THE DIETHYLAMINOETHOXYETHYL ESTER OF DIETHYLPHENYLACETIC ACID. A NEW ANTITUSSIVE AGENT

BY V. PETROW, O. STEPHENSON AND A. M. WILD

From The Chemical Research Laboratories, The British Drug Houses, Ltd., London, N.1.

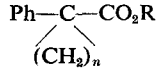
Received August 11, 1957

The preparation is described of some dialkylaminoethoxyethyl esters (X) of diethylphenylacetic acid and of some corresponding esters of 1-phenyl*cyclo*pentane-1-carboxylic acid and 4-phenyltetrahydropyran-4-carboxylic acid. These were required for biological study which revealed that the diethylaminoethoxyethyl ester (X; R = R′ = Et) of diethylphenylacetic acid (Oxeladin) was the most potent antitussive agent of the present series.

THERE is a need for a new antitussive agent resembling codeine as a cough suppressant, but differing from it in not producing constipation even at minimal dose levels. In seeking such a product we turned to derivatives of phenylacetic acid as such compounds often show antispasmodic properties and, less frequently, antitussive action.

Interest in C-substituted phenylacetic acid esters stemmed from the discovery of Trasentin (β-diethylaminoethyl diphenyl acetate) in 1936. In 1938 Halpern[1] described a series of esters of C-alkylphenyl acetic acids in which the alkyl group ranged from ethyl to heptyl. The preparation of many other compounds of related type followed in quick succession[2–5]. Diethylaminoethyl phenylethyl acetate, first described by Halpern, was introduced as an antitussive, some years ago.

In 1946 Rubin and Wishinsky[6] described the preparation of a novel series of esters of C-disubstituted acetic acids in which the α-carbon atom formed an integral part of

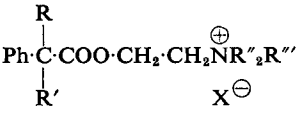


(I)

a *cyclo*hexane (I; $n = 5$) or *cyclo*hexanone nucleus and soon afterwards Weston[7] reported the synthesis of a closely related group of esters, and in particular the diethylaminoethyl esters of structure (I; $n = 2$ or 5). The series was further extended by Tilford, van Campen, Jr., and Shelton[8] who, *inter alia*, esterified 1-phenyl*cyclo*hexane-1-carboxylic acid (I; n=5,R=H) with dimethylaminoethoxyethanol. They failed to study the antitussive properties of the resulting ester, but reported that it was more potent than the corresponding dimethylaminoethyl ester against the acetylcholine and barium chloride induced spasms of the isolated rabbit jejunum, but less active in antagonising the effect of histamine on the isolated guinea pig intestine. The antitussive properties of the dimethylaminoethoxyethyl ester were subsequently reported by Levis, Preat and Moyersoons[9], who examined a number of derivatives of type (I; $n = 2$, 3, 4 and 5), and

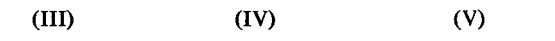
concluded that optimal activity was attained in the diethylaminoethoxyethyl ester of 1-phenyl*cyclo*pentane-1-carboxylic acid (I; $n = 4$; $R = \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot NEt_2$).

Our own studies in the antitussive field have dealt largely with esters of diethylphenyl acetic acid. Very little information is available on the biological properties of compounds of this type apart from a publication by Jensen, Hansen and Hammer[10] describing the spasmolytic activity of the quaternary esters (II).



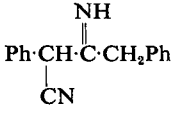
(II) (where R = R′ = Et)

We therefore prepared a series of typical esters containing the dialkyl aminoethyl moiety. Their study as antitussives by David and his colleagues[11] revealed the superiority of the dialkylaminoethoxyethyl ester type (X), which was chosen for detailed study. Before embarking on this project, however, it proved necessary to develop a preparative method for diethylphenyl acetic acid (V) itself.

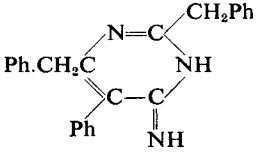


(III) (IV) (V)

αα-Diethylphenylacetonitrile (IV) was prepared after Bodroux and Taboury[12] by heating the disodium derivative of phenylacetonitrile with ethyl iodide in ether. It was converted in low yield into the acid (V) by heating with amyl alcoholic potassium hydroxide. In our hands αα-diethylphenylacetonitrile (IV) was obtained in 85 per cent yield by condensation of an excess of ethyl chloride with the disodium salt of phenylacetonitrile, prepared *in situ* using sodium in liquid ammonia. The product so formed was free from unchanged nitrile and from the monoethylated material, but was admixed with very small quantities of toluene and of 3-phenylpentane, which were readily separated by distillation. The last compound probably arises through reduction of the product (IV) by the reducing metal. Alternatively, the alkylated nitrile (IV) was obtained in 85 per cent yield by condensing phenylacetonitrile with ethyl chloride or bromide in toluene using sodamide as condensing agent. Attempts to effect the alkylation with potassium *tert.*-butoxide in *tert.*-butanol led to the formation of substantial quantities of phenylacetonitrile self-condensation products such as (VI) and (VII).



