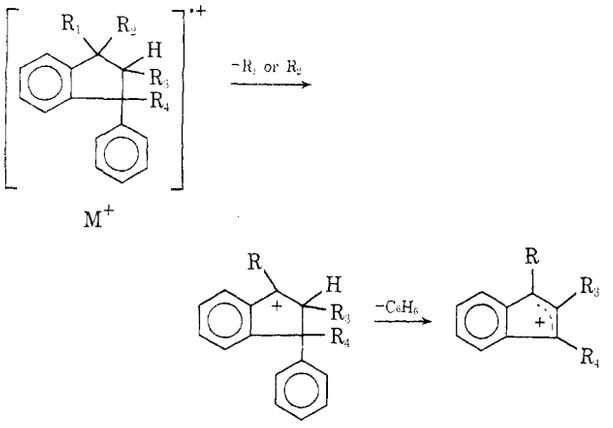

reaction time, in addition to the dimerization and reduction products **4** and **9** obtained through paths A and C, there was formed also compound **10**. This compound is a product of a secondary reaction of the cyclic dimer **4** obtained through path A. To prove this point, pure **4** was submitted to the reaction under the drastic conditions to yield **10** as the major product[21]

(21) Adams[9] reported a somewhat similar degradation of **2** to 1,1,3-triphenylindan when **2** was heated with $AlCl_3$ at 110° for 6 hr.

(*ca.* 73% of the fraction that underwent reaction). Based on the nmr data (splitting of the methyl) we conclude that, in the degradation process of **4** to **10**, the substitution of phenyl by hydrogen occurred on the phenyl in position 1 next to the methyl rather than one of the two geminal phenyls in position 3 (see above).

Acknowledgment.—This project has been supported in part by a grant from the National Council for Research and Development (Israel).

Registry No.—**1**, 98-83-9; **2**, 3910-35-8; **3**, 530-48-3; **4**, 19303-32-3; **5**, 41906-71-2; **6**, 637-50-3; **7**, 30170-60-6; **8**, 41906-72-3; **9**, 612-00-0; **10**, 30098-24-9; **11**, 103-30-0; **12**, 41906-73-4; **13**, 1520-42-9; **14**, 645-49-8; EADC, 563-43-9.

Supplementary Material Available.—A figure with the nmr spectra of compounds **2**, **4**, and **10** as well as two tables summarizing the nmr and mass spectral data for all the products discussed will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4040.

A General Synthesis of 3-(Substituted benzoyl)-3-Substituted Alkanoic Acids

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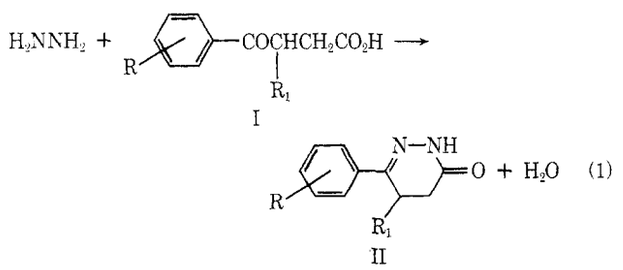
A general method for the preparation of 3-(substituted benzoyl)-3-substituted alkanoic acids is described. The key feature of the method is the conversion of a quaternary salt (V) derived from the Mannich base of a phenone into the corresponding γ-keto nitrile (VI), hydrolysis of which furnishes the acid. The transformation of V into VI by cyanide proceeds in two stages: (1) β elimination, and (2) conjugate hydrocyanation of the resulting enone. The efficiency of the method is compared to (1) the preparation of γ-keto esters by alkylation of enamines with ethyl bromoacetate and (2) the reduction of β-benzoylcrotonic acids obtained by condensation of phenones with glyoxalic acid.

