phenomenon being currently taken to account for other anomalous n.m.r. data,[21] as well as in some loss of entropy attributed to restricted freedom of rotation.[22]

Interestingly, when the σ^* values in Fig. 1 are replaced by the K_{A} values of the corresponding primary amines, the resulting plot is quite similar to Fig. 1, indicating again that the base strength of primary amines is not greatly dependent on steric effects.

It may be noted that the alicyclic esters examined show little deviation; here substituents are held back rigidly enough to cause no interference.

The chemical shift changes of two esters for which no σ^*-values exist at present have also been determined. The size of the *allyl* group should lead to no serious steric effects, so that the value of +0.17–0.19 found for σ^* is probably very realistic, especially when compared to that of +0.13 for the methallyl group. Assuming similar steric factors to be operating for the *n*-butyl and *n-amyl* groups, the σ^*-value for the latter is placed at −0.14 to −0.16.

Conclusions

While there exists a general correspondence between the electron-donating properties of alkyl groups of esters and the chemical shifts of protons attached to the acyl group, no linear correlation is obtained, a fact which may be explained in part by the magnetic anisotropy of aromatic substituents present and in part by steric factors related to the size and type of the aliphatic groups, especially by means of Newman's Rule of Six.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO, CHICAGO 37, ILLINOIS]

The Preparation of 1-Carboxy-4-substituted Bicyclo[2.2.2]octanes[1]

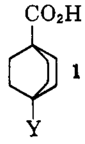
BY HANS D. HOLTZ[2] AND LEON M. STOCK

RECEIVED APRIL 4, 1964

Syntheses of 1-carboxy-4-substituted bicyclo[2.2.2]octanes are described.

Introduction

The 1,4-disubstituted bicyclo[2.2.2]octane acids (**1**) are excellent models for the study of the influence of nonconjugative polar effects and the mode of transmission of these polar effects to reaction sites.



1

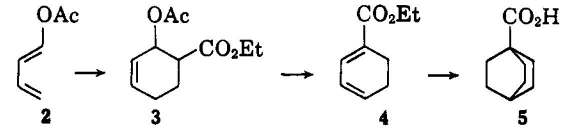
Roberts and Moreland[3] first recognized the utility of this structure and several members of the series were prepared.[4] More recently, Ritchie and Lewis examined the dependence of the polar effects on the nature of the solvent.[5]

The major advantages of the bicyclo[2.2.2]octane system dictated its choice as one of the models for our studies. Methods for the preparation of these acids are summarized in this report.

Results and Discussion

The synthesis of 1-carboxybicyclo[2.2.2]octane (**5**) is outlined in Chart I.

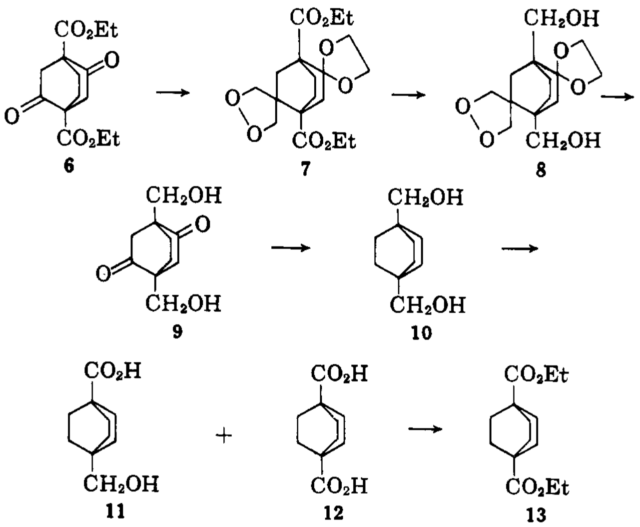
CHART I



The sequence is a composite of two other known routes to the parent acid **5**.[6,7] The Diels–Alder condensation of 1-acetoxybuta-1,3-diene (**2**) with ethyl acrylate yielded 1-carbethoxy-2-acetoxycyclohex-3-ene (**3**). The stereochemistry of this compound has not been established. The adoption of ethyl acrylate rather than methyl acrylate[6] allowed the preparation of a solid ester (**3**) rather than the liquid methyl ester employed by Sayigh.[6] The diene **4** was obtained by the pyrolysis of the ethyl ester **3** under basic conditions. The subsequent transformations in this sequence follow the synthesis described by Grob and his associates.[7]

Other methods were employed for the preparation of the disubstituted acids. One approach is summarized in Chart II.

CHART II



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(1) Chemistry of the bicyclo[2.2.2]octanes. Part II. This research was supported by Grants G 14211 and G 25190 from the National Science Foundation.

(2) Esso Educational Foundation Fellow, 1961–1962; Union Carbide Corporation Fellow, 1962–1963.

(3) J. D. Roberts and W. T. Moreland, *J. Am. Chem. Soc.*, **75**, 2167 (1953).

(4) J. D. Roberts, W. T. Moreland, and W. Frazer, *ibid.*, **75**, 637 (1953).

(5) C. D. Ritchie and E. S. Lewis, *ibid.*, **84**, 591 (1962).

(6) A. A. Sayigh, Thesis, Columbia University Libraries, 1952.

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

The known[4,8] condensation of diethyl succinate to 1,4-dicarbethoxy-2,5-diketocyclohexane and the subsequent incorporation of the ethano bridge was employed as the first step in this sequence. In the alkylation, monoglyme and 1,2-dibromoethane were employed as cosolvents to achieve a high concentration of the alkyl halide and to take advantage of the accelerating influence[9] of the ethereal solvent on this reaction. The yields of 1,4-dicarbethoxy-2,5-diketobicyclo[2.2.2]-octane (**6**) approached 40% of the theoretical quantity based on the succinate ester.

