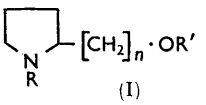
116. *Pharmacodynamic Compounds. Part III.* Antitussives derived from 1-Alkylpyrrolidinyl and 1-Alkylpiperidyl Alcohols.*

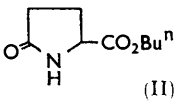
By F. P. Doyle, M. D. Mehta, G. S. Sach, R. Ward, and (in part) P. S. Sherman.

α-Alkoxy-αα-diphenylacetic and α-cyclohexyl-α-methoxy-α-phenylacetic acids have been esterified with various 1-alkylpyrrolidinyl- and 1-alkylpiperidyl-alkanols, to give compounds having antitussive activity.

The effect of replacing the hydroxy-group in pharmacodynamically active dialkylaminoalkyl αα-diphenylglycollates by alkoxyl has been investigated by several workers,[1] but little attention has hitherto been paid to similar structural changes in the esters of cyclic amino-alcohols. In a previous paper[2] we described αα-diphenylglycollates and other esters of several 1-alkyl-2-pyrrolidinyl alcohols, some of which exhibited spasmolytic activity.[3] We now report the synthesis of α-alkoxy-αα-diphenylacetates and α-cyclohexyl-α-methoxy-α-phenylacetates of various 1-alkylpyrrolidinyl- and 1-alkylpiperidyl-alkanols.



(I)



(II)

The three 1-alkyl-2-hydroxymethylpyrrolidines (I; R = Et, Pr^n, Bu^n, R′ = H; $n = 1$) were prepared by acylation of 2-hydroxymethylpyrrolidine[2] with the appropriate acid anhydride, followed by reduction of the *ON*-diacyl derivative with lithium aluminium hydride, but 2-hydroxymethyl-1-isopropylpyrrolidine (I; R = Pr^i, R′ = H; $n = 1$) was obtained by alkylation of the potassium derivative of butyl 5-oxopyrrolidine-2-carboxylate[2] (II) with isopropyl iodide followed by reduction.

1-Ethyl-4-hydroxypiperidine was prepared by a modification of the general method of McElvain and Rorig.[4] The 1-ethyl-2-, -3-, and -4-hydroxymethylpiperidine were prepared by the hydrogenation of the appropriate ethyl pyridinecarboxylates to yield the corresponding piperidyl esters, which were acylated with acetic anhydride and then reduced with lithium aluminium hydride.

Many of the esters were made by transesterification of alkyl α-alkoxy-αα-diphenylacetates with basic alcohols. In other cases the alkoxy-substituent was introduced last, by heating α-halogeno-αα-diphenylacetic ester hydrochlorides under reflux with anhydrous methanol, ethanol, etc. The latter method could not be used for the preparation of α-cyclohexyl-α-methoxyphenylacetates. When α-cyclohexyl-α-phenylglycollic acid was treated with phosphorus pentachloride some dehydrohalogenation occurred during distillation of the product, as suggested by Smith *et al.*[5] If crude undistilled α-chloro-α-cyclohexyl-α-phenylacetyl chloride was heated under reflux with methanol and then hydrolysed with alkali, a mixture was obtained from which α-cyclohexyl-α-methoxy-α-phenylacetic acid was isolated as its water-insoluble sodium salt. The other components of the mixture were α-cyclohexyl-α-phenylglycollic acid and gummy unsaturated material. Evidently the α-chlorine atom is less readily replaced than that present in α-chloro-αα-diphenylacetyl chloride. More forcing conditions, such as heating the acid chloride with

* Part II, *J.*, 1961, 633.

[1] Klosa, *Arch. Pharm.*, 1954, **287**, 321; 1955, **288**, 42; Boehringer Sohn, B.P. 716,700/1951; Gilman, *J. Pharmacol.*, 1942, **74**, 290; Hirt, *Helv. Chim. Acta*, 1949, **32**, 87; Büchi, Lauerner, Meyer, and Lieberherr, *ibid.*, 1951, **34**, 373; Blicke and Biel, *J. Amer. Chem. Soc.*, 1954, **76**, 3161; Wander A.-G., B.P. 641,571/1950.

[2] Doyle, Mehta, Sach, and Pearson, *J.*, 1958, 4458.

[3] Acred, Atkins, Bainbridge, Brown, Quinton, and Turner, *Brit. J. Pharmacol.*, 1957, **12**, 447.

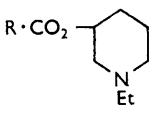
[4] McElvain and Rorig, *J. Amer. Chem. Soc.*, 1948, **70**, 1820.

[5] Smith, Buehler, Magee, Nayak, and Glenn, *J. Org. Chem.*, 1959, **24**, 1301.

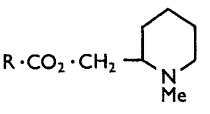
methanol under pressure, favoured the elimination. Repeated treatment of methyl α-cyclohexyl-α-phenylglycollate with methyl iodide and silver oxide failed to methylate the hydroxyl group. Reaction of α-cyclohexyl-α-methoxy-α-phenylacetic acid with diazomethane yielded the methyl ester, which was used in transesterifications.

Two esters in which the oxygen of the alkoxy-group was replaced by sulphur were prepared by the transesterification of methyl α-ethylthio-αα-diphenylacetate with 1-alkyl-2-hydroxymethylpyrrolidines.

Although the ester (I; R = Et, R′ = MeO·CPh$_2$·CO; n = 1) was recovered unchanged on rapid distillation at 0·1 mm., it rearranged completely to the piperidyl isomer (III) when heating at 200° for 2 hr., as shown by comparison with an authentic sample and by reduction of the product with lithium aluminium hydride to 1-ethyl-3-hydroxypiperidine. To avoid this thermal isomerisation of the pyrrolidinyl esters to the corresponding piperidyl ones,[6] they were converted into solid derivatives without prior distillation. There was shown no thermal rearrangement to the corresponding piperidyl isomer when 2-hydroxymethylpyrrolidine was heated under reflux with butyric anhydride, since an identical product was obtained by treatment with butyryl chloride under mild conditions. To find if the scope of the rearrangement could be extended, 2-(α-methoxy-αα-diphenylacetoxymethyl)-1-methylpiperidine (IV) was heated at 200° for 4 hours, but ring expansion to the azacycloheptane (V) did not take place.



