447. *Synthetic Analgesics and Related Compounds. Part I. Amidines and 4 : 5-Dihydroglyoxalines.*

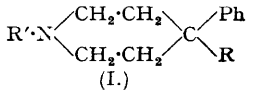
By Walter Wilson.

Several cyano-compounds related to amidone and pethidine have been converted into the corresponding *N*-phenylamidines and 4 : 5-dihydroglyoxalines. Tertiary cyanides were abnormally unreactive. The cyanide (II; R = CN), an intermediate in the production of amidone, with 2-aminoethylammonium toluene-*p*-sulphonate at 200° afforded a 2-imino-pyrrolidine and not the expected 4 : 5-dihydroglyoxaline.

The conversion, into amidines and 4 : 5-dihydroglyoxalines, of various cyano-compounds related to pethidine (I; R = CO_2Et, R′ = Me) and amidone (II; R = COEt) has been studied, fusion techniques (cf., especially, Oxley and Short, *J.*, **1946**, 147; **1947**, 497) being used. The present experiments have been restricted mainly to reaction with anilinium arylsulphonates (giving *N*-phenylamidines) and 2-aminoethylammonium toluene-*p*-sulphonate (giving 2-substituted 4 : 5-dihydroglyoxalines) at 200°. Basic cyanides were used as their salts with benzenesulphonic or toluene-*p*-sulphonic acid.

Improved methods for preparing benzhydryl cyanide have recently been described (Reid and Turner, *J. Amer. Chem. Soc.*, 1948, **70**, 3515; U.S.P., 2,447,419; Ginsburg and Baizer, *J. Amer. Chem. Soc.*, 1949, **71**, 2254). The material used in the present work was obtained by boiling diphenylacetamide with thionyl chloride (cf. Freeman, Ringk, and Spoerri, *ibid.*, **1947**, **69**, 858), yields being satisfactory if the time of heating was not prolonged. Long heating gave large amounts of α-chlorobenzhydryl cyanide (IV; R = CN, R′ = Cl), identified by acid hydrolysis to benzophenone cyanohydrin (IV; R = CN, R′ = OH). An attempt to convert the chloro-cyanide into the anilino-cyanide (Miller, Plöchl, and Rohde, *Ber.*, 1892, **25**, 2056) afforded only aniline hydrochloride and benzophenone. The mechanism of formation of the chloro-cyanide remains obscure. Pure benzhydryl cyanide gave only traces of the chloro-cyanide on prolonged boiling with pure thionyl chloride, and the reaction was not catalysed by small amounts of iodine, red phosphorus, ammonium chloride, or ferric chloride. It is possible that, under appropriate conditions, thionyl chloride behaves as a chlorinating reagent by decomposing as follows (cf. sulphuryl chloride and peroxide catalysts, Kharasch and Brown,

J. Amer. Chem. Soc., 1939, **61**, 2142; also Patai and Bergmann, *ibid.*, 1950, **72**, 1034) : $2SOCl_2 \longrightarrow 2SO + 2Cl \longrightarrow S + SO_2 + 2Cl$.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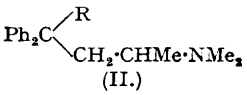
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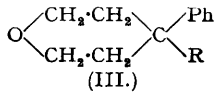
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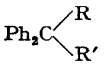
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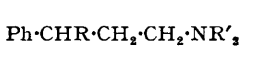
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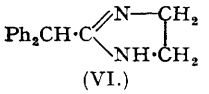
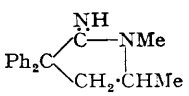
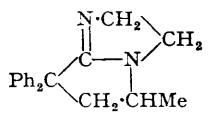

(VI.)

Benzhydryl cyanide (IV; R = CN, R′ = H) readily afforded both the *N*-phenylamidine and the 4 : 5-dihydroglyoxaline (VI) (cf. Jílek and Protiva, *J.*, 1950, 188). The tertiary cyanide (IV; R = CN, R′ = Et) did not react with amine salts under the conditions used; the allyl analogue (IV; R = CN, R′ = CH_2·CH:CH_2) also failed to react with ethylenediamine salts.

The tetrahydropyran (III; R = CN) and two cyanides (I; R = CN, R′ = Me or CH_2Ph) of pethidine type were converted in good yields into the 2-substituted 4 : 5-dihydroglyoxalines on prolonged heating with ethylenediamine salts. The tetrahydropyran (III; R = CN) gave heterogeneous melts with ammonium or anilinium benzenesulphonates, which may account for the non-formation of amidines. Conversion of the other two cyanides into amidines was not examined.

