Acylation of 2,2,6,6-Tetramethylpiperidine and 2,2,5,5-Tetramethylpyrrolidine

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Treatment of 2,2,6,6-tetramethylpiperidine with carbonyl dichloride caused ring fission with loss of hydrogen chloride to give a mixture of 1,1,5-trimethylhex-4-enyl isocyanate and 1,1,5-trimethylhex-5-enyl isocyanate which on treatment with sodium carbonate gave *N*-(1,1,5-trimethylhex-4-enyl)-*N'*-(1,1,5-trimethylhex-5-enyl)urea. Ring fission also occurred on treatment with acetic anhydride or acetyl chloride, giving a mixture of *N*-(1,1,5-trimethylhex-4-enyl)acetamide and *N*-(1,1,5-trimethylhex-5-enyl)acetamide, although conditions could be modified to give 1-acetyl-2,2,6,6-tetramethylpiperidine. Treatment of 2,2,5,5-tetramethylpyrrolidine with carbonyl dichloride gave the 1-chlorocarbonyl derivative, which reacted normally with alcohols and amines.

THE possibility that *NNN'N'*-tetrasubstituted ureas might act as carriers of pharmacologically active substances into the brain of animals led us to attempt the synthesis of a symmetrical urea (1) derived from 2,2,6,6-tetramethylpiperidine (2), the precursor of the hypotensive agent, pempidine tartrate [1] (3), which was readily accessible to us.

Treatment of 2,2,6,6-tetramethylpiperidine (2) with carbonyl dichloride afforded an oil from which a waxy solid slowly separated after treatment with aqueous alkali. Repeated crystallisations gave a product which, although having correct analytical figures for the urea (1), was shown by its i.r. spectrum to contain a secondary amino-group. Distillation of the crude oil under reduced pressure gave a low-boiling fraction that contained no halogen but possessed the chemical properties of an isocyanate. G.l.c. showed it to be a mixture of two compounds in the ratio *ca.* 4 : 5, which on the basis of elemental analysis and i.r., n.m.r., and mass spectra were assigned the isomeric structures (4) and (5). If excess of carbonyl dichloride was used in the original reaction, a small amount of a 1-chlorocarbonyl derivative (6) was isolated as a high-boiling fraction. Its cyclic structure has not been confirmed. Trituration of the residue obtained after distillation with light petroleum gave a waxy solid, identical with that obtained before. This product could also be obtained by treatment of the mixture of isomers (4) and (5), or of the putative 1-chloro-compound (6), with aqueous sodium carbonate. On the basis of elemental analysis and i.r., n.m.r., and mass spectra it was assigned the structure (7).

Treatment of the mixture of isocyanates (4) and (5) with ammonia afforded a single product having analytical figures consistent with a monosubstituted urea. On the basis of n.m.r. and mass spectra it was assigned the structure (8), derived from the isocyanate (4). As the yield of this urea (8) was significantly higher than that theoretically possible from the amount of the isocyanate (4) present in the mixture of isocyanates used, some isomerisation had probably occurred during the reaction.

A considerable difference in reactivity between the isomeric isocyanates (4) and (5) is therefore suggested both by the absence of a urea isomeric with (8) and derived from (5) when the mixture of (4) and (5) is treated with ammonia, and by the isolation of the unsymmetrical urea (7), when the mixture is treated with aqueous sodium hydroxide or sodium carbonate.