We required a general synthesis of 3-(substituted benzoyl)-3-substituted propionic acids (I) in order to evaluate a series of pharmacologically interesting 6-(substituted phenyl)-5-substituted 4,5-dihydro-3-(2*H*)-pyridazinones (II),[1] which are readily prepared by reaction of I with hydrazine (eq 1).[1,2] Many of the procedures



described in the literature for the preparation of I rely on anionic condensations between ketones and esters,[3] and do not appear applicable to those reactants having substituents containing active hydrogens (see below). Those acid catalyzed procedures, *e.g.*, Friedel–Crafts condensations, compatible with substituents possessing active hydrogens usually give mixtures containing the isomeric 3-(substituted benzoyl)-2-substituted propionic acid.[1,4] In this paper we describe a method of apparent generality for the preparation of I; moreover, its effectiveness is compared with that of two other procedures.

The general method is based on an improved synthesis of γ-keto nitriles (VI), the hydrolysis of which readily furnish I (see Scheme I).[5,6] The preparation of certain γ-keto nitriles by treatment of Mannich bases with aqueous alkali cyanide has been reported by Knott,[6] and we have used a modification of this procedure to prepare the requisite intermediates. Thus, ketones III were converted into Mannich bases IV using the procedure of Back,[7] and reaction of the crude IV with methyl iodide furnished the quaternary salts

(1) W. V. Curran and A. Ross, *J. Med Chem.*, submitted for publication.

(2) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **75**, 1117 (1953), and references cited therein.

(3) (a) W. H. Puterbaugh and R. L. Readshaw, *J. Amer. Chem. Soc.*, **82**, 3635 (1960); (b) W. Cocker, L. O. Hopkins, L. Mabrouk, J. McCormick, and T. B. H. McMurray, *J. Chem. Soc.*, 2230 (1960); (c) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958); (d) J. A. Marshall and S. F. Brady, *ibid*, **35**, 4068 (1970); (e) W. E. Bachmann and G. D. Johnson, *J. Amer. Chem. Soc.*, **71**, 3463 (1949).

(4) A. G. Peto in "Friedel-Crafts and Related Reactions," Vol. III, Part 1, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, pp 573, 583.

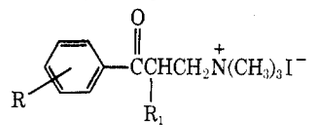
(5) C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937).

(6) E. B. Knott, *J. Chem. Soc.* 1190 (1947).

(7) W. Back, *Arch. Pharm. (Weinheim)*, **303**, 491 (1970).

TABLE I

[β-(SUBSTITUTED BENZOYL)ALKYL]TRIMETHYLAMMONIUM IODIDES (V)

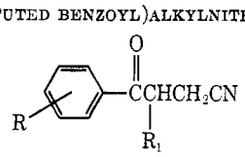


Compd	R	R_1	Yield,[a] %	Crystn solvent	Mp, °C	Formula[b]
1	*o*-NO_2	H	64	Acetone	152–155	$C_{12}H_{17}IN_2O_3$[c]
2	*o*-NO_2	CH_3	61	Acetone	168–170, 195–200 dec	$C_{13}H_{19}IN_2O_3$[d]
3	*m*-NO_2	CH_3	93	Acetone	206–208	$C_{13}H_{19}IN_2O_3$
4	*p*-Br	CH_3	93	Acetone	184–185	$C_{13}H_{19}BrINO$
5	*p*-Cl	CH_3	82	Acetone	171–173	$C_{13}H_{19}ClINO$[e]
6	*p*-F	CH_3	91	Acetone	186–187	$C_{13}H_{19}FINO$[f]
7	H	CH_3	92	Acetone–ether	149–151	$C_{13}H_{20}INO$
8	*p*-F	C_2H_5	71	Acetone–ether	164–165	$C_{14}H_{21}FINO$
9	*p*-NHAc	CH_3	85	Acetone	206–207	$C_{15}H_{23}IN_2O_2$
10	*p*-F	C_6H_5	85	Acetone–ether	168–170	$C_{18}H_{21}FINO$[c]
11	H	C_6H_5	77	Acetone–ether	191–192	$C_{18}H_{22}INO$

[a] Overall for two stages from the corresponding phenone. [b] Satisfactory analytical data (±0.4% for C, H, I, N) were reported for all compounds except as noted. [c] N analysis only. [d] I: calcd, 33.56; found, 34.38. [e] I: calcd, 34.52; found, 34.01. [f] I: calcd, 36.14; found, 36.70.

