NOTES

Nuclear Magnetic Resonance Studies. XXIII. Long-range ^1H–^1H Couplings (J_{HCCOCH}) in some Methyl Bicyclo[2.2.1]heptane-2-carboxylates[1]

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The methoxyl proton signals of several 3-substituted 2-carbomethoxybicyclo[2.2.1]hept-5-enes and -heptanes appear as doublets because of ^1H–^1H coupling over five σ-bonds (^5J). The dependence of these long-range coupling constants on the nature and orientation of 2- and 3- substituents is discussed in terms of the probable conformations of the 2-carbomethoxyl groups.

Les signaux des protons du groupe méthoxy de quelques carbométhoxy-2 bicyclo[2.2.1]heptènes-5 et heptanes substitués en position-5 apparaissent sous forme de doublets par suite du couplage ^1H–^1H à travers cinq liaisons σ (^5J). La relation entre ces constantes de couplage à longue distance et la nature et l'orientation des substituants en position-2 et -3 est discutée à la lumière des conformations probables des groupes carbométhoxy-2.

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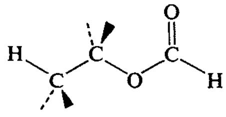
Long-range proton–proton coupling interactions over five bonds, ^5J, have been reported for a variety of systems (1) but the majority of these occur through an unsaturated bonding network. There are relatively few reports of coupling constants between protons separated by five σ-bonds. One of the first reported examples, however, is the long-range coupling observed in the spectra of formic acid esters (2) between the formyl proton and the protons on the β-carbon of the alkyl group, **1**. Other carboxylic acid esters were expected to exhibit similar interactions since the nearest protons are separated by five bonds, **2**, and Hayamizu and Yamamoto (3) subsequently reported measurements of these couplings for a series of 14 saturated aliphatic esters as well as for three unsaturated systems. These compounds exhibit a small, but readily resolved, ^5J splitting either in the methoxyl signals of the methyl esters or in the α-proton absorption of the substituted acetates with values in the range, 0.1–0.25 Hz. Although the signs are not easily determined, the authors assumed these to be positive by analogy with the results for several saturated formic acid esters (4); in the latter series the five-bond couplings are +0.52 ± 0.1 Hz (4). A few additional examples have been reported more recently by Riggs and Verma (5) who ascribed the couplings to transmission through planar "extended-W" σ-bond systems (**1** and **2**) with the ester group serving to maintain "the necessary degree of planarity". It had been suggested earlier (6), however, that the contribution of resonance forms such as **3** may be a factor although five-bond couplings are known in systems in which such resonance forms cannot contribute. Examples of the latter include $^5J_{14}$ and $^5J_{25}$ for the equatorial protons in pyranose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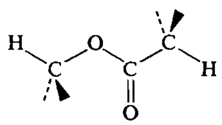
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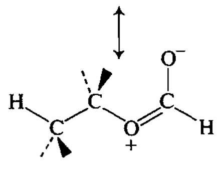
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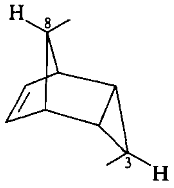
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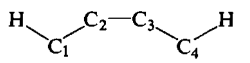
[1] For Part XXII, see Stothers *et al.* (13).
[2] Holder of NRCC scholarships, 1966–1970.

derivatives (7), similarly, $^5J_{25}$ for 1,3-dioxane (8) and $^5J_{3_x8_s}$ in **4** (9). According to Barfield and Chakrabarti (1), the indirect mechanism for coupling over five bonds in a fragment of σ-bonds, *e.g.* **5**, leads to a dependence on dihedral angles specified as in eq. 1; where ϕ and ϕ' are

$$[1] \quad {}^5J_{\mathrm{HH}} = (A\cos^2\phi + B\cos\phi + C)(A\cos^2\phi' + B\cos\phi' + C)$$

dihedral angles involving the terminal C—H bonds (see **6**); maximum coupling occurs for $\phi = \phi' = 180°$, but $^5J_{\mathrm{HH}}$ is independent of the dihedral angle about the central C_2—C_3 bond in **5**. In the course of an investigation of the ^1H and ^{13}C spectra of an extensive series of 3-substituted norbornene- and norbornane-2-carboxylic acid derivatives, **7** and **8**, we have observed five-bond coupling constants in several methyl esters between the methoxyl protons and the C-2 methine proton, *i.e.* J_{HCCOCH}, which we wish to report here.