(III)



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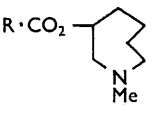


(V)

[R = MeO·CPh$_2$]

Three of the esters, 1-ethyl-2-(α-methoxy-αα-diphenylacetoxymethyl)pyrrolidine, its piperidyl isomer (III), and 3-(α-methoxy-αα-diphenylacetoxymethyl)-1-methylpyrrolidine were resolved into their optical isomers by using (+)-tartaric acid. An attempt was also made to obtain an enantiomorph of the first of these by esterifying 1-ethyl-2-hydroxymethylpyrrolidine which had been prepared from L-glutamic acid through the 5-oxopyrrolidine (II), with subsequent alkylation and reduction. Partial racemisation must have occurred, since the product had a lower specific rotation than that of the corresponding enantiomorph resulting from resolution of the racemic compound.

The pharmacological properties of the new compounds have been investigated by Mr. D. M. Brown and his colleagues of these laboratories, who found that the acid addition salts of the alkoxy-esters possess much less atropine-like activity than the corresponding glycollates, but that some of them have high antitussive activity, which is reduced by quaternisation. The optical isomers show no improvement in activity over the racemic compounds.

Experimental

Infrared absorption spectra were determined by using a Grubb-Parsons double-beam spectrometer. The specimens were examined as ~3% solutions in carbon tetrachloride or in cyclohexane.

1-Methyl-2-hydroxymethylpyrrolidine,[7] 1-alkyl-2-2′-hydroxyethylpyrrolidines [2] (I; R = Me or Et, R′ = H; n = 2), 1-methyl- and 1-ethyl-3-hydroxymethylpyrrolidine,[8] 1-methyl- and 1-ethyl-3-hydroxypyrrolidine,[9] 1-methyl- and 1-ethyl-3-hydroxypiperidine,[7] and 2-, 3-, and 4-hydroxymethyl-1-methylpiperidine [10] were prepared by known methods.

Butyl 1-Isopropyl-5-oxopyrrolidine-2-carboxylate.—A solution of butyl 5-oxopyrrolidine-2-carboxylate [2] (25 g.) in dry benzene (50 ml.) was added to a stirred suspension of " molecular potassium " (5·3 g.) in benzene (50 ml.). After the mixture had been heated under reflux for

[6] Brain, Doyle, and Mehta, *J.*, 1961, 633; Biel, Abood, and Hoya, Abs. Papers, 138th Meeting Amer. Chem. Soc., 1960, p. 19-O; Biel, *Chem. Eng. News*, 1960, **38**, No. 38, p. 50.
[7] Soulal, B.P. 820,503/1959.
[8] Wu and Feldkamp, *J. Org. Chem.*, 1961, **26**, 1519.
[9] Lunsford, U.S.P. 2,830,997/1958.
[10] Feldkamp, Faust, and Cushman, *J. Amer. Chem. Soc.*, 1952, **74**, 3831.

1 hr., isopropyl iodide (23 g.) in benzene was added and heating was continued for a further 1 hr. The mixture was cooled, washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residual liquid gave *butyl 1-isopropyl-5-oxopyrrolidine-2-carboxylate* (10·4 g., 40%), b. p. 116—117°/0·05 mm., n_D^{19} 1·4621 (Found: C, 62·9; H, 9·25; N, 6·5. $C_{12}H_{21}NO_3$ requires C, 63·4; H, 9·3; N, 6·2%).

1-Ethyl-4-oxopiperidine.—Treatment of diethyl *N*-ethyl-ββ′-iminodipropionate [11] with sodium hydride in benzene by the method given by McElvain and Rorig [4] for the *N*-methyl homologue yielded *ethyl 1-ethyl-4-oxopiperidine-3-carboxylate hydrochloride* (70%) plates (from ethanol), m. p. 140—141° (Found: C, 51·05; H, 7·8; N, 5·85; Cl, 15·1. $C_{10}H_{18}ClNO_3$ requires C, 51·0; H, 7·7; N, 5·9; Cl, 15·0%). The oxopiperidine (68 g.) was heated under reflux with 5N-hydrochloric acid (276 ml.) until the solution no longer gave a red colour with ferric chloride. After the solution had been concentrated to a small volume *in vacuo*, it was neutralised with potassium hydroxide pellets, then extracted with ether continuously for 24 hr. The ether extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled to yield 1-ethyl-4-oxopiperidine (14·2 g., 39%), b. p. 76—80°/33 mm., n_D^{20} 1·4625 [*2,4-dinitrophenylhydrazone hydrochloride*, needles (from ethanol), m. p. 216° (Found: C, 45·3; H, 5·3; Cl, 10·45; N, 19·9. $C_{13}H_{18}ClN_5O_4$ requires C, 45·4; H, 5·3; Cl, 10·3; N, 20·4%)].

Hydrogenation of Ethyl Pyridinecarboxylates.—Ethyl pyridine-2-carboxylate (65 g.) was hydrogenated in acetic acid (100 ml.) and water (50 ml.) over platinum oxide (3·2 g.). The catalyst was filtered off and washed with water, and the filtrates were saturated with anhydrous potassium carbonate, then extracted continuously with ether for 24 hr. The ether extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled, to give ethyl piperidine-2-carboxylate (49 g., 73%), b. p. 91—93°/9 mm., n_D^{20} 1·4565 (lit.,[12] b. p. 93—94°/11 mm., n_D^{25} 1·4547) [*picrate* m. p. 114—116° (Found: C, 43·7; H, 4·6; N, 14·3. $C_{14}H_{18}N_4O_9$ requires C, 43·5; H, 4·7; N, 14·5%)].

