Transmission of Substituent Effects in Semirigid Aliphatic Systems. I. Synthesis of a Model

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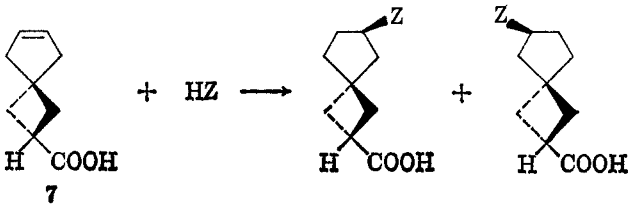
The synthesis of spiro[3.4]-6-octene-2-carboxylic acid is described. The method involves a malonic ester cyclization of 1,1-dimethylol-3-cyclopentene-di-*p*-toluenesulfonate followed by hydrolysis and decarboxylation. The choice and potential utility of this system in separating field and inductive substituent effects is discussed.

Substituent effects which do not find their origin in steric or resonance interactions may be broadly classified as polar effects.[1] In recent years interest has grown in the possibility of evaluating the relative importance of field and inductive effects[2] in this polar component of the total substituent effect.

A careful consideration of previous work in this area[4] points to the need for constructing new molecular systems which may allow a direct experimental separation of field and inductive effects, if indeed they are separable.

We are now initiating such a study. Several criteria may serve as a guide to a successful venture in this direction. First it would appear profitable to limit initial investigations to aliphatic systems or aromatic systems in which one or more saturated carbon atoms intervene between the substituent and the reaction center. Second, long flexible-chain aliphatic or large, flexible alicyclic compounds should be avoided because of ambiguities of interpretation of data resulting from possible steric interactions in coiled conformations. Third, the molecular systems chosen should be sufficiently rigid to allow accurate calculation or measurement of distances between substituents and reaction centers. And finally, it would appear desirable to construct isomeric models in which the inductive effect, if important, would be constrained to operate through identical chain lengths and in which field effects would be expected to differ.

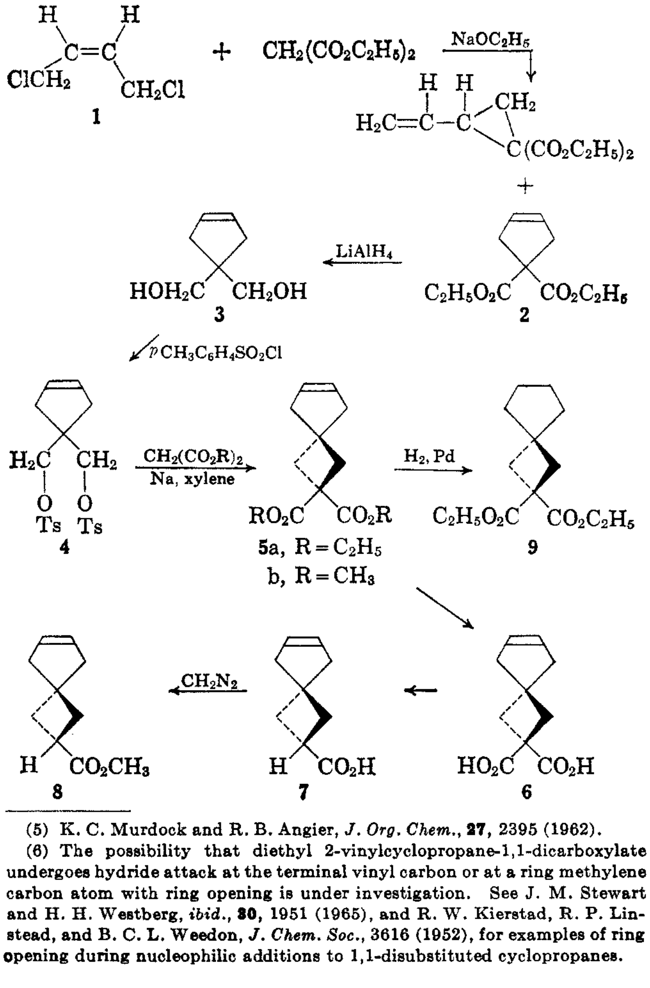
The first model in this study which would seem to satisfy these criteria incorporates the spiro[3.4]octane skeleton. Our first objective was to prepare spiro[3.4]-6-octene-2-carboxylic acid (7), and is described below. Studies of additions to the double bond and the properties of the products will be reported separately.



