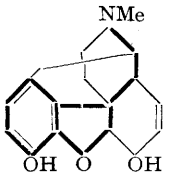
68. *Synthetic Analgesics. Part I. Synthesis of Basic Benzofuran Derivatives and certain 4-Phenylpiperidine Compounds.*

By F. Bergel, J. W. Haworth, A. L. Morrison, and H. Rinderknecht.

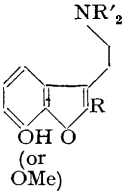
Attempts to synthesise basic benzofuran derivatives as forming part of the morphine molecule and possibly possessing analgesic properties are described. Although 3-β-dialkylaminoethylcoumarones could not be obtained from 2-hydroxy-β-dialkylaminopropiophenones, yet 2-*dimethylaminomethyl*-6-*methoxycoumaranone* and 2-*β-piperidinopropionyl*-7-*methoxycoumarone* were synthesised. By using the method of Eisleb (*Ber.*, 1941, **74**, 1433) 4-(2′-*hydroxyphenyl*)-1-*methylpiperidine*-4-*carboxylic acid lactone* and its 3′-*methoxy*-analogue were prepared from the corresponding phenylacetonitriles. A related *coumaran* was obtained when 4-*acetyl*-4-(2′-*methoxyphenyl*)-1-*methylpiperidine*—from the corresponding nitrile with methylmagnesium iodide—was reduced, and the product treated with concentrated hydrobromic acid. Attempts to reduce 4-arylpiperidine-4-nitriles with sodium and alcohol to primary amines failed, for the nitrile group was removed; on catalytic hydrogenation the secondary amine was formed.

The synthesis of true analgesics has long been the object of research; work in this field before 1938 has been adequately reviewed by Fourneau (*Chim. Ind.*, 1938, **39**, 1043) and by Small, Eddy, Mosettig, and Himmelsbach (Publ. Health Service, Suppl. No. 138, U.S. Treasury Dept., Washington, 1938). Much attention has been directed to the study of synthetic substances whose structures embrace certain features found in the morphine molecule (I), but although some such compounds show promising pharmacological properties, none so far obtained can seriously compete with morphine or a number of its derivatives.

In taking up the study of synthetic analgesics, we decided first to attempt the preparation of basic derivatives of benzofuran which forms part of the morphine molecule, for this group has not been studied previously. Although we then failed to prepare representatives of 3-β-dialkylaminoethylcoumarones or coumarans of type (II; R′ = alkyl), we did prepare a 2-dialkylaminocoumaranone (cf. III) and a 2-β-piperidinopropionyl-coumarone derivative (cf. IV).



(I.)



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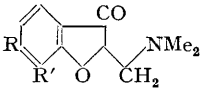

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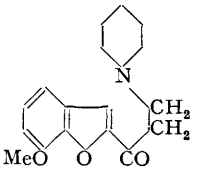
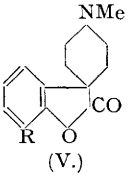


(IV.)

While we were engaged on the above work, Eisleb and Schaumann (*Deut. med. Wochenschr.*, 1939, **65**, 967) announced the synthesis of a new analgesic, ethyl 4-phenyl-1-methylpiperidine-4-carboxylate. Methods for its preparation and that of similar piperidine derivatives were later reported by Eisleb (*Ber.*, 1941, **74**, 1433) and in patent literature (B.P. 501,135; U.S.PP. 2,167,351, 2,242,575), and the pharmacological properties of 42 compounds of this series were described by Schaumann (*Arch. Path. Exp. Pharm.*, 1940, **196**, 109).

In view of the interesting physiological properties of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (Dolantin, Dolantal, Demerol, or, according to the British Pharmacopœia Commission, Pethidine) and its close relation to substances of our own working scheme, we extended our original work to the preparation of *iso*-coumaranones of type (V) and of a coumaran of type (VI), using Eisleb's general method (*loc. cit.*) for the preparation of the required 4-phenylpiperidine-4-nitriles in which phenylacetonitriles are condensed with ββ′-dichlorodiethylamines. We have also obtained several other new 4-phenylpiperidine compounds.



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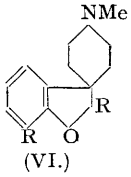

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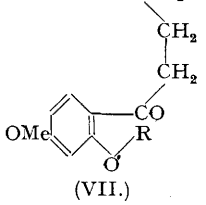

(VII.)