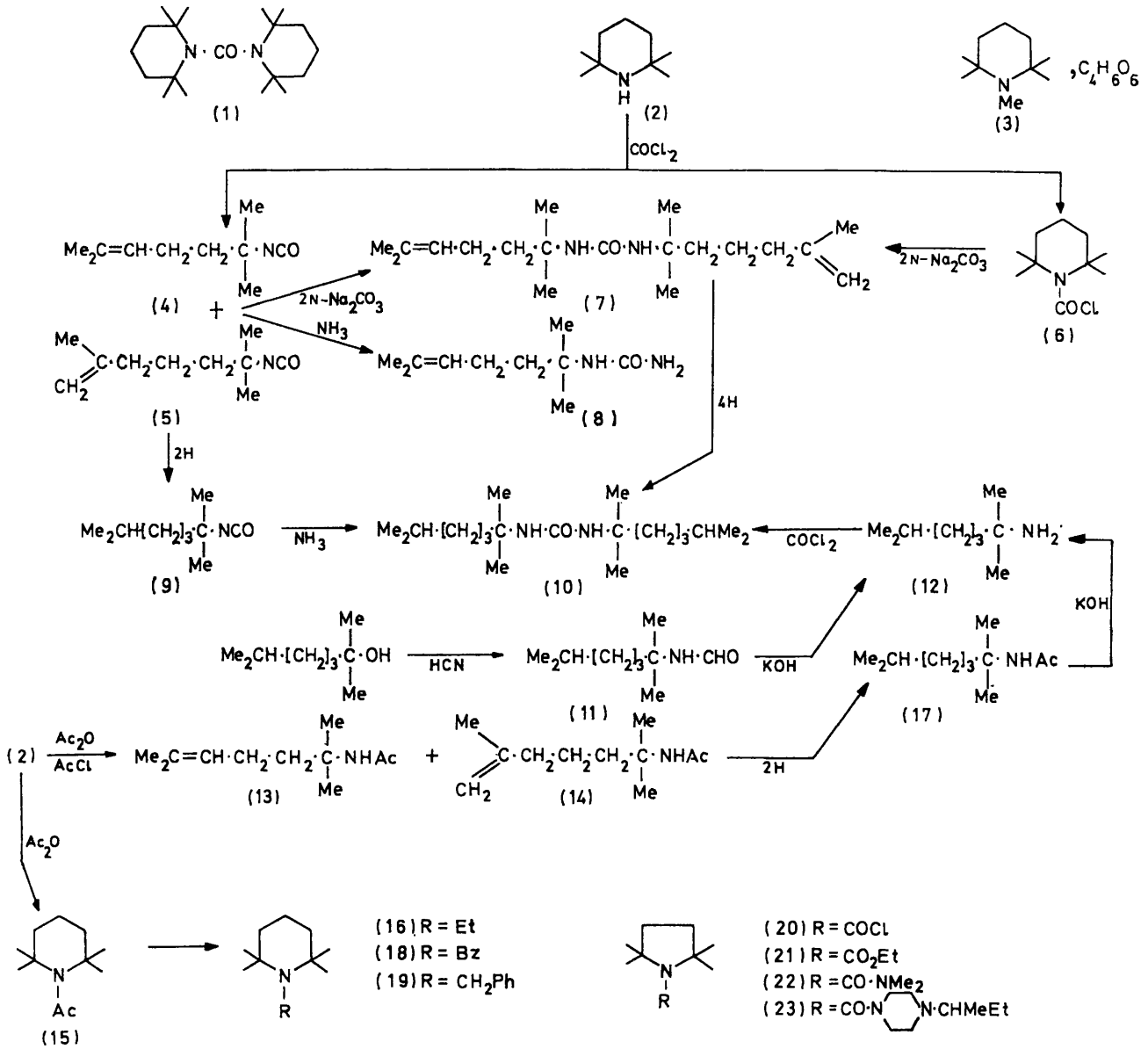
Catalytic reduction of the mixture of isocyanates (4) and (5) gave the single isocyanate (9), which with ammonia afforded the symmetrical urea (10), which was also obtained by catalytic reduction of the urea (7). The structure (10) was confirmed by comparison with an authentic sample synthesised from 2,6-dimethylheptan-2-ol [2] [the formamido-compound (11) was hydr-

[1] G. E. Lee, W. R. Wragg, S. J. Corne, N. D. Edge, and H. W. Reading, *Nature*, 1958, **181**, 1717.

[2] J. Pastureau and Mll. Zamenhof, *Bull. Soc. chim. France*, 1926, **39**, 1435.

olysed to the amine (12), which was treated with carbonyl dichloride].

