Table VI

Properties of the *para*-Substituted Benzylidene Derivatives of Lincomycin

Compd no.	Substituent	Formula	Equiv wt Calcd	Equiv wt Found	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % S	Found, % Cl
II	*p*-Cl[a]	$C_{25}H_{38}N_2O_6SCl_2$	567.6	567	53.09	6.77	4.95	5.67	12.54	52.24	7.10	4.65	5.63	11.79
III	*p*-H[a]	$C_{25}H_{39}N_2O_6SCl$	531.1	532	56.53	7.40				55.66	7.59			
IV	*p*-CH_3[a]	$C_{26}H_{41}N_2O_6SCl$	545.1	541	57.28	7.58	5.56	5.88	6.50	56.03	7.76	5.58	5.95	6.31
V	*p*-OCH_3	$C_{26}H_{40}N_2O_7S$	524.6	524	59.53	7.69	5.34	6.10		59.77	7.66	5.34	6.17	
VI	*p*-OH	$C_{25}H_{38}N_2O_7S$	510.7	498	58.80	7.50	5.49	6.28		58.11	7.76	5.42	6.16	

[a] Hydrochloride salts.

distillation. Crystallization was induced with seed crystals. After standing in the refrigerator overnight, the white needlelike crystals were removed by filtration and washed with ether–hexane 1:1. The recovery was 13.2 g after drying at 65° under high vacuum. An additional 4.7 g of product was obtained by adding hexane to the mother liquor giving a total recovery of 17.9 g. Tlc on silica gel G (acetone–ether, 8:2) showed a single compound with R_f 0.8. The compound was recrystallized by dilution of an acetone–ether solution of the compound with hexane.

Kinetic Measurements.—The hydrolysis of lincomycin acetals was followed by observing the appearance of aldehyde in the ultraviolet region of the Cary Model 11 or 15 spectrophotometers. Table VII shows that the progress of the hydrolysis reactions can be followed by observing the appearance of the product spectrophotometrically, since the molar absorptivity of reactant is small compared to that of the product.

In the acidic pH region the rates were fast enough to allow following the complete reaction on the Cary recording spectrophotometer. The Cary 5-cm cell was thermostated to the required temperature within ±0.5°. In the pH region 7–9 the reaction solutions were sealed in ampoules and thermostated in a 70° oil bath for the required times and then assayed on the Cary. The A_∞ values for the 70° runs were calculated from the initial concentration of acetal. The buffers used were chloride for pH 1–3, acetate for pH 3–7, and phosphate for pH 7–9. Potassium chloride was used to adjust the ionic strength to 0.1.

Table VII

Molar Absorptivities of Lincomycin Acetals and Corresponding Aldehydes at the Wavelength of Maximum Absorbance of the Aldehyde

Product	Product, λ_{max}, mμ	a_M (product)	a_M[a] (reactant)
Benzaldehyde	249	11,200	186
p-Chlorobenzaldehyde	260	16,100	247
p-Methoxybenzaldehyde	285	16,800	236
p-Tolualdehyde	262	16,100	275
p-Hydroxybenzaldehyde	284 (pH 1–5)	15,800	500 (pH 1–5)
p-Hydroxybenzaldehyde	330 (pH 9–10)	27,000	400 (pH 9–10)

[a] Molar absorptivity of the lincomycin acetal at λ_{max} of the corresponding aldehyde.

Registry No.—II HCl, 16315-42-7; III HCl, 16315-43-8; IV HCl, 16394-31-3; V, 16315-44-9; VI, 16315-45-0.

Some Structural and Acidity Relationships in Olefinic Carboxylic Acids

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In an attempt to resolve some contradictions between reported experimental data and arguments which relate acidity and structure in β-substituted acrylic acids, the *cis–trans* isomer pairs of β-methyl-, β-ethyl-, β-isopropyl-, β-*t*-butyl-, and β-phenylacrylic acids, and *cis*- and *trans*-2-methylcyclopropanecarboxylic acids were prepared and their dissociation constants were determined by potentiometric titration. The results are shown in Table II. In contrast with earlier reports, the *cis*- and *trans*-β-methylacrylic acids (crotonic acids) have essentially the same dissociation constants. The results remove an inconsistency as to the effect of a *cis*-β-methyl group on the acidity of α,β-olefinic acids, and it is suggested that replacement of a *cis*-β hydrogen by a methyl group results in a decrease in acidity of 0.43–0.44 pK. The general trend in difference of acidity between *cis* and *trans* isomers with increasing size of β substituent is consistent with steric interaction between the *cis*-β substituent and the carboxyl group resulting in an increasing twisting of the carboxyl group out of the olefinic plane.

