822. *Some 2-Aminoalkylcyclohexylamines and Derivatives of Potential Pharmacological Interest.*

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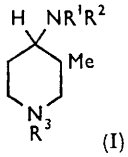
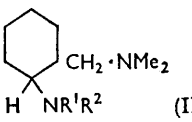
The synthesis of 2-dimethylaminomethyl-, 2(2-dimethylaminoethyl-, and 2-(4-phenylpiperazylmethyl)-cyclohexylamine is described. The successive benzoylation, reduction, and acetylation of these amines is reported. Attempts to obtain isomeric forms of 2-dimethylaminomethylcyclohexylamine are outlined.

Several 4-aminopiperidine derivatives (I),[1] possess significant pharmacological activities including the induction of analgesia and short duration sympathetic blockade. The



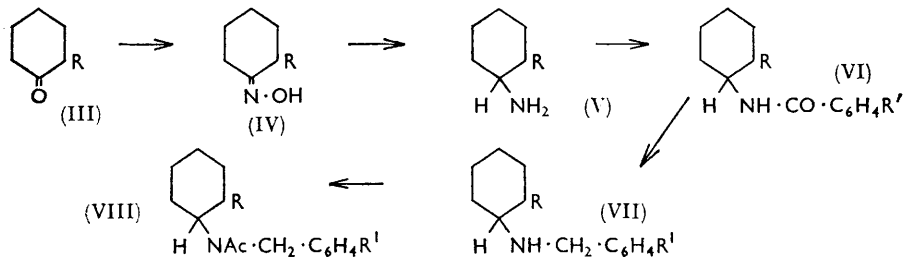
(I)



(II)

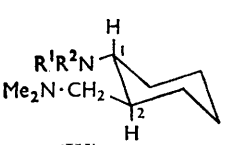
R^1 = H,COMe, COEt
R^2 = $CH_2C_6H_4R^4$
R^3 = lower alkyl or aralkyl
R^4 = H,Cl,F

synthesis of the less rigid analogues (II), presently reported, was undertaken as a further study of the relationship of molecular rigidity to pharmacological activity.[2] The reaction sequence employed is shown below.



R = (a) $CH_2 \cdot NMe_2$; (b) $[CH_2]_2 \cdot NMe_2$; (c) $CH_2 \cdot N$ NPh; R^1 = H, *m*-F or *p*-Cl

The diamine (Va), previously reported to be formed by reductive amination of the ketone (IIIa) [3] and by catalytic hydrogenation of the oxime (IVa),[4] was made in improved yield by reducing the oxime (IVa) (base or hydrochloride) with lithium aluminium hydride. It was acylated by hot benzoyl (or a substituted benzoyl) chloride in toluene or a benzoyl chloride-sodium hydrogen carbonate mixture in chloroform. Treatment of the resultant amides (VIa) with lithium aluminium hydride gave the benzylamino-amines (VIIa); the *p*-chlorobenzyl derivative (VIIa; R^1 = *p*-Cl) was obtained in two isomeric forms indicating that the precursor amide (VIa; R^1 = *p*-Cl) and diamine (Va) were not isomerically pure. The configuration of the derivatives (II) has not been established but is probably *trans*-($CH_2 \cdot NMe_2$/NR^1R^2) on steric grounds. The n.m.r. spectrum of the acetyl derivative (VIIIa; R^1 = *m*-F) shows a one proton signal centred at τ 6·6 that must be due either to the C-1 or C-2 hydrogen atom. The signal approximates to a quartet (J = 7 c./sec.) and has a half height width (25 c./sec.) consistent with its arising from an axial proton flanked by two protons of the same (axial) conformation in support of the *trans* configuration (IX).[5]



(IX)

[1] Chignell, Ph.D. Thesis, London, 1962.
[2] Casy, Harper, and Dimmock, *J.*, 1964, 3635.
[3] Smith and Day, *J. Amer. Chem. Soc.*, 1955, **77**, 3541.
[4] Nazarov and Kuznetsov, *Doklady Akad. Nauk S.S.S.R.*, 1956, **111**, 358.
[5] Lemieux, Kullnig, Bernstein, and Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6098.