(VI)



(VII)

Hydrolysis of αα-diethylphenylacetonitrile (IV) to the required acid (V) was accomplished in 90 per cent yield employing potassium hydroxide in ethylene glycol under reflux.

Conversion of diethylphenylacetic acid (V) into the dialkylaminoethoxyethyl esters (X) was effected in several ways:

$$\underset{\text{(VIII)}}{Ph{\cdot}CEt_2{\cdot}COCl} + \underset{\text{(IX)}}{HO{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2NRR'} \longrightarrow \underset{\text{(X)}}{Ph{\cdot}CEt_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2NRR'}$$

(i) by reaction of the acid chloride (VIII) with the appropriate amino alcohol (IX) in a solvent such as benzene, when the product (X) separated as the hydrochloride;

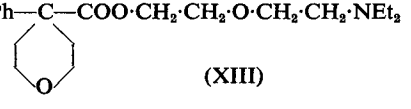
(ii) by interaction of the acid (V) with the chloroalkamine (XI) in *iso*-propanol[13]:

$$\text{(V)} + \underset{\text{(XI)}}{Cl{\cdot}CH_2CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NRR'} \rightarrow \text{(X)}$$

and (iii) by condensing the potassium salt of αα-diethylphenylacetic acid with ββ′-dichlorodiethyl ether in ethylene glycol solution to give the β-chloroethoxyethyl ester (XII), which passed smoothly into the required basic ester (X) on reaction with the appropriate amine.

$$\underset{\text{(XII)}}{Ph{\cdot}CEt_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2Cl}$$

By applying the above methods, and in particular method (iii), we obtained the diethylamino-, ethylmethylamino-, ethylpropylamino-, di-*n*-butylamino-, di-*n*-hexylamino-, *N*-pyrrolidino-, *N*-Δ^3-piperideino- and *N*-piperidinoethoxyethyl esters of diethylphenylacetic acid. In addition, we prepared the *N*-pyrrolidino-, *N*-Δ^3-piperideino- and *N*-piperidinoethoxyethyl esters of 1-phenyl*cyclo*pentane-1-carboxylic acid [*cf.* (I; $n = 4$)] as well as the diethylaminoethoxyethyl ester of 4-phenyltetrahydropyran-4-carboxylic acid (XIII).



(XIII)

Biological study of the above esters by David and his colleagues showed clearly that the diethylaminoethoxyethylester (X; R = R′ = Et) of diethylphenylacetic acid was a potent antitussive agent and the most active compound of the present series[11]. The free base (X; R = R′ = Et) formed a colourless, odourless oil, b.p. 140° at 0·1 mm., which was quite stable on exposure to air. Its salts with hydrochloric, carbonic, benzoic, cinnamic and other organic acids were difficult to crystallise. The citrate, in contrast, formed small needles, m.p. 90° to 91° which were readily soluble in water (> 80 per cent w/w at 25°) to give solutions of only moderate acidity. It thus proved suitable for pharmaceutical presentation.

EXPERIMENTAL

αα-Diethylphenylacetonitrile (IV). (*a*) To *ca.* 2 litres of liquid ammonia in a 5-litre three-necked flask fitted with stirrer and Drikold condenser was added 2 g. of ferric nitrate as catalyst followed portionwise by sodium metal (200 g. = 8·7 g. atoms). The mixture was stirred for 1 hour after addition of sodium was complete to ensure formation of sodamide. Phenylacetonitrile (468 g., 4 moles) was then run in with stirring over about 20 minutes. As soon as the addition of nitrile was complete a solution of ethyl chloride (650 ml. = *ca.* 9 mole) in toluene was added slowly. The apparatus was surrounded by a Drikold bath and the rate of addition of ethyl chloride regulated to control the exothermic reaction. The mixture was stirred for one hour after the addition of ethyl chloride was complete and the ammonia was then allowed to evaporate freely from the mixture (usually overnight).

A current of nitrogen was passed through the apparatus and water (2 litres) added slowly to the mixture with stirring.

