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Studies on Benzhydryl Derivatives. IV.[1] Synthesis and Anti-inflammatory Activity of 2-*O*-(Diphenylacetyl)salicylic Acids

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A synthetic route to 2-*O*-(diphenylacetyl)salicylic acid derivatives was developed and the effects of the products on the heat-denaturation of albumin and on heat-induced erythrocytolysis were examined (*in vitro* anti-inflammation test). Trichloroethyl salicylate was acylated with diphenylacetic acid and its derivatives in the presence of methanesulfonyl chloride and pyridine, and the products were deprotected with zinc-acetic acid to give 2-*O*-(diphenylacetyl)salicylic acid derivatives. Their biological effects resembled those of ibuprofen.

Keywords——benzhydryl derivative; trichloroethyl ester; acylation with methanesulfonyl chloride-pyridine; acylation with DCC-4-dimethylaminopyridine; anti-inflammatory assay *in vitro*

Considerable knowledge exists on the usefulness of acetylsalicylic acid as a drug, but little attention has been paid to the synthesis and bioactivity of other acylated derivatives of salicylic acid.

On the other hand, there have been a number of reviews on the involvement of the benzhydryl group in many types of drugs,[2] and the authors have studied the synthesis and bioactivity of compounds containing this group.[1,3]

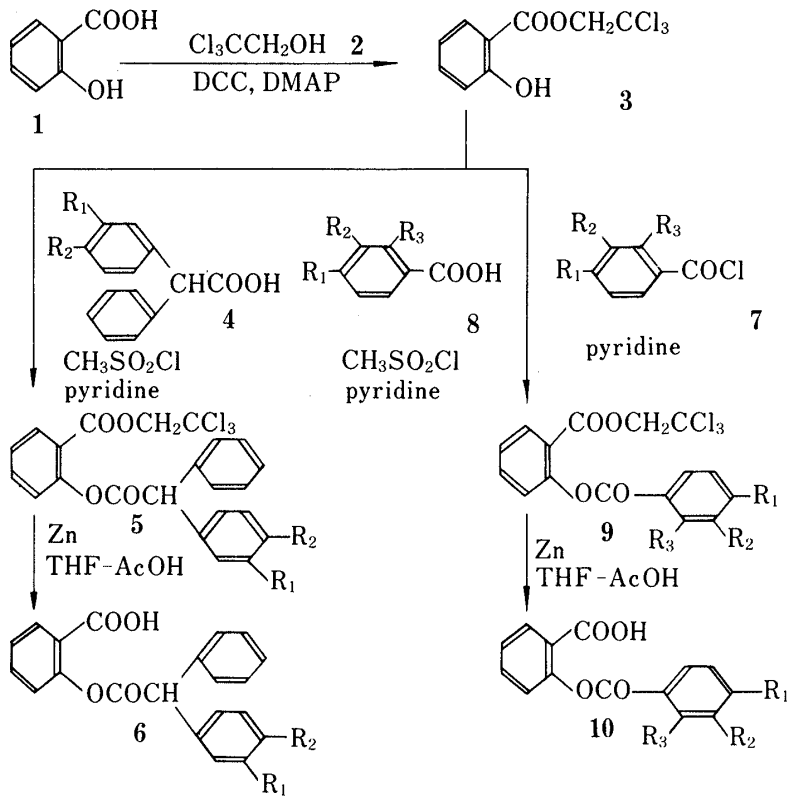
In this work, we studied the synthesis of 2-*O*-(diphenylacetyl)salicylic acids and related 2-*O*-(phenylacetyl)salicylic acids. The inhibitory effects of the products on the heat denaturation of bovine serum albumin and on heat-induced erythrocyte lysis as indicators of anti-inflammatory activity were also examined.

Known synthetic methods for 2-*O*-acylsalicylic acid include the reaction of an alkali metal salt of salicylic acid with acyl chlorides[4] and the reaction of salicylic acid with acyl chlorides in the presence of dimethylaniline[5] or pyridine[6] (the reaction in pyridine appears to give the best yield). Application of these procedures to the preparation of 2-*O*-(diphenylacetyl)salicylic acid was not effective. Therefore, we investigated the acylation of salicylic acid protected by a 2,2,2-trichloroethyl ester, which can be easily removed by treatment with Zinc in acetic acid.[7]

Heating of salicylic acid (**1**) with 2,2,2-trichloroethanol (**2**) in concentrated sulfuric acid gave the desired ester (**3**) but the yield was not reproducible. An improvement was obtained by reacting **1** with **2** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP)[8] in tetrahydrofuran.