The expected *N*-phenylamidines and 4 : 5-dihydroglyoxalines were easily prepared from the two basic cyanides (V; R = CN, R′ = Me or Et) obtained by aminoalkylation of benzyl cyanide. However, similar but tertiary basic cyanides derived from benzhydryl cyanide were unreactive. Thus 3-dimethylamino-1-cyano-1 : 1-diphenylpropane (as the toluene-*p*-sulphonate) was unchanged on heating (200°) with 2-aminoethylammonium toluene-*p*-sulphonate. The homologous (±)-cyanide (II; R = CN) was converted in moderate yield into a basic compound, m. p. 103°, which was not, however, the dihydroglyoxaline. The stereoisomeric (+)-cyanide (II; R = CN) similarly afforded the dextro-rotatory isomer, believed to be 2-imino-3 : 3-diphenyl-1 : 5-dimethylpyrrolidine (VII). Evidently, the ethylenediamine used does not enter into the composition of this molecule. Similar compounds have been obtained by heating salts of basic cyanides of the amidone series (Blicke and Zambito, Abstr. 111th Meeting Amer. Chem. Soc., 1947, 3K). An alternative structure (VIII) for the compound of m. p. 103° was considered improbable in view of the formation of the dextrorotatory isomer : during the formation of (VIII) racemisation would be expected.

(VII.) 


(VIII.)

Abnormal or particularly ready cyclisations affording five-membered ring compounds for *gem*-diphenyl compounds have been commented on elsewhere (Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454; Wilson, *J.*, 1948, 1993; Clarke, Mooradian, Lucas, and Slauson, *J. Amer. Chem. Soc.*, 1949, **71**, 2821; Walton, Ofner, and Thorpe, *J.*, 1949, 648; Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500). Experiments are proceeding on the independent synthesis of compounds of types (VII) and (VIII).

The resistance to amidine and 4 : 5-dihydroglyoxaline formation shown by the tertiary cyanides was possibly caused by steric factors. Normal reactions were observed only with those tertiary cyanides in which the α-carbon atom was contained in a piperidine or tetrahydropyran ring.

The compounds prepared in this work, which combine features of the potent synthetic analgesics with the amidine and 4 : 5-dihydroglyoxaline groups, are being assayed for biological activity. No outstanding activity has as yet been observed.

Experimental.

α-Chlorobenzhydryl Cyanide.—Boiling diphenylacetamide for 5—8 hours with excess of thionyl chloride gave satisfactory yields of benzhydryl cyanide (Reid and Turner, *J. Amer. Chem. Soc.*, 1948, **70**, 3515; Freeman, Ringk, and Spoerri, *ibid.*, 1947, **69**, 858). After prolonged boiling (30 hours), however, the product contained about 40% of an oil. Removal of benzhydryl cyanide by low-temperature crystallisation from light petroleum (b. p. 40—60°) and distillation of the soluble fraction

gave evil-smelling *α-chlorobenzhydryl cyanide*, b. p. 140°/1 mm. (Found: N, 6·15; Cl, 14·7. $C_{14}H_{10}NCl$ requires N, 6·15; Cl, 15·6%).

Hydrolysis. The foregoing chloro-compound was boiled with water for 2½ hours. The resulting unstable benzophenone cyanohydrin recrystallised from light petroleum (b. p. 40—60°) as white crystals, m. p. 120°. The product gave an intense red colour with concentrated sulphuric acid and was immediately hydrolysed by cold dilute sodium hydroxide to hydrogen cyanide and benzophenone (2 : 4-dinitrophenylhydrazone, m. p. 239°) (cf. Wittig and Pockels, *Ber.*, 1936, **69**, 790).

4-*Cyano*-4-*phenyl*-1-*benzylpiperidine* (I; R = CN; R′ = CH_2Ph).—This was prepared by the I.G.Farbenind. (Hoechst) process (B.I.O.S. Final Report No. 766, p. 62; Eisleb, *Ber.*, 1941, **74**, 1433). The *benzenesulphonate* formed needles (from *iso*propanol), m. p. 194—195° (Found: N, 6·6. $C_{25}H_{26}O_3N_2S$ requires N, 6·45%).

