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THE CARBOMETHOXY CHEMICAL SHIFT AS A CRITERION OF STEREOCHEMISTRY IN CERTAIN ARYL CYCLOPROPANECARBOXYLATES

G. L. Krueger, F. Kaplan, M. Orchin, and W. H. Faul
Department of Chemistry
University of Cincinnati
Cincinnati, Ohio - 45221

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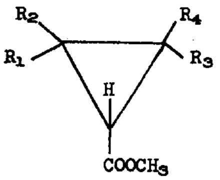
The reactions of styrenes and stilbenes with diazoacetic esters give mixtures of cis- and trans-2-aryl- and 2,3-diarylcyclopropanecarboxylates. Analogous mixtures are obtained from 2-(1,4) and 4-vinylpyridine. Although in the past stereochemical configuration of these isomers has been established by various methods,(1,2,3,4,5,6) we now wish to report that assignments may be made by analysis of the nuclear magnetic resonance (n.m.r.) chemical shifts of the carbomethoxy protons. The carbomethoxy group gives a sharp intense peak. The chemical shift for a series of compounds of known stereochemistry has been measured; the data are summarized in Table I. On the basis of the relationship between chemical shift and stereochemistry it is possible to assign configurations to other structurally related compounds isolated either as separate stereoisomers or as a mixture of cis- and trans-isomers.

With respect to the aryl and diarylcyclopropane derivatives of known stereochemistry, the assignment of a resonance peak to the carbomethoxy group is unambiguous. The partially deuterated carbomethoxy

TABLE I

Chemical Shifts of Carbomethoxy Group in Cyclopropane Derivatives



Compound	R_1	R_2	R_3	R_4	$COOCH_3$[a]
1	H	H	H	H	220.2[b]
2	H	C_6H_5[d]	H	H	220.8
3	H	C_6H_5[e]	H	C_6H_5	224.2
4	H	C_6H_5	H	p-$CH_3OC_6H_5$	224.3
5	H	p-$CH_3OC_6H_5$	H	p-$CH_3OC_6H_5$	224.6
6	C_6H_5[d]	H	H	H	203.2
7	C_6H_5	H	H	C_6H_5	208.1
8[c]	C_6H_5	H	H	p-$CH_3OC_6H_5$	208.6, 209.9
	p-$CH_3OC_6H_5$	H	H	C_6H_5	
9	p-$CH_3OC_6H_5$	H	H	p-$CH_3OC_6H_5$	209.7
10	C_6H_5	H	C_6H_5	H	209.4
11	p-$CH_3OC_6H_5$	H	C_6H_5	H	211.3
12	p-$CH_3OC_6H_5$	H	p-$CH_3OC_6H_5$	H	211.5

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a) Chemical shifts are in cps from tetramethylsilane using a Varian Associates A-60 Spectrometer at 60 Mc. Samples were 15% or less w/w solutions in chloroform or deuterochloroform. The audio-oscillation side band technique was used to calibrate spectra.

b) Spectrum 112, "High Resolution NMR Spectra Catalogue," Varian Associates, Palo Alto, California (1962).

c) A spectrum of a mixture of isomeric compounds was obtained.

d) Corresponding carboxylic acids were provided by Dr. Paul Craig, Smith, Kline and French Laboratories, Philadelphia, Pa.

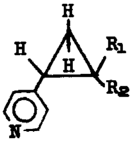
group in compounds 4, 5, 8, 9, 11, and 12 (Table I) were prepared in order to differentiate RCO_2CH_3 resonance peaks from those of $ArOCH_3$. The chemical shifts of the carbomethoxy group of 15% w/w solutions in chloroform or deutereochloroform were insensitive to dilution; however, a change in solvent resulted in significant changes in the positions of the peaks. The positions of the carbomethoxy resonances in 15% w/w solutions in carbon tetrachloride were at higher fields and varied from 0 to 7 cps. compared to chloroform solutions.

When aryl groups are exclusively trans to the carbomethoxy group (the reference group for cis and trans assignment) as in 2, 3, 4, and 5, the chemical shifts range from 220.2 to 224.6 cps. A single trans phenyl group results in a small difference in chemical shifts of the carbomethoxy groups of compounds 1 and 2 (0.6 cps), but the addition of a second trans aryl group results in a decreased shielding of the carbomethoxy group by approximately 3.5 cps.

