LOCAL ANAESTHETIC ACTIVITY IN DIETHYLAMINOACETYL DERIVATIVES OF SUBSTITUTED BENZYLAMINES

By R. F. Collins and B. J. Large

From the Research Laboratories, May and Baker Ltd., Dagenham, Essex

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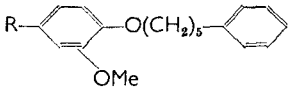
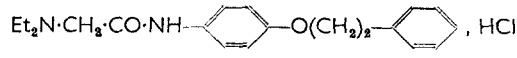
Six diethylaminoacetyl derivatives of general formula (III) are more potent than lignocaine as local anaesthetics. All cause erythema or necrosis of guinea-pig skin on intradermal injection except III, R = NH_2, R′ = H, and R″ = $O(CH_2)_2Ph$. This compound is several times more potent than lignocaine and in equipotent concentrations did not cause any tissue damage to skin on intradermal injection.

Local anaesthetic activity was first discovered by us in several aminophenoxyalkanes (Collins, Davis, Edge, Hill, Reading and Turnbull, 1959), including the primary amine (*Ia*) and its diethylamino-acetyl derivative (*Ib*). None of these compounds was as active as lignocaine and all caused erythema or necrosis of the skin after intradermal injection. A subsequent publication by Borovansky, Sekera and Vrba (1960) reported local anaesthetic activity in a compound (II) of this type but, although we



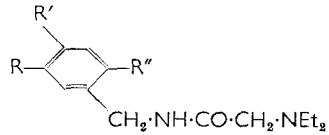
(*Ia*) R = NH_2, $MeSO_3H$
(*Ib*) R = $NH\,CO{\cdot}CH_2{\cdot}NEt_2$, HCl



(II)

found it to be more active than lignocaine, this compound also caused erythema and necrosis of guinea-pig skin on intradermal injection.

A claim by Dalal and Trivedi (1960), that diethylaminoacetyl derivatives of substituted benzylamines possessed local anaesthetic activity, led us to investigate a small group of related compounds (III) listed in Table I. Here we found much greater local anaesthetic activity, but tissue damage usually resulted from injection into the skin. One member of this series (III, R = NH_2, R′ = H, R″ = $O(CH_2)_2Ph$) (compound 8315), was several times as active as lignocaine in the tests described, and did not cause damage to the skin after intradermal injection of an equipotent concentration. In this respect it was the best compound examined.



(III)

Pharmacological Methods

The compounds were examined for local anaesthetic activity by four tests.

(1) *Surface Anaesthesia: Corneal Reflex Test of the Guinea-pig*

Eight albino guinea-pigs of either sex, weighing 400 to 500 g. were used for each compound (four animals on each of two concentrations). Concentrations, in normal saline from 1 to 2 per cent w/v for lignocaine and, for example, 0·005 to 0·02 per cent w/v for compound 8554, were continuously instilled into the conjuctival sac for 5 min. after which the eye was washed with 0·9 per cent w/v saline. The corneal reflex was tested by lightly touching the cornea with a rabbit's whisker six times at 5 min. intervals for 30 min., and the degree of anaesthesia was estimated by counting the times that the blink reflex could not be obtained during this period. For example, a score of 27 failures out of a possible maximum of 36 gave 75 per cent anaesthesia. Percentage anaesthesia was plotted against log concentration and relative potencies were abstracted by reading from the abscissa the concentration of each compound which produced 50 per cent anaesthesia.

(2) *Plexus Anaesthesia in Frogs* (Bülbring and Wadja, 1945)

Using 16 frogs the time for onset of anaesthesia was estimated for 3 concentrations of lignocaine (0·1, 0·2 and 0·5 per cent w/v in saline). Except for compounds 9329 and 9393 where three concentrations were used, each compound was then examined at two concentrations, these being chosen to give times within the range of the lignocaine results; 4 frogs were used at each concentration. Time for onset of anaesthesia was plotted against log concentration.

