ture for 30 min. The mixture was filtered into 1 l. of water to precipitate an oil that crystallized on rubbing. Filtration gave 26.41 g of solid, mp 88–93°. Extraction of the filtrate with ether and recrystallization of the material from CH_2Cl_2–petroleum ether gave an additional 1.66 g (90%) of material, mp 82–86°, having suitable purity for further use. The preparation and characterization of other acids prepared by this procedure is given in Table IV.

1-(1-Phenylpropenyl)pyrrolidine.—This enamine was prepared by the procedure outlined by Stork.[11] A solution of 13.4 g (0.10 mol) of propiophenone, 11.6 ml (0.14 mol) of pyrrolidine, and 100 mg of *p*-toluenesulfonic acid in 30 ml of benzene was heated under reflux with water removal by a Dean–Stark trap for 23 hr. The mixture was evaporated *in vacuo* and the residual gum was dissolved in 30 ml of benzene. To the solution was added 11.6 ml of pyrrolidine and 100 mg of *p*-toluenesulfonic acid and the mixture was again heated under reflux with water collection for 18 hr. The solvent was removed and the residue was distilled to give 9.60 g (51%) of enamine, bp 83–85° (0.6 mm), ir max 5.94 μ. Sollenberger and Martin[12] report bp 139.5–140° (13 mm).

Ethyl β-Benzoylbutyrate.—To a boiling solution of 3.74 g (20 mmol) of the above enamine in 30 ml of ethanol was added dropwise a solution of 3.3 ml (30 mmol) of ethyl bromoacetate in 10 ml of ethanol. The solution was heated at reflux for 90 min and then for an additional 60 min with 20 ml of water. The alcohol was evaporated and the residue was diluted with water. The product was isolated with methylene chloride and vacuum distilled to give 2.53 g (61%) of ester, bp 108–116° (0.6 mm), ir max 5.76, 5.95, 6.29 μ. This product was characterized further by its conversion into the known 4,5-dihydro-5-methyl-6-phenyl-3(2*H*)-pyridazinone, mp 151–153° (lit.[1] mp 147–149°), by reaction with hydrazine in ethanol containing a catalytic amount of acetic acid.

Ethyl β-(*o*-Acetamidobenzoyl)propionate.—Application of the above transformations to 17.7 g (0.10 mol) of *o*-acetamidoacetophenone gave 3.11 g (12%) of product as an orange oil following chromatography on a synthetic magnesia–silica adsorbent: ir max 3.10, 5.78, 5.88, 6.06, 6.30, 6.58 μ. This material was converted directly into the 4,5-dihydro-3(2*H*)-pyridazinone without further purification.

Preparation of the β-Benzoyl-β-Substituted Acrylic Acids (IX).—The following preparation of β-(*p*-bromobenzoyl)crotonic acid illustrates the general procedure. A solution of 36.00 g (0.24 mol) of tartaric acid in 72 ml of water was added to a mechanically stirred, ice-cooled mixture of 51.36 g (0.24 mol) of sodium metaperiodate in 300 ml of water containing 4.8 ml of concentrated sulfuric acid. Stirring was continued at ice-bath temperature for 5 min and then at room temperature for 25 min, whereafter 50.95 g (0.24 mol) of *p*-bromopropiophenone, a solution of 36.00 g of sodium hydroxide in 660 ml of water, and 600 ml of ethanol were added in the indicated sequence. The resulting mixture was stirred at room temperature for 15 hr, whereafter it was heated at steam-bath temperature for 1 hr. The cooled mixture was diluted with water sufficient to dissolve the solids. The solution was extracted with ether to remove 8.11 g (16%) of *p*-bromopropiophenone. Dissolved ether was removed from the aqueous solution under reduced pressure, and the concentrate was rendered acid to Congo Red paper by addition of 3 *N* hydrochloric acid solution. The precipitated solid was collected and recrystallized with the aid of activated carbon from benzene–heptane to give 31.40 g (49%) of tan crystals, mp 140–143° (lit.[14] mp 144.5–145.0°). The preparation of other β-benzoyl-β-substituted acrylic acids is summarized in Table IV.

Acknowledgment.—We thank Dr. D. S. Allen, Jr., for helpful discussions, and we are indebted to Messrs. W. Fulmor and L. Brancone and their associates for the spectral data and microanalyses, respectively.

Registry No.—**1**, 42075-08-1; **2**, 42075-09-2; **3**, 42075-10-5; **4**, 42075-11-6; **5**, 42075-12-7; **6**, 42075-13-8; **7**, 31035-03-7; **8**, 42075-15-0; **9**, 42075-16-1; **10**, 42075-17-2; **11**, 31035-04-8; **12**, 42075-19-4; **13**, 42075-20-7; **14**, 42075-21-8; **15**, 42075-22-9; **16**, 42075-23-0; **17**, 42075-24-1; **18**, 13866-36-9; **19**, 42075-26-3; **22**, 42075-27-4; **23**, 42075-28-5; **25**, 42075-29-6; **26**, 42071-57-8; **27**, 42071-58-9; **28**, 42071-59-0; **29**, 42071-60-3; **30**, 6307-19-3; **31**, 42071-62-5; **32**, 42071-63-6; **33**, 42071-64-7; **34**, 42071-65-8; **36**, 42071-66-9; 1-(1-phenylpropenyl)pyrrolidine, 31889-28-8; ethyl β-benzoylbutyrate, 40394-84-1; ethyl β-(*o*-acetamidobenzoyl)-propionate, 42071-69-2.

