

40. Synthetic Mydriatics. Diphenylchloroacetyl Chloride as a Reagent for the Preparation of Benzoic Esters of Tertiary Amino-alcohols.

By F. E. KING and D. HOLMES.

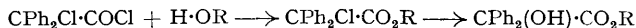
The benzoic esters of β -dimethylaminoethanol, 4-diethylaminobutan-2-ol, *trans*-2-dimethyl- and -diethyl-aminocyclohexanol and phenyl- β -dimethylaminoethylcarbinol, mostly in the form of their simple quaternary salts, have been prepared for evaluation as mydriatics. A convenient synthesis has been developed in which the tertiary amino-alcohols, or their hydrochlorides or metho-chlorides, are esterified with diphenylchloroacetyl chloride, the resulting chloro-esters being converted into the corresponding esters of benzoic acid by heating with water.

VARIOUS benzoic esters of amino-alcohols have from time to time been the subject of pharmacological investigations, and the recent work of Blicke and Maxwell (*J. Amer. Chem. Soc.*, 1942, **64**, 428; 1943, **65**, 1967) and of Ford-Moore and Ing (this vol., p. 55) has shown that certain quaternary salts of the simple dialkylaminoethyl benzoates possess mydriatic properties comparable with those of atropine. Extending these synthetical experiments to other benzoic esters, for example, those of secondary and/or cyclic alcohols—which consequently have rather more in common with the natural base—a new method for the preparation of benzoic esters has been elaborated.

Hitherto, the mydriatic benzoates have been obtained either by the action of salts of the basically substituted halides on potassium benzoate, or by heating the free aminoalkyl halides with benzoic acid in an organic solvent (Horenstein and Pählicke, *Ber.*, 1938, **71**, 1645; Blicke and Maxwell, *loc. cit.*). The preparation of the necessary halides is, however, sometimes inconvenient, and experiments were undertaken to synthesise the required esters by the method generally used for tropeines, *viz.*, the action of the acetylated hydroxy-acid chloride on the amino-alcohol, followed by hydrolysis of the protecting acetyl group.

Acetylbenzoic acid was obtained by acetylation with acetic anhydride at 100°, as described by La Mer and Greenspan (*J. Amer. Chem. Soc.*, 1934, **56**, 956), who showed that the recrystallised derivative is a monohydrate requiring prolonged vacuum desiccation over sulphuric acid for complete dehydration. Our attempts to hasten the removal of water by heating, etc., gave uncrystallisable products, but shaking in ether solution with anhydrous copper sulphate gave the dehydrated acid in two or three days. Hurd and Williams (*ibid.*, 1936, **58**, 967) claim that the action of boiling thionyl chloride on the anhydrous acid gives acetylbenzoyl chloride in 48% yield, but they have not recorded an analysis for their product, and, despite many attempts under various conditions, we have failed to obtain a homogenous specimen of the desired compound.

While searching for some more stable substituted benzoic acid for use during the acid chloride stage, the labile character of the halogen atom in diphenylchloroacetic acid and its derivatives was noted (cf. Bickel, *Ber.*, 1889, **22**, 1538). The chloro-acid chloride is readily obtained from benzoic acid in one operation, and so the synthesis indicated by the following equation was investigated :



Later, a reference to the use of this method for the synthesis of benzyl- ψ -tropine was encountered (Wolfe and Hromatka, D.R.-P. 655,404; *Chem. Centr.*, 1938, **I**, 2755), but no practical details are to be found in available sources.

