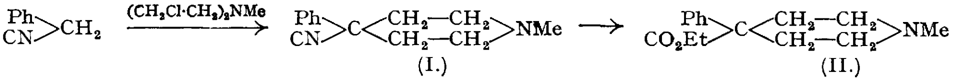
84. *Search for New Analgesics. Part I. Homologues of Pethidine and Related Compounds.*

By E. Walton and (in part) M. B. Green.

αα-Bis-(β′-bromoethyl)phenylacetic ester (IV) has been found to react with primary amines to give a series of pethidine *analogues* (V). With ammonia it reacted exceptionally to give 3-(*β-aminoethyl*)-3-*phenyl*-2-*pyrrolidone* (IX; R = H).

α-(β′-Bromoethyl)-α-phenylbutyrolactone (VII; X = Br) reacted with amines in two ways. With ammonia, the lower primary amines, and secondary amines, it gave aminoethyl lactones (VIII), but with higher primary amines, pyrrolidones (VI) were formed.

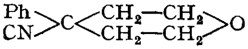
The analgesic drug, pethidine (II), was first synthesised by Eisleb (*Ber.*, **1941**, **74**, **1433**), by condensing phenylacetonitrile with bis-(β-chloroethyl)methylamine to give 4-phenyl-1-methylpiperidine-4-nitrile (I), which was then converted into the corresponding ethyl ester :—



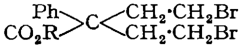
(I.) (II.)

Probably the main disadvantage of this process lies in the use of the powerful vesicant bis-(β-chloroethyl)-methylamine.

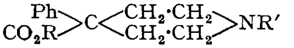
The original object of this research was therefore an alternative synthesis of pethidine avoiding the use of the vesicant, and this was eventually achieved by converting 4-cyano-4-phenylpentamethylene oxide (III) (Eisleb, *loc. cit.*) into αα-bis-(β′-bromoethyl)phenylacetic acid (IV; R = H) and treating the ethyl ester of the latter with methylamine. As this method has recently been recorded by Bergel, Morrison, and Rinderknecht (J., **1944**, 267), it is unnecessary to describe it further here. The reactions of the dibromo-acid (IV; R = H) and its immediate derivatives have, however, been more extensively studied by us, with a view to the synthesis of homologues of pethidine and related compounds.



(III.)



(IV.)



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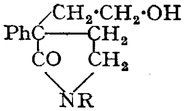

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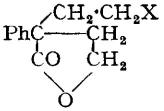
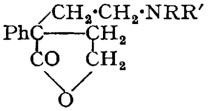
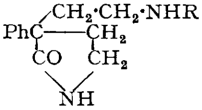


(VII.)



(VIII.)



(IX.)

The acid (IV; R = H), on attempted distillation or treatment with dilute alkali, gave good yields of α-(β′-bromoethyl)-α-phenylbutyrolactone (VII; X = Br), which on stronger hydrolysis formed α-(β′-hydroxyethyl)-α-phenylbutyrolactone (VII; X = OH) (compare Bergel *et al.*, *loc. cit.*). Esterification with either diazomethane or diazoethane, however, stabilised the molecule sufficiently for further synthetic work.

Both the ester (IV; R = Et) and the bromo-lactone (VII; X = Br) have now been found to give a series of derivatives on treatment with amines. With ammonia, the ester (IV) gave neither norpethidine (V; R = Et, R′ = H) as expected nor its amide, but 3-(β-*aminoethyl*)-3-*phenyl*-2-*pyrrolidone* (IX; R = H), the structure of which was confirmed by *N*-methylation to 3-(β-methylaminoethyl)-3-phenyl-2-pyrrolidone (IX; R = Me) and by conversion with nitrous acid into α-(β′-hydroxyethyl)-α-phenylbutyrolactone (VII; X = OH). With the primary amines, ethylamine, *n*-propylamine, *n*-butylamine and benzylamine, however, (IV) reacted normally to give a series of pethidine homologues (V), together with smaller amounts of the corresponding lactones (VIII) or lactams (VI), but with aniline only 1 : 3-*diphenyl*-3-(β-*hydroxyethyl*)-2-*pyrrolidone* (VI; R = Ph) was obtained. Attempts to prepare open-chain bis-(dialkylamino)-compounds from (IV) have so far been unsuccessful.