The acylation of **3** with diphenylacetyl chloride was unsuccessful, but the reaction of **3** with the free acid (**4**), DCC, and DMAP gave the desired acylate (**5a**) in 51% yield.

Esterification in the presence of arylsulfonyl chloride in pyridine,[9] which is recommended for the preparation of sterically hindered esters, was modified by using methanesul-



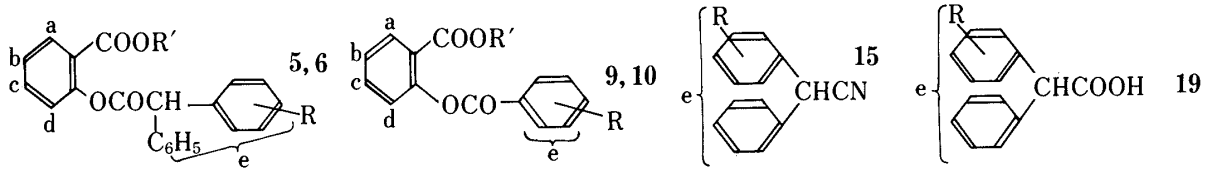
Compd.	R_1	R_2	mp (°C)	Recryst. from	Yield (%)	Compd.	R_1	R_2	R_3	mp (°C)	Recryst. from	Yield (%)
5a	H	H	90—91	Me_2CO–*n*-Hexane	78	**9a**	H	H	Cl	125—126	Et_2O–*n*-Hexane	71
5b	H	Cl	95—96	Me_2CO–*n*-Hexane	83	**9b**	Cl	H	H	83—85	*n*-Hexane	70
5c	Cl	Cl	95—96	*n*-Hexane	77	**9c**	H	Cl	Cl	102—103	$CHCl_3$	96
5d	H	MeO	106—108	EtOH	80	**9d**	MeO	H	H	84	$CHCl_3$	68
6a	H	H	128—129	Benzene	73	**10a**	H	H	Cl	156—157	$CHCl_3$	70
6b	H	Cl	123—124	Me_2CO–*n*-Hexane	75	**10b**	Cl	H	H	145—146	Benzene	43
6c	Cl	Cl	118—120	Et_2O–*n*-Hexane	88	**10c**	H	Cl	Cl	165—166	$CHCl_3$	45
6d	H	MeO	125—126	Et_2O–*n*-Hexane	80	**10d**	MeO	H	H	137—138	Benzene	75

Chart 1

fonyl chloride-pyridine and the yield of **5a** increased to 78%. The intermediate (**5a**) thus obtained was treated with zinc dust in tetrahydrofuran-acetic acid mixture, giving 2-*O*-(diphenylacetyl)salicylic acid (**6a**). The analogs (**6b—d**) and several aromatic 2-*O*-acylsalicylic acids (**10a—d**) were synthesized in the same way. The synthetic routes to the substituted diphenylacetic acids (**4a—d**) are depicted in Chart 2.

The 2-*O*-acylsalicylic acids (**6a** and **10a—b**) inhibited the heat-denaturation of bovine serum albumin[10] a concentration-dependent manner in the test solution (Table II) and the inhibition rates were 80—90% at 1 mM for all five compounds. The diphenylacetyl derivative (**6a**) showed the strongest inhibition among them and had activity comparable to that of ibuprofen, but less than that of flufenamic acid. The next strongest compounds were **10a** and **10b**, followed by **10c**, and **10d** was then weakest.

