Hypotensive Amines: Unbridged Cyclohexane Analogues of Mecamylamine

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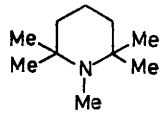
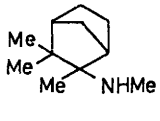
Some polyalkylcyclohexylamines related to pempidine have been prepared as potential ganglion-blocking agents, and their methylation has been examined. An *N*-formyl derivative, prepared *via* the Ritter reaction, showed anomalous behaviour on hydrolysis. No useful pharmacological activity was found.

THE highly active ganglion-blocking agent pempidine [1] (I) may be regarded as being derived [2] from mecamylamine (II) [3] by removal of the methylene bridge, and replacement of the exocyclic methylamino-group by an endocyclic basic centre. We report studies on the related type (III; $R^2 = NH_2$ or NHMe) in which only the former modification has been effected.

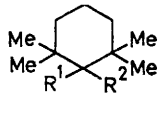
Catalytic hydrogenation of 2,2,6,6-tetramethylcyclohexanone oxime [4] under mild conditions gave the cyclohexylamine [5] (III; $R^1 = H$, $R^2 = NH_2$). Reaction of this with formaldehyde–formic acid readily afforded the fully *N*-methylated base (III; $R^1 = H$, $R^2 = NMe_2$), but attempts to effect mono-*N*-alkylation by quaternation of the *N*-benzylidene derivative (III; $R^1 = H$, $R^2 = N{:}CHPh$) with methyl iodide resulted in some concomitant fission of the basic grouping with production of ammonium iodide and methylamine hydriodide, in addition to a low yield of the hydriodide of the desired base (III; $R^1 = H$, $R^2 = NHMe$). The formation of these fission products is probably not due to intrinsic instability of the cyclohexylamines (III; $R^1 = H$, $R^2 = NH_2$) or (III; $R^1 = H$, $R^2 = NHMe$); the former was stable to concentrated hydrogen iodide at 150° for 6 hr.



(I)



(II)



(III)

Homologous compounds of the type (III; $R^1 = Me$), more closely analogous to mecamylamine (II), were obtained *via* a Grignard reaction on 2,2,6,6-tetramethylcyclohexanone which gave, in our hands, a solid tertiary carbinol (III; $R^1 = Me$, $R^2 = OH$) previously described as a liquid.[6] Reaction of this carbinol with sodium cyanide and concentrated sulphuric acid in acetic acid,[7] followed by hydrolysis with concentrated alkali gave the required base (III; $R^1 = Me$, $R^2 = NH_2$) in low yield, accompanied by a substantial amount of the *N*-formyl derivative (III; $R^1 = Me$, $R^2 = NH{\cdot}CHO$). This latter derivative proved unexpectedly resistant to alkaline hydrolysis even with boiling 10% ethanolic potassium hydroxide; hydrolysis with concentrated mineral acids led to fission of the basic group and the formation of ammonium halides. Controlled hydrolysis with 2N-hydrochloric acid, however, gave a moderate yield of the same primary amine (III; $R^1 = Me$, $R^2 = NH_2$) as had been isolated directly from the Ritter reaction.

Attempted mono-*N*-alkylation of this primary amine with methyl iodide (1 mol.) and potassium carbonate gave a low yield of a mixture of two isomeric bases which were separated by preparative g.l.c. (see Experimental section).

The slower-running base formed a hydriodide (A) (m.p. 202—203°) which was identical with the hydriodide of an authentic sample of (III; $R^1 = Me$, $R^2 = NHMe$) prepared by reduction with lithium aluminium hydride of the *N*-formyl compound (III; $R^1 = Me$, $R^2 = NH{\cdot}CHO$). The faster-running base formed a hydriodide (B) (m.p. 201—202°), the i.r. spectrum of which differed only slightly from that of (A), but its structure has not been further investigated.

The n.m.r. spectrum of the base (III; $R^1 = Me$, $R^2 = NHMe$) and its salts showed six methyl peaks instead of the expected three (see Experimental section). One possible explanation for this is that the molecule exists in a twist-boat conformation, which is prevented from assuming the normal chair form by steric crowding. The results of variable temperature n.m.r. studies are not inconsistent with this view. Other possible explanations such as skeletal rearrangements, or restricted rotation of the methylamino-group are considered less likely. Similar complex spectra were observed with the compound (III; $R^1 = Me$, $R^2 = NH_2$) and its salts (see Experimental section).