Similarly were prepared: ethyl piperidine-3-carboxylate (78%), b. p. 116—120°/23 mm., n_D^{20} 1·4610 (lit.,[13] b. p. 102—104°/7 mm., n_D^{19} 1·4592) [*picrate*, m. p. 121—122° (Found: C, 43·25; H, 4·75; N, 14·6. $C_{14}H_{18}N_4O_9$ requires C, 43·5; H, 4·7; N, 14·5%)], and -4-carboxylate (55%), b. p. 120—122°/28 mm., n_D^{21} 1·4615 (picrate, m. p. 177—178°) (lit.,[14] b. p. 100—101°/10 mm.; picrate, m. p. 177—178°).

N-Acylation of Pyrrolidines and Piperidines.—2-Hydroxymethylpyrrolidine [2] was heated under reflux for 1·5 hr. with an excess of the appropriate acid anhydride and then distilled to give:

2-Acetoxymethyl-1-acetylpyrrolidine (83%), needles (from light petroleum), m. p. 52—53° (Found: C, 58·6; H, 8·25; N, 7·2. $C_9H_{15}NO_3$ requires C, 58·4; H, 8·1; N, 7·6%).

1-Propionyl-2-propionyloxymethylpyrrolidine (71%), b. p. 112—114°/0·1 mm., n_D^{20} 1·4720 (Found: C, 61·8; H, 8·8; N, 6·9. $C_{11}H_{19}NO_3$ requires C, 62·0; H, 8·9; N, 6·6%).

1-Butyryl-2-butyryloxymethylpyrrolidine (87%), b. p. 113°/0·05 mm., n_D^{24} 1·4672 (Found: C, 64·1; H, 9·2; N, 6·2. $C_{13}H_{23}NO_3$ requires C, 64·7; H, 9·6; N, 5·8%).

Similarly, treatment of the ethyl piperidinecarboxylates with acetic anhydride yielded *ethyl 1-acetylpiperidine-2-* (69%), b. p. 94—95°/0·06 mm., n_D^{20} 1·4731 (Found: C, 60·3; H, 8·5; N, 6·8. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%), *-3-carboxylate* (83%), b. p. 120°/1 mm., n_D^{22} 1·4780 (Found: C, 60·5; H, 8·9; N, 7·0%), and *-4-carboxylate* (89%), b. p. 103—104°/0·01 mm., n_D^{23} 1·4790 (Found: C, 60·2; H, 8·95; N, 7·2%).

Preparation of Basic Alcohols.—The following compounds were prepared by the reduction of a suitable intermediate with lithium aluminium hydride in ether, as previously described: [2]

1-Ethyl-2-hydroxymethylpyrrolidine (83% yield from 2-acetoxymethyl-1-acetylpyrrolidine), b. p. 68—70°/12 mm., n_D^{20} 1·4691 (lit.,[15] b. p. 82—84°/24 mm., n_D^{25} 1·4662 for the alkanol prepared by hydrogenation of diethyl pyrrolidine-1,2-dicarboxylate).

2-Hydroxymethyl-1-propylpyrrolidine (41% yield from 1-propionyl-2-propionyloxymethylpyrrolidine), b. p. 44°/0·05 mm., n_D^{22} 1·4659 (analysis was unsatisfactory).

2-Hydroxymethyl-1-isopropylpyrrolidine (40% yield from butyl 1-isopropyl-5-oxopyrrolidine-2-carboxylate), b. p. 54—56°/0·2 mm., n_D^{21} 1·4721 (lit.,[7] b. p. 94—98°/17 mm.).

[11] Fuson, Parham, and Reed, *J. Amer. Chem. Soc.*, 1946, **68**, 1239.
[12] Singer and McElvain, *J. Amer. Chem. Soc.*, 1935, **57**, 1135.
[13] McElvain and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2745.
[14] Grob and Renk, *Helv. Chim. Acta*, 1954, **37**, 1672.
[15] Signaigo and Adams, *J. Amer. Chem. Soc.*, 1936, **58**, 709.

1-*Butyl*-2-*hydroxymethylpyrrolidine* (87% yield from 1-butyryl-2-butyryloxymethylpyrrolidine), b. p. 63—64°/0·6 mm., n_D^{23} 1·4638 (Found: C, 68·7; H, 12·6; N, 9·0. $C_9H_{19}NO$ requires C, 68·8; H, 12·1; N, 8·9%).

1-Ethyl-4-hydroxypiperidine (69% yield from 1-ethyl-4-oxopiperidine), b. p. 101°/12 mm., n_D^{20} 1·4810 (lit.,[16] b. p. 105—110°/15 mm., n_D^{33} 1·4769) [*picrate* yellow needles (from propan-2-ol), m. p. 109·5—112° (Found: C, 43·8; H, 5·0; N, 15·5. $C_{13}H_{18}N_4O_8$ requires C, 43·55; H, 5·1; N, 15·6%)].

1-Ethyl-2-hydroxymethylpiperidine (80% yield from ethyl 1-acetylpiperidine-2-carboxylate), b. p. 92—93°/10 mm., n_D^{20} 1·4842 (lit.,[17] b. p. 102°/16 mm., n_D^{23} 1·4834) [*benzoate hydrochloride* prisms (from ethyl methyl ketone), m. p. 158—160° (Found: C, 63·6; H, 7·9; Cl, 12·6. $C_{15}H_{22}ClNO_2$ requires C, 63·5; H, 7·8; Cl, 12·5%)].

1-Ethyl-3-hydroxymethylpiperidine (68% yield from ethyl 1-acetylpiperidine-3-carboxylate), b. p. 120—125°/17 mm., n_D^{20} 1·4808 (lit.,[18] b. p. 115—116°/10 mm.) [*benzoate hydrochloride* needles (from ethyl methyl ketone), m. p. 182—184° (Found: C, 63·8; H, 7·85; Cl, 12·7%)].

1-Ethyl-4-hydroxymethylpiperidine (78% yield from ethyl 1-acetylpiperidine-4-carboxylate), b. p. 120°/15 mm., n_D^{20} 1·4790 (lit.,[19] b. p. 90—92°/0·15 mm.) [benzoate, isolated as the *hydrogen* (+)-*tartrate*, prisms (from propan-2-ol), m. p. 118—120° (Found: C, 57·4; H, 7·0. $C_{19}H_{27}NO_8$ requires C, 57·4; H, 6·85%)].

