818. *The Synthesis of 2-Imino-3-phenyl- and -3 : 3-diphenylpyrrolidines.*

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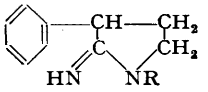
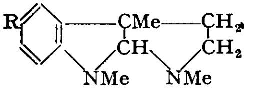
Under conditions appropriate to the formation of amidines, 3-halogeno-1-phenyl- and -1 : 1-diphenyl-propyl cyanides have been converted into 2-iminopyrrolidines.

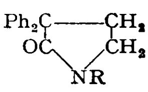
2-IMINO-3-PHENYLPYRROLIDINES, *e.g.*, (I), possess certain structural features of the physostigmine (eserine) ring-system (II) and for that reason appeared to merit pharmacological examination; moreover Blicke and Zambito (Abstr. 111th Meeting Amer. Chem. Soc., April 1947, p. 3K) have reported that the somewhat related 1-ethyl-3 : 3-diphenyl-2-pyrrolidone (III; R = Et) has decided analgesic activity. The preparation of compounds of type (I) and of the analogous 2-imino-3 : 3-diphenylpyrrolidines (IV) was therefore undertaken, starting from 3-halogeno-1-phenyl- and -1 : 1-diphenyl-propyl cyanides as follows.

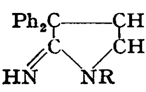
The monophenyl-cyanide (V) was readily converted into the hydrochloride of the imino-ether (VI), but treatment with ammonia gave, not the corresponding amidine, but the hydrochloride of 2-imino-3-phenylpyrrolidine (I; R = H), which amine was also formed when the chloro-cyanide (V) was heated with alcoholic ammonia. Heating the cyanide (V) with aniline benzenesulphonate and even with aniline gave the *N*-phenyl base (I; R = Ph). This imino-pyrrolidone was hydrolysed by nitrous acid to the related 1 : 3-diphenylpyrrolidone, a reaction which excludes the alternative 3-phenyl-2-phenyliminopyrrolidine structure.

Although Blicke and Zambito (*loc. cit.*) presume the intermediate formation of an imino-ether salt in converting 3-diethylamino-1 : 1-diphenylpropyl cyanide into 1-ethyl-2-imino-3 : 3-diphenylpyrrolidine (IV; R = Et), we were unable to prepare imino-ethers from either 3-chloro- or 3-bromo-1 : 1-diphenylpropyl cyanide (Pinner conditions, 44 days). However, when the bromo-cyanide was heated with aniline or aniline benzenesulphonate, 2-imino-1 : 3 : 3-triphenylpyrrolidine (IV; R = Ph) was obtained, the assigned constitution being sustained by hydrolysis of the base with nitrous acid to 1 : 3 : 3-triphenyl-2-pyrrolidone (III; R = Ph).


(I)

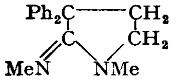

(Physostigmine; R = Me·NH·CO·O)
(II)

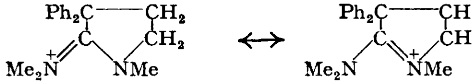

(III)


(IV)

$NC\cdot CHPh\cdot CH_2\cdot CH_2Cl$
(V)

$EtO\cdot C(:NH)\cdot CHPh\cdot CH_2\cdot CH_2Cl,HCl$
(VI)


(VII)


(VIII)

In a later personal communication from Professor Blicke, heating in a stream of hydrogen chloride is given as a method by which the diethylamino-cyanide is cyclised to the imino-pyrrolidine (IV; R = Et).