The bromo-lactone (VII; X = Br) with amines formed two distinct types of products. With ammonia, methylamine, ethylamine, and the secondary amines diethylamine, piperidine, methylaniline, and benzylmethylamine, it gave a series of *aminoethyl lactones* (VIII), whereas with the higher primary amines *n*-butylamine, aniline, benzylamine and *cyclo*hexylamine, it yielded feebly basic *hydroxyethyl lactams* of type (VI). With *n*-propylamine both α-(β′-*n*-propylaminoethyl)-α-phenylbutyrolactone (VIII; R = n-C_3H_7, R′ = H) and 3-*phenyl*-3-(β-*hydroxyethyl*)-1-n-*propyl*-2-*pyrrolidone* (VI; R = n-C_3H_7) were formed.

These lactones and lactams showed varying tendencies towards interconversion. Thus α-(β′-aminoethyl)-α-phenylbutyrolactone (VIII; R = R′ = H) existed only in the form of its *hydrochloride*, for with alkali the latter gave the feebly basic 3-(β-*hydroxyethyl*)-3-*phenyl*-2-*pyrrolidone* (VI; R = H), which required excess of acid for reconversion into the neutral hydrochloride of (VIII).

α-(β-Methylaminoethyl)-α-phenylbutyrolactone (VIII; R = Me, R′ = H) was more stable. Its *hydrochloride* yielded the corresponding base on neutralisation, and a crystalline *derivative*, m. p. 151°, with *p*-nitrobenzoyl chloride. On the other hand, preliminary heating of the hydrochloride led to the rapid evolution of hydrogen chloride and the formation of a feebly basic oil, probably 3-phenyl-1-methyl-3-(β-hydroxyethyl)-2-pyrrolidone (VI; R = Me), which gave a p-*nitrobenzoyl* derivative melting at 110—112°.

The *hydrochlorides* of both α-(β′-ethylaminoethyl)-α-phenylbutyrolactone (VIII; R = Et, R′ = H) and α-(β′-*n*-propylaminoethyl)-α-phenylbutyrolactone (VIII; R = n-C_3H_7, R′ = H) also evolved hydrogen chloride on heating to give feebly basic oils (VI ?), but crystalline *p*-nitrobenzoyl derivatives could not be obtained in these cases. Some preliminary attempts to reconvert these crude hydroxyethyl lactams into the corresponding lactones were also unsuccessful.

Several of the compounds described in this paper have been tested for spasmolytic and analgesic activity by Mr. R. H. Thorp at the Wellcome Physiological Research Laboratories, Beckenham, and although spasmolytic activity is still retained to a certain extent in most of these compounds, analgesic activity has been completely abolished. Detailed results will be published elsewhere.

EXPERIMENTAL.

αα-Bis-(β′-bromoethyl)phenylacetic Acid (IV; R = H).—4-Cyano-4-phenylpentamethylene oxide (7·6 g.) was heated with fuming hydrobromic acid (*d* 1·81) (60 ml.) in a sealed tube at 100° for 7 hours. When cold, the resulting brown crystalline mass was washed with water and crystallised from petrol (b. p. 80—100°) (500 ml.), forming needles, m. p. 118° (Found : C, 41·4; H, 4·0; Br, 45·4. Calc. for $C_{12}H_{14}O_2Br_2$: C, 41·2; H, 4·0; Br, 45·7%).

α-(β′-Bromoethyl)-α-phenylbutyrolactone (VII; X = Br).—This was readily prepared from the corresponding acid (IV; R = H) by straight distillation. After melting, the acid (7 g.) evolved hydrogen bromide to give the lactone (4·1 g.), b. p. 204—210°/13 mm. (Found : C, 53·1; H, 4·9; Br, 29·9. Calc. for $C_{12}H_{13}O_2Br$: C, 53·5; H, 4·9; Br, 29·7%). Treatment of the dibromo-acid with cold alkali or even warm water yielded the same lactone.