Preparation of Glycollates.—The crude α-chloro-αα-diphenylacetate hydrochloride (4 g.) obtained by treating 1-ethyl-2-hydroxymethylpyrrolidine (1·1 g.) with α-chloro-αα-diphenylacetyl chloride (3·6 g.) as in the method of King and Holmes,[20] was dissolved in water (*ca.* 80 ml.) and set aside for 1 hr. at room temperature, and the solution was saturated with sodium chloride (*ca.* 30 g.) and then extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and distilled to leave a gum, which on crystallisation from ethyl acetate yielded 2-(αα-*diphenylglycolloyloxymethyl*)-1-*ethylpyrrolidine hydrochloride* (1·8 g., 46%) as needles, m. p. 144—145° (Found: C, 67·2; H, 7·0; Cl, 9·5. $C_{21}H_{26}ClNO_3$ requires C, 67·1; H, 7·0; Cl, 9·4%) [*ethiodide*, prisms (from ethanol), m. p. 174° (Found: C, 55·7; H, 6·5; I, 25·8. $C_{23}H_{30}INO_3$ requires C, 55·7; H, 6·1; I, 25·6%)]. In a similar way the following αα-diphenylglycollates were isolated:

2-(αα-*Diphenylglycolloyloxymethyl*)-1-*propylpyrrolidine hydrochloride* (73%) (from ethyl methyl ketone), m. p. 159—160° (Found: C, 67·8; H, 7·2; Cl, 9·1. $C_{22}H_{28}ClNO_3$ requires C, 67·7; H, 7·2; Cl, 9·1%).

2-(αα-*Diphenylglycolloyloxymethyl*)-1-*isopropylpyrrolidine hydrochloride* (15%), needles (from ethyl methyl ketone), m. p. 165—166° (Found: C, 67·5; H, 7·1; Cl, 9·2%).

1-*Butyl*-2-(αα-*diphenylglycolloyloxymethyl*)*pyrrolidine hydrochloride* (68%), needles (from ethyl methyl ketone), m. p. 171—172° (Found: C, 68·3; H, 7·2; Cl, 8·8. $C_{23}H_{30}ClNO_3$ requires C, 68·4; H, 7·5; Cl, 8·8%).

Preparation of α-Alkoxy-αα-diphenylacetates.—*Method* (A). The basic alcohol was treated with α-chloro-αα-diphenylacetyl chloride in ethyl methyl ketone, and the resulting α-chloro-αα-diphenylacetate hydrochloride was heated under reflux with the appropriate anhydrous alkanol for 16 hr. Distillation of the excess of alkanol left a gum which crystallised.

Method (B). The following example is typical. A solution of 2-(αα-diphenylglycolloyloxymethyl)-1-ethylpyrrolidine hydrochloride (3·7 g.) in chloroform (50 ml.) was saturated with hydrogen bromide at 0°. After 24 hr. the solvent was removed *in vacuo* and the residual gum was crystallised from acetone, to give 2-(α-*bromo*-αα-*diphenylacetoxymethyl*)-1-*ethylpyrrolidine hydrobromide* (3·8 g., 86%) as prisms, m. p. 135—136° (Found: C, 51·9; H, 5·5; Br, 32·25. $C_{21}H_{25}Br_2NO_2$ requires C, 52·2; H, 5·2; Br, 33·05%). Treatment of this compound with methanol as in method (A) yielded 1-*ethyl*-2-(α-*methoxy*-αα-*diphenylacetoxymethyl*)*pyrrolidine hydrobromide* (No. 13, Table 1).

Method (C). Alkyl α-alkoxy-αα-diphenylacetates [21] were transesterified with the appropriate

[16] Coan, Jaffa, and Pappa, *J. Amer. Chem. Soc.*, 1956, **78**, 3701.
[17] Shen, Rogers, and Sarett, U.S.P. 3,031,452/1962.
[18] Kallischnigg and Krastinat, G.P. 1,032,252/1958.
[19] Shapiro, Soloway, Shapiro, and Freedman, *J. Org. Chem.*, 1960, **25**, 291.
[20] King and Holmes, *J.*, 1947, 164.
[21] (*a*) Klinger, *Annalen*, 1912, **390**, 371; (*b*) Brain, Doyle, Hardy, Long, Mehta, Miller, Nayler, Soulal, Stove, and Thomas, *J.*, 1962, 1445.

basic alcohol as in the following example. To a boiling solution of 3-hydroxy-1-methylpiperidine (8 g.) and ethyl α-ethoxy-αα-diphenylacetate (13·3 g.) in heptane (150 ml.), a solution of sodium (0·13 g.) in ethanol (3 ml.) was added dropwise in 15 min. and the ethanol–heptane azeotrope was distilled through a Dufton column (10″) fitted with a reflux head. More heptane was added at approximately the same rate as it was removed. After 2·5 hr. the reaction mixture was cooled, washed with water to remove any alcohol, then extracted with N-hydrochloric acid (3 × 50 ml.). Neutralisation of the extracts with sodium hydroxide liberated an oil which was extracted into ether, dried ($MgSO_4$), and treated with ethereal hydrogen chloride; the resulting solid recrystallised from ethanol–ether to give 3-(*α-ethoxy-αα-diphenylglycolloyloxy*)-1-*methylpiperidine hydrochloride* (15·3 g., 84%) (No. 4, Table 2).

All the esters listed in Table 2 were prepared by this method.