The basic alcohol chosen for the first experiments was choline, since benzylcholine chloride (β -dimethylaminoethyl benzoate methochloride) was already known from the work of Ford-Moore and Ing (*loc. cit.*). Starting from β -aminoethanol, which was methylated by the formic acid-paraformaldehyde method (cf. *J.*, 1945, 278), choline chloride was prepared from the resulting dimethylaminoethanol by converting it into the methiodide, which was then treated with silver chloride. The product obtained by heating the dry metho-salt with diphenylchloro-

acetyl chloride—presumably the diphenylchloroacetylcholine chloride—gave β -dimethylaminoethyl benzilate methochloride on dissolving in boiling water. The process was then applied to the readily prepared 4-diethylaminobutan-2-ol, a reduction product of the corresponding Mannich ketone, and it was shown that the identical *diphenylchloroacetate hydrochloride* was obtainable from either the free diethylaminobutanol or its hydrochloride. Hydrolysis with boiling water and neutralisation gave the crystalline 4-diethylamino-2-butyl benzilate. The amine methiodide on double decomposition with silver chloride gave the benzilate *methochloride*, which proved to have only about 6% of the mydriatic activity of atropine.

In view of the presence in tropine of a cyclic secondary alcohol group, new syntheses were undertaken with amino-cyclohexanols. 2-Amino-cyclohexanols are obtainable from cyclohexene oxide, which reacts with simple amines to give products of *trans*-configuration (cf. Godchot and Mousseron, *Compt. rend.*, 1932, **194**, 981). *trans*-2-Dimethylaminocyclohexanol, formed when dimethylamine is used (Kötz and Merkel, *J. pr. Chem.*, 1926, **113**, 63), gave on heating with diphenylchloroacetyl chloride the expected *chloro-ester hydrochloride*, and this was hydrolysed to the *benzilate hydrochloride* by dissolving in boiling water. The free base combined without difficulty with methyl iodide, and the *methiodide* and corresponding *methochloride* were readily crystallised. On the other hand, formation of the *ethiodide*, from which an *ethochloride* was prepared, was appreciably slower. An attempt to condense *trans*-2-dimethylaminocyclohexanol *methochloride* with diphenylchloroacetyl chloride, as an alternative route to the foregoing benzilate methochloride, was unsuccessful.

Homologues in the 2-diethylaminocyclohexanol series have also been synthesised, the *trans*-diethylaminocyclohexanol (Brunel, *Ann. Chim. Phys.*, 1905, **6**, 259) reacting readily with the chloro-acid chloride at 100—105°. The resulting 2-diethylaminocyclohexyl *diphenylchloroacetate hydrochloride* was rapidly hydrolysed to the *benzilate hydrochloride* by boiling water. Heating with methyl iodide in a sealed tube was necessary to obtain the methiodide, which was converted into the *benzilate methochloride* in the usual way. The diethylamino-ester failed to react with ethyl iodide, except under conditions which led to decomposition.

The mydriatic properties of ephedrine, adrenaline, and similar amino-alcohols likewise encouraged investigations on the benzilic esters of this series. Phenyl- β -dimethylaminoethylcarbinol, which can readily be prepared from the corresponding ketone (Mannich and Heilner, *Ber.*, 1922, **55**, 359), is a homologue of the ephedrine type, and the preparation of its benzilate was therefore attempted. The action of diphenylchloroacetyl chloride on the free base failed, however, to give a crystalline product, and when the amine hydrochloride was substituted, dehydration ensued giving γ -phenylallyldimethylamine, isolated as *hydrochloride*. The identity of the unsaturated base was proved by reduction to γ -phenylpropyldimethylamine, which was characterised by the melting points of its known salts. Nevertheless, the properties of the unsaturated hydrochloride are not in agreement with those already recorded by Mannich and Chang (*ibid.*, 1933, **66**, 419) for the apparently identical salt, and it is probable that the two compounds are *cis-trans*-isomerides.

In the meantime, further experiments with 2-diethylaminocyclohexanol had shown that, on mixing diphenylchloroacetyl chloride with *twice* the theoretical quantity of amino-alcohol in an inert solvent, ester formation occurs in the cold, the second molecule of the base precipitating as hydrochloride. The application of this technique to phenyl- β -dimethylaminoethylcarbinol resulted in the formation of a high yield of the chloro-ester, hydrolysed by boiling water to the required *benzilate*, from which was obtained the crystalline *methochloride*.