The action of methylamine on 3-bromo-1 : 1-diphenylpropyl cyanide produced a mixture of 2-imino-1-methyl-3 : 3-diphenylpyrrolidine (IV; R = Me) and 1-methyl-2-methylimino-3 : 3-diphenylpyrrolidine (VII), separated by crystallisation of the picrates. The existence of the iminopyrrolidine (IV; R = Me) has been postulated by Morrison and Rinderknecht (*J.*, 1950, 1478) but the compound was not characterised. The reaction leading to the production of (VII) is indicated by the formation of the ditertiary base when the monomethyl compound (IV; R = Me) was heated with excess of methylamine. Similarly, the action of methyl iodide on (IV; R = Me) gives the tertiary base (VII); excess of the reagent on both (IV; R = Me) and (VII) afforded the identical quaternary product isolated in the form of a methopicrate. This is unquestionably the 2-*N*-dimethyl compound for the cation of which the resonance structure (VIII) can be postulated.

Biological tests were carried out through the kindness of Dr. G. E. Ullyot of the Smith, Kline, and French Laboratories, Philadelphia. They show that the iminopyrrolidines (I; R = Ph), (IV; R = Me), (IV; R = Ph), and (VII) fail to antagonise leptazol(metrazol)-induced convulsions in mice, and that (IV; R = Me) and (VII) are without analgesic activity.

EXPERIMENTAL

3-Hydroxy-1-phenylpropyl Cyanide.—The preparation of 3-hydroxyl-1-phenylpropyl cyanide due to Knowles and Cloke (*J. Amer. Chem. Soc.*, 1932, **54**, 2028) was found unsatisfactory (yields 22%) and has even been reported to fail completely (Anker and Cook, *J.*, 1948, 806). The following modification affords consistent yields of *ca.* 50%.

Sodamide (40 g., 2 mols.), powdered in a ball-mill and dispersed in benzene (80 c.c.) and ether (300 c.c.), was slowly treated with benzyl cyanide (60 g.), and the mixture heated under reflux for 2 hours. Ethylene chlorohydrin (41 g., 1 mol.) was then added at 0° during 2 hours and next day the mixture was shaken with water. 3-Hydroxy-1-phenyl cyanide was isolated from the dried organic solution by distillation and had b. p. 141—145°/1—1·2 mm., n_D^{21} 1·5409, d_4^{20} 1·0587, $[R_L]_D$ 46·21 (calc. 46·28).

A solution in ether with *p*-nitrobenzoyl chloride and 2N-sodium hydroxide gave the p-*nitrobenzoyl* ester which crystallised from methanol in prisms, m. p. 76° (Found : N, 9·0. $C_{17}H_{14}O_4N_2$ requires N, 9·0%). The *toluene*-p-*sulphonate*, similarly prepared, was an oil, b. p. 142—150°/2 mm. (Found : N, 4·7. $C_{17}H_{17}O_3NS$ requires N, 4·4%).

4-*Chloro*-1-*ethoxy*-1-*imino*-2-*phenylbutane Hydrochloride* (VI).—A mixture of 3-chloro-1-phenylpropyl cyanide (27 g.), prepared from the foregoing hydroxy-cyanide by the method of Anker and Cook (*loc. cit.*), and ethanol (7 g.) was treated with hydrogen chloride (6·6 g., 1·2 mols.) at 0° and kept at that temperature for 5 days. The *imino-ether hydrochloride* (28·3 g., 72%) then precipitated by dry ether formed prisms, m. p. 96° (Found : N, 5·5. $C_{12}H_{16}ONCl,HCl$ requires N, 5·3%). Treatment with sodium picrate in ice-cold aqueous solution gave the *picrate* which crystallised from ethanol as yellow needles, m. p. 127—128° (Found : N, 12·6 $C_{12}H_{16}ONCl,C_6H_3O_7N_3$ requires N, 12·3%).