α-Cyclohexyl-α-methoxy-α-phenylacetic Acid.—α-Cyclohexyl-α-phenylglycollic acid [22] (10 g). was heated with phosphorus pentachloride (17·4 g.) at 120° for 1 hr. Phosphorus oxychloride was distilled off *in vacuo*, then anhydrous methanol (100 ml.) was added to the residue, the mixture heated under reflux for 24 hr., and the solvent removed. The crude ester was hydrolysed by heating it for 5 hr. with a solution of potassium hydroxide (20 g.) in water (60 ml.) and methanol (100 ml.). The mixture was poured into water, washed with ether, acidified, and extracted with ether. After drying ($MgSO_4$), evaporation of the ether extract left an oil, which crystallised under light petroleum (25 ml.) to give a solid (6·4 g.), m. p. 96—100°. A suspension of this in water (45 ml.) was treated with a solution of sodium hydroxide (5 g.) in water (20 ml.). The solid dissolved and then a precipitate of the sodium salt was formed rapidly, which was filtered off. [Acidification of the filtrate yielded α-cyclohexyl-α-phenylglycollic acid (1·2 g., 12%).] The acid regenerated from the sodium salt was crystallised from ethyl methyl ketone–light petroleum, to give *α-cyclohexyl-α-methoxy-α-phenylacetic acid* (3·5 g.,

TABLE 1.

Compounds, $RO\cdot CPh_2\cdot CO\bullet[CH_2]_n$–N(R′)

No.	R	R′	*n*	Posn. in ring	Salt	Form and solvent	M. p.	Method of prepn.	Yield (%)
1	Me	Me	0	3	HCl	Needles, EtOAc–Et_2O	128—129°	C	28
2	Et	Me	0	3	HCl	Needles, COMeEt	143—145	C	23
3	Me	Et	0	3	HCl	Needles, EtOH–Et_2O	137—138	C	37
4	Et	Et	0	3	HCl	Needles, EtOH–Et_2O	131—132	C	57
5	Me	Me	1	2	HCl	Needles, COMeEt–Et_2O	146—147	B	86
6	Me	Me	1	2	MeI	Needles, COMeEt	139—140 *		
7	Et	Me	1	2	HBr	Microcrystals, COMeEt–Et_2O	150—151	B	53
8	Et	Me	1	2	MeI	Plates, COMeEt–Et_2O	167—168		
9	Pr^n	Me	1	2	Hel	Microcrystals, COMeEt	153—154	B	49
10	Bu^n	Me	1	2	HCl	Prisms, $COMe_2$	74—76	C	26
11	CH_2Ph	Me	1	2	HCl	Prisms, MeOH–Et_2O	146—148	B	4
12	Me	Et †	1	2	HCl	Needles, COMeEt	181—182	C	69
13	Me	Et ‡	1	2	HBr	Needles, COMeEt–EtOAc	182—183	B	67
14	Me	Et †	1	2	PTS §	Needles, COMeEt	120—121	C	
15	Et	Et †	1	2	HCl	Needles, EtOH–Et_2O	141—143	C	69
16	Me	Pr^n ‡	1	2	HCl	Needles, COMeEt–EtOAc	171—172	A	63
17	Et	Pr^n ‡	1	2	HCl	Plates, COMeEt–Et_2O	150—151	A	35
18	Me	Pr^i †	1	2	HCl	Needles, COMeEt–Et_2O	107—109	C	30
19	Et	Pr^i †	1	2	HCl	Plates, COMeEt–Et_2O	135—137	C	68
20	Me	Bu^n ‡	1	2	HCl	Needles, EtOAc	143—145	A	36
21	Me	Me	1	3	HBr	Prisms, EtOAc–Et_2O	147—149	C	74
22	Me	Me	1	3	EDS ¶	Microcrystals, $COMe_2$–Et_2O	121—122·5		
23	Me	Me	1	3	MeI	Plates, $COMe_2$	135·5—136		
24	Et	Me	1	3	DBT **	Prisms, EtOH–Et_2O	134—135	C	66
25	Me	Et	1	3	HCl	Needles, $COMe_2$	149—150	C	43
26	Et	Et	1	3	DHC ††	$COMe_2$	102—104	C	61
27	Me	Me	2	2	HCl	Prisms, COMeEt–EtOAc	150—152	A	57
28	Et	Me	2	2	HBr	Needles, COMeEt	163—164	B	38
29	Me	Et	2	2	HCl	Needles, EtOAc	146—148	B	
30	Et	Et	2	2	HCl	Plates, EtOAc	135—137	B	56

[22] Smith, Alderman, Shacklett, and Welch, *J. Amer. Chem. Soc.*, 1949, **71**, 3772.

TABLE 1. (*Continued.*)

	Found (%)				Required (%)		
No.	C	H	Hal	Formula	C	H	Hal
1	66·7	6·6	9·9	$C_{20}H_{24}ClNO_3$	66·4	6·7	9·8
2	67·3	7·1	9·7	$C_{21}H_{26}ClNO_3$	67·1	7·0	9·4
3	67·0	6·9	9·7	$C_{21}H_{26}ClNO_3$	67·1	7·0	9·4
4	67·8	7·5	9·1	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
5	66·65	7·0	9·5	$C_{21}H_{26}ClNO_3$	67·1	7·0	9·4
6	54·9	5·7	26·5	$C_{22}H_{28}INO_3$	54·9	5·9	26·35
7	60·7	6·7	18·8	$C_{22}H_{28}BrNO_3$	60·8	6·45	18·4
8	56·1	6·2	25·4	$C_{23}H_{30}INO_3$	55·7	6·1	25·6
9	68·3	7·8	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
10	66·25	8·4	8·2	$C_{24}H_{32}ClNO_3,H_2O$	66·1	7·85	8·1
11	71·4	6·5	8·0	$C_{27}H_{30}ClNO_3$	71·7	6·7	7·8
12	67·9	7·5	9·2	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
13	60·9	6·4	18·2	$C_{22}H_{28}BrNO_3$	60·8	6·45	18·4
14	66·3	6·7	6·3 ‡‡	$C_{29}H_{35}NO_6S$	66·3	6·7	6·1 ‡‡
15	68·6	7·5	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
16	68·3	7·3	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
17	68·6	8·0	8·8	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5
18	68·4	7·7	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
19	69·1	7·3	8·6	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5
20	68·8	7·8	8·5	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5
21	59·9	6·4	19·0	$C_{21}H_{25}BrNO_3$	59·9	6·2	19·2
22	60·6	6·3	6·8 ‡‡	$C_{44}H_{56}N_2O_{12}S_2$	60·8	6·5	7·4 ‡‡
23	54·8	5·9	26·5	$C_{22}H_{28}INO_3$	54·9	5·9	26·35
24	70·0	6·6		$C_{62}H_{68}N_2O_{14}$	70·0	6·4	
25	68·0	7·5	9·2	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
26	62·4	6·5		$C_{29}H_{37}NO_{10}$	62·25	6·6	
27	67·95	6·9	9·1	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
28	61·7	6·7	18·0	$C_{23}H_{30}BrNO_3$	61·6	6·7	17·85
29	68·2	7·2	9·1	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
30	68·9	7·1	8·5	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5