(3) *Infiltration Anaesthesia: Subcutaneous Injection into the Mouse Tail* (Bianchi, 1956)

Two per cent w/v solutions of each compound were prepared in distilled water and dilutions were made in 0·9 per cent w/v saline. Ten mice were used at each of 3 doses for each compound. Subcutaneous injections of 0·1 ml. were made in the tail about 1 cm. from the root and an artery clip applied to the tail at 15 min. intervals after injection up to 4 hr. A positive response occurred, usually within 5 sec., when a mouse attempted to remove the clip. A negative response was recorded, indicating local anaesthesia, when the mouse failed to attempt to dislodge the clip within 30 sec. The number of mice, out of ten, which gave a negative response was converted to percentage anaesthesia. Since maximal effects were observed 15 min. after injection, percentage anaesthesia at this time was plotted against log concentration. A comparison of the duration of action was afforded by extending the observations up to 4 hr. after injection.

(4) *Infiltration Anaesthesia: Intradermal Injection into the Skin of the Guinea-pig*

This method was based on that of Bülbring and Wadja (1945), as modified by Somers and Edge (1947). The compounds were injected intracutaneously in Latin square designs such that 9 fully grown albino guinea-pigs were used when comparing any compound with lignocaine

at 3 different concentrations. Graphs were plotted relating log concentration of the anaesthetic to the degree of anaesthesia 30 min. after injection. Since the lines obtained for all compounds were approximately parallel, relative potencies were calculated as the antilog of the differences in concentration between each compound and lignocaine in producing the same degree of anaesthesia.

Toxicity

Local toxicity to the skin was estimated by two methods.

(*a*) Observations were made on the mice used in test No. 3 for local anaesthetic activity, and a numerical score was allotted to each according to the severity of the local reaction. Three grades were easily distinguished ranging from erythema to severe necrosis. Daily observations were made up to 7 days, the maximum effect being usually observed after 4 days.

(*b*) The compounds were injected intradermally in a volume of 0·2 ml. into the shaved backs of guinea-pigs. Two concentrations of each compound were chosen, these were equipotent in local anaesthetic activity in test No. 4, with two concentrations of lignocaine (0·5 and 1·0 per cent). Each concentration was injected once into 4 guinea-pigs which were examined at intervals up to 7 days and the degree of irritation noted; six grades could be detected varying from slight erythema to severe necrosis. Confirmatory tests were made by histological examination of the skin and subcutaneous tissue.

Toxicity in mice. Albino mice of either sex weighing between 15 and 20 g. were injected intravenously and subcutaneously with the compounds under test, 30 to 40 mice being used for each LD50 determination. Observations were made up to 4 days after injection, though deaths usually occurred within 24 hr. of injection.

Pharmacological Results

All the results are summarised in Tables I and II.

Local Anaesthetic Activity

Test 1. Two experiments were carried out. In one, the figures were: lignocaine 1·0, compounds 7663, 0·0086, 8112, 0·10, 8315, 0·25 and 8554, 0·0044 per cent; in the second the figures were: lignocaine 1·78, compounds 9329, 0·02 and 9393, 0·08 per cent. The most potent compound was compound 8554 which was 224 times as effective as lignocaine.

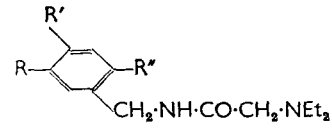
Test 2. One experiment was made for the estimation of conduction anaesthesia. With the exception of compound 8554, concentrations from 0·1 to 0·5 per cent w/v were used as this gave times for onset of anaesthesia similar to those for lignocaine in the same concentrations. The graphs when plotted were not parallel but the differences from lignocaine were so slight that the compounds have been accorded a figure approximately equal to lignocaine. Compound 9329 is quoted as less active because a linear relationship between log concentration

and effect did not exist; anaesthesia developed in about 20 min. regardless of concentration. Compound 8554 (0·05 per cent) gave a mean time to anaesthesia equal to that of lignocaine (0·5 per cent), thus showing a relative potency 10 times that of lignocaine.