TABLE II

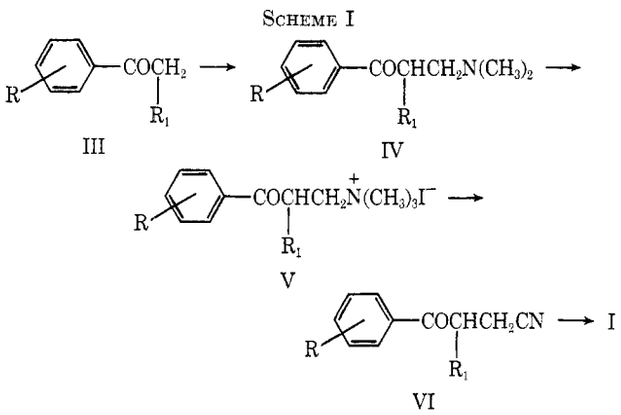
β-(SUBSTITUTED BENZOYL)ALKYLNITRILES (VI)



Compd	R	R_1	Reaction solvent	Yield, %	Recrystn solvent	Mp, °C	Molecular formula[a]
12	*o*-NO_2	H	MeOH	59	Acetone–hexane	73–74	$C_{10}H_8N_2O_3$
13	*m*-NO_2	CH_3	H_2O	92	Et_2O	63–64	$C_{11}H_{10}N_2O_3$
14	*p*-NHAc	CH_3	MeOH-H_2O	92	Acetone–petroleum ether	131–132	$C_{13}H_{14}N_2O_2$
15	*p*-NHAc	C_2H_5	H_2O	57[b]	Acetone–petroleum ether	129–130	$C_{14}H_{16}N_2O_2$
16	*p*-NHAc	*n*-C_3H_7	H_2O	40[b]	Acetone–petroleum ether	103–105	$C_{15}H_{18}N_2O_2$
17	*p*-F	C_6H_5	MeOH	91	Et_2O–petroleum ether	82–85	$C_{16}H_{12}FNO$[c]
18	H	C_6H_5	MeOH	97	Et_2O–petroleum ether	87–88	$C_{16}H_{13}NO$

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds. [b] Overall yield for three stages from the 4′-acetamidophenone, the last characterized intermediate. [c] F: calcd, 7.50; found, 7.72.

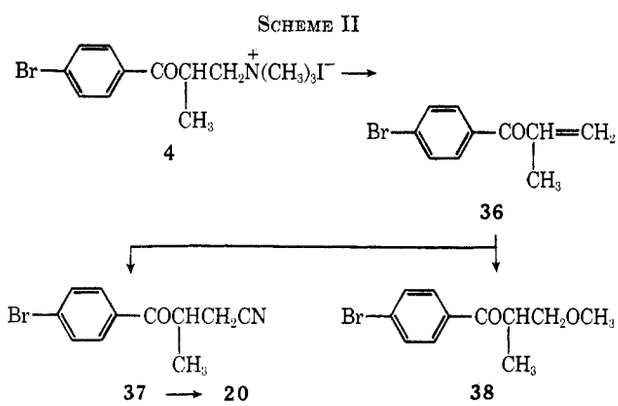
SCHEME I



(V) of Table I. Exposure of V to aqueous or methanolic solutions of potassium cyanide effected smooth, efficient conversion into the γ-keto nitriles (VI) of Table II. Those nitriles that were liquid were converted directly into the γ-keto acids I (see Table III) without purification. The present procedure for the preparation of VI appears to be more efficient and general than that of Knott.

Examination of the reaction of [2-(*p*-bromobenzoyl)-propyl]trimethylammonium iodide (**4**) with potassium cyanide showed that conversion of V into VI proceeds in two stages: (1) β elimination[8] to ketone **36** and (2) conjugate hydrocyanation.[5,9] Thus, reaction of **4** with aqueous cyanide gave 63% of the α,β-unsaturated ketone **36** and 37% of nitrile **37** (Scheme II).

