath temperature and acidified with concentrated hydrochloric acid. The mixture was extracted with several portions of ether and the resulting ethereal solution was dried over anhydrous magnesium sulfate. The ether solution was separated from the drying agent and the solvent was removed on a steam bath. Recrystallization from water gave 1.49 g. (85%) of **9**, m.p. 188–190°. A sample of the material, recrystallized from water three times, gave colorless prisms, m.p. 200–201°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.57; H, 7.12. Found: C, 60.64; H, 7.20.

The infrared spectrum (KBr pellet) exhibits a broad band at 1700 cm.$^{-1}$ attributable to unconjugated acid groups.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Anhydride (**10**).—To 20 ml. of thionyl chloride, under anhydrous conditions, was added 1 g. of previously dried **9**. The mixture was stirred at reflux until solution occurred (1 hr.). The thionyl chloride was removed under reduced pressure. Crystallization of the residue from cyclohexane gave 0.82 g. (92%) of **10** in the form of colorless plates, m.p. 163.5–164.5°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.71. Found: C, 66.67; H, 6.76.

The infrared spectrum (CCl_4) exhibits bands at 1800, 1875, and 1200 cm.$^{-1}$ attributable to a cyclic 5-membered anhydride.

Bicyclo[2.2 2]octane-1,2-dicarbonyl Chloride (**11**).—To 15 g. (0.076 mole) of dry **9** under a nitrogen atmosphere was added 31.8 g. (0.152 mole) of phosphorus pentachloride. The solids were mixed by shaking, whereupon an exothermic reaction occurred, accompanied by the formation of a liquid. When the reaction had subsided the mixture was heated to 140° and kept at this temperature, with stirring, for 16 hr. Fractionation of the liquid under reduced pressure gave 16.7 g. (95%) of **11**, b.p. 121–122° (0.3 mm.), $n^{25}D$ 1.5199.

The infrared spectrum (CH_2Cl_2) showed a strong band at 1800 cm.$^{-1}$ attributable to the acyl chloride groups and weak band at 1870 cm.$^{-1}$ attributable to the small quantity of cyclic anhydride which codistills with the acid chloride.

1-Diethylaminobutadiene (**12**) was prepared by the method of Hünig and Kahanek[14] in 42% yield, b.p. 66–67° (9–10 mm.) [lit.[21] b.p. 64–66° (10 mm.)].

Ethyl *cis*-2-diethylaminocyclohex-3-ene-1-carboxylate (**13**) was prepared by the reaction of **12** with ethyl acrylate[14] in 72% yield, b.p. 70–76° (0.07–0.14 mm.) [lit.[14] b.p. 80–83° (0.2 mm.)].

Ethyl 1,3-cyclohexadiene-1-carboxylate (**14**) was prepared from **13** by the method of Grob, Ohta, Renk, and Weiss[4] in 50% yield, b.p. 98–100° (17 mm.), $n^{25}D$ 1.4988 [lit.[4] b.p. 90–92° (11 mm.)].

The ultraviolet spectrum of the product in ethanol has a maximum at 292 mμ (ϵ 8260); the infrared spectrum (CCl_4) exhibits bands at 1710 and 1640 cm.$^{-1}$ attributable to a conjugated ester and carbon–carbon double bonds.

***exo* and *endo* Isomers of Diethyl Bicyclo[2.2.2]oct-5-ene-1,2-(and 1,3)-dicarboxylate** (**15**).—To 75 mg. of hydroquinone was added 9.8 g. (0.0981 mole) of freshly distilled ethyl acrylate (b.p. 99°) and 5 g. (0.0327 mole) of **14**. The resulting solution was refluxed under nitrogen in the dark for 24 hr. and then was allowed to stand for 20 hr. at 0°. Fractionation gave 4.16 g. (50%) of a pale yellow liquid boiling at 90–94° (0.03 mm.). Gas-liquid chromatography indicated a mixture of four major components in the ratio of 5:30:1:8 (listed in the order of elution). They were assigned as follows: diethyl bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (**15A**), diethyl bicyclo[2.2.2]oct-5-ene-1,*endo*-2-dicarboxylate (**15B**), diethyl bicyclo[2.2.2]oct-5-ene-1,-*exo*-3-dicarboxylate (**15C**), and diethyl bicyclo[2.2.2]oct-5-ene-1,-*endo*-3-dicarboxylate (**15D**). The ratio of **A** + **B** *vs.* **C** + **D** was 3.9 to 1. The esters were separated on a preparative g.l.p.c. column containing 25% 550 silicone oil on 60–80-mesh Chromosorb P (Johns Mansville firebrick). Ester **15C** was not isolated.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.63; H, 7.99. Found for **15A**: C, 66.03; H, 8.16. Found for **15B**: C, 66.38; H, 8.02. Found for **15D**: C, 66.97; H, 8.11.