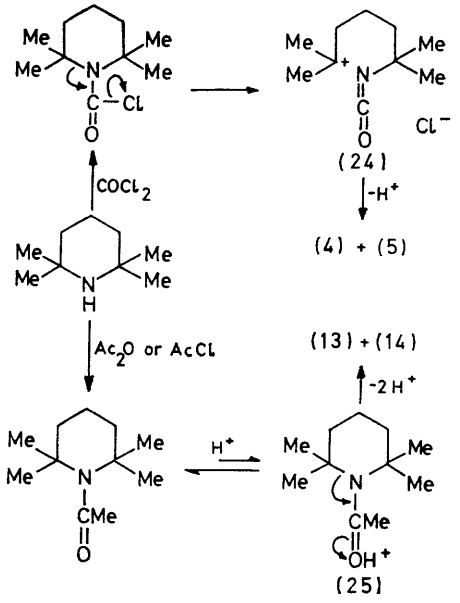
2,2,6,6-Tetramethylpiperidine (2) was boiled with excess of acetic anhydride under reflux, and the solution was then stirred with water. Extraction with ether gave an oil, which was separated into four fractions by distillation under reduced pressure. The lower-boiling fraction slowly solidified, and elemental analysis and n.m.r. and mass spectra showed it to be a 1 : 2 complex of 2,2,6,6-tetramethylpiperidine with acetic acid. It was readily decomposed with dilute alkali to give the parent amine (2). Examination of the middle fractions by g.l.c. showed that they were almost identical, containing two components in the ratio *ca.* 10 : 1. On the basis of elemental analysis and i.r., n.m.r., and mass spectra they were assigned structures (13) and (14), the former being the predominant isomer. If the original reaction mixture was not poured into water, but fractionated under reduced pressure, some 1-acetyl derivative (15) was also isolated. Its structure was confirmed by analysis, spectral determinations, and reduction with lithium aluminium hydride to the known 1-ethyl-2,2,6,6-tetramethylpiperidine (16).[3] Evidence to support the assigned structures of the mixed isomers (13) and (14) was obtained by catalytic reduction to the single compound (17), and hydrolysis of this to the amine (12). Treatment of 2,2,6,6-tetramethylpiperidine with acetyl chloride gave a mixture of the isomers (13) and (14) in the ratio *ca.* 10 : 1.



Scheme 1

[3] E. H. P. Young, B.P. 832,290.

Treatment of benzoyl chloride with 2,2,6,6-tetramethylpiperidine to give the 1-benzoyl derivative (18), previously reported by Leonard and Normensen,[4] was successfully repeated albeit in poor yield, but reactions with methanesulphonyl chloride, toluene-*p*-sulphonyl chloride, and benzyl chloride were unsuccessful, although Simon and Vvendenskii [5] have described the preparation of the 1-benzyl derivative (19) by this route. Unchanged amine (2) was recovered in all these experiments and no evidence was obtained for ring fission.



SCHEME 2

Acetylation of 2,2,5,5-tetramethylpyrrolidine with boiling acetic anhydride was reported by Lunt [6] to give an 80% yield of the 1-acetyl derivative. Under less stringent conditions, reaction with formic acetic anhydride gave a 40% yield of the 1-formyl derivative,[6] but no evidence of formylation was observed under similar conditions with 2,2,6,6-tetramethylpiperidine.[7] Treatment with carbonyl dichloride afforded the 1-chlorocarbonyl derivative (20) in good yield, and no evidence of ring fission was obtained. The chlorocarbonyl compound (20) was characterised by conversion into the urethane (21) and the ureas (22) and (23).

Molecular models of 2,2,6,6-tetramethylpiperidine and 2,2,5,5-tetramethylpyrrolidine show that the nitrogen atom in the six-membered ring is sterically hindered, whereas in the five-membered ring compound it is not. The observed fission of the six-membered ring can therefore be associated with the relief of steric strain.

The reaction pathways shown in Scheme 2 are proposed for the *N*-acylation reactions of 2,2,6,6-tetramethylpiperidine.

The yield of approximately equal amounts of isocyanates (4) and (5) in the carbonylation reaction suggests that the reaction proceeds *via* a carbonium ion (24). In the acetylation reaction, an equilibrium situation is proposed involving a protonated species (25), to account for the observed increase in the yield of the mixture of (13) and (14) when the reaction mixture was treated with acetic acid, or (better still) when the reaction was carried out in the presence of sulphuric acid. The preponderance of (13) over (14) in the mixture of isomers obtained in all the reactions so far carried out suggests a concerted mechanism for the reaction pathway from (25), rather than the involvement of a carbonium ion.

No evidence of the presence of the desired symmetrical urea (1) has been obtained in attempts to condense the 1-chlorocarbonyl compound (6) with its parent amine (2).