From the attempted *NN*-dimethylation of the primary amine (III; $R^1 = Me$, $R^2 = NH_2$) with formaldehyde and formic acid only trimethylamine was isolated (as the hydriodide); treatment with excess of methyl iodide and potassium carbonate also led to deamination and the formation of 1,1,3,3-tetramethyl-2-methylenecyclohexane.

The basic cyclohexylamine derivatives prepared had only low ganglion-blocking activity, less than one-tenth that of mecamylamine or pempidine.

[1] A. Spinks and E. H. P. Young, *Nature*, 1958, **181**, 1397.
[2] G. E. Lee, W. R. Wragg, S. J. Corne, N. D. Edge, and H. W. Reading, *Nature*, 1958, **181**, 1717.
[3] J. H. Moyer, R. Ford, E. Dennis, and C. A. Handley, *Proc. Soc. Exp. Biol. Med.*, 1955, **90**, 402.
[4] A. Haller and R. Cornubert, *Bull. Soc. chim. France*, 1927, (4) **41**, 367; R. Cornubert, *ibid.*, p. 894.
[5] M. Protiva, M. Rajsner, V. Trcka, M. Vanecek, and Z. J. Vejdelek, *Experientia*, 1959, **15**, 54; Z. J. Vejdelek, M. Rajsner, and M. Protiva, *Coll. Czech. Chem. Comm.*, 1960, **25**, 245.
[6] R. Cornubert, C. Borrell, M. de Demo, J. Garnier, R. Humeau, H. le Bihan, and G. Sarkis, *Bull. Soc. chim. France*, 1935, (5) **2**, 195.
[7] J. J. Ritter and J. Kalish, *J. Amer. Chem. Soc.*, 1948, **70**, 4048; *cf.* R. Jacquier and H. Christol, *Bull. Soc. chim. France*, 1957, 596, 600.

Protiva and his co-workers [5] have studied the ganglion-blocking and hypotensive activity of some related alkylcycloalkylamines, including the compound (III; $R^1 = NH_2$, $R^2 = H$).

EXPERIMENTAL

2,2,6,6-Tetramethylcyclohexanone (III; $R^1R^2 = :O$) was prepared by repeated methylation of 2-methylcyclohexanone essentially as described by Haller and Cornubert [4] except that the final fractional distillation was carried out with a forty-plate variable take-off Dixon column (*cf.* ref. 8) to give 41% overall yield of pure (by g.l.c.) tetramethylketone, b.p. 186—187·5°/756 mm., n_D^{20} 1·4471 (lit.,[8] b.p. 185°, n_D^{20} 1·4470). The oxime was best prepared by refluxing the ketone with hydroxylamine hydrochloride and sodium acetate in dry ethanol for 96 hr. (57% yield; m.p. 150—151°) (lit.,[4] m.p. 151°).

2,2,6,6-*Tetramethylcyclohexylamine* (III; $R^1 = H$, $R^2 = NH_2$).—2,2,6,6-Tetramethylcyclohexanone oxime (10 g.) in ethanol (250 ml.) was hydrogenated over Raney nickel at 60° and 500 lb./in.^{2} The filtered mixture was acidified with ethereal hydrogen chloride and evaporated. The residue (from acetone) gave the pure hydrochloride (8·6 g., 76%), sublimes >300° (lit.,[5] m.p. >300°) (Found: C, 62·6; H, 11·7; Cl, 18·7; N, 7·05. Calc. for $C_{10}H_{22}ClN$: C, 62·7; H, 11·5; Cl, 18·55; N, 7·3%). The *picrate* had m.p. 241—242° (from water) (Found: C, 49·8; H, 6·4; N, 14·85. $C_{16}H_{24}N_4O_7$ requires C, 50·0; H, 6·25; N, 14·55%). The free *base* had b.p. 100—101°/40 mm., n_D^{23} 1·4638 (Found: C, 78·1; H, 13·4; N, 8·8. $C_{10}H_{21}N$ requires C, 77·5; H, 13·5; N, 9·0%). Attempts to prepare this compound by direct reductive amination of 2,2,6,6-tetramethylcyclohexanone proved unsuccessful.