Results and Discussion

The synthetic route to 7 is shown in Chart I. The *cis*-dichloride (1) was prepared from the corresponding diol using thionyl chloride. The cyclization of 1 with diethyl malonate leads to the desired 1,1-dicarbethoxy-3-cyclopentene (2) contaminated with sizable amounts of the vinylcyclopropane isomer as previously reported by Murdock and Angier.[5] The cyclopentenediol (3) was isolated from the reaction products derived from the lithium aluminum hydride reduction of the mixture of diesters.[6] Characterization of this diol including

Chart I



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[1] R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

[2] The concise definitions used by Roberts and Moreland[3] are useful and are included here in slightly modified form. The term *field effect* is meant to describe that part of the electrical influence of a polar or dipolar substituent which is transmitted to the reaction site through space (including solvent and the molecular cavity bearing the groups) in accord with the laws of classical electrostatics. The term *inductive effect* is used to designate that portion of the electrical influence of a group which is transmitted through a chain of covalently bound atoms primarily by polarization of the intervening σ-bonding electrons.

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

[4] (a) N. Bjerrum, *Z. Physik. Chem.*, **106**, 219 (1923); (b) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 513 (1938); (c) F. H. Westheimer and M. W. Shookhoff, *J. Am. Chem. Soc.*, **61**, 555, 1977 (1939); (d) M. Kilpatrick and W. H. Mears, *ibid.*, **62**, 3047 (1940); (e) J. H. Elliott and M. Kilpatrick, *J. Phys. Chem.*, **45**, 472 (1941); (f) J. D. Roberts and R. A. Carboni, *J. Am. Chem. Soc.*, **77**, 5554 (1955); (g) C. Tanford, *ibid.*, **79**, 5348 (1957); (h) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3539, 3541, 3546, 3548 (1962); (i) H. D. Holtz and L. M. Stock, *ibid.*, **86**, 5188 (1964); (j) C. F. Wilcox, Jr., and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965); (k) K. Bowden, *Can. J. Chem.*, **43**, 3354 (1965); (l) P. E. Peterson, C. Casey, E. V. P. Tao, A. Agtarap, and G. Thompson, *J. Am. Chem. Soc.*, **87**, 5163 (1965); (m) M. J. S. Dewar and A. P. Marchand, *ibid.*, **88**, 354 (1966).

[5] K. C. Murdock and R. B. Angier, *J. Org. Chem.*, **27**, 2395 (1962).

[6] The possibility that diethyl 2-vinylcyclopropane-1,1-dicarboxylate undergoes hydride attack at the terminal vinyl carbon or at a ring methylene carbon atom with ring opening is under investigation. See J. M. Stewart and H. H. Westberg, *ibid.*, **30**, 1951 (1965), and R. W. Kierstad, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952), for examples of ring opening during nucleophilic additions to 1,1-disubstituted cyclopropanes.