The amino-ketone (IIIb) (obtained by alkylation of ethyl 2-oxocyclohexanecarboxylate and decarboxylation of the product [6]) gave an oxime which, on treatment with lithium aluminium hydride, formed the diamine (Vb); this was successively benzoylated, reduced, and acetylated to give the series (VIb—VIIIb; R^1 = *m*-F). The ketone (IIIc), obtained from a Mannich reaction between cyclohexanone, formaldehyde, and phenylpiperazine hydrochloride, was used as precursor of the series (VIc—VIIIc; R^1 = *m*-F). These compounds required purification by chromatography and, in contrast to the dimethylaminomethyl (and ethyl) analogues, did not readily form crystalline derivatives.

Attempts were made to obtain isomeric forms of the oxime (IVa) and the diamine (Va) but fractional crystallisation of the corresponding hydrochlorides failed to reveal a second isomer in either case. The indistinct melting behaviour of the diamine (Va) hydrochloride made investigation of its isomeric composition difficult. It was considered that catalytic hydrogenation of the oxime (IVa) might yield a different isomeric form of the diamine (Va), since this reduction mode converts 2-methylcyclohexanone oxime into *cis*-2-methylcyclohexylamine [7] while use of lithium aluminium hydride leads to the *trans*-isomer.[8] The oxime (IVa) proved difficult to reduce catalytically at atmospheric pressure and the product, finally obtained in low yield, was identical with the diamine derived by hydride reduction. Chignell [1] similarly found catalytic and chemical reduction of *N*-phenethyl-3-methyl-4-piperidone oxime to lead to the same diamine. In a further attempt to obtain the diamine (Va) in isomeric forms, the two isomers (VIIa; R^1 = *p*-Cl) were catalytically debenzylated. Conditions successfully applied to *N*-benzylpiperidines [9] failed in the present case probably due to the deactivating influence of the *p*-chloro-substituent; [10] reaction was induced by increasing the proportion of catalyst (10% palladium on carbon) to substrate and heating the reaction mixture. The major isomer (VIIa; R^1 = *p*-Cl) gave a diamine (Va) hydrochloride identical with that derived from the oxime; the minor gave a diamine salt which, from melting point evidence (it melted over a lower temperature range than and depressed the melting point of the sample derived from the major isomer) appeared to be a second isomer. The high-resolution infrared spectra of the two samples, although similar, were not superimposable.

Some pharmacological properties of certain of these compounds have been investigated. In the hot plate test, with pethidine as standard (activity = 1), the activities of the acetyl derivatives (VIIIa; R^1 = H and *m*-F) and the amide (VI; R^1 = *p*-Cl) were 0·14, 0·4, and 0·22, respectively; the major isomer of the benzylaminoamine (VII; R^1 = *p*-Cl) had an activity of 0·33, the minor isomer being inactive. Only the amide (VIa; R^1 = *m*-F) showed a significant effect in the electroshock test (it was 35% as active as diphenylhydantoin) while all compounds tested lacked activity in the antiamphetamine and antireserpine tests.

Experimental

Some analyses were by Mr. G. S. Crouch, School of Pharmacy, University of London. Equivalent weights of bases and salts were determined by titration with 0·02N-perchloric acid in glacial acetic acid with Oracet Blue B as indicator.