EXPERIMENTAL

Attempted Preparation of Bis-(2,2,6,6-tetramethylpiperidino)formaldehyde (1) (carried out by L. G. KING).—Carbonyl dichloride (3·8 g, 0·038 mol) in anhydrous benzene (30 ml) was added dropwise during 0·25 h to a stirred solution of 2,2,6,6-tetramethylpiperidine (21·2 g, 0·15 mol) in anhydrous benzene (100 ml). The reaction temperature was controlled at 15 ± 3°, and after the addition the mixture was stirred at room temperature for a further 1·5 h. 2,2,6,6-Tetramethylpiperidine hydrochloride (13·1 g, 98·5%; sublimes at 300°) was filtered off, and the filtrate was heated at 60° for 1 h. The solution was filtered and concentrated under reduced pressure to give an oil, which, after trituration with 2N-sodium hydroxide, solidified overnight. The solid was triturated with 2N-hydrochloric acid and dissolved in methanol (50 ml), and the filtered solution was diluted with water (100 ml). The waxy solid (3·25 g), which was filtered off and dried (silica gel) was crystallised from light petroleum (b.p. 40—60°) to give white crystals (1 g), m.p. 113—116° (shrinks at 106°) (Found: C, 73·7; H, 11·7; N, 9·1. Calc. for $C_{19}H_{36}N_2O$: C, 74·0; H, 11·7; N, 9·1%); the i.r. spectrum showed a strong NH band.

Reaction of Carbonyl Dichloride with 2,2,6,6-Tetramethylpiperidine (Molar Proportions 1 : 2).—A solution of carbonyl dichloride (4·2 ml) in anhydrous benzene (30 ml) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (34 g) in anhydrous benzene (160 ml) at 10°. The mixture was stirred for a further 1·5 h at ambient temperature, then heated at 60° for 1 h, and the precipitated 2,2,6,6-tetramethylpiperidine hydrochloride (21 g, 92%) was filtered off. The filtrate was concentrated under reduced pressure to remove the solvent and the residue was fractionated to give unchanged 2,2,6,6-tetramethylpiperidine (1·2 g), b.p. 40—42° at 10 mmHg., and a mixture of *1,1,5-trimethylhex-4-enyl isocyanate* (4) and *1,1,5-trimethylhex-5-enyl isocyanate* (5) (5·2 g, 38·5%), b.p. 75—80° at 10 mmHg (Found: C, 72·4; H, 10·3; N, 8·25. $C_{10}H_{17}NO$ requires C, 71·9; H, 10·2; N, 8·25%), τ 4·93 (t, CH_2–CH=C), 5·33 (CH_2=C), 8 (m, –CH_2–CH_2–C=), 8·35 (s, =CMe), and 8·66 (s, Me_2C), M^+ (mass spectrum) 167 (fragmentation pattern consistent with assignments of structure). The mixture of isomers [(4) and (5) in the ratio 4 : 5] could be separated by

[4] N. J. Leonard and E. W. Normensen, *J. Amer. Chem. Soc.*, 1949, **71**, 2808.
[5] I. B. Simon and V. P. Vvedenskii, *J. Gen. Chem.* (*U.S.S.R.*), 1964, **34**, 403.
[6] E. Lunt, Proceedings of the International Symposium, Polish Academy of Sciences, Warsaw, Sept., 1963 (Pergamon, Oxford).
[7] E. Lunt, personal communication.

preparative g.l.c. (5% Apiezon L on Chromolay G at 80° at 1 atmosphere pressure). The structure of each isomer was consistent with its n.m.r. spectrum.

The residue (6·3 g) from the distillation was dissolved in anhydrous light petroleum (b.p. 40—60°), and the filtered solution was concentrated to remove most of the solvent (to *ca.* 5 ml) and cooled to 0°. The white crystals were filtered off and washed with anhydrous light petroleum (b.p. 40—60°) which had been precooled in acetone–solid carbon dioxide. The i.r. spectrum of the product (3·8 g, 30%), m.p. 123—125° was identical with that obtained by King (above), and on the basis of its n.m.r. spectrum, it was assigned the structure N-(1,1,5-*trimethylhex*-4-*enyl*)-N′-(1,1,5-*trimethylhex*-5-*enyl*)*urea* (7) (Found: C, 73·4; H, 11·6; N, 9·1. $C_{19}H_{36}N_2O$ requires C, 74·0; H, 11·7; N, 9·1%), τ 4·89 (t, $^-CH{=}C$), 5·31 ($CH_2{=}C$), 5·7 (NH), 8·3 and 8·4 (each s, =CMe), and 8·71 (s, Me_2C), M^+ (mass spectrum) 308 (fragmentation consistent with the assignment of structure).

