PREPARATION OF ANTIDOTES FOR ANTICHOLINESTERASE POISONING

I. PARPANIT ANALOGUES[1]

R. A. B. BANNARD, J. H. PARKKARI, AND I. W. COLEMAN
Defence Research Chemical Laboratories, Ottawa, Ontario

Manuscript received June 13, 1962

ABSTRACT

Interaction of potassium 1-phenylcyclopentanecarboxylate and 2-diethylaminoethyl chloride in absolute ethanol proved the most satisfactory of four methods examined for the preparation of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate hydrochloride (Parpanit). This procedure was used to obtain 2-(ethyl-2′-fluoroethylamino)ethyl (I), 2-(ethylisopropylamino)-ethyl (II), 2-diisopropylaminoethyl (III), 2-pyrrolidinoethyl (IV), and 2-piperidinoethyl (V) 1-phenylcyclopentanecarboxylate hydrochlorides. 2-Diethylaminoethyl 1-(*p*-nitrophenyl)-cyclopentanecarboxylate hydrochloride (VI) was also prepared in this way but was obtained more conveniently by direct nitration of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate. The preparation of intermediates required in these syntheses is described.

Preliminary results are given on the potency of these compounds as substitutes for atropine sulphate in the usual oxime and atropine sulphate treatment of mice which have been poisoned with Sarin.

In connection with extension of our studies on the usefulness of substitutes for atropine in the treatment of Sarin poisoning (1, 2) it became necessary to prepare certain analogues of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate hydrochloride, which is known commercially as Parpanit, Panparnit, Caramiphen hydrochloride, or Pentaphen. Many compounds of this type have been synthesized previously and the method most frequently employed has been interaction of the acid chloride with the requisite aminoalcohol in an aromatic solvent (3–8) (method 1). Other procedures which have been utilized less frequently include transesterification of ethyl 1-phenylcyclopentanecarboxylate with an aminoalcohol and sodium in xylene (8–11) (method 2); interaction of an alkali metal salt of the acid and an aminoalkyl halide in a hydrocarbon solvent (5, 7, 12–14) (method 3); treatment of the acid chloride with an aminoalcohol hydrochloride in a hydrocarbon solvent (5) (method 4); and heating the acid with an aminoalkyl chloride hydrochloride in an alcohol (5) (method 5). Method 2 was considered unsuitable for preparation of the compounds required because it sometimes furnishes very poor yields (11). It was not clear, however, which of the other four procedures referred to above would be most satisfactory. Accordingly, the merits of methods 1, 3, 4, and 5 were briefly examined with respect to yield and manipulative convenience for preparation of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate hydrochloride (3).

Interaction of equimolar quantities of 1-phenylcyclopentanecarboxylic acid chloride and 2-diethylaminoethanol in anhydrous benzene under reflux for 2 hours furnished the ester hydrochloride in 65% yield. Prolonging the period of reflux did not improve the yield (method 1).

When potassium 1-phenylcyclopentanecarboxylate was heated under reflux in absolute ethanol for 18 hours with a 20 mole% excess of 2-diethylaminoethyl chloride, followed by treatment with hydrogen chloride, an 80% yield of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate hydrochloride was obtained. Lengthening the period of reflux did not improve the yield but the latter decreased to ca. 60% when heating periods shorter than 12 hours were employed (method 3).

[1]*Issued as D.R.C.L. Report No. 374.*

Interaction of equimolar quantities of 1-phenylcyclopentanecarboxylic acid chloride and 2-diethylaminoethanol hydrochloride in dry benzene at reflux temperature for 48 hours gave a 51% yield of the desired material. The yield decreased sharply when shorter reflux periods were used (method 4).

When equimolar quantities of 1-phenylcyclopentanecarboxylic acid and 2-diethylaminoethyl chloride hydrochloride were heated under reflux in absolute ethanol for 48 hours only a 29% yield of the desired ester hydrochloride was obtained (method 5).

From the foregoing results it is evident that method 3 is superior to the others examined on the basis of yield. It is also best from the standpoint of manipulative convenience, since the other methods either required much longer periods of heating under reflux and/or furnished products of inferior quality, which necessitated multiple recrystallizations to provide material equivalent to that obtained by method 3. This method was therefore adopted for preparation of the esters shown in Table II and was satisfactory in all cases.