* The salt crystallised from methanol as prisms, m. p. 90—91°, and from ethanol as needles, m. p. 156—158°, but gave incorrect analyses. It crystallized from propanol or butanol as needles, m. p. 139—140°. † The corresponding basic alkanol was prepared by Soulal's method.[7] ‡ Product obtained from a basic alkanol derived from L-glutamic acid. § Toluene-*p*-sulphonate. ¶ Ethane-disulphonate. ** Dibenzoyl-(+)-tartrate. With E. A. Twamley. †† Dihydrogen citrate. ‡‡ Analysis for sulphur.

32%) as prisms, m. p. 111—112° (Found: C, 72·6; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). The mother-liquor yielded a gum which readily discharged the colour of cold aqueous potassium permanganate, indicating the presence of dehydrohalogenated material. Treatment of the acid with ethereal diazomethane yielded the *methyl ester* (96%) as colourless plates (from aqueous methanol), m. p. 43—45° (Found: C, 73·3; H, 8·5. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

2-(α-*Cyclohexyl*-α-*methoxy*-α-*phenylacetoxymethyl*)-1-*methylpyrrolidine*.—Transesterification of 2-hydroxymethyl-1-methylpyrrolidine with methyl α-cyclohexyl-α-methoxy-α-phenylacetate gave 2-(α-cyclohexyl-α-methoxyphenylacetoxymethyl)-1-methylpyrrolidine, isolated as the *hydrogen di*-p-*toluoyl*-(+)-*tartrate* [23] (34%), needles (from ethyl methyl ketone–light petroleum), m. p. 128—129° (Found: C, 67·0; H, 6·7. $C_{41}H_{49}NO_{11}$ requires C, 67·3; H, 6·75%); the *picrate* formed yellow needles (from methanol), m. p. 119—121° (Found: C, 56·6; H, 6·0; N, 9·4. $C_{27}H_{34}N_4O_{10}$ requires C, 56·3; H, 6·1; N, 9·7%). The following esters were prepared similarly:

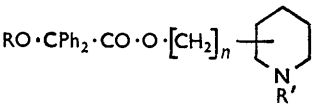
2-(α-*Cyclohexyl*-α-*methoxy*-α-*phenylacetoxymethyl*)-1-*ethylpyrrolidine dihydrogen citrate monohydrate* (36%), prisms (from acetone–ether), m. p. 130° (loss of water at 86—88°) (Found: C, 59·05; H, 7·5. $C_{28}H_{43}NO_{11}$ requires C, 59·05; H, 7·6%).

3-(α-*Cyclohexyl*-α-*methoxy*-α-*phenylacetoxy*)-1-*methylpiperidine hydrochloride* (22%), needles (from ethyl methyl ketone), m. p. 187—189° (Found: C, 66·2; H, 8·5; Cl, 9·3. $C_{21}H_{32}ClNO_3$ requires C, 66·0; H, 8·4; Cl, 9·3%); *hydrogen di*-p-*toluoyl*-(+)-*tartrate*, needles (from ethyl methyl ketone–light petroleum), m. p. 128—129° (Found: C, 67·2; H, 6·9. $C_{41}H_{49}NO_{11}$ requires C, 67·3; H, 6·75%).

2-[2-(α-*Cyclohexyl*-α-*methoxy*-α-*phenylacetoxy*)*ethyl*]-1-*methylpyrrolidine hydrochloride* (31%),

[23] Stoll and Hoffman, *Helv. Chim. Acta*, 1943, **26**, 922.

TABLE 2.

Compounds, 

No.	R	R′	*n*	Posn. in ring	Salt	Form and solvent	M. p.	Yield (%)
1	Me	Me	0	3	HCl	Amorphous	178—180° *	72
2	Me	Me	0	3	DHC †	Prisms, $COMe_2$	130—131	
3	Me	Me	0	3	MeI	Needles, COMeEt–Et_2O	211—212	
4	Et	Me	0	3	HCl	Needles, EtOH–Et_2O	206—207	84
5	Bu^n	Me	0	3	HCl	Needles, COMeEt–Et_2O	183—185	78
6	Me	Et	0	3	HCl	Needles, $COMe_2$	189—189·5	49
7	Me	Et	0	3	EtI	Plates, EtOH–Et_2O	146·5—148	
8	Et	Et	0	3	HCl	Needles, EtOH–Et_2O	171—172	39
9	Me	Me	0	4	HCl	Needles, EtOH–Et_2O	234—235 ‡	61
10	Et	Me	0	4	HCl	Needles, EtOH–Et_2O	192—194 §	64
11	Me	Et	0	4	HCl	Prisms, EtOH–COMeEt	217—218	51
12	Et	Et	0	4	HCl	Needles, EtOH–COMeEt	195—196	71
13	Me	Me	1	2	HCl	Prisms, EtOH–Et_2O	187—188	59
14	Me	Me	1	2	MeI	Needles, COMeEt	164—166	
15	Et	Me	1	2	HCl	Needles, EtOH–Et_2O	199—200	70
16	Me	Et	1	2	HCl	Needles, COMeEt	182—183	33
17	Et	Et	1	2	HCl	Needles, COMeEt	160—161	57
18	Me	Me	1	3	HCl	Needles, Pr^iOH–Et_2O	162—164	55
19	Et	Me	1	3	HCl	Needles, Pr^iOH–Et_2O	162—164	61
20	Me	Et	1	3	HCl	Prisms, COMeEt–Et_2O	158	41
21	Et	Et	1	3	HCl	Plates, COMeEt–Et_2O	153—154·5	55
22	Me	Me	1	4	HCl	Prisms, COMeEt	173—174	72
23	Et	Me	1	4	HCl	Prisms, COMeEt	183—184	45
24	Me	Et	1	4	HCl	Needles, COMeEt	160—162	40
25	Et	Et	1	4	HCl	Prisms, COMeEt	176	72