The toluene layer was separated and the toluene removed under reduced pressure on the steambath. The residual oil was distilled at reduced pressure to yield the product as an oil (590 g.), b.p. 145° at 30 mm. or 155° at 45 mm. $n_D^{20} = 1{\cdot}5040$. Found: C, 82·9; H, 8·3; N, 8·2. Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·7; N, 8·1 per cent.

(*b*) (With Mr. A. J. Thomas, B.Sc.) To a stirred suspension of powdered sodamide (32 g.; 0·8 mole) in dry toluene (250 ml.) in a flask fitted with a Drikold condenser, was added phenylacetonitrile (46·8 g., 0·4 mole) over 5 minutes, the temperature of the mixture rising to *ca.* 45°. The mixture was then cooled to 5° and a solution of ethyl chloride (64·5 g., 1·0 mole) in toluene (100 ml.) added at such a rate that the temperature of the mixture was kept at *ca.* 5°. The addition took 45 minutes and stirring was then continued for 3 hours at 5° to 10°. The reaction was then completed by heating at 70° for 2 hours. The mixture was cooled to room-temperature, water (500 ml.) added with stirring and the aqueous layer just acidified with hydrochloric acid. The toluene layer was separated and washed with water. After removal of the toluene the residual oil was distilled under reduced pressure and the product (59 g.) collected at 144° to 146° at 30 mm. $n_D^{20} = 1{\cdot}5040$.

αα-Diethylphenylacetic acid (V). To αα-diethylphenylacetonitrile (450 g.) in a stainless steel vessel was added a solution of potassium hydroxide (320 g.) in ethylene glycol (1300 ml.). The mixture was heated to reflux and water (36 ml.) distilled off. The mixture was refluxed gently for 24 hours when evolution of ammonia had ceased. It was cooled, poured into water and the mixture extracted with a little light petroleum (b.p. 60° to 80°) to remove non-acidic material. Acidification of the aqueous layer with hydrochloric acid, followed by cooling, yielded diethylphenylacetic acid. This was collected and purified by crystallisation from 50 per cent aqueous methanol. After drying at 50° to 60° in a current of air it had m.p. 93° to 94°. As an alternative the acid could be purified by rapid distillation and had b.p. 195° at 30 mm.

2-(*β-Chloroethoxy)ethyl diethylphenylacetate* (XII). To sodium hydroxide (40 g.) in ethylene glycol (300 ml.) was added diethylphenylacetic acid (192 g.) which was dissolved by warming. 2:2′-Dichlorodiethyl ether (300 g., 2·1 moles) was added and the mixture heated under reflux for 1 hour, when it was poured into water and the oily layer separated and distilled at reduced pressure to remove unchanged 2:2′-dichlorodiethyl ether. The required *chloro-ester* (254 g.) had b.p. 130° at 0·5 mm. Found: C, 64·3; H, 7·6; Cl, 12·2. $C_{16}H_{23}O_3Cl$ requires C, 64·3; H, 7·8; Cl, 11·9 per cent.

2-(*β-Diethylaminoethoxy)ethyl diethylphenylacetate* (X; R = R′ = Et). A mixture of 2-(β-chloroethoxy) ethyl diethylphenylacetate (120 g.), diethylamine (84 g. = 2·9 mole equivs.) and *n*-hexanol (480 ml.) was heated under reflux for 6 hours.

The hexanol and excess diethylamine were removed in steam. The cooled residue was acidified with hydrochloric acid and extracted with toluene to remove non-basic impurities. It was then basified with aqueous sodium hydroxide and extracted with toluene. After removal of the toluene the residual oil was distilled at 0·5 mm. to yield the *product* (111 g.) as an oil, b.p. 150°. Found: C, 71·6; H, 9·8; N, 4·2. $C_{20}H_{23}O_3N$ requires C, 71·5; H, 9·9; N, 4·2 per cent.

The base (150 g.) was added with stirring to a hot solution of citric acid monohydrate (100 g.) in ethyl acetate (2·5 litres). The *citrate* separated in small needles on cooling. After crystallisation from ethyl acetate it had m.p. 90° to 91°. Found: C, 58·8; H, 7·8; N, 2·7. $C_{26}H_{41}O_{10}N$ requires C, 59·2; H, 7·8; N, 2·7 per cent.

2-(*β-N-Piperidinoethoxy)-ethyl diethylphenylacetate* (X; NRR′ = piperidino). A mixture of 2-(β-chloroethoxy)ethyl diethylphenylacetate (20 g.) and piperidine (30 g.) was heated gently under reflux for 1 hour. The cooled mixture was acidified with dilute hydrochloric acid and extracted with ether to remove non-basic material. The aqueous phase was basified with aqueous sodium hydroxide and extracted with ether. The ether extract was dried and the ether and excess of piperidine removed under reduced pressure. The residual oil was fractionated *in vacuo* to yield the product, b.p. 165° at 0·5 mm.