In our first experimental series we prepared from 2-hydroxy-4-methoxyacetophenone (pæonol) with paraformaldehyde and secondary bases (cf. Mannich, *Ber.*, 1922, **55**, 356) β-*dimethylamino*-2-*hydroxy*-4-*methoxypropiophenone* (VII; R = H), its 2-*acetoxy*-derivative (VII; R = Ac), and β-*piperidino*-2-*hydroxy*-4-*methoxypropiophenone*. The glycollic acid or ethyl glycollate ether of pæonol, treated in a similar manner, yielded 2-β-*dimethylaminopropionyl*-5-*methoxyphenoxyacetic acid* (VII; R = $CH_2 \cdot CO_2H$), its *ethyl* ester, and the two corresponding *piperidino*-compounds. When the potassium salt of (VII; R = H) was treated with an α-halogeno-ketone, according to the method of Kunkell and Kessler (*Ber.*, 1903, **36**, 1260), who prepared 2-benzoyl-3-methylcoumarone from *o*-hydroxyacetophenone and ω-bromoacetophenone, the desired coumarone (cf. II; R = COPh) was not formed; instead, when ω-bromoacetophenone was used, only ω-dimethylamino-

acetophenone and 2-hydroxy-4-methoxyphenyl vinyl ketone could be isolated. When (VII; R = $CH_2 \cdot CO_2H$) or its ethyl ester was caused to react with acetic anhydride and sodium acetate, according to Kostanecki and Tambor's conditions (*Ber.*, **1909**, **42**, 905), again the molecule was disrupted.

On the other hand, when (VII; R = Ac) was brominated to *α-bromo-β-dimethylamino-2-acetoxy-4-methoxypropiophenone* and the acetyl groups removed with hydrobromic acid, the free phenol yielded with potassium carbonate in acetone the very unstable 2-dimethylaminomethyl-6-methoxycoumaranone (III; R = OMe, R′ = H).

Another basic benzofuran derivative was prepared when *7-methoxy-2-acetylcoumarone*, obtained from *o*-vanillin with chloroacetone in presence of potassium hydroxide according to Stoermer (*Ber.*, **1903**, **36**, 2865), was condensed with paraformaldehyde and piperidine hydrochloride to give *2-β-piperidinopropionyl-7-methoxycoumarone* (IV)

Eisleb's method enabled us to approach our original goal (cf. II) to some extent. First, we prepared the *iso*coumaranones, *4-(2′-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid lactone* (V; R = H) and its *3′-methoxy*-derivative (V; R = OMe) in the following manner: 2-methoxyphenylacetonitrile, *2-benzyloxyphenylacetonitrile*, and 2 : 3-dimethoxyphenylacetonitrile were prepared from 2-methoxy-, 2-benzyloxy-, and 2 : 3-dimethoxy-benzaldehyde, respectively, according to Robertson (J., **1933**, 489) through the stages of azlactone, pyruvic acid, and pyruvic acid oxime. Condensation of the above nitriles with ββ′-dichlorodiethylmethylamine gave *4-(2′-methoxyphenyl)-1-methylpiperidine-4-nitrile*, the corresponding *benzyloxy*-compound and *4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine-4-nitrile*. Hydrolysis of the benzyloxy-compound with hydrochloric acid and of the dimethoxy-compound with concentrated hydrobromic acid yielded the *iso*coumaranones (V; R = H and R = OMe).

We failed to prepare the desired corresponding coumarans (cf. VI) by the action of alkylmagnesium halides on these lactones. We were, however, partly successful when *4-acetyl-4-(2′-methoxyphenyl)-1-methylpiperidine*, from 4-(2′-methoxyphenyl)-1-methylpiperidine-4-nitrile with methylmagnesium iodide (cf. Winthrop Chem. Co., U.S.P. 2,248,018, 1941; *Chem. Abstr.*, 1941, **35**, 6394), was reduced with sodium and alcohol, and the crude product treated with concentrated hydrobromic acid. The basic oil thus formed gave a *picrate* whose analysis indicated that the desired coumaran (VI; R = H, R′ = Me) had been synthesised. Reduction of 4-acetyl-4-phenyl-1-methylpiperidine readily yielded *4-phenyl-4-(α-hydroxyethyl)-1-methylpiperidine* On the other hand, attempts to prepare a ketone from 4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine-4-nitrile were completely unsuccessful.