Attempts to correlate structural features and acidity in carboxylic acids and then interpret the correlations have fascinated chemists over the years. One such correlation, that *cis* isomers of α,β-olefinic carboxylic acids are more acidic than the corresponding *trans* isomers, has been explained by Ingold[2] in terms of steric inhibition of resonance. Thus, "On account of size only we expect a methyl, or a phenyl, or a chlorine substituent, if *cis*-related to the carboxyl group, to cause a twisting of the latter out of the ethylenic plane, and thus to strengthen the acid."[2] That is, the noncoplanarity of the ethylenic and carboxyl groups interferes with the conjugation between these groups which results in destabilization of the acid relative to the corresponding anion, and consequently an increase of acidity. Some doubts about the completeness of this explanation have been raised.[3] Specifically, using published values of acidity constants,[4] it is difficult to see why replacement of a *cis*-β hydrogen by a methyl group should result in ΔpK values of +0.15, +0.43, −0.37, and +0.43 in acrylic acid, *trans*-crotonic acid, methacrylic acid, and *trans*-β-ethylacrylic acid. That is, steric inhibition of resonance, a *cis*-β-methyl group interacting with a carboxyl group, seems to be inadequate to explain acidity changes of different size and even different sign brought about by a constant change in structure. The present work was carried out in order to examine systematically acidity relationships in *cis–trans* pairs of α,β-olefinic carboxylic acids and to use the

(1) Based on the M.S. Thesis of E. A. McCoy.

(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 744.

(3) L. L. McCoy and G. W. Nachtigall, *J. Amer. Chem. Soc.*, **85**, 1321 (1963).

(4) Taken from the values compiled in Table II by McCoy and Nachtigall.[3]

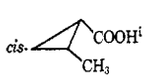
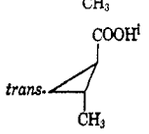
results, if possible, to clarify the difficulties indicated for the "steric inhibition of resonance" explanation.

Experimental Section

Materials.—*trans*-Cinnamic acid and *trans*-crotonic acid were commercial materials recrystallized to constant melting point. *cis*-2-Methylcyclopropanecarboxamide which was converted into the corresponding acid by treatment with nitrous acid was supplied by Dr. D. Applequist. All of the other acids were prepared by methods described in the literature. The melting points and boiling points of the acids and references for their preparation are given in Table I. These physical constants were used only to characterize the acids. Purity and isomeric identity were established for the olefinic acids by nuclear magnetic resonance spectra, and for the cyclopropane acids by infrared spectra.[5] The spectra indicated that all of the acids were isomerically pure (<1% isomeric impurity); for the *cis*-alkyl substituted olefinic acids this is in agreement with observations by Rappe and Adestrom[6]. Less than 1% impurity was present in all acids except the *cis*-β-ethyl-, *cis*-β-isopropyl-, and *cis*-β-*t*-butylacrylic acids which were not distilled so as to minimize possibility of isomerization, but in these cases the only impurity (about 4–6%) appeared to be residual amounts of the solvent ether used in their isolation.[6] These spectral results with regard to impurities were confirmed by the titration results.

TABLE I

PHYSICAL PROPERTIES OF SEVERAL α,β-OLEFINIC ACIDS

Acid	Mp, °C	Bp, °C (mm)
cis-$CH_3CH{=}CHCOOH$[a]		42–42.5 (1.9) [80–81 (26)][b]
trans-$CH_3CH{=}CHCOOH$	71.4–71.8 (71.6)[c]	
trans-$CH_3CH_2CH{=}CHCOOH$[d]		64–65 (1.3) [105 (19)][d]
trans-$(CH_3)_2CHCH{=}CHCOOH$[d]		71–73 (1.3–1.4) [113 (20)][d]
trans-$(CH_3)_3CCH{=}CHCOOH$[e]	61–63.5 (62–63°)[e]	
cis-$C_6H_5CH{=}CHCOOH$[f]	64–67.4 (42, 58, 68)[g]	
trans-$C_6H_5CH{=}CHCOOH$	134–134.6 (132.5–133.5)[h]	
		93–95° (22) [91.0–91.5° (14)][i]
		84–85 (8) [90–91 (11)][i]

[a] Reference 6. [b] A. Dadieu, A. Pongratz, and K. W. F. Kohlrausch, *Monatsh. Chem.*, **60**, 211 (1932). [c] "The Merck Index," 6th ed, Merck and Co., Inc., Rahway, N. J., 1952, p 285. [d] A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, **130**, 2343 (1928). [e] R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Amer. Chem. Soc.*, **72**, 4359 (1950). [f] A solution of *trans*-cinnamic acid in benzene was irradiated with uv light and the resulting *cis–trans* mixture was separated by Faseeh's method [*Pakistan J. Sci. Res.*, **3**, 63 (1951)]. [g] H. Stobbe, *Ann.*, **402**, 187 (1914). [h] C. Paul and W. Hartman, *Ber.*, **42**, 3930 (1909). [i] Reference 5.