Reaction of Excess of Carbonyl Dichloride with 2,2,6,6-*Tetramethylpiperidine*.—2,2,6,6-Tetramethylpiperidine (21 g) in anhydrous benzene (60 ml) was added dropwise during 1·5 h to a stirred solution of carbonyl dichloride (60 ml) in anhydrous benzene (240 ml) at 0°. A solid carbon dioxide–acetone condenser was used to minimise loss of carbonyl dichloride. Afterwards the mixture was stirred for 1 h at 0°, and nitrogen was then bubbled through for 24 h to remove excess of carbonyl dichloride. 2,2,6,6-Tetramethylpiperidine (21 g) in anhydrous benzene (60 ml) was then added dropwise during 1 h at 0°, and the mixture was stirred overnight at ambient temperature. 2,2,6,6-Tetramethylpiperidine hydrochloride (31·5 g ≡ 25 g of amine) was filtered off, and after removal of benzene under reduced pressure, the residue was fractionated to give (*a*) a mixture of 1,1,5-trimethylhex-4-enyl isocyanate (4) and 1,1,5-trimethylhex-5-enyl isocyanate (5) (12·5 g, 63%), and (*b*) a viscous oil (1·2 g), b.p. 52—55° at 0·1 mmHg., probably 1-*chlorocarbonyl*-2,2,6,6-*tetramethylpiperidine* (6) (Found: C, 59·3; H, 8·7; Cl, 16·8; N, 7·1. $C_{10}H_{18}ClNO$ requires C, 58·95; H, 8·85; Cl, 17·45; N, 6·9%).

N-(1,1,5-*Trimethylhex*-4-*enyl*)-N′-(1,1,5-*trimethylhex*-5-*enyl*)*urea* (7).—(*a*) The mixture of isocyanates (4) and (5) (10 g) and 2N-sodium carbonate (100 ml) were stirred and heated on a steam-bath for 7 h, then cooled. The solid was filtered off, washed with water, dried (H_2SO_4), and crystallised from light petroleum (b.p. 40—60°) to give white crystals (7·65 g, 82%), m.p. 123—125°.

(*b*) 1-Chlorocarbonyl-2,2,6,6-tetramethylpiperidine (1 g) and 2N-sodium carbonate (20 ml) were treated similarly to give white crystals (0·6 g, 79%), m.p. 123—125°.

N-(1,1,5-*Trimethylhex*-4-*enyl*)*urea* (8).—The mixture of (4) and (5) (10 g) and conc. aqueous ammonia (50 ml) were stirred overnight at ambient temperature. The solid was filtered off, washed with water, and crystallised from ethanol to give white *crystals* (7 g, 63%), m.p. 119—120° (Found: C, 64·9; H, 10·8; N, 15·0. $C_{10}H_{20}N_2O$ requires C, 65·2; H, 10·85; N, 15·2%). The structure was consistent with the n.m.r. and mass spectra.

1,1,5-*Trimethylhexyl Isocyanate* (9).—The mixture of isocyanates (4) and (5) (1 g) in ethyl acetate (10 ml) was hydrogenated at atmospheric pressure over Adams catalyst (0·1 g). Uptake of hydrogen (150 ml, 98%) was complete in 0·75 h, and after removal of the catalyst and solvent the residue was fractionated under reduced pressure to give a yellow *oil* (0·6 g, 60%), b.p. 83—85° at 16 mmHg (Found: C, 70·8; H, 11·1; N, 8·2. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·25; N, 8·3%).

NN′-*Bis*-(1,1,5-*trimethylhexyl*)*urea* (10).—(*a*) The disubstituted urea (7) (4·5 g) in ethanol (80 ml) was hydrogenated at atmospheric pressure over Adams catalyst (0·4 g). Uptake of hydrogen (810 ml, 99%) was complete in 1 h, and after removal of the catalyst and solvent the residue (4·5 g) was crystallised from aqueous ethanol to give white crystals (4·2 g, 93%), m.p. 131—132°, identical with an authentic sample (Found: C, 73·2; H, 12·8; N, 8·9. Calc. for $C_{19}H_{40}N_2O$: C, 73·1; H, 12·8; N, 9·0%).

(*b*) 1,1,5-Trimethylhex-4-enyl isocyanate (0·6 g) was dissolved in conc. aqueous ammonia (6 ml). After a few minutes an oil separated which slowly solidified, and next day the solid (0·5 g) crystallised from aqueous ethanol as white crystals (0·25 g, 45%), m.p. 133—134°, identical with an authentic sample.