Benzyldi-(2-chloroethyl)amine.—A toluene solution of the chloro-amine (described by Eisleb, *loc. cit.*) was used in the above process. Such solutions were conveniently assayed by adding saturated methanolic picric acid and weighing the insoluble *picrate*. This formed yellow prisms, m. p. 129·5—130·5°, from acetone (Found: N, 12·15. $C_{17}H_{18}O_7N_4Cl_2$ requires N, 12·2%).

Alcoholysis of 4-*Cyano*-4-*phenyl*-1-*benzylpiperidine.*—The cyanide (56·3 g.), water (6 c.c.) and sulphuric acid (28·5 c.c.) were heated alone and then with slow addition of absolute ethanol (cf. *op. cit.*, p. 62). The crude product (46 g.) was recrystallised from water and identified as 4-*phenyl*-1-*benzylpiperidine*-4-*carboxyamide hydrochloride*, prisms, m. p. 275° (Found: N, 8·0; Cl, 10·1. $C_{19}H_{23}ON_2Cl$ requires N, 8·5; Cl, 10·7%).

Authentic 4-*Phenyl*-1-*benzylpiperidine*-4-*carboxyamide.*—The 4-carboxylic acid (Eisleb, *loc. cit.*) (5 g.) was heated with excess of thionyl chloride and then mixed with aqueous ammonia (*d* 0·88). The impure amide (1·9 g.; m. p. 92—97°) was filtered off and converted by hydrogen chloride in glacial acetic acid into the hydrochloride, white prisms (from acetone), m. p. 276°, not depressed on admixture with the material from the previous experiment (Found: N, 8·5%). Acidification of the ammoniacal mother-liquors gave some unchanged acid (1·7 g.).

3-*Dialkylamino*-1-*cyano*-1-*phenylpropanes* (V; R = CN).—The 3-dimethylamino-compound was obtained from 2-dimethylaminoethyl chloride and benzyl cyanide (Clarke, Mooradian, Lucas, and Slauson, *J. Amer. Chem. Soc.*, 1949, **71**, 2821) and converted into the *toluene*-p-*sulphonate*, m. p. 111° (from *iso*propanol–ether) (Found: N, 7·55. $C_{19}H_{24}O_3N_2S$ requires N, 7·8%). The 3-diethylamino-analogue (Eisleb, *loc. cit.*; Heilbron, Cook, and Brown, *J.*, 1949, S106) similarly gave a *toluene*-p-*sulphonate*, m. p. 105° (Found: C, 64·95; H, 7·1. $C_{21}H_{28}O_3N_2S$ requires C, 65·0; H, 7·25%).

3-*Dimethylamino*-1-*cyano*-1 : 1-*diphenylpropane.*—The base (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500) with toluene-*p*-sulphonic acid monohydrate (1 mole) in *iso*propanol afforded the *toluene*-p-*sulphonate*, m. p. 174—175° (74%) (Found: C, 68·9; H, 6·2. $C_{25}H_{28}O_3N_2S$ requires C, 68·8; H, 6·4%).

(±)-3-*Dimethylamino*-1-*cyano*-1 : 1-*diphenylbutane* (II; R = CN).—The base has been adequately described (Bockmühl and Ehrhart, *Annalen*, 1948, **561**, 52; also Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454; Attenburrow, Elks, Hems, and Speyer, *J.*, 1949, 510). By use of a 5% excess of hydrated benzenesulphonic acid in acetone–ethyl acetate, the *benzenesulphonate* was obtained (65%). Crystallised from acetone–ethyl acetate, this had m. p. 158—159° (Found: N, 6·55. $C_{25}H_{28}O_3N_2S$ requires N, 6·4%).

(+)-3-*Dimethylamino*-1-*cyano*-1 : 1-*diphenylbutane.*—The (±)-cyanide was resolved with tartaric acid (Walton, Ofner, and Thorpe, *J.*, 1949, 652; Buck *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 4195). The (+)-cyanide was converted into the (+)-*toluene*-p-*sulphonate* in acetone. Crystallised from methanol–ether, this had m. p. 154° (Found: N, 6·5. $C_{25}H_{28}O_3N_2S$ requires N, 6·4%).

N-*Phenyldiphenylacetamidine.*—Heating benzhydryl cyanide (7·6 g.) and anilinium benzenesulphonate (10 g.) at 195—200° for 4 hours, trituration with acetone, and recrystallisation of the product (13·5 g., 76%; m. p. 164—167°) from *iso*propanol–ether gave the *amidinium benzenesulphonate*, m. p. 174—176° (Found: N, 6·3. $C_{26}H_{24}O_3N_2S$ requires N, 6·3%).

