166. 2,3,6,7-*Tetrahydro-5-methyl-7,7-diphenyl-5*H-*pyrrolo*[1,2-*a*]-*imidazole.*

By M. W. GITTOS and W. WILSON.

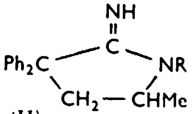
The compound (III) has been synthesised by two methods and found to be identical with the product obtained previously by heating together salts of 3-dimethylamino-1,1-diphenylbutyl cyanide and ethylenediamine.

SEVERAL years ago, one of us[1] obtained a base, m. p. 103°, by heating together arenesulphonates of ethylenediamine and (±)-3-dimethylamino-1,1-diphenylbutyl cyanide (I); the corresponding dextrorotatory base, m. p. 130°, was obtained similarly from the (+)-cyanide.[1,2] The two most likely structures for the product appeared to be (II; R = Me) and (III); the former was later excluded by synthesis of such a compound here [2] and by Cymerman and Gilbert.[3] The bicyclic structure (III) was not originally favoured, particularly in view of the observed retention of optical activity when the (+)-amino-cyanide was treated with ethylenediamine. The compound (III) has now been synthesised, and found to be identical with the base, m. p. 103°, obtained from 3-dimethylamino-1,1-diphenylbutyl cyanide.

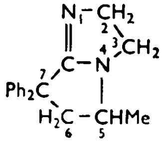
In one synthesis the bromo-cyanide (IV) was treated with ammonia, affording the 2-iminopyrrolidine (II; R = H). The formation of 2-iminopyrrolidines from γ-halogenated cyanides and ammonia or amines has been established previously;[4,5] the compound (II; R = H) had been recognised previously by Cymerman and Gilbert[3] amongst the products obtained by fusing 3-dimethylamino-1,1-diphenylbutyl cyanide with ammonium benzenesulphonate. Heating its hydrochloride with ethanolamine afforded the 2-2'-hydroxyethyliminopyrrolidine (V); the corresponding 2'-chloroethyl compound cyclised readily in dilute alkali, to afford the hydropyrroloimidazole (III).

$Ph_2C(CN)\cdot CH_2\cdot CHMe\cdot NMe_2$

(I)



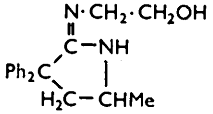
(II)



(III)

$Ph_2C(CN)\cdot CH_2\cdot CHMeBr$

(IV)



(V)

$Ph_2C(CN)\cdot CH_2\cdot CHMe\cdot NH\cdot CH_2\cdot CH_2\cdot NH_2$

(VI)

A simpler, although perhaps less unequivocal, synthesis was effected by heating the bromo-cyanide (IV) with ethylenediamine. It is envisaged that substances such as (VI) and (II; R = $CH_2\cdot CH_2\cdot NH_2$) are formed as intermediates.

Arising out of this work, experiments were performed on amine-exchange by 2-iminopyrrolidines. For reaction to occur, either the pyrrolidine or the amine (but not both) must be in the form of a salt; these observations are consistent with the previous experiments of King, Latham, and Partridge,[4] and those of Oxley and Short[6] on the simpler but analogous ammonolysis of *N*-arylamidines.

As an alternative approach to the synthesis of hydropyrroloimidazoles an attempt was made to prepare iminopyrrolidines unsubstituted on both nitrogen atoms, by hydrogenation of *N*-benzyl derivatives. However, the benzyl group persisted on hydrogenation of compound (VII), and after hydrolysis only the amino-alcohol (VIII) was obtained.

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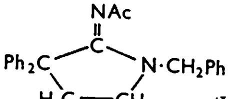
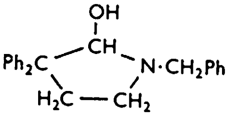
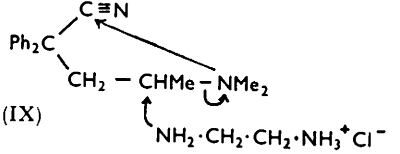
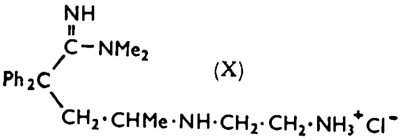
[1] Wilson, *J.*, 1950, 2173.
[2] Wilson, *J.*, 1952, 3524.
[3] Cymerman and Gilbert, *J.*, 1952, 3529.
[4] King, Latham, and Partridge, *J.*, 1952, 4268.
[5] Gittos and Wilson, *J.*, 1955, 2371.
[6] Oxley and Short, *J.*, 1949, 449.