When we tried to prepare primary amines directly from 4-arylpiperidine-4-nitriles with the aim of eventually obtaining coumarans, the action of sodium and alcohol eliminated the nitrile group in every case, giving 4-arylpiperidines. 4-Phenyl-1-methylpiperidine-4-nitrile gave 4-phenyl-1-methylpiperidine, identical with the product obtained by decarboxylation of 4-phenyl-1-methylpiperidine-4-carboxylic acid (cf. Eisleb, *loc. cit.*) 4-(2′-Benzyloxyphenyl)-1-methylpiperidine-4-nitrile yielded *4-(2′-hydroxyphenyl)-1-methylpiperidine* by simultaneous removal of the benzyl group, and 4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine-4-nitrile gave *4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine*, which on hydrolysis with concentrated hydrobromic acid gave the *dihydroxy*-compound. That this elimination of the nitrile group is not confined to tertiary arylpiperidine nitriles was shown by the formation of *γ-phenyl-n-amyldiethylamine* from *γ-diethylamino-α-phenyl-α-ethylbutyronitrile*, prepared by condensation of α-phenylbutyronitrile with β-chloroethyldiethylamine.

Catalytic hydrogenation of 4-phenyl-1-methylpiperidine-4-nitrile yielded mainly *bis-(4-phenyl-1-methylpiperidyl-4-methyl)amine*, m. p. 91—93°.

The results of the pharmacological tests of some of the above compounds will be published elsewhere.

Experimental.

β-Dimethylamino-2-acetoxy-4-methoxypropiophenone Hydrochloride (VII; R = Ac).—Acetylpæonol (12·5 g.), paraformaldehyde (2·4 g.), and dimethylamine hydrochloride (5·4 g.) in ethyl alcohol (15 c.c.) were refluxed for 1 hour. More paraformaldehyde (1·0 g.) was then added, and the refluxing continued for 1 hour. On cooling, the *hydrochloride* of *β-dimethylamino-2-acetoxy-4-methoxypropiophenone* separated as a crystalline mass (10·1 g.), and a further 1·2 g. separated on addition of acetone (20 c.c.) and ether (100 c.c.) to the mother-liquors. When crystallised from ethyl alcohol, it had m. p. 175° (Found: C, 55·9; H, 6·9. $C_{14}H_{20}O_4NCl$ requires C, 55·8; H, 6·7%).

β-Dimethylamino-2-hydroxy-4-methoxypropiophenone Hydrochloride (VII; R = H).—The above acetyl derivative (5·0 g.) was refluxed for 1 hour with aqueous hydrochloric acid (15 c.c.). The solution was then evaporated to dryness in a vacuum, the residue taken up in hot alcohol, and ether added, whereupon the *hydrochloride* of (VII; R = H) was precipitated as a white solid. After crystallisation from alcohol–ethyl acetate, it had m. p. 166—167°. It gave a deep red coloration with ferric chloride (Found: C, 55·3; H, 7·0; N, 5·3. $C_{12}H_{18}O_3NCl$ requires C, 55·6; H, 6·9; N, 5·4%).

β-Piperidino-2-hydroxy-4-methoxypropiophenone Hydrochloride.—A mixture of pæonol (1·0 g.), paraformaldehyde (0·5 g.), and piperidine hydrochloride (0·8 g.) in alcohol (3 c.c.) was refluxed for 6 hours. After cooling, ether was added, and the resulting oily precipitate solidified on standing. The solid (1·4 g.) was filtered off, and after crystallisation from ethyl acetate–alcohol, the *hydrochloride* of *β-piperidino-2-hydroxy-4-methoxypropiophenone* was obtained in colourless needles, m. p. 188—189° (Found: C, 60·1; H, 7·3; N, 4·3. $C_{15}H_{22}O_3NCl$ requires C, 60·0; H, 7·3; N, 4·7%).

Reaction of β-Dimethylamino-2-hydroxy-4-methoxypropiophenone with Bromoacetophenone.—The base hydrochloride (2·6 g.) was dissolved in a solution of potassium hydroxide (1·12 g.) in water (3 c.c.), and a solution of bromoacetophenone (2·0 g.) in alcohol (16 c.c.) added. The mixture was boiled for 3 hours, alcohol removed, and the residue poured into dilute sodium hydroxide. After extraction with ether, the extract was washed with water, dried over sodium sulphate, and evaporated. The residue was again taken up in dry ether, and alcoholic hydrogen chloride added, precipitating a hydrochloride, m. p. 173—174° after crystallisation from ethyl acetate–alcohol. This showed no depression in m. p. on admixture with an authentic specimen of the hydrochloride of β-dimethylaminoacetophenone (m. p. 173—174°)

prepared from bromoacetophenone and dimethylamine. The material soluble in sodium hydroxide was precipitated as a dark oil by passing carbon dioxide into the solution. This was extracted with ether, the extract dried over sodium sulphate, and the ether distilled. A viscous phenolic oil remained, which on treatment with 2 : 4-dinitrophenylhydrazine gave a product, m. p. 244—245°, apparently the 2 : 4-*dinitrophenylhydrazone* of 2-hydroxy-4-methoxyphenyl vinyl ketone (Found : C, 53·8; H, 3·8; N, 16·7. $C_{10}H_{14}O_6N_4$ requires C, 53·6; H, 3·9; N, 15·7%).