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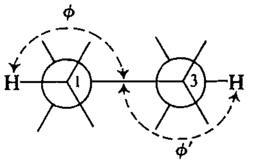

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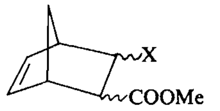

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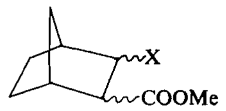

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The data are listed in Table 1 for a series of 22 norbornene-2-carboxylic methyl esters and 20 methyl norbornane-2-carboxylates. Most of these were obtained by measurements of the wiggle-beat patterns (10) produced by rapid scanning through the methoxyl signals. Although the methoxyl absorption appears as a closely spaced doublet in the normal spectrum, more precise measurements of the spacing are possible with the wiggle-beat technique; the precision of the tabulated data is judged to be ±0.02 Hz.

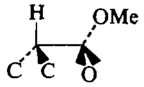
It is apparent that the long-range coupling in the *exo*-esters is independent of the nature of the *endo*-3-substituents and is slightly attenuated by increasingly bulky *exo*-3-substituents. As expected these ^5J values are independent of the nature of the 5,6 bond; ^5J is essentially the same in both the norbornene and norbornane derivatives. Greater variations in ^5J are found for the *endo*-esters, with the largest values exhibited by the *exo*-3-substituted compounds, averaging 0.27 Hz in the norbornenes. The coupling appears to be slightly smaller in the corresponding norbornanes while ^5J for the *endo*-3-substituted *endo*-2 esters is comparable to that found for the *exo*-esters. There is no marked trend attributable to substituent polarity, but all ^5J values are equal to or smaller than the ^5J for the corresponding unsubstituted esters.

TABLE 1. Long-range J_{HCCOCH} values* for some 2-carbomethoxynorbornenes **7** and -norbornanes **8**

C-3 Substitution	*endo*-2-COOMe		*exo*-2-COOMe	
	7	**8**	**7**	**8**
endo-OCH_3	0.18	—	0.19	0.19
endo-Cl	0.18	0.15†	0.18	0.18
endo-Br	0.17	0.17	0.19	0.18
endo-I	0.16	<0.1‡	0.19	0.18
endo-CH_3	0.21	0.18	0.18	0.20
Nil	0.27	0.24	0.18	0.19
exo-OCH_3	0.29	0.23	0.17	—
exo-Cl	0.28	0.23	0.16	0.17
exo-Br	0.28	0.24	0.16	0.14
exo-I	0.28	0.24	0.14	0.13
exo-CH_3	0.27	0.24	0.15	0.14

*In Hz, for CCl_4 solutions.
†By direct measurement of spacing in methoxyl absorption.
‡No wiggle-beat observed, splitting of methoxyl signal not resolved.

These results may be compared with the previously reported values for various acetates (3, 5) as well as with the data for the methyl *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylates, 0.30 and 0.16 Hz, respectively. The latter value is comparable to ^5J of 0.19 Hz for methyl isobutyrate, an acyclic analog for the cyclic systems. Since the methoxyl group is essentially unhindered in each of the cyclic systems and consequently ϕ can be the same in each, the variation in ^5J must arise from differences in the relative orientation of the carbonyl group with respect to the α-methine proton. There is a general tendency for carbonyl groups to eclipse one of the bonds to the α-carbon (11). Thus the two nonequivalent rotamers available to the cyclohexanecarboxylates may be represented as **9** and **10**, of which **9** will be destabilized in the *cis*-4-*t*-



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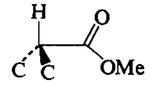