Test 3. The compounds were tested in two groups in different experiments. In the first the concentrations producing 50 per cent anaesthesia were as follows: compounds 7663, 0·21, 8112, 0·34, 8315, 0·20 and 8554, 0·24 per cent, compared with 0·58 per cent for lignocaine. In the second

TABLE I

RELATIVE ANAESTHETIC POTENCIES AND TOXICITIES OF DIETHYLAMINOACETYL DERIVATIVES OF SUBSTITUTED BENZYLAMINES

General formula 

Compound No.	R	R′	R″	Test	Anaesthetic activity (approx.) lignocaine = 1	LD50 (mg./kg.) (mice) i.v.	s.c.
7663	NH_2	H	OC_8H_{17}	1 2 3 4	118 ≃1 3 10	8 (87–115)	—
8112	Et_2NCH_2CONH	H	OC_8H_{17}	1 2 3 4	10 ≃1 1·75 7	37·5 (92–109)	550 (87–115)
8315	NH_2	H	$O(CH_2)_2Ph$	1 2 3 4	4 ≃1 3 4	26 (92–109)	225 (77–130)
8554	H	H	OC_8H_{17}	1 2 3 4	224 10 2·3 47	5 (78–128)	290 (87–115)
9329	H	OC_8H_{17}	H	1 2 3 4	87 <1 0·6 ≃3	42 (80–125)	>2000 —
9393	H	H	$O(CH_2)_2Ph$	1 2 3 4	22 ≃1 0·8 5	14 (86–116)	>1000 —

All compounds were tested as the mono- or dihydrochlorides. The LD50 values for lignocaine hydrochloride were 15 mg./kg. (limits 87–115 per cent for P = 0·95) by i.v. injection and 390 mg./kg (limits 81–124 per cent) by s.c. injection. Figures in brackets under LD50 show the fiducial limits (per cent) for P = 0·95.

experiment the figures were: lignocaine 0·15, compounds 9329, 0·24 and 9393, 0·18 per cent. Lignocaine used as a standard had a duration of action about 45 min., compounds 8315 and 9393 about 1 hr., whereas the remainder had an action lasting 2 hr. or more.

Test 4. The relative activities shown in Table I were obtained from one experiment. Concentrations of lignocaine from 0·1 to 0·4 per cent were used and the concentrations of compound 8554, the most active compound in this test, ranged from 0·0025 to 0·01 per cent.

Effect of Adrenaline on Local Anaesthetic Action

One experiment was made to determine the effect of adrenaline on the anaesthetic activity of compound 8315. These results were obtained after 5 hr. by the guinea-pig intradermal test, and the results are shown in Table II. All dilutions of compound 8315 and lignocaine were made in 1:200,000 adrenaline hydrochloride solution. Adrenaline potentiated the local anaesthetic activity of compound 8315 to a greater degree than that of lignocaine (concentrations were used which were equipotent when compound 8315 and lignocaine were used alone without adrenaline.)

TABLE II

EFFECT OF ADRENALINE HYDROCHLORIDE ON LOCAL ANAESTHETIC ACTIVITY OF COMPOUND 8315, USING THE GUINEA-PIG INTRADERMAL WHEAL TEST

Compound	Concentration (per cent)	Percentage anaesthesia after 5 hr.	
		(*a*) In aqueous solution	(*b*) In 1:200,000 adrenaline hydrochloride solution
Lignocaine	1	42	54
	0·5	33	58
Compound 8315	1	75	96
	0·5	58	88
	0·25	50	83
	0·125	33	79

Toxicity

Local toxicity to the skin. All the compounds, with the exception of compound 8315, caused slight to severe necrosis of the skin, with an inflammatory cellular reaction in concentrations which were equipotent with lignocaine in producing anaesthesia by intradermal injection. Lignocaine produced but a slight inflammatory cellular infiltration at a concentration of 1 per cent. Compound 8315 at 0·25 per cent produced almost identical reactions and at 1 per cent gave rise to moderate necrosis of the skin and localised muscle degeneration.

Toxicity in mice. The LD50 figures for intravenous and subcutaneous injection are shown in Table I. Compound 8315 was less toxic than lignocaine on intravenous injection but more toxic on subcutaneous injection. All the compounds, including lignocaine, produced loss of the righting reflex with an increase in respiration rate; death was usually preceded by tonic convulsions except for lignocaine where no convulsions were observed.

DISCUSSION

The small series of diethylaminoacetyl derivatives of substituted benzylamines described in this paper showed interesting local anaesthetic properties, as determined by several tests in mice, guinea-pigs and frogs for infiltration, conduction and topical anaesthesia.