The infrared spectra of the esters (CCl_4) exhibit bands at 1730 and 1615 cm.$^{-1}$ attributable to unconjugated ester groups and a carbon–carbon double bond. The spectra of the three isolated esters were very similar with only minor differences in the fingerprint region.

Diethyl Bicyclo[2.2.2]octane-1,2(and 1,3)-dicarboxylate (**16**).—To 200 mg. of platinum oxide was added 5 ml. of 95% ethanol. The catalyst was reduced and 2 g. (0.00994 mole) of **15** was added in 5 ml. of ethanol. Upon completion of the hydrogenation (uptake 0.01 mole of hydrogen) the solution was separated from the catalyst and the solvent was removed under reduced pressure. Fractionation of the residue gave 1.82 g. (95%) of a colorless liquid, b.p. 110–113° (0.07 mm.). Two major components were shown by g.l.p.c. in the ratio of 3.8 to 1, assigned as **16A** and **16B**, respectively. The two components were separated on a

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(13) The *endo* designation for **5** and **6** refers to a *syn* relation of a substituent to the *unsubstituted bridge*. In all other cases the *endo* designation refers to a *syn* relation of a substituent to an *unsaturated* bridge.

(14) S. Hünig and H. Kahanek, *Chem. Ber.*, **90**, 238 (1957).

g.l.p.c. column containing 25% 550 silicone oil on 60–80-mesh Chromosorb P.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.10; H, 8.73. Found for **16A**: C, 66.04; H, 8.81. Found for **16B**: C, 66.16; H, 8.75.

The infrared spectra of the esters (CCl_4) show a band at 1730 cm.$^{-1}$ (ester). The spectra of the two esters are very similar with only minor variations in the fingerprint region.

Bicyclo[2.2.2]octane-1,2(and 1,3)-dicarboxylic Acid (9, 17).—To a solution of 0.8 g. (0.00315 mole) of **16** in 8 ml. of absolute ethanol was added 0.53 g. (0.00945 mole) of potassium hydroxide and 2 ml. of water. The solution was refluxed for 4 hr. At the end of this period the bulk of the ethanol was removed under reduced pressure and 10 ml. of water was added. The resulting solution was acidified with concentrated hydrochloric acid and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration of the mixture and evaporation of the solvent gave 0.61 g. of a yellow solid, a mixture of **9** and **17**. A 95-mg. sample of this mixture was treated with 2.5 ml. of thionyl chloride for 2 hr. Evaporation of the excess thionyl chloride and recrystallization of the residue from cyclohexane afforded 31 mg. of bicyclo[2.2.2]octane-1,2-dicarboxylic anhydride (**10**), m.p. 163–164°, m.m.p. 163–164°, identical in infrared spectrum with the material prepared by the sequence of Chart I.

A second portion of the mixture of **9** and **17** (0.3 g.) was dissolved in ether and treated with ethereal diazomethane. Ether was removed through a Vigreux column and the residue was distilled to give 0.21 g. of a colorless liquid. Two components were indicated by g.l.p.c. in the ratio of 2 to 1. The compounds were separated on a g.l.p.c. column containing 25% 550 silicone oil on 60–80-mesh Chromosorb P. The major component had the same retention time and infrared spectrum as **8**.

Bicyclo[2.2.2]octane-1,3-dicarboxylic Acid (17).—To 42 mg. (0.000163 mole) of **16B** was added 1.24 ml. of absolute ethanol. To this was added 0.326 ml. of a solution of 8.3 g. of potassium hydroxide in 100 ml. of water (27.4 mg., 0.000489 mole). The resulting solution was refluxed for 4 hr. Water (10 ml.) was added and the solution was acidified with concentrated hydrochloric acid. The acidified solution was extracted with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave 62 mg. of a yellow semisolid material. Sublimation and crystallization from acetone–hexane gave 14 mg. (44%) of **17** in the form of colorless needles, m.p. 206–208°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.57; H, 7.12. Found: C, 60.44; H, 7.02.