The base was converted into the *citrate*, m.p. 73° after crystallisation from ethyl acetate. Found: C, 59·6; H, 7·5; N, 2·7. $C_{27}H_{41}O_{10}N$ requires C, 60·1; H, 7·7; N, 2·6 per cent.

2-(*β-N-Δ³-Piperideino ethoxy)ethyl diethylphenylacetate* (X; NRR′ = Δ³-piperideino) was prepared as for the preceding analogue using Δ³-piperideine in place of piperidine. The *citrate* had m.p. 80° after crystallisation from ethyl acetate. Found: C, 60·3; H, 7·1; N, 2·4. $C_{27}H_{39}O_{10}N$ requires C, 60·3; H, 7·3; N, 2·6 per cent.

2-(*β-N-Pyrrolidinoethoxy)ethyl diethylphenylacetate* (X; NRR′ = pyrrolidino). A mixture of 2-(β-chloroethoxy) ethyl diethylphenylacetate (30 g.) and pyrrolidine (20 g.) was heated under reflux for 3 hours then cooled and acidified with dilute hydrochloric acid. After extraction with ether to remove non-basic impurities the aqueous layer was basified with aqueous sodium hydroxide and extracted with ether. The ether was

dried, the solvent removed and the oil distilled at 1·0 mm. to yield the *product*, b.p. 170°. Found: C, 71·4; H, 9·9; N, 4·1. $C_{20}H_{31}O_3N$ requires C, 72·0; H, 9·4; N, 4·2 per cent.

2-(β-N-*Ethylmethylaminoethoxy*)*ethyl diethylphenylacetate* (X; R = Et, R′ = Me). A mixture of 2-(β-chloroethoxy)-ethyl diethylphenylacetate (25 g.), ethylmethylamine (30 ml.) and *n*-hexanol (200 ml.) was heated under reflux for 6 hours, when hexanol and excess amine were distilled off. The cooled residue was acidified with dilute hydrochloric acid, extracted with ether to remove unchanged chloroester, then basified with aqueous sodium hydroxide. The separated oil was extracted with ether and isolated by distillation *in vacuo*. The *product* had b.p. 140° at 0·5 mm. Found: C, 70·9; H, 9·5; N, 4·3. $C_{19}H_{31}O_3N$ requires C, 71·0; H, 9·7; N, 4·4 per cent.

2-(β-N-*Ethylpropylaminoethoxy*)-*ethyl diethylphenylacetate* (X; R = Et, R′ = *n*-Pr) was an oil, b.p. 155° at 0·2 mm. Found: C, 72·1; H, 10·0; N, 4·4. $C_{21}H_{35}O_3N$ requires C, 72·2; H, 10·1; N, 4·0 per cent.

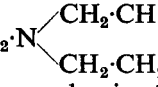
2-(β-N-*Di*-n-*butylaminoethoxy*)*ethyl diethylphenylacetate* (X; R = R′ = *n*-Bu). A mixture of 2-(β-chloroethoxy) ethyl diethylphenylacetate (20 g.) di-*n*-butylamine (30 g.) and *n*-hexanol (80 ml.) was heated under reflux for 20 hours. The hexanol and excess of di-*n*-butylamine were removed in steam. The residue was cooled and basified directly since the hydrochloride of the product is soluble in organic solvents. Extraction with ether yielded the *product*, isolated as an oil, b.p. 169° at 1·0 mm. Found: C, 73·7; H, 10·3; N, 3·4. $C_{24}H_{41}O_3N$ requires C, 73·6; H, 10·6; N, 3·6 per cent.

2-(β-N-*Di-n-hexylaminoethoxy*)*ethyl diethylphenylacetate* (X; R = R′ = *n*-hexyl). A mixture of 2-(β-chloroethoxy)ethyl diethylphenylacetate (20 g.) and di-*n*-hexylamine (35 g.) in *n*-hexanol (40 ml.) was heated under reflux for 2 hours. The *product* had b.p. 190° at 0·03 mm. Found: C,74·4, H, 10·6; N, 3·1. $C_{28}H_{49}O_3N$ requires C, 75·1; H, 11·0; N, 3·1 per cent.