Ethyl 2-β-Dimethylaminopropionyl-5-methoxyphenoxyacetate (VII; R = $CH_2{\cdot}CO_2Et$).—A mixture of ethyl 5-methoxy-2-acetylphenoxyacetate (3·75 g.; prepared from pæonol and bromoacetic ester), paraformaldehyde (1·0 g.), dimethylamine hydrochloride (1·25 g.), and alcohol (4 c.c.) was refluxed for 1 hour, more paraformaldehyde (0·25 g.) then being added and the refluxing continued for a further hour. After cooling, a little ether was added, and the *hydrochloride* of (VII; R = $CH_2{\cdot}CO_2Et$) separated as a white crystalline mass; recrystallised from ethyl acetate–alcohol, it had m. p. 149° (Found : C, 54·7; H, 6·9. $C_{16}H_{24}O_5NCl$ requires C, 55·6; H, 6·9%).

The corresponding *piperidino*-compound, prepared in the same manner, separated from alcohol–ethyl acetate in colourless prisms, m. p. 134° (Found : C, 59·2; H, 7·1; N, 3·5. $C_{19}H_{28}O_5NCl$ requires C, 59·2; H, 7·3; N, 3·6%).

2-β-Dimethylaminopropionyl-5-methoxyphenoxyacetic acid (VII; R = $CH_2{\cdot}CO_2H$).—Repetition of the above experiment but with the acid in place of the ester, gave the *hydrochloride* of (VII; R = $CH_2{\cdot}CO_2H$) in good yield. Crystallisation from alcohol gave colourless needles, m. p. 197° (Found : C, 53·1; H, 6·3; N, 3·9. $C_{14}H_{20}O_5NCl$ requires C, 53·0; H, 6·3; N, 4·3%).

The corresponding *piperidino*-compound melted at 183—184° after crystallisation from alcohol (Found : C, 57·4; H, 6·8; N, 3·7. $C_{17}H_{24}O_5NCl$ requires C, 57·1; H, 6·7; N, 3·9%).

Reaction of Ethyl 2-β-Dimethylamino-5-methoxyphenoxyacetate with Acetic Anhydride and Sodium Acetate.—When the hydrochloride of (VII; R = $CH_2{\cdot}CO_2Et$) (0·5 g.) was refluxed with acetic anhydride (5 c.c.) and sodium acetate (1·5 g.) for 45 minutes and the resulting solution worked up, only a nitrogen-free solid (m. p. 112°) could be isolated. The reaction also failed when (VII; R = $CH_2{\cdot}CO_2H$) was treated in the same manner.

α-Bromo-β-dimethylamino-2-acetoxy-4-methoxypropiophenone Hydrobromide.—To a solution of β-dimethylamino-2-acetoxy-4-methoxypropiophenone hydrochloride (4·5 g.) in glacial acetic acid (40 c.c.), warmed to 40°, was added dropwise with stirring during 1 hour a solution of bromine (2·4 g.) in acetic acid (20 c.c.). The acetic acid was then distilled under reduced pressure, leaving a viscous oil which was washed with ether. On addition of a little alcohol this formed a solid, white mass (6·2 g.) of the required compound, which formed plates from alcohol, m. p. 161° (Found : C, 40·2; H, 4·9; N, 3·7; Br, 36·7. $C_{14}H_{19}O_4NBr_2$ requires C, 39·6; H, 4·5; N, 3·3; Br, 37·7%).

The above *acetyl* compound was hydrolysed by heating for three hours with an equal amount of 50% hydrobromic acid in about 20 parts of 95% alcohol. Addition of ether then precipitated the *hydrobromide* of the *hydroxy*-compound as a white solid, obtained as needles, m. p. 179°, from alcohol and giving a deep red coloration with ferric chloride (Found : C, 38·2; H, 4·5; Br, 41·0. $C_{12}H_{17}O_3NBr_2$ requires C, 37·6; H, 4·4; Br, 41·7%).