Conformational and Configurational Studies of Some Diethyl 2,3-Diarylsuccinates Using Nuclear Magnetic Resonance

LEON GORTLER,* KARL BRANDSPIGEL, ELOISE HARMAN, SUSAN HECHT, AND RANDI LEAVITT

Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn, New York 11210

Received July 30, 1971

The diethyl 2,3-diarylsuccinates, I-H, II-H, I-Cl, I-OMe, I-NH_2, and I-NO_2 have been synthesized and their nmr spectra examined. I-H, II-H, I-Cl, I-OMe, and I-NO_2 have been equilibrated with their respective stereoisomers. In each case the threo isomer predominated at equilibrium and the equilibrium constant increased with the electron-withdrawing power of the substituent. The J_{HCCH} obtained for the benzylic protons in I-NO_2 and II-NO_2 (12 Hz) and other characteristics of the nmr spectra indicate that predominant conformers for the erythro and threo isomers are IA and IIA, respectively.

As a result of stereochemical questions raised by our earlier work on the thermal decomposition of *meso*-di-*tert*-butylperoxy 2,3-diphenylsuccinate,[1] we have synthesized a series of *erythro*-diethyl 2,3-diarylsuccinates (I-H, I-Cl, I-OMe, I-NH_2 and I-NO_2) and the threo isomer II-H and examined their nmr spectra in some detail.

Our initial intent was to use the coupling constant for the benzylic protons in conjunction with the Karplus equation[2] to establish the major conformer for each succinate isomer (Figure 1). This relationship has been used with considerable success in cyclic and acyclic systems,[3] although some apparent exceptions have been observed.[4]

The compounds I-H, II-H, I-Cl, I-OMe, and I-NO_2 were subjected to base-catalyzed equilibration and the respective equilibrium constants determined. The equilibration of 2,3-diphenylsuccinic acid had been observed as early as 1890 by Anschütz,[5] and the equilibration of the unsubstituted esters was studied in some detail by

(1) L. M. Bobroff, L. B. Gortler, D. J. Sahn, and H. Wiland, *J. Org. Chem.*, **31**, 2678 (1966).

(2) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(3) A review of the literature pertaining to acyclic systems can be found in C. A. Kingsbury, *J. Org. Chem.*, **35**, 1319 (1970), and the preceding papers in the series.

(4) (a) D. C. Best, G. Underwood, and C. A. Kingsbury, *Chem. Commun.*, 627 (1969), and references therein. (b) W. T. Borden, Harvard University, 1971, private communication. Both diastereomers of 2,2-dimethyl-4-phenyl-3-pentanol have a J_{HCCH} for the methine protons of about 3.5 Hz.

(5) R. Anschütz and P. Bendix, *Justus Liebigs Ann. Chem.*, **259**, 61 (1890).

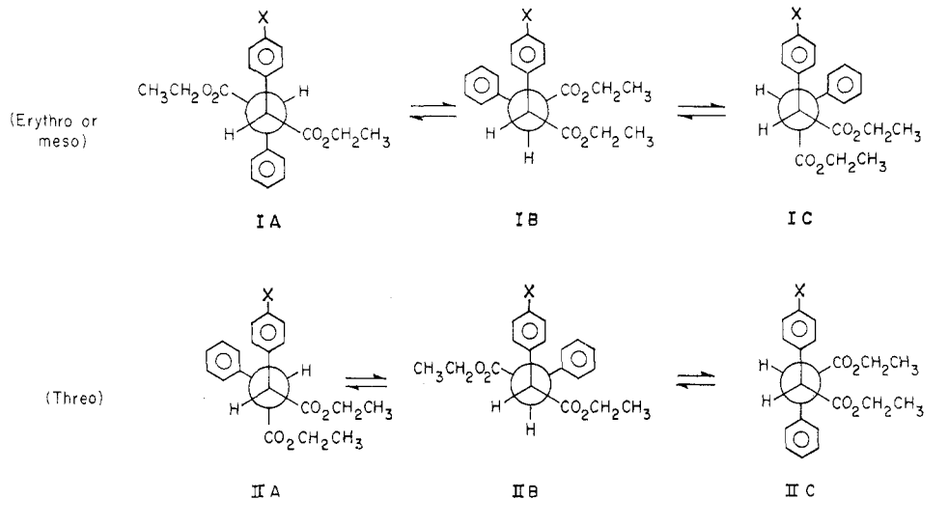
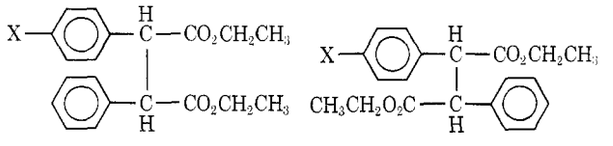


Figure 1.



I (erythro or meso)
I-H, X = H
I-Cl, X = Cl
I-OMe, X = OMe
I-NH_2, X = NH_2
I-NO_2, X = NO_2

II (threo)
II-H
II-Cl
II-OMe
II-NO_2

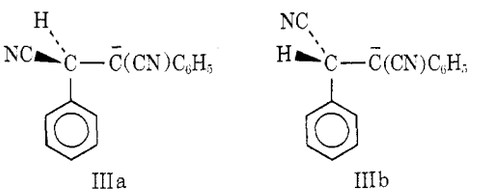
Wren and Still.[6] No equilibrium constants were determined in these earlier studies.