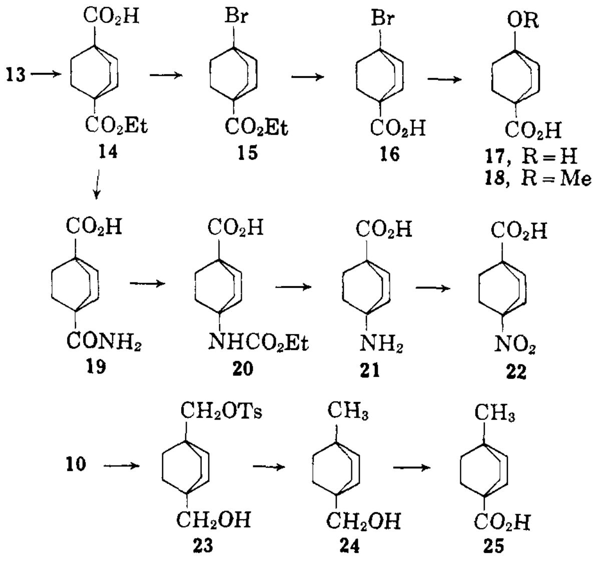
The reduction of the ketone functions presents a serious problem. Attempts to reduce diketodiester **6** under basic conditions result in the destruction of the bicyclic ring system or lead to the formation of other undesirable products. Thus, the alkaline hydrolysis of **6** gives 1,3,6,8-tetracarboxyhexane.[10] The Wolff–Kishner reduction of **6** yields pyrazalones.[8] Guha reported that the conventional Clemmensen reduction proceeded satisfactorily.[8] Unfortunately, this procedure failed to yield a significant quantity of the desired product.[4] More recently, it has been found that a modified Clemmensen method (anhydrous ethanol solvent with reagents at high dilution) yields the reduction product **13**.[11] Roberts' group achieved the reduction of **6** to **13** by the Raney nickel desulfurization of the dithioketal of **6**.[4] We selected to examine the route outlined in Chart II, since this sequence offered an opportunity to obtain other 1,4-substituted derivatives useful in our program.

Treatment of 1,4-dicarbethoxy-2,5-diketobicyclo-[2.2.2]octane (**6**) with ethylene glycol in the presence of catalytic amounts of *p*-toluenesulfonic acid in refluxing benzene from which water was continuously separated yielded the diketal **7**. Lithium aluminum hydride reduction of the diketaldiester **7** provided the diketaldiol **8**. The ligands were then removed by acid hydrolysis to give 1,4-dihydroxymethyl-2,5-diketobicyclo[2.2.2]octane **9**. Wolff–Kishner reduction of this product proceeded satisfactorily to yield 1,4-dihydroxymethylbicyclo[2.2.2]octane (**10**). The alkaline permanganate oxidation of the diol **10** gave, under selected conditions, an easily separated mixture of 53% 1-carboxy-4-hydroxymethylbicyclo[2.2.2]octane (**11**) and 23% 1,4-dicarboxybicyclo[2.2.2]octane (**12**).

With excess oxidizing agent the diacid **12** was obtained. The diacid **12** and the diester **13** prepared from it were identical in all respects with the compounds described in the literature, securing the structures of the other previously unknown substances prepared in this sequence.

The intermediates produced through the reactions outlined in Chart II were converted to other substituted acids by the methods summarized in Chart III.

CHART III



The half-hydrolysis of diester **13** was accomplished by the known procedure.[4] The conversion of **14** to the bromoester **15** was achieved by the Cristol modification of the Hunsdiecker reaction.[12] Since the bridgehead radical formed in the course of the reaction is nonselective,[13] bromotrichloromethane was employed as the solvent to avoid contamination of the product. Acid hydrolysis of the ester **15** yielded the known bromoacid **16**.[4] Basic hydrolysis of **15** or **16** gave the hydroxy acid **17**. The hydroxy group was methylated by treatment of **17** with sodium hydride and methyl iodide.

The half-ester **14** was also converted to the amino acid **21** by the known sequence.[4] Alkaline permanganate oxidation[14] of **10** provided 1-carboxy-4-nitrobicyclo[2.2.2]octane (**22**).[15] The low yield step in this conversion is the Hoffman rearrangement of the amide **19** to the urethan **20**. In preliminary work yields of the urethan were 30% or less as reported,[4,11] with some starting material recovered and the bulk of the material converted to the diacid (**12**). The failure to achieve a better yield of **20** appeared to be associated with the reaction of bromine with the solvent. In subsequent experiments we used somewhat larger amounts of bromine and protected the reaction mixture from light; the urethan was then obtained in 60–70% yield with only a minor amount of the diacid produced.

1-Carboxy-4-methylbicyclo[2.2.2]octane (**25**) was first produced (see also Chart IV) from diol **10** by tosylation, lithium aluminum hydride reduction of the tosylate, and subsequent alkaline permanganate oxidation of 1-hydroxymethyl-4-methylbicyclo[2.2.2]octane (**24**). The neopentyl character of the tosylate **23** did not adversely influence the yield of **24** obtained in the hydride displacement reaction.

Colonge and Viullemet recently reported the synthesis of several 1-hydroxy-3-keto-4-substituted bicyclo[2.-2.2]octanes (**26**)[16] from the readily available 3-substituted 3-acetylpimelonitriles.[17] These trisubstituted bicyclo[2.2.2]octanes were converted to 4-methyl- **25**, 4-ethyl- **31**, and 4-phenyl-1-carboxybicyclo[2.2.2.]octane (**32**) by the sequence shown in Chart IV.