Finally, a lower homologue of the foregoing amino-alcohol, *i.e.*, phenyldimethylaminomethylcarbinol, was prepared, and characterised by its crystalline *hydrochloride* and *methiodide*.

The specific character of the β -aminoethanol grouping in conferring mydriatic properties in the series of benzilic esters is emphasised by tests, kindly carried out by Professor J. H. Burn, F.R.S., and Miss E. Bülbring, Department of Pharmacology, Oxford, which revealed that none of the new benzilic esters described in this paper possesses more than very slight mydriatic activity.

EXPERIMENTAL.

Acetylbenzilic Acid (cf. La Mer and Greenspan, *loc. cit.*).—A solution of benzilic acid (50 g.) in acetic anhydride (100 c.c.) was heated for 10 hours on a steam-bath, cooled, and as much water added as possible without causing turbidity (*ca.* 25 c.c.). Within 2 or 3 hours the crystalline acetate had begun to separate, and from then on further small quantities of water were added at intervals to a total of *ca.* 200 c.c. The resulting acetylbenzilic acid monohydrate (51—55 g.) had m. p. 96—97°. Dissolution in alcohol (150 c.c.) at 40° (charcoal) and precipitation with water (200 c.c.) gave the pure acetyl compound (42 g., 68%), m. p. 97°. Acetylation in presence of sulphuric acid (5 g./100 c.c. acetic anhydride) or sodium acetate (12—13 g./100 c.c.) effected no significant improvement in yield.

In attempting to prepare the anhydrous acetyl derivative, benzoic acid was treated with acetyl chloride as in the preparation of acetylmandelic acid (*Org. Synth.*, IV, 1). It was necessary to heat the mixture to dissolve the acid, and evaporation left an uncrystallisable syrup. When the mixture of acid and acetyl chloride was left overnight at room temperature, large colourless tablets were formed, m. p. 117—118° after crystallisation from benzene-petroleum, which were probably diphenylchloroacetic acid.

La Mer and Greenspan obtained the anhydrous acetylated acid by 3 weeks' desiccation at room temperature. In trying to shorten the time of drying, a specimen of the acid monohydrate was heated at 50—55°/15 mm. in presence of phosphoric anhydride for 2 hours. A colourless sticky glass had then formed, and the odour of acetic acid was detected. Evaporation of a solution of the hydrate (4 g.) in anhydrous benzene (100 c.c.) at 35°/16 mm. also gave a non-crystalline product. The recrystallised hydrate (20 g.) was therefore dissolved in dry ether (200 c.c.) to which anhydrous copper sulphate (20 g.) was added. After being shaken at intervals for 2—3 days, the solution was filtered and evaporated below 25° under reduced pressure, and the anhydrous acid (15.5 g.), m. p. ca. 103°, obtained by trituration with light petroleum.

Following Hurd and Williams (*loc. cit.*), the anhydrous acid was heated for 2 hours with purified thionyl chloride. Distillation at 15 mm. was accompanied by considerable decomposition and gave a reddish-yellow product (30—35% yield), but, as recorded by the American authors, it afforded a crystalline anilide. An ether solution (200 c.c.) of the anhydrous acid (8.6 g.) and thionyl chloride (2½ mol.) which 2½ hours later was gently refluxed for 30 minutes, gave on distillation at 0.5 mm. (air-bath at 155°) a pale yellow oil (2.9 g.), but analysis showed it to be impure. Similarly, experiments in which both hydrated and anhydrous acetylbenzoic acid were left with thionyl chloride for various times (up to 15 hours) at room temperature, the surplus reagent then being removed under reduced pressure, also failed to give a homogeneous product.

Diphenylchloroacetyl Chloride (cf. Bickel, *loc. cit.*; Billman and Hidy, *J. Amer. Chem. Soc.*, 1943, 65, 760).—When the energetic reaction between phosphorus pentachloride (38 g., 2.08 mols.) and benzoic acid (20 g., 1 mol.) had subsided, the mixture was heated at 100° for 15 minutes. Phosphoryl chloride was then removed under diminished pressure at 60—70°, and the residue shaken with ice and water. The solid product was taken up in light petroleum (b. p. 45—55°), dried (Na₂SO₄), the solution evaporated and diphenylchloroacetyl chloride obtained as a colourless solid, m. p. 50—51°, b. p. 139—143°/0.15—0.2 mm., yield 75%.