By topical application to the cornea of the guinea-pig all six compounds were considerably more potent than lignocaine. Compounds

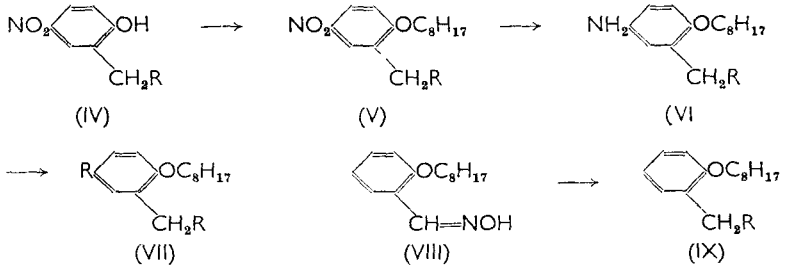
7663, 8554 and 9329 were 100 to 200 times as active as lignocaine but only in this test; by the other tests they were generally only 1 to 50 times as active.

In the small group of compounds tested all those with the OC_8H_{17} grouping produced a severe local reaction, on injection into guinea-pig skin, in concentrations which were equipotent (as local anaesthetics) with lignocaine. The only compound which was as well tolerated as lignocaine, namely 8315, possessed an $O(CH_2)_2Ph$ grouping. It should be noted however that one other compound with this grouping (9393) caused moderate necrosis.

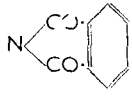
It is difficult to explain why these compounds should show such high activity on the cornea. Pertinent to this point are some observations of relative surface tension by a capillary rise method: one per cent aqueous solutions showed the following order: lignocaine > 8315 > 7663, 8112, 8554, 9329 and 9393. Lowering of surface tension may play some part in permitting the compounds to penetrate more readily into the cornea than into other tissues.

Chemical Methods

Compound 7663 (VI*a*) was synthesised from the known 2-diethylamino-acetamidomethyl-4-nitrophenol (IV*a*) by alkylation to the n-octyl ether (V*a*) and subsequent catalytic reduction. In a second route, 2-chloro-



(*a*) R = NH·CO·CH_2·NEt_2, (*b*) R = Cl, (*c*) R = NHCOMe

(*d*) R = NH_2 (e) R = $NHCOCH_2Cl$ (*f*) R = 

methyl-4-nitrophenol (IV*b*) was converted successively into 2-acetamido-methyl-4-nitrophenol (IV*c*) and its n-octyl ether (V*c*). Hydrolysis gave the primary amine (V*d*), which was chloroacetylated to (V*e*), treated with diethylamine, yielding (V*a*), and then reduced. A third route utilised 5-nitro-2-n-octyloxybenzyl chloride (V*b*) available from concurrent work. From this the 2-phthalimidomethyl compound (V*f*) was prepared and was hydrolysed to the amine (V*d*), subsequent stages being as already described. The nitro-amine (V*d*) was also used for the synthesis of compound 8112 (VII*a*) by reduction to the diamine (VI*d*), chloro-acetylation, and treatment of the product (VII*e*) with diethylamine.

The phenethyl ether 8315 was obtained from 2-acetamidomethyl-4-nitrophenol (IV*c*) by a route similar to the second one described above.

Compound 8554 was prepared from the octyl ether of salicylaldehyde via the oxime (VIII) followed by reduction to the amine (IX*d*), chloroacetylation, and reaction with diethylamine. Compound 9393 was similarly obtained from the corresponding phenethyl ether of salicylaldehyde, and 9329, the *para*-isomer of compound 8554, was likewise prepared from *p*-hydroxybenzaldehyde.

EXPERIMENTAL

1-(2-Diethylaminoacetamidomethyl-4-nitrophenoxy)-n-octane hydrochloride (V*a*). (*a*) 2-Diethylaminoacetamidomethyl-4-nitrophenol (IV*a*) (11 g.) (Einhorn and Mauermayer, 1905) was dissolved in a solution prepared from sodium (0·82 g.) and ethanol (30 ml.). n-Octyl bromide (7·5 g.) was added, the mixture was refluxed (12 hr.), ethanol was removed and the residue was extracted with ether. The ethereal solution was washed with N aqueous sodium hydroxide and water, dried and saturated with dry hydrogen chloride. The product was crystallised from ethanol giving (*1-(2-diethylaminoacetamidomethyl-4-nitrophenoxy)-n-octane hydrochloride* (3·5 g.), m.p. 168–170°. Found: N, 9·7; Cl, 8·5. $C_{21}H_{35}N_3O_4$, HCl requires N, 9·8; Cl, 8·3 per cent.