unequivocal nmr proton assignments has been described.[7] Conversion of **3** to the corresponding ditosylate (**4**) proceeded in 90% yield. The nmr spectrum of **4** clearly shows that no isomerization of the double bond occurred. Cyclization to **5a** was effected in a solution of boiling xylene containing sodio diethyl malonate according to a general procedure developed by Buchta and Geibel.[8] The unsaturated dimethyl ester (**5b**) was prepared similarly from **4** using sodio dimethyl malonate. The nmr spectra for **5a** and **b** are in complete agreement with the proposed structures. In addition to the protons of the ester groups they each show three singlets (τ 4.52, 7.28, and 7.60 for **5a** and τ 4.43, 7.48, and 7.57 for **5b**) with integrated areas in the ratios 1:2:2. Catalytic hydrogenation of **5a** to the corresponding known[8] saturated spirane diester (**9**) serves as confirmation of the structure of **5a**. Basic hydrolysis of **5a** to diacid **6** proceeded in high yield (88%), but difficulty was encountered in effecting the decarboxylation. Although 3-cyclopentene-1,1-dicarboxylic acid reportedly[5] undergoes smooth thermal decarboxylation in high yield (93%) and similar successes have been reported in thermal decarboxylations of cyclobutane 1,1-dicarboxylic acids, the thermal decomposition of **6** was accompanied by extensive polymerization. The highest yield of **7** obtained by this procedure was 56%. However, when a sample of the diacid (**6**) was boiled in a solution of pyridine for several hours and then worked up by continuous ether extraction of an acidic aqueous solution of the products, the desired monoacid was obtained in 95% yield. This method would appear to be particularly useful for decarboxylation of substituted malonic acids bearing other thermally unstable groups.

In preparation for hydroboration studies, **7** has been converted to methyl ester **8** by treatment with diazomethane.

Experimental Section[9]

1,1-Dimethylol-3-cyclopentene-di-*p*-toluenesulfonate (4).—To a stirred solution of 15.0 g (0.117 mole) of diol **3** in 100 ml of dry pyridine, was added, in portions, 50.0 g (0.263 mole) of *p*-toluenesulfonyl chloride. The solution was stirred under a nitrogen atmosphere for 3 hr at 0°. The resultant pasty mixture was poured into cold 6 *N* hydrochloric acid. The crude ditosylate (49 g) was collected on a filter and then recrystallized from methanol affording 46 g (90%) of colorless crystals, mp 108–110°. A small portion of **4** was recrystallized again from methanol giving a product which melted at 110.5–111.5°.

Anal. Calcd for $C_{21}H_{24}O_6S_2$: C, 57.78; H, 5.54; S, 14.69. Found: C, 57.93; H, 5.63; S, 14.37.

The infrared spectrum (5% in chloroform) shows strong bands at 1183 (S=O) and at 1374 cm^{-1} (CH_3). The nmr spectrum (9% in chloroform) shows four singlets at τ 4.50, 6.10, 7.56, and 7.85 attributable to vinyl, CH_2OTs, CH_3, and allyl protons, respectively. The corresponding peak intensities were found in ratios of 1:2:3:2. The aromatic protons were masked by the solvent.

Diethyl Spiro[3.4]-6-octene-2,2-dicarboxylate (5a).—Sodium (3.5 g, 0.15 g-atom) was dispersed in 200 ml of xylene by heating the solvent until the sodium melted and then stirring the mixture vigorously. To the granular sodium suspension was added, dropwise, 33.0 g (0.206 mole) of diethyl malonate. This mixture was then heated until a red-brown solution was obtained. To this solution was added in several portions 30.0 g (0.0688 mole) of ditosylate **4**. The solution was then heated to boiling (approximately 150°) for 38 hr under an atmosphere of nitrogen. The solution was cooled and poured into 200 ml of water. The organic layer was separated and the aqueous phase was extracted with three 150-ml portions of xylene. The combined xylene extract was washed with 1 *N* hydrochloric acid and water, and then dried over magnesium sulfate. The extract was concentrated under reduced pressure. To the viscous residue was added 25 ml of methanol. After standing overnight at 0° the solution deposited 11.2 g (37%) of unreacted ditosylate. Solvent was again removed and the residue distilled. The main fraction was collected from 98 to 105° at 0.2 mm ($n^{20}D$ 1.4622) and amounted to 7.16 g (66% based on unrecovered **4**). A thin layer chromatograph of this sample on silica gel revealed the presence of only one product (5% ethyl acetate in benzene used as eluent solvent). An analytical sample was collected from a vapor phase chromatographic column (packed with 20% silicone oil on firebrick) at 210°.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.42; H, 8.19.