α-(β′-Hydroxyethyl)-α-phenylbutyrolactone (VII; X = OH).—The bromo-lactone (VII; X = Br) (10 g.) was warmed with *N*-methyl-alcoholic potassium hydroxide (100 ml.) for 1 minute; the oil then went into solution and potassium bromide separated. The filtrate was evaporated to remove alcohol, diluted with water, and washed with ether. The aqueous portion, probably consisting of a solution of potassium αα-bis-(β′-hydroxyethyl)phenylacetate,* was acidified and extracted with ether. The dried ethereal extract on distillation yielded the hydroxy-lactone as a colourless oil, b. p. 220°/15 mm., slightly soluble in hot water (Found : C, 70·6; H, 7·2. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·8%). The p-*nitrobenzoate* formed tablets, m. p. 116—117° (Found : N, 4·4. $C_{19}H_{17}O_6N$ requires N, 4·0%).

Methyl and ethyl αα-bis-(β′-bromoethyl)phenylacetates (IV; R = Me and Et) were formed by esterification of the corresponding acid with a slight excess of an ethereal solution of diazomethane and diazoethane respectively. On removal of the ether, they were obtained as oils, which readily decomposed into the lactone (VII; X = Br) on heating.

3-(β-*Aminoethyl*)-3-*phenyl*-2-*pyrrolidone* (IX; R = H).—The crude ethyl ester (IV; R = Et) (10 g.) and ethyl-alcoholic ammonia (40 ml.) were heated under pressure at 95° for 3 hours. After removal of the alcohol and ammonia, the residue was filtered from ammonium bromide (which was washed with acetone), basified with dilute caustic soda solution, and well extracted with ether or chloroform. The extract, after removal of solvent, crystallised from benzene in tablets (2·4 g.), m. p. 113—114°, very soluble in hot water, but crystallisable from dilute caustic soda solution (Found : C, 70·1; H, 7·9; N, 13·7. $C_{12}H_{16}ON_2$ requires C, 70·6; H, 7·8; N, 13·8%). The *pyrrolidone* tended to absorb carbon dioxide on exposure.

The *hydrochloride* crystallised from alcohol–ether in rectangular plates, m. p. 150—153° (Found : C, 59·6; H, 7·1; N, 11·8; Cl, 14·9. $C_{12}H_{16}ON_2$,HCl, requires C, 59·8; H, 7·1; N, 11·6; Cl, 14·8%). Treatment of an aqueous solution of the hydrochloride with an excess of sodium nitrite and hydrochloric acid yielded an oil, which was extracted with ether and treated with *p*-nitrobenzoyl chloride. A crystalline *p*-nitrobenzoate, m. p. 113—116°, was formed, identical with that obtained from the hydroxy-lactone (VII; X = OH) (*q.v.*).

3-(β-*Methylaminoethyl*)-3-*phenyl*-2-*pyrrolidone* (IX; R = Me).—A mixture of the pyrrolidone (IX; R = H) (0·5 g.), methyl iodide (0·4 g.), and sodium carbonate (0·15 g.) in alcohol (3 ml.) was refluxed for 5 minutes. The residue, after removal of the volatile constituents, was made strongly alkaline and extracted with chloroform. The oily extract formed a *hydrochloride*, which crystallised from alcohol–ether in feathery needles, m. p. 177—178° (Found : C, 61·3; H, 7·5; N, 10·6; Cl, 14·1. $C_{13}H_{18}ON_2$,HCl requires C, 61·3; H, 7·5; N, 11·0; Cl, 14·0%).

Methyl and Ethyl 4-*Phenyl*-1-*methylpiperidine*-4-*carboxylates* (V; R = Me and Et, R′ = Me).—The methyl ester (IV; R = Me) (10 g.) and 27% w/v methyl-alcoholic methylamine (50 ml.) were heated in a sealed tube at 120—130° for 3 hours. The methyl alcohol was removed, and the residue made strongly alkaline with caustic soda and extracted with ether. The extract on distillation gave a lower fraction, b. p. 185—210°/16 mm., which, on treatment with hydrochloric acid, yielded methyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride, crystallising from acetone in prisms (1 g.), m. p. 201—202°, identical with that obtained by Eisleb's method (B.P. 501,135).