(*b*) 5-Nitro-2-n-octyloxybenzyl chloride (V*b*) (118 g.) (Collins, unpublished) in acetone (1 litre) was refluxed (0·5 hr.) with sodium iodide (59 g.): sodium chloride was then filtered off. A solution of potassium hydroxide (84 per cent, 25·4 g.) and phthalimide (93·5 g.) in water (200 ml.) was added and the mixture was refluxed (24 hr.) and cooled. The product was recrystallised from ethanol, giving *1-(4-nitro-2-phthalimidomethylphenoxy)-n-octane* (V*f*) (75 g.), m.p. 103–105°. Found: N, 6·8. $C_{23}H_{26}N_2O_5$ requires N, 6·8 per cent.

A solution of this compound (15 g.) in ethanol (50 ml.) and aqueous hydrazine (60 per cent w/v, 6·25 ml.) was refluxed (3 hr.), ethanol was removed and the residue was extracted with a mixture of concentrated hydrochloric acid (16 ml.) and water (26 ml.). The filtered solution was basified with aqueous sodium hydroxide and extracted with ether, yielding 1-(2-aminomethyl-4-nitrophenoxy)-n-octane (V*d*) (10 g.). A solution of this base (21 g.) in acetic acid (150 ml.) containing anhydrous sodium acetate (5 g.) was treated with chloroacetyl chloride (6·55 ml.). After 30 min. the mixture was poured into water and the product was recrystallised from aqueous acetic acid to yield *1-(2-chloroacetamidomethyl-4-nitrophenoxy)-n-octane* (V*e*) (10·4 .g), m.p. 85–88°. Found: N, 7·5; Cl, 9·3. $C_{17}H_{25}ClN_2O_4$ requires N, 7·8; Cl, 9·9 per cent. The chloroacetyl derivative (10·3 g.) was refluxed (3 hr.) with diethylamine (30 ml.) and the excess of diethylamine was removed. An ether solution of the residue was washed with water, dried and treated with hydrogen chloride, yielding 1-(2-diethylaminoacetamidomethyl-4-nitrophenoxy)-n-octane hydrochloride (7·6 g.), m.p. 168–171°, not depressed by a sample prepared as in (*a*).

(*c*) 2-Chloromethyl-4-nitrophenol (IV*b*) (300 g.) and acetamide (900 g.) were heated (1 hr.) at 170–180°. The mixture was cooled and poured into water to yield *2-acetamidomethyl-4-nitrophenol* (IV*c*) (303 g.), m.p. 194–196° (from ethyl acetate). Found: C, 51·4; H, 5·0; N, 13·2. $C_9H_{10}N_2O_4$ requires C, 51·4; H, 4·8; N, 13·3 per cent.

This compound (147 g.) was dissolved in 2-ethoxyethanol (1 litre) and treated with sodium hydroxide (28 g.) in water (30 ml.) then n-octyl bromide (135 g.). After 8 hr. reflux the solution was diluted with water and the product was recrystallised from aqueous methanol to yield 1-(*2-acetamidomethyl-4-nitrophenoxy*)-*n-octane* (V*c*) (182 g.), m.p. 73–74°. Found: C, 63·6; H, 8·1; N, 8·6. $C_{17}H_{24}N_2O_3$ requires C, 63·6; H, 8·1; N, 8·7 per cent. A mixture of this compound (182 g.) with hydrochloric acid (200 ml.) and water (200 ml.) was refluxed (8 hr.) and the hydrochloride was collected. It was suspended in water and treated with excess of sodium hydroxide to yield an oil, 1-(2-aminomethyl-4-nitrophenoxy)-n-octane (V*d*) (169 g.). The remaining stages were as in (*b*).