The infrared spectrum (neat) of the diester **5a** shows a strong band at 1745 cm^{-1} (ester C=O). The nmr spectrum (12% in benzene) shows the following features (chemical shift in τ values, relative number of protons from peak areas, and assignments): A singlet at 4.52, two protons, vinyl hydrogen; a quartet centered at 5.98, four protons, CH_2 in ethyl groups; a triplet centered at 9.03, six protons, CH_3 in ethyl groups; a singlet at 7.28, four protons, allyl protons; a singlet at 7.60, four protons, cyclobutane methylene protons. The chemical shifts (listed in the same order) observed in carbontetrachloride (10% solution) are τ 4.43, 5.83, 8.74, 7.48, and 7.56. The assignments for the cyclopentene and cyclobutane methylene protons must be considered tentative at this time and may in fact be reversed.[10] This is true also for the assignments given for **5b** and **6**.

Dimethyl Spiro[3.4]-6-octene-2,2-dicarboxylate (5b).—The same procedure used in the preparation of **5a** was employed. The reaction was carried out in 100 ml of xylene starting with 1.75 g (0.0761 g-atom) of sodium, 13.6 g (0.103 mole) of dimethyl malonate and 15.0 g (0.0344 mole) of the ditosylate **4**. The same isolation procedure yielded 8.9 g (59%) of unreacted **4** and 1.2 g of impure **5b**, bp approximately 95° (0.45 mm). A vapor phase chromatogram[11] indicated that the sample was comprised of approximately 85% **5b**. The major contaminant was dimethyl malonate. A pure sample of the dimethyl ester **5b** was collected from a preparative vapor phase chromatography column (silicone on firebrick) at 180°.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.32; H, 7.19. Found: C, 64.11; H, 7.37.

The nmr spectrum (9% in carbon tetrachloride) shows the following features: a singlet at τ 4.43 two protons, vinyl hydrogen; a singlet at 6.29, six protons, OCH_3; a singlet at 7.48, four protons, allyl protons; and a singlet at 7.57, four protons, cyclobutane methylene protons.

Spiro[3.4]-6-octene-2,2-dicarboxylic Acid (6).—A mixture of 4.16 g of potassium hydroxide in 37 ml of ethanol and 6.10 g (0.0242 mole) of the diethyl ester **5a** was boiled under reflux for 1 hr. The resulting slurry was cooled and filtered. The insoluble dipotassium salt was rinsed with 30 ml of ethanol and then

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[7] E. J. Grubbs and D. J. Lee, *J. Org. Chem.*, **29**, 3105 (1964).

[8] E. Buchta and K. Geibel, *Ann.*, **648**, 36 (1961).

[9] The melting points were determined on a Fisher-Johns apparatus and are corrected. The infrared spectra were obtained using either Perkin-Elmer Models 321 or 621 infrared recording spectrophotometer unless otherwise indicated. Nmr spectra were obtained with a Varian Model A-60 spectrometer. Tetramethylsilane served as the reference standard for chemical shifts. The elemental analyses were performed by either West Coast Analytical Laboratories, Inc., or by Mr. C. F. Geiger.