SCHEME II

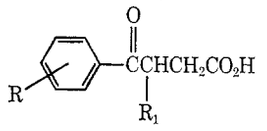


Ketone **36** gives a mixture of the same substances when treated similarly. Methanol is a more effective solvent for the conversion of either the quaternary salt or

(8) S. Patai, S. Weinstein, and Z. Rappoport, *J. Chem. Soc.*, 1741 (1962).
(9) W. Nagata, M. Yoshioka, and S. Hirai, *J. Amer. Chem. Soc.*, **94**, 4635 (1972), and references cited therein.

Table III

β-(Substituted benzoyl)alkanoic Acids (I)

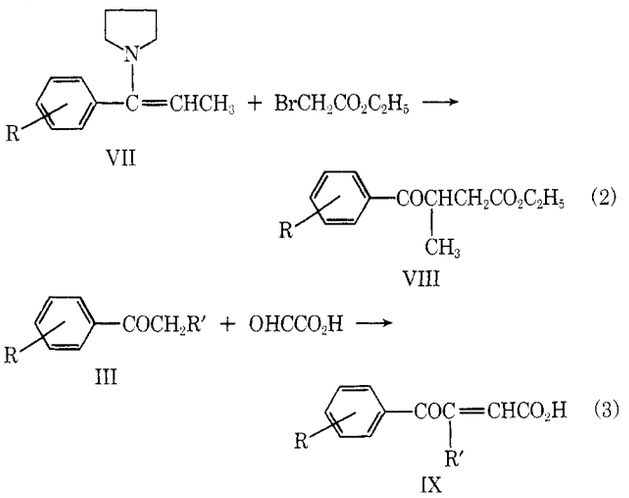


Compd	R	R1	Yield, % — Method — A	B	Recrystn solvent	Mp, °C	Molecular formula[a]
19	o-NO_2	H	68		Ether–petroleum ether	95–97	$C_{10}H_9NO_5$
20	p-Br	CH_3	86[b]	90	Ether–petroleum ether	95–96[c]	$C_{11}H_{11}BrO_3$
21	p-Cl	CH_3	82[b]	78	Petroleum ether	79–82[d]	$C_{11}H_{11}ClO_3$
22	p-F	CH_3	87[b]	94	Ether–petroleum ether	57–58	$C_{11}H_{11}FO_3$
23	m-NO_2	CH_3	87		CH_2Cl_2–petroleum ether	89–90	$C_{11}H_{11}NO_5$
24	H	CH_3	95		Ether–petroleum ether	57–58[e]	$C_{11}H_{12}O_3$
25	p-NH_2	CH_3	73		Acetone–benzene	121–123	$C_{11}H_{13}NO_3$
26	p-F	C_2H_5	91[b]	94	Ether–petroleum ether	80–81	$C_{12}H_{13}FO_3$
27	p-NH_2	C_2H_5	82		Acetone–petroleum ether	128–129	$C_{12}H_{15}NO_3$
28	p-NH_2	C_3H_7	69		CH_2Cl_2–petroleum ether	110–111	$C_{13}H_{17}NO_3$[f]
29	p-F	C_6H_5	63		Ether–petroleum ether	114–115	$C_{16}H_{13}FO_3$
30	H	C_6H_5	91	64	Ethanol–H_2O	147–149[g]	$C_{16}H_{14}O_3$

[a] Satisfactory analyses (±0.4% for C, H, F, N) were reported for all new compounds except as noted. [b] Overall yield from the last crystalline intermediate, the quaternary ammonium salt V. [c] Lit.[14] mp 95.5°. [d] Lit.[3a] mp 81.0–82.5°. [e] Lit.[3b] mp 58°. [f] C: calcd, 66.36; found, 65.79. [g] A dimorph of the reported form having mp 163°: A. M. Cragg, F. M. Dean, and G. Winfield, *J. Chem. Soc.*, 2431 (1959).

