306. *Synthetic Analgesics. Part IX. Synthesis of Compounds Related to Amidone.*

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Two compounds in the amidone series, 1-methylallylamino-3 : 3-diphenylhexan-4-one and 1-diallylamino-3 : 3-diphenylhexan-4-one have been prepared but found to possess slight analgesic action. A new synthesis of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (amidone nitrile) is described.

In attempts to prepare the nitroso-derivative of the substance formed by hydrogenation of 3-benzhydrylmethylamino-1 : 1-diphenylpropyl cyanide, 3 : 3-diphenyl-1-methylpyrrolid-2-one was isolated.

The preparation of amidone was first described in Report No. PB-981, U.S.A. Office of the Publication Board, Department of Commerce, and more recently an improved synthesis of the intermediate 3-dimethylamino-1 : 1-diphenylbutyl cyanide has been reported by Schultz, Robb, and Sprague (*J. Amer. Chem. Soc.*, 1947, **69**, 2454).

In the preparation of amidone from this nitrile by treatment with ethylmagnesium iodide in toluene, it was found that, when the toluene solution of the Grignard reaction mixture was decomposed by warm 2N-sulphuric acid, amidone sulphate separated and after cooling could be filtered off in at least 90% yield.

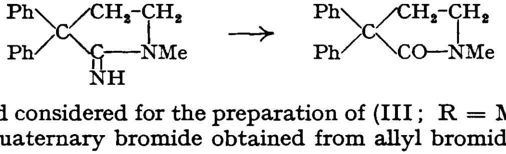
It was early recognised that one of the disadvantages of amidone was the definite depressant effect it exerted on respiration. We considered, in view of the work of Hart and McCawley (*J. Pharm. Exp. Ther.*, 1944, **82**, 339) and of Unna (*ibid.*, 1943, **79**, 27) on *N*-allylnormorphine, that it would be of interest to make and test substances of the amidone series which carried allyl groups on the nitrogen atom.

Benzhydryl cyanide and ethylene dichloride in presence of sodamide gave 3-chloro-1 : 1-diphenylpropyl cyanide (I) (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500) which, when heated with methylallylamine, gave 3-methylallylamino-1 : 1-diphenylpropyl cyanide (II; R = Me, R′ = $CH_2{:}CH{\cdot}CH_2$), whence ethylmagnesium iodide afforded 1-methylallylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = $CH_2{:}CH{\cdot}CH_2$). In a similar manner from diallylamine, 3-diallylamino-1 : 1-diphenylpropyl cyanide (II; R = R′ = $CH_2{:}CH{\cdot}CH_2$), and 1-diallylamino-3 : 3-diphenylhexan-4-one (III; R = R′ = $CH_2{:}CH{\cdot}CH_2$) were prepared. Methylallylamine was obtained most readily by applying the method of Decker and Becker (*Annalen*, 1913, **395**, 362) to unsaturated amines.

$$Ph_2C(CN){\cdot}CH_2{\cdot}CH_2Cl \qquad Ph_2C(CN){\cdot}CH_2CH_2{\cdot}NRR' \xrightarrow{C_2H_5{\cdot}MgI} Ph_2C(COEt){\cdot}CH_2{\cdot}CH_2{\cdot}NRR'$$

(I.) (II.) (III.)

Two other methods of preparing compounds of type (III; R = Me, R′ = $CH_2{:}CH{\cdot}CH_2$) were tried. Benzhydrylmethyl-2-chloroethylamine, obtained by chlorination of benzhydrylmethyl-2-hydroxyethylamine, was condensed with benzhydryl cyanide to give 3-benzhydrylmethylamino-1 : 1-diphenylpropyl cyanide (II; R = Me, R′ = $CHPh_2$). Although previous work had shown that it was not practicable to remove a benzyl group from a tertiary amine and leave a nitrile group in the same molecule unaffected (cf. Bergel, Hindley, Morrison, and Rinderknecht, *J.*, 1944, 269), it was hoped in view of work described in B.P. 607,772 that this would be possible where a benzhydryl group was involved. Hydrogenation of (II; R = Me, R′ = $CHPh_2$) proceeded slowly and gave a small amount of product, b. p. 155—160°/0·3 mm., which on addition of 2N-hydrochloric acid gave a crystalline hydrochloride, m. p. 226—228°. Heating an aqueous solution of this salt with potassium nitrite gave a neutral product, m. p. 146—148°, which instead of the expected nitroso-derivative proved to be 3 : 3-diphenyl-1-methylpyrrolid-2-one (V). The formation of this compound can be explained by the intermediate formation of 2-imino-3 : 3-diphenyl-1-methylpyrrolidine (IV), which has not been characterised.