N,N,2,2,6,6-*Hexamethylcyclohexylamine* (III; $R^1 = H$, $R^2 = NMe_2$).—Methylation of 2,2,6,6-tetramethylcyclohexylamine (13 g.) with formaldehyde–formic acid by the Eschweiler–Clarke [9] procedure gave, after work-up, the N,N-*dimethyl derivative* (12·5 g., 81%) as a solid, m.p. 70—71° (Found: C, 78·45; H, 13·6; N, 7·5. $C_{12}H_{25}N$ requires C, 78·7; H, 13·65; N, 7·65%). The *hydrochloride* had m.p. 216—217° (from propan-2-ol–ether)(Found: Cl, 15·0; N, 5·85. $C_{12}H_{26}ClN,H_2O$ requires Cl, 15·0; N, 5·9%); the *hydriodide* had m.p. 240—241° (decomp.) (from propan-2-ol–ether) (Found: I, 40·55; N, 4·2. $C_{12}H_{26}IN$ requires I, 40·8; N, 4·5%); and the *picrate* had m.p. 208—209° (from water)(Found: C, 52·6; H, 7·05; N, 13·6. $C_{18}H_{28}N_4O_7$ requires C, 52·4; H, 6·8; N, 13·6%).

N,2,2,6,6-*Pentamethylcyclohexylamine* (III; $R^1 = H$, $R^2 = NHMe$).—2,2,6,6-Tetramethylcyclohexylamine [from the hydrochloride (11 g.)] in dry benzene (400 ml.) was refluxed with a slight excess of benzaldehyde in a Dean and Stark separator until no more water was evolved. After evaporation of the benzene the crude residual benzylidene compound was dissolved in methyl iodide (100 ml.) and the mixture was heated in a sealed tube at 150° for 6 hr. After removal of excess of methyl iodide the residual gum was triturated with ether and the semi-solid quaternary salt was dissolved in a mixture of ethyl acetate (100 ml.) and water (1 ml.). The solution was refluxed for 2 hr., concentrated to two-thirds volume, and left at 0° overnight to give crude hydriodide (2·3 g.), m.p. 214—238°. Extraction with hot propan-2-ol (15 ml.) and filtration from residual solid (mainly ammonium iodide), gave on cooling, the N-*methyl amine hydriodide* (0·4 g., 2%), m.p. 250—252° (Found: I, 41·7; N, 4·4; H_2O, 1·5. $C_{11}H_{24}IN,0·25H_2O$ requires I, 42·1; N, 4·65; H_2O, 1·5%). Further amounts were later recovered from mother liquors as the *picrate* (1·25 g., 6%), which had m.p. 212—214° (from water) (Found: C, 51·6; H, 6·6; N, 14·1. $C_{17}H_{26}N_4O_7$ requires C, 51·3; H, 6·5; N, 14·05%). From the propan-2-ol mother liquors on dilution with ether was obtained methylamine hydriodide (0·2 g.), m.p. 266—268° (Found: I, 79·5; N, 8·5. Calc. for CH_6IN: I, 80·3; N, 8·75%) (lit.,[10] m.p. 263—265°).

1,2,2,6,6-*Pentamethylcyclohexanol* (III; $R^1 = Me$, $R^2 = OH$).—2,2,6,6-Tetramethylcyclohexanone (100 g.) in ether (100 ml.) was added to a Grignard solution prepared from magnesium (15·8 g.) and methyl iodide (93 g.) in ether (150 ml.), and the whole was refluxed for 18 hr. The complexes were decomposed by pouring on to ammonium chloride (85 g.) and ice–water (300 ml.); the ether layer was separated and the aqueous layer was extracted with ether (2 × 250 ml.). The ether extracts were washed with sodium thiosulphate solution and water, dried (Na_2SO_4), and evaporated. The residue was distilled to give the alcohol (103 g., 93%), b.p. 98—102°/20 mm. (lit.,[6] b.p. 104—109°/28 mm.). Trituration with ice-cold light petroleum (b.p. 40—60°) gave the solid *alcohol*, m.p. 48—49° (Found: C, 77·5; H, 12·9. $C_{11}H_{22}O$ requires C, 77·7; H, 12·95%).

1,2,2,6,6-*Pentamethylcyclohexylamine* (III; $R^1 = Me$, $R^2 = NH_2$).—(a) *Ritter reaction.* 1,2,2,6,6-Pentamethylcyclohexanol (20 g.) was treated with sodium cyanide (6·1 g.), concentrated sulphuric acid (12·2 ml.), and glacial acetic acid (22·5 ml.) under the general conditions of Ritter and Kalish; [7] the crude mixture was treated with water (48 ml.) followed by a solution of sodium hydroxide (60 g.) in water (120 ml.), refluxed for 4 hr., then steam distilled until 1 l. of distillate had been collected. The steam distillate was acidified with hydrochloric acid, non-basic material (13 g.) (believed to be mainly 1,1,3,3-tetramethyl-2-methylenecyclohexane, b.p. 67°/10 mm.) was extracted with ether, and the aqueous layer was basified and extracted with ether. The dried ether extracts, treated with ethereal hydrogen chloride gave 1,2,2,6,6-*pentamethylcyclohexylamine hydrochloride*, sublimes >315° (from acetone) (0·4 g., 2%) (Found: Cl, 17·35; N, 6·8. $C_{11}H_{24}ClN$ requires Cl, 17·6; N, 6·95%), δ(Me) (5% soln. in $CDCl_3$) 0·99 (2), 1·09, 1·16, and 1·58 p.p.m.