1-(*4-Amino-2-diethylaminoacetamidomethylphenoxy*)-*n-octane* (compound 7663; VIa). The corresponding nitro-compound (11 g.) was hydrogenated at Adams's platinum oxide (220 mg.) in ethanol (200 ml.) at 60°/70 lb. per sq. in. The product was treated with ethereal hydrogen chloride to yield 1-(*4-amino-2-diethylaminoacetamidomethylphenoxy*)-*n-octane dihydrochloride* (9 g.), softens from 85°. Found: N, 9·6; Cl, 16·0. $C_{21}H_{37}N_3O_2$, 2HCl required N, 9·6; Cl, 16·3 per cent. The (−)-*di-p-toluoyltartrate* had m.p. 106–110°. Found: C, 65·7; H, 7·3; N, 5·0. $C_{21}H_{37}N_3O_2,C_{20}H_{18}O_8$ requires C, 65·7; H, 7·3; N, 5·6 per cent.

1-(*4-Diethylaminoacetamido-2-diethylaminoacetamidomethylphenoxy*)-*n-octane dihydrochloride* (compound 8112, VIIa). 1-(2-Aminomethyl-4-nitrophenoxy)-n-octane (V*d*) (12 g.) was hydrogenated as above at 30°/200 lb. per sq. in. The hydrochloride of the resulting 1-(4-amino-2-aminomethylphenoxy)-n-octane (VI*d*) was dissolved in acetic acid (100 ml.) containing anhydrous sodium acetate (14 g.). Chloroacetyl chloride (12 ml.) was added and the mixture was stirred (2 hr.) then poured into water. The crude product, which slowly solidified, was recrystallised from methanol to yield 1-(*4-chloroacetamido-2-chloroacetamidomethylphenoxy*)-n-*octane* (VII*e*) (7·2 g.), m.p. 137–139°. Found: N, 7·0; Cl, 17·5. $C_{19}H_{26}Cl_2N_2O_3$ requires N, 7·0; Cl, 17·7 per cent. This compound (5·3 g.) was refluxed (3 hr.) with diethylamine (22 ml.), the excess of diethylamine was removed, the residue was treated with water and extracted with ether. The washed and dried ethereal solution was concentrated, and the base was converted with ethereal hydrogen chloride into 1-(*4-diethylaminoacetamido-2-diethylaminoacetamidomethylphenoxy*)-*n-octane dihydrochloride* (6·5 g.), m.p. 83–85°. Found: N, 10·2; Cl, 12·6. $C_{27}H_{48}N_4O_3$,2HCl requires N, 10·2; Cl, 12·9 per cent.

1-(*4-Amino-2-diethylaminoacetamidomethylphenoxy*)-*2-phenylethane dihydrochloride* (compound 8315). A solution of 2-acetamidomethyl-4-nitrophenol (IV*c*) (35 g.) and sodium hydroxide (6·7 g.) in 2-ethoxyethanol (240 ml.) and water (8 ml.) was refluxed (7 hr.) with 2-phenyl-

ethyl bromide (30·8 g.). The mixture was cooled and poured into water (240 ml.). The crude product was recrystallised from methanol yielding 1-(2-acetamidomethyl-4-nitrophenoxy)-2-phenylethane (24 g.), m.p. 139–141°. Hydrolysis of this compound (24 g.) was effected by refluxing (8 hr.) with a mixture of hydrochloric acid (50 ml.) and water (50 ml.). The hydrochloride which separated from the cooled mixture was suspended in water and basified with sodium hydroxide, giving 1-(2-aminomethyl-4-nitrophenoxy)-2-phenylethane (19 g.) as an oil. To the base in acetic acid (150 ml.) containing anhydrous sodium acetate (4·7 g.), chloroacetyl chloride (6 ml.) was added. The mixture was stirred (5 min.), kept 30 min., and treated with water (160 ml.). The product (10 g.), m.p. 103–105°, was recrystallised from benzene to yield 1-(2-*chloroacetamidomethyl*-4-*nitrophenoxy*)-2-*phenylethane* (5·4 g.), m.p. 117–119°. Found: N, 7·8; Cl, 10·3. $C_{17}H_{17}ClN_2O_4$ requires N, 8·0; Cl, 10·2 per cent.