1-Phenylcyclopentanecarbonitrile was prepared by interaction of phenylacetonitrile and tetramethylene dibromide with sodamide in liquid ammonia, following the general method of Case (15) as modified by Tilford and co-workers (9). The nitrile was hydrolyzed to the acid in 93% yield by the action of 48% hydrobromic acid, by modification of the method used by Weston (5) for preparation of 1-phenylcyclohexanecarboxylic acid. Interaction of the acid and thionyl chloride in dry benzene furnished the acid chloride in 79% yield. Potassium 1-phenylcyclopentanecarboxylate was obtained in 97% yield by neutralization of an alcoholic solution of the acid with 10% alcoholic potassium hydroxide. 1-(*p*-Nitrophenyl)cyclopentanecarboxylic acid was prepared in 80% yield by nitration of 1-phenylcyclopentanecarboxylic acid. The nitro group was concluded to be para to the phenylcyclopentanecarboxylic acid group on the basis of the infrared absorption pattern of the compound in the 1650- to 2000-cm^{-1} region (16). The potassium salt of this acid was readily obtained by the method employed for preparation of potassium 1-phenylcyclopentanecarboxylate.

2-(Ethyl-2′-fluoroethylamino)ethanol was prepared in 78% yield from 2-ethylaminoethanol and 2-fluoroethyl bromide (17), which were caused to react in dry benzene in the presence of anhydrous potassium carbonate. 2-(Ethylisopropylamino)ethanol was obtained similarly and in 41% yield from isopropylaminoethanol and ethyl bromide and was characterized as the halogen acid salts shown in Table I. Isopropylaminoethanol was prepared from isopropylamine and ethylene oxide following Biel's method (18) and characterized as the hydrochloride.

2-Diethylaminoethanol, N-(2-hydroxyethyl)pyrrolidine, N-(2-hydroxyethyl)piperidine, 2-(ethyl-2′-fluoroethylamino)ethanol, 2-(ethylisopropylamino)ethanol, and 2-diisopropylaminoethanol were converted to the corresponding chloride hydrochlorides in the yields given in Table I by treating them with thionyl chloride in dry chloroform (cf. Bartlett *et al.* (19)). These salts were treated with 20% aqueous sodium hydroxide and the free bases were recovered by ether extraction. The latter compounds were not analyzed but were kept at 4° until required in the esterifications.

Finally, 2-diethylaminoethyl 1-(*p*-nitrophenyl)cyclopentanecarboxylate hydrochloride (VI), which had been obtained by esterification of potassium 1-(*p*-nitrophenyl)cyclopentanecarboxylate with 2-diethylaminoethyl chloride, was prepared in 65% yield by direct nitration of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate. The identity of the two samples was established by comparison of melting points and infrared spectra.

The effectiveness of Parpanit analogues I–VI (Table II) as substitutes for atropine