Hydrochloride of 2-Dimethylaminomethyl-6-methoxycoumaranone (III; R = OMe, R′ = H).—The foregoing hydrobromide (1·0 g.) was mixed with powdered potassium carbonate (8·0 g.) and boiled with acetone (20 c.c.) for 1—2 minutes. The acetone solution was filtered, the carbonate washed with ether (20 c.c.), and the washings added to the filtrate. Addition of alcoholic hydrogen chloride then precipitated the hydrochloride of (III; R = OMe, R′ = H) as a white crystalline solid (0·4 g.), m. p. 144—145°. The product gave a very faint coloration with ferric chloride, showing the presence of traces of starting material. Attempts to crystallise it, however, resulted in polymerisation, with production of a *substance* with an indefinite m. p. (Found : C, 54·9; H, 5·8; N, 4·6. $C_{12}H_{16}O_3NCl$ requires C, 55·9; H, 6·2; N, 5·4%). The *picrate*, prepared by addition of aqueous picric acid to a solution of the hydrochloride, separated in needles, m. p. 123—124°, which, however, decomposed on attempted recrystallisation (Found : N, 11·6. $C_{18}H_{18}O_{10}N_4$ requires N, 12·4%).

7-Methoxy-2-acetylcoumarone.—*o*-Vanillin (20 g.) in water (30 c.c.) containing potassium hydroxide (7·4 g.), chloroacetone (12 g.), and absolute ethanol (150 c.c.) were refluxed for 4 hours. After cooling, water was added until no more oily precipitate was formed. This was extracted with ether, and the ether dried and evaporated. The residue, recrystallised from ethanol or light petroleum (b. p. 60—80°), formed colourless, soft needles, m. p. 92°; yield 10 g. (Found : C, 69·4; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

2-β-Piperidinopropionyl-7-methoxycoumarone Hydrochloride (IV).—The above coumarone (6 g.) was mixed with paraformaldehyde (2 g.), piperidine hydrochloride (4·5 g.), and absolute ethanol (10 c.c.) and refluxed for 6 hours. The solution was left overnight, then treated with acetone and ether, a solid being precipitated. This was dissolved in water, and when concentrated sodium carbonate solution was added an oil was formed which was extracted with ether. After drying, the solvent was removed. As the base decomposed when distillation was attempted in a high vacuum, the substance after removal of low-boiling bases in a vacuum desiccator (yield *ca.* 6 g.) was transformed into a *hydrochloride* in the usual manner; m. p. 170—172° from absolute alcohol (Found : N, 4·3. $C_{17}H_{22}O_3NCl$ requires N, 4·3%). When the base (1·38 g.), regenerated from the hydrochloride, was submitted to catalytic hydrogenation in absolute methanol (45 c.c.) in presence of platinic oxide (0·2 g.), 135 c.c. of hydrogen were taken up very slowly (1 mol. of hydrogen requires 120 c.c.). As the hydrochloride did not crystallise properly, a *picrate* was formed, m. p. 158—159° after crystallisation from water (Found : C, 53·3; H, 5·4. $C_{23}H_{26}O_{10}N_4$ requires C, 53·3; H, 5·0%).

Azlactone of 2-Benzyloxybenzaldehyde.—A mixture of 2-benzyloxybenzaldehyde (10 g.), hippuric acid (14 g.), sodium acetate (15 g.), and acetic anhydride (50 c.c.) was heated on the steam-bath for 1 hour, and the *azlactone* formed isolated by addition of ethyl alcohol (125 c.c.) and water (150 c.c.), and cooling; recrystallised from alcohol, it had m. p. 167—169° (Found : N, 3·9. $C_{23}H_{17}O_3N$ requires N, 3·9); yield 63%.

2-Benzyloxyphenylpyruvic Acid.—The above azlactone (10 g.) was refluxed with 10% aqueous sodium hydroxide (100 c.c.) for 5 hours in nitrogen, water (250 c.c.) was added, and the cooled solution saturated with sulphur dioxide. The precipitated benzoic acid was filtered off, the filtrate extracted twice with ether, boiled to remove ether, acidified to Congo-red with hydrochloric acid (20%), boiled to remove sulphur dioxide, and cooled in the ice chest. The *pyruvic acid* which separated, crystallised from 50% aqueous acetic acid, had m. p. 119—120° (Found : C, 71·0; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%); yield 70%.

2-Benzyloxyphenylacetonitrile.—The above acid was converted into its oxime by dissolving it (3 g.) in 10% aqueous sodium hydroxide (30 c.c.), adding hydroxylamine hydrochloride (3 g.), heating it at 50° for 5 minutes, and 24 hours later acidifying the mixture with hydrochloric acid. The crude oxime (3·2 g.) was not purified, but after being dried it was warmed with acetic anhydride (5 c.c.) until evolution of carbon dioxide had ceased, and the solution was poured into ice. The ethereal extract was washed free from acid with water, dried, and concentrated. Crystallised from light petroleum (b. p. 60—80°), the *nitrile* had m. p. 75—77° (Found : N, 6·2. $C_{15}H_{13}ON$ requires N, 6·3%); yield 90%.