[10] An examination of the nmr spectra of numerous olefinic compounds and their saturated analogs reveals that protons even remotely located from the carbon–carbon double bonds undergo small upfield shifts upon hydrogenation. It was hoped that this might prove useful in making assignments for the ring methylene protons in **5a**, **5b**, and **6**. Accordingly we compared the chemical shifts of the exocyclic (CH_2O) methylene protons (τ 6.33) in **3** and in 1,1-dimethylol cyclopentane (τ 6.41) under identical conditions (dilute carbon tetrachloride). Hydrogenation in this case causes an upfield shift of 0.08 ppm. In **5a** the two singlets for the two sets of ring methylene protons absorb at τ 7.48 and 7.56. In **9** the one singlet remaining in this region is at τ 7.61 (the cyclopentane protons appear as a singlet at τ 8.42). In this case either the lower field peak in **5a** represents the cyclobutane methylene protons and undergoes a 0.13-ppm upfield shift upon hydrogenation or the higher field singlet in **5a** represents the cyclobutane protons and moves 0.05-ppm upfield when hydrogenated. The latter appears a little more likely in light of the comparison with **3**, but these results are only suggestive. Definitive assignments must await isotopic substitution as employed[7] in making unequivocal assignments for the protons in **3**.

[11] The column was packed with silicone oil on firebrick and maintained at 160°.

dissolved in 30 ml of water. This solution was acidified with 10 ml of 50% sulfuric acid. The solution deposited the crude diacid as colorless crystals. One recrystallization from 20 ml of water afforded 3.75 g (88%) of the diacid **6**, mp 165–169°. An analytical sample was prepared by recrystallizing a small portion again from water, mp 166.5–168°.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17; neut equiv, 98.1. Found: C, 61.12; H, 5.98; neut equiv, 99.3.

The nmr spectrum of **6** was obtained as a 5% solution in trifluoroacetic acid with tetramethylsilane as an external standard. It shows three singlets at τ 4.29, 7.10, and 7.35 with relative intensities of 1:2:2. The lowest field peak is attributable to vinyl hydrogen and the remaining singlets to cyclopentene and cyclobutane methylene protons. The infrared spectrum (potassium bromide disk using a Perkin-Elmer Infracord recording spectrophotometer) showed absorption bands at 1705 (C=O) and a broad envelope band in the region 2700–3500 cm^{-1} attributable to a combination of O—H and C—H stretching vibrations.

Spiro[3.4]-6-octene-2-carboxylic Acid (7). A. Pyrolytic Decarboxylation without Solvent.—A 0.900-g (0.00459 mole) sample of diacid **6** was placed in a sublimator fitted with a cold finger well which was filled with Dry Ice and acetone. The sample was heated to 185° at atmospheric pressure. At this temperature the diacid underwent thermal decarboxylation and monoacid **7** condensed on the cold finger and on the upper side walls of the sublimator. Considerable polymerization occurred during the decarboxylation. The crude monoacid was recrystallized from dilute acetic acid affording in two crops, 0.675 g (56%) of colorless crystals, mp 35–38.5°. A small sample recrystallized from dilute acetic acid showed a melting point of 36–37°.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95; neut equiv, 152. Found: C, 71.08, 71.03; H, 8.49, 8.48; neut equiv, 151.7.

B. Decarboxylation in Boiling Pyridine.—Diacid **6** (2.15 g, 0.0110 mole) was dissolved in 12 ml of pyridine and boiled under reflux for 5.5 hr. The solution was cooled, acidified with 28 ml of 6 *N* hydrochloric acid, and continuously extracted with ether for 18 hr. The ether extract was dried and concentrated leaving 1.67 g of the monoacid as a brown solid, mp 25–29°. This sample was dissolved in ether, treated with activated charcoal, filtered, and concentrated to give the nearly colorless acid (1.59 g, 95%), mp 32–36°.

Methyl Spiro[3.4]-6-octene-2-carboxylate (8).—The ester was prepared by dropwise addition of an ethereal solution of diazomethane[12] to 1.59 g (0.0105 mole) of monoacid **7**. After removing the solvent, the ester was obtained as a pale yellow oil (1.64 g, 99%). A gas chromatogram[13] of this product exhibited only one peak. A small sample (150 mg) was distilled through a Hickman still under reduced pressure (2 mm), pot temperature 49°, affording 133 mg of a colorless oil, $n^{23.5}\mathrm{D}$ 1.4867.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.95; H, 8.38.

