The Conformational Analysis of Saturated Heterocycles. Part XLII.[1] 1,2-Dimethylhexahydropyridazine †

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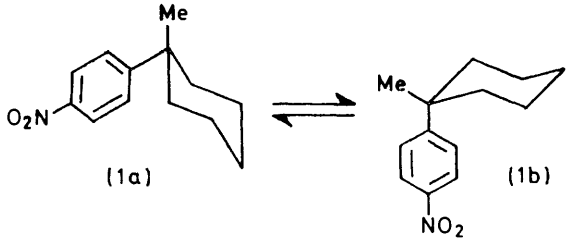
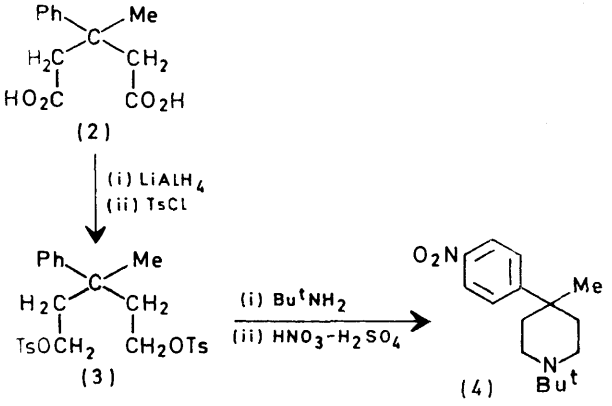
Variable-temperature n.m.r. spectra and electric dipole moments are used to study the conformations of 1,2-dimethylhexahydropyridazine and some of its derivatives. All three conformations of the parent compound (*N*-methyl groups both equatorial, both axial, and one axial/one equatorial) are approximately equally populated.

RECENTLY, much interest has been shown in the conformations of tetrasubstituted hydrazine derivatives. In addition to acyclic tetra-alkyl derivatives of hydrazine [2] and 1,2-diacyl cyclic hydrazines,[3,4] *NN'*-dialkyl derivatives of cyclic hydrazines with three-,[5] five-,[6] simple six-[4,6] and bridged six-[7] membered rings have all been studied. However, with few exceptions,[8] this work has all been concerned with the determination of activation energies for inversion and other kinetic processes, and little data is available on the equilibrium behaviour of alkyl derivatives in unstrained six-membered rings.



We have now studied the conformational equilibria of 1,2-dimethylhexahydropyridazine using electric dipole moment measurements in conjunction with low-temperature n.m.r. spectroscopy for comparison with related work on hexahydropyrimidines [9] and hexahydrotetrazines.[10]

Preparation of Compounds.—1-Methyl-1-*p*-nitrophenylcyclohexane [(1a) ⇌ (1b)] was prepared by nitration of 1-methyl-1-phenylcyclohexane.[11] 1-t-Butyl-4-methyl-4-*p*-nitrophenylpiperidine (4) ‡ was prepared from 3-methyl-3-phenylglutaric acid (2) [12] by the method of Scheme 1. 1,3-Dimethyl-3-phenylpiperidine (7) was



SCHEME 1

† Preliminary communication, R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *Chem. Comm.*, 1971, 644.

‡ This was originally prepared as a model compound; it was subsequently found not to be necessary for this purpose, but the report of its preparation is retained.

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[7] J. E. Anderson and J. M. Lehn, *J. Amer. Chem. Soc.*, 1967, **89**, 81; E. L. Allred, C. L. Anderson, R. L. Miller, and A. L. Johnson, *Tetrahedron Letters*, 1967, 525.

[8] J. Wagner, W. Wojnarowski, J. E. Anderson, and J. M. Lehn, *Tetrahedron*, 1969, **25**, 657.

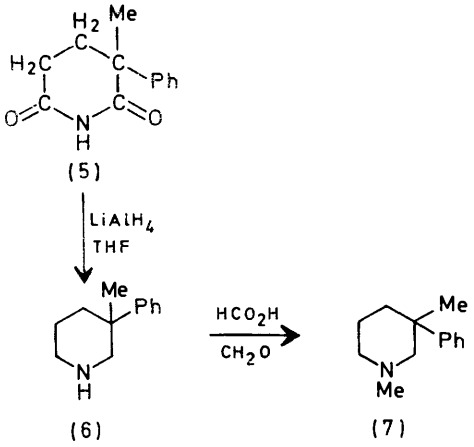
[9] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131.

[10] R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, and A. C. Richards, unpublished results.

[11] J. Linsk, *J. Amer. Chem. Soc.*, 1950, **72**, 4257.