β-Dimethylaminoethanol.—Ethanamine (30.5 g., 1 mol.) was neutralised with anhydrous formic acid (46 g., 2 mol.) and the solution cautiously heated with paraformaldehyde (30 g., 2 mol.). At ca. 100° a vigorous evolution of carbon dioxide occurred, after which the dark red liquid was heated at 130—140° for 30 minutes. Distillation gave a colourless aqueous solution (45 g.), b. p. 100—135°/748 mm., of *β*-dimethylaminoethanol identified by the picrolonate, which separated from alcohol in long yellow needles, m. p. 195—197° (Knorr and Matthes, *Ber.*, 1901, 34, 3484, give m. p. 197°) (Found: C, 47.9; H, 5.6. Calc. for C₄H₁₁ON, C₁₆H₈O₈N₂: C, 47.6; H, 5.4%). The aqueous base (44.5 g.) was dissolved in methyl alcohol (30 c.c.) and treated with methyl iodide (70 g.). After refluxing for 30 minutes the solution was evaporated and the crystalline residue (77 g., indicating a 67% yield in the ethanamine methylation) was recrystallised from methyl alcohol. Choline iodide was thus obtained in shining deliquescent plates, m. p. ca. 262—264° (efferv.). The chloride obtained therefrom by treating it in aqueous methyl alcohol with silver chloride, crystallised from acetone containing a little alcohol in deliquescent needles, m. p. >300°.

β-Dimethylaminoethyl Benzilate Methochloride.—A mixture of diphenylchloroacetyl chloride (2.6 g., 1 mol.) and choline chloride (1.4 g., 1 mol.) was heated for 1 hour in an oil-bath at 110°, hydrogen chloride being evolved. The product, a clear glassy solid, failed to crystallise and it was therefore dissolved in boiling water (18—20 c.c.). Next day, the voluminous crystalline mass (2.8 g.) which had formed was crystallised from ethyl acetate containing a little methyl alcohol. The methochloride separated in sheaves of minute prisms, m. p. 216° (efferv.) [Ing records m. p. 216° (decomp.)] (Found: C, 65.1; H, 6.8. Calc. for C₁₈H₂₁O₃N, CH₃Cl: C, 65.2; H, 6.9%).

4-Diethylamino-2-butyl Diphenylchloroacetate Hydrochloride.—(a) A mixture of 4-diethylaminobutan-2-ol hydrochloride (2.2 g.) and diphenylchloroacetyl chloride (3.75 g.) when heated at 100° for 50 minutes evolved hydrogen chloride. The resulting clear amber syrup was dissolved in acetone, and the *hydrochloride* crystallised on standing in colourless, stout rectangular prisms (3 g.), m. p. 120° (Found: C, 64.3; H, 6.9. C₂₂H₂₈O₂NCl, HCl requires C, 64.4; H, 7.1%).

(b) Using the free amino-alcohol (1.8 g.), which reacted exothermally with the acid chloride (3.9 g.), a clear syrup was formed which solidified during heating at 100° for 30 minutes. By treatment with acetone the identical hydrochloride (5 g.) (m. p. and mixed m. p.) was obtained, the higher yield being due to more economical crystallisation.

4-Diethylamino-2-butyl Benzilate.—The foregoing diphenylchloroacetate hydrochloride (5 g.), which is sparingly soluble in cold water, was heated on a steam-bath with water (40 c.c.) for 4 minutes. Next day, the clear solution was evaporated to dryness under diminished pressure, but the residue could not be crystallised, and it was therefore redissolved and the solution neutralised with aqueous sodium hydroxide. The liberated hydroxy-ester was removed in ether which was dried and evaporated, leaving a gum that later solidified. The *benzilate* separated from a small quantity of light petroleum in thick prisms, m. p. 44° (Found: C, 74.4; H, 8.2. C₂₂H₂₉O₃N requires C, 74.4; H, 8.2%). When dissolved in alcoholic picrolonic acid a deep yellow *picrolonate*, m. p. 141°, was obtained (Found: C, 61.7; H, 6.0. C₂₂H₂₉O₃N, C₁₀H₈O₈N₄ requires C, 62.0; H, 6.0%).