Warm dilute ammonia precipitated the free *amidine* (7·2 g.; m. p. 156°), crystallising from aqueous methanol in minute needles, m. p. 150° (Found: N, 9·8. $C_{20}H_{18}N_2$ requires N, 9·8%). After 16 hours in the air the crude material (initial m. p. 156°) had m. p. 141—149° (shrinking at 135°). Crystallisation failed to restore the material to its original m. p. The dry material became electrically charged when ground with a spatula.

2-*Benzhydryl*-4 : 5-*dihydroglyoxaline* (cf. Jílek and Protiva, *loc. cit.*).—Benzhydryl cyanide (1·9 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.) were heated at 200° for 3½ hours and the base (2·05 g.) was precipitated by aqueous ammonia. It crystallised from aqueous methanol in needles, m. p. 143—145° (Found: N, 12·05. Calc. for $C_{16}H_{16}N_2$: N, 11·9%). Jílek and Protiva, *loc. cit.*, give m. p. 133—135°; Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 3195, gives 137°. The hydrochloride formed prisms (from ethanol), m. p. 182°, resolidifying with change of crystalline form and remelting at 197° (Found: N, 9·85. Calc. for $C_{16}H_{17}N_2Cl$: N, 10·25%) (Jílek and Protiva, *loc. cit.*, give m. p. 180—182°; Ciba, Austrian P. 150,307, give 192—193°).

Reaction Between 1-*Cyano*-1 : 1-*diphenylpropane and* 2-*Aminoethylammonium Toluene*-p-*sulphonate.*—The benzhydryl cyanide in the previous experiment was replaced by 1-cyano-1 : 1-diphenylpropane (2·2 g.) (b. p. 158—162°/2 mm.; Ramart-Lucas, *Ann. Chim.*, 1913, [viii], **30**, 417; Klingemann, *Annalen*, 1893, **275**, 85). The minute yield of base was recrystallised from aqueous ethanol, affording 2-benzhydryl-4 : 5-dihydroglyoxaline (0·2 g.), m. p. 140° not depressed on admixture with an authentic specimen (Found: N, 12·2%).

4-Phenyl-4-(4 : 5-dihydroglyoxalin-2-yl)tetrahydropyran (III ; R = dihydroglyoxalin-2-yl).—4-Cyano-4-phenyltetrahydropyran (7·6 g.) (Eisleb, *loc. cit.*) and 2-aminoethylammonium toluene-*p*-sulphonate (9·2 g.) were heated at 200° for 14 hours, then cooled, and triturated with acetone. The solid (13 g., 80·5% ; m. p. 260°) on recrystallisation from water afforded the pure *dihydroglyoxalinium toluene-p-sulphonate* as white needles, m. p. 263—264° (Found : N, 6·6. $C_{21}H_{26}O_4N_2S$ requires N, 6·95%). The salt was dissolved in water, excess of sodium hydroxide added (no precipitate), and the base (6·1 g. ; m. p. 125—128°) isolated by extraction with chloroform. It was converted directly into the *hydrochloride*, small prisms (from acetone–ethanol), m. p. 247—248° (Found : N, 10·5. $C_{14}H_{19}ON_2Cl$ requires N, 10·5%).

4-Phenyl-4-(4 : 5-dihydroglyoxalin-2-yl)-1-methylpiperidine (I ; R = dihydroglyoxalin-2-yl ; R′ = Ph).—4-Cyano-4-phenyl-1-methylpiperidine (10 g.) (Eisleb, *loc. cit.*) in methanol–ethyl acetate afforded the *benzenesulphonate* (12·9 g.), prisms, m. p. 168—168·5° (Found : N, 7·95. $C_{19}H_{22}O_3N_2S$ requires N, 7·8%). This salt (3·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.), heated at 200° for 15 hours and then triturated with acetone, gave a salt (4·2 g. ; m. p. 245—260°), which was dissolved in water, basified with sodium hydroxide, and extracted with chloroform, to afford a base (1·5 g. ; m. p. 112—114°) which could not be satisfactorily recrystallised. The *dihydrochloride* crystallised from ethanol–ether in small prisms, m. p. 336—337° (Found : N, 13·7. $C_{15}H_{23}N_3Cl_2$ requires N, 13·3%).