This work has enabled us to establish the absolute configurations of the substituted diarylsuccinates and to assign the major conformer for each isomer.

Results and Discussion

Synthesis of the Esters.—Most of the esters were prepared through the condensation of the appropriate para-substituted benzaldehyde and benzyl cyanide followed by addition of hydrogen cyanide to yield the mono-para-substituted 2,3-diphenylsuccinonitrile. The procedure developed by Davis[7] permits the condensation and addition to proceed together. The dinitrile was hydrolyzed and the resulting acid was esterfied. The *p*-nitro ester, however, could not be made directly using either *p*-nitrobenzaldehyde or *p*-nitrobenzyl cyanide. This direct synthesis apparently fails because of difficulty in adding HCN to the 2-phenyl-3-*p*-nitrophenylacrylonitrile. An indirect synthesis starting with *p*-acetamidobenzaldehyde yielded small quantities of the *p*-nitro ester.

The fact that only one diastereomer, I-H, I-Cl, I-OMe, I-NH_2 and I-NO_2, was obtained in each synthesis is an interesting, if not surprising, phenomenon. The stereoselective addition of hydrogen cyanide to (*Z*)-2,3-diphenylacrylonitrile is known,[7b] but is difficult to rationalize on mechanistic grounds. The addition surely goes through the anions IIIa and IIIb[8] which



IIIa IIIb

should, on protonation, yield a mixture of diastereomers. We strongly suspect that the erythro dinitriles are far less soluble than the threo isomers and precipitate as they are formed; *i.e.*, the product ratio is determined by the solubility of the products. We are currently investigating this problem.

Absolute Configuration of the Diastereomers.—The fact that I-H, I-Cl, I-OMe, I-NH_2, and I-NO_2 were all obtained in essentially the same way, *i.e.*, from a selectively produced dinitrile, is one basis for assigning stereochemistry to these isomers. Compound I-H is well characterized[6a] as the *meso*-diethyl 2,3-diphenylsuccinate. The other I compounds, by analogy, can be assigned the same absolute configuration.

We have also used the chemical shift of the methyl protons to determine the stereochemistry of the various isomers. Compound I-H has a methyl triplet in the nmr centered at δ 0.88 ($CDCl_3$). The equally well characterized[6a] threo isomer, II-H, has a methyl triplet centered at δ 1.16. Compound I-OMe has two methyl triplets[9] centered at δ 0.90 and 0.93. Compound II-OMe, observed only in a mixture with I-OMe, has a single methyl triplet at δ 1.18.[10] Two upfield triplets are also observed for I-Cl, I-NH_2, and I-NO_2 (Table I). Compound II-Cl has a single downfield triplet, and II-NO_2 has two closely spaced downfield triplets (chemical shift difference of about 0.8 Hz).

All of the I compounds, then, have methyl absorption

(6) (a) H. Wren and C. J. Still, *J. Chem. Soc.*, **107**, 444 (1915); (b) *ibid.*, **111**, 513 (1917); (c) *ibid.*, **111**, 1019 (1917).

(7) (a) R. B. Davis, *J. Amer. Chem. Soc.*, **80**, 1752 (1958); (b) N. Rabjohn, Ed., "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, pp 392–395.

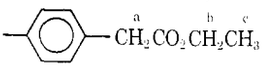
(8) C. A. Fyfe, *Can. J. Chem.*, **47**, 2331 (1969); D. J. Kroeger and R. Stewart, *J. Chem. Soc. B*, 217 (1970).

(9) When the 60- and 100-MHz spectra were compared, we found the resonance positions of the two triplets changed with respect to one another but the coupling constants remained the same. We are, therefore, dealing with two triplets and not the splitting of a single triplet.

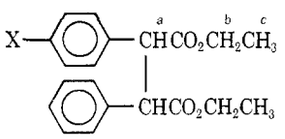
(10) The nmr data for II-OMe, II-Cl, and II-NO_2 were obtained from spectra of mixtures.

TABLE I

NMR DATA.[a] PROTON CHEMICAL SHIFTS, δ[b]

Ethyl Phenylacetates 

Registry no.	X	a	b	c
101-97-3	H	3.51 (s)	4.06 (q, 6.5)	1.13 (t, 6.5)
14062-18-1	OMe	3.48 (s)	4.08 (q, 7)	1.17 (t, 7)
14062-24-9	Cl	3.50 (s)	4.08 (q, 6.5)	1.17 (t, 6.5)
5445-26-1	NO_2	3.74 (s)	4.18 (q, 6.5)	1.25 (t, 6.5)

Diethyl 2,3-Diarylsuccinates, 

Compd	a	b	c
I-H	4.38 (s)	3.84 (q, 7)	0.88 (t, 7)
II-H	4.22 (s)	4.14 (q, 7)	1.16 (t, 7)
I-OMe	4.31 (s)	3.88 (q, 7)[c]	0.90 (t, 7)
			0.93 (t, 7)
II-OMe	4.18 (s)	4.14 (q, 7)	1.18 (t, 7)
I-Cl	4.34 (s)	3.84 (q, 7)[d]	0.90 (t, 7)
		3.88 (q, 7)	0.94 (t, 7)
II-Cl	4.20 (s)	4.15 (q, 7)	1.18 (t, 7)
$I-NH_2$	4.31 (s)	3.85 (q, 7)	0.88 (t, 7)
		3.87 (q, 7)	0.92 (t, 7)
$I-NO_2$	4.34 (d, 12)	3.86 (q, 7)[d]	0.92 (t, 7)
	4.51 (d, 12)	3.88 (q, 7)	0.96 (t, 7)
$II-NO_2$	4.17 (d, 12)	4.11 (q, 7)	1.20 (t, 7)
	4.42 (d, 12)		1.21 (t, 7)