TABLE I

2-Aminoethanol derivatives

Compound	M.p. (°C)	% yield	Solvent for recrystallization	Empirical formula	Analysis							
					Calculated %				Found %			
					C	H	N	X	C	H	N	X
2-Isopropylaminoethanol hydrochloride	69–70	75	Ethanol–ether	$C_5H_{14}NOCl$	43.01	10.11	10.03	25.40	43.13	9.99	10.09	25.46
2-(Ethylisopropylamino)ethanol hydrochloride	85–86	73	Ethanol–ether	$C_7H_{18}NOCl$	50.14	10.82	8.35	21.15	50.23	10.80	8.32	21.17
2-(Ethylisopropylamino)ethanol hydrobromide	71–72	72	Ethanol–ether	$C_7H_{18}NOBr$	39.63	8.55	6.60	37.67	39.90	8.68	6.65	37.59
2-(Ethylisopropylamino)ethanol hydriodide	76–77	38	Ethanol–ether	$C_7H_{18}NOI$	32.44	7.00	5.41	48.98	32.50	6.95	5.56	49.28
2-(Ethylisopropylamino)ethyl chloride hydrochloride	120–121	92	Acetone–ether	$C_7H_{17}NCl_2$	45.17	9.21	7.53	38.10	45.11	9.40	7.63	38.01
2-(Ethyl-2′-fluoroethylamino)-ethyl chloride hydrochloride	147–147.5	66	Methanol–ether	$C_6H_{14}NCl_2F$	37.91	7.42	7.37		37.73	7.30	7.30	
2-Diisopropylaminoethyl chloride hydrochloride	130–131*	84	Acetone–ether	$C_8H_{19}NCl_2$	48.00	9.57	7.00	35.43	48.27	9.44	6.96	35.44
2-Pyrrolidinoethyl chloride hydrochloride	169.5–170.5†	77	Ethanol–ether	$C_6H_{13}NCl_2$	42.37	7.70	8.24	41.69	42.60	7.61	7.97	41.56
2-Piperidinoethyl chloride hydrochloride	225–227‡	79	Ethanol	$C_7H_{15}NCl_2$	45.66	8.21	7.61	38.52	45.84	7.99	7.49	38.40

*J. B. Wright *et al.* (23) report m.p. 132°.
†J. B. Wright *et al.* (24) report m.p. 173.5–174°.
‡J. G. M. Dunlop (25) reports m.p. 231°.

TABLE II

1-Phenyl- and 1-(*p*-nitrophenyl)-cyclopentanecarboxylate hydrochlorides

Compound	M.p. (°C)	% yield	Empirical formula	Analysis							
				Calculated %				Found %			
				C	H	N	X	C	H	N	X
1-Phenylcyclopentanecarboxylate hydrochloride											
2-(Ethyl-2′-fluoroethylamino)ethyl (I)	131.5–132.5	77	$C_{18}H_{27}NO_2ClF$	62.87	7.92	4.07		62.74	8.11	4.07	
2-(Ethylisopropylamino)ethyl (II)	130–131	61	$C_{19}H_{30}NO_2Cl$	67.13	8.90	4.12	10.43	67.37	8.70	4.07	10.42
2-Diisopropylaminoethyl (III)	134–134.5	75	$C_{20}H_{32}NO_2Cl$	67.87	9.11	3.96	10.02	67.87	9.32	4.09	10.10
2-Pyrrolidinoethyl (IV)	142.5–143	83	$C_{18}H_{26}NO_2Cl$	66.75	8.09	4.33	10.95	66.64	8.17	4.34	10.93
2-Piperidinoethyl (V)	163.5–164.5	82	$C_{19}H_{28}NO_2Cl$	67.54	8.35	4.15	10.49	67.55	8.28	4.07	10.51
1-(*p*-Nitrophenyl)cyclopentanecarboxylate hydrochloride											
2-Diethylaminoethyl (VI)	182–182.5	51*	$C_{18}H_{27}N_2O_4Cl$	58.29	7.34	7.56	9.56	58.50	7.13	7.39	9.53

*Recrystallized from ethanol–ether, all others recrystallized from acetone–ether.

sulphate in the usual pyridine-2-aldoxime methanesulphonate (P-2-S) and atropine treatment of Sarin-poisoned mice is shown in Table III. The method of bioassay was

TABLE III

Atropine substitute activity of Parpanit analogues in protection of Sarin-poisoned mice

Compound	Atropine substitute activity PR-1*	Compound	Atropine substitute activity PR-1*
Atropine	2.03	III	4.5
Parpanit	3.2	IV	2.6
I	1.2	V	2.0
II	1.8	VI	1.3

*PR-1 = (LD_{50} Sarin in treated animals)/(LD_{50} Sarin in untreated controls).

identical with that described previously (1). Compounds III and IV are the only members of the group which exhibit greater protective ability than atropine sulphate. The marked improvement in protective effectiveness displayed by the diisopropyl analogue III relative to Parpanit suggests that further improvement in atropine substitute activity in the Parpanit molecule may result by placing suitable bulky electron-donating substituents on the nitrogen atom.