Titrations.—Except for minor modifications, *e.g.*, change in volume of acid solution titrated to 10 ml and use of a smaller syringe buret, the titrations were carried out at 25.0° essentially as described in earlier work.[3] Data from these titrations were used to calculate thermodynamic acidity constants[3] which are reported as pK values in Table II.

Discussion

The values shown in Table II lead to a number of conclusions and suggestions. Thus, the pK value for *cis*-crotonic acid determined here is appreciably different from that reported in the literature, but its use removes one of the difficulties which initiated this work. That is, the replacement of the *cis*-β hydrogen in acrylic acid (pK 4.26[4]) by a methyl group to give *cis*-crotonic acid (pK 4.70, this work) gives a ΔpK of +0.44, a value consistent with two of the other cases cited earlier. The reason for the discrepancy between the value reported for *cis*-crotonic acid (pK 4.41[4,7]) and the value determined in this work is not clear. The acid used in the previous work was converted into its sodium salt which was purified; the free acid was liberated from the sodium salt in solution by treatment with hydrochloric acid to obtain the *cis*-crotonic acid free from isomerism in solution.[7] Neither the method of preparation nor the means of determining the purity of the acid, prior to or following purification, are indicated by Larsson and Adell.[7] In the absence of such information, it is suggested that the relatively low pK value reported could be attributed to the presence of a slight excess of hydrochloric acid used in treating the sodium salt or the presence of β-chlorocrotonic acid, a possible precursor of the *cis*-crotonic acid used. We suggest that the reported pK value for angelic acid, also determined by Larsson and Adell,[7] may be incorrect. On the basis that in these compounds under consideration replacement of a *cis*-β hydrogen by a methyl group should produce a constant ΔpK (0.43–0.44), we suggest that the pK for angelic acid should be approximately 5.09.[8]

The pK value for *cis*-crotonic acid observed in this work brings into question the earlier correlation that *cis* acids are stronger than the corresponding *trans* acids. The pK values for the *cis* isomers of both crotonic and β-ethylacrylic acid are, within experimental error, the same as those for the *trans* isomers and it is only with the β-isopropylacrylic acid that a significant difference in pK is apparent. This suggests that in terms of steric effects, the *cis*-β-methyl and *cis*-β-ethyl groups have no more effect on acidity than a *cis*-β hydrogen. It should be noted that the present results for *cis*-crotonic acid remove (invalidate) one of the most frequently cited examples of *cis* acids being stronger than the isomeric *trans* acids.

In spite of this correction, the ΔpK values in Table II clearly show the trend that as the size of the *cis*-β substituent increases the *cis* isomer becomes increasingly more acidic than the *trans* isomer. The ΔpK values differ in a manner similar to the conformational free-energy differences between axial and equatorial orientation for these substituents attached to cyclohexane. This suggests that the substituent interaction with the carboxyl group in the acids is essentially the same as it

(5) Reproductions of the infrared spectra of the cyclopropane compounds were sent to us by Dr. Applequist. A method of isomeric analysis using the infrared spectra has been reported: D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **82**, 2372 (1960).

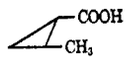
(6) C. Rappe and R. Adestrom, *Acta Chem. Scand.*, **19**, 383 (1965).

(7) E. Larsson and B. Adell, *Z. Phys. Chem.* (Leipzig), **A159**, 315 (1932).

(8) (a) We believe this constant ΔpR value for a *cis*-β-methyl group will hold only so long as there is no appreciable steric interaction between ethylenic substituents located *trans* to the carboxyl group. However, where such interaction does occur, a buttressing effect may result which in turn may cause the *cis*-β-methyl group to interact more strongly with the carboxyl group. Thus, ΔpK for the tiglic acid–trimethylacrylic acid pair may be appreciably less than the 0.43–0.44 range indicated by the acid pairs considered in this work. (b) The value 5.09 is our suggested value only if the methacrylic acid pK value of 4.66 is correct. This value, determined also by Larsson and Adell,[7] used acid for which no data concerning preparation or purity was cited. For reference purposes, we feel the pK of methacrylic acid also should be redetermined. (c) This value of 0.43–0.44 is the same as that suggested by Branch and Calvin ("The Theory of Organic Chemistry," Prentice-Hall Co., Inc., New York, N. Y., 1946, pp 237–238) for the effect of β-alkyl groups (*cis* or *trans*) on acidity constants.