[a] Solvent, $CDCl_3$; internal standard, TMS. [b] When the signal is not a singlet, the value is that for the center of the pattern. The splitting pattern followed by the coupling constant in hertz is given in parentheses after the chemical shift: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [c] Broad bands. Probably more than one quartet. CH_3O absorbs at δ 3.77 for I-OMe and δ 3.67 for II-OMe. [d] With higher resolution further splitting of the quartets was observed (see Figure 2). The methylene protons are diastereotopic and the pattern is probably that for an ABX_3 spin system.

at upfield positions (less than δ 1.0), and all of the II compounds have methyl absorption at downfield positions (above δ 1.0). This suggests that all of the I compounds have the erythro configuration, and all of the II compounds have the threo configuration.

The upfield and downfield chemical shifts and the appearance of double and single triplets can be explained in terms of the predominant conformer and will be discussed in detail below.

Equilibration of the Diastereomers.—The equilibration of the diastereomers, I $\rightleftarrows$ II, was effected by refluxing an ethanol solution of the erythro isomer containing a small quantity of sodium ethoxide until the ratio of the two isomers no longer changed. In one experiment we started with the threo isomer, II-H, and the result was the same. Before analysis, the mixture of isomers was isolated and then redissolved in $CDCl_3$. The equilibrium constants were calculated from the integration of the methyl proton region of the spectra (see Figure 2B). The results of our measurements are tabulated in Table II.

The analyses were reproducible to $\pm 5\%$, and had an accuracy of about $\pm 10\%$ determined using synthetic mixtures of I-H and II-H. In cases where the threo methyl triplet overlapped with the erythro methyl triplet(s), the integrals of the outside peaks were compared (see Figure 2). This comparison favors a $K_{\text{threo/erythro}} > 1$ because the methyl signal is not completely symmetrical and the downfield peaks, those closest to the methylene signal, are larger than the upfield peaks. The nonsymmetry of the triplets is minimal, however, because of the large chemical shift differences between methyl and methylene (*ca.* δ 3). Any errors from this source are already included in the accuracy errors mentioned above. The areas under the benzylic proton signals could not be measured since they overlapped the methylene peaks, but a visual comparison yielded the same qualitative result, $K_{\text{threo/erythro}} > 1$, as that obtained from integration of the methyl signals.

TABLE II

EQUILIBRIUM CONSTANTS FOR I $\rightleftarrows$ II IN ETHANOL AT 78°

Compd[a]	$K_{\text{threo/erythro}}$[b]
I-OMe	1.25
I-H	1.35
II-H	1.37
I-Cl	1.5
$I-NO_2$	2.5

[a] Compound with which equilibration was started. [b] Equilibrium constants have an accuracy of $\pm 10\%$.

Although the K values could be off by as much as 10%, the trend of the equilibrium constants is obvious. The more electronegative the substituent, the larger the equilibrium constant. If, indeed, IA and IIA (Figure 1) are the predominant conformers (see below), the major factor determining the position of equilibrium must be the decreasing repulsion of the gauche aryl groups as the substituent becomes more electronegative. Such a decrease in aryl repulsion would favor conformer IIA and the K value would increase. The total repulsion must be a composite of steric and electronic effects, $R_{\text{total}} = R_{\text{steric}} + R_{\text{electronic}}$, and the electronic factor must decrease significantly, or perhaps change sign, as one aryl group becomes more electrophilic. The correlation with the Hammett σ function is not linear, but this is not surprising. The change in K, however, is in the direction we would expect for an "acid–base," or charge-transfer, like π interaction between the two aryl groups.

On examination of a model of II we find that, when the aryl groups are gauche, the least steric interaction is obtained when the π orbitals are facing each other. The rings are not parallel, but the 1 carbon atoms, those attached to the benzylic carbons, are about 3 Å apart, well within the van der Waals overlap distance of 3.7 Å.[11] The 4 carbons, those in the para positions, however, are 5 to 6 Å apart. Some distortion of the bond angles and bond distances may be necessary to maximize the attractive forces.

Conformational Analysis.—Our initial objective was the determination of the major ground-state conformer for the diethyl 2,3-diarylsuccinates using the Karplus relationship. The only compounds for which an AB coupling constant could be obtained for the two benzylic hydrogens were $I-NO_2$ and $II-NO_2$ (see Figure 2). The coupling constant for each isomer is 12.0 Hz. This coupling constant must be close to the maximum expected for trans protons in this system. Bothner-By[12]

(11) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 28. The half thickness of an aromatic ring is given as 1.85 Å.

(12) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962).