EXPERIMENTAL[2, 3]

1-Phenylcyclopentanecarbonitrile

This compound was prepared in 64% yield (b.p. 144–148° at 12 mm pressure; n_D^{25} 1.5323) using the procedure of Tilford and co-workers (9), who report b.p. 148–153° at 20 mm pressure.

1-Phenylcyclopentanecarboxylic Acid

1-Phenylcyclopentanecarbonitrile (34.2 g, 0.020 mole) was heated under reflux with 48% hydrobromic acid (140 ml) for 3 days. The precipitated acid was collected by filtration, washed with water, and dissolved in ether (500 ml). The ether solution was extracted with 10% sodium hydroxide (2×150 ml) and the alkaline extract was acidified with 10% hydrochloric acid. The resultant precipitate was recrystallized from aqueous alcohol, yielding 35.5 g (93.4%) of light fawn plates, m.p. 159–160°. Case (15) reports m.p. 158–159°.

1-Phenylcyclopentanecarboxylic Acid Chloride

Thionyl chloride (11.9 g, 0.10 mole) was added dropwise to a mechanically stirred solution of 1-phenylcyclopentanecarboxylic acid (9.5 g, 0.05 mole) in anhydrous benzene (100 ml). Stirring was continued for 2 hours at room temperature, after which the solution was heated under reflux for 2 hours. Distillation *in vacuo* furnished 8.20 g (78.5%) of pale yellow oil, b.p. 114–115° at 4 mm pressure; n_D^{25} 1.5418. Levshina and Sergievskaya (13) report b.p. 149–150° at 20–23 mm pressure.

Potassium 1-Phenylcyclopentanecarboxylate

A solution of 1-phenylcyclopentanecarboxylic acid (3.80 g, 0.020 mole) in absolute ethanol (100 ml) was titrated with 10% ethanolic potassium hydroxide using phenolphthalein as external indicator. Removal of the solvent *in vacuo* followed by two recrystallizations from ethanol–ether gave 4.42 g (97.0%) of fine colorless needles which did not melt below 350°. Calc. for $C_{12}H_{13}O_2K$: C, 61.07; H, 5.74; K, 17.13%. Found: C, 61.18; H, 5.74; K, 17.08%.

1-(p-Nitrophenyl)cyclopentanecarboxylic Acid

1-Phenylcyclopentanecarboxylic acid (5.00 g, 0.0263 mole) was added portionwise with stirring to fuming nitric acid (75 ml) kept at −10°. Stirring was continued for a further hour at 0°, after which the reaction mixture was poured onto crushed ice (300 g). The resultant precipitate was collected by filtration and recrystallized from methanol, yielding 4.93 g (80.0%) of colorless to light tan platelets, m.p. 179–182°. Calc. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96%. Found: C, 60.94; H, 5.52; N, 5.98%. This procedure is based on that used by Rubin and Wishinsky (20) for preparation of 1-(*p*-nitrophenyl)cyclohexanecarboxylic acid.

[2]*All melting points and boiling points are uncorrected.*

[3]*Microanalyses were performed by J. G. Helie of these laboratories.*

Potassium 1-(p-Nitrophenyl)cyclopentanecarboxylate

This compound was prepared in 96% yield from the corresponding acid, using the method described for potassium 1-phenylcyclopentanecarboxylate and was obtained as fawn needles, m.p. 225°, after recrystallization from methanol–ether. Calc. for $C_{12}H_{12}NO_4K$: C, 50.56; H, 4.43; N, 5.12; K, 14.31%. Found: C, 50.81; H, 4.57; N, 4.93; K, 14.38%.

2-(Ethyl-2′-fluoroethylamino)ethanol

A mixture of 2-ethylaminoethanol (Eastman, 67.0 g, 0.750 mole), 2-fluoroethyl bromide (120 g, 0.940 mole) (17), anhydrous potassium carbonate (103 g, 0.750 mole), and dry benzene (475 ml) was heated under reflux with stirring for 40 hours. The solid which separated from the cooled solution was collected by filtration and washed with benzene. The benzene was removed by distillation and the residue fractionated *in vacuo*, yielding 79.0 g (78.0%) of 2-(ethyl-2′-fluoroethylamino)ethanol as a colorless liquid, b.p. 71–72° at 8 mm pressure; n_D^{25} 1.4330. Equivalent weight: Calc. for $C_6H_{14}NOF$: 135. Found: 134.