The formation of the bicyclic compound (III) from (I) and ethylenediamine involves an unexpected displacement of the dimethylamino-group; this furthermore occurs with retention of optical activity with the (+)-cyanide (I). The reaction appears to be an S_N2 displacement facilitated by the neighbouring cyano-group (cf. amine exchange by β-cyano-amines, studied by Cymerman-Craig *et al.*[7]). The initial stage in the reaction may be represented by the scheme (IX); the feasibility of this scheme is indicated by the evolution of dimethylamine when the base (I) (as toluene-*p*-sulphonate) is heated with benzylamine and by the earlier demonstration of intramolecular interactions between the basic nitrogen and cyano-group in γ-cyano-amines.[2,5] Further transformations, for example, through (X), might be expected to afford the bicyclic compound (III). Direct attack of $NH_2{\cdot}CH{\cdot}CH{\cdot}NH_3^+Cl^-$ at the cyano-group of (I) is very unlikely, in view of the resistance of tertiary cyanides of this type to amidine formation.[8]


(VII)


(VIII)


(IX)


(X)

EXPERIMENTAL

*3-Bromo-*1,1-*diphenylbutyl Cyanide* (IV).—Tetrahydro-2-imino-5-methyl-3,3-diphenylfuran, m. p. 116—117°, was made (73% yield) from diphenylmethyl cyanide, propylene oxide, and sodamide.[8] The derived hydrochloride was heated with phosphorus tribromide, affording the bromo-cyanide,[9] b. p. 135—139°/0·01 mm., m. p. 41—43° (78% yield).

2-*Imino*-5-*methyl*-3,3-*diphenylpyrrolidine* (II; R = H).—The above bromo-cyanide (31·4 g.) and ammonia (18 g.) in ethanol (200 c.c.) were heated in an autoclave at 120° for 16 hr. The ethanol was distilled off, the residue mixed with dilute hydrochloric acid, and neutral material removed by extraction with benzene–ether (1 : 1). Addition of alkali precipitated the pyrrolidine (5 g., 20%), m. p. 149—150° (Cymerman and Gilbert[3] give m. p. 149·5—151·5°). The *hydrochloride*, recrystallised from acetone–ether, had m. p. 114—116° (Found: N, 8·3, 8·45. $C_{17}H_{18}N_2,HCl,2H_2O$ requires N, 8·65%).

Amine Exchange by 2-*Iminopyrrolidines.*—(*a*) A mixture of 2-imino-1-methyl-3,3-diphenylpyrrolidine hydrochloride (1 g.) and methylammonium chloride (2·5 g.) was heated at 240° for 6 hr. Unchanged iminopyrrolidine hydrochloride (87%) was recovered through the free base.

(*b*) 2-Imino-1-methyl-3,3-diphenylpyrrolidine hydrochloride (1 g.) and benzylamine (5 c.c.) were boiled under reflux for 5 hr., aqueous alkali was added, and the bases were extracted in ether. Ether and benzylamine were removed in a vacuum and the residue was treated with hydrogen chloride in ether. Recrystallisation of the product from acetone gave 2-*benzylimino*-1-*methyl*-3,3-*diphenylpyrrolidine hydrochloride* (0·6 g., 46%), m. p. 120—122° (Found: N, 7·3. $C_{24}H_{24}N_2,HCl$ requires N, 7·45%). Treatment of the hydrochloride with aqueous potassium nitrate gave the sparingly soluble *nitrate* as needles (from ethanol–ether), m. p. 144—145° (Found: N, 10·3. $C_{24}H_{24}N_2,HNO_3$ required N, 10·4%).

2-2′-*Hydroxyethylimino*-5-*methyl*-3,3-*diphenylpyrrolidine* (V).—2-Imino-5-methyl-3,3-diphenylpyrrolidine hydrochloride (4 g.) and ethanolamine (30 c.c.) were boiled together for 2 hr.; ammonia was evolved. The excess of ethanolamine was distilled off in a vacuum, the

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[7] Bauer, Cymerman, and Sheldon, *J.*, 1951, 3311; Cymerman-Craig, Moyle, Nicholson, and Werner, *J.*, 1955, 3628; Bates, Cymerman-Craig, Moyle, and Young, *J.*, 1956, 388.

[8] Wilson, *J.*, 1948, 1984.

[9] Nelson, Easton, Gardner, and Stevens, *J. Amer. Chem. Soc.*, 1947, **69**, 2941.

residue treated with concentrated hydrochloric acid, and the solid product recrystallised from ethanol–ether, to yield 2-2′-*hydroxyethylimino*-5-*methyl*-3,3-*diphenylpyrrolidine hydrochloride* (3·5 g., 83%), m. p. 226—228° (Found: N, 7·95. $C_{19}H_{22}N_2O,HCl$ requires N, 8·45%).

2-2′-*Chloroethylimino*-5-*methyl*-3,3-*diphenylpyrrolidine Hydrochloride*.—The foregoing hydroxyethyl compound (3 g.) was boiled for 30 min. with thionyl chloride (2 c.c.) in chloroform (50 c.c.). The chloroform was distilled off and the residue recrystallised from ethanol–ether. The *chloroethyl hydrochloride* (2·7 g., 87%) had m. p. 145—147° (Found: N, 7·65. $C_{19}H_{21}ClN_2,HCl$ requires N, 8·0%).