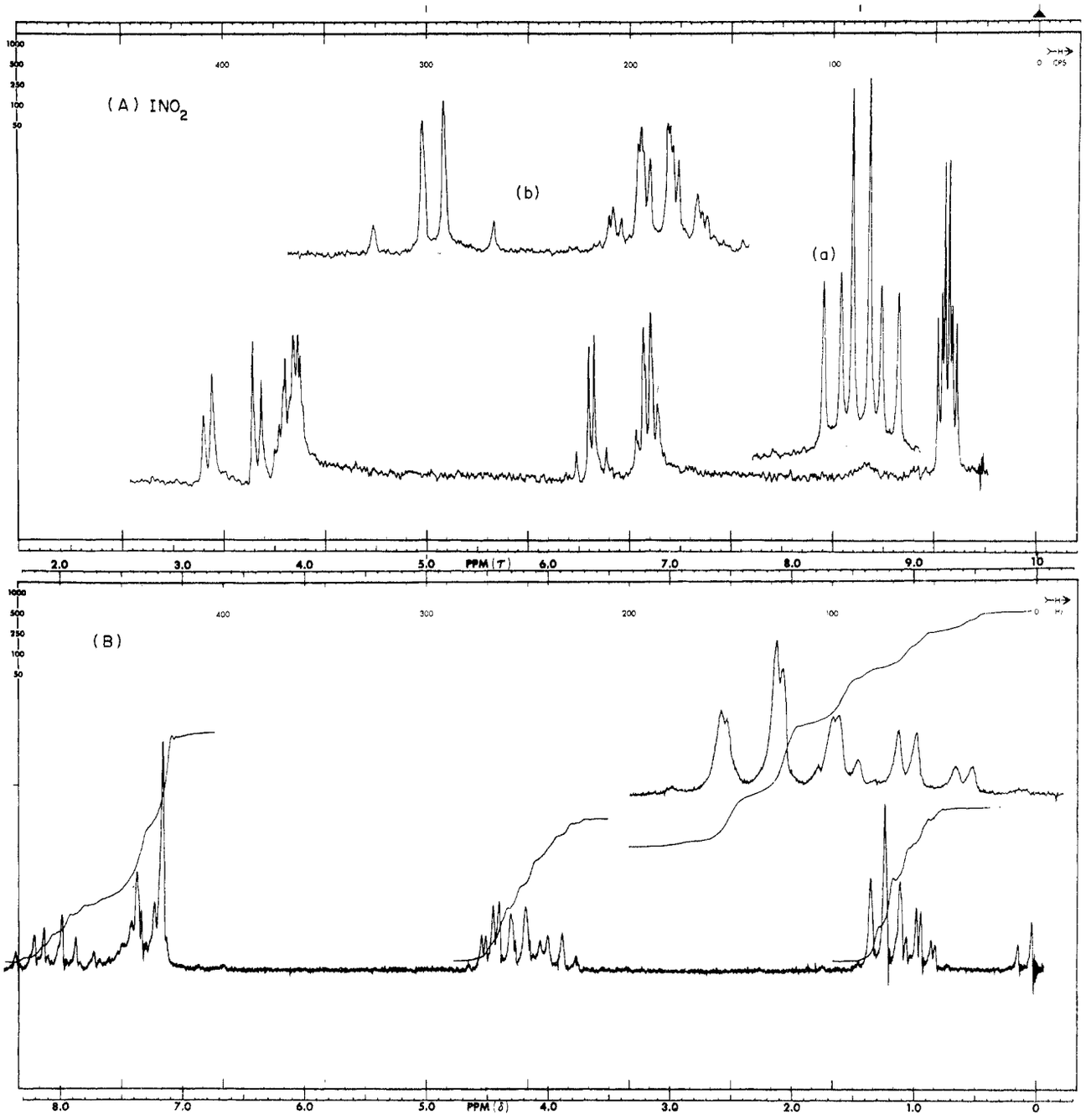


Figure 2.—(A) INO_2, 100 MHz, sweep width 1000 Hz, $CDCl_3$. Inserts: (a) methyl triplets, sweep width 250 Hz; (b) benzylic protons (an AB quartet) and methylene multiplet (two quartets, each with $J = 7$ Hz; each quartet is further split into a doublet, $J =$ 0.6 and 1.5 Hz), sweep width 250 Hz. (B) Equilibrium mixture of INO_2 and $IINO_2$, 60 MHz, sweep width 500 Hz, $CDCl_3$. Insert: methyl signals, sweep width 100 Hz.

uses values of 3 and 13 Hz for J_g and J_t in his analysis of the 2,3-diphenylbutanes, and values of 1 and 11 Hz for the 2,3-dibromobutanes since electronegative groups tend to decrease the size of the coupling constant. We can assume, then, that J_t for our system must lie between 11 and 13 Hz (12 Hz is obviously the lower limit). If this assumption is correct, conformers IA and IIA must account for over 90% of their respective isomers, at least for the *p*-nitro compounds.

The fact that only I-NO_2 and II-NO_2 had an observable coupling constant for the benzylic protons is not surprising. The insensitivity of the chemical shift of benzylic protons to changes in the para substituent can be observed in the ethyl phenylacetates (Table I) with only the *p*-nitro compound showing a significant shift from the unsubstituted ester. A similar insensitivity of the chemical shift of benzylic protons to substituent has been observed by Indictor and coworkers in a study of 2-aryl-1,3-dioxolanes and heteroatomic analogs.[13] Here, too, the *p*-nitro group is anomalous.

As we argued in the previous section, the trend in the equilibrium constants is consistent with a preponderance of conformers IA and IIA. This suggests that a similar conformer distribution exists for all of the compounds, not just the *p*-nitro compounds.