2-*Imino*-3-*phenylpyrrolidine* (I; R = H).—(i) A solution of 4-chloro-1-ethoxy-1-imino-2-phenylbutane hydrochloride (28·3 g.) in 10% ethanolic ammonia (270 c.c., 18 mols.) was set aside at room temperature for 5 days. It was then concentrated to precipitate ammonium chloride, 2-*imino*-3-*phenylpyrrolidine hydrochloride* (11·4 g., 54%) being obtained by evaporation of the filtrate and crystallisation of the residue from *iso*propanol as hygroscopic prisms, m. p. 186° (Found : C, 60·8; H, 6·7; N, 14·7. $C_{10}H_{12}N_2,HCl$ requires C, 61·0; H, 6·8; N, 14·2%). The *picrate* crystallised from ethanol in yellow needles, m. p. 195° (Found : N, 17·7. $C_{10}H_{12}N_2,C_6H_3O_7N_3$ requires N, 18·0%).

With sodium hydroxide solution the hydrochloride gave 2-*imino*-3-*phenylpyrrolidine* which was collected in chloroform and crystallised from carbon tetrachloride in rods, m. p. 93° (Found : N, 17·4. $C_{10}H_{12}N_2$ requires N, 17·5%). Treated with benzenesulphonic acid it afforded the *benzenesulphonate* which separated from *iso*propanol in prisms, m. p. 147° (Found : N, 8·8. $C_{10}H_{12}N_2,C_6H_6O_3S$ requires N, 8·8%).

(ii) 3-Chloro-1-phenylpropyl cyanide (18 g.), ammonium chloride (0·1 g.), and 8·7% ethanolic ammonia (60 c.c., 3 mols.) were heated at 130° for 90 hours. Ammonium chloride (2·65 g.) was collected and the concentrated filtrate basified and extracted with chloroform. The base was isolated as the picrate which when recrystallised from ethanol was obtained as needles (7·8 g., 20%), m. p. and mixed m. p. 195°.

2-*Imino*-1 : 3-*diphenylpyrrolidine* (I; R = Ph).—(i) 3-Chloro-1-phenylpropyl cyanide (6·3 g.) and aniline benzenesulphonate (8·8 g., 1 mol.) were heated at 210° until hydrogen chloride evolution had almost ceased (*ca.* 1¾ hours). The product was dissolved in hot *iso*propanol (50 c.c.) and light petroleum (b. p. 80—100°) (20 c.c.); recrystallisation of the solid (9·4 g., 68%), m. p. 136—140°, which separated in the cold afforded 2-*imino*-1 : 3-*diphenylpyrrolidine benzenesulphonate* as plates, m. p. 147—149° (Found : N, 6·7. $C_{22}H_{22}O_3N_2S$ requires N, 7·1%).

Treatment of the residual *iso*propanol–petroleum solution with aqueous sodium hydroxide gave additional product as the free *base*, which separated from light petroleum in plates, m. p. 98° (Found : C, 80·8; H, 6·7; N, 11·9. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8; N, 11·9%). 2-*Imino*-1 : 3-*diphenylpyrrolidine picrate* crystallised from ethanol in yellow rods, m. p. 222—223° (Found : N, 15·0. $C_{16}H_{16}N_2,C_6H_3O_7N_3$ requires N, 15·0%).

(ii) When the solid obtained by heating a mixture of 3-chloro-1-phenylpropyl cyanide (2·6 g.) and aniline (1·3 g., 1 mol.) at 185° for 2¼ hours was dissolved in water, 2-imino-1 : 3-diphenylpyrrolidine (1·5 g., 44%) was obtained by the addition of sodium hydroxide. The crystallised product and its benzenesulphonate and picrate had the above recorded m. p.s and mixed m. p.s.

1 : 3-*Diphenyl*-2-*pyrrolidone*.—Mixed solutions of 2-imino-1 : 3-diphenylpyrrolidine (2·4 g.) in 2N-hydrochloric acid (5 c.c., 1 mol.) and of sodium nitrite (3·5 g., 5 mols.) in water (15 c.c.) were heated to 80—83° with the dropwise addition of 2N-hydrochloric acid (30 c.c., 6 mols.). The brown solid (1·3 g., 53%) which had separated after cooling was crystallised from light petroleum and then aqueous ethanol, 1 : 3-*diphenyl*-2-*pyrrolidone* thus being obtained as silky needles, m. p. 81—82° (Found : C, 80·6; H, 6·6; N, 6·2. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4; N, 5·9% .