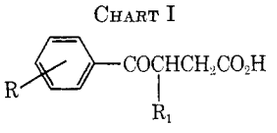
the enone into the nitrile, and the reaction is conveniently monitored by tlc. As reaction proceeds from intermediate **36**, two more polar products, which remain after disappearance of **4** and **36**, appear in the chromatogram. One of these is keto nitrile **37**; nmr spectroscopy of a fraction rich in the second product suggests it to be methoxy ketone **38**. The formation of this product by competitive 1,4 addition of solvent is not a serious factor, for acid hydrolysis of the mixture gave 86% of γ-keto acid **20**.[10]

We also examined the condensation of an enamine with ethyl α-bromoacetate (eq 2)[11] and base-catalyzed condensation of glyoxylic acid with the appropriate ketone (eq 3)[3c,d] as alternative routes to γ-keto acids. Alkylation of the pyrrolidine enamine of propiophenone[12] (VII, R = H) with ethyl bromoacetate gave 61% of ethyl β-benzoylbutyrate (VIII, R = H). However, this procedure proved to be limited, for its application to *o*-acetamidoacetophenone gave only 12% of ethyl β-(*o*-acetamidobenzoyl)propionate. Moreover, the enamine derived from *p*-acetamidopropiophenone and morpholine could not be separated from unreacted ketone, and attempts to utilize this mixture were abortive.



The procedure of eq 3 was somewhat more versatile. Thus, condensation of glyoxylic acid, generated *in situ* by periodate oxidation of tartaric acid,[3c,d] with the appropriate ketone III gave the β-substituted acrylic acids (IX) listed in Table IV; however, the yields of product were disappointing (13–47%). Reduction of the halobenzoyl (**31**, **32**, **34**) and benzoyl (**35**) derivatives with zinc in acetic acid gave 64–94% of the corresponding β-(substituted benzoyl)alkanoic acids (Table III). Yet a similar reduction of the acid **33** did not give β-(*m*-aminobenzoyl)butyric acid. Moreover, the isomeric acid could not be prepared from *p*-acetamidopropiophenone by this sequence, since condensation of the ketone with glyoxylic acid failed. In addition to the above shortcomings, comparison of the overall yield of I by this two-step procedure with that produced by the Mannich sequence demonstrates superiority for the latter method (see Chart I).[13]

Chart I



Compd	R	R1	% yield — A[a]	B[b]
20	p-Br	CH_3	80	44
21	p-Cl	CH_3	67	32
22	p-F	CH_3	79	44
23	m-NO_2	CH_3	74	*c*
26	p-F	C_2H_5	65	12

[a] Synthesis *via* Mannich reaction. [b] Synthesis *via* glyoxylic acid condensation. [c] Not achieved.

(10) The fate of methoxy ketone **38** under these conditions was not determined; acid-catalyzed elimination of methanol and conversion of the resulting **36** into other nonacidic products is apparent.

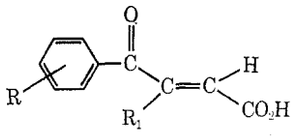
(11) (a) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **76**, 2029 (1954); (b) G. Stork, A. Brizzolava, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(12) P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, **92**, 4261 (1970).

(13) The direct preparation of certain γ-keto esters and γ-keto nitriles by conjugate addition of benzaldehyde and *p*-chlorobenzaldehyde to α,β-unsaturated esters and nitriles was described after completion of this work: H. Stetter and M. Schreckenberg, *Angew. Chem. Int. Ed. Engl.*, **12**, 81 (1973).

TABLE IV

β-BENZOYL-β-SUBSTITUTED ACRYLIC ACIDS



Compd	R	R_1	Yield, %	Recrystn solvent	Mp, °C	Formula[a]
31	*p*-Cl	CH_3	41	Benzene–heptane	128	$C_{11}H_9ClO_3$
32	*p*-F	CH_3	47	Benzene–heptane	97–99	$C_{11}H_9FO_3$
33	*m*-NO_2	CH_3	33	Benzene–heptane	137–139	$C_{11}H_9NO_5$
34	*p*-F	C_2H_5	13	Ether–hexane	88–89	$C_{12}H_{11}FO_3$
35	H	C_6H_5	44	Benzene–heptane	120–123[b]	$C_{16}H_{14}O_3$

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds. [b] Trans isomer, mp 128°: E. P. Kohler, W. D. Peterson, and C. L. Bickel, *J. Amer. Chem. Soc.*, **56**, 2000 (1934). Cis isomer, mp 140–141°: C. R. Bauer and R. E. Lutz, *J. Amer. Chem. Soc.*, **75**, 5997 (1953).