2-Dimethylaminomethylcyclohexylamine (Va) *Dihydrochloride.*—A suspension of 2-dimethylaminomethylcyclohexanone oxime (IVa) (64·1 g., 0·38 mole), m. p. 157—158·5° (reported [11] m. p. 158°), in ether (300 ml.) was added during 7·5 hr. to a stirred mixture of lithium aluminium hydride (21·5 g., 0·56 mole) and ether (250 ml.). The mixture was then heated under reflux for 12 hr., decomposed with water (45 ml.), and filtered. The filtrate was dried ($MgSO_4$) and evaporated and the product distilled to give the diamine (Va) (8·0 g.), b. p. 76—82°/26 mm. (reported [4] b. p. 112—113/30 mm.). The residue was treated with excess of ethanolic hydrogen

[6] Grewe, *Ber.*, 1943, **76**, 1072.
[7] Anziani and Cornubert, *Compt. rend.*, 1945, **221**, 103; *Bull. Soc. chim. France*, 1948, 859.
[8] Smith, Maienthal, and Tipton, *J. Org. Chem.*, 1952, **17**, 294.
[9] Casy, Beckett, Hall, and Vallance, *J. Medicin. Pharmaceut. Chem.*, 1961, **4**, 535.
[10] Baltzly and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 3410.
[11] Mannich and Braun, *Ber.*, 1920, **53***B*, 1874.

chloride and crystallised from ethanol to give the diamine (Va) dihydrochloride (9·5 g.), m. p. 219—221·5° (decomp.) (reported [3] m. p. 214·5—215·5°). An analytical sample melted at 230° (Found: C, 47·1; H, 9·5; N, 12·2%; Equiv., 122. Calc. for $C_9H_{22}Cl_2N_2$: C, 47·2; H, 9·7; N, 12·2%; Equiv., 115). A mixture of the diamine (Va) (3·5 g.), benzenesulphonyl chloride (4·0 g.), sodium hydrogen carbonate (1·9 g.), and chloroform (30 ml.) was heated under reflux for 5 hr., cooled, and extracted with hydrochloric acid. The free base (3 g.) recovered as usual, was treated with excess of ethanolic hydrogen chloride and crystallised from ethanol–ether to give N-*benzenesulphonyl*-2-*dimethylaminomethylcyclohexylamine hydrochloride* (1·25 g.), m. p. 169°. An analytical sample melted at 172—173° (Found: C, 52·8; H, 7·8; N, 8·2%; Equiv., 339. $C_{15}H_{25}ClN_2O_2S,\frac{1}{2}H_2O$ requires C, 52·6; H, 7·7; N, 8·2%; Equiv., 342). It had a broad absorption band near 3400 cm.$^{-1}$ (H_2O).

2-(2-*Dimethylaminoethyl*)*cyclohexanone Oxime* (IVb) *Hydrochloride*.—Hydroxylamine hydrochloride (22·8 g., 0·33 mole) in methanol (170 ml.) was added to 2-(2-dimethylaminoethyl)cyclohexanone [11] (58·5 g., 0·35 mole) in methanol (15 ml.). Next day the mixture was evaporated and water removed by azeotropic distillation with benzene and alcohol. A portion of the residue (4·3 g.) was treated with a slight excess of ethanolic hydrogen chloride and crystallised from ether–ethanol to give the *oxime* (IVb) *hydrochloride* (1·7 g.), m. p. 173·5—174° (Found: C, 54·6; H, 9·7; N, 13·0%; Equiv., 224. $C_{10}H_{21}ClN_2O$ requires C, 54·4; H, 9·6; N, 12·7%; Equiv., 221).

2-(2-*Dimethylaminoethyl*)*cyclohexylamine* (Vb) *Dihydrochloride*.—Reduction of the impure oxime (IVb) hydrochloride (0·32 mole) with lithium aluminium hydride (0·92 mole), as described for (IVa), gave the diamine (Vb). It formed a *dihydrochloride*, m. p. 208—210°, from ethanol–ether (Found: C, 49·2; H, 9·8; N, 11·6. $C_{10}H_{24}Cl_2N_2$ requires C, 49·4; H, 9·95; N, 11·5%).