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butylcyclohexyl systems because of nonbonded interactions between the carbonyl oxygen and the axial 3-(5-)proton. In **10**, $\phi = 180°$ (*vs.* 60° in **9**); consequently the increase in ^5J for an axial carbomethoxyl relative to that for the equatorial group is readily rationalized. The difference in ^5J values for *exo*- and *endo*-carbomethoxyl groups bonded to the norbornenyl and norbornyl skeletons without 3-substituents may be explained similarly since the rotamer in which the carbonyl bond of an *endo*-COOMe eclipses the C_1—C_2 bond is destabilized by interaction with C-6. The fact that, relative to the unsubstituted cases, ^5J is essentially unaffected by *trans*-vicinal substitution, *i.e.* by *endo*-3 and *exo*-3-substituents in the *exo*- and *endo*-esters, respectively, is consistent with this view. In each series, however, *cis*-vicinal substitution tends to decrease ^5J. This tendency suggests that the decrease results from a steric effect which reduces the relative population in the rotamer corresponding to **10** but dipolar repulsion between electronegative atoms at C-3 and the carbonyl oxygen produces the same effect. In addition, there may be an attractive interaction between the 3-substituents and the ethereal oxygen because of resonance forms corresponding to **3**. In any event the dependence of these five-bond couplings on molecular geometry appears to be qualitatively consistent with eq. 1 as predicted earlier (1).

Experimental

Spectra

All spectra were determined with a Varian HA-100 spectrometer equipped with a Sanborn 151 recorder for the wiggle-beat measurements, using 5 mol % solutions in carbon tetrachloride. The precision of the data is estimated to be ±0.02 Hz, although repeated measurements showed less scatter for individual cases. The beat frequency of the wiggles produced by rapidly scanning through the methoxyl absorption gives the separation directly. Decoupling experiments confirmed the origins of the observed coupling.

Materials

All of the methyl esters were prepared from the carboxylic acids by reaction with diazomethane in ether. The carboxylic acids are, for the most part, known compounds and were prepared by the Diels–Alder reaction of freshly distilled cyclopentadiene with the appropriate substituted acrylic acid except for the 3-methoxy derivatives (see below). In each case both isomers formed, with the *endo*-acid as the major product; the *exo*-acid was readily separated from the *endo*-isomer using the iodolactone method. Hydrogenation in ethyl acetate over platinum oxide furnished the norbornanecarboxylic acids. Three of the 3-iodo derivatives have not been described previously; their melting points and elemental analyses are as follows.

exo-3-Iodo-*endo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid; m.p. 136–138°.

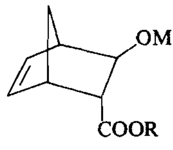
Anal. Calcd. for $C_8H_9O_2I$: C, 36.38; H, 3.44; I, 48.06. Found: C, 36.43; H, 3.44; I, 48.21.

exo-3-Iodo-*endo*-bicyclo[2.2.1]heptane-2-carboxylic acid; m.p. 139–141°.

Anal. Calcd. for $C_8H_{11}O_2I$: C, 36.11; H, 4.17; I, 47.70. Found: C, 36.09; H, 3.90; I, 48.05.

endo-3-Iodo-*exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid; m.p. 105–106°.

Anal. Calcd. for $C_8H_9O_2I$: C, 36.38; H, 3.44; I, 48.06. Found: C, 36.26; H, 3.70; I, 48.13.



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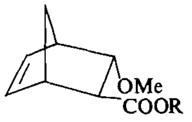

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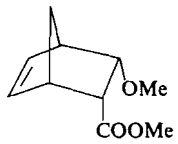

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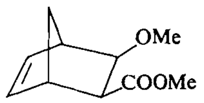

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*3-Methoxybicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Esters **11–14***