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined in pressed KBr disks on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were measured in methanol solution with a Cary Model 11 recording spectrometer. Nmr spectra were determined in deuteriochloroform on a Varian HR-100 spectrometer using tetramethylsilane as an internal standard. All evaporations were carried out at reduced pressure. The petroleum ether used was that fraction boiling at 30–60°.

Preparation of the [(Substituted benzoyl)alkyl]trimethylammonium Iodides (V).—The following preparation of [2-(*p*-acetamidobenzoyl)propyl]trimethylammonium iodide (**9**) illustrates the general procedure. A solution of 21.0 g (0.257 mol) of dimethylamine hydrochloride in 15.2 ml (0.203 mol) of 37% aqueous formaldehyde was allowed to stand at room temperature for 30 min. To the solution was added 105 ml (1.1 mol) of acetic anhydride and the mixture was swirled until a clear solution resulted and spontaneous gentle boiling began. To the still warm solution was added 32.8 g (0.172 mol) of *p*-acetamidopropiophenone and the mixture was heated on the steam bath for 2 hr. The reaction mixture was evaporated on a water bath at 55–60°. To destroy the excess reagents the residue was treated with 350 ml of acetone and the solution was boiled for 5 min and then evaporated. The residual gum was dissolved in 350 ml of water and washed with three 250-ml portions of methylene chloride. The aqueous solution was stirred in an ice bath with 250 ml of methylene chloride and rendered alkaline by the dropwise addition of 2.5 *N* sodium hydroxide solution. The methylene chloride solution was separated and the aqueous solution was extracted with an additional 250 ml of methylene chloride. The combined organic extracts were washed with saline, dried, and evaporated, leaving 40 g of 4′-(3-dimethylamino-2-methylpropionyl)acetanilide as a liquid which was used without further purification. A solution of this material and 22 ml (0.33 mol) of iodomethane in 400 ml of acetone was stirred at reflux temperature for 18 hr. The mixture was cooled and 51.9 g (85%) of methiodide, mp 206–207°, was collected by filtration. The characterization of this substance and the other Mannich base quaternary salts is given in Table I.

Preparation of the β-(Substituted benzoyl)alkylnitriles (VI).—The following preparation of 4′-(3-cyano-2-methylpropionyl)acetanilide (**14**) illustrates the general procedure. To a stirred solution of 88.0 g (1.35 mol) of potassium cyanide in 1.76 l. of water was added a solution of 220 g (0.565 mol) of [2-(*p*-acetamidobenzoyl)propyl]trimethylammonium iodide (**9**) in 440 ml of methanol and 2.2 l. of water. An oil separated and gradually became a white solid during 4 hr of stirring. The solid was collected and washed liberally with water, affording 119 g (92%) of nitrile, mp 127–130°. Characterization of this substance and others prepared in a similar manner is given in Table II. Absence of an entry corresponding to the acids obtained by method B in Table II signifies a liquid product, which was used without attempted purification.

A similar reaction in methanol between 3.40 g of potassium cyanide and 9.00 g of [2-(*p*-bromobenzoyl)propyl]trimethylammonium iodide (**4**) gave, after 3 hr, a binary product mixture (R_f 0.31, 0.54 on silica plates), which was partially separated on a column (5 × 46 cm) prepared from a synthetic magnesia–silica absorbent using heptane–methylene chloride (4:1) as the solvent system. The material (2.12 g) eluted by this solvent was a mixture of **37** and **4′-bromo-3-methoxy-2-methylpropiophenone (38)** as indicated by tlc and the distinctive nmr spectrum: *inter alia* $\delta^{TMS}_{CDCl_3}$ 3.30 (s, OCH_3). Further elution of the column with methylene chloride gave 3.40 g (62%) of **3-(*p*-bromobenzoyl)-butyronitrile (37)**, the homogenity of which was indicated by tlc and ir.