2-Isopropylaminoethanol

2-Isopropylaminoethanol, b.p. 169–170°, n_D^{25} 1.4388, was prepared in 78% yield by the method of Biel (18), who reported b.p. 169–171°. This compound was characterized as the hydrochoride, m.p. 69–70° (see Table I).

2-(Ethylisopropylamino)ethanol

A mixture of 2-isopropylaminoethanol (28.8 g, 0.280 mole), anhydrous potassium carbonate (38.7 g, 0.280 mole), ethyl bromide (30.5 g, 0.280 mole), and anhydrous benzene (50 ml) was heated under reflux with stirring for 5 hours. The solid was removed by filtration and discarded. The filtrate was dried over anhydrous magnesium sulphate, then distilled *in vacuo*, yielding 15.2 g (39.4%) of colorless oil, b.p. 95° at 57 mm; n_D^{25} 1.4380. Brill (21) reports b.p. 175°. This compound was further characterized as the hydrochloride, m.p. 85–86°, and hydrobromide, m.p. 71–72°, which were prepared by conventional methods (see Table I). The hydriodide was prepared directly as follows. A mixture of 2-isopropylaminoethanol (11.3 g, 0.11 mole), ethyl iodide (15.6 g, 0.10 mole), and 90% ethanol (50 ml) was heated under reflux for 24 hours, then kept at room temperature for 3 days. Volatiles were removed *in vacuo*; the oily residue was dissolved in water (100 ml) and extracted with ether (6×15 ml). The aqueous layer was concentrated and dried at 0.001 mm pressure, yielding an oil which crystallized on standing. Three recrystallizations from ethanol–ether gave 9.88 g (39.7%) of 2-(ethylisopropylamino)ethanol hydriodide as colorless needles, m.p. 76–77° (see Table I).

Dialkylaminoethyl Chloride Hydrochlorides

These compounds were all prepared in the same manner, by interaction of thionyl chloride with the dialkylaminoethanol in anhydrous chloroform. The preparation of 2-diisopropylaminoethyl chloride hydrochloride is typical.

A solution of thionyl chloride (5 ml, 8.3 g, 0.07 mole) in dry chloroform (5 ml) was added dropwise to a stirred solution of 2-diisopropylaminoethanol (7.26 g, 0.05 mole) in dry chloroform (50 ml) kept at −10°. The mixture was heated under reflux for 6 hours, and methanol (5 ml) was added. Removal of solvents, first at water pump pressure, then at 0.001 mm, followed by recrystallization of the solid residue from acetone–ether, gave 7.25 g (72.5%) of 2-diisopropylaminoethyl chloride hydrochloride as colorless needles, m.p. 130–131°. The dialkylaminoethyl chloride hydrochlorides prepared are shown in Table I.

Dialkylaminoethyl Chlorides

These compounds were prepared from the corresponding hydrochlorides according to the method used by Breslow and co-workers for the preparation of 2-diethylaminoethyl chloride (22). The preparation of 2-(ethylisopropylamino)ethyl chloride is typical.

A mixture of 2-(ethylisopropylamino)ethyl chloride hydrochloride (4.65 g, 0.025 mole), ice-cold 20% aqueous sodium hydroxide (5 ml), crushed ice (10 g), and ice-cold ether (25 ml) was stirred vigorously for 5 minutes. The ether layer was decanted and the aqueous layer extracted with ice-cold ether (2×15 ml). The combined extracts were dried for 3 hours at 4° over anhydrous magnesium sulphate. The drying agent was removed by filtration and the ether was removed *in vacuo*, yielding 2.85 g (76.0%) of colorless oil. No attempt was made to characterize the product and it was used immediately in the esterification conducted according to method 3. The dialkylaminoethyl chlorides are unstable on storage at room temperature but may be kept at 4° for periods up to 2 weeks without separation of solid, which is considered to be the cyclic dimer (cf. Breslow *et al.* (22) and Wright *et al.* (24)). The following dialkylaminoethyl chlorides were prepared by this method and yields are given in parentheses: 2-(ethylisopropylamino)ethyl (76), 2-(ethyl-2′-fluoroethylamino)ethyl (87), 2-diisopropylaminoethyl (89), 2-pyrrolidinoethyl (82), 2-piperidinoethyl (83).