2-(4-*Phenylpiperazylmethyl*)*cyclohexanone* (IIIc).—Phenylpiperazine (238 g., 1·47 mole) in ethanol was treated with a slight excess of ethanolic hydrogen chloride, the solvent evaporated, and the residue heated under reflux for 20 min. with aqueous formaldehyde (40%; 110 ml., c·48 mole), cyclohexanone (721 g., 7·35 mole), water (20 ml.), and concentrated hydrochloric grid (40 ml.), and left at room temperature overnight. Water (350 ml.) was added and the organic phase extracted with hydrochloric acid. The acid extract, after being washed with ether, was basified with aqueous sodium hydroxide and extracted with benzene (6 × 600 ml.). The dried extract ($MgSO_4$) was evaporated to give the impure piperazyl ketone (IIIc) (248 g.) [*dipicrate*, m. p. 134—137°, from ethanol (Found: C, 47·1; H, 4·4; N, 15·8%; Equiv., 367. $C_{29}H_{30}N_8O_{15}$ requires C, 47·7; H, 4·1; N, 15·3%; Equiv., 365)].

2-(4-*Phenylpiperazylmethyl*)*cyclohexylamine* (Vc) *Trihydrochloride*.—The piperazyl ketone (IIIc) gave an oxime dihydrochloride, m. p. 235—236° (prepared as described for IVb), that could not be obtained analytically pure. It was reduced with excess of lithium aluminium hydride as described above to give the triamine (Vc) characterised as a *trihydrochloride*, m. p. 215° (decomp.) (Found: C, 52·5; H, 7·6; N, 11·2. $C_{17}H_{30}Cl_3N_3$ requires C, 53·3; H, 7·9; N, 11·0%).

N-*Benzoyl*-2-*dimethylaminomethylcyclohexylamine* (VIa; R^1 = H).—Benzoyl chloride (20 g.) in chloroform (50 ml.) was added to a stirred mixture of the diamine (Va) (8 g.), sodium hydrogen carbonate (8·6 g.), and chloroform (50 ml.), the product heated under reflux for 4 hr., cooled, and filtered. The filtrate, after being washed with water, was dried (Na_2SO_4), and evaporated, and the residue crystallised from ethanol–ether to give the N-*benzoyldiamine* (VIa; R^1 = H) *hydrochloride*, m. p. 212·5—214° (Found: C, 65·3; H, 8·4. $C_{16}H_{25}ClN_2O$ requires C, 64·7; H, 8·5%). The N-p-*Chlorobenzoyldiamine* (VIa; R^1 = *p*Cl) *hydrochloride*, similarly prepared, had m. p. 239—240·5° (decomp.) (from acetone) (Found: Cl, 21·7; N, 8·1%; Equiv., 335. $C_{16}H_{24}Cl_2N_2O$ requires Cl, 21·3; N, 8·4%; Equiv., 333).

2-*Dimethylaminomethyl*-N-m-*fluorobenzoylcyclohexylamine* (VIa; R^1 = *m*-F) *Hydrochloride*.—A solution of *m*-fluorobenzoyl chloride (30·5 g.) and the diamine (Va) in toluene (60 ml.) was heated under reflux for 20 hr. The crystals (15·7 g.) which separated on cooling were crystallised from ethanol–ether to give the N-m-*fluorobenzoyldiamine* (VIa, R^1 = *m*-F) *hydrochloride*, m. p. 215—217° (Found: C, 61·1; H, 7·7; N, 9·1. $C_{16}H_{24}ClFN_2O$ requires C, 61·0; H, 7·7; N, 8·9%).

N-m-*Fluorobenzoyl*-2-(4-*phenylpiperazylmethyl*)*cyclohexylamine* (VIc; R^1 = *m*-F).—A mixture of *m*-fluorobenzoyl chloride (35 g.), the piperazylamine (Vc) (20 g.) and toluene (145 ml.) was heated under reflux for 2 hr. and then evaporated, and the residue extracted with hydrochloric acid. The free base (3·4 g.), a portion of the total (26·5 g.) recovered as usual, was

chromatographed on alumina; benzene–alcohol eluates gave an oil (1·55 g.) that solidified on trituration with petroleum (b. p. 60—80°). The solid was crystallised from the same solvent to give the N-m-*fluorobenzoylpiperazylamine* (VIc; R = *m*-F), m. p. 127·5—128° (Found: C, 73·1; H, 7·7; N, 10·8. $C_{24}H_{30}FN_3O$ requires C, 72·9; H, 7·65; N, 10·6%) [*dipicrate*, m. p. 179°, from ethanol (Found: C, 50·65; H, 4·4; N, 14·7. $C_{36}H_{36}FN_9O_{15}$ requires C, 50·6; H, 4·25; N, 14·8%)].