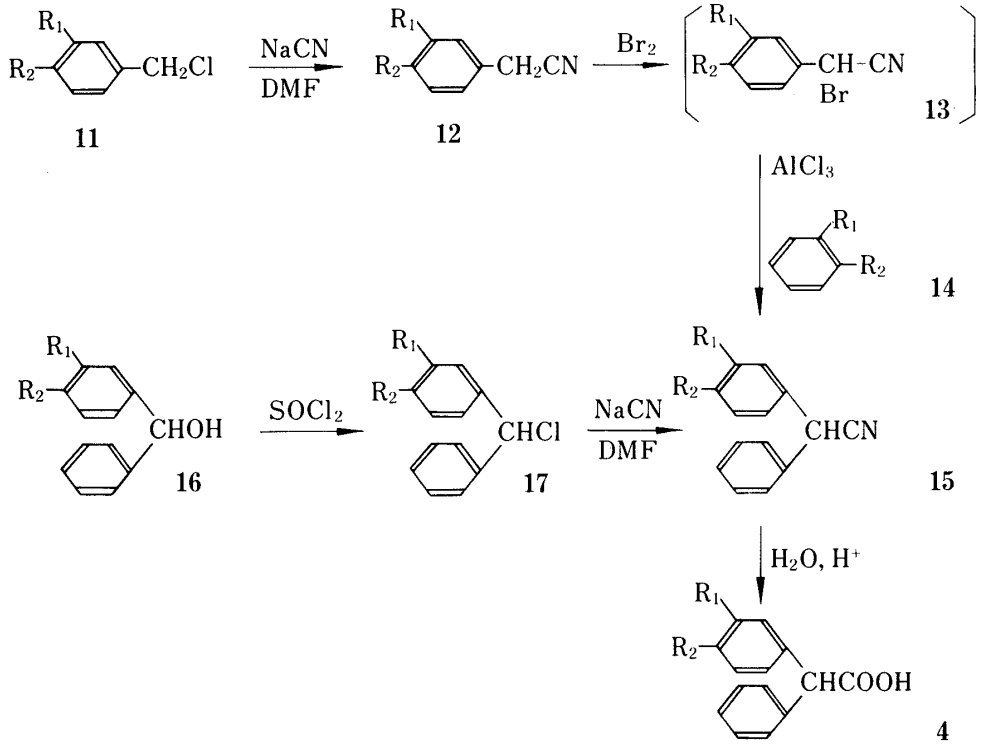
TABLE I. Spectral and Analytical Data for Synthesized Compounds



Compound	IR_{max}^{Nujol} cm^{-1} ν (COO)	NMR ($CDCl_3$) δ (J, Hz)					Formula	Analysis (%) Calcd (Found)		
		CH_2	CH	a	d	e		C	H	Cl
5a	1740	4.80 s	5.41 s	8.12 dd (8, 2.5)	7.01 dd (7.5, 2)	7.2—7.8 m	$C_{23}H_{17}Cl_3O_4$	59.57 (59.72	3.70 3.84	22.94 23.11)
5b	1725	4.82 s	5.40 s	8.15 dd (7.5, 2)	7.00 dd (8, 2)	7.3—7.7 m	$C_{23}H_{16}Cl_4O_4$	55.45 (55.54	3.24 3.41	28.46 28.58)
5c	1730	4.86 s	5.34 s	8.13 dd (8, 1.8)	7.02 dd (8, 1.1)	7.2—7.4 m	$C_{23}H_{15}Cl_5O_4$	51.87 (52.06	2.84 2.75	33.28 33.01)
5d	1725	4.81 s	5.34 s	8.12 dd (7.5, 2)	7.02 dd (6.5, 2)	7.2—7.4 m	$C_{24}H_{19}Cl_3O_5$	58.38 (58.09	3.88 3.76	21.54 21.30)
6a	1765 1685	—	5.50 s	7.95 dd (8, 2)	7.05 dd (8, 2)	7.2—7.7 m	$C_{21}H_{16}O_4$	75.89 (75.88	4.85 4.84)	—
6b	1770 1690	—	5.23 s	8.15 dd (7.5, 2.5)	7.05 dd (7.5, 2.5)	7.4—7.8 m	$C_{21}H_{15}ClO_4$	68.75 (68.89	4.15 4.22	9.66 9.74)
6c	1755 1695	—	5.28 s	8.12 dd (8, 2.5)	7.04 dd (8, 1)	7.2—7.7 m	$C_{21}H_{14}Cl_2O_4$	62.86 (63.04	3.52 3.47	17.67 17.56)
6d	1760 1675	—	5.31 s	8.10 dd (8, 2)	7.05 dd (8, 1.1)	6.9—7.6 m	$C_{22}H_{18}O_5$	72.92 (72.81	5.01 5.16)	—
9a	1730	4.82 s	—	8.10 dd (8, 2.5)	7.01 dd (8, 1)	7.2—7.4 m	$C_{16}H_{10}Cl_4O_4$	47.09 (47.15	2.47 2.55	34.76 34.80)
9b	1725	4.82 s	—	8.05 dd (8, 2)	7.02 dd (8, 1)	7.2—7.5 m	$C_{16}H_{10}Cl_4O_4$	47.09 (47.26	2.47 2.48	34.76 34.69)
9c	1730	4.80 s	—	8.02 dd (7.5, 2)	7.25 dd (8, 1)	7.4—7.9 m	$C_{16}H_9Cl_5O_4$	43.42 (43.40	2.05 2.31	40.06 40.12)
10a	1735 1680	—	—	—	—	7.3—8.3 m	$C_{14}H_9ClO_4$	60.77 (60.58	3.28 3.50	12.82 12.88)
10b	1730 1680	—	—	—	—	7.3—8.3 m	$C_{14}H_9ClO_4$	60.77 (60.81	3.28 3.42	12.82 12.99)
10c	1740 1705	—	—	—	—	7.3—8.2 m	$C_{14}H_8Cl_2O_4$	54.04 (54.14	2.63 2.63	22.79 22.77)
10d	1720 1680	—	—	—	—	7.0—8.3 m	$C_{15}H_{12}O_5$	66.17 (66.09	4.44 4.64)	—
15b	—	—	5.12 s	—	—	7.3—7.4 m	$C_{14}H_{10}ClN$	73.85 (73.85	4.43 4.65	15.57 15.29)
15c	—	—	5.08 s	—	—	7.1—7.5	$C_{14}H_9Cl_2N$	64.14 (64.40	3.46 3.22	27.05 27.23)