---

[8] P. C. Guha, *Ber.*, **72**, 1359 (1939).

[9] H. D. Zook and T. J. Russo, *J. Am. Chem. Soc.*, **82**, 1258 (1960).

[10] P. C. Guha and C. Krishnamurthy, *Ber.*, **72**, 1374 (1939).

[11] C. F. Wilcox and J. S. McIntyre, unpublished results; J. S. McIntyre, Thesis, Cornell University Libraries, 1962, p. 40.

[12] S. J. Cristol and W. C. Firth, *J. Org. Chem.*, **26**, 280 (1961).

[13] F. W. Baker, H. D. Holtz, and L. M. Stock, *ibid.*, **28**, 514 (1963).

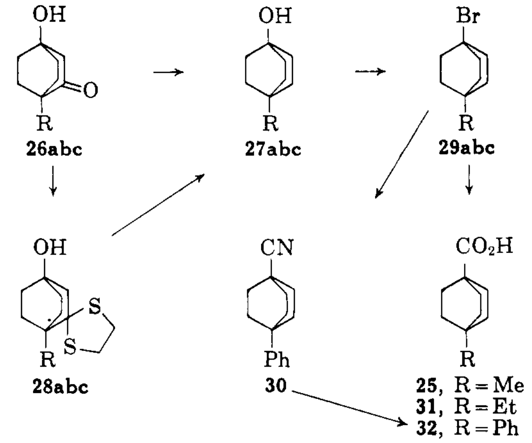
[14] N. Kornblum, R. J. Clutter, and W. M. Jones, *J. Am. Chem. Soc.*, **78**, 4003 (1956).

[15] The preparation of **22** from **14** was carried out by Miss N. Santo.

[16] J. Colonge and H. Viullemet, *Bull. soc. chim. France*, 2238 (1961).

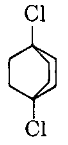
[17] H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.*, **64**, 2850, 2857 (1942).

CHART IV[a]



[a] For a, R = Me; b, R = Et; c, R = Ph.

4-Methyl- (**27a**) and 4-ethylbicyclo[2.2.2]octanol-1 (**27b**) were conveniently prepared by the Clemmensen reduction of **26a** and **26b**. Vapor phase chromatography of the isolated products indicated the presence of impurities of undetermined structure. These contaminants were removed by chromatography on alumina. The yield of the 4-phenyl derivative **27c** in the Clemmensen reduction was very poor and it was best prepared by another route. The thioketal **28c** was readily obtained and reduced under Wolff–Kishner conditions according to the procedure of Georgian and his associates.[18] The alcohols **27a** and **27b** were also prepared by the reduction of the thioketals **28ab**. The alcohols obtained by the two methods were identical in all respects. Reaction of the alcohols **27abc** with Lucas reagent at 50° easily converted them to the bromides **29abc**. The carboxyl function was introduced by treatment of the bromides with silver sulfate in sulfuric acid in the presence of carbon monoxide generated by the decomposition of formic acid.[19,20] The methyl derivative **25** obtained by this route was identical with the acid obtained by the method of Chart III securing a structure proof for the methyl compounds of Chart IV and indicating the unrearranged character of the other products. Unfortunately, 1-bromo-4-phenylbicyclo[2.2.2]octane (**29c**) reacted rapidly with sulfuric acid to yield an uncharacterized water-soluble substance, presumably the sulfonic acid. An alternate route to the phenyl acid **32** was devised. The bromo compound **29c** was converted to the cyanide **30** in 47% yield by treatment with cuprous cyanide in pyridine.[21] This procedure was the most satisfactory of several alternative methods that were examined. The nitrile **30** was then hydrolyzed to the acid **32**.



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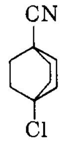

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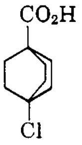

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The recently discovered method[22] for the conversion of perchlorocoumalin to 1,4-dichlorobicyclo[2.2.2]octane (**33**) provided a convenient starting point for the preparation of 1-carboxy-4-chlorobicyclo[2.2.2]octane (**36**). The Koch procedure failed with the 1,4-dichloro derivative **33**.[19,20] It proved necessary to heat the sulfuric acid solution to 70° before silver chloride was precipitated. After hydrolysis, 1-chloro-4-hydroxybicyclo[2.2.2]octane (**34**) was isolated in addition to starting material rather than the acid **36**. The treatment of the dichloride with cuprous cyanide for 3 days in refluxing N-methylpyrrolidone gave the cyanide **35** in poor yield.[23,24] The ready availability of the starting material made the preparation practical. Hydrolysis of the cyanide yielded the desired acid **36**. In conclusion, the synthetic methods which involve bicyclo[2.2.2]octylcarbonium ions are often accomplished with remarkable ease. The 1-bromo-4-alkylbicyclo[2.2.2]octanes are easily ionized by reaction with silver ion. At 0°, in sulfuric acid solvent, the precipitation of silver bromide begins upon the admixture of the reagents. The ion has sufficient stability to allow capture by carbon monoxide. Moreover, hydrobromic acid–zinc bromide reagent is equally effective for the conversion of 4-substituted bicyclo[2.2.2]octan-1-ols to the corresponding bromides. The unsubstituted bromides and alcohols react similarly.[8,13]

The influence of one halogen substituent on the other in 1,4-dichlorobicyclo[2.2.2]octane appreciably alters the velocity of the reactions. A mixture of the dihalide, silver sulfate, and sulfuric acid must be heated to 70° before the precipitation of silver chloride is detectable. The observed substituent effect is very large. Nevertheless, it is possible to accomplish these reactions as shown by the conversion of 1,4-dichlorobicyclo[2.2.2]octane (**33**) to 1-hydroxy-4-chlorobicyclo[2.2.2]octane (**34**).