The corresponding ethyl ester (pethidine) was obtained in a similar manner but in better yield as a lower fraction, b. p. 175—180°/14 mm. (cf. Bergel *et al.*, *loc. cit.*).

4-*Phenyl*-1-*methylpiperidine*-4-*carboxyamide* was prepared from the corresponding acid chloride by established methods (B.P. 501,135) for comparison with the isomeric 3-(β-methylaminoethyl)-3-phenyl-2-pyrrolidone (*q.v.*). The amide crystallised from water in needles, m. p. 125° (Found : C, 71·4; H, 8·3; N, 12·2. $C_{13}H_{18}ON_2$ requires C, 71·6; H, 8·3; N, 12·8%). The hydrochloride had m. p. 247° (Found : C, 60·9; H, 7·4; N, 10·9; Cl, 14·0. Calc. for $C_{13}H_{18}ON_2$,HCl : C, 61·3; H, 7·5; N, 11·0; Cl, 14·0%).

Ethyl 4-*Phenyl*-1-*ethylpiperidine*-4-*carboxylate* (V; R = R′ = Et).—The dibromo-ethyl ester (IV; R = Et) (12 g.) and 28% w/v ethyl-alcoholic ethylamine (45 ml.) were heated under pressure for 3 hours at 90—95°. The ethereal extract, obtained as described above for the methyl ester, gave a first fraction, b. p. 182—195°/15 mm., which yielded a *hydrochloride*, very soluble in water but crystallising from alcohol–ether in octagonal plates, m. p. 171° (Found : C, 64·5; H, 7·8; N, 5·1; Cl, 12·4. $C_{16}H_{23}O_2N$,HCl requires C, 64·6; H, 8·1; N, 4·7; Cl, 11·9%).

Ethyl 4-*Phenyl*-1-n-*propylpiperidine*-4-*carboxylate* (V; R = Et, R′ = *n*-C_3H_7).—The ethyl ester (IV; R = Et) (5 g.) and *n*-propylamine (8 ml.), warmed under reflux for 2 hours and worked up as previously described, gave a fraction (2 g.), b. p. 190—203°/20 mm., which formed a *hydrochloride* crystallising from alcohol–ether in hexagonal prisms, m. p. 196° (Found : C, 65·5; H, 8·2; N, 4·8; Cl, 11·4. $C_{17}H_{25}O_2N$,HCl requires C, 65·5; H, 8·4; N, 4·5; Cl, 11·4%).

Ethyl 4-*Phenyl*-1-n-*butylpiperidine*-4-*carboxylate* (V; R = Et, R′ = *n*-C_4H_9).—The same ester (10 g.) and *n*-butylamine (10 g.), refluxed for 3 hours and worked up as described above, gave a fraction (1·8 g.), b. p. 225—230°/13 mm., which was only partly soluble in acid. The base was therefore extracted with hydrochloric acid and, after being washed with ether, the aqueous solution was evaporated. The resulting *hydrochloride* crystallised from alcohol–ether in prisms, m. p. 183° (Found : N, 4·4; Cl, 10·9. $C_{18}H_{27}O_2N$,HCl requires N, 4·3; Cl, 10·9%).

Ethyl 4-*Phenyl*-1-*benzylpiperidine*-4-*carboxylate* (V; R = Et, R′ = C_7H_7).—The ester (IV) (10 g.) and benzylamine (20 g.) gave the hydrochloride, m. p. 242°, as square leaflets from water (Found : Cl, 9·9. Calc. for $C_{21}H_{25}ON_2$,HCl : Cl, 9·9%) (cf. Eisleb, *loc. cit.*).