4-Diethylamino-2-butyl Benzilate Methochloride.—The addition of methyl iodide (3 g.) to a dry ether solution of the benzilic ester (3 g.) soon gave a flocculent amorphous precipitate. This could not be crystallised, but was dissolved next day in water (40 c.c.) and methyl alcohol (20 c.c.), shaken with freshly precipitated silver chloride (3 g.), and heated on a steam-bath before filtration. Evaporation under diminished pressure gave a clear gum which crystallised in contact with acetone, in which the *methochloride* is very sparingly soluble. By precipitation from a very small volume of ethyl alcohol with

hot ethyl acetate the pure salt was obtained in spheroidal aggregates of prisms, m. p. after drying in a vacuum, 173—175° (Found: C, 67.7; H, 7.5. $C_{22}H_{29}O_2N, CH_3Cl$ requires C, 68.1; H, 7.9%).

trans-2-Dimethylaminocyclohexanol.—The preparation of the dimethylaminocyclohexanol from cyclohexene (*Org. Synth.*, V, 31) followed closely the method of Kötze and Merkel (*loc. cit.*). The product, b. p. 83—83.5°/13 mm., was obtained in 93% yield, and gave a *picrate* crystallising from ethanol in fine pale yellow needles, m. p. 149—150° (Found: C, 45.4; H, 5.4. $C_8H_{17}ON, C_6H_5O_7N_3$ requires C, 45.2; H, 5.4%). The amine methiodide separated from alcohol-ethyl acetate in stout rods, m. p. 217—217.5° (Wilson and Read, *J.*, 1935, 1273, record m. p. 214°), and the *methochloride* in colourless deliquescent needles, m. p. 253—254° (decomp.), from ethyl acetate containing ethanol. An attempt to convert this compound into a diphenylchloroacetate did not succeed, apparently owing to the insolubility of the metho-salt in the fused acid chloride.

2-Dimethylaminocyclohexyl Diphenylchloroacetate Hydrochloride.—When molten diphenylchloroacetyl chloride (10 g.), supercooled to 40°, was added with stirring to 2-dimethylaminocyclohexanol (5 g.), an exothermic reaction occurred accompanied by slight charring. The pasty mass, frequently stirred, was heated at 105—110° for 2½ hours and afterwards refluxed with dry acetone (10 c.c.). When cold, the product was collected and washed with acetone which left the *diphenylchloroacetate hydrochloride* as a colourless solid (10.8 g., 76%), m. p. 178—185°. A sample recrystallised from dry acetone-methyl alcohol by precipitation with ether separated in spherical aggregates of small plates, m. p. 185.5—186.5° (decomp.) (Found: C, 64.3; H, 6.8; N, 3.6; Cl, 17.2. $C_{22}H_{26}O_2NCl, HCl$ requires C, 64.7; H, 6.7; N, 3.4; Cl, 17.4%).

2-Dimethylaminocyclohexyl Benzilate.—The chloro-ester hydrochloride (10 g.), m. p. 178—185°, was dissolved in hot water (10 c.c.) and, after 5 minutes at 100°, the crystalline solid which had precipitated was taken up in alcohol (100 c.c.) and water (20 c.c.). On cooling, the *benzilate hydrochloride* (8.8 g., 90%) separated in rods, m. p. 227—229° (decomp.) raised by one crystallisation from aqueous alcohol to 230—231° (decomp.) (Found: C, 67.7; H, 7.3. $C_{22}H_{27}O_2N, HCl$ requires C, 67.8; H, 7.2%). The free base, liberated from the powdered hydrochloride by aqueous ammonia and isolated with ether, was a straw-coloured gum which could not be crystallised. A portion in alcoholic solution was converted into the *picrate* which, crystallised from alcohol-acetone (4:1), formed deep yellow lustrous plates, m. p. 186—187° (Found: C, 57.9; H, 5.3. $C_{22}H_{27}O_2N, C_6H_5O_7N_3$ requires C, 57.7; H, 5.3%).