In contrast, the reactions of bridgehead halides with cuprous cyanide, presumably a reaction of both nucleophilic and electrophilic character, are much slower. The reaction of bromobenzene with sodium thiophenolate is a second-order reaction which proceeds easily at 175°.[25] The reaction of this nucleophile with the bridgehead halide is not detectable under the same conditions.

Experimental[26]

1-Carbethoxy-2-acetoxycyclohex-3-ene (**3**).—Acetoxybutadiene[27] (241 g., 2.15 moles), ethyl acrylate (370 g., 3.7 moles), dry benzene (400 ml.), and hydroquinone (1 g.) were refluxed for 30 hr. The solvents were distilled *in vacuo* to yield a residue which solidified upon cooling. Recrystallization from cyclohexane gave **3** (170 g., 37%, m.p. 50–51°).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.30; H, 7.60. Found: C, 62.45; H, 7.84.

Compound **3** was converted to 1-carbethoxycyclohexa-1,3-diene (**4**) by the method of Sayigh[6] and thence to 1-carboxybicyclo[2.2.2]octane (**5**) *via* the sequence described by Grob and his associates.[7] All intermediates and products exhibited physical properties compatible with literature data.[6,7,26]

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(22) J. C. Kauer, French Patent 1,345,138 (1963); *Chem. Abstr.*, **60**, 14407 (1964).

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(24) L. Friedman and H. Shechter, *ibid.*, **26**, 2522 (1961).

(25) Unpublished results of F. W. Baker.

(26) All melting points are uncorrected. Infrared spectra were recorded on Perkin–Elmer Model 21 or Beckman IR7 recording spectrophotometers; n.m.r. spectra were recorded with a Varian A60 Model spectrometer. Microanalyses were performed by Mr. W. Saschek. Detailed synthetic procedures for all compounds encountered in this work are reported in the Ph.D. Thesis of H. D. Holtz, University of Chicago Libraries, 1963.

(27) K. K. Georgieff and A. Dupre, *Can. J. Chem.*, **38**, 1070 (1960).

1,4-Dicarbethoxy-2,5-diketobicyclo[2.2.2]octane (6).—Sodium hydride (2 moles, 50% in mineral oil) was suspended in monoglyme (800 ml.) in a flask fitted with a stirrer, condenser, addition funnel, and vented to a wet test meter. *t*-Butyl alcohol (5 g.) was added and the temperature raised to 60°. Diethyl succinate (348 g., 2 moles) was added at such a rate as to keep hydrogen evolution under control. Stirring was continued for 1 hr. after the calculated amount of hydrogen had evolved. The monoglyme and ethanol were distilled *in vacuo*. Dry 1,2-dibromoethane (800 ml.) and monoglyme (200 ml.) were added to the disodium salt of 2,5 diketocyclohexane-1,4-diester. The temperature was slowly raised to 80–90°. The course of the alkylation was followed by the determination of the pH of hydrolyzed samples. The reaction was usually complete (pH 7–8) within 4 to 6 days. The system was then set for steam distillation. Dibromide and monoglyme were removed and the residue was allowed to crystallize. The crude product was collected and mineral oil removed by washing the solid with cyclohexane. The material was recrystallized from ethanol and then washed with 1% potassium hydroxide until the washings were no longer yellow and again recrystallized from ethanol to give 6 (110 g., 40%, m.p. 111–112°).

Ethylenediketal of 1,4-Dicarbethoxy-2,5-diketobicyclo[2.2.2]-octane (7).—Diketodiester 6 (170 g., 0.6 mole), benzene (600 ml.), *p*-toluenesulfonic acid (1 g.), and ethylene glycol (93 g., 1.5 moles) were refluxed until water no longer separated in a trap (3 days). The solution was cooled and shaken with 10% potassium hydroxide and the layers were separated. Benzene was evaporated and cyclohexane (200 ml.) was added to the hot residue. After several days large clear crystals of 7 (161 g., 73%, m.p. 84–86°) were collected and dried. An analytical sample, recrystallized from cyclohexane, melted at 85–86°.

Anal. Calcd. for $C_{18}H_{26}O_8$: C, 58.72; H, 7.10. Found: C, 58.61; H, 7.09.

Diketal of 1,4-Dimethylhydroxy-2,5-diketobicyclo[2.2.2]octane (8).—Diketaldiester 7 (110 g., 0.30 mole) was dissolved in ether (500 ml.) and added to a stirred suspension of lithium aluminum hydride (25 g., 0.66 mole) in ether over a period of 4.5 hr. Reflux was continued for 5 hr. and the excess hydride destroyed. Water (150 ml.) and dilute sulfuric acid (1:10, 500 ml.) were added. The ether layer was separated and dried. The aqueous layer was extracted with methylene chloride for 6 days. The ether layer yielded a viscous residue (36 g.) which solidified on long standing to give 8. An analytical sample recrystallized from cyclohexane–acetone had m.p. 100–101°.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.70; H, 7.75. Found: C, 58.93; H, 7.46.

The methylene chloride extract yielded 40 g. of a mixture of mostly 8 and some 9; yield 89%.