The *azlactone* of 2-methoxybenzaldehyde was prepared from the aldehyde (18 g.), hippuric acid (20·6 g.), sodium acetate (9·5 g.), and acetic anhydride (74 c.c.); recrystallised from alcohol, it had m. p. 154—156° (Found : N, 5·0. $C_{17}H_{13}O_3N$ requires N, 5·0%). When this was hydrolysed exactly as described for the benzyloxy-compound, it yielded the crude pyruvic acid, the oxime of which, without purification, was treated with acetic anhydride and gave 2-methoxyphenylacetonitrile, m. p. 66—69° (cf. Pschorr *et al.*, *Ber.*, 1900, **33**, 162).

The *azlactone* of 2 : 3-dimethoxybenzaldehyde was prepared from the aldehyde (8·39 g.), hippuric acid (9 g.), acetic anhydride (32 c.c.), and sodium acetate (4·1 g.), and after crystallising from ethyl alcohol had m. p. 167—168° (Found : N, 4·3. $C_{18}H_{15}O_4N$ requires N, 4·5%). From this azlactone, 2 : 3-dimethoxybenzyl cyanide (cf. Montequi, *Anal. Soc. Fis. Quím.*, 1929, **27**, 692) was prepared in the following manner. The azlactone (5 g.) was boiled with 10% aqueous sodium hydroxide (50 c.c.) for 5 hours in nitrogen, the solution cooled to 50°, and hydroxylamine hydrochloride (3 g.) added. After 24 hours, excess of dilute hydrochloric acid was added, and the precipitated mixture of oxime and benzoic acid was dried, warmed with acetic anhydride (10 c.c.) until evolution of carbon dioxide had ceased, and decomposed with ice water; the ethereal extract of the nitrile was washed free from acid with dilute sodium carbonate solution, dried, and concentrated. The pure *nitrile* had b. p. 158—160°/12 mm. (Found : N, 7·5. $C_{10}H_{11}O_2N$ requires N, 7·9%).

4-(2′-*Benzyloxyphenyl*)-1-*methylpiperidine*-4-*nitrile Hydrochloride*.—Powdered sodamide (2·8 g.) was added to a solution of 2-benzyloxyphenylacetonitrile (7·1 g.) and ββ′-dichlorodiethylamine (5 g.) in toluene (30 c.c.) at room temperature with stirring, and the reaction completed by refluxing for one hour. After addition of water to the cooled solution, the mixture was extracted with ether. The ether–toluene solution was extracted with dilute hydrochloric acid, and the extract washed with ether, and made alkaline with dilute sodium hydroxide solution. The precipitated base was extracted with ether, and after removal of the ether the base was purified by warming with light petroleum (b. p. 100—120°), the impurities remaining undissolved. On passing dry hydrogen chloride into this solution, the *hydrochloride* of the base was formed. Recrystallised from ethyl alcohol–ethyl acetate, it had m. p. 220—221° (Found : C, 69·8; H, 6·5. $C_{20}H_{23}ON_2Cl$ requires C, 70·1, H, 6·7%).

Hydrochloride of 4-(2′-*Hydroxyphenyl*)-1-*methylpiperidine*-4-*carboxylic Acid Lactone* (V; R = H).—The above hydrochloride (4 g.) was heated with concentrated hydrochloric acid (24 c.c.) in a sealed tube at 120—130° for 5 hours. After cooling, water was added, and the aqueous solution extracted with ether, and made alkaline with dilute sodium carbonate solution; a base was liberated, the dry ethereal solution of which gave a crystalline *hydrochloride* with ethyl-alcoholic hydrogen chloride. It was purified by sublimation at 200°/0·2 mm. and had m. p. 260—263°. When kept free from moisture the hydrochloride retained this m. p., but on exposure to the atmosphere, the m. p. fell to *ca.* 180°, at which temperature a gas was given off and the original hydrochloride, m. p. 260—263°, was re-formed (Found : C, 59·7; H, 6·6; N, 5·1. $C_{13}H_{16}O_2NCl,\frac{1}{2}H_2O$ requires C, 59·4; H, 6·5; N, 5·3%).

4-(2′ : 3′-*Dimethoxyphenyl*)-1-*methylpiperidine*-4-*nitrile*.—2 : 3-Dimethoxyphenylacetonitrile (8 g.) and ββ′-dichlorodiethylmethylamine (7 g.) were condensed in toluene (50 c.c.) at 80° by the gradual addition of sodamide (4 g.) with stirring, followed by refluxing for 1 hour. On being worked up in the previously described manner, the *nitrile* was obtained as a crystalline solid (m. p. 107—110°) after distillation at 155—157°/0·06 mm. (Found : C, 69·7; H, 7·5; N, 10·8. $C_{15}H_{20}O_2N_2$ requires C, 69·3; H, 7·7; N, 10·8%). The picrate, crystallised from alcohol, had m. p. 194—196°.

