THE STRUCTURE OF "6-METHYLMETHADONE"

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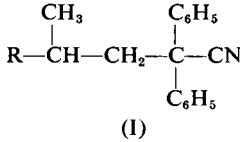
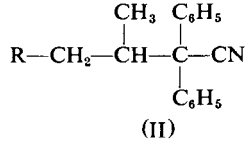
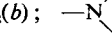
THE reaction of 1-amino-2-chloropropanes or 2-amino-1-chloropropanes with diphenylmethyl cyanide has been shown to give pairs of isomeric cyanides[1,2,3,4,5] (I and II).

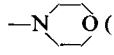


(I)



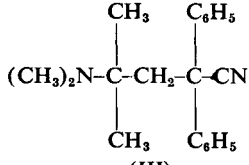
(II)

R = $-N(CH_3)_2$(*a*); $-N(C_2H_5)_2$(*b*);  (*c*);

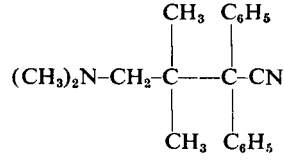
 (*d*); $-N(CH_2)_6$(*e*) $-N(CH_2)_7$(*f*).

The hindered character of the cyanide group in isomers II (*a*, *b*, *c*, and *d*) is shown by the isolation of stable ketimines from the cyanide-Grignard complexes[2,3,4]. Furthermore, the cyanide group of the dimethylamino-compound (II*a*) is resistant both to hydrolytic agents and to the action of sodamide[2].

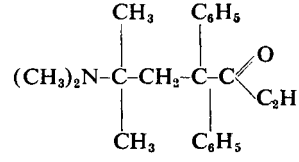
In a recent paper[6], the authors reported that condensation of 1-chloro-2-dimethylamino-2-methylpropane with diphenylmethyl cyanide gave two isomeric cyanides, namely 3-dimethylamino-3-methyl-1:1-diphenylbutyl cyanide (III) and 3-dimethylamino-2:2-dimethyl-1:1-diphenylpropyl cyanide (IV). The two cyanides (A and B) varied greatly in their reactions. Ethyl magnesium bromide yielded a ketone with the cyanide (A) but failed to react with cyanide (B). The latter was also recovered unchanged after treatment with lithium ethyl and attempted hydrolysis with 20 per cent. hydrobromic acid. These facts demonstrated the hindered nature of the cyanide group in (B) and consequently structure (III) was allocated to the less hindered cyanide (A), and structure (V) "6-methylmethadone" to the derived ketone.



(III)



(IV)

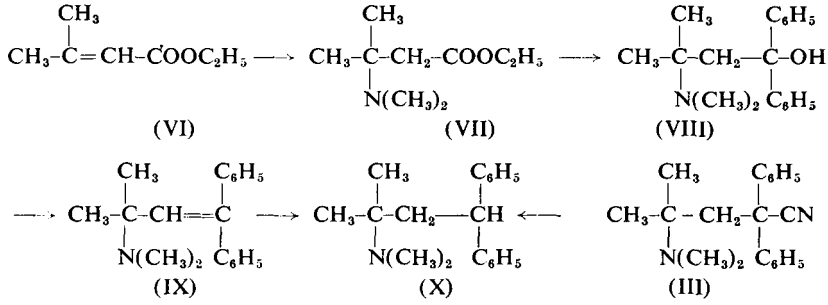


(V)

The allocation of formula (III) to the cyanide A has now been confirmed by an unequivocal chemical method, the reactions employed being illustrated in Table I.

Ethyl 3-dimethylamino-3-methylbutyrate (VII) was obtained from a mixture of ethyl 3:3-dimethylacrylate (VI) and dimethylamine in ethanol

TABLE I



which had been allowed to stand for 16 days at room temperature. An attempt to improve the yield by heating the mixture under pressure was unsuccessful. The amino-ester (VII), on treatment with phenylmagnesium bromide, gave 3-dimethylamino-3-methyl-1 : 1-diphenylbutan-1-ol (VIII), which was dehydrated by a concentrated hydrochloric acid-glacial acetic acid mixture to the corresponding amino-butene (IX). Catalytic reduction of the amino-butene (IX) gave 3-dimethylamino-3-methyl-1 : 1-diphenylbutane (X) ; this was identical with the product obtained by the cleavage of cyanide (A) with sodamide. Thus, cyanide (A) is 3-dimethylamino-3-methyl-1 : 1-diphenyl-butyl cyanide (III) and the derived ketone, 6-dimethylamino-6-methyl-4 : 4-diphenylheptan-3-one (V).

Experimental

All m.pts. are uncorrected.

Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London.

Equivalent weights of the bases and the picrate were determined by titration with 0·02N perchloric acid in glacial acetic acid using crystal violet as indicator.