The dimethylamino-benzilate (2.8 g.) was treated with methyl iodide (8 g.) and the mixture refluxed for 1 hour. The excess of reagent was evaporated and the residue taken up in alcohol-acetone (1:1). Recrystallisation of the product (3.5 g., m. p. ca. 150°) from alcohol-ethyl acetate gave the pure *methiodide* (3 g.) as aggregates of colourless shining plates, m. p. 145—146° (Found: C, 54.0; H, 6.2; I, 24.6. $C_{22}H_{27}O_2N, CH_3I, H_2O$ requires C, 53.8; H, 6.3; I, 25.6%).

The crude methiodide (2.9 g.) was dissolved in hot aqueous methyl alcohol and shaken for 10 minutes with freshly precipitated silver chloride (1.5 mol.). The product obtained by evaporation of the filtered solution was a pale yellow friable mass which by crystallisation from acetone-methyl alcohol gave the *methochloride* in colourless plates, m. p. 217—217.5° (decomp.) (Found: C, 68.2; H, 7.7; Cl, 8.9. $C_{22}H_{27}O_2N, CH_3Cl$ requires C, 68.4; H, 7.5; Cl, 8.8%).

When the dimethylamino-benzilate (2.7 g.) dissolved in ether (4 c.c.) was treated with ethyl iodide scarcely any reaction occurred, and so the mixture was refluxed for 7—8 hours. The solvents were then evaporated, and the clear gum was dissolved in methyl alcohol and the solution cautiously diluted with water. Recrystallisation from aqueous methanol gave the pure *ethiodide* (2.6 g.) in lustrous plates, m. p. 144—145° (Found: C, 55.5; H, 6.7. $C_{22}H_{27}O_2N, C_2H_5I, CH_3OH$ requires C, 55.5; H, 6.7%).

An aqueous methyl alcoholic solution of the ethiodide (2.3 g.) was shaken with silver chloride (1.1 mols.) for ½ hour, and the filtered liquid then evaporated. On dissolving the residue in the minimum amount of methyl alcohol and diluting with acetone, the *ethochloride* (1.4 g.) crystallised as a cake of colourless prisms, which after recrystallisation and drying at 100°/18 mm. had m. p. 185—186° (decomp.) (Found: C, 68.5; H, 7.7; Cl, 8.1. $C_{22}H_{27}O_2N, C_2H_5Cl$ requires C, 69.0; H, 7.7; Cl, 8.5%).

2-Diethylaminocyclohexyl Diphenylchloroacetate Hydrochloride.—(a) Molten diphenylchloroacetyl chloride (7.8 g.) supercooled to 30° was mixed with 2-diethylaminocyclohexanol (5 g.). After the initial reaction and heating at 100—105° for 30 minutes, a solid product was obtained which after being refluxed and washed with acetone was crystallised from ethyl acetate containing a little methyl alcohol. The *diphenylchloroacetate hydrochloride* (7.9 g.) was finally obtained in colourless cubes, m. p. 193—194° (decomp.) after slight sintering above 191° (Found: C, 65.8; H, 7.1. $C_{24}H_{30}O_2NCl, HCl$ requires C, 66.0; H, 7.2%).

(b) 2-Diethylaminocyclohexanol (2 g., 2 mols.) was mixed with the acid chloride (1.6 g., 1 mol.) in dry benzene (25 c.c.). After standing overnight, the nearly theoretical quantity of the amino-alcohol hydrochloride, m. p. 167—169°, had precipitated (Brunel, *loc. cit.* gives m. p. 168°). The filtrate was saturated with dry hydrogen chloride and then evaporated to dryness. The residual gum dissolved in dry acetone and diluted with ether gave the above hydrochloride (1.7 g., 68%), m. p. 190—192°.