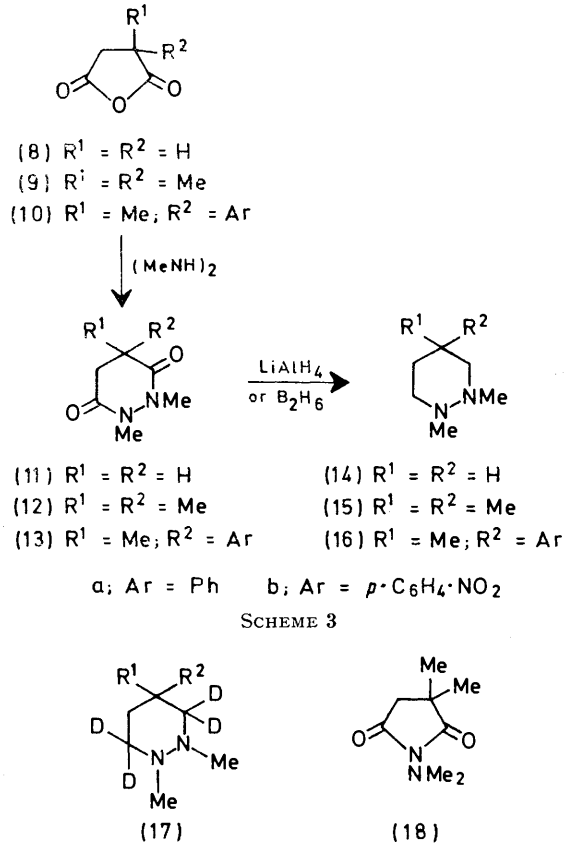
[12] S. M. McElvain and D. H. Clemens, *J. Amer. Chem. Soc.*, 1958, **80**, 3915.

prepared from 2-methyl-2-phenylglutarimide (5) * by the method of Scheme 2.



SCHEME 2

The 1,2-dimethylhexahydropyridazines [(14), (15), and (16)] were prepared (Scheme 3) by reduction of the diones [(11), (12), and (13)] which themselves came from



SCHEME 3

the corresponding substituted succinic anhydrides [(8), (9), and (10)]. The method of Rosen and Popp [13] was used for the anhydride to dione stage, but for (15) a modification of the method of Feuer *et al.*[14] gave superior results. The preparation of (12) gave some of the amine succinimide (18), presumably from 1,1-dimethylhydrazine present in the 1,2-isomer as an impurity. The 3,3,6,6-tetradeuterio-analogues (17) of the hexahydropyridazines [(15) and (16)] were obtained by reduction of the precursor diones with hexadeuteriodiborane.

* Gift from CIBA.

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EXPERIMENTAL

1-Methyl-1-p-nitrophenylcyclohexane (1).— 1-Methyl-1-phenylcyclohexane [11] (6·9 g) in glacial acetic acid (19 ml) was slowly added to premixed nitric acid (*d* 1·5; 37·5 ml) and glacial acetic acid (16 ml), at 0°. The whole was stirred for 1 h, poured onto ice, and extracted with benzene. The extracts were washed with water, aqueous sodium hydroxide, again with water, and were then dried ($MgSO_4$). Benzene was removed *in vacuo*, and the product was fractionated. The middle fraction was chromatographed in benzene on silica gel, to give 1-methyl-1-*p*-nitrophenylcyclohexane (4 g, 46%), b.p. 130°/0·1 mm (lit.,[15] 145—150°/3 mm), homogeneous by g.l.c. (2 m, ¼ in. O.D. stainless-steel column, 15% PPG on Chromosorb W, column temperature 100°, nitrogen flow rate 15 lb f in^{-2}; τ ($CDCl_3$) 1·76, 2·37 (A_2B_2, 4H), 7·8—8·6 (m, 10H), and 8·75 (s, 3H).

3-Methyl-3-phenylpentane-1,5-diol.— 2-Methyl-2-phenylglutaric acid [14] (14·8 g) in dry ether (100 ml) was slowly added to lithium aluminium hydride (10 g) under dry diethyl ether (100 ml). The mixture was heated under reflux for 1 h and then cooled; water was added cautiously followed by 2N-sulphuric acid (100 ml). The ethereal layer was separated and the aqueous layer was extracted with ether (5 × 50 ml). The combined extracts were dried ($MgSO_4$), the ether removed, and the residue was recrystallised from benzene to give the diol (11·2 g, 87%), m.p. 72° (lit.,[12] 68—73°). The diol (26·8 g) was treated [16] at 0° in pyridine with toluene-*p*-sulphonyl chloride (58 g), to give the *ditosylate* (3) (46 g, 48%), m.p. 63·5° (Found: C, 62·2; H, 6·1. $C_{26}H_{30}S_2O_6$ requires C, 62·1; H, 6·0%); τ ($CDCl_3$) 2·1—2·8 (m, 13H), 6·12 (t, 4H, *J* 7 Hz), 7·6 (s, 6H), 7·98 (t, 4H, *J* 7 Hz), and 8·7 (s, 3H).