TABLE I (continued)

Compound	IR_{max}^{Nujol} cm^{-1} ν (COO)	NMR ($CDCl_3$) δ (J, Hz)					Formula	Analysis (%) Calcd (Found)		
		CH_2	CH	a	d	e		C	H	Cl
15d	—	—	5.09 s	—	—	7.1—7.4	$C_{15}H_{13}NO$	80.69 (80.59	5.87 5.89)	—
4b	1690						$C_{14}H_{11}ClO_2$	68.16 (68.26	4.49 4.38	14.37 14.52)
4c	1660						$C_{14}H_{10}Cl_2O_2$	59.81 (59.97	3.59 3.64	25.22 25.52)
4d	1680						$C_{15}H_{14}O_3$	74.36 (74.44	5.83 5.91)	



Compound	R_1	R_2	mp (°C)	Recryst. from	Yield (%)
15b	H	Cl	74—75	iso-PrOH	70[a]
4b	H	Cl	117—118	Me_2CO–*n*-Hexane	90
15c	Cl	Cl	59—62	*n*-Hexane	53[a]
4c	Cl	Cl	152—153	Benzene	82
15d	H	MeO	130—131	EtOH	10[a], 16[b]
4d	H	MeO	97—98	AcOEt–*n*-Hexane	84

a) Prepared from **12**. *b*) Prepared from **16d**.

Chart 2

The inhibition test on erythrocyte lysis induced by heat treatment[11] (Table III) revealed moderate potency of all five compounds at 0.30 mM and higher. Small differences in potency were observed among these compounds, and **10b** and **10c** showed inhibitory effects equivalent

Table II. Inhibitory Effect of 2-*O*-Acylsalicylic Acids on Heat Denaturation of Bovine Serum Albumin

Concentration[b] (mM)	Inhibition (%)[a]				
	0.01	0.03	0.10	0.30	1.00
Compound					
6a	20.3	34.6	62.7	88.5	92.2
10a	14.3	26.3	35.9	60.4	91.2
10b	14.3	23.0	31.8	61.8	89.9
10c	8.3	12.9	17.5	39.6	82.9
10d	0.9	4.1	4.6	26.7	80.2
Flufenamic acid	31.6	67.6	89.2	97.2	97.7
Ibuprofen	16.9	37.7	74.5	97.7	98.6

a) Results are average values of two measurements.
b) Test compounds were dissolved in dimethylsulfoxide (final concentration: 1%)–0.9% NaCl solution.