α-(β′-Aminoethyl)-α-phenylbutyrolactone (VIII; R = R′ = H) *and* 3-(β-*Hydroxyethyl*)-3-*phenyl*-2-*pyrrolidone* (VI; R = H).—The bromo-lactone (VII; X = Br) (10 g.) and saturated ethyl-alcoholic ammonia (40 ml.) were heated under pressure for 3 hours at 90—95°. After removal of alcohol, the residue was treated with water (90 ml.) and dilute hydrochloric acid until just blue to Congo-paper, and left overnight. The resulting solid, consisting of 3-(β-*hydroxyethyl*)-3-*phenyl*-2-*pyrrolidone*, crystallised from water in needles (4·3 g.), m. p. 85—90°, containing water of crystallisation, and from benzene in hexagonal leaflets, m. p. 111—112° (Found : C, 70·2; H, 7·3; N, 7·1. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3; N, 6·8%). The pyrrolidone was insoluble in dilute hydrochloric acid, but with concentrated acid it formed *α-(β′-aminoethyl)-α-phenylbutyrolactone hydrochloride*, which crystallised from alcohol–ether in needles, m. p. indefinite (75—150°) (Found : C, 55·7; H, 6·9; N, 5·4; Cl, 13·8. $C_{12}H_{15}O_2N$,HCl,H_2O requires C, 55·5; H, 6·9; N, 5·4; Cl, 13·7%). The hydrochloride was very soluble in water, forming a stable neutral solution, but with alkali it reverted to the pyrrolidone.

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* Attempts to isolate the free acid were unsuccessful, as the oil, on acidification, although at first soluble in alkali, rapidly became insoluble during extraction, etc.

α-(β′-Methylaminoethyl)-α-phenylbutyrolactone (VIII; R = H, R′ = Me).—The bromo-lactone (5 g.) and 27% methyl-alcoholic methylamine (20 ml.) were heated under pressure at 90—95° for 3 hours. The alcohol-free residue was made strongly alkaline and extracted with ether. In this way, the methylamino-lactone was obtained as an oil, b. p. 225—240°/17 mm. (slight decomp.). The methylamino-lactone was also obtained as a second fraction in the preparation of (V; R = Me or Et, R′ = Me) (*q.v.*). Its *hydrochloride* crystallised from alcohol–ether in hexagonal prisms, m. p. 178° (Found: C, 61·1; H, 6·9; N, 5·5; Cl, 14·2. $C_{13}H_{17}O_2N$,HCl requires C, 61·1; H, 7·0; N, 5·5; Cl, 13·9%). Heated with *p*-nitrobenzoyl chloride at 150—200° for 1 minute, the hydrochloride gave a p-*nitrobenzamido*-derivative, which crystallised from alcohol in prisms, m. p. 151° (Found: C, 65·0; H, 5·5; N, 7·8. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·4; N, 7·6%). On the other hand, when heated alone up to 280°, it evolved hydrogen chloride, leaving a residual oil, which failed to solidify. The oil, probably 3-phenyl-1-methyl-3-(β-hydroxyethyl)-2-pyrrolidone (VI; R = Me), dissolved in concentrated hydrochloric acid, but reappeared on dilution. It formed a p-*nitrobenzoate* crystallising from alcohol in rectangular plates, m. p. 110—112° (Found: C, 65·2; H, 5·6; N, 7·8. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·4; N, 7·6%).

α-(β′-Ethylaminoethyl)-α-phenylbutyrolactone (VIII; R = H, R′ = Et).—The bromolactone (5 g.) and 28% ethyl-alcoholic ethylamine (20 ml.), worked up as described in the previous example, yielded the ethylamino-lactone as an oily base, which was also obtained as a residual oil in the preparation of (V; R = R′ = Et) (*q.v.*). On heating under reflux at normal pressure for 10—15 minutes, it showed signs of changing into the corresponding lactam of type (VI). The crude base formed a *hydrochloride*, which crystallised from alcohol–ether in rectangular plates (1·9 g.), m. p. 194° (Found: C, 62·3; H, 7·1; N, 5·3; Cl, 13·5. $C_{14}H_{19}O_2N$,HCl requires C, 62·3; H, 7·4; N, 5·2; Cl, 13·2%).