(c) *Unambiguous synthesis*. N-(1,1,5-*Trimethylhexyl*)-*formamide* (11). A stirred mixture of 2,6-dimethylheptan-2-ol (73·1 g), acetic acid (63·5 ml), and sodium cyanide (27·5 g) was warmed to 60°, and a mixture of conc. sulphuric acid (68 ml) and acetic acid (63·5 ml) was added at such a rate as to maintain the reaction temperature at 55—65° (0·75 h). The mixture was then stirred at 55—60° for 2·5 h, kept at ambient temperature for 24 h, poured into water (1·2 l), and neutralised at $<5°$ with 15% w/v sodium hydroxide. Extraction with ether (4 × 500 ml), afforded the *amide*, an almost colourless oil (73·9 g, 85%), b.p. 99—100° at 0·1 mmHg (Found: C, 70·2; H, 12·7; N, 8·25. $C_{10}H_{21}NO$ requires C, 70·2; H, 12·3; N, 8·2%).

1,1,5-*Trimethylhexylamine* (12). The amide (11) (20 g), potassium hydroxide (67 g), and diethylene glycol (200 ml) were refluxed for 0·25 h. The mixture was then distilled; an azeotrope of the product and water was obtained, b.p. 114—120°, which was dissolved in ether. The solution was dried ($MgSO_4$), the solvent was removed, and the residue was distilled to give the *amine*, a colourless oil (14·9 g, 89%), b.p. 60° at 10 mmHg (Found: C, 75·8; H, 15·1; N, 10·0. $C_9H_{21}N$ requires C, 75·5; H, 14·7; N, 9·8%).

The urea (10). Carbonyl dichloride (0·15 ml) in anhydrous benzene (5 ml) was added dropwise to a stirred solution of the amine (12) (1 g) in anhydrous benzene. Stirring was continued overnight, the solvent was removed under reduced pressure, and the semi-solid residue was then refluxed with N-sodium carbonate (10 ml) for 4 h. The solid which separated was filtered off, dried (H_2SO_4), and crystallised from light petroleum (b.p. 40—60°) to give white *crystals* (0·35 g, 64%), m.p. 130—131° (Found: C, 73·3; H, 12·9; N, 9·0. $C_{19}H_{40}N_2O$ requires C, 73·1; H, 12·8; N, 9·0%).

Reaction of 2,2,6,6-*Tetramethylpiperidine with Acetic Anhydride*.—(*a*) 2,2,6,6-Tetramethylpiperidine (31 g) and acetic anhydride (310 ml) were refluxed for 1 h. The solution was cooled and poured on ice (750 g). The mixture was stirred for 1 h, saturated with sodium chloride, and extracted with ether. The extract was washed with 2N-sodium carbonate, dried (Na_2SO_4), and evaporated. After the residue was fractionated at 0·1 mmHg to give fractions (i), b.p. 78—92°, (ii) 94—96°, (iii) 96—98°, and (iv) 120—150°. Fraction (i) solidified and crystallised from light petroleum (b.p. 60—80°) as white *crystals* (2·65 g), m.p. 106—109°, smelling strongly of acetic acid (Found: C, 59·8; H, 10·4; N, 5·75. $C_9H_{19}N,2C_2H_4O_2$ requires C, 59·9; H, 10·4; N, 5·4%). Eight weeks after its preparation, n.m.r. and mass spectra showed the product to be a protonated cyclised species

which lost $MeCO^+$ in the mass spectrum. The compound appeared to change on storage. Fractions (ii) and (iii) were combined and redistilled to give a colourless oil (11·8 g, 29·5%), b.p. 76—82° at 0·04 mmHg (Found: C, 71·4; H, 11·5; N, 7·6. Calc. for $C_{11}H_{21}NO$: C, 72·1; H, 11·5; N, 7·65%). The product showed one major and one minor peak (*ca.* 9 : 1) by g.l.c., and n.m.r. determinations showed it to be a mixture of *N*-(1,1,5-*trimethylhex*-4-*enyl*)-*acetamide* (13) and *N*-(1,1,5-*trimethylhex*-5-*enyl*)*acetamide* (14), in the ratio 10 : 1, τ 2·85 (–NH–CO–), 4·89 (t, C=CH–), 5·4 (CH_2=C), 8·15 (s, OAc), 8·35 and 8·41 (MeC=), and 8·73 (s, Me_2C), M^+ (mass spectrum) 183 (fragmentation pattern consistent with assignments of structure). Fraction (iv) was not investigated further.