2-*Imino*-1 : 3 : 3-*triphenylpyrrolidine* (IV; R = Ph).—(i) 3-Bromo-1 : 1-diphenylpropyl cyanide (5 g.) and aniline benzenesulphonate (4·2 g., 1 mol.) were mixed and heated at 210° for 3¼ hours. Extraction with water left unchanged bromo-cyanide (2·4 g., 48%), and treatment of the solution with aqueous sodium hydroxide gave 2-*imino*-1 : 3 : 3-*triphenylpyrrolidine* (1·75 g., 34%) which crystallised from *iso*propanol in plates, m. p. 128° (Found: N, 8·9. $C_{22}H_{20}N_2$ requires N, 9·0%). The *picrate* formed orange-yellow prisms (from ethanol), m. p. 206—208° (Found : N, 12·8. $C_{22}H_{20}N_2,C_6H_3O_7N_3$ requires N, 12·9%).

(ii) The action of aniline (1 mol.) on 3-bromo-1 : 1-diphenylpropyl cyanide (1 mol.) at 185° for 2½ hours gave the foregoing pyrrolidine (61%), m. p. and mixed m. p. 128°.

1 : 3 : 3-*Triphenyl-2-pyrrolidone* (III; R = Ph).—Treatment of 2-imino-1 : 3 : 3-triphenylpyrrolidine (1·55 g.) with nitrous acid as described for the preparation of 1 : 3-diphenyl-2-pyrrolidone gave 1 : 3 : 3-*triphenyl-2-pyrrolidone* (1·5 g., 97%) which crystallised from ethanol in plates, m. p. 117—118° (Found : N, 4·6. $C_{22}H_{19}ON$ requires N, 4·5%).

1-*Methyl-2-methylimino-*3 : 3-*diphenylpyrrolidine* (VII).—(i) 3-Bromo-1 : 1-diphenylpropyl cyanide (60 g.) (Bockmühl and Ehrhart, *Annalen*, 1948, **561**, 52), methylamine (39·3 g., 6·5 mols.), and ethanol (35 c.c.) were heated under pressure at 100° for 13 hours. The residue left on evaporation was treated with 2N-sodium hydroxide (130 c.c.), the mixed amines were extracted with chloroform, and the solution was dried and heated to remove solvent and residual methylamine. Fractionation of the hydrochlorides obtained by treatment in ethereal solution with hydrogen chloride failed to separate the products, but crystallisation of the picrates (83 g.), m. p. 135—139°, from ethanol gave the less soluble 1-*methyl-2-methylimino-*3 : 3-*diphenylpyrrolidine picrate* (18·5 g., 19%) as yellow rods, m. p. 180—182° (Found : C, 58·7; H, 4·6; N, 14·3. $C_{18}H_{20}N_2,C_6H_3O_7N_3$ requires C, 58·4; H, 4·7; N, 14·2%). 1-*Methyl-2-methylimino-*3 : 3-*diphenylpyrrolidine*, liberated from the picrate by lithium hydroxide (cf. Burger, *J. Amer. Chem. Soc.*, 1945, **67**, 1615) and collected in chloroform, crystallised from aqueous methanol in needles, m. p. 106° (Found : C, 81·5; H, 7·5; N, 10·7. $C_{18}H_{20}N_2$ requires C, 81·8; H, 7·6; N, 10·6%). The *hydrochloride* separated from *iso*propanol in long prisms, m. p. 292—293° (decomp.) (Found : C, 70·5; H, 6·8; H, 9·7. $C_{18}H_{20}N_2,HCl$ requires C, 72·0; H, 7·0; N, 9·3%). The *picrolonate*, prepared in methanol, formed yellow prisms, m. p. 216° (Found : C, 63·4; H, 5·4; N, 16·2. $C_{18}H_{20}N_2,C_{10}H_8O_5N_4$ requires C, 63·6; H, 5·3; N, 15·9%).