N-*Benzyl*-2-*dimethylaminomethylcyclohexylamine* (VIIa; R = H).—The *N*-benzoyldiamine (VIa; R = H) (8·7 g.) in ether (6·5 ml.) was added to lithium aluminium hydride (2·54 g.) in ether (75 ml.), the mixture heated under reflux for 15 hr., decomposed with water (5 ml.), and filtered. The filtrate was washed with water, dried ($MgSO_4$), and evaporated; the residue was treated with excess of ethanolic hydrogen chloride and crystallised from ethanol–ether to give the N-*benzyldiamine* (VIIa; R = H) *dihydrochloride*, m. p. 245·5—246° (Found: C, 59·2; H, 9·1; N, 8·5%; Equiv., 167. $C_{16}H_{28}Cl_2N_2,\frac{1}{2}H_2O$ requires C, 58·5; H, 8·9; N, 8·5%; Equiv., 164). It had a broad absorption band near 3400 cm.$^{-1}$ (H_2O). Similarly prepared were the *N*-benzyldiamine (VIIa; R^1 = *m*-F and *p*-Cl) (VIIb and VIIc, R′ = *m*-F). The *N*-*m*-Fluorobenzyldiamine (VIIa; R′ = *m*-F) gave a *dihydrochloride*, m. p. 231—232·5° (Found: C, 56·6; H, 8·2; N, 8·2%; Equiv., 175. $C_{16}H_{27}Cl_2FN_2$ requires C, 56·9; H, 8·1; N, 8·3%; Equiv., 169), and a *monohydrochloride*, m. p. 199—201·5° (decomp.) (Found: C, 63·0; H, 8·6; N, 9·8; Cl, 11·8%; Equiv., 157. $C_{16}H_{26}ClFN_2$ requires C, 63·9; H, 8·7; N, 9·3; Cl, 11·8%; Equiv., 150). The *N*-*p*-Chlorobenzyldiamine (VIIa; R^1 = *p*-Cl) gave a *dihydrochloride* (*isomer A*), m. p. 233—235° (Found: C, 54·9; H, 7·5; N, 7·8. $C_{16}H_{27}Cl_3N_2$ requires C, 54·3; H, 7·7; N, 7·9%), and a *dihydrochloride* (*isomer B*), m. p. 198·5—200° (Found: C, 54·6; H, 7·8; N, 8·0; Cl, 29·8%; Equiv., 176. $C_{16}H_{27}Cl_3N_2$ requires Equiv., 177). The ratio of isomers A : B was 3·3 : 1 (the minor isomer separated from the mother-liquors after prolonged storage at 5°). The *N*-*m*-Fluorobenzyldiamine (VIIb; R′ = *m*-F) gave a *dihydrochloride*, m. p. 268—269° (Found: C, 58·2; H, 8·6; N, 8·2%; Equiv., 180. $C_{17}H_{29}Cl_2FN_2$ requires C, 58·1; H, 8·3; N, 8·0%; Equiv., 176). The *N*-*m*-Fluorobenzylpiperazylamine (VIIc; R^1 = *m*-F) (purified by chromatography on alumina) was isolated as an oil (Found: C, 75·2; H, 8·2; N, 10·6. Calc. for $C_{24}H_{32}FN_3$: C, 75·6; H, 8·5; N, 11·0%).