The above chloroacetyl derivative (9·8 g.) was refluxed (3 hr.) with diethylamine and worked up in the usual way. The product was converted into the hydrochloride, which was recrystallised from ethanol to yield 1-(2-*diethylaminoacetamidomethyl*-4-*nitrophenoxy*)-2-*phenylethane hydrochloride* (8·7 g.), m.p. 215–217°. Found: N, 9·9; Cl, 8·6. $C_{21}H_{27}N_3O_4$,HCl requires N, 10·0; Cl, 8·4 per cent. Hydrogenation of this compound (8·65 g.) over Raney nickel in ethanol (150 ml.) at 57°/70 lb. per sq. in. gave the hygroscopic 1-(4-*amino*-2-*diethylamino-acetamidomethylphenoxy*)-2-*phenylethane hydrochloride* (6·0 g.), m.p. 138–142°. Found: N, 11·2; Cl, 8·7. $C_{21}H_{29}N_3O_2$,HCl requires N, 10·7; Cl, 9·0 per cent. It was converted into the *dihydrochloride*, m.p. 89–115° (efferv.). Found: N, 9·6; Cl, 16·1. $C_{21}H_{29}N_3O_2$,2HCl requires N, 9·8; Cl, 16·6 per cent.

1-(2-*Diethylaminoacetamidomethylphenoxy*)-*n-octane* (compound 8554; IXa). Redistilled salicylaldehyde (24·4 g.), n-octyl bromide (46 g.), ethanol (100 ml.) and anhydrous potassium carbonate (33 g.) were refluxed (18 hr.) with stirring. The solvent was removed and the residue was extracted with ether. The washed and dried extract was concentrated and the residue was distilled to yield o-*octyloxybenzaldehyde** (40·2 g.), b.p. 130–133°/0·02 mm.n_D^{20} 1·5118. Found: C, 76·7; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5 per cent. The aldehyde (13 g.) in ethanol (100 ml.) was mixed with hydroxylamine hydrochloride (4 g.) in water (20 ml.) and potassium hydroxide (4 g.) in water (10 ml.). The mixture was refluxed (30 min.) and poured into water. The product was dried and recrystallised from ethanol or light petroleum (b.p. 40–60°) to yield o-*octyloxybenzaldoxime* (VIII) (7·4 g.), m.p. 33–36°. Found: N, 5·4. $C_{15}H_{23}NO_2$ requires N, 5·6 per cent.

The oxime (10 g.) in dry ethanol (100 ml.) was reduced with powdered sodium (10 g.) added in portions. Solvent was removed, water was added, and the amine was taken up in ether. The extract was shaken with 2N aqueous hydrochloric acid, the acid solution was basified and the

* Prepared by Dr. D. A. A. Kidd of these laboratories.

amine was re-extracted into ether. The dried ethereal solution was concentrated and distilled giving o-*octyloxybenzylamine* (IXd) (4·9 g.), b.p. 156°/0·02 mm. n_D^{20} 1·5049. This amine (4·8 g.), in acetic acid (50 ml.) containing anhydrous sodium acetate (1·7 g.), was treated with chloroacetyl chloride (2·4 g.) as before. The mixture was diluted with water and the product was dried and recrystallised from light petroleum (b.p. 40–60°) to yield crude 1-(2-chloroacetamidomethylphenoxy)-n-octane (IXe) (5·5 g.), m.p. 49–50°. Found: N, 4·6; Cl, 10·0. $C_{17}H_{26}ClNO$ requires N, 4·5; Cl, 11·4 per cent. The low chlorine analysis was due to contamination with the corresponding acetyl derivative.

The crude chloroacetyl derivative (5·4 g.) was treated with diethylamine in the usual way. The hydrochloride obtained was dissolved in water and extracted with ether to remove non-basic material (the acetyl derivative) and the aqueous solution was then basified and extracted with ether. Distillation gave 1-(*2-diethylaminoacetamidomethylphenoxy*)-*n-octane* (2·8 g.), b.p. 175–180°/0·04 mm. Found; C, 72·1; H, 10·5; N, 7·9. $C_{21}H_{36}N_2O_2$ requires C, 72·4; H, 10·4; N, 8·0 per cent. The hydrochloride was obtained as a pale yellow gum which could not be crystallised.