Table III. Inhibitory Effect of 2-*O*-Acylsalicylic Acids on Heat-Induced Erythrocyte Lysis

Concentration[b] (mM)	Inhibition (%)[a]				
	0.01	0.03	0.10	0.30	1.00
Compound					
6a	−0.1	−0.2	2.4	6.5	33.7
10a	1.6	2.3	3.1	9.7	30.9
10b	1.7	3.3	5.6	16.5	39.5
10c	−0.8	−0.1	1.3	3.4	24.0
10d	1.1	2.0	6.9	17.8	40.9
Flufenamic acid	25.6	46.9	54.6	−17.6	−18.3
Ibuprofen	—	—	—	—	41.6

a) Results are average values of three measurements.
b) Test compounds were dissolved in dimethylsulfoxide (final concentration: 1%)–0.9% NaCl solution.

to that of ibuprofen, *i.e.*, about 40% at 1.00 mM.

Anti-inflammation tests *in vitro* revealed positive effects of these compounds. They differed from flufenamic acid in the effect on erythrocyte lysis (Table III), *i.e.*, the latter showed inhibition at lower concentration but activation at higher concentration, and the activity of the test compounds rather resembled that of ibuprofen. The results are encouraging, and further studies on these compounds and other 2-*O*-(diphenylacetyl)salicylic acids (**6b—d**) to test their anti-inflammatory activities *in vivo* are in progress.

Experimental

2,2,2-Trichloroethyl Salicylate (3)——a) A mixture of salicylic acid (**1**, 10 g, 65 mmol), 2,2,2-trichloroethanol (**2**, 30 g, 195 mmol), and conc. H_2SO_4 (3 ml) was heated at 100 °C for 4 h. After cooling, the mixture was agitated with $CHCl_3$ (20 ml) and the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated off and the residue was distilled to remove 2,2,2-trichloroethanol (bp_{25} 63 °C); the fraction of $bp_{1.5}$ 110 °C was collected. Recrystallization gave 9 g of a solid (C_6H_6), mp 56—57 °C (45%). IR ν_{max}^{Nujol} cm^{-1} 1690 (ν_{COO}). NMR ($CDCl_3$): 5.0 (2H, s, CH_2), 6.90 (3-H, dd, J=7, 2 Hz), 7.05 (5-H, s, br), 7.55 (4-H, m), 7.95 (6-H, dd, J=8, 2 Hz). *Anal.* Calcd for $C_9H_7Cl_3O_3$: C, 40.11; H, 2.62; Cl, 39.47. Found: C, 40.23; H, 2.58; Cl, 39.61.

b) DCC (0.82 g, 4.0 mmol) in THF (5 ml) was added dropwise to a solution of **1** (0.5 g, 3.6 mmol), **2** (0.6 g, 4.0 mmol), and DMAP (44.2 mg, 0.36 mmol) in THF (10 ml) with efficient cooling and stirring. After additional cooling and stirring for 3 h, the stirring was continued overnight at room temperature. The separated *N,N'*-dicyclohexylurea was filtered off. The filtrate was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$ (20 ml). The solution was washed successively with 5% HCl, 5% Na_2CO_3, and H_2O. The solution was dried (Na_2SO_4) and the solvent was removed by distillation. The residue was distilled, $bp_{0.25}$ 75—100 °C (bath temperature), 0.75 g, mp 56—57 °C (77%). The product was shown to be identical with an authentic sample by comparison of the IR spectra.

2,2,2-Trichloroethyl 2-*O*-Acylsalicylates (5 and 9, General Procedure)——a) After the addition of 2.5 equivalents of 1 N methanesulfonyl chloride in toluene to a solution of 1 equivalent of **4** or **8** in 10 times the weight of anhydrous pyridine with stirring, one equivalent of **3** was added to the mixture and the whole was continuously stirred for 10 h at room temperature. The mixture was extracted with AcOEt, the organic layer was dried (Na_2SO_4), and the solvent was removed by distillation to leave a crude product. Compounds **5a—d** and **9a—c** were obtained by this procedure. The yields, physical properties, and analytical data are listed in Chart 1 and Table I.

b) **3** was added to a cooled mixture of 4-methoxybenzoyl chloride (1.6 g) in pyridine (10 ml). The mixture was refluxed for 2 h and the solvent was distilled off. The residue was extracted with AcOEt and the organic layer was dried (Na_2SO_4). The solution was distilled to remove the solvent. The remaining crude **9d** was used directly in the next step. 1.8 g (47%). IR_{max}^{neat} cm^{-1}: 1720 (ν_{COO}).