1,4-Dimethylhydroxy-2,5-diketobicyclo[2.2.2]octane (9).—Diketodiol 9 was prepared by refluxing diketal 8 (24 g., 0.08 mole) in dilute hydrochloric acid (1:10, 100 ml.) for 8 hr. After cooling, the reaction mixture was neutralized with potassium hydroxide and the water was removed *in vacuo*. Crude 9 was dissolved in acetone and the solution filtered. The removal of acetone *in vacuo* gave a residue sufficiently pure for the next step. Compound 9 (b.p. 190° (0.5 mm.)) yielded a 2,4-dinitrophenylhydrazone with a broad melting point.

Anal. Calcd. for the dinitrophenylhydrazone, $C_{22}H_{22}N_8O_{10}$: N, 20.07. Found: N, 19.50.

1,4-Dimethylhydroxybicyclo[2.2.2]octane (10).—Diketodiol 9 (25 g., 0.126 mole), 100% hydrazine hydrate (25 ml., 0.48 mole), and a solution of potassium hydroxide (40 g.) in diethylene glycol (180 ml.) were allowed to react in the usual way. After dilution with water, the product was extracted into ether. The removal of the solvent yielded a residue which crystallized in 6–8 hr. in a refrigerator. Recrystallization from benzene gave pure 10 (8.0 g., 41%, m.p. 107–108°).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.60; H, 10.65. Found: C, 70.55; H, 10.68.

1-Hydroxymethylbicyclo[2.2.2]octane-4-carboxylic Acid (11).—Diol 10 (12 g., 0.07 mole) was dissolved in water (500 ml.) and potassium hydroxide (2.0 g.) added. The solution was stirred and potassium permanganate (13 g., 0.082 mole) added in small portions over a period of 6 hr. When the violet color had disappeared, the reaction mixture was filtered and the manganese dioxide residue was washed with dilute aqueous base. The combined filtrates were extracted with ether. The residue from the evaporated ether solution solidified yielding 2.0 g. of diol 10. The basic solution was evaporated to 75 ml. Acidification gave a heavy white precipitate which was filtered, washed with water, and dried. The dry material was sublimed at 145–150° (0.5 mm.) to yield 11 (5.7 g., 53%). A small portion was recrystallized from acetone; m.p. 187–188°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.20; H, 8.75. Found: C, 65.30; H, 8.83.

The residue (2.7 g., 23%) in the sublimator was diacid 12. This known compound[8] (m.p. 391–393°) was also prepared by oxidation with excess permanganate in 85% yield.

Ethyl bicyclo[2.2.2]octane-1,4-dicarboxylate (13) was prepared by acid-catalyzed esterification of 12. Ethyl hydrogen bicyclo-[2.2.2]octane-1,4-dicarboxylate (14) was prepared from 13 by the method of Roberts, *et al.*[4] Compound 14 was converted to 1-bromo-4-carboxybicyclo[2.2.2]octane (15) by the method of Baker, *et al.*[13] This substance was hydrolyzed by Roberts' method[4] to 1-bromo-4-carboxybicyclo[2.2.2]octane (16). 1-Hydroxy-4-carboxybicyclo[2.2.2]octane (17) was prepared from 16 by Roberts' approach.[4] These known compounds exhibited physical properties in good agreement with the literature.[4,26]

1-Methoxy-4-carboxybicyclo[2.2.2]octane (18).—Hydroxy acid 17 (1.5 g., 0.00882 mole) and sodium hydride (2.5 g., 53% dispersion in mineral oil) were refluxed in monoglyme (50 ml.) under nitrogen. When hydrogen evolution ceased, methyl iodide (25 ml.) was added. The solution was refluxed for 24 hr. After cooling, aqueous base was added and the layers separated. The aqueous layer was acidified and extracted with ether. The ether solution yielded 200 mg. of crude 18. The organic layer was concentrated and dilute aqueous base was added to the residue and the solution refluxed for 24 hr. The basic solution was then acidified and extracted with ether. Acid 18 (1 g.) was obtained by evaporation of the ether. The crude acid fractions were combined, and dissolved in aqueous potassium hydroxide, and the acid was regenerated. The precipitate was collected and sublimed at 100° (0.5 mm.) to yield 18 (0.7 g., 43%, m.p. 160–166°). The product was crystallized from water to give large colorless plates, m.p. 168–169.5°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.20; H, 8.75. Found: C, 65.17; H, 8.68.

Ethyl 4-carboxamidobicyclo[2.2.2]octane-1-carboxylate (19) with the correct physical properties was prepared from the half-ester 14 by the known procedure.[4,26]

Ethyl 4-(N-Carbethoxy)aminobicyclo[2.2.2]octane-1-carboxylate (20).—A solution of 19 (2.13 g., 0.0095 mole) in ethanol (30 ml.) with sodium ethoxide (0.02 mole) was prepared and protected from light. Excess bromine (2.0 g., 0.012 mole) was added dropwise in the dark at room temperature. After addition, the solution was refluxed for 15 min. and the product isolated according to the procedure of Roberts' group.[4] The yield of urethan 27, m.p. 95–97°, was 1.6 g. (62%). Yields of 30% or less were obtained when the reaction was carried out in light.

1-Carboxy-4-aminobicyclo[2.2.2]octane (21).—The high melting amino acid was prepared and isolated by the known method.[4]

1-Carboxy-4-nitrobicyclo[2.2.2]octane (22).—The oxidation method of Kornblum, Clutter, and Jones[14] was used. The hydrochloride of 21 (0.28 g., 0.014 mole) was dissolved in a basic solution (5 ml.) of potassium permanganate (0.65 g.) in water and stirred. After 1 day, the manganese dioxide was removed by filtration and the residual oxidizing agent in the filtrate destroyed. The solution was acidified, and the product collected and sublimed at 150° (0.5 mm.) to yield 22 (m.p. 251–253°, 20%).