The infrared spectrum (KBr) has a band at 1700 cm.$^{-1}$ attributable to carboxylic acid functions. The spectrum was similar to that of **9** with only minor differences in the fingerprint region.

Bromo Lactone in the Bicyclo[2.2.1]heptane System (18).—To a stirred solution of 5 g. (0.0328 mole) of a 3:1 mixture of *endo* and *exo* methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate in 50 ml. of chloroform, cooled to 0°, was added dropwise 5.3 g. (0.0328 mole) of bromine. When the addition of the bromine was complete the solvent was removed under reduced pressure, giving a dark green oil (color developed during concentration). Decolorization with Norit and crystallization from ether–pentane gave 3.3 g. (62% based on the amount of *endo* isomer) of the bromo lactone of bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid in the form of colorless cubic crystals, m.p. 68–70°. A sample recrystallized from ether–pentane afforded material of melting point 67.5–69° (lit.[15] m.p. 67.5–68.5°).

The infrared spectrum ($CHCl_3$) has bands at 1775 and 1010 cm.$^{-1}$ attributable to the five-membered ring lactone.

Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*endo*-2-dicarboxylate (19).—To 15 ml. of absolute methanol-sodium methoxide solution (from 51 mg. of sodium) under a nitrogen atmosphere was added 500 mg. (0.00233 mole) of **7**. The resulting pale yellow solution was refluxed under nitrogen for 13.5 hr., cooled, and 134 mg. (0.00223 mole) of glacial acetic acid was added. The methanol was removed under reduced pressure. Ether and water were added to the residue and the water solution was further extracted with ether. The combined ether extracts were washed with 10% sodium bicarbonate and water and dried over anhydrous magnesium sulfate. The solution was filtered and the ether was removed under reduced pressure. Distillation of the residue gave 352 mg. (70%) of a yellow liquid. Gas–liquid chromatography indicated two compounds in the ratio of 3.5 to 1. Comparison of retention indicated that the smaller peak was the starting material. Since, as indicated subsequently, reduction of the mixture gave only one component, **8**, the major component was designated as **19**. The two components were separated on a g.l.p.c. column containing 25% 710 silicone oil on 80–100-mesh Chromosorb P. The major component **19** crystallized and was recrystallized from pentane giving colorless cubic crystals, m.p. 44–45.5°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.24; H, 7.21. Found: C, 64.17; H, 7.21.

The infrared spectrum (CCl_4) of **19** had bands at 1730 and 1615 cm.$^{-1}$ attributable to an unconjugated ester group and a carbon-carbon double bond. The n.m.r. data are given in the discussion.

Dimethyl Bicyclo[2.2.2]octane-1,2-dicarboxylate (8).—Platinum oxide (10 mg.) was suspended in 1 ml. of absolute methanol, the catalyst was reduced, and 75 mg. (0.00334 mole) of the mixture containing **19** and **7** was added in 1.5 ml. of methanol. The amount of hydrogen absorbed was 0.0036 mole. Removal of the methanol under reduced pressure gave 72 mg. (94%) of a liquid, identical in infrared spectrum with **8**. Gas-liquid chromatography showed only one component which had the same retention time as **8**.

Bromo Lactone in Bicyclo[2.2.2]octane System (20).—To 2 ml. of methanol-free chloroform (passed through silica gel) cooled to 0° was added 100 mg. (0.000446 mole) of ester mixture **19** and **7** (80% **19**) and 71 mg. (0.000446 mole) of bromine in 2 ml. of chloroform. The reaction mixture was allowed to stand in the dark for 24 hr. at 0°. The resulting solution was washed with 5 ml. of 5% sodium sulfite, 5 ml. of water, and 5 ml. of saturated sodium chloride solution, and dried over magnesium sulfate. The chloroform was removed under reduced pressure leaving 172 mg. of a pale yellow oil. Addition of a small amount of ether caused the oil to crystallize to a white solid weighing 63 mg., m.p. 124–130°. Recrystallization from ether–pentane gave 43 mg. (44% based on the amount of *endo* isomer) of the bromo lactone of 1-carbomethoxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid, m.p. 128.5–129.5°. A sample recrystallized from acetone–hexane melted at 129–130°.

Anal. Calcd. for $C_{11}H_{13}O_4Br$: C, 45.67; H, 4.53; Br, 27.65. Found: C, 45.63; H, 4.52; Br, 27.92.