2-Diethylaminocyclohexyl Benzilate.—The crude chloro-ester hydrochloride (9.7 g.) was boiled with water (15 c.c.) for 2 minutes. On cooling, the *benzilate hydrochloride* separated, and when recrystallised from aqueous alcohol formed colourless prisms, m. p. 204—205° (decomp.) (Found: C, 69.0; H, 7.8; Cl, 8.5. $C_{24}H_{31}O_2N, HCl$ requires C, 69.0; H, 7.7; Cl, 8.5%).

The free *benzilate* (5.9 g.) was liberated from the powdered hydrochloride (7.1 g.) by ammonia and collected in ether (Found on a specimen distilled at 0.025 mm., air-bath at 195°: C, 75.7; H, 8.1. $C_{24}H_{31}O_2N$ requires C, 75.6; H, 8.2%). It gave a *picrate* crystallising from ethanol-acetone in star-shaped clusters of slender yellow needles, m. p. 169—169.5° (Found: C, 59.0; H, 5.65. $C_{24}H_{31}O_2N, C_6H_5O_7N_3$ requires C, 59.0; H, 5.6%). The base (2.9 g.), a straw-coloured gum, was refluxed in ether solution with methyl iodide (5 mols.) for 4 hours, and the product isolated by evaporation of the solvents was dissolved in the minimum of methyl alcohol and diluted with water. The product which separated over-night, washed first with methyl alcohol and then ether, gave a crystalline residue (1.1 g.); unchanged base (2.1 g.) was recovered from the washings. Treatment of the latter with methyl iodide in a sealed tube at 100° for 2 hours gave a further 0.7 g. of solid; total yield, 46%. The product

was difficult to recrystallise and was therefore treated with silver chloride in aqueous methyl alcohol to give, after evaporation of the filtered solution, the *methochloride*, which recrystallised from methyl alcohol-acetone in minute octahedra, m. p. 200—200.5° (decomp.) (Found: C, 69.4; H, 8.2; Cl, 8.6. $C_{24}H_{31}O_3N, CH_3Cl$ requires C, 69.5; H, 7.9; Cl, 8.2%).

γ-Phenylallyldimethylamine.—Phenyl-β-dimethylaminoethylcarbinol hydrochloride (Mannich and Heilner, *loc. cit.*) (6 g.) was treated with diphenylchloroacetyl chloride (7.4 g.) and heated to 115°, whereat the amber-coloured fluid slowly evolved hydrogen chloride for 7 hours. The product obtained by dissolution in boiling ethyl acetate and precipitation with ether crystallised from alcohol-ethyl acetate giving the required *hydrochloride* (2.9 g.) in long thin plates, m. p. 190.5—191° (Found: C, 66.9; H, 8.2; N, 6.5; Cl, 18.0. $C_{11}H_{15}N, HCl$ requires C, 66.8; H, 8.2; N, 7.1; Cl, 17.9%). Mannich and Chang (*loc. cit.*) give m. p. 147°, but in view of the manner of its preparation their compound may be the *cis*-isomeride.

The free base, liberated by ammonia and isolated with ether, was a straw-coloured oil characterised by the *picrate*, aggregates of pale yellow plates, m. p. 124—125° (Found: C, 52.2; H, 4.7. $C_{11}H_{15}N, C_6H_3O_3N_3$ requires C, 52.3; H, 4.7%). The vigorous reaction of the base with methyl iodide gave a *methiodide*, which formed pale cream plates, m. p. 182—183° after 2 crystallisations from alcohol (Found: C, 47.9; H, 6.1; I, 42.2. $C_{11}H_{15}N, CH_3I$ requires C, 47.5; H, 6.0; I, 41.9%).