The proximity of a single cis phenyl group as in 6 results in a large upfield shift of 17.0 cps for the carbomethoxy resonance peak compared to the unsubstituted compound 1. The addition of a second aryl group, at the 3-position cis as in 10, 11, and 12 or trans as in 7, 8, and 9 to the 2-aryl and 1-carbomethoxy groups, lead to a deshielding of the carbomethoxy group of 6.2 to 8.3 cps and 4.9 to 6.5 cps respectively.

These data indicate that the chemical shift of the carbomethoxy group may be used to determine the cis-trans stereochemistry of isomeric compounds. An aryl substituent cis to the carbomethoxy group gives a chemical shift appearing in the region from 203 to 212 cps. The presence of one or two cis aryl substituents cannot be ascertained by this method, but in the absence of any cis aryl substituent the carbomethoxy resonance occurs between 220 and 225 cps. The influence of other types of substituents and solvent systems on the chemical shift cannot be assumed to be negligible and caution should be exercised in extension of this technique. The chemical shift of the aryl methoxy group appears to be of little value for the assignment of stereochemistry.

Our work on arylcyclopropanecarboxylates formed the basis of structure assignments for the corresponding pyridyl compounds. The presence of stereoisomeric cyclopropane derivatives obtained by reaction of 4-vinylpyridine with methyl diazoacetate can be determined from the n.m.r. spectrum of vacuum-distilled samples in carbon tetrachloride solution, approximately 30% w/w.

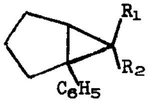


13. R_1 = COOMe, R_2 = H

14. R_1 = H, R_2 = COOMe

The cyclopropane protons of both isomers appear as a complex multiplet (4 protons) from 70 to 160 cps. Two sharp peaks (3 protons) at 218.7 and 203.7 cps, two quartets (2 protons) at 413.8 and 422.7 cps and a multiplet (2 protons) in the region of 498-506 cps are present. The δ COOMe for the cis-isomer, 14, was assigned 203.7 cps and that for the trans-isomer, 13, 218.7 cps, in agreement with similar values reported in Table I. The ratio of trans- to cis-isomer was approximately 2:1. The ratio of protons in the two quartets at 413.8 and 422.7 cps was approximately 2:1 indicating that two pyridyl protons in the 3'- and 5'- positions of the cis-stereoisomer were deshielded more than those of the trans-isomer, presumably due to the anisotropic effect of the carbonyl group.

As a final illustration of the value of n.m.r. data for configurational assignment, the chemical shifts of the carbomethoxy groups in the isomeric compounds 15 and 16 were determined. The values are 221.0 and 202.5 cps and the compound with the absorption at 202.5 cps correctly indicates the presence of an aryl group cis- to the carbomethoxy group (cpd. 16).



15. R_1 = COOMe, R_2 = H

16. R_1 = H, R_2 = COOMe

The isomeric 1-phenylbicyclo[3,1,0]cyclohexane-2-carboxylic acids, m.p. 74.5-77° and 137-138° (4) from which methyl esters 15 and 16 were respectively derived, were kindly provided by Dr. Albert Carr of the Wm. S. Merrell Co., Cincinnati, Ohio. All 2,3-diarylcyclopropanecarboxylic acids were previously prepared by Dr. John Blatchford.(5) Methyl esters (cpds 2-12, 15, 16) were prepared by reaction of diazomethane with free acids in solution. Partially deuterated esters were prepared by using ethereal solutions of diazomethane which had been stirred with a solution of NaOD in D_2O for approximately one hour in an ice bath. The mixture of methyl 2-(4-pyridyl)cyclopropanecarboxylates was prepared from 4-vinylpyridine (Reilly Tar and Chemical Corp.) and methyl diazoacetate(7) in a manner described for the synthesis of ethyl 2-(2-pyridyl)cyclopropanecarboxylates.(4) The n.m.r. spectrum was determined for a sample boiling 115-117° C./2.5 mm. Hg.

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