The infrared spectrum (10% solution in carbon tetrachloride) shows a sharp band at 1732 (ester C=O) and a medium intensity band at 3060 cm^{-1} (*cis*-disubstituted olefin C—H stretch). The nmr spectrum (10% solution in carbon tetrachloride) shows a singlet at τ 4.40, a singlet at 6.37, a quartet centered 7.08, and a complex multiplet in the region from 7.45 to 8.0. The ratios of the corresponding integrated areas closely approximate 2:3:1:8. The proton assignments in this order are vinyl hydrogen, methyl ester hydrogen, the single hydrogen at C_2 (split by *cis* and *trans* hydrogens at C_1 and C_3), and the remaining methylene hydrogens. The coupling constant associated with splitting of the tertiary proton at C_2 is 8 cps.

Diethyl Spiro[3.4]octane-2,2-dicarboxylate (9).—A sample of unsaturated diethyl ester **5a** (0.863 g, 0.00342 mole) was hydrogenated in an ethanolic solution containing palladium on charcoal. After hydrogen uptake ceased, the catalyst was separated, the ethanol was distilled, and the product was finally distilled through a Hickman still affording 0.510 g (59%) of **9**, $n^{24}\mathrm{D}$ 1.4530. The sample distilled when the pot temperature reached 110° (1.5 mm) [lit.[8] bp 104–105° (0.2 mm)]. This sample proved to be approximately 98% pure. A pure sample was collected from a vapor phase chromatography column (Apiezon on Chromosorb W). The nmr spectrum of **9** (in dilute CCl_4) shows a quartet and triplet centered at τ 5.84 and 8.76, respectively, attributed to the ester protons and two singlets at 7.61 and 8.42 attributed to the cyclopentane and cyclobutane protons, respectively. The ratios of integrated areas are in accord with these assignments.

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[12] The diazomethane was generated from Du Pont EXR-101 which contains 70% N,N′-dinitroso-N,N′-dimethylterephthalamide and 30% mineral oil.

[13] The chromatogram was obtained with a 6-ft column packed with silicone oil suspended on Chromosorb W.

Indoles, Benzofurans, Phthalides, and Tolanes *via* Copper(I) Acetylides

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The reaction of cuprous acetylides with *o*-iodoanilines, *o*-halophenols, and *o*-halocarboxylic acids is a general and convenient route to 2-substituted indoles, 2-substituted benzofurans, and 3-alkylidenephthalides. The reaction to produce indoles is markedly dependent upon solvent. *o*-Aminotolanes are smoothly cyclized to indoles by treatment with cuprous iodide in dimethylformanide. *ortho*-Substituted tolanes and polyacetylenes are readily prepared from the acetylides.

We have briefly described the beginnings of a tolane and heterocyclic synthesis based upon the substitution of aryl iodides with cuprous acetylides.[1] We now wish to portray the general scope and utility of these reactions and to correct some errors present in the original studies.

A series of recent reports[2] have delineated the sensitivity of aryl halides toward substitutions with a variety of ligands of cuprous salts (reactions 1 and 2).

$$\mathrm{ArX + CuY \longrightarrow ArY + CuX} \qquad (1)$$

$$\mathrm{ArX + HY + Cu_2O \longrightarrow ArY + Ar\dot{H} + Ar_2} \qquad (2)$$

The ease of replacement of halogen (X) was found to be in the order I > Br > Cl ≫ F, while the efficacy of the cuprous species varied with the nature of the ligand (Y) in the sequence Cl > Br > I > CN > SPh > SCN. A rate expression first order in each reactant was obtained (eq 1). Moreover, as a part of the same study, cuprous acetate was found to dehalogenate reductively *o*-bromonaphthalene (eq 3) in pyridine.

[1] C. E. Castro and R. D. Stephens, *J. Org. Chem.*, **28**, 2163 (1963); R. D. Stephens and C. E. Castro, *ibid.*, **28**, 3313 (1963).

[2] R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1097, 1108, 1117 (1964).