2-*O*-Acylsalicylic Acids (6 and 10, General Procedure)——One equivalent of **5** or **9** was dissolved in 10 volumes of a mixture of THF–90% AcOH (1 : 1). Zinc dust (same weight as that of the starting material) was added to the solution and the mixture was stirred for 30 min at room temperature. After the removal of the excess zinc by filtration, the solvent was distilled off from the filtrate. The residue was mixed with the same volume of H_2O and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried (Na_2So_4) and the solvent was evaporated off to leave a crude product, which was recrystallized to give the pure substance.

Compounds **6a—d** and **10a—d** were obtained by this procedure and the details, yield, physical properties, and spectral data are summarized in Chart 1 and Table I.

Effects of 6a, 10a, b, c, and d on Heat Denaturation of Albumin[10]——A mixture of 3.6 ml of 0.75% bovine serum albumin (Fraction V, powder) in 0.2 M phosphate buffer, pH 5.3, and 0.4 ml of test compound at the desired concentration in 10% dimethylsulfoxide–0.9% NaCl solution was incubated at room temperature for 15 min and then treated at 63 °C for 10 min. The reaction mixture was cooled immediately and the turbidity of the solution was measured at 660 nm. The protection from denaturation was calculated from the difference between the control and the sample.

Inhibitory Effect of 6a, 10a, b, c, and d on Heat-Induced Erythrocyte Lysis[11]——Rat erythrocytes freshly obtained from heparinized blood were suspended in 0.15 M phosphate buffer, pH 7.4, at 5% on a volume basis. To 3.6 ml of this erythrocyte suspension was added 0.4 ml of test compound dissolved in 10% dimethylsulfoxide–0.9% NaCl solution (the pH had previously been adjusted to pH 7.4 with 0.1 N NaOH). The test tubes were rotated gently. After being kept standing at room temperature for 15 min, the mixture was treated at 53 °C in a water bath for 20 min. The heat-treated sample was cooled in an ice bath for 5 min then centrifuged at 2500 rpm for 10 min to obtain the supernatant. The absorption of the supernatant at 540 nm was measured. The inhibition of erythrocyte lysis was calculated from the difference in optical density between the sample and the control (blank).

α-(4-Chlorophenyl)phenylacetonitrile (15b)——Br_2 (34.8 g, 0.22 mol) was added dropwise to stirred 4-chlorobenzyl cyanide (30 g, 0.2 mol) at 110 °C over a period of 1 h. After continuous heating for 15 min at 105—110 °C, N_2 was introduced into the reaction mixture to remove HBr produced. The mixture was dissolved in anhydrous C_6H_6. The solution was added to a mixture of $AlCl_3$ and C_6H_6 under reflux with stirring over a period of 2 h, and the whole mixture was refluxed for an additional 1 h. After cooling, the mixture was added to ice (250 g)–conc. HCl (25 ml). The H_2O layer was extracted with Et_2O and the extract was combined with the C_6H_6 layer. The organic solution was washed successively with H_2O, saturated $NaHCO_3$, and H_2O. The dried (Na_2SO_4) solution was concentrated under reduced pressure to leave crude crystals, which were recrystallized (Chart 2 and Table I).

α-(4-Chlorophenyl)phenylacetic Acid (4b)——A mixture of **15b** (1.7 g, 0.75 mmol), H_2SO_4 (17 ml), and H_2O (17 ml) was refluxed for 8 h with stirring. The reaction mixture was diluted with ice–H_2O (51 ml) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave the crude acid, which was recrystallized (Chart 2 and Table I).

3,4-Dichlorophenylacetonitrile (12c)——3,4-Dichlorobenzyl chloride (5.6 g, 30.1 mmol) and NaCN (6.4 g, 130.6 mmol) were dissolved in DMF (20 ml) and the mixture was heated at 80 °C for 2 h. After cooling, the mixture was dissolved in $CHCl_3$ (100 ml) and the solution was washed with H_2O and dried (Na_2SO_4). The solvent was removed to leave an oil, which was distilled to obtain crystals, $bp_{0.48}$ 110—116 °C (3.6 g, 65%). IR_{max}^{Nujol} cm^{-1}: 2215 (ν_{CN}). NMR δ ($CDCl_3$): 3.75 (2H, s, CH_2), 7.41—7.58 (3H, m, C_6H_3).