N-*Acetyl*-N-*benzyl*-2-*dimethylaminomethylcyclohexylamine* (VIIIa; R^1 = H).—A stirred mixture of the *N*-benzyldiamine (VIIa; R^1 = H) (3·85 g.), acetic anhydride (10 ml.), and glacial acetic acid (10 ml.) was heated under reflux for 30 min. The product was evaporated under reduced pressure and the residue treated with excess of ethanolic hydrogen chloride and crystallised from ethanol–ether to give the N-*acetyldiamine* (VIIIa; R^1 = H) *hydrochloride* (2·9 g.), m. p. 215° (analytical sample, m. p. 225°) (Found: C, 66·2; H, 9·3; N, 8·4. $C_{18}H_{29}ClN_2O$ requires C, 66·5; H, 9·0; N, 8·6%). The following *N*-acetyl derivatives (VIII) were similarly prepared. The *N*-acetyl-*N*-*m*-fluorobenzyldiamine (VIIIa; R^1 = *m*-F) [*hydrochloride*, m. p. 217—219° (Found: C, 62·8; H, 8·3; N, 8·1%; Equiv., 350. $C_{18}H_{28}ClFN_2O$ requires C, 63·0; H, 8·2; N, 8·15%; Equiv., 343)]. The *N*-acetyl-*N*-*p*-chlorobenzyldiamine (VIIIa; R^1 = *p*-Cl) [obtained from the isomeric mixture (VIIa; R^1 = *p*-Cl)] [*hydrochloride*, m. p. 231—232° (Found: C, 60·4; H, 7·8; N, 7·7%; Equiv. 358. $C_{18}H_{28}Cl_2N_2O$ requires C, 60·2; H, 7·9; N, 7·8%; Equiv., 359)]. The *N*-acetyl derivative (VIIIb; R^1 = *m*-F) was obtained as an oil (Found: C, 70·9; H, 9·4. Calc. for $C_{19}H_{29}FN_2O$: C, 71·2; H, 9·1%), as was also the piperazyl analogue (VIIIc; R^1 = *m*-F) (Found: C, 73·7; H, 8·0. Calc. for $C_{26}H_{34}FN_3O$: C, 73·8; H, 8·0%). Both oils had intense absorption peaks at 1640 cm.$^{-1}$ (tertiary amide).

Catalytic Reductions.—A mixture of the oxime (IVa) hydrochloride (5·0 g.) in glacial acetic acid (90 ml.) and platinum on carbon (5%, 0·5 g.) was shaken with hydrogen at atmospheric pressure, being warmed at intervals. After 5 days the mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in water and the free base isolated by using benzene; it was treated with excess of ethanolic hydrogen chloride and crystallised from ethanol–ether to give the diamine (Va) hydrochloride (0·9 g., 16% yield), m. p. 234—236° undepressed by mixture with a sample obtained by hydride reduction (the two samples had identical infrared spectra). Oxime (IVa) hydrochloride (0·36 g.) was recovered from the mother-liquors. Use of 0·5N-hydrochloric acid as solvent and platinum on alumina (10%, 1 g.) as catalyst led to an even lower yield of the same diamine (0·65 g. from 5 g. of oxime hydrochloride).

The *N*-*p*-Chlorobenzyldiamine (VIIa; R^1 = *p*-Cl) hydrochloride (*isomer* A) (1·5 g.) in

ethanol (15 ml.) and palladium on charcoal (10%, 1·5 g.) were shaken with hydrogen as above for 7·5 hr. The mixture was filtered, the filtrate evaporated, and the residue (1·4 g.) crystallised from ethanol–ether to give the diamine (Va) hydrochloride (0·7 g., 72% yield), m. p. 231° (decomp.) undepressed by mixture with material obtained by hydride reduction of the oxime (IVa). When isomer B (VIIa; $R^1 = p$-Cl) (1·0 g.) was subjected to the same treatment, the diamine (Va) hydrochloride (0·43 g., 66% yield), m. p. 209—216° (decomp.), was isolated; it depressed the melting point of the previous sample, and oxime-derived diamine hydrochloride to 222—227 and 223—225°, respectively.

The n.m.r. spectrum was obtained on a 60 M.c. Varian (A-60) instrument (carbon tetrachloride solution with tetramethylsilane as internal standard).

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