4-(2′-*Hydroxy*-3′-*methoxyphenyl*)-1-*methylpiperidine*-4-*carboxylic Acid Lactone* (V; R = OMe).—The above nitrile (2 g.) in hydrobromic acid (*d* 1·3; 20 c.c.) was heated in a nitrogen-filled sealed tube at 120° for 5 hours. On cooling a crystalline hydrobromide separated. It was sublimed in a high vacuum and had m. p. 265—270°. The free *lactone* was obtained by shaking this hydrobromide with a mixture of ether and dilute sodium carbonate solution, and treating the ethereal solution with diazomethane to methylate a small amount of phenolic by-product. Recrystallised from light petroleum (b. p. 60—80°), it had m. p. 115—117° (Found : C, 68·2; H, 6·7; N, 5·9; OMe, 11·5. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7; OMe, 12·5%).

4-(2′-*Methoxyphenyl*)-1-*methylpiperidine*-4-*nitrile*.—Powdered sodamide (12 g.) was gradually added with stirring to a solution of 2-methoxyphenylacetonitrile (22 g.) and ββ′-dichlorodiethylmethylamine (24 g.) in toluene (50 c.c.) at 80°, and the mixture refluxed for 2 hours. On being worked up as previously described, the product was obtained crystalline from light petroleum (b. p. 60—80°); m. p. 97—99° (Found : C, 72·7; H, 8·1; N, 12·1. $C_{14}H_{18}ON_2$ requires C, 72·9; H, 7·8; N, 12·1%). The picrate from alcohol, had m. p. 250°.

4-*Acetyl*-4-(2′-*methoxyphenyl*)-1-*methylpiperidine*.—A solution of methylmagnesium iodide in benzene (50 c.c.) was prepared from magnesium (2 g.) and methyl iodide (11·4 g.), the ether and excess of methyl iodide being removed by distillation, and to the filtered solution was added 4-(2′-methoxyphenyl)-1-methylpiperidine-4-nitrile (4·6 g.), and the mixture refluxed for 16 hours. A little ice and 20% sulphuric acid (20 c.c.) were then added, and the aqueous acid layer made alkaline with aqueous sodium hydroxide; the ketone was thus obtained as an oil, whose *picrate*, recrystallised from alcohol, had m. p. 197—200° (Found : N, 11·9. $C_{21}H_{24}O_9N_4$ requires N, 11·8%). The oxime, from aqueous methanol, had m. p. 150—153°.

4-*Phenyl*-4-(α-*hydroxyethyl*)-1-*methylpiperidine*.—4-Acetyl-4-phenyl-1-methylpiperidine (2 g.) was dissolved in absolute alcohol (50 c.c.), and sodium (4 g.) slowly added. The reaction was completed by heating for 2 hours at 120° under reflux. Some of the alcohol was then distilled off, and the residue treated with water and extracted with ether, which on drying and evaporating left the secondary *alcohol*; after crystallising from light petroleum (b. p. 80—100°) this had m. p. 117—119° (Found : N, 6·6; $C_{14}H_{21}ON$ requires N, 6·4%). The acetate, prepared by treatment of the alcohol with acetic anhydride in pyridine, was an oil, b. p. 113—115°/0·1 mm.

2-*Methyl*-3-4′-spiro-(1′-*methylpiperidine*)*coumaran* (VI; R = H; R′ = Me).—4-Acetyl-4-(2′-methoxyphenyl)-1-methylpiperidine (2·8 g.) was dissolved in absolute alcohol (60 c.c.), sodium (4·8 g.) gradually added, and the solution finally heated at 120° for 2 hours; most of the alcohol was then distilled off, water added, and the precipitated oil extracted with ether. It did not give any crystalline derivatives. The crude alcohol (2·3 g.) was heated in a pressure bottle with hydrobromic acid (*d* 1·7; 10 c.c.) at 120° for 5 hours. On being made alkaline with sodium hydroxide solution and then extracted with ether, this afforded an oil (1 g.), b. p. *ca.* 150°/0·2 mm. It gave a *picrate*, m. p. 182—184° (Found : N, 13·0. $C_{20}H_{22}O_8N_4$ requires N, 12·6%).