2-(β-N-*Pyrrolidinoethoxy*)-*ethyl*-1-*phenyl*-1-cyclo*pentane carboxylate* (I; $n = 4$, R = $-CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}N\begin{matrix}CH_2-CH_2\\ \\ CH_2-CH_2\end{matrix}$).—A solution of 1-phenyl*cyclo*pentanoyl chloride (12 g.) in chloroform (12 ml.) was treated with 2-(β-*N*-pyrrolidinoethoxy)ethanol (12 g.) in chloroform (12 ml.) and the mixture heated under reflux for 1 hour. After removal of the chloroform the residue was acidified with dilute hydrochloric acid and extracted with ether to remove by-products. The aqueous phase was basified with aqueous sodium hydroxide and extracted with ether. The *product* was an oil, b.p. 168° to 172° at 0·4 mm. Found: C, 72·4; H, 8·7; N, 4·0. $C_{20}H_{29}NO_3$ requires C, 72·5; H, 8·8; N, 4·2 per cent.

2-(β-N-*Piperidinoethoxy*)-*ethyl*-1-*phenyl*-1-cyclo*pentane carboxylate* (I; $n = 4$, R = $CH_2CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}N\begin{matrix}CH_2-CH_2\\ \\ CH_2-CH_2\end{matrix}CH_2$).—Condensation of 1-phenyl *cyclo*pentanoyl chloride with 2-(β-*N*-piperidinoethoxy)-ethanol

was carried out as described in the previous example. The base was obtained as an oil b.p. 180° at 0·6 mm. It was converted to its *hydrobromide* which separated from ethanol-ether in needles, m.p. 89°. Found: C, 59·5; H, 7·6; N, 3·2. $C_{21}H_{32}O_3NBr$ requires C, 59·1; H, 7·6; N, 3·3 per cent.

2-(β-N-Δ^3-*Piperideinoethoxy*)-*ethyl*-1-*phenyl*-1-cyclo*pentane carboxylate* (I; $n = 4$, R = $-CH_2CH_2\cdot O\cdot CH_2\cdot CH_2\cdot N$ ).—This was prepared as for the pyrrolidino analogue by condensing 1-phenyl*cyclo*pentanoyl chloride with 2-(β-*N*-Δ^3-piperideinoethoxy)-ethanol. The base was converted directly into the *hydrobromide* which separated from ethanol-ether in needles, m.p. 84°. Found: C, 59·0; H, 7·2; N, 3·0; Br, 18·9. $C_{21}H_{30}O_3NBr$ requires C, 59·4; H, 7·1; N, 3·3; Br, 18·9 per cent.

2-(β-N-*Diethylaminoethoxy*)-*ethyl*-4-*phenyl-tetrahydropyran*-4-*carboxylate* (XIII).—4-Phenyltetrahydropyranoyl chloride was prepared by a slight variation of the method used by Eisleb[14].

Condensation of the acid chloride (11·5 g.) with 2-β-diethylaminoethoxy) ethanol (11·5 g.) in dry chloroform (25 ml.) yielded the base as an oil b.p. 179° at 0·2 mm.

The base was converted into the *hydrobromide* which separated from *iso*propanol/ether in needles, m.p. 101°. Found: C, 55·7; H, 7·5; N, 2·8 Br, 18·1. $C_{20}H_{32}O_4NBr$ requires C, 55·8; H, 7·5; N, 3·3; Br, 18·6 per cent.

References

1. Halpern, *Arch. int. Pharmacodyn.*, 1938, **59**, 149.
2. Wagner-Jauregg, Arnold and Born, *Ber.*, 1939, **72**, 1551.
3. Meier and Hoffmann, *Helv. Med. Acta.*, 1941, **7**, 106.
4. Hoffmann, *Helv. Chim. Acta*, 1941, **24**, 36.
5. Cheyney and Bywaters, *J. Amer. chem. Soc.*, 1942, **64**, 970.
6. Rubin and Wishinsky, *ibid.*, 1946, **68**, 828.
7. Weston, *ibid.*, 1946, **68**, 2345.
8. Tilford, van Campen and Shelton, *ibid.*, 1947, **69**, 2902.
9. Levis, Preat and Moyersoons, *Arch. int. Pharmacodyn.*, 1955, **103**, 200.
10. Jensen, Hansen and Hammer, *Acta chem. scand.*, 1952, **6**, 615.
11. David, Leith-Ross and Vallance, *J. Pharm. Pharmacol.*, 1957, **9**, 446.
12. Bodroux and Taboury, *C.R. Acad. Sci., Paris*, 1910, **150**, 1241; *Bull. Soc. Chim.*, 1910, [4], **7**, 666; 733; 847.
13. Horenstein and Pahlicke, *Ber.*, 1938, **71**, 1644.
14. Eisleb, *Ber.*, 1941, **74**, 1447.