When the unsaturated amine hydrochloride was heated with aqueous permanganate the odour of benzaldehyde was noticed. The salt was reduced in the presence of palladised charcoal, and *γ*-phenylpropyldimethylamine hydrochloride, m. p. 139—146°, obtained by crystallisation from acetone in very deliquescent needles (literature, 146°). For the amine picrate, m. p. 100—101° was observed (Mannich and Heilner found 103°).

γ-Dimethylamino-α-phenylpropyl Benzilate.—When diphenylchloroacetyl chloride (1.5 g., 1 mol.) dissolved in dry ether (20 c.c.) was slowly added to a solution of phenyl-β-dimethylaminoethylcarbinol (2 g., 2 mol.), a solid (1.2 g.) separated which was identified by its m. p. 135—136° as the amino-alcohol hydrochloride. After 12 hours the solution was filtered, treated with dry hydrogen chloride, and evaporated. The residue solidified when washed with ether, and had m. p. ca. 80°, but was difficult to recrystallise satisfactorily, and was therefore directly hydrolysed by heating with boiling water for 5 minutes. The *γ-dimethylaminoethyl-α-phenylpropyl benzilate* (1.76 g., 80%), isolated by treatment with ammonia and ether extraction, distilled at 0.02 mm. (bath at 175—180°), and then separated from light petroleum in asteroid clusters, m. p. 98.5—99.5° (Found: C, 76.9; H, 6.8. $C_{25}H_{27}O_3N$ requires C, 77.1; H, 6.9%).

Heating with methyl iodide gave a glassy methiodide converted by silver chloride in hot aqueous methanol into a *methochloride*, which was isolated, by evaporation and recrystallisation from acetone containing a trace of ethanol, in long slender needles, m. p. 211—212° (Found: C, 70.7; H, 7.0; Cl, 8.0. $C_{25}H_{27}O_3N, CH_3Cl$ requires C, 71.0; H, 6.9; Cl, 8.1%).

Phenyldimethylaminomethylcarbinol.—Dimethylaminoacetophenone, b. p. 122—122.5°/14—15 mm., was obtained in 60% yield from dimethylamine and bromoacetophenone in benzene (cf. v. Braun and Weissbach, *Ber.*, 1929, **62**, 2425). The amino-ketone (7.2 g.) in dry ethanol (40 c.c.) was hydrogenated at N.T.P. using platinum oxide catalyst, 70% absorption occurring in 3 hours. Complete reduction required 24 hours, after which the product was distilled, whereby the *amino-alcohol* was obtained as a pale straw-coloured oil (5.7 g., 78%), b. p. 94—97°/1 mm., n_D^{20} 1.517 (Found: C, 72.6; H, 9.3. $C_{10}H_{15}ON$ requires C, 72.7; H, 9.15%). The *methiodide* crystallised from ethanol in colourless stout prisms, m. p. 226° (Found: C, 43.4; H, 5.6; I, 41.75. $C_{10}H_{15}ON, CH_3I$ requires C, 43.0; H, 5.9; I, 41.3%). Pharmacological data are given for the amino-alcohol by Alles and Knoefel (*Arch. int. Pharmacodyn.*, 1934, **47**, 96) but its preparation has not been recorded. An optically active form of the base is known from the methylation of a natural product (Men'shikov and Rubinstein, *J. Gen. Chem. Russia*, 1943, **13**, 801).

When diphenylchloroacetyl chloride (1 mol.) and the alcohol (2 mol.) reacted in ether solution, the amine *hydrochloride* separated and was obtained by crystallisation from ethanol-ethyl acetate (1 : 3) as glistening minute plates, m. p. 150—151° (Found: C, 59.7; H, 7.9. $C_{10}H_{15}ON, HCl$ requires C, 59.5; H, 8.0%). Evaporation of the ethereal filtrate treated with hydrogen chloride left a syrup which on solution in ethyl acetate gave needles, m. p. 142—143.5°; but the product was not analytically pure.

This paper is published with the permission of the Chief Scientific Officer, Ministry of Supply.

DYSON PERRINS LABORATORY, OXFORD.

[Received, June 11th, 1946.]