562. *The Synthesis of Neurotropic and Musculotropic Stimulators and Inhibitors. Part IV. Benzilic Acid Derivatives.*

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In view of their structural relation to both " Trasentin " and " Benadryl," 2-dialkylaminoalkyl α-(2-dialkylaminoethoxy)-αα-diphenylacetates (IV) were prepared. Some of them possess valuable spasmolytic properties.

Treatment of sodium α-(2-dimethylaminoethoxy)-αα-diphenylacetate with thionyl chloride gave 3-keto-4-methyl-2 : 2-diphenylmorpholine.

In 1945, Loew, Kaiser, and Moore (*J. Pharm. Exp. Ther.*, 1945, **83**, 120) reported that 1-(2-dimethylaminoethoxy)-1 : 1-diphenylmethane (I; " Benadryl ") possessed pronounced histaminolytic properties. We had previously observed that allyl 1-methyl-4-phenylpiperidine-4-carboxylate was a more powerful histaminolytic than the corresponding ethyl ester (pethidine) and we therefore considered that allyl α-(2-dimethylaminoethoxy)-αα-diphenylacetate (II;

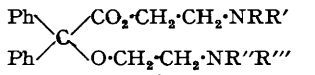
$Ph_2CH{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$ (I.) $Ph_2C(CO_2R){\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NR'R''$ (II.)

R = allyl, R′ = R″ = Me) might be a generally valuable spasmolytic. We also visualised that if in (II; R = allyl) the allyl radical were replaced by a 2-diethylaminoethyl radical, the resulting compound (IV; R = R′ = Et; R″ = R‴ = Me) would contain features of both " Benadryl " and the well-established neurotropic spasmolytic " Trasentin " (III). Alkyl esters of α-(2-dialkylaminoethoxy)-αα-diphenylacetic acid and -α-phenylacetic acid were readily obtained by condensing the sodio-derivatives of alkyl benzilates and alkyl mandelates with dialkyl-2-chloroethylamines. Not until 1946 (*Chem. Abstr.*, 1946, **40**, 1175) did we learn that CIBA had already prepared such esters by an identical method (B.P. 558,653; U.S.P. 2,387,447). The preparation of new esters is given in the Experimental section.

The first method employed to prepare the dibasic esters (IV) was to hydrolyse the alkyl esters (II; R′ = Et) with sodium hydroxide and condense the conveniently isolated sodium salt of the

acid with dialkyl-2-chloroethylamines, as described in the Experimental part. Later it was found that the dibasic esters were even more readily prepared from the corresponding ethyl

$Ph_2CH{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$ (III.)



(IV.)

$Ph_2C(COEt){\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$ (V.)

esters by transesterification using the basic alcohol in presence of a small amount of its sodium derivative. A number of dibasic esters were made by this general method and their properties are given in the table.

It was also of interest to prepare the ketone (V), as its structural similarity to amidone indicated that it might possess both spasmolytic and analgesic properties.

The preparation of 1-(2-diethylaminoethoxy)-1 : 1-diphenylbutan-2-one is described in B.P. 558,653, but as we failed to repeat this experiment, it was decided to attempt the preparation of (V) by the action of ethylmagnesium halide on the piperidide of α-(2-dimethylaminoethoxy)-αα-diphenylacetic acid. Treatment of the sodium salt of this acid with thionyl chloride (cf. G.P. 262,883) and reaction of the resultant crude product with piperidine gave only a non-basic product. The action of thionyl chloride was more closely investigated and it was found that the neutral product, m. p. 97—98°, was formed in 75% yield, and from analysis and properties was undoubtedly 3-keto-4-methyl-2 : 2-diphenylmorpholine. This reaction is analogous to those described by Tiffeneau and Führer (*Bull. Soc. chim.*, 1914, **15**, 168), wherein certain acid chlorides and bromides react with certain tertiary bases to give disubstituted amides and alkyl halides. More recently it has been reported that attempts to make the acid chloride by treatment of γ-dimethylamino-αα-diphenylvaleric acid with thionyl chloride yielded 1 : 5-dimethyl-3 : 3-diphenylpyrrolid-2-one (Gardner, Easton, and Stevens, *J. Amer. Chem. Soc.*, 1948, **70**, 2906). It is interesting to note that whereas γ-diethylamino-αα-diphenylbutyric acid is readily converted by the action of thionyl chloride into 1-ethyl-3 : 3-diphenylpyrrolid-2-one, δ-diethylamino-αα-diphenylvaleric acid does not give the 2-piperidone on similar treatment but simply the acid chloride (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500). α-(2-Dimethylaminoethoxy)-αα-diphenylacetopiperidide and the corresponding 2-diethylaminoethylamide were finally prepared from ethyl α-(2-dimethylaminoethoxy)-αα-diphenylacetate by Bodroux's method (*Compt. rend.*, 1904, **138**, 1427). All attempts to prepare a ketone by treating the piperidide with ethylmagnesium iodide were unsuccessful, the starting material being recovered (cf. Burton, *J.*, 1930, 2400).