(IV.) (V.)

The alternative method considered for the preparation of (III; R = Me, R′ = $CH_2{:}CH{\cdot}CH_2$) was to hydrogenate the quaternary bromide obtained from allyl bromide and 1-benzylmethylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2Ph) (Dupré *et al.*, *loc. cit.*) so as to remove the benzyl group. Hydrogenation of the quaternary salt with palladium–barium sulphate catalyst and 1 mole of hydrogen gave a product which could be separated into two fractions on distillation at 0·1 mm. Fraction 1 had b. p. 146°/0·1 mm. and analysed as 1-methylallylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = $CH_2{:}CH\cdot CH_2$) or 1-methylpropylamino-3 : 3-diphenylhexan-4-one (R = Me, R′ = Pr^n), while fraction 2 had b. p. 180—190°/0·1 mm. and analysed as 1-benzylmethylamino-3 : 3-diphenylhexan-4-one (III; R = Me, R′ = CH_2Ph). This result indicates that an allyl group is just as susceptible to hydrogenolysis as a benzyl group (cf. Howton, *J. Amer. Chem. Soc.*, 1947, **69**, 2555).

The original German method for synthesising amidone involves a considerable waste of material, as at least two isomeric nitriles are formed in the reaction of the base from 2-chloropropyldimethylamine hydrochloride and benzhydryl cyanide, only one of which gives amidone. In a search for a more economical preparative method for amidone nitrile we explored the possibilities of the following synthesis: Benzhydryl cyanide was condensed with 1-chloro-2 : 2-diethoxyethane to give 2-cyano-2 : 2-diphenylpropaldehyde diethyl acetal (VI), which on acid hydrolysis gave the corresponding aldehyde (VII), characterised by its azine. Treatment of (VII) with 1 mole of methylmagnesium iodide gave a product b. p. 154—156°/0·1 mm., which analysed correctly for the expected secondary alcohol (VIII). It might be expected that the product should be 2-imino-3 : 3-diphenyl-5-methyltetrahydrofuran, as prepared by Easton, Gardner, and Stevens (*J. Amer. Chem. Soc.*, 1947, **69**, 2941) by the condensation of benzhydryl cyanide and propylene oxide, but we did not obtain it crystalline as reported. On treatment with thionyl chloride in presence of dimethylaniline, a crude chloro-compound was obtained which on condensation with dimethylamine gave a small yield of 3-dimethylamino-1 : 1-diphenylbutyl cyanide, isolated and identified as its picrate.

$Ph_2C(CN)\cdot CH_2\cdot CH(OEt)_2$ (VI.)

$Ph_2C(CN)\cdot CH_2\cdot CHO$ (VII.)

$Ph_2C(CN)\cdot CH_2\cdot CHMe\cdot OH$ (VIII.)

When tested for analgesic action (III; R = Me, R′ = $CH_2{:}CH\cdot CH_2$) and (III; R = R′ = $CH_2{:}CH\cdot CH_2$) had respectively one-half and one-eighth of the potency of (III; R = R′ = Me).

EXPERIMENTAL.

2-*Dimethylamino*-4 : 4-*diphenylheptan*-5-*one* (*Amidone*).—When the toluene solution of the Grignard complex from ethylmagnesium iodide and 3-dimethylamino-1 : 1-diphenylbutyl cyanide was heated with excess of 2N-sulphuric acid on the water-bath for 30 minutes, amidone sulphate crystallised out on cooling. It was filtered off and suspended in water, and excess of sodium hydroxide solution added to liberate the free base which was taken up in ether. After drying of the ethereal solution, amidone hydrochloride was formed by addition of alcoholic hydrogen chloride and obtained pure (m. p. 232—233°) in 91% yield (Found: C, 72·8; H, 8·0; N, 4·4. Calc. for $C_{21}H_{28}ONCl$: C, 72·95; H, 8·1; N, 4·05%).