Dialkylaminoethyl 1-Phenyl- and 1-(p-Nitrophenyl)-cyclopentanecarboxylate Hydrochlorides

(a) Method 1.—Freshly distilled diethylaminoethanol (Eastman, 5.85 g, 0.050 mole) dissolved in dry benzene (25 ml) was added dropwise with stirring to a solution of freshly prepared 1-phenylcyclopentanecarboxylic acid chloride (10.4 g, 0.050 mole) in dry benzene (100 ml) at 25°. The solution was heated under reflux with stirring for 2 hours, during which time a precipitate separated. The mixture was cooled to room

temperature and anhydrous ether (400 ml) was added to complete precipitation. The precipitate was recrystallized three times from acetone, yielding 10.9 g (69.0%) of 2-diethylaminoethyl 1-phenylcyclopentanecarboxylate hydrochloride as colorless needles, m.p. 142–143°. Swiss Patent 234,452 (3) reports m.p. 145–146° for this compound.

(b) Method 3.—Potassium 1-phenylcyclopentanecarboxylate (2.28 g, 0.01 mole) dissolved in absolute ethanol (25 ml) was added in one portion to freshly prepared 2-diethylaminoethyl chloride (1.62 g, 0.012 mole) dissolved in absolute ethanol (10 ml). The solution immediately became turbid and a precipitate began to separate. The mixture was heated under reflux for 18 hours and, after cooling to 0°, the precipitated inorganic salt was collected and discarded. The filtrate was evaporated to dryness *in vacuo* and the oily residue was extracted with anhydrous ether (4×25 ml). The ether solution on saturation with dry hydrogen chloride gave a precipitate which was recrystallized once from acetone, yielding 2.61 g (80.0%) of colorless needles, m.p. 145–147°.

(c) Method 4.—A mixture of 1-phenylcyclopentanecarboxylic acid chloride (4.18 g, 0.02 mole), 2-diethylaminoethanol hydrochloride (Eastman, 3.07 g, 0.02 mole), and dry benzene (50 ml) was heated under reflux for 2 days. The precipitate which separated on cooling was collected and the filtrate was evaporated to dryness *in vacuo*. The combined residue and precipitate were recrystallized from acetone, yielding 3.32 g (51.0%) of colorless needles, m.p. 140–141.5°.

(d) Method 5.—A mixture of 1-phenylcyclopentanecarboxylic acid (1.90 g, 0.01 mole) and 2-diethylaminoethyl chloride hydrochloride (1.72 g, 0.01 mole) in absolute ethanol (50 ml) was heated under reflux for 2 days. The dark precipitate was collected, discarded, and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized three times from acetone, yielding 0.96 g (28.6%) of colorless needles, m.p. 144–146°.

The products from the four methods were shown to be identical with an authentic sample of Parpanit (2-diethylaminoethyl 1-phenylcyclopentanecarboxylate hydrochloride), kindly provided by Geigy Pharmaceuticals, Montreal, by comparison of melting points and infrared spectra.

The other esters of 1-phenylcyclopentanecarboxylic acid and 1-(*p*-nitrophenyl)cyclopentanecarboxylic acid shown in Table II were prepared by method 3.

2-Diethylaminoethyl 1-(p-Nitrophenyl)cyclopentanecarboxylate Hydrochloride (VI) by Nitration of 2-Diethylaminoethyl 1-Phenylcyclopentanecarboxylate

2-Diethylaminoethyl 1-phenylcyclopentanecarboxylate (5.00 g, 0.0153 mole) was added portionwise with stirring during a period of 1 hour to fuming nitric acid (75 ml) kept at −15°. The reaction mixture was stirred at 0° for an additional hour then poured onto crushed ice (200 g). The resultant mixture was neutralized with ice-cold 10% sodium hydroxide and extracted with ether (4×50 ml). The extract was dried over anhydrous magnesium sulphate, filtered to remove the desiccant, and saturated with hydrogen chloride. The precipitated solid was recrystallized twice from ethanol–ether, yielding 3.63 g (65.2%) of colorless crystals, m.p. 182–182.5° alone and in admixture with an authentic sample of 2-diethylaminoethyl 1-(*p*-nitrophenyl)cyclopentanecarboxylate hydrochloride (VI). The infrared spectra of the two samples were also identical.