The results of pharmacological testing of the above compounds will be reported elsewhere (Forbes and Marshall, *Brit. J. Pharmacol.*, in the press). Preliminary clinical results indicate that 2-diethylaminoethyl α-(2-dimethylaminoethoxy)-αα-diphenylacetate (Ro 3—0131) may possess valuable spasmolytic properties (Norman and Wrigley, *Acta Allerg.*, 1948, **1**, 382).

Experimental.

Allyl Mandelate.—A solution of mandelic acid (20 g.) and concentrated sulphuric acid (2 ml.) in allyl alcohol (100 ml.) was heated on the steam-bath for 16 hours. The excess of allyl alcohol was then distilled off *in vacuo* and the residue made alkaline with ice-cold sodium carbonate solution. The *ester* was extracted with ether and distilled, having b. p. 152—154°/12 mm. The oil crystallised on storage and then had m. p. 30—32° (yield, 17 g.) (Found: C, 68·0; H, 6·5%; I.V., 125·6. $C_{11}H_{12}O_3$ requires C, 68·75; H, 6·25%; I.V., 131).

Allyl Benzilate.—Benzilic acid (20 g.) was esterified with allyl alcohol as described above and the *ester* obtained as an oil, b. p. 158—160°/0·8 mm. (Found: C, 76·3; H, 6·3. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

Allyl α-(2-Dimethylaminoethoxy)-α-phenylacetate.—Allyl mandelate (10 g.) was added to powdered sodium (1·2 g.) in dry toluene (80 ml.), and when the sodium had reacted 2-chloroethyldimethylamine (8 g.) was added and the solution heated under reflux for 3 hours. When the reaction mixture was worked up for basic material, the *ester* was obtained as an oil, b. p. 128—130°/0·1 mm. (Found: C, 68·1; H, 8·3; N, 5·1. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·0; N, 5·5%).

Allyl α-(2-Dimethylaminoethoxy)-αα-diphenylacetate.—This *ester*, prepared in a similar way from allyl benzilate, was obtained as an oil, b. p. 175—178°/0·05 mm. (Found: C, 73·8; H, 7·5; N, 4·7. $C_{21}H_{25}O_3N$ requires C, 74·1; H, 7·4; N, 4·1%).

Ethyl α-(2-Dimethylaminoethoxy)-αα-diphenylacetate.—To powdered sodium (11·5 g.) in toluene (550 ml.) was added gradually with cooling and stirring ethyl benzilate (128 g.) in toluene (150 ml.). When all the sodium had dissolved a dried solution of 2-chloroethyldimethylamine, liberated from the hydrochloride (85 g.), in toluene (150 ml.) was slowly added and the solution heated under reflux for 5 hours. The cooled toluene solution was then exhaustively extracted with 2N-hydrochloric acid (six times), the acid extract washed with ether and made alkaline with sodium hydroxide solution, and the

precipitated base taken up in ether. The ethereal solution, after being washed with water and dried (Na_2SO_4), was concentrated and the residual oil distilled to give the *ester*, b. p. 165—167°/0·3 mm. (120 g., 73·5%) (Found : N, 4·3. $C_{20}H_{25}O_3N$ requires N, 4·3%).

Sodium α-(2-*Dimethylaminoethoxy*)-αα-*diphenylacetate*.—Sodium (4·6 g.) was dissolved in ethanol (174 ml.), and the above ester (43·5 g.) in ethanol (174 ml.), and water (8·5 ml.), added. When the solution was heated, the *sodium* salt started to separate. Heating was continued for 1 hour, the mixture cooled in ice and filtered, and the sodium salt washed first with ice-cold alcohol and then with dry ether. It melted at 303—304° (decomp.) (35·5 g., 83·1%) (Found : Na, 7·2. $C_{18}H_{20}O_3NNa$ requires Na, 7·2%).

α-(2-*Dimethylaminoethoxy*)-αα-*diphenylacetic Acid Hydrochloride*.—The above sodium salt (1 g.) dissolved when its suspension in water was made acid with concentrated hydrochloric acid, and a crystalline product separated, which, after cooling, was filtered off and washed with dry acetone. The *hydrochloride* (0·8 g.) melted at 112—114° (Found : Cl, 10·7; N, 3·9. $C_{18}H_{22}O_3NCl$ requires Cl, 10·6; N, 4·1%).