2,3,6,7-*Tetrahydro*-5-*methyl*-7,7-*diphenyl*-5H-*pyrrolo*[1,2-*a*]*imidazole* (III).—(*a*) The above chloroethyl compound (1·5 g.) was mixed with an excess of 5N-sodium hydroxide. The oily base was isolated by ether-extraction and boiled for 15 min. with sodium iodide (10 mg.), ethanol (7·5 c.c.), and water (7·5 c.c.). An excess of 5N-sodium hydroxide was then added and the precipitated solid recrystallised from aqueous methanol, to give the *bicyclo-compound* (1·0 g., 84%) (Found: C, 82·3; H, 7·5; N, 10·1. $C_{19}H_{20}N_2$ requires C, 82·55; H, 7·3; N, 10·15%), as prisms, m. p. 103°, m. p. not depressed on admixture with the previously unidentified product from ethylenediamine and (±)-3-dimethylamino-1,1-diphenylbutyl cyanide.[1] Attempts to resolve the product with (+)-tartaric or (+)-camphor-10-sulphonic acid were not successful. The infrared spectrum was virtually identical with those of the (±)- and (+)-bases made previously from 3-dimethylamino-1,1-diphenylbutyl cyanide.[1]

(*b*) 3-Bromo-1,1-diphenylbutyl cyanide (2·8 g.) and ethylenediamine (25 c.c.) were boiled together for 21 hr., and an excess of ethylenediamine was removed in a vacuum. The residue was dissolved in dilute hydrochloric acid, neutral products were removed by extraction with ether, and the solution was made alkaline with potassium hydroxide. The precipitated bicyclo-compound (0·3 g., 10%) had m. p. 102—103°.

(*c*) 3-Dimethylamino-1,1-diphenylbutyl cyanide benzenesulphonate (11 g.) was heated with 2-aminoethylammonium toluene-*p*-sulphonate (5·8 g.) at 200° for 27 hr. as described in the earlier paper.[1] The bicyclo-compound (1·0 g., 14·5%) had m. p. 103° (Found: C, 82·7; H, 7·5; N, 10·5%). The *picrate* (from ethanol) had m. p. 166—168° (Found: C, 59·85; H, 4·75. $C_{19}H_{20}N_2,C_6H_3O_7N_3$ requires C, 59·4; H, 4·6%).

(*d*) Repetition of experiment (*c*) but at 240° for 4 hr. gave a reduced yield of the bicyclo-compound, isolated as the picrate, m. p. 165—167°.

Hydrogenation of 2-*Acetimido*-1-*benzyl*-3,3-*diphenylpyrrolidine* (VII).—The acetimido-compound (1·75 g.) and Adams platinum oxide (0·05 g.) in glacial acetic acid (30 c.c.) were shaken in hydrogen at 1 atm. Absorption of hydrogen (1 mol.) ceased after ½ hr. The syrupy product was boiled for 5 hr. with concentrated hydrochloric acid (30 c.c.), and the solid recrystallised from water, affording 1-*benzyl*-2-*hydroxy*-3,3-*diphenylpyrrolidine hydrochloride* (1·2 g., 69%) as prisms, m. p. 224—226° (Found: N, 3·35. $C_{23}H_{23}NO,HCl$ requires N, 3·8%). The derived *base* (VIII) crystallised from aqueous methanol and had m. p. 69—70° (Found: N, 4·5. $C_{23}H_{23}NO$ requires N, 4·25%). 1-Benzyl-2-imino-3,3-diphenylpyrrolidine resisted hydrogenation.

Action of Benzylamine on 3-*Dimethylamino*-1,1-*diphenylbutyl Cyanide*.—The basic cyanide toluene-*p*-sulphonate (5 g.) and benzylamine (25 c.c.) were boiled under reflux for 20 hr. The volatile amine evolved was collected in dilute hydrochloric acid and treated with toluene-*p*-sulphonyl chloride and alkali, to give *NN*-dimethyltoluene-*p*-sulphonamide, m. p. and mixed m. p. 79°. The reaction mixture was basified and the oily product separated and treated with ethereal hydrogen chloride, affording dibenzylammonium chloride (0·65 g.), m. p. and mixed m. p. 262°. The other products remained as syrups; the dibenzylammonium chloride was an artefact, as the following experiment shows.

A mixture of benzylammonium chloride (1 g.) and benzylamine (30 c.c.) was boiled under reflux for 16½ hr. Benzylamine was removed in a vacuum and the product recrystallised, giving dibenzylammonium chloride (1 g.), m. p. and mixed m. p. 262°.

The authors thank Dr. D. H. Whiffen for infrared absorption spectra.

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[*Received, September 8th,* 1961.]