ACKNOWLEDGMENT

We are indebted to Mr. J. R. Blanchfield for preparation of some of the 1-phenylcyclopentanecarboxylic acids used in this work and for providing the 2-diisopropylaminoethanol.

REFERENCES

1. I. W. Coleman, P. E. Little, and R. A. B. Bannard. Can. J. Biochem. and Physiol. **40**, 815 (1962).
2. I. W. Coleman, P. E. Little, and R. A. B. Bannard. Can. J. Biochem. and Physiol. **40**, 827 (1962).
3. J. R. Geigy A-G. Swiss Patent No. 234,452 (January 16, 1945); Chem. Abstr. **43**, 6229[b] (1949).
4. H. Martin and F. Häfliger. U.S. Patent No. 2,404,588 (July 23, 1946); Chem. Abstr. **40**, 6501[2] (1946).
5. A. W. Weston. J. Am. Chem. Soc. **68**, 2345 (1946).
6. J. R. Geigy A-G. Swiss Patent No. 240,160 (May 1, 1946); Chem. Abstr. **43**, 6655[h] (1949).
7. A. W. Weston. U.S. Patent No. 2,704,284 (March 15, 1955); Chem. Abstr. **50**, 1903[i] (1956).
8. H. G. Morren. Brit. Patent No. 753,779 (August 1, 1956); Chem. Abstr. **51**, 7443[c] (1957).
9. C. H. Tilford, M. G. Van Campen, and R. S. Shelton. J. Am. Chem. Soc. **69**, 2902 (1947).
10. M. G. Van Campen and C. H. Tilford. U.S. Patent No. 2,474,796 (June 28, 1949); Chem. Abstr. **44**, 3018[b] (1950).
11. J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprenzler. J. Am. Chem. Soc. **74**, 1485 (1952).
12. T. Ito. Jap. Patent No. 5278 (December 12, 1952); Chem. Abstr. **48**, 8820[d] (1954).
13. K. V. Levshina and S. I. Sergievskaya. Zhur. Obshchei Khim. **22**, 2189 (1952).
14. W. A. Lott and J. Krapcho. U.S. Patent No. 2,688,025 (August 31, 1954); Chem. Abstr. **49**, 11697[i] (1955).
15. F. H. Case. J. Am. Chem. Soc. **56**, 715 (1934).

16. R. N. JONES and C. SANDORFY. *In* Technique of organic chemistry. Vol. IX. Chemical applications of spectroscopy. *Edited by* A. Weissberger. Interscience Publishers, Inc., New York. 1956. p. 397.
17. F. W. HOFFMANN. J. Org. Chem. **15**, 425 (1950).
18. J. H. BIEL. J. Am. Chem. Soc. **71**, 1306 (1949).
19. P. D. BARTLETT, S. D. ROSS, and C. G. SWAIN. J. Am. Chem. Soc. **71**, 1415 (1949).
20. M. RUBIN and H. WISHINSKY. J. Am. Chem. Soc. **68**, 828 (1946).
21. H. C. BRILL. J. Am. Chem. Soc. **54**, 2484 (1932).
22. D. S. BRESLOW, R. S. YOST, H. G. WALKER, and C. R. HAUSER. J. Am. Chem. Soc. **66**, 1921 (1944).
23. J. B. WRIGHT, E. H. LINCOLN, R. V. HEINZELMAN, and J. H. HUNTER. J. Am. Chem. Soc. **72**, 3536 (1950).
24. J. B. WRIGHT, H. G. KOLLOFF, and J. H. HUNTER. J. Am. Chem. Soc. **70**, 3098 (1948).
25. J. G. M. DUNLOP. J. Chem. Soc. **101**, 2002 (1912).