(*b*) 2,2,6,6-Tetramethylpiperidine (13·4 g) and acetic anhydride (134 ml) were refluxed for 1 h. Excess of acetic anhydride was removed under reduced pressure, and the waxy residue was refluxed for 3 h with acetic acid (134 ml). Excess of acetic acid was removed under reduced pressure, and the residual oil was dissolved in ether. The solution was washed with water, dried ($MgSO_4$), and evaporated. Fractionation of the residue gave an oil (11·5 g, 66%), b.p. 90—91° at 0·07 mmHg. The i.r. spectrum was identical with that of the mixture of *N*-acetyl compounds (13) and (14) obtained from (*a*).

(*c*) 2,2,6,6-Tetramethylpiperidine (31 g), acetic anhydride (310 ml), and conc. sulphuric acid (5 ml) were refluxed for 1 h. The solution was cooled and poured on ice (750 g). The mixture was stirred for 1 h, saturated with sodium chloride, and extracted with ether. The extract was washed with 2N-sodium carbonate, dried (Na_2CO_3), and evaporated. Fractionation of the residue gave a colourless oil (12·9 g, 74%), b.p. 92—94° at 0·1 mmHg. The i.r. spectrum was identical with that of the mixture of *N*-acetyl compounds (13) and (14) obtained from (*a*).

(*d*) 2,2,6,6-Tetramethylpiperidine (8 g) and acetic anhydride (80 ml) were refluxed for 1 h, and excess of acetic anhydride was removed under reduced pressure. The residual waxy solid was dissolved in ether, and the solution was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Distillation of the residue gave a fraction, b.p. 95—100° at 0·05 mmHg, which solidified. Crystallisation from light petroleum (b.p. 40—60°) with cooling to <60° gave white prisms (3·5 g, 34%), m.p. 68—70° (Found: C, 72·5; H, 11·3; N, 7·6. $C_{11}H_{21}NO$ requires C, 72·1; H, 11·5; N, 7·65%). The n.m.r. {τ 7·97 (s, Ac), 8·28 (s, $[CH_2]_3$), and 8·58 (s, Me_2C)}, mass (M^+ 183), and i.r. spectra showed the product to be 1-*acetyl*-2,2,6,6-*tetramethylpiperidine* (15).

1-*Ethyl*-2,2,6,6-*tetramethylpiperidine* (16).— 1-Acetyl-2,2,6,6-tetramethylpiperidine (1·83 g) in anhydrous ether (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0·35 g) in anhydrous ether (10 ml). The reaction was slightly exothermic and after being refluxed for 7 h the mixture was kept at ambient temperature overnight. Excess of lithium aluminium hydride was decomposed with water (ice cooling), and the mixture was extracted with ether. The extract was washed with a little water and dried ($MgSO_4$). It afforded a colourless oil (0·65 g, 38·5%), b.p. 82—83° at 10 mmHg (Found: C, 77·4; H, 13·6; N, 8·4. Calc. for $C_{11}H_{23}N$: C, 78·0; H, 13·6; N, 8·3%), i.r. spectrum identical with that of an authentic specimen.

Reaction of 2,2,6,6-*Tetramethylpiperidine with Acetyl Chloride*.—Acetyl chloride (3·85 ml) was added dropwise to the stirred 2,2,6,6-tetramethylpiperidine (7·6 g) in anhydrous benzene (15 ml). A highly exothermic reaction ensued, and some solid separated. The mixture was refluxed for 48 h, 2,2,6,6-tetramethylpiperidine hydrochloride (4·7 g, 98%) was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in ether; the solution was washed with 2N-hydrochloric acid and water, and dried ($MgSO_4$). Removal of the solvent followed by distillation gave an oil (0·8 g, 15·8%), b.p. 88—92° at 0·08 mmHg, i.r. spectrum identical with that of the ring-opened products obtained by use of acetic anhydride–acetic acid.