*α-(β′-*n*-Propylaminoethyl)-α-phenylbutyrolactone* (VIII; R = H, R′ = *n*-C_3H_7) *and 3-Phenyl-3-(β-hydroxyethyl)-1-*n*-propyl-2-pyrrolidone* (VI; R = *n*-C_3H_7).—A mixture of the bromo-lactone (5 g.) and *n*-propylamine (10 g.) was left for 12 hours and then refluxed for 2 hours. After removal of the excess of *n*-propylamine, the mixture was made alkaline to indigo-carmine and extracted with ether. The ether-free extract was dissolved in concentrated hydrochloric acid, the solution evaporated to dryness to remove excess of acid, and again treated with water; it then only partly redissolved. The resulting water–oil mixture was extracted with ether to give an aqueous portion (A), and an ethereal extract (B). The portion (A), on repeated evaporation with alcohol, eventually yielded the *hydrochloride* of α-(β′-*n*-propylaminoethyl)-α-phenylbutyrolactone as a solid, which crystallised from alcohol–ether in needles (0·2 g.), m. p. 167—168° (Found: C, 63·5; H, 7·7; N, 5·1; Cl, 12·5. $C_{15}H_{21}O_2N$,HCl requires C, 63·5; H, 7·8; N, 4·9; Cl, 12·5%). The extract (B) was dried and distilled in a vacuum. The first fraction up to 220° contained diminishing traces of halogen and became increasingly soluble in concentrated hydrochloric acid. The second fraction, b. p. 228—230°/11 mm., was a colourless halogen-free syrup, consisting of *3-phenyl-3-(β-hydroxyethyl)-1-*n*-propyl-2-pyrrolidone* (Found: C, 72·3; H, 8·4; N, 6·1. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5; N, 6·1%). It dissolved readily in cold concentrated hydrochloric acid, but reappeared as an oil on dilution.

α-(β′-Diethylaminoethyl)-α-phenylbutyrolactone (VIII; R = R′ = Et).—The bromo-lactone (7 g.), diethylamine (10 ml.), and alcohol (10 ml.), heated under pressure at 90—95° for 4 hours and worked up in the usual manner, yielded *α-(β′-diethylaminoethyl)-α-phenylbutyrolactone* as an oily base, b. p. 214—220°/17 mm. (Found: C, 73·5; H, 8·8; N, 5·4. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%). The *hydrochloride* was obtained as an uncrystallisable syrup (Found: Cl, 11·9. $C_{16}H_{23}O_2N$,HCl requires Cl, 11·9%). Attempts to prepare it in crystalline form by passing dry hydrogen chloride into an ethereal solution of the base were unsuccessful.

α-(β′-Piperidinoethyl)-α-phenylbutyrolactone (VIII; RR′ = C_5H_{10}).—A mixture of the bromo-lactone (3 g.) and piperidine (3 g.), refluxed for 3 minutes and then worked up in the usual way, gave the hydrochloride, which crystallised from alcohol–ether in rhombs, m. p. 216—218° (Found: C, 66·1; H, 7·4; N, 5·0; Cl, 11·5. Calc. for $C_{17}H_{23}O_2N$,HCl: C, 65·9; H, 7·7; N, 4·5; Cl, 11·5%).

α-(β′-Methylanilinoethyl)-α-phenylbutyrolactone (VIII; R = Me, R′ = Ph).—The bromo-lactone (5 g.) and methylaniline (10 ml.) were refluxed for 3 hours and then steam-distilled to remove excess of methylaniline. The residue was basified, and the ethereal extract again steam-distilled to remove the remaining traces of methylaniline. The residual oil was now strongly acidified with hydrochloric acid—most of the oil dissolved—cleaned with ether, and the aqueous layer evaporated to dryness. The residual gum solidified on treatment with alcohol–ether to *α-(β′-methylanilinoethyl)-α-phenylbutyrolactone hydrochloride*, which crystallised from the same solvents in hexagonal prisms (2·4 g.), m. p. 160—165° (Found: N, 4·5; Cl, 10·4. $C_{19}H_{21}O_2N$,HCl requires N, 4·2; Cl, 10·7%). The hydrochloride was soluble in water in high concentration, giving an acid solution, but on dilution the base was liberated as an oil.