(13) N. Indictor, J. W. Horodniak, H. Jaffe, and D. Miller, *J. Chem. Eng. Data*, **14**, 76 (1969).

In the section concerned with the stereochemistry of the diastereomers we observed that the methyl signals for erythro isomers were always upfield with respect to the methyl signals of their threo counterparts. This result is best explained by a carbethoxy–aryl gauche interaction where the methyl lies over the aromatic π cloud and is shielded by the induced diamagnetic field above and below the plane of the ring.[14] In the erythro isomers there is at least one carbethoxy–aryl gauche interaction in each of the conformers, and, in IA, the supposed predominant conformer, there are two such interactions. In IIA, the major conformer for the threo compounds, there are no carbethoxy–aryl gauche interactions and the chemical shift for these methyl protons is about the same as that for the ethyl phenylacetates (Table I). If there were significant contributions from IIB and IIC we would expect to see some upfield shift of the methyl signal.

For each of the substituted compounds in series I, two methyl groups were observed. This is reasonable since the methyl groups are magnetically nonequivalent in each of the conformers, assuming, of course, that the carbethoxy groups interact differently with phenyl and substituted phenyl. The fact that only one methyl triplet is observed for II-Cl and II-OMe can be explained only by the predominance of conformer IIA. In this conformation, the carbethoxy groups are essentially in the same magnetic environment. If IIA is the predominant conformer, the chemical shifts for the methyl signals should differ no more than do the methyl signals in the ethyl phenylacetates (Table I). In an nmr spectrum of a mixture of ethyl phenylacetate and ethyl *p*-chlorophenylacetate taken at 60 MHz, the methyl groups were indistinguishable. The methyl in ethyl *p*-nitrophenylacetate is shifted significantly from that of the unsubstituted compound (δ 1.25 *vs.* 1.13), and this probably explains the appearance of the two closely spaced triplets in II-NO_2.

Interaction of the carbethoxy group with the phenyl or substituted phenyl attached to the same carbon must be minimal. If such interactions were more important than the gauche interactions, we would expect the spectra of the diastereomers to be more alike.

All of the evidence, then, demands that IIA be the predominant conformer for the compounds in series II. The arguments are not so overwhelming for IA, but the size of the benzylic proton coupling constant, energy considerations, especially the three large group interactions in IB and IC *vs.* two such interactions in IA, and some of the spectral evidence, leaves little doubt that this is the predominant conformer in series I.

Experimental Section

Preparation of the Erythro Nitriles.—2,3-Diphenylsuccinonitrile, 2-*p*-methoxyphenyl-3-phenylsuccinonitrile, and 2-*p*-chlorophenyl-3-phenylsuccinonitrile were prepared using procedure A of R. B. Davis.[7]

***erythro*-2-*p*-Acetamidophenyl-3-phenylsuccinonitrile.**—A solution of 30.6 g (0.63 mol) of sodium cyanide in 50 ml of water was heated until the solid dissolved. Absolute methanol (200 ml) was added, the solution was heated to reflux, and 25 ml (0.21 mol) of freshly distilled benzyl cyanide was added all at once. Solid *p*-acetamidobenzaldehyde (41 g, 0.25 mol) was added to the stirred, refluxing solution over 45 min. The *p*-acetamidobenzaldehyde did not go completely into solution. An additional 15 ml (0.13 mol) of freshly distilled benzyl cyanide was added to the reaction mixture followed by the addition of 150 ml of absolute methanol. Following these additions, the solution was refluxed for 1.5 hr. During this period it turned green. The solution was cooled in an ice bath. The precipitate, a yellow solid, was collected and washed with cold 75% methanol–water, with water, and again with 75% methanol–water. The crude solid weighed 26.6 g (37%). Recrystallization from glacial acetic acid yielded a colorless solid, mp 265–268°.

Preparation of the Erythro Acids.—2,3-Diphenylsuccinic acid, 2-*p*-methoxyphenyl-3-phenylsuccinic acid, and 2-*p*-chlorophenyl-3-phenylsuccinic acid were prepared by hydrolysis of the corresponding dinitriles using the procedure of Wawzonek.[15] Melting points of the various acids after recrystallization from acetic acid follow: unsubstituted acid, mp 248–249° (lit.[16] mp 252°); *p*-methoxy acid, mp 225–227° (lit.[17] mp 227°); *p*-chloro acid, mp 247–254° (lit.[18] 249–250°).

***threo*-2,3-Diphenylsuccinic Acid.**—This acid was prepared by a modification of the method of Corey and Casanova.[19] A 3-g portion of *erythro*-2,3-diphenylsuccinic acid that had been recrystallized from acetic acid was heated to 300° in a Wood's metal bath. After 5 min, the white acid had been completely converted to a yellow oil. The oil was cooled and triturated with a minimal amount of ether while warming over a steam bath. The ether solution was dried over magnesium sulfate, filtered, and some of the solvent evaporated. The crude anhydride was collected by suction filtration and recrystallized from ether. The faint yellow crystals, 1.3 g (48%), of *threo*-2,3-diphenylsuccinic anhydride had a melting point of 113–114° (lit.[5] mp 115–116°).

The anhydride (5 g, 0.02 mol) was dissolved by heating in a minimal amount of 10% sodium carbonate. After the solution was filtered, the threo acid was precipitated by acidification. The acid (5 g, 0.019 mol, 95%) was collected and recrystallized from ethanol. The acid melted at 178°, resolidified, and melted again at 220–224°. This behavior is essentially that reported in the literature,[20] mp 183°, 220–221°.