Extraction of the residual liquors from the steam distillation with ether gave crude *N*-formyl-1,2,2,6,6-pentamethylcyclohexylamine (1·0 g., 4%), m.p. 183—185° [from light petroleum (b.p. 60—80°)] (Found: C, 73·2; H, 11·9; N, 7·2%). This was shown by n.m.r. to contain a small isomeric impurity, which was removed by a short reflux with ethanolic potassium hydroxide (10% w/v) to give the pure *formamido-compound*, m.p. 195—196° (Found: C, 73·5; H, 11·7; N, 6·8. $C_{12}H_{23}NO$ requires C, 73·4; H, 11·7; N, 7·15%), δ (10% soln. in $CDCl_3$) 8·12 (1H, d, *J* 12 Hz, CHO), and 0·93 (6H), 1·08 (6H), and 1·32 (3H) (each s, 5 × Me) p.p.m.

If the original Ritter reaction mixture was heated at 60—65° for 18 hr., instead of 15 min., after addition of the acetic–sulphuric acid mixture, the yield of formamido-compound was raised to 23%. The recovered methylene-

[8] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

[9] M. L. Moore, *Org. Reactions*, 1949, **5**, 323.

[10] H. Biltz and F. Max, *Annalen*, 1921, **423**, 300.

cyclohexane could also be reprocessed to give an additional 8% of formyl compound.

(b) *Hydrolysis of formamido-compound* (III; R^1 = Me, R^2 = NH·CHO).—The formamido-compound proved unexpectedly stable to alkaline hydrolysis, being recovered substantially unchanged after refluxing with 10% ethanolic potassium hydroxide for 3 hr.

When the formamido-compound was refluxed with concentrated hydrochloric or hydrobromic acid, the amino-group was rapidly lost and the only solid product isolated was ammonium chloride or ammonium bromide respectively. This breakdown must occur during the hydrolysis, as the 1,2,2,6,6-pentamethylcyclohexylamine itself is recovered substantially unchanged after being refluxed with strong mineral acid, as are its *N*-methyl derivatives and 2,2,6,6-tetramethylcyclohexylamine.

The hydrolysis was finally effected by refluxing the *N*-formyl compound (11 g.) with 2N-hydrochloric acid (250 ml.) for 2 hr. The mixture was cooled, some neutral material was removed with ether, and the aqueous layer, cooled in ice, was basified with sodium hydroxide (50% w/w). The liberated base was extracted with ether (3 × 200 ml.), and the extracts were dried and evaporated to give 1,2,2,6,6-*pentamethylcyclohexylamine* (5·0 g., 53%), m.p. 131—132° (Found: C, 78·15; H, 13·45; N, 8·6. $C_{11}H_{23}N$ requires C, 78·2; H, 13·6; N, 8·3%), δ (2% soln. in 1,2,4-trichlorobenzene) 1·3—1·8 (exchangeable, NH_2) and methyl singlets at 0·79, 0·80, 0·85, 0·99, and 1·15 p.p.m. The *picrate* decomposed at 206—220° with formation of ammonium picrate (m.p. 286—287°) (Found: C, 51·55; H, 6·85; N, 14·0. $C_{17}H_{26}N_4O_7$ requires C, 51·3; H, 6·5; N, 14·1%).