	Found (%)				Required (%)		
No.	C	H	Hal	Formula	C	H	Hal
1	67·1	7·1	9·4	$C_{21}H_{26}ClNO_3$	67·1	7·0	9·4
2	61·0	6·5	—	$C_{27}H_{33}NO_{10}$	61·0	6·25	—
3	55·0	6·0	26·3	$C_{22}H_{28}INO_3$	54·9	5·9	26·35
4	67·9	6·9	8·9	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
5	68·8	7·9	8·5	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5
6	67·9	7·5	9·0	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
7	57·05	6·9	24·7	$C_{24}H_{32}INO_3$	56·6	6·3	24·9
8	68·4	7·5	9·0	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
9	67·3	7·0	9·5	$C_{21}H_{26}ClNO_3$	67·1	7·0	9·4
10	67·4	7·4	9·3	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
11	68·0	7·3	9·2	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
12	68·6	7·8	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
13	67·65	7·5	8·8	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
14	55·7	6·5	25·3	$C_{23}H_{30}INO_3$	55·7	6·1	25·6
15	68·4	7·8	8·6	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
16	68·6	7·6	8·9	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
17	68·9	7·7	8·4	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5
18	67·6	7·5	9·05	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
19	68·4	7·65	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
20	68·5	7·8	8·8	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
21	69·0	7·7	8·4	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5
22	67·9	7·4	9·2	$C_{22}H_{28}ClNO_3$	67·7	7·2	9·1
23	68·2	7·6	8·7	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
24	68·6	7·8	8·7	$C_{23}H_{30}ClNO_3$	68·4	7·5	8·8
25	69·1	7·9	8·5	$C_{24}H_{32}ClNO_3$	68·9	7·7	8·5

* M. p. after heating at 80°/1 mm. This compound crystallised from a variety of solvents as needles, m. p. 196—198° (moist samples softened at *ca.* 115°), but failed to give correct analyses (Cannon, *J. Org. Chem.*, 1960, **25**, 959, gives m. p. 109—111°). † Dihydrogen citrate. ‡ Klosa and Delmar (*J. prakt. Chem.*, 1962, **16**, 71) give m. p. 232—234°. § Klosa and Delmar (*loc. cit.*) give m. p. 178—180°.

plates (from ethyl methyl ketone–ether), m. p. 73—75° (Found: C, 66·5; H, 8·9; Cl, 8·6. $C_{22}H_{34}ClNO_3$ requires C, 66·7; H, 8·65; Cl, 8·95%).

2-(α-*Ethylthio-αα-diphenylacetoxymethyl*)-1-*methylpyrrolidine*.—Treatment of α-ethylthio-αα-diphenylacetic acid [21b] with ethereal diazomethane gave the *methyl ester* (86%), prisms (from light petroleum), m. p. 71—72° (Found: C, 71·5; H, 6·6; S, 11·35. $C_{17}H_{18}O_2S$ requires C, 71·3; H, 6·3; S, 11·2%), which on transesterification with 2-hydroxymethyl-1-methylpyrrolidine yielded 2-(α-ethylthio-αα-diphenylacetoxymethyl)-1-methylpyrrolidine (19%), isolated as its *hydrogen* (+)-*tartrate*, prisms (from ethyl methyl ketone), m. p. 146—147° (Found: C, 60·2; H, 6·8; S, 6·4. $C_{26}H_{33}NO_8S$ requires C, 60·1; H, 6·4; S, 6·2%).

1-*Ethyl*-2-(α-*ethylthio-αα-diphenylacetoxymethyl*)*pyrrolidine hydrogen* (+)-*tartrate hemihydrate* (36%) was obtained similarly, as prisms (from ethyl methyl ketone), m. p. 102—105° (Found: C, 59·65; H, 6·5; S, 5·95. $C_{54}H_{72}N_2O_{17}S_2$ requires C, 59·7; H, 6·7; S, 5·9%).

Thermal Rearrangement of 1-*Ethyl*-2-(α-*methoxy-αα-diphenylacetoxymethyl*)*pyrrolidine*.—The ester was regenerated from a sample of the pure hydrochloride. When the ester was heated at 200° for 2 hr. and then distilled (b. p. 160—163°/0·05 mm., n_D^{20} 1·5482), it rearranged to 1-ethyl-3-(α-methoxy-αα-diphenylacetoxy)piperidine, as shown by the following evidence: (i) The infrared spectrum of the base was identical with that of the authentic piperidyl ester (No. 6, Table 2). (ii) The hydrochloride did not depress the m. p. of the authentic piperidyl ester hydrochloride. (iii) Reduction of the ester with lithium aluminium hydride in ether yielded an oil (69%), b. p. 82—84°, n_D^{21} 1·4678, which had an infrared spectrum and hydrochloride identical with those of 1-ethyl-3-hydroxypiperidine. [The residue from the distillation was 2-methoxy-2,2-diphenylethanol (88%), m. p. 90—91° (from light petroleum) (lit.,[24] m. p. 89·6—90·2°).]

However, when the pyrrolidyl ester was distilled rapidly (b. p. 171—173°/0·02 mm., n_D^{20} 1·5458), there was virtually no change in the infrared spectrum.