Table II

The Acid Dissociation Constants (pK) of Several α,β-Olefinic Carboxylic Acids at 25.0°

No.[h]	Acid	pK_{trans}	pK_{cis}	ΔpK
1	$CH_3CH{=}CHCOOH$	4.74 ± 0.02 (4.69,[a] 4.71,[b] 4.71,[c] 4.69,[d] 4.71[e])	4.70 ± 0.01 (4.41[f])	0.04
2	$CH_3CH_2CH{=}CHCOOH$	4.74 ± 0.02 (4.69[a])	4.70 ± 0.02	0.04
3	$(CH_3)_2CHCH{=}CHCOOH$	4.75 ± 0.02 (4.70[a])	4.63 ± 0.03	0.12
4	$(CH_3)_3CCH{=}CHCOOH$	4.88 ± 0.02	4.12 ± 0.02	0.76
5	$C_6H_5CH{=}CHCOOH$	4.50 ± 0.01 (4.44[g])	3.93 ± 0.02 (3.88[g])	0.57
6		5.00 ± 0.02	5.02 ± 0.01	−0.02

[a] D. J. G. Ives, R. P. Linstead, and H. L. Riley, *J. Chem. Soc.*, 561 (1933). [b] B. Saxton and G. W. Waters, *J. Amer. Chem. Soc.*, **59**, 1048 (1937). [c] E. Larsson and B. Adell, *Z. Phys. Chem.* (Leipzig), **A157**, 342 (1931). [d] W. L. German, G. H. Jeffery, and A. I. Vogel, *J. Chem. Soc.*, 1604 (1937). [e] L. Otvos and F. Sirokman, *Acta Univ. Szeged., Acta Phys. Chem.*, **2**, 118 (1956); pK determined at 18°. [f] Reference 7. [g] F. F. J. Dippy and R. H. Lewis, *J. Chem. Soc.*, 1008 (1937). [h] Registry no.: 1 (*trans*), 107-93-7, (*cis*), 503-64-0; 2 (*trans*), 13991-37-2, (*cis*), 16666-42-5; 3 (*trans*), 16666-43-6, (*cis*), 1775-44-6; 4 (*trans*), 16666-45-8, (*cis*), 1577-94-2; 5 (*trans*), 140-10-3, (*cis*), 102-94-3; 6 (*trans*), 6202-94-4, (*cis*), 6142-57-0.

is with the axial hydrogens in cyclohexane, *i.e.*, their steric effectiveness is a function of their conformational orientation and not their gross size.[9] An increased twisting of the carboxyl group relative to the ethylenic bond as the effective size of the substituent increases and a consequent increase in "steric inhibition of resonance" is consistent with the ΔpK values observed.[10]

In the sense that, at a maximum, the carboxyl group can be twisted perpendicular to the ethylenic plane, we expect that the effect of substituents on the relative acidity of *cis* and *trans* pairs should reach a maximum with increasing effective size of the *cis*-β substituent. With further increases in size, the *cis*-β substituent should begin to hinder solvation of the carboxyl group,[11] and we would expect a gradual decrease in the difference of acidity between *cis* and *trans* isomers.

The cyclopropane compounds were examined with the initial thought that a *cis*-2 substituent would restrict the carboxyl group to an orientation approaching perpendicular to the cyclopropane ring; such an orientation should enhance the conjugation of the cyclopropane ring and the carboxyl group, and thus *decrease* the acidity of the *cis* isomer relative to the *trans*. Unfortunately, the results do not permit any definite conclusion, *i.e.*, the methyl group might be of inadequate size to restrict the carboxyl group (see discussion of the crotonic acids), or the carboxyl group might already be restricted by conjugation in the *trans* case.

Acknowledgment.—We wish to thank the National Science Foundation for support of part of this work. We also want to thank Mr. Bruce Smart for purifying the *trans* isomers of crotonic and cinnamic acids.

(9) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 44, 45.

(10) Recently [J. Steigman and D. Sussman, *J. Amer. Chem. Soc.*, **89**, 6406 (1967)], an alternative to the "steric inhibition of resonance" explanation for the increased acidity of *ortho*-substituted benzoic acids relative to benzoic acid has been presented. This alternate "solvent structure" explanation also has as its starting point the twisting of the carboxyl group out of the plane of the benzene ring. To the extent that the π system of an olefin can affect solvent structure analogously to the π system of a benzene ring, this explanation would be applicable to the present compounds.

(11) G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955).