4-*Phenyl*-1-*methylpiperidine*.—Sodium (2·8 g.) was added gradually to a solution of 4-phenyl-1-methylpiperidine-4-nitrile (2 g.) in absolute alcohol (34 c.c.) and the solution heated at 130° for 30 minutes; more sodium (1 g.) and alcohol (10 c.c.) were then added, and heating at 130° continued for further 150 minutes. The mixture was poured into water and extracted with ether; the oil (1·5 g.) obtained had b. p. 120—122°/10 mm. This formed a *picrate* which, crystallised from alcohol, had m. p. 239—240°, alone or mixed with the picrate of 4-phenyl-1-methylpiperidine (m. p. 239—240°), prepared by decarboxylation of 4-phenyl-1-methylpiperidine-4-carboxylic acid (cf. B.P. 501,135) (Found : C, 54·2; H, 5·0; N, 13·4. $C_{18}H_{20}O_7N_4$ requires C, 53·5; H, 5·0; N, 13·9%).

4-(2′-*Hydroxyphenyl*)-1-*methylpiperidine*.—4-(2′-Benzyloxyphenyl)-1-methylpiperidine-4-nitrile (3·1 g.) was reduced with sodium (2·5 g.) and absolute alcohol (25 c.c.) as previously described, and after addition of water to the reaction mixture, the solution was neutralised (phenolphthalein) with dilute hydrochloric acid; 4-(2′-*hydroxyphenyl*)-1-*methylpiperidine* was precipitated as a solid which, crystallised from benzene, had m. p. 179—181° (Found : C, 75·6; H, 8·8; N, 7·5. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%).

4-(2′ : 3′-*Dimethoxyphenyl*)-1-*methylpiperidine*.—4-(2′ : 3′-Dimethoxyphenyl)-1-methylpiperidine-4-nitrile (2·6 g.) on reduction with sodium (5 g.) and absolute alcohol (30 c.c.) gave the above *piperidine* as a colourless liquid, b. p. 125—127°/1 mm. (Found : N, 6·9. $C_{14}H_{21}O_2N$ requires N, 6·0%). The *picrate*, from alcohol, had m. p. 159—162° (Found : N, 11·7. $C_{20}H_{22}O_9N_4$ requires N, 12·1%).

4-(2′ : 3′-*Dihydroxyphenyl*)-1-*methylpiperidine*.—The above piperidine (1·2 g.) in 66% hydrobromic acid (10 c.c.)

and acetic acid (5 c.c.) was heated under reflux for 4 hours and then made alkaline with sodium carbonate solution. A little sodium hydrosulphite was added, and the solution extracted with ether, the *dihydroxy*-compound being obtained as a white solid which, crystallised from benzene–alcohol, had m. p. 200—205° (Found : C, 69·4; H, 8·3; N, 6·6. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2; N, 6·8%).

γ-Diethylamino-α-phenyl-α-ethylbutyronitrile was prepared by condensing α-phenylbutyronitrile (8 g.) with β-chloroethyldiethylamine (8·6 g.) in dry toluene (50 c.c.), powdered sodamide (2·7 g.) being added gradually with stirring, and the reaction completed by heating at 130—140° under reflux for one hour. Isolated in the usual way, it was obtained as a colourless oil, b. p. 161—166°/10—12 mm. (Found : N, 11·0. $C_{16}H_{24}N_2$ requires N, 11·4%); yield 9 g.

γ-Phenyl-n-*amyldiethylamine*, formed when the above nitrile (3 g.) was reduced with sodium (4 g.) and absolute alcohol (30 c.c.) as previously described, is a colourless oil, b. p. 134°/15 mm. (Found : N, 7·0. $C_{15}H_{25}N$ requires N, 6·4%).

Bis-(4-*phenyl*-1-*methylpiperidyl*-4-*methyl*)*amine*.—4-Phenyl-1-methylpiperidine-4-nitrile (3 g.), dissolved in absolute alcohol (40 c.c.), was hydrogenated in presence of charcoal (2 g.) and 5% aqueous palladium chloride (5 c.c.), three further 5-c.c. portions of the latter being added during the hydrogenation. When the hydrogen uptake had ceased, the alcoholic solution was freed from catalyst, concentrated to small bulk, excess sodium hydroxide solution added, and the liberated base taken up in ether. The secondary *amine* distilled at 160—170°/0·05 mm.; recrystallised from light petroleum (b. p. 60—80°), it had m. p. 90—93° (Found : C, 80·0; H, 9·6; N, 10·4. $C_{26}H_{37}N_3$ requires C, 79·8; H, 9·5; N, 10·7%).

RESEARCH DEPARTMENT, ROCHE PRODUCTS LTD., WELWYN GARDEN CITY. [*Received, January 5th*, 1944.]