1-(2-*Diethylaminoacetamidomethylphenoxy*)-2-*phenylethane* (compound 9393). This compound was similarly prepared from salicylaldehyde. The following intermediates were obtained (yields are given in parentheses): o-(2-*Phenylethoxy*)*benzaldehyde* (57 per cent), m.p. 71–73·5° (from ethanol). Found: C, 78·4; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·5; H, 6·2 per cent. o-(2-*Phenylethoxy*)*benzaldoxime* (95 per cent), m.p. 90–92° [from light petroleum (b.p. 80–100°)]. Found: C, 74·6; H, 6·5; N, 6·0. $C_{15}H_{15}NO_2$ requires C, 74·7; H, 6·2; N, 5·8 per cent. o-(2-*Phenylethoxy*)*benzylamine* (50 per cent), b.p. 148–155°/0·05 mm. Found: C, 79·5; H, 7·7; N, 6·0. $C_{15}H_{17}NO$ requires C, 79·2; H, 7·5; N, 6·2 per cent. 1-(2-*Chloroacetamidomethylphenoxy*)-2-*phenylethane* (71 per cent), m.p. 96–98° [from light petroleum (b.p. 80–100°)]. Found: N, 4·6; Cl, 11·5. $C_{17}H_{18}ClNO_2$ requires N, 4·6; Cl, 11·7 per cent. 1-(2-*Diethylaminoacetamidomethylphenoxy*)-2-*phenylethane* (57 per cent), b.p. 210–220°/0·1 mm. Found: C, 73·8; H, 8·5; N, 8·1. $C_{21}H_{28}N_2O_2$ requires C, 74·0; H, 8·2; N, 8·2 per cent. The hydrochloride was a yellow gum.

1-(4-*Diethylaminoacetamidomethylphenoxy*)-*n-octane* (compound 9329). This compound was similarly prepared from *p*-hydroxybenzaldehyde. The following intermediates were obtained: p-*Octyloxybenzaldehyde* (83 per cent), b.p. 134–144°/0·1 mm. Found: C, 76·3; H, 9·6. $C_{15}H_{22}O_2$ requires C, 77·0; H, 9·4 per cent. p-*Octyloxybenzaldoxime* (77·5 per cent), m.p. 81–83° (from aqueous ethanol). Found: N, 5·7. $C_{15}H_{23}NO_2$ requires N, 5·6 per cent. p-*Octyloxybenzylamine* (32 per cent), b.p. 130–140°/0·05 mm. Found: C, 76·4; H, 10·6; N, 5·8. $C_{15}H_{25}NO$ requires C, 76·5; H, 10·6; N, 5·9 per cent. 1-(4-*Chloroacetamidomethyl-phenoxy*)-*n-octane* (76 per cent), m.p. 97–99° (from aqueous acetic acid). Found: N, 4·75; Cl, 12·3. $C_{17}H_{26}ClNO_2$ requires N, 4·5; Cl, 11·5 per cent. 1-(4-*Diethylaminoacetamidomethylphenoxy*)-*n-octane* (48

per cent), m.p. 53–54° [from light petroleum (b.p. 40–60°)]. Found: C, 72·3; H, 10·3; N, 8·2. $C_{21}H_{36}N_2O_2$ requires C, 72·5; H, 10·3; N, 8·05 per cent.

REFERENCES

Bianchi, C. (1956). *Brit. J. Pharmacol.*, **11**, 104–106.
Borovansky, A., Sekera, A. and Vrba, C. (1960). *J. Amer. pharm. Ass., Sci. Ed.*, **49**, 57–58.
Bülbring, E. and Wadja, I. (1945). *J. Pharmacol.*, **85**, 78–84.
Collins, R. F., Davis, M., Edge, N. D., Hill, J., Reading, H. W. and Turnbull, E. R. (1959). *Brit. J. Pharmacol.*, **14**, 467–476.
Dalal, S. S. and Trivedi, J. J. (1960). *J. Indian chem. Soc.*, **37**, 437–439.
Davis, M. (1962). *J. chem. Soc.*, 178–181.
Einhorn, A. and Mauermayer, T. (1905). *Liebig's Ann.*, **343**, 282–310.
Somers, G. F. and Edge, N. D. (1947). *Quart. J. Pharm. Pharmacol.*, **20**, 380–391.

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