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.60; H, 6.57; N, 7.04. Found: C, 54.56; H, 6.67; N, 6.77.

1-Hydroxymethyl-4-tosyloxymethylbicyclo[2.2.2]octane (23).—Diol 10 (6 g., 0.035 mole) and *p*-toluenesulfonyl chloride (2.3 g., 0.012 mole) were dissolved in pyridine (15 ml.). The reaction mixture was maintained at 0° for 4 hr. and at room temperature for 32 hr. The crude product was isolated in the usual manner. Residual diol (4.0 g.) was removed by sublimation at 100° (0.5 mm.). The residue was chromatographed on alumina. Elution with benzene–ether yielded a small amount of the ditosylate. Elution with ethyl acetate gave product 23 (3 g., 78% yield based on unrecovered starting diol). The product was recrystallized from benzene; m.p. 128–129.5°.

Anal. Calcd. for $C_{17}H_{24}O_4S$: C, 62.80; H, 7.45. Found: C, 63.08; H, 7.46.

1-Hydroxymethyl-4-methylbicyclo[2.2.2]octane (24).—Tosylate 23 (1.6 g., 0.00493 mole) was dissolved in tetrahydrofuran (25 ml.) and added dropwise to a stirred suspension of lithium aluminum hydride (1 g., 0.025 mole) in the same solvent (75 ml.). The mixture was refluxed for 48 hr. The ether solution of the product obtained in the usual way was washed with 4 *N* potassium hydroxide and dried. Evaporation of the ether gave the crude product (1 g.).

1-Methyl-4-carboxybicyclo[2.2.2]octane (25).—Crude alcohol **24** (0.3 g.), potassium permanganate (0.7 g.), and potassium hydroxide (one pellet) were shaken for 4 hr. in water (25 ml.). Ethanol was added to destroy excess oxidizing agent. The mixture was filtered and the residue washed with dilute aqueous base. The filtrate and washings were combined and condensed. The aqueous solution was acidified and the precipitate collected, dried, and sublimed at 100° (0.5 mm.). The sublimate was recrystallized from methanol–water to give white crystals of **25** (0.25 g., m.p. 187–188°).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.40; H, 9.58. Found: C, 71.52; H, 9.60.

The 3-acetyl-3-R-pimelonitriles (R = CH_3, C_2H_5, C_6H_5) were prepared as described by Bruson and Riener.[17] These compounds were hydrolyzed to the corresponding acids by the known procedure[17] and thence converted to 4-acetyl-4-R-cyclohexanones by procedures adapted from the techniques reported by Colonge and Vuillemet.[16,26] The $n^{25}\text{D}$ of 4-acetyl-4-ethylcyclohexanone was found to be 1.4775 in poor agreement with the reported value 1.475.[16] An analysis of the compound was obtained for a complete characterization.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.40; H, 9.58. Found: C, 71.33; H, 9.64.

These acetylcyclohexanones were converted to the corresponding 4-R-bicyclo[2.2.2]octan-3-ones by the methods of Colonge and Vuillemet.[16]

1-Hydroxy-4-methylbicyclo[2.2.2]octane (27a).—Ketol **26a** (5 g., 0.0324 mole), ethanol (50 ml.), and water (70 ml.) were added to a mercury amalgam (prepared from 100 g. of zinc) followed by concentrated hydrochloric acid (40 ml.). The reaction mixture was stirred, heated to reflux, and 350 ml. of concentrated hydrochloric acid added at a rate to keep hydrogen evolution vigorous. When the amalgam was consumed, the cooled solution was extracted with ether. The ether was washed with aqueous base and dried. The solvent was removed and the residue analyzed by v.p.c. The chromatograph revealed one major (90% of total area) and three minor peaks. The impure product was chromatographed on alumina. Elution with *n*-hexane–acetone yielded a white crystalline solid which was sublimed at 70° (25 mm.) to provide **27a** (1.5 g., 33%, m.p. 103–104°). The infrared spectrum showed OH absorption but no carbonyl. The n.m.r spectrum at 60 Mc. showed three singlet peaks at 0.85, 1.7, and 3 p.p.m. from TMS attributable to methyl, methylene, and OH absorptions, respectively.

Anal. Calcd. for $C_9H_{16}O$: C, 77.05; H, 11.50. Found: C, 77.13; H, 11.91.

1-Hydroxy-4-ethylbicyclo[2.2.2]octane (17b).—Compound **27b** was prepared from ketoalcohol **26b** by the method described for the methyl homolog. The yield of product, m.p. 104.5–106°, was 40%.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.70; H, 11.51.

Ethylenedithioketals of 1-Hydroxy-4-substituted 3-Bicyclo[2.2.2]octan-3-one (28abc).—Compounds **28abc** were prepared by the method of Roberts, *et al.*[4] Thioketal **28a** (4-methyl-) was recrystallized from cyclohexane; m.p. 112–113°.

Anal. Calcd. for $C_{11}H_{18}OS_2$: C, 57.32; H, 7.87. Found: C, 57.55; H, 7.76.

Thioketal **28b** (4-ethyl-) was recrystallized from cyclohexane and sublimed at 90° (0.5 mm.), m.p. 94–94.5°.

Anal. Calcd. for $C_{12}H_{20}OS_2$: C, 58.94; H, 8.25. Found: C, 58.99; H, 8.51.