***erythro*-2-*p*-Aminophenyl-3-phenylsuccinic Acid.**—A solution of 15.9 g (0.055 mol) of *erythro*-2-*p*-acetamidophenyl-3-phenylsuccinonitrile in 60 ml of acetic acid, 40 ml of sulfuric acid, and 40 ml of water was refluxed for 3 days. After cooling to room temperature, the solution was diluted with an equal volume of water and neutralized to pH 6 with 6 *N* sodium hydroxide. The solid was collected by suction filtration and washed thoroughly with water to dissolve solid salts. The water-insoluble solid, presumably the zwitterionic amino acid (5.6 g, 0.02 mol, 36%), did not melt.

Preparation of the Erythro Esters. Diethyl 2-*p*-Aminophenyl-3-phenylsuccinate (I-NH_2).—A solution of 5.6 g (0.02 mol) of *erythro*-2-*p*-aminophenyl-3-phenylsuccinic acid in 125 ml of ethanol and 5 ml of concentrated sulfuric acid was refluxed for 3 days. The solution was cooled to room temperature and neutralized with 20% sodium carbonate, and the ethanol was removed at reduced pressure. Ether and additional aqueous base were added to the mixture remaining. The layers were separated and the water layer was washed three times with ether. The combined ether layers were dried over magnesium sulfate and filtered, and the ether was evaporated. The solid was recrystallized from ethanol, yielding 1 g (0.003 mol, 15%) of colorless I-NH_2: mp 136.5–137°; nmr ($CDCl_3$) δ 6.4–7.7 (m, 9, aromatic), 4.31 (s, 2, benzylic), 3.83 (q, J = 7 Hz, $-OCH_2-$), 3.87 (q, J = 7 Hz, $-OCH_2-$), broad $-NH_2$ signal, center *ca.* 3.63, overlapped methylene signals (total integral for $-OCH_2-$ and $-NH_2$ was 6), 0.88 (t, J = 7 Hz, $-CH_3$), 0.92 (t, J = 7 Hz, $-CH_3$) (total integral for two methyl triplets was 6).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.70; H, 6.77; N, 4.48.

Using essentially the same procedure, the following esters were prepared: I-H, mp 139–140° (lit.[6a] mp 140–141°); II-H, mp 78–82° (lit.[6a] mp 82–83.5°); I-OMe, mp 101–102° (lit.[17] mp 102°); and I-Cl, mp 112–113° (from known acid and nmr perfect for diester).

(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 97.

(15) S. Wawzonek, *J. Amer. Chem. Soc.*, **62**, 745 (1940).

(16) W. Roser, *Justus Liebigs Ann. Chem.*, **247**, 152 (1888).

(17) J. A. McRae and A. S. Townsend, *Can. J. Res.*, **11**, 628 (1934).

(18) F. J. Villani and N. Sperber, U. S. Patent 2,852,526 (1958); *Chem. Abstr.*, **53**, 8163*i* (1958).

(19) E. J. Corey and J. Casnova, Jr., *J. Amer. Chem. Soc.*, **85**, 165 (1963).

(20) K. L. Reimer, *Chem. Ber.*, **14**, 1803 (1881).

erythro-**Diethyl 2-*p*-Nitrophenyl-3-phenylsuccinate (I-NO_2).**—The *p*-amino ester, I-NH_2, was oxidized to I-NO_2 using the procedure of Emmons:[21] mp 105–106° (from ethanol) (lit.[22] mp 101°); nmr ($CDCl_3$) δ 7.1–8.3 (m, 9, aromatic), 4.34 (d) and 4.51 (d) (2, benzylic), 3.86 (q) and 3.88 (q) (4, $-OCH_2-$), 0.92 (t) and 0.96 (t) (6, $-CH_3$).

Equilibration Procedure.—To a solution of 0.12 g (3.24×10^{-4} mol) of I-NO_2 in 20 ml of absolute ethanol was added 1 ml (3.24×10^{-5} mol of NaOEt) of a solution prepared from 7.4 mg of sodium dissolved in 10 ml of absolute ethanol. Upon addition of the base, the yellow ester solution turned light brown. The solution was heated at reflux under nitrogen for 24 hr. The reaction was terminated by acidification of the solution with dilute HCl and then pouring it into a beaker of ice. The brown color disappeared when the acid was added. The water–ethanol was milky white at this point. The ethanol was evaporated and the remaining aqueous mixture was washed three times with ether. The ether extracts were combined, dried over magnesium sulfate, and filtered. Evaporation of the ether left 113.9 mg of an oily, yellow solid. This material was analyzed as described in the discussion of the equilibrations.

Equilibrations of I-H, II-H, I-Cl, and I-OMe were carried out using the same procedure. However, no color changes accompanied these equilibrations and these esters were easily collected by suction filtration of the melted ice solution as opposed to the extraction procedure described above.

The nmr spectra were taken using Varian A-60 and Varian HA-100 spectrometers. $CDCl_3$ containing TMS was used as the solvent in all cases.

Acknowledgment.—Our thanks to the National Science Foundation for its support of this research. K. B., S. H., E. H., and R. L. were National Science Foundation Undergraduate Research Participants (GY-7540).