4-Phenyl-1-benzyl-4-(4 : 5-dihydroglyoxalin-2-yl)piperidine (I ; R = dihydroglyoxalin-2-yl ; R′ = Me).—4-Cyano-4-phenyl-1-benzylpiperidinium benzenesulphonate (4·3 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.) after 31 hours at 200° afforded a crude salt (3·0 g. ; m. p. 171—175°), which was dissolved in water and basified with sodium hydroxide. The solid precipitate (1·3 g. ; m. p. 153—154°) was recrystallised from aqueous ethanol. The *dihydroglyoxaline* formed prisms, m. p. 155—156° (Found : N, 13·2. $C_{21}H_{25}N_3$ requires N, 13·1%) ; the *dihydrochloride*, crystallised from methanol–ether, had m. p. 215—218° (Found : N, 10·8. $C_{21}H_{27}N_3Cl_2$ requires N, 10·7%).

*5-Dialkylamino-*N* : 2-diphenylbutyramidines.*—3-Dimethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (2·7 g.) and anilinium toluene-*p*-sulphonate (2·7 g.) were heated for 6½ hours at 200°, dissolved in water, and treated with aqueous ammonia to give a base (1·95 g.), m. p. 114—116°. Recrystallisation from benzene–light petroleum (b. p. 100—120°) afforded the *5-dimethylamino-amidine* as small pearly needles, m. p. 123·5—124° (Found : C, 77·05 ; H, 8·5. $C_{18}H_{23}N_3$ requires C, 77·0 ; H, 8·2%). Similarly, 3-diethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (3·9 g.) was converted into the *5-diethylamino-amidine* (1·2 g.), small crystals [from benzene–light petroleum (b. p. 100—120°)], m. p. 104·5—15·5° (Found : C, 77·6 ; H, 8·8. $C_{20}H_{27}N_3$ requires C, 77·8 ; H, 8·75%).

2-(3-Dialkylamino-1-phenylpropyl)-4 : 5-dihydroglyoxalines.—3-Dimethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (3·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (2·3 g.), heated at 200° for 7 hours and then triturated with acetone, gave a salt (2·95 g. ; m. p. 223—224°). After recrystallisation from aqueous ethanol, the *3′-dimethylaminoditoluene-*p*-sulphonate* formed needles, m. p. 233—234° (Found : C, 58·5 ; H, 6·3. $C_{28}H_{37}O_6N_3S_2$ requires C, 58·4 ; H, 6·4%). The free base was an oil.

Similarly, 3-diethylamino-1-cyano-1-phenylpropane toluene-*p*-sulphonate (3·9 g.) afforded the *3′-diethylamino-ditoluene-*p*-sulphonate* (3·2 g.), prisms m. p. 127°, from *iso*propanol–ether (Found : C, 58·85, 59·0 ; H, 6·6, 6·8. $C_{30}H_{41}O_6N_3S_2$ requires C, 59·7 ; H, 6·8%). The free base was an oil.

Reaction between (±)-3-Dimethylamino-1-cyano-1 : 1-diphenylbutane and Ethylenediamine.—The (±)-cyanide benzenesulphonate (11 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (5·8 g.) were heated at 200° for 27½ hours. Trituration with cold acetone gave a crystalline salt (2·75 g. ; m. p. 184—189°), which was dissolved in water ; the base (1·5 g. ; m. p. 100—102°) was precipitated by aqueous sodium hydroxide. Several crystallisations from aqueous methanol afforded (±)-*2-imino-3 : 3-diphenyl-1 : 5-dimethylpyrrolidine* as prisms, m. p. 103°, becoming white and opaque when dry (Found : C, 82·3 ; H, 7·5 ; N, 10·1. $C_{18}H_{20}N_2$ requires C, 81·9 ; H, 7·6 ; N, 10·6%). The compound was not acetylated by acetic anhydride in pyridine and was largely recovered unchanged after prolonged boiling with concentrated hydrochloric acid, or with potassium hydroxide in ethylene glycol.

Reaction between the (+)-Cyanide and Ethylenediamine.—The above reaction was repeated with the dextrorotatory cyanide. The resultant crude salt (2 g. ; m. p. 150—160°) was converted into the (+)-pyrrolidine (1·3 g.), which crystallised from aqueous methanol in needles, m. p. 130° ; $[\alpha]_D^{17}$ +157° (*c*, 1·29 in methanol) (Found : C, 82·1 ; 82·4 ; H, 6·95 ; 7·05 ; N, 10·75%). The compound was unchanged after treatment with acetic anhydride in pyridine.

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