N-(1,1,5-*Trimethylhexyl*)*acetamide* (17).—The mixture of acetyl derivatives of 2,2,6,6-tetramethylpiperidine (11 g) in ethyl acetate (33 ml) was hydrogenated at atmospheric pressure over Adams catalyst (1·1 g). Uptake of hydrogen (1560 ml, 100%) was complete in 2 h, and after removal of the catalyst and the solvent the residue was distilled to give the *amide*, an almost colourless oil (7·6 g, 69%), b.p. 90° at 0·05 mmHg (Found: C, 71·0; H, 12·3; N, 7·4. $C_{11}H_{23}NO$ requires C, 71·4; H, 12·4; N, 7·55%). Hydrolysis with potassium hydroxide in diethylene glycol by a similar procedure to that previously described for the corresponding formamide derivative gave the amine (12), identical with an authentic sample.

1-Benzoyl-2,2,6,6-tetramethylpiperidine (18) was prepared in 13% yield by the method of Leonard and Normensen;[4] m.p. 90—91°. The structure was consistent with the i.r. spectrum.

2,2,5,5-*Tetramethylpyrrolidine*-1-*carbonyl Chloride* (20).—Carbonyl dichloride (8 ml) was added dropwise to a stirred solution of 2,2,5,5-tetramethylpyrrolidine (20 g) in anhydrous benzene (70 ml) precooled to 5°. The reaction was exothermic and was controlled at 20°, an acetone–solid carbon dioxide condenser being attached to the flask to minimise loss of carbonyl dichloride. The mixture was stirred overnight at ambient temperature, 2,2,5,5-tetramethylpyrrolidine hydrochloride (11 g, 86%) was filtered off, and the solvent was removed under reduced pressure. The residue of the *carbonyl chloride* solidified and was crystallised from light petroleum (b.p. 40—60°) to give white crystals (11·65 g, 78%), m.p. 69—70° (Found: C, 57·3; H, 8·9; N, 7·2. $C_9H_{16}ClNO$ requires C, 57·1; H, 8·5; N, 7·4%).

1-(NN-*Dimethylcarbamoyl*)-2,2,5,5-*tetramethylpyrrolidine* (22).—Dimethylamine (1·05 g ≡ 1·48 ml) in anhydrous benzene (20 ml) was added dropwise to a stirred ice-cooled solution of 2,2,5,5-tetramethylpyrrolidine-1-carbonyl chloride (2·1 g) in anhydrous benzene (20 ml). The mixture was stirred overnight at ambient temperature, dimethylamine hydrochloride (0·8 g, 90%) was filtered off, and the solvent was removed under reduced pressure. The residual *amide* crystallised as white prisms (1·5 g, 65%), m.p. 31—33° [from light petroleum (b.p. 40—60°)] (Found: C, 67·4; H, 11·3; N, 13·9. $C_{11}H_{22}N_2O$ requires C, 67·1; H, 11·1; N, 14·1%).

1-(4-*s*-*Butylpiperazin*-1-*ylcarbonyl*)-2,2,5,5-*tetramethylpyrrolidine* (23).—2,2,5,5-Tetramethylpyrrolidine-1-carbonyl chloride (5·65 g), *N*-s-butylpiperazine (8·5 g), and anhydrous benzene (60 ml) were refluxed overnight. The mixture was cooled, *N*-s-butylpiperazine hydrochloride (4·6 g, 87%) was filtered off, and the solvent was removed under reduced pressure. The residue was extracted with light petroleum (b.p. 60—80°), and the combined extracts were evaporated. The solid crystallised from light petroleum (b.p. 40—60°)

with cooling to $<60°$ to give white crystals of the *amide* (4·7 g, 54%), m.p. 52° (Found: C, 68·9; H, 11·3; N, 14·2. $C_{17}H_{33}N_3O$ requires C, 69·0; H, 11·2; N, 14·2%). The structure was consistent with its i.r. spectrum.

Ethyl-2,2,5,5-tetramethylpyrrolidine-1-carboxylate (21).—1-Chlorocarbonyl-2,2,5,5-tetramethylpyrrolidine (4·65 g) was added in one portion to anhydrous ethanol (46·5 ml). The reaction was mildly exothermic, the temperature rising to 35°. After 24 h at ambient temperature, the solvent was removed under reduced pressure, and the residue was dissolved in anhydrous ether (20 ml) and filtered from a little insoluble material; the solvent was removed, and the residue was distilled to give the *ethoxycarbonyl* compound as a colourless oil (3·8 g, 78%), b.p. 95° at 14 mmHg (Found: C, 66·3; H, 10·7; N, 7·5. $C_{11}H_{21}NO_2$ requires C, 66·2; H, 10·6; N, 7·1%). The i.r. spectrum was in accord with the assignment of structure.

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