Thioketal **28c** (4-phenyl-) was recrystallized from 95% ethanol; m.p. 190–191°.

Anal. Calcd. for $C_{16}H_{20}OS_2$: C, 65.70; H, 6.89. Found: C, 65.55; H, 6.70.

4-Phenyl-1-hydroxybicyclo[2.2.2]octane (27c).—Attempts to prepare **27c** by the method used for **27a** and **27b** failed. It (**27c**) was prepared from dithioketal **28c** by the desulfurization method of Georgian, *et al.*[18] Dithioketal **28c** (25 g., 0.085 mole) and hydrazine hydrate (45 ml.) were dissolved in a solution of potassium hydroxide (40 g.) in diethylene glycol (220 ml.). The reaction was carried out in the usual way. The residue obtained by ether extraction was poured into 75 ml. of hot cyclohexane and after cooling fine white needles precipitated. The product was dried and sublimed at 120° (0.5 mm.). The total yield of sublimate **27c**, m.p. 122–123°, was 7 g., 40%.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.10; H, 8.96. Found: C, 83.33; H, 9.20.

This procedure gave only small amounts of **27a** and **27b** when applied to thioketals **28a** and **28b**. These thioketals were reduced to alcohols **27a** and **27b** by Raney nickel desulfurization.[4] The products of this reaction were identical in all respect with the alcohols described above.

1-Bromo-4-substituted Bicyclo[2.2.2]octanes (29abc).—Compounds **29abc** were prepared from **27abc** by the method of Sayigh.[6] Bromide **29a** (4-methyl) was sublimed at 70° (1 mm.), m.p. 92–94°.

Anal. Calcd. for $C_9H_{15}Br$: C, 53.17; H, 7.44; Br, 39.32. Found: C, 53.42; H, 7.36; Br, 39.35.

Bromide **29b** (4-ethyl) was purified in the same way; m.p. 34–35°.

Anal. Calcd. for $C_{10}H_{17}Br$: C, 55.3; H, 7.88; Br, 36.80. Found: C, 55.25; H, 7.88; Br, 36.86.

Bromide **29c** was purified in the same way; m.p. 109–110°.

Anal. Calcd. for $C_{14}H_{17}Br$: C, 63.40; H, 6.46; Br, 30.13. Found: C, 63.48; H, 6.42; Br, 30.21.

1-Carboxy-4-ethylbicyclo[2.2.2]octane (31).—Acid **31** was prepared from bromide **29a** by the method described by Koch[19] and used by Stetter, *et al.*,[20] for the conversion of bromoadamantane to the corresponding acid. Concentrated sulfuric acid (98%, 150 ml.) and silver sulfate (1.3 g., 0.0042 mole) were cooled to 5° and a solution of bromide **29a** in *n*-hexane (5 ml.) was added followed by dropwise addition of 98% formic acid (1 ml.) over a period of 3 hr. When carbon monoxide evolution ceased, the solution was poured on ice (600 g.) and the product isolated in the usual way and sublimed at 105° (1 mm.). The sublimed product was recrystallized from methanol–water, yielding white platelets of **31** (0.7 g., 49%, m.p. 170.5–171°).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.50; H, 9.87. Found: C, 72.47; H, 9.71.

1-Carboxy-4-methylbicyclo[2.2.2]octane (25) was prepared in 30% yield by the method used for **31**. The product was identical in all respects with the acid obtained by the oxidation of **24**.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.40; H, 9.58. Found: C, 71.52; H, 9.60.

1-Cyano-4-phenylbicyclo[2.2.2]octane (30).—Compound **30** was prepared from the corresponding bromide **29c** by a method described by Reinhardt for biadamantyl dibromide.[21] Bromide **29c** (4 g., 0.015 mole), cuprous cyanide (5 g., 0.056 mole), and pyridine (25 ml.) were heated slowly to 210° as pyridine distilled. After cooling, the residue was extracted with benzene for 24 hr. to give **30** (1.3 g.). Recrystallization from methanol gave an analytical sample, m.p. 142–143.5°. The substance exhibited a C≡N absorption at 2275 cm.$^{-1}$.

1-Carboxy-4-phenylbicyclo[2.2.2]octane (32).—Nitrile **30** (0.2 g., 0.0094 mole), ethanol (7 ml.), water (2 ml.), and potassium hydroxide (0.5 g., 0.0089 mole) were refluxed for 18 hr. The ethanol was evaporated, water (5 ml.) was added, and the reaction mixture was filtered. The filtrate was acidified, and the white precipitate collected and washed with water. It was then sublimed at 150° (1 mm.) to yield **42** (0.17 g., 77%, m.p. 293–294°).

Anal. Calcd. for $C_{15}H_{18}O$: C, 78.15; H, 7.87. Found: C, 78.34; H, 7.83.

1,4-Dichlorobicyclo[2.2.2]octane (33).—Perchlorocoumalin (kindly donated by Hooker Chemical Co.) was converted to 1,4-dichlorobicyclo[2.2.2]octane by Kauer's[22] method. The product had m.p. 239–240°.

1-Chloro-4-hydroxybicyclo[2.2.2]octane (34).—Silver sulfate (8.63 g., 0.0279 mole) was dissolved in sulfuric acid (96%, 200 ml.), and dichloride **43** (5.0 g., 0.0279 mole) added. *n*-Heptane (20 ml.) was added and the temperature was slowly raised to 70° when a heavy white precipitate formed. The reaction mixture was cooled to 5° and filtered into ice (500 g.). The aqueous solution was extracted with ether. Removal of ether yielded a residue which was sublimed at 120° (1 mm.) and chromatographed on alumina. Elution with cyclohexane gave starting material (1.9 g.). Elution with ether–acetone gave chloroalcohol **34** (1.6 g., 58%) which was recrystallized from methanol–water and sublimed at 100° (1 mm.), m.p. 173–175°.