Registry No.—I-H, 13638-89-6; I-OMe, 41915-54-2; I-Cl, 41915-55-3; I-NH_2, 41915-56-4; I-NO_2, 41915-57-5; II-H, 41915-58-6; II-OMe, 41939-32-6; II-Cl, 41915-59-7; II-NO_2, 41915-60-0; *erythro*-2-*p*-acetamidophenyl-3-phenylsuccinonitrile, 41915-61-1; benzyl cyanide, 140-29-4; *p*-acetamidobenzaldehyde, 122-85-0; *erythro*-2-*p*-methoxyphenyl-3-phenylsuccinic acid, 41915-62-2; *erythro*-2-*p*-chlorophenyl-3-phenylsuccinic acid, 41915-63-3; *threo*-2,3-diphenylsuccinic acid, 41915-64-4; *erythro*-2,3-diphenylsuccinic acid, 41915-65-5; *erythro*-2-*p*-aminophenyl-3-phenylsuccinic acid, 41915-66-6.

(21) W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3470 (1954).
(22) J. Hoch and D. Legay, *C. R. Acad. Sci., Ser. C*, **255**, 2975 (1962).

Catalytic Mechanism of Intermolecularly Carboxylate-Assisted Acyl Transfer[1,2]

ANNIE ELIZABETH WILLIAMS,[3] J. K. LEE, AND RICHARD L. SCHOWEN*[4]

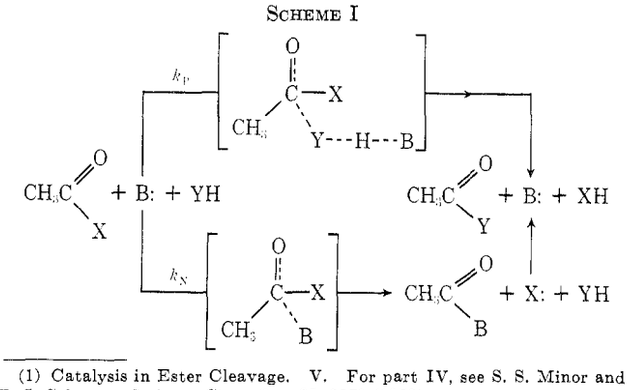
Department of Chemistry, University of Kansas, Lawrence, Kansas 66044

Received March 30, 1973

The methanolysis of *p*-nitrophenyl benzoate in methanolic buffers of sodium phenylacetate and phenylacetic acid is general base catalyzed and leads to both methyl benzoate (in 17–54% yield, depending on the buffer-component concentrations) and methyl phenylacetate (in corresponding 83–46% yield). This shows that at least a part of the catalyzed reaction occurs by a nucleophilic mechanism to generate benzoic phenylacetic anhydride, which then rapidly methanolyzes. Synthesis of this anhydride and its methanolysis shows the yield of methyl phenylacetate, under conditions of the kinetic study, to be 96.5 ± 0.6%. The data cited above show that the yield of this product from the phenylacetate-catalyzed part of the ester methanolysis is identical with that from the anhydride methanolysis, demonstrating that the sole mechanism of general-base catalysis in this system is the nucleophilic mechanism. This further supports the view that alcoholysis reactions prefer nucleophilic rather than protolytic general catalysis, in comparison to hydrolysis reactions.

The discrimination of the protolytic (k_P) and nucleophilic (k_N) mechanisms (Scheme I) of general base catalyzed acyl transfer processes,[5] which are usually kinetically indistinguishable, is of interest not only from standpoint of solution chemical dynamics, but also because of the role of such catalysis in the action of enzymes[6] and in medicinal chemistry.[7] For example, it appears that the imidazole ring of the active-site His-57 of α-chymotrypsin can function either as a protolytic catalyst or as a nucleophilic catalyst in the acylation of the nearby Ser-195 hydroxyl group, with the choice of catalytic mechanism depending on the structure of the substrate.[8] Very good leaving groups favor the nucleophilic mechanism, as is expected from the comprehensive investigation of Gold, Oakenfull, and Riley.[9] These workers studied the acetate-catalyzed hydrolysis of a series of aryl acetates, trapping the acetic anhydride intermediate formed in nucleophilic catalysis with aniline, and found that leaving groups more reactive than *p*-nitrophenoxide give preferential nucleophilic catalysis and less reactive leaving groups give preferential protolytic catalysis: *p*-nitrophenoxide itself produced 56% nucleophilic and 44% protolytic catalysis. The direct application of these results to enzymic systems such as α-chymotrypsin and the other "serine

SCHEME I



(1) Catalysis in Ester Cleavage. V. For part IV, see S. S. Minor and R. L. Schowen, *J. Amer. Chem. Soc.*, **95**, 2279 (1973).
(2) This research was supported by a grant from the National Institutes of Health and was carried out in part at the Computation Center of the University of Kansas. Further details may be found in A. E. Williams, M. S. Thesis in Chemistry, University of Kansas, 1972.
(3) Education Professions Development Act Fellow, 1970–1972.
(4) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.
(5) (a) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967); (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969; (c) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971.
(6) R. M. S. Smellie, Ed., "Chemical Reactivity and Biological Role of Functional Groups in Enzymes," Academic Press, New York, N. Y., 1970.
(7) R. D. Gandour and R. L. Schowen, *Ann. Rep. Med. Chem.*, **7**, 279 (1972).
(8) C. D. Hubbard and J. F. Kirsch, *Biochemistry*, **11**, 2483 (1972).
(9) V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. B*, 515 (1968).