(ii) 2-Imino-1-methyl-3 : 3-diphenylpyrrolidine (from 5 g. of the picrate) was heated under pressure at 105° with methyl iodide (2 g., 1 mol.) and acetone (2 c.c.) for 15 hours. The brown crystalline product (2 g.), m. p. 238—248°, was shaken with chloroform and 2N-sodium hydroxide, and the chloroform solution evaporated, whereupon the residue gave 1-methyl-2-methylimino-3 : 3-diphenylpyrrolidine picrate (16%), m. p. and mixed m. p. 181—182°.

(iii) 2-Imino-1-methyl-3 : 3-diphenylpyrrolidine, from the picrate (1 g.), was heated with 33% alcoholic methylamine (5 c.c.) and methylamine hydrochloride (0·05 g.) in ethanol (5 c.c.) at 105° for 4 days. After evaporation of volatile substances the product gave a picrate (27%), m. p. 180—181° alone or mixed with 1-methyl-2-methylimino-3 : 3-diphenylpyrrolidine picrate.

2-*Imino-*1-*methyl-*3 : 3-*diphenylpyrrolidine* (IV; R = Me).—The alcoholic solution from which 1-methyl-2-methylimino-3 : 3-diphenylpyrrolidine picrate was originally isolated contained the more soluble *picrate* of 2-imino-1-methyl-3 : 3-diphenylpyrrolidine which crystallised in clusters of orange prisms (14·1 g., 15%), m. p. 147—149° (Found : C, 57·6; H, 4·4; N, 14·6. $C_{17}H_{18}N_2,C_6H_3O_7N_3$ requires C, 57·6; H, 4·4; N, 14·6%). The free base obtained by treatment with lithium hydroxide failed to solidify. The *hydrochloride* crystallised from *iso*propanol in prisms, m. p. 224—225° (Found, in sample dried at 130° in a vacuum : C, 70·9; H, 7·4; N, 9·3. $C_{17}H_{18}N_2,HCl$ requires C, 71·2; H, 6·7; N, 9·8%), and the *picrolonate* from ethanol in yellow prisms, m. p. 189° (Found : C, 63·0; H, 4·8; N, 16·0. $C_{17}H_{18}N_2,C_{10}H_8O_5N_4$ requires C, 63·0; H, 5·1; N, 16·3%). A solution of the pyrrolidine in hydrochloric acid treated with sodium nitrite (5 mols.) on a steam-bath gave 1-methyl-3 : 3-diphenyl-2-pyrrolidone (57%), m. p. 145° (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 500, record m. p. 146·5—147°) (Found : N, 5·4. Calc. for $C_{17}H_{17}ON$: N, 5·6%); 33% of the original pyrrolidine was recovered.

1-*Methyl-2-methylimino-*3 : 3-*diphenylpyrrolidine Methopicrate.*—(i) 2-Imino-1-methyl-3 : 3-diphenylpyrrolidine was heated under reflux with potassium carbonate and excess of methyl iodide in acetone solution for several hours. The acetone was then distilled and the residue shaken with 2N-sodium hydroxide and chloroform. The product obtained from evaporation of the chloroform solution was dissolved in warm aqueous lactic acid (20%) and mixed with a solution of sodium picrate in water, thus causing the precipitation of 1-*methyl-2-methylimino-*3 : 3-*diphenylpyrrolidine methopicrate* which crystallised from ethanol in orange plates (67%), m. p. 188° (Found : C, 59·5; H, 4·8; N, 13·8. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0; N, 13·9%). (ii) When 1-methyl-2-methylimino-3 : 3-diphenylpyrrolidine was heated under reflux with methyl iodide (1 mol.) the methopicrate (yield 65%) obtained from the product had m. p. 188° alone or mixed with the sample derived from the 2-imino-1-methylpyrrolidine.

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