Anal. Calcd. for $C_8H_{13}ClO$: C, 59.80; H, 8.16; Cl, 22.05. Found: C, 59.81; H, 8.38; Cl, 22.20.

1-Cyano-4-chlorobicyclo[2.2.2]octane (35) was prepared under reaction conditions discussed by Newman and Boden for aryl halides.[23] Dichloride **33** (7 g., 0.0394 mole), cuprous cyanide (5 g., 0.0558 mole), and N-methylpyrrolidone (20 ml.) were refluxed 14 hr.; additional cuprous cyanide (5 g., 0.0558 mole) was added and reflux was continued for 72 hr. The product was isolated by the method recommended by Friedman and Shechter.[24] The material isolated (4 g.) was sublimed at 110° (1 mm.) and then chromatographed on acid-washed alumina. Elution with carbon tetrachloride gave starting dichloride **33** (2.1 g.). Elution with acetone yielded **35** (1.2 g., 26%, m.p. 107–109°). The C≡N absorption was at 2280 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.70; H, 7.13; Cl, 20.88. Found: C, 63.75; H, 7.25; Cl, 20.70.

1-Chloro-4-carboxybicyclo[2.2.2]octane (36).—Compound **35** (2.5 g., 0.0148 mole) was hydrolyzed with concentrated hydrochloric acid (140 ml.) at reflux for 18 hr. After cooling, the mixture was poured into cold water and the product taken up in ether. The ether solution was extracted with cold 3 *N* potassium hydroxide (50 ml.). The basic solution was acidified and the white precipitate collected, washed with water and sublimed at 120° (1 mm.). The sublimate was recrystallized from methanol–water to yield **46** (1.9 g., 68%, m.p. 268–269°).

Anal. Calcd. for $C_9H_{13}ClO_2$: Cl, 18.78. Found: Cl, 18.77.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO, CHICAGO 37, ILLINOIS]

Dissociation Constants for 4-Substituted Bicyclo[2.2.2]octane-1-carboxylic Acids. Empirical and Theoretical Analysis[1]

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Thermodynamic dissociation constants for ten 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in 50% (weight) ethanol–water at 25° have been measured. The σ_I-parameters yield a very precise correlation of the available results for 14 acids in the series. The σ_m and F,F'-constants offer a reasonable but less precise correlation. A theoretical treatment of the data based on Tanford's modification of the Kirkwood–Westheimer model yields calculated values of log (K_X/K_H) in only fair agreement with experiment. This model does, however, predict ΔpK_A for most substituents, hydrogen and alkyl excluded, with good accuracy. A theoretical dissection of log (K/K_H) into cavity and solvent terms reveals the major importance of the cavity transmission of the embedded end of the dipole as suggested by Dewar and Grisdale. Finally, the variations in D_E which are necessary for the identification of linear free energy relationships with electrostatic theory are shown to be the natural consequence of the structures of the acids.

Introduction

The energy change associated with the influence of dipolar and charged groups on the dissociation constants of acids may, in principle, be calculated from electrostatic theory. The early contributions of Bjerrum, Eucken, Smallwood, and Ingold are well known,[3,4] as is the approach of Kirkwood and Westheimer.[3–6] While highly useful for the interpretation of many experimental facts, the Kirkwood–Westheimer theory has proved less reliable for the computation of log (K_X/K_H) for dissociation of substituted carboxylic acids. Roberts and Moreland, for example, found a serious discrepancy between the calculated and experimental log (K_X/K_H) values for 4-bromo- and 4-cyanobicyclo[2.2.2]octane-1-carboxylic acids.[7] Errors of this nature led Tanford to re-examine the approach.[8] He pointed out that the most critical factor was the depth of the dipolar substituent within the cavity and showed that the adoption of a new definition of the cavity size greatly improved the agreement between theory and experiment. The discrepancy, however, remains significant.

More recently, Dewar and Grisdale proposed a somewhat different model.[9] They suggested that substituent effects could be adequately treated by consideration of the charge associated with the end of the dipole embedded within the molecular cavity. Using this idea, they devised a set of substituent parameters capable of the generation of the σ-constants for linear free energy relationships for any structural class. In the past decade, the application of such relationships to aliphatic molecules has been under study. Taft and his associates have shown the many applications of the polar substituent constants, σ_I.[10–12] These constants are related to σ^*, the original polar parameters, by the equation: $\sigma_I = \sigma' = 0.45\sigma^*$.[13] The σ'-constants were assessed from data for the bicyclic acids by the equation of ρ for the ionization of the benzoic acids with that of the aliphatic acids.[7] This approximation is difficult to substantiate empirically or theoretically.[14]

Neither the theoretical nor the empirical foundations of substituent dipole effects are completely secure. Uncertainties remain largely because the information on desirable model compounds is insufficient. Among the aliphatics only three series of carboxylic acids incorporating the substituent in a rigid structure free from resonance or steric interactions—1,4-bicyclo[2.2.2]octane,[7] 1,4-*trans*-cyclohexane,[15] and 1,3-adamantane[16]—have been examined. While these studies provide a basis for a discussion of the problem and for the initiation of new work, we thought it desirable to supplement the known results[7,17,18] for the bicyclo[2.2.2]octane series before undertaking the investiga-

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