3-*Methylallylamino*-1 : 1-*diphenylpropyl Cyanide* (II; R = Me, R′ = $CH_2{:}CH\cdot CH_2$).—3-Chloro-1 : 1-diphenylpropyl cyanide (14·8 g.), sodium iodide (8·7 g.), and methylallylamine (13 ml.) in methanol (30 ml.) were heated in a pressure-bottle for 36 hours at 100°. On working up of the product for basic material the *cyanide* was obtained as an oil, b. p. 152°/0·3 mm. (6·5 g.) (Found: C, 82·1; H, 7·6; N, 10·1. $C_{20}H_{22}N_2$ requires C, 82·8; H, 7·6; N, 9·6%).

1-*Methylallylamino*-3 : 3-*diphenylhexan*-4-*one* (III; R = Me, R′ = $CH_2{:}CH\cdot CH_2$).—To a Grignard solution in dry benzene (50 ml.), prepared from magnesium (3·7 g.) and ethyl iodide (17·5 g.), was added the above cyanide (6·5 g.), and the solution heated under reflux for 16 hours. The product was then heated on the boiling water-bath with a solution of concentrated hydrochloric acid (75 ml.) in water (250 ml.) for 3½ hours. The aqueous portion was then made alkaline and the base extracted with ether. After drying and concentration of the ethereal solution the *ketone* was obtained as an oil, b. p. 158°/0·5 mm. (6·2 g.) (Found: C, 82·5; H, 8·4; N, 4·7. $C_{22}H_{27}ON$ requires C, 82·3; H, 8·4; N, 4·4%). It forms a *methiodide*, m. p. 160—161° (Found: N, 3·2. $C_{23}H_{30}ONI$ requires N, 3·0%).

3-*Diallylamino*-1 : 1-*diphenylpropyl Cyanide* (II; R = R′ = $CH_2{:}CH\cdot CH_2$).—3-Chloro-1 : 1-diphenylpropyl cyanide (7 g.) and diallylamine (12 ml.) in ethyl alcohol (15 ml.) were heated at 155° for 16 hours under pressure. On being worked up as previously described, the *cyanide* (4·6 g.) was obtained as an oil, b. p. 162—163°/0·5 mm. (Found: C, 82·6; H, 7·1; N, 9·2. $C_{22}H_{24}N_2$ requires C, 83·5; H, 7·6; N, 8·9%).

1-*Diallylamino*-3 : 3-*diphenylhexan*-4-*one* (III; R = R′ = $CH_2{:}CH\cdot CH_2$).—From the above cyanide the *ethyl ketone* was obtained in the normal manner as an oil, b. p. 154°/0·2 mm., in about 50% yield (Found: C, 82·85; H, 8·3; N, 4·3. $C_{24}H_{29}ON$ requires C, 83·0; H, 8·4; N, 4·0%).

Methylallylamine.—Allylamine (22·8 g.) was slowly mixed with benzaldehyde (44·5 g., 1·05 moles), ether was added, and the water formed was separated. The residue was dried by distilling off benzene and then heated with methyl iodide (75 g., 1·3 moles) in a pressure-bottle at 80° for 16 hours. The dark viscous oil which was formed became crystalline and was triturated with benzene, and the solid filtered off with exclusion of moisture. The solid was then decomposed with water, and the aqueous portion, after being thoroughly extracted with ether, concentrated to a smaller volume and made alkaline with 50% sodium hydroxide solution. The methylallylamine which separated had b. p. 62—64° and weighed 20·1 g. (71%). When the base was prepared by decomposition of the quaternary salt from allyl bromide and the Schiff's base from methylamine and benzaldehyde, the yield was only 14%.

Benzhydrylmethyl-2-*hydroxyethylamine*.—A mixture of benzhydrylmethylamine (25·9 g.) and ethylene oxide (6 g.) was heated in a closed vessel at 100° for 24 hours and the product then distilled to give the *alcohol* as an oil, b. p. 145—148°/0·4 mm. (27·7 g.) (Found : C, 80·6; H, 8·1; N, 5·1. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9; N, 5·8%).