Ethyl 3 : 3-*dimethyl acrylate* (*VI*). This was prepared by the method described by Perkin[7] and had b.pt. 152° to 156° C. (Perkin[7] gives b.pt. 154° to 155° C.)

Ethyl 3-*dimethylamino*-3-*methylbutyrate* (*VII*). A mixture of ethyl 3 : 3-dimethylacrylate (VI) (10 g.) and a 33 per cent. solution of dimethyl amine in ethanol (25 ml.) was allowed to stand for 16 days at room temperature. The mixture was then fractionally distilled under reduced pressure, unchanged ester distilling at 64–66°/18 mm. and the crude amino-ester (VII) (1·7 g.) at 95° to 100°/18 mm. The latter gave a *picrate*, yellow needles from ethanol, m.pt. 137° to 138° C. Found: C, 44·9; H, 5·5; N, 13·7 per cent. Equiv. wt. 410. $C_{15}H_{22}O_9N_4$ requires C, 44·8; H, 5·5; N, 13·9 per cent. Equiv. wt. 402.

3-*dimethylamino*-3-*methyl*-1 : 1-*diphenylbutan*-1-*ol* (VIII). The crude amino-ester (VII) (1·7 g.) in ether (5 ml.) was added drop by drop to a stirred, ice-cooled solution of phenylmagnesium bromide in ether prepared from magnesium (0·7 g.) and bromobenzene (4·7 g.). The mixture, after stirring for ½ hour at room temperature, was poured on to crushed ice and

ammonium chloride (2 g.) and acidified with glacial acetic acid. The solid which separated was washed with ether, the free base liberated with dilute solution of ammonia, filtered off, and crystallised from ethanol to give colourless crystals of the *amino-butanol* (VIII) (0·45 g.) m.pt. 144° to 145° C. Found: C, 80·2; H, 8·8; N, 5·0 per cent. Equiv. wt., 287. $C_{19}H_{25}ON$ requires C, 80·6; H, 8·8; N, 4·9 per cent. Equiv. wt., 283.

3-*methyl*-3-*dimethylamino*-1 : 1-*diphenylbut*-1-*ene picrate*. A mixture of the amino-butanol (VIII) (0·5 g.), concentrated hydrochloric acid (1 ml.), and glacial acetic acid (3·3 ml.) was refluxed for ½ hour. The solvent was removed under reduced pressure to give the crude amino-butene hydrochloride which formed a *picrate*, yellow needles from ethanol, m.pt. 155° C. Found: C, 60·8; H, 5·3; N, 11·3 per cent. $C_{25}H_{26}O_7N_4$ requires C, 60·7; H, 5·3; N, 11·3 per cent.

3-*dimethylamino*-3-*methyl*-1 : 1-*diphenylbutane* (*X*). A mixture of the crude amino-butene hydrochloride (0·5 g.) in ethanol (10 ml.) and 5 per cent. palladiumised charcoal (0·5 g.) was shaken for 4 hours with hydrogen at room temperature and pressure. The mixture was filtered and the solvent removed under reduced pressure, the residue shaken with water, and the non-basic material extracted with ether. The basic material was then liberated with dilute solution of ammonia, extracted with ether and, after drying over anhydrous sodium sulphate, the solvent removed. The residual yellow oil (0·11 g.) rapidly solidified and the solid was crystallised from ethanol to give colourless plates of the *amino-butane* (X) m.pt. 94° to 95° C. Found: C, 85·8; H, 9·5; N, 5·3 per cent. $C_{19}H_{25}N$ requires C, 85·4; H, 9·4; N, 5·2 per cent.

Cleavage of Cyanide A.

A mixture of cyanide A (2·4 g.), sodamide (1·4 g.), and dry toluene (15 ml.) was refluxed for 12 hours. After cooling, the excess of sodamide was decomposed with water and the base extracted with dilute hydrochloric acid. The free base was liberated with dilute solution of ammonia, filtered off and crystallised from ethanol to give colourless plates (1·5 g.) of 3-*dimethylamino*-3-*methyl*-1 : 1-*diphenylbutane* (*X*) m.pt. 94·5° to 95° C. Found: C, 85·3; H, 9·3; N, 5·2 per cent. Equiv. wt. 266. $C_{19}H_{25}N$ requires C, 85·4; H, 9·4; N, 5·2 per cent. Equiv. wt. 267. The melting point of the product of cleavage was undepressed when mixed with a specimen of the amino-butane (X) derived from 3-dimethylamino-3-methyl-1 : 1-diphenyl-butan-1-ol (VIII).

Summary

The structure of "6-methylmethadone" has been shown to be 6-dimethylamino-6-methyl-4 : 4-diphenylheptan-3-one (V).

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