2-Allyl *p*-Bromophenyl Ketone (36).—A mixture of 29.13 g (0.071 mol) of [2-(*p*-bromobenzoyl)propyl]trimethylammonium iodide (**4**) and 10.5 g (0.162 mol) of potassium cyanide in 650 ml of water was mechanically stirred in a baffle flask for 22 hr. The products were isolated with methylene chloride in the usual manner to give 16.81 g of a liquid that was dissolved in hexane–methylene chloride (4:1) and adsorbed onto a column (5 × 46 cm) prepared from this system and a synthetic magnesia–silica adsorbent. Elution of the column with hexane–methylene chloride (4:1, 5.5 l.) gave 10.1 g (63%) of ketone as white crystals, mp 45–47°. A sample was recrystallized twice from petroleum ether at −78° to give white crystals: mp 50–51°; uv max 258 nm (ε 12,800); ir max 6.04, 6.14, 6.28 μ; nmr $\delta^{TMS}_{CDCl_3}$ 2.06 (d, 2, J = 0.8 Hz, CH_3), 5.58 (d, 1, J = 0.8 Hz, HC=CCH_3), 5.90 (d, 1, J = 0.8 Hz, HC=CCH_3), 7.58 (s, 4, aryl H).

Anal. Calcd for $C_{10}H_9BrO$: C, 53.37; H, 4.03. Found: C, 53.39; H, 3.93.

Elution of the column with 3 l. of methylene chloride gave 6.87 g (37%) of **3-(*p*-bromobenzoyl)butyronitrile (37)** as a colorless liquid, ir max 4.50, 5.95, 6.31 μ.

3-(*p*-Bromobenzoyl)butyronitrile (37).—A solution of 8.70 g (39.6 mmol) of 2-allyl *p*-bromobenzoyl ketone (**36**) and 5.80 g (89 mmol) of potassium cyanide in 150 ml of methanol was stirred at room temperature for 3 hr to give 9.55 g (96%) of product as a liquid, the ir spectrum of which was identical with that prepared from quaternary salt **4** and acid hydrolysis of which gave 7.71 g (75%) of **3-(*p*-bromobenzoyl)butyric acid (20)**, mp 93–96°.

Use of water as the reaction medium and chromatography of the crude product as described above gave 38% of ketone **36** and 46% of nitrile **37**.

Preparation of the β-(Substituted benzoyl)alkanoic Acids (I). Method A.—A solution of 23.2 g (0.10 mol) of 4′-(3-cyano-2-methylpropionyl)acetanilide (**14**) and 230 ml of 6 *N* hydrochloric acid was stirred at reflux temperature for 1 hr. The solution was evaporated and the residue was triturated with acetone, affording, in two crops, 28 g of a mixture of amino acid hydrochloride and ammonium chloride. A 1.22-g sample of this material was dissolved in 12 ml of water and the solution was brought to pH 4 by the dropwise addition of 1.0 *N* sodium hydroxide solution. The ice-cooled solution deposited 690 mg of 3-(*p*-aminobenzoyl)-butyric acid (**25**) as white crystals, mp 119–123°. The characterization of this substance is given in Table III.

Those compounds of Table III lacking an amino group were isolated by extraction of cooled acid solution with CH_2Cl_2, removal of solvent, and recrystallization.

Method B.—A mixture of 31.40 g (0.116 mol) of β-(*p*-bromobenzoyl)crotonic acid[14] and 15.2 g of zinc dust in 168 ml of glacial acetic acid and 68 ml of water was stirred at steam-bath tempera-

(14) R. E. Lutz and R. J. Taylor, *J. Amer. Chem. Soc.*, **55**, 1168 (1933).

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.

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

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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).