These isomers were prepared using a modification of the method described by Miller (12). Propynoic acid (60 g) was added to freshly distilled cyclopentadiene (100 g) at such a rate that the temperature was maintained below 45°, after which the mixture was stirred for 2 h at 40°. Excess cyclopentadiene was removed by evaporation under vacuum and the residue refluxed with methanol (400 ml) containing concentrated H_2SO_4 (2 ml). Polymeric material was removed by filtration and excess methanol evaporated under vacuum. The residue was poured into ice-water and the product (130 g) extracted with methylene chloride which, after removal of solvent, appeared to contain *ca.* 25% of the desired 3-methoxyl substituted esters while the remainder was 2-carbomethoxybicyclo[2.2.1]hepta-2,5-diene. This mixture was dissolved in methanol (250 ml) and benzyltrimethylammonium methoxide (5 g; 40% solution in methanol) was added before the solution was refluxed for 9 h. After removal of methanol, the residue was dissolved in CH_2Cl_2, extracted twice with water, and dried over Na_2SO_4. Fractional distillation of the residue obtained after evaporation of solvent yielded a major fraction containing the *trans* isomers, b.p. 46°/0.4 mm consisting of 94% **11** and 6% **12**. Hydrolysis with 10% Na_2CO_3 solution (200 ml) afforded, by CH_2Cl_2 extraction, a solid residue from which the *endo*-acid (**11**, R = H) was recrystallized from ethyl acetate to yield 22 g, m.p. 109–110°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 64.32; H, 7.19. Found: C, 64.19; H, 7.13.

Neutralization of the mother liquors with 20% NaOH solution, followed by the reaction with I_2/KI solution permitted isolation of 3.5 g of the minor component (**12**, R = H) *ca.* 95% pure; the contaminant was **11**. Repeated attempts to crystallize **12** failed and the product was esterified to give **12** (R = Me) which was employed for the spectral study. Gas chromatography on a column of diethylene glycol succinate (5% on Chromosorb P, 80/100 mesh) and the proton spectrum showed that **11** (R = Me) was the only contaminant. The higher boiling fractions 48–69°/0.4 mm, shown by gas chromatography to contain varying amounts of **11** and **12** (R = Me) as well as the *cis*-isomers **13** and **14**, were combined and dissolved in pentane. At Dry Ice temperatures, **13** slowly crystallized from solution and, after several recrystallizations, 1.69 g, m.p. 28–30° was obtained. A small sample of **14** (0.1 g) was isolated by preparative gas chromatography on a 15′ × 3/8″ column of diethylene glycol succinate (15% on Chromosorb P, 80/100 mesh) at 180°. The retention times (min) for the four isomers were **11**, 34; **12**, 39.5; **14**, 41.5; **13**, 57.5, at a helium flow rate of 120 ml/min. Analytical g.l.c. indicated that the sample of **14** was at least 97% pure.

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Preparation of 5-Aminomethyl-2-thienylacetic Acid from 1-Methylthio-2-(2′-thienyl)ethyne

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A five-step synthesis of 5-aminomethyl-2-thienylacetic acid is described starting from a 2-thienylethynyl thioether.

On décrit une synthèse qui permet de transformer en cinq étapes le méthylthio-1 (thiényl-2)-2 éthyne en acide aminométhyl-5 thiényl-2 acétique.

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In a recent program we required 5-aminomethyl-2-thienylacetic acid. After several unsuccessful attempts to obtain this material via chloromethylation or amidomethylation of 2-thienylacetic acid (or ester) we investigated the use of 1-methylthio-2-(2′-thienyl)ethyne (**1**) as possible starting material. Compound **1** was readily available from 4-(2′-thienyl)-1,2,3-thiadiazole by treatment with *n*-butyllithium at −60° followed by reaction of the resulting lithium 2-thienylethynethiolate with methyl iodide (1).

Lithiation of **1** with *n*-butyllithium at −60° and subsequent reaction with formaldehyde provided the 5-hydroxymethyl thiophene derivative **2** which gave the chloromethyl compound **3** by reaction with thionyl chloride and triethylamine in methylene chloride (Scheme 1). Reaction of **3** with potassium phthalimide in dimethylformamide gave **4**, which could be hydrolyzed to 5-phthalimidomethyl-2-thienylacetic acid (**5**). The hydrolysis was carried out in two stages; **4** was first heated under reflux with dilute sulfuric acid and methanol to give the methylester of **5** which was