1-t-Butyl-4-methyl-4-phenylpiperidine.— 3-Methyl-3-phenylpentane-1,5-diol ditoluene-*p*-sulphonate (8·3 g) and tertiary butylamine (200 ml, b.p. 43—46°, refractionated) were kept sealed for four days. Colourless needles were filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in ether, and the solution was washed with aqueous potassium hydroxide followed by water, and dried (Na_2SO_4), and distilled to give the *piperidine* (2·0 g, 51%), as an oil, b.p. 95—100°/0·2 mm, which was homogeneous by g.l.c. (2 m, ¼ in O.D. stainless-steel column, 15% PPG on Chromosorb W, column temperature 110°, nitrogen flow rate 15 lb f in^{-2}); τ ($CDCl_3$) 2·65 (s, 5H), 7·43 (t, 4H, *J* 5·4 Hz), 8·0 (t, 2H, *J* 5·4 Hz), 8·8 (s, 3H), 9·0 (s, 9H); *m/e* 231 (molecular ion), 174 (loss of butyl group), 77 (formation of a phenyl cation).

1-t-Butyl-4-methyl-4-p-nitrophenylpiperidine (4).—Nitric acid (*d* 1·49; 1 ml) was added dropwise during 1 h to 1-t-butyl-4-methyl-4-phenylpiperidine (2·0 g) in sulphuric acid (*d* 1·84; 2·9 g) at 0°. After being stirred for a further hour, the mixture was poured onto ice, neutralised with aqueous potassium hydroxide, and extracted with ether. The dried

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(Na_2SO_4) extracts were evaporated *in vacuo*, and the yellow residue was recrystallised from light petroleum. The product was purified by column chromatography on alumina (Woelm/neutral) with ethyl acetate as eluant, to give the *piperidine* (1·8 g, 75%), m.p. 95°; τ ($CDCl_3$) 1·76, 1·90, 2·41, 2·55 (A_2B_2, 4H), 7·43 (t, 4H, *J* 5·4 Hz), 8·0 (t, 2H, *J* 5·4 Hz), 8·23 (t, 2H, *J* 5·4 Hz), 8·8 (s, 3H), and 9·0 (s, 9H).

3-*Methyl*-3-*phenylpiperidine* (6).— 2-Methyl-2-phenylglutarimide (5) (Ciba), m.p. 103—104° (lit.,[17] 104—105°) (3·50 g) in tetrahydrofuran (50 ml) was added dropwise to lithium aluminium hydride (1·55 g) stirred under tetrahydrofuran under nitrogen. After three days at reflux, the mixture was worked up according to Mićović and Michailović.[18] Fractional distillation of the dried (Na_2SO_4) solution afforded the substituted *piperidine* (2·57 g, 85·5%), as an oil, b.p. 85—86°/0·35 mm; $\nu_{max.}$ (liquid film) 3290, 3090, 3060, 3030, 1600, 1580, 1500, 760, and 700 cm^{-1}, which was characterised as the *picrate* (95% ethanol), m.p. 178—179° (Found: C, 53·6; H, 5·2; N, 13·7. $C_{18}H_{20}N_4O_7$ requires C, 53·5; H, 5·0; N, 13·9%).

1,3-*Dimethyl*-3-*phenylpiperidine* (7).—3-Methyl-3-phenylpiperidine (2·06 g), formaldehyde, and formic acid were allowed to react under standard conditions [19] to give the desired *piperidine* (1·86 g, 83·4%) as an oil, b.p. 98—99°/0·45 mm; $\nu_{max.}$ (liquid film), 3090, 3060, 3030, 2780, 1600, 1570, 1500, 765, and 700 cm^{-1}; τ (CCl_4, 60 MHz) 2·74 (m, 5H), 7·6 (m, 4H, CH_2N), 7·84 (s, 3H, CH_3N), 8·44 (m, 4H, C–CH_2CH_2–C), and 8·77 (s, 3H). The *picrate* (95% ethanol) had m.p. 127—128° (Found: C, 54·8; H, 5·4; N, 13·1. $C_{19}H_{22}N_4O_7$ requires C, 54·5; H, 5·3; N, 13·4%).

1,2-*Dimethylhexahydropyridazine* (14).—The pyridazine (4·5 g, 79%) had b.p. 139—140°/760 mm (lit.,[20] 140—141°/760 mm) and was homogeneous by g.l.c.

1,2,4,4-*