Benzhydrylmethyl-2-*chloroethylamine Hydrochloride.*—The above alcohol (27·7 g.) was dissolved in chloroform (85 ml.), and thionyl chloride (17 g.) added slowly with cooling and shaking. The mixture was heated under reflux for 2 hours, some of the chloroform and the excess of thionyl chloride were then distilled off, and acetone was added to the residue, whereupon the *hydrochloride* crystallised. Recrystallised from chloroform–acetone it melted at 193—195° (Found : Cl′, 12·0. $C_{16}H_{19}NCl_2$ requires Cl′, 12·0%).

3-*Benzhydrylmethylamino*-1 : 1-*diphenylpropyl Cyanide* (II; R = Me, R′ = $CHPh_2$).—To a solution of benzhydryl cyanide (9·6 g.) and benzhydrylmethyl-2-chloroethylamine base (liberated from 16·5 g. of its hydrochloride) in dry toluene (150 ml.), sodamide powder (2·0 g.) was added and the reaction mixture refluxed for 2 hours with vigorous stirring. After cooling it was extracted 3 times with 2N-hydrochloric acid. The aqueous part and the insoluble hydrochloride of the reaction product were treated with 50% sodium hydroxide solution, the freed base was extracted with ether, and the ethereal extract washed with water, dried (Na_2SO_4), and evaporated. The residue was distilled in a high vacuum to give the *cyanide* (9 g.) as a resinous, amber-coloured substance, which solidified and after two recrystallisations from light petroleum (b. p. 60—80°) melted at 120—123° (Found : C, 85·9; H, 6·6; N, 6·8. $C_{30}H_{28}N_2$ requires C, 86·6; H, 6·7; N, 6·7%).

3 : 3-*Diphenyl*-1-*methylpyrrolid*-2-*one.*—The above nitrile (4·2 g.) dissolved in warm alcohol was shaken with a palladium–barium sulphate catalyst (prepared *in situ* from 0·4 g. of barium sulphate and 0·5 ml. of 10% palladium chloride solution) in presence of hydrogen. The uptake of hydrogen proceeded slowly until 0·8 mole had been absorbed, whereafter it ceased. The alcoholic solution was then filtered, made acid, and evaporated to dryness, and the residue dissolved in water and extracted with ether to remove the diphenylmethane formed. The aqueous portion was made alkaline and extracted with ether, and the extracted base distilled at 155—160°/0·3 mm. (1·6 g.). This base, when treated with 2N-hydrochloric acid, gave a hydrochloride, m. p. 226—228°, analysis of which (C, 67·6; H, 7·2; N, 10·7%) did not agree with the theoretical values for 3-methylamino-1 : 1-diphenylpropyl cyanide (II; R = Me, R′ = H) hydrochloride, or, of course, for the isomeric 2-imino-3 : 3-diphenyl-1-methylpyrrolidine hydrochloride. In an attempt to make a nitroso-derivative of (II; R = Me, R′ = H), an aqueous solution of the hydrochloride, m. p. 226—228°, was heated with potassium nitrite, whereupon a neutral substance, m. p. 146—148° [from light petroleum (b. p. 60—80°)], was formed. This compound, from its properties and analysis, would appear to be 3 : 3-diphenyl-1-methylpyrrolid-2-one (Dupré *et al.*, *loc. cit.*) (Found : C, 80·8; H, 6·7; N, 5·2. Calc. for $C_{17}H_{17}ON$: C, 81·3; H, 6·8; N, 5·6%).

Benzylmethylallyl-4-*keto*-3 : 3-*diphenylhexylammonium Bromide.*—Reaction of 1-benzylmethylamino-3 : 3-diphenylhexan-4-one in ether with allyl bromide gave the quaternary *salt*, m. p. 171—174° (from acetone) (Found : C, 70·4; H, 6·9; N, 2·8. $C_{29}H_{34}ONBr$ requires C, 70·8; H, 6·9; N, 2·8%).