The infrared spectrum ($CHCl_3$) has bands at 1730 and 1790 cm.$^{-1}$ attributable to an unconjugated ester group and a 5-membered lactone.

Attempted Lactonization of Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (7).—A sample of **7** was subjected to the preceeding bromination conditions, employing the same work-up procedure. Evaporation of the chloroform gave 165 mg. of a pale yellow oil which could not be crystallized. The infrared spectrum of the oil ($CHCl_3$) showed a band at 1730 cm.$^{-1}$ attributable to unconjugated ester groups. There was no band in the region where lactone absorption is expected.

Dimethyl Bicyclo[2.2.2]octane-1,*endo*-2-dicarboxylate (19) from Diethyl Bicyclo[2.2.2]octane-1,*endo*-2-dicarboxylate (15B).—To 75 mg. (0.000298 mole) of **15B** (containing 0.6% of **15A**) under a nitrogen atmosphere, was added 5 ml. of collidine and 399 mg. (0.00298 mole) of pulverized lithium iodide. The mixture was refluxed under nitrogen for 24 hr. After cooling, the reaction mixture was poured into a mixture of 5 ml. of concentrated hydrochloric acid and 5 g. of ice. The resulting yellow solution was extracted with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether under reduced pressure gave 65 mg. of a pale yellow semisolid material.

The crude solid was dissolved in 10 ml. of ether, cooled to 0°, and treated with an ethereal solution of diazomethane. The latter was added until a permanent yellow color occurred. The excess diazomethane was decomposed with 4 drops of glacial acetic acid. Evaporation of the ether under reduced pressure gave 74 mg. of a yellow oil. Gas–liquid chromatography of the liquid indicated two components in the ratio of 33 to 1. Comparison with mixture **19**, **7** indicated that the compounds had the same retention times. Purification of the major component on a column containing 25% 710 silicone oil on 80–100-mesh Chromosorb P gave a colorless oil which was crystallized from pentane. The infrared spectrum of the solid (CCl_4) was the same as the spectrum of **19**.

Diethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (15A) from Its *endo* Isomer 15B.—To 23.3 mg. (0.093 mmole) of **15B** under a nitrogen atmosphere was added 0.41 ml. of a 0.228 *M*

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(15) C. D. VerNooy and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **77**, 3583 (1955).

solution of ethanolic sodium ethoxide, and 7.5 ml. of absolute ethanol. The resulting solution was refluxed for 20 hr. under nitrogen. At the end of this period 5.6 mg. (0.093 mmole) of glacial acetic acid was added to neutralize the base. Evaporation of the solvent under reduced pressure left a small quantity of liquid which was extracted with two 10-ml. portions of ether. Drying of the ethereal solution over magnesium sulfate and evaporation of the solvent gave 10 mg. (43%) of a colorless oil. Gas–liquid chromatography of the oil on a column containing 20% XF-1150[16] on 80–100-mesh Chromosorb P showed two peaks in the ratio of 5 to 1. The lesser component was eluted first and had the same retention time as **15A**. The larger peak had the same retention time as **15B**.

Diethyl Bicyclo[2.2.2]octane-1,3-dicarboxylate (16B) from Diethyl Bicyclo[2.2.2]oct-5-ene-1,*endo*-3-dicarboxylate (15D).— A 12.5-mg. sample of **15D** (containing 4.2% of **15B**) was hydrogenated by platinum oxide in ethanol (1 ml.). Removal of the catalyst and evaporation of the solvent under reduced pressure gave 12.3 mg. (98%) of a colorless liquid giving two peaks on a g.l.p.c. column containing 25% 710 silicone oil on Chromosorb P. The two peaks were in the ratio of 23 to 1. The major component had the same infrared spectrum and retention time as **16B**-

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[16] A nitrile–silicon polymer obtained from General Electric.

The Lactones of *cis*- and *trans*-2-Hydroxycycloheptaneacetic Acid[1]

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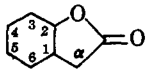
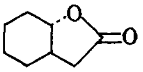
The *cis*- and *trans*-lactones of 2-hydroxycycloheptaneacetic acid have been prepared and equilibrated at various temperatures. The *cis* isomer predominates slightly in the temperature range 384–423°K. The thermodynamic quantities have been calculated and the conformations are discussed and contrasted with those of the cyclohexane analogs. Two examples of what appears to be partial *cis*-electrophilic addition to the cycloheptene double bond have been observed.