α-(3,4-Dichlorophenyl)phenylacetonitrile (15c)——Br_2 (2.8 g, 17.5 mmol) was added to stirred **12c** (3 g, 16.1 mmol) at 105—115 °C over a period of 1 h. Heating was continued for an additional 15 min. HBr produced was removed by the introductions of N_2 into the reaction mixture, then the mixture was dissolved in anhydrous C_6H_6

(2.5 ml). The solution was added dropwise to a refluxing mixture of $AlCl_3$ (2.15 g, 16.1 mmol) and C_6H_6 (6.8 ml) with stirring. The mixture was refluxed with stirring for an additional 1 h. The cooled solution was mixed with ice (20 g)–conc. HCl (2 ml) and the H_2O layer was extracted with Et_2O. The extract was combined with the C_6H_6 layer and the solution was washed successively with H_2O, saturated $NaHCO_3$, and H_2O, then dried (Na_2SO_4). Evaporation of the solvent left an oil, which was chromatographed on a silica gel column. The eluate with C_6H_6 was concentrated and the residue was recrystallized (Chart 2 and Table I).

α-(3,4-Dichlorophenyl)phenylacetic Acid (4c)——The nitrile **15c** (7.4 g, 28.2 mmol) was added to a mixture of H_2SO_4–AcOH–H_2O (1 : 1 : 1, 220 ml) and the whole was refluxed for 5 h. The cooled reaction mixture was diluted with ice–H_2O (220 ml) and extracted with $CHCl_3$. The organic layer was extracted with 10% Na_2CO_3. The extract was acidified with conc. HCl to obtain crystals which were further purified by recrystallization (Chart 2 and Table I).

α-(4-Methoxyphenyl)phenylacetonitrile (15d)——a) Br_2 (6.2 g, 38.8 mmol) was added dropwise to benzyl cyanide (5.3 g, 44.8 mmol) at 105—110 °C with stirring over a period of 30 min, and the heating was continued for an additional 30 min. Anisole (14.5 g, 134.5 mmol) was added to the mixture and $AlCl_3$ (5 g, 37.5 mmol) was added in small portions to the mixture at 45—50 °C. The whole was heated at 100 °C for 1 h, then poured into ice–H_2O (80 ml) and conc. HCl (10 ml) was added. The H_2O layer was extracted, with Et_2O and the extract was combined with the organic layer. The solution was washed with H_2O and then with saturated $NaHCO_3$ and H_2O. The solution was dried (Na_2SO_4) and evaporation of the solvent left an oil, which was distilled to collect the fraction of $bp_{0.5}$ 150—160 °C (bath temp.). The solidified distillate was purified by recrystallization (Chart 2 and Table I).

b) $SOCl_2$ (1 ml, 14.0 mmol) was added dropwise to a solution of 1-(4-methoxyphenyl)-1-phenylmethanol (**16d**) (1 g, 4.6 mmol) in $CHCl_3$ (10 ml) under stirring and cooling. After stirring for 10 min, the solvent and excess $SOCl_2$ were removed by distillation under reduced pressure. Addition of $CHCl_3$ to the residue followed by concentration was repeated twice and the residue was dissolved in DMF (2 ml). The solution was heated with NaCN (0.25 g, 5.1 mmol) for 3 h at 80 °C. Dilution of the reaction mixture with H_2O (10 ml) precipitated a solid which was recrystallized to give the pure product (0.17 g, 16% from **16d**). The product was shown to be identical with an authentic sample by mixed melting point determination and comparison of IR spectra.

α-(4-Methoxyphenyl)phenylacetic Acid (4d)——The nitrile **15d** (6.35 g, 0.03 mol) was added to a mixture of H_2SO_4–AcOH–H_2O (1 : 1 : 1, 153 ml) and the whole was heated at 100 °C for 5 h with stirring. The cooled solution was diluted with ice–H_2O (120 ml) and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried (Na_2SO_4). The solvent was removed by distillation to give the crude acid, which was recrystallized (Chart 2 and Table I).

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