Reaction of Butyryl Chloride with 2-*Hydroxymethylpyrrolidine*.—To a solution of 2-hydroxymethylpyrrolidine [2] (10 g.) in chloroform (50 ml.), butyryl chloride (26·4 g.) in chloroform (50 ml.) was added dropwise in 5 min. The mixture was heated under reflux for 2 hr., the solvent removed *in vacuo*, and the residue treated with ether, which precipitated some 2-*butyryloxymethylpyrrolidine hydrochloride* (3 g., 14%, plates (from ethyl acetate), m. p. 87—87·5° (Found: C, 52·0; H, 9·0; Cl, 16·9. $C_9H_{18}ClNO_2$ requires C, 52·0; H, 8·7; Cl, 17·1%). The ethereal filtrate was evaporated *in vacuo*, to leave 1-butyroyl-2-butyroyloxymethylpyrrolidine (19·5 g., 80%) as an oil which had an infrared spectrum identical with that of the product from the reaction of 2-hydroxymethylpyrrolidine with butyric anhydride (see above); *i.e.*, no ester rearrangement had occurred at the b. p. of butyric anhydride.

Optical Resolution of Basic Esters.—(i) 1-*Ethyl*-3-(α-*methoxy-αα-diphenylacetoxy*)*piperidine*. The free base (30 g.) was added to a solution of (+)-tartaric acid (12·7 g.) in acetone (175 ml.), and the mixture was kept at room temperature for 3 days. A solid separated (m. p. 132—137°), which was recrystallised twice from acetone to give a hydrogen (+)-tartrate (11 g., 26%), m. p. 140—141°, $[\alpha]_D^{19}$ −1·73° (*c* 10·4 in H_2O), which was basified and treated with ethereal hydrogen chloride. Recrystallisation of the hydrochloride from acetone yielded (−)-1-*ethyl*-3-(α-*methoxy-αα-diphenylacetoxy*)*piperidine hydrochloride* (4 g., 12%), m. p. 187—189°, $[\alpha]_D^{21}$ −14·2° (*c* 9·96 in H_2O) (Found: C, 67·6; H, 7·2; Cl, 9·0. $C_{22}H_{28}ClNO_3$ requires C, 67·8; H, 7·2; Cl, 9·1%). The mother-liquors from the recrystallisation of the tartrate were evaporated and the residue was converted into a hydrochloride as before, from which was isolated by fractional crystallisation from acetone (+)-1-*ethyl*-3-(α-*methoxy-αα-diphenylacetoxy*)*piperidine hydrochloride* (3·7 g., 11%), m. p. 187—189°, $[\alpha]_D^{22}$ +13·85° (*c* 10 in H_2O) (Found: C, 68·1; H, 7·5; Cl, 9·35%).

(ii) 1-*Ethyl*-2-(α-*methoxy-αα-diphenylacetoxymethyl*)*pyrrolidine*. Treatment of the free base with (+)-tartaric acid in acetone as in the preceding example yielded a *hydrogen* (+)-*tartrate* (30%), m. p. 124°, $[\alpha]_D^{18}$ +3·26° (*c* 10 in H_2O) (Found: C, 62·3; H, 6·6; N, 3·2. $C_{26}H_{33}NO_9$ requires C, 62·0; H, 6·6; N, 2·8%). From this was obtained (−)-1-*ethyl*-2-(α-*methoxy-αα-diphenylacetoxymethyl*)*pyrrolidine hydrochloride* (3·8 g., 17%), m. p. 185—186° (from acetone), $[\alpha]_D^{18}$ −8·36° (*c* 5 in H_2O) (Found: C, 67·8; H, 7·2; N, 3·6; Cl, 9·1. $C_{22}H_{28}ClNO_3$ requires C, 67·8; H, 7·2; N, 3·6; Cl, 9·1%). The mother-liquors from the recrystallisation of the tartrate were evaporated, then the residue was basified and treated with (−)-tartaric acid in

[24] Winstein, Lindegren, Marshall, and Ingraham, *J. Amer. Chem. Soc.*, 1953, **75**, 147.

acetone, to give the hydrogen (−)-tartrate (27%), m. p. 124°, $[\alpha]_D^{18}$ −3·00° (*c* 10 in H_2O), and thence (+)-1-*ethyl*-2-(α-*methoxy*-αα-*diphenylacetoxymethyl*)*pyrrolidine hydrochloride* (25%), m. p. 185°, $[\alpha]_D^{19}$ +8·12° (*c* 5 in H_2O) (Found: C, 68·1; H, 7·4; Cl, 9·1%).

The ester hydrochloride derived from L-glutamic acid (No. 12, Table 1) had m. p. 181—182°, $[\alpha]_D^{20}$ +6·5° (*c* 4·2 in H_2O).

(iii) 3-(α-*Methoxy*-αα-*diphenylacetoxymethyl*)-1-*methylpyrrolidine*. This ester was resolved by making use of both (+)- and (−)-tartaric acid, as in the preceding example. Thus the *hydrogen* (+)-*tartrate dihydrate* (26%), needles (from acetone), m. p. 69—70°, $[\alpha]_D^{19}$ +7·21° (*c* 2·25 in H_2O) (Found: C, 57·15; H, 6·7. $C_{25}H_{35}NO_{11}$ requires C, 57·1; H, 6·7%) yielded (+)-3-(α-*methoxy*-αα-*diphenylacetoxy*)*methyl*-1-*methylpyrrolidine hydrobromide* (14%) as prisms (from ethyl acetate), m. p. 160—161·5°, $[\alpha]_D^{17}$ +1·32° (*c* 2·17 in H_2O) (Found: C, 59·8; H, 6·2; Br, 19·1. $C_{21}H_{26}BrNO_3$ requires C, 59·9; H, 6·2; Br, 19·2%). Similarly the *hydrogen* (−)-*tartrate dihydrate* (30%), m. p. 68—70·5°, $[\alpha]_D^{21}$ −7·16° (*c* 2·1 in H_2O) (Found: C, 57·3; H, 6·8%), yielded (−)-3-(α-*methoxy*-αα-*diphenylacetoxymethyl*)-1-*methylpyrrolidine hydrobromide* (13%), m. p. 160—161·5°, $[\alpha]_D^{21}$ −1·15° (*c* 2·17 in H_2O) (Found: C, 59·8; H, 6·2; Br, 19·4%).

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