The lactone of *cis*-2-hydroxycyclohexaneacetic acid[3–6] (I) is more stable than the *trans* isomer (II),[7] the *trans* compound being convertible to the *cis* under the influence of sulfuric acid–acetic acid.[3,5] An analogous acid-catalyzed rearrangement is well known in the santonin series where the allylic position of the lactone ether oxygen renders the isomerization more facile,[8] but many other instances of this stability relationship among lactones of substituted 2-hydroxycyclohexaneacetic acid could be cited.[9]

In the last decade, a group of new sesquiterpene lactones has been discovered in which the γ-lactone ring is fused onto the seven-membered ring portion of perhydroazulene skeleton.[10] In discussions dealing with the stereochemistry of the new lactones, it has been tacitly assumed[11] that commonly accepted generalizations about γ-lactones fused onto six-membered rings can be extended to γ-lactones fused onto seven-membered rings. Because of our interest in naturally occurring perhydroazulenic lactones, we decided to examine this supposition by the synthesis and study of the previously unreported title compounds III and IV.



I



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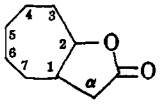

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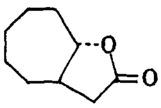

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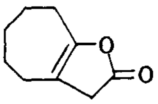
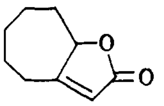


V



VI

The energetics of *cis*- and *trans*-ring fusion to cycloheptanes have, in the meantime, been considered by Hendrickson,[12] with particular reference to the *cis*- and *trans*-bicyclo[5.3.0]decanes (perhydroazulenes). The conclusion was reached that the energy difference between *cis*- and *trans*-perhydroazulene was likely to be virtually negligible, experimental support for this having been provided by Allinger and Zalkow.[13] When a lactone is substituted for a five-membered ring, inspection of Dreiding models suggests that in the *cis* isomer III the favored twist-chair conformation[12] of the cycloheptane ring may be destabilized somewhat because of angle strain. Of the two *trans*-forms of IV, the 2e-3e isomer appears to be affected only slightly, the 3e-4e isomer more so. The over-all effect is difficult to assess but would not be expected to alter the stability relationships significantly.

Lactone III was prepared from VI, or more conveniently from the mixture of V and VI prepared by cyclization of 2-oxocycloheptaneacetic acid.

Lactone IV was synthesized in a manner similar to that adopted by Newman and Vander Werf[3] for the preparation of II. However, the first step, the reaction of cycloheptene oxide with malonate ion, was exceedingly slow as compared with the analogous reaction of cyclohexene oxide which reacts at least 10 times as rapidly.

The reasons for this difference in reactivity are not quite clear. It has been shown that cyclohexene oxide reacts with methoxide ion about 1.5 times as fast as

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[1] Supported in part by a grant from the National Science Foundation (NSF-G 14396).

[2] Abstracted from a thesis submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy, 1963.

[3] M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

[4] J. Klein, *J. Org. Chem.*, **23**, 1209 (1958).

[5] J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959).

[6] E. H. Charlesworth, H. J. Campbell, and D. L. Stachiw, *Can. J. Chem.*, **37**, 877 (1959).

[7] S. Coffey, *Rec. trav. chim.*, **42**, 387 (1923).

[8] Y. Abe, T. Miki, M. Sumi, and T. Toga, *Chem. Ind.* (London), 953 (1956); H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 504 (1956); M. Sumi, *J. Am. Chem. Soc.*, **80**, 4869 (1958); D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962); W. Cocker, B. Donnelly, H. Gobinsingh, T. B. H. McMurray, and M. A. Nisbet, *ibid.*, 1262 (1963).

[9] See, for example, M. Hinder and M. Stoll, *Helv. Chim. Acta*, **36**, 1995 (1953); W. Klyne, *J. Chem. Soc.* 3072 (1953).

[10] The most recent review of this rapidly moving field is already very much out of date, T. Nozoe and S. Ito, *Fortschr. Chem. Org. Naturstoffe*, **19**, 32 (1961).

[11] See, for example, J. W. Huffman, *Experientia*, **16**, 120 (1960). The complications have been recognized by J. B. Hendrickson and R. Rees, *Chem. Ind.* (London), 1424 (1962).

[12] J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

[13] N. L. Allinger and V. B. Zalkow, *ibid.*, **83**, 1144 (1961).