N,1,2,2,6,6-*Hexamethylcyclohexylamine* (III; R^1 = Me, R^2 = NHMe).—(a) *By reduction of* N-*formyl*-1,2,2,6,6-*pentamethylcyclohexylamine*. A solution of the formyl compound (5·25 g.) in dry ether (70 ml.) was added with stirring to a suspension of lithium aluminium hydride (1·1 g.) in dry ether (50 ml.) cooled in ice. The mixture was then stirred and refluxed for 18 hr., then worked up by the usual procedure.[11] The filtered ether solution was extracted with 2N-hydrochloric acid (20 ml.) and the aqueous extracts were basified with sodium hydroxide and extracted with ether. The bulked ether extracts were made just acid with ethanolic hydriodic acid and evaporated to give crude material (3·95 g., 48%), which yielded N,1,2,2,6,6-*hexamethylcyclohexylamine hydriodide*, m.p. 203° (from propan-2-ol–ether) (Found: I, 40·9; N, 4·35. $C_{12}H_{26}IN$ requires I, 40·8; N, 4·5%), δ(Me) (10% soln. in $CDCl_3$) 0·98, 1·06, 1·20, 1·32, 1·49, and 2·67br p.p.m. The free base (generated *in situ* from the hydriodide) showed the methyl singlets at δ 0·85, 0·88, 0·92, 0·95, 1·33, and 2·36 p.p.m. (10% soln. in 1,2,4-trichlorobenzene). On heating to 190° the spectrum of the free base in 1,2,4-trichlorobenzene showed complex changes with broadening and emergence of new methyl peaks at δ 0·83, 0·88 (2), 0·93, 1·15, and 2·18 p.p.m., the original spectrum being again observed after cooling. The *picrate* had m.p. 192—193° (from water) (Found: C, 52·7; H, 6·8; N, 13·5. $C_{18}H_{28}N_4O_7$ requires C, 52·5; H, 6·8; N, 13·6%).

(b) *By methylation of* 1,2,2,6,6-*pentamethylcyclohexylamine*. A mixture of 1,2,2,6,6-pentamethylcyclohexylamine (2·15 g.), methyl iodide (0·8 ml., 1 equiv.), and anhydrous potassium carbonate (1·92 g.) in dry acetone (10 ml.) was refluxed for 16 hr., then cooled; ether (70 ml.) was added and the inorganic salts were filtered off. The filtrate was evaporated to dryness to give, in addition to a considerable amount of neutral material, a mixture of two basic components which were separated by preparative g.l.c. on glycerol αα′-bis-(*p*-nonylphenyl) ether–Embacel at 182° to give (as slower-running component) *N*,1,2,2,6,6-hexamethylcyclohexylamine, isolated as a hydriodide (A) (0·1 g., 3%), m.p. 202—203° (from propan-2-ol–ether), and identical (mixed m.p. and i.r. spectrum with the sample prepared in (a) (Found: C, 46·3; H, 8·6; I, 40·9. Calc. for $C_{12}H_{26}IN$: C, 46·3; H, 8·4; I, 40·8%), together with (faster-running component) an isomeric base, isolated as a hydriodide (B) (0·1 g, 3%), m.p. 201—202° (decomp.) (mixed m.p. with *N*,1,2,2,6,6-hexamethylcyclohexylamine hydriodide depressed to 195—196°) (Found: C, 46·5; H, 8·7; I, 41·1%).

Attempted Preparation of N,N,1,2,2,6,6-*Heptamethylcyclohexylamine* (III; R^1 = Me, R^2 = NMe_2).—(a) *Eschweiler–Clarke methylation*. 1,2,2,6,6-Pentamethylcyclohexylamine (2 g.) was treated in the usual way [9] with formic acid (90% w/w; 2·7 ml.) and formalin (40% w/v; 2·7 ml.). After the work-up, the basic product was converted into the hydriodide, which gave, as the only isolated product, trimethylamine hydriodide, m.p. 250—255° (decomp.) (0·21 g., 10%) (Found: C, 19·8; H, 5·7; I, 67·6; N, 7·4. Calc. for $C_3H_{10}IN$: C, 19·3; H, 5·35; I, 68·0; N, 7·5%) (lit.,[12] m.p. *ca.* 260°).

(b) *With excess of methyl iodide and potassium carbonate*. 1,2,2,6,6-Pentamethylcyclohexylamine (1 g.) was added to a mixture of methyl iodide (5 ml.) and anhydrous potassium carbonate (1·78 g.) in dry acetone (5 ml.) and the whole was refluxed for 24 hr. Further portions of methyl iodide (2 × 5 ml.) were added and refluxing was continued for a further 40 hr. The mixture was cooled, dry ether (100 ml.) was added and the inorganic salts were removed. Evaporation of the ether gave a neutral oil (0·9 g.), from which was isolated [by g.l.c. on glycerol αα′-bis-(*p*-nonylphenyl) ether–Embacel at 182°] a solid, m.p. 72—75°, believed (analytical and i.r. data) to be 1,1,3,3-*tetramethyl*-2-*methylenecyclohexane* (Found: C, 85·7; H, 12·9. $C_{11}H_{20}$ requires C, 86·8; H, 13·2%), >C=CH_2 i.r. bands at 889, 1640, 1790, and 3080 $cm.^{-1}$.

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[11] L. H. Amundsen and L. S. Nelson, *J. Amer. Chem. Soc.*, 1951, **73**, 242.

[12] M. Delépine, *Ann. Chim. Phys.*, 1896, (7) **8**, 439.