2-*Diethylaminoethyl* α-(2-*Dimethylaminoethoxy*)-αα-*diphenylacetate*.—(*a*) To a stirred suspension of the above sodium salt (26·8 g.) in toluene (150 ml.) was added a dried solution of 2-chloroethyldiethylamine, liberated from the hydrochloride (21·6 g.), in toluene (50 ml.), and the mixture refluxed gently with stirring for 2½ hours. The sodium chloride (5·0 g.; theor., 4·9 g.) was filtered off, and the toluene solution exhaustively extracted with 2N-hydrochloric acid. The base was precipitated by addition of excess of 2N-sodium hydroxide solution and taken up in ether, and the ethereal solution washed five times with water. After being dried, the ethereal solution was concentrated and the residual oil distilled, to give the *ester*, b. p. 170°/0·05 mm., $n_D^{17\cdot5}$ 1·5290 (24·7 g., 75%) (Found : C, 72·1; H, 8·7; N, 7·1. $C_{24}H_{34}O_3N_2$ requires C, 72·3; H, 8·55; N, 7·0%).

(*b*) To dry 2-diethylaminoethanol (5·35 g.) and dry toluene (20 ml.) in a flask fitted with a short fractionating column and a ratio still head, was added sodium (0·05 g.,), and the solution was heated until it refluxed (b. p. 110°). Ethyl 1-(2-dimethylaminoethoxy)-1 : 1-diphenylacetate (10 g.) in toluene (20 ml.) was then added slowly, the vapour temperature falling to 80°. Toluene and alcohol were then distilled off until all the ester had been added and the vapour temperature had risen to 110°. The toluene solution was then worked up as described in (*a*) to give 9·6 g. (79%) of product, b. p. 178°/0·1 mm., n_D^{20} 1·5282 (Found : C, 72·8; H, 8·6; N, 7·2%). The esters recorded in the Table were prepared in the same way.

Ethyl α-(2-*Morpholinoethoxy*)-αα-*diphenylacetate*.—To powdered sodium (1·8 g.) in toluene (80 ml.) at room temperature was added slowly with stirring ethyl benzilate (20 g.) in toluene (25 ml.). When all the sodium had reacted 1-2′-chloroethylmorpholine (16 g.) in toluene (25 ml.) was added and the reaction mixture refluxed for 4 hours. When worked up as described above the *ester* was obtained as an oil, b. p. 166—167°/0·1 mm. (18·6 g.) (Found : C, 71·4; H, 7·5; N, 4·5. $C_{22}H_{27}O_4N$ requires C, 71·55; H, 7·3; N, 3·8%).

Sodium α-(2-*Morpholinoethoxy*)-αα-*diphenylacetate*.—Hydrolysis of the above ester (16 g.) with alcoholic sodium hydroxide gave the *sodium* salt, m. p. 273—274° (decomp.) (14 g.) (Found : N, 3·9; Na, 6·3. $C_{20}H_{22}O_4NNa$ requires N, 3·9; Na, 6·3%).

Esters, $Ph_2C(CO_2R)\cdot O\cdot CH_2\cdot CH_2\cdot NMe_2$, *etc.*

R =	B. p., at mm.	Yield, %.	Formula.	Required, %. C.	H.	N.	Found, %. C.	H.	N.
$CH_2\cdot CH_2\cdot NMe_2$	168—170° 0·2 mm.	—	$C_{22}H_{30}O_3N_2$	71·35	8·1	7·5	72·3	8·2	7·1
$CH_2\cdot CH_2\cdot N<([CH_2]_2)_2>O$	194—196° 0·1 mm.	75	$C_{25}H_{34}O_3N_2$	73·2	8·3	6·8	72·8	8·3	7·2
$CH_2\cdot CH_2\cdot N<^{Me}_{CH_2\cdot CH:CH_2}$	184—186° 0·1 mm.	60·8	$C_{24}H_{32}O_3N_2$	72·7	8·1	7·1	73·4	8·3	7·1
$CH_2\cdot CH_2\cdot N(CH_2\cdot CH:CH_2)_2$	150° 0·05 mm.	64	$C_{26}H_{34}O_3N_2$	73·9	8·05	6·6	73·3	8·45	6·5
$CH_2\cdot CH_2\cdot N<([CH_2]_2)_2>O$	192—194° 0·1 mm.	56	$C_{24}H_{32}O_4N_2$	—	—	6·8	—	—	6·75
$CH_2\cdot CH_2\cdot NMePr^i$	166—170° 0·2 mm.	67	$C_{24}H_{34}O_3N_2$	—	—	7·1	—	—	6·7
$CHMe\cdot CH_2\cdot NMe_2$	182—184° 0·1 mm.	88	$C_{25}H_{36}O_3N_2$	—	—	6·8	—	—	6·8
$CH_2\cdot CH_2\cdot NEt_2$ *	180—184° 0·05 mm.	80	$C_{26}H_{38}O_3N_2$	73·2	8·9	6·6	73·3	9·3	6·3

* $NMePr^i$ replaces NMe_2 in the general formula.