Hydrogenation of this salt (1·8 g.) in alcohol with freshly prepared palladium–barium sulphate (0·1 g.) proceeded slowly until 1 mole of hydrogen (90 ml.) had been absorbed, then becoming much slower. The hydrogenation was interrupted and the alcohol distilled off. The residue was treated with 2N-sodium hydroxide and extracted with amyl alcohol. The amyl-alcoholic extract was washed and distilled. The product was obtained as a thick oil which gave two fractions : (i) b. p. 146°/0·1 mm., and (ii) b. p. 180—190°/0·1 mm. From its analysis the first fraction may be 1-methylallylamino-3 : 3-diphenylhexan-4-one or 1-methylpropylamino-3 : 3-diphenylhexan-4-one (Found : C, 82·0; H, 8·8; N, 4·0. Calc. for $C_{22}H_{27}ON$: C, 82·3; H, 8·4; N, 4·4%). The second fraction analysed as 1-benzylmethylamino-3 : 3-diphenylhexan-4-one (Found : C, 83·8; H, 8·0; N, 3·9. Calc. for $C_{26}H_{29}ON$: C, 84·1; H, 7·8; N, 3·8%).

2-*Cyano*-2 : 2-*diphenylpropaldehyde Diethyl Acetal* (VI).—To benzhydryl cyanide (5·0 g.) and chloroacetaldehyde diethylacetal (4·0 g.) in dry benzene (30 ml.) sodamide (1·1 g.) was added, with stirring, and the mixture then refluxed for 2 hours. The benzene solution was well washed with water, the benzene distilled off, and the residue distilled, giving the *cyanide* as an oil, b. p. 145°/0·3 mm. (Found : C, 77·9; H, 7·2; N, 4·7. $C_{20}H_{23}O_2N$ requires C, 77·7; H, 7·4; N, 4·5%).

2-*Cyano*-2 : 2-*diphenylpropaldehyde* (VII).—The above acetal (3·4 g.) was hydrolysed by shaking it with 15% hydrochloric acid (13·5 ml.) in an atmosphere of nitrogen for 24 hours. The mixture was extracted with ether, the ethereal solution washed with a solution of potassium carbonate, and then with water, and dried (Na_2SO_4) and the ether distilled off. The residue distilled at 130—150°/0·6 mm. and became partly solid when kept overnight. After being pressed on porous plate and recrystallised from light petroleum (b. p. 60—80°), the *aldehyde* had m. p. 92—94° (yield 42%) (Found : C, 82·1; H, 5·7; N, 5·75. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The *azine* prepared from the aldehyde (2·85 g.) and 90% hydrazine hydrate (0·23 ml.) had m. p. 182—184° after recrystallisation from ethyl alcohol (Found : C, 82·1; H, 5·8; N, 12·2. $C_{32}H_{26}N_4$ requires C, 82·4; H, 5·6; N, 12·0%).

3-*Dimethylamino*-1 : 1-*diphenylbutyl Cyanide* (II; R = R′ = Me).—To the above aldehyde (5·0 g.) in ether (50 ml.) was added an ethereal solution of methylmagnesium iodide containing one molar equivalent, at 0° with stirring. A solid formed at once and stirring was continued for 30 minutes at room temperature. The Grignard complex was then decomposed with ammonium chloride solution, and the ethereal layer separated, washed with water, and dried (Na_2SO_4). After removal of the ether the residue was distilled in a high vacuum giving an oil at 154—156°/0·1 mm., which analysed correctly as the secondary *alcohol* (VIII) (Found : C, 81·0; H, 6·1; N, 5·6. $C_{17}H_{17}ON$ requires C, 81·25; H, 6·8; N, 5·6%).

To a mixture of the above compound (3·6 g.) and dimethylaniline (1·7 g.) in benzene (30 ml.) was added, with cooling and shaking, thionyl chloride (2·0 ml.) in benzene (10 ml.). The mixture was heated under reflux for 2 hours and then poured into ice-water, the benzene layer was separated, washed with water, and concentrated, and the residue distilled at 156°/0·2 mm., giving a product (2·0 g.) containing 10·2% of Cl (Calc. for $C_{17}H_{16}NCl$: Cl, 13·2%).

This crude chloro-compound (1·5 g.) was heated with 25% aqueous dimethylamine (10 ml.) for 6 hours at 130° in a sealed tube. On working up in the usual way, about 0·2 g. of basic material was obtained, which gave a picrate, m. p. 148—149·5°, which showed no depression in m. p. when mixed with an authentic specimen of 3-dimethylamino-1 : 1-diphenylbutyl cyanide picrate of m. p. 149—150° (Found : C, 59·7; H, 5·6; N, 14·3. Calc. for $C_{25}H_{25}O_7N_5$: C, 59·2; H, 4·9; N, 13·8%).

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