α-(β′-Benzylmethylaminoethyl)-α-phenylbutyrolactone (VIII; R = Me, R′ = CH_2Ph).—The bromo-lactone (2 g.) and benzylmethylamine (3 ml.) were heated together for 2—3 minutes, the internal temperature being allowed to rise to 195°. After cooling, the mixture was made alkaline to indigo-carmine, and the ethereal extract treated with sodium sulphate and bicarbonate to remove caustic alkali. The residue was then repeatedly evaporated with water in a vacuum in an attempt to remove traces of benzylmethylamine. After several experiments, the following method of working up was found to give the best results: The oil was redissolved in ether and fractionally extracted with small quantities of dilute hydrochloric acid. The first acid extraction (alkaline reaction) gave hydrochloride, m. p. 115—155°. The second acid extraction (still alkaline) gave crude benzylmethylamine hydrochloride, m. p. 170—176°. The third extraction (approaching neutrality) yielded a similar product. The fourth extraction, however, a very slight excess of dilute hydrochloric acid being used, gave crude *α-(β′-benzylmethylaminoethyl)-α-phenylbutyrolactone hydrochloride* (1·6 g.), which crystallised from alcohol–ether in minute rectangular prisms, m. p. 165—166° (Found: C, 69·2; H, 7·0; N, 4·3; Cl, 10·5. $C_{20}H_{23}O_2N$,HCl requires C, 69·5; H, 7·0; N, 4·1; Cl, 10·3%). The hydrochloride was very soluble in water, giving neutral solutions. Careful addition of a little concentrated hydrochloric acid threw out the hydrochloride as an oil, but it redissolved on further addition of this acid.

*3-Phenyl-3-(β-hydroxyethyl)-1-*n*-butyl-2-pyrrolidone* (VI; R = *n*-C_4H_9).—The bromo-lactone (10 g.) and *n*-butylamine (10 g.) were heated together on the steam-bath for 3 hours. The product was made strongly alkaline and extracted with ether. The extract was dried and evaporated, and the residue dissolved in concentrated hydrochloric acid. The resulting solution, on dilution with water, gave an oil, which on extraction and distillation yielded the *pyrrolidone* (2·5 g.) as a fraction, b. p. 234—236°/12 mm. (Found: C, 73·7; H, 8·8; N, 5·4. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%). In properties it resembled its propyl analogue (*q.v.*).

1 : *3-Diphenyl-3-(β-hydroxyethyl)-2-pyrrolidone* (VI; R = Ph).—The bromo-lactone (3 g.) was boiled with an excess of aniline for 3 minutes. Dilute hydrochloric acid was added to remove aniline, and the remaining oil cooled and scratched until it solidified. Crystallised from benzene–petrol, it gave the *pyrrolidone* in octagonal tablets (2·3 g.), m. p. 100—101° (Found: C, 77·0; H, 6·8; N, 5·4. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%). The pyrrolidone dissolved in warm concentrated hydrochloric acid, but separated unchanged on cooling. There was no reaction with methyl iodide. Its p-*nitrobenzoate* crystallised from alcohol in hexagonal prisms, m. p. 136—137° (Found: C, 69·7; H, 5·0; N, 6·5. $C_{25}H_{22}O_5N_2$ requires C, 69·7; H, 5·1; N, 6·5%).

*3-Phenyl-1-*cyclo*hexyl-3-(β-hydroxyethyl)-2-pyrrolidone* (VI; R = C_6H_{11}), obtained by similar methods from the bromo-lactone and *cyclo*hexylamine, crystallised from benzene–petrol in minute tablets, m. p. 61°, which dissolved in cold concentrated hydrochloric acid, but came out on dilution (Found: C, 75·5; H, 9·0; N, 5·1. $C_{18}H_{25}O_2N$ requires C, 75·3; H, 8·8; N, 4·9%).

3-*Phenyl*-1-*benzyl*-3-(β-*hydroxyethyl*)-2-*pyrrolidone* (VI; $R = C_7H_7$), obtained from the bromo-lactone and benzylamine (spontaneous reaction above 90°), crystallised from benzene–petrol in small needles, m. p. 123—124° (Found: C, 77·3; H, 7·2; N, 5·0. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·1; N, 4·7%).

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