2-*Diethylaminoethyl* α-(2-*Morpholinoethoxy*)-αα-*diphenylacetate*.—Condensation of the above sodium salt (7 g.) with 2-chloroethyldiethylamine (2·9 g.) by heating them in boiling toluene (50 ml.) for 4 hours gave the basic *ester* as an oil, b. p. 200°/0·4 mm. (7·0 g.) (Found : C, 71·0; H, 8·05; N, 6·45. $C_{26}H_{36}O_4N_2$ requires C, 70·9; H, 8·2; N, 6·4%).

2-*Morpholinoethyl* α-(2-*Morpholinoethoxy*)-αα-*diphenylacetate*.—In a similar way the sodium salt (7·0 g.) on condensation with 2-chloroethylmorpholine (4 g.) gave the basic *ester*, b. p. 228—230°/0·1 mm. (6·2 g.) (Found : C, 68·8; H, 7·4; N, 6·4. $C_{26}H_{34}O_5N_2$ requires C, 68·7; H, 7·5; N, 6·2%).

Ethyl α-(2-N-*Methyl*-N-iso*propylaminoethoxy*)-αα-*diphenylacetate*.—2-*N*-Methyl-*N*-*iso*propylaminoethanol was prepared by methylation of 2-*iso*propylaminoethanol with formaldehyde and formic acid (cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571). A fraction, b. p. 66—76°/15 mm.,

of the product was analysed (Found: N, 12·2. Calc. for $C_6H_{15}ON$: N, 11·9%). This impure product (40 g.) in chloroform (80 ml.) was treated with thionyl chloride (37 ml.) in chloroform (70 ml.) and left at room temperature overnight. The chloroform and excess of thionyl chloride were distilled off, and alcohol (30 ml.) was added. On addition of dry ether a sticky solid separated, which, even after recrystallisation from alcohol–ether, was very hygroscopic and not suitable for analysis. The crude hydrochloride (31 g.) was therefore used for the next stage of the synthesis. Ethyl benzilate (46·4 g.) was treated with sodium (4·16 g.) in toluene (100 ml.); 2-chloroethylmethyl*iso*propylamine, prepared from the hydrochloride (31 g.), was added and the mixture heated for 7 hours under reflux. Worked up in the described manner, the *ester* was obtained as an oil, b. p. 176—180°/0·2 mm. (Found: N, 4·2. $C_{22}H_{29}O_3N$ requires N, 3·9%).

3-*Keto*-4-*methyl*-2 : 2-*diphenylmorpholine*.—Sodium 1-(2-dimethylaminoethoxy)-1 : 1-diphenylacetate (10 g.) was added in small portions to thionyl chloride (20 ml.), and the mixture heated under reflux for 1 hour. It was then poured on ice, whereupon an oil separated and crystallised after some time. It was filtered off and dried *in vacuo* over phosphoric oxide. Recrystallised from *cyclo*hexane it gave the pure *ketomorpholine*, m. p. 97—98° (7·2 g.) (Found: C, 77·0; H, 6·2; N, 5·2. $C_{17}H_{17}O_2N$ requires C, 76·7; H, 6·3; N, 5·2%).

α-(2-*Dimethylaminoethoxy*)-αα-*diphenylacetopiperidide*.—To a solution of methylmagnesium iodide, prepared from magnesium (1·2 g.) and methyl iodide (7·1 g.), in benzene (50 ml.), was added dry piperidine (4·25 g.) in benzene (20 ml.), and the mixture stirred for 30 minutes. Ethyl 1-(2-dimethylaminoethoxy)-1 : 1-diphenylacetate (8·1 g.) in benzene (20 ml.) was then added and the mixture heated under reflux for 1 hour with stirring. To the ice-cooled reaction mixture N-hydrochloric acid (100 ml.) was added. The aqueous layer was made alkaline with sodium hydroxide solution, and sufficient ammonium chloride added to dissolve the magnesium hydroxide. The base was extracted with ether and gave, on distillation, the pure *piperidide*, b. p. 195—206°/0·5 mm., which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 94—96° (4·8 g.) (Found: C, 75·4; H, 8·2; N, 7·6. $C_{23}H_{30}O_2N_2$ requires C, 74·7; H, 8·1; N, 7·2%). The corresponding 2-*diethylaminoethylamide* was prepared in the same way from *NN*-diethylethylenediamine and was obtained as an oil, b. p. 195—197°/0·5 mm. (Found: C, 72·8; H, 8·8; N, 10·5. $C_{24}H_{35}O_2N_3$ requires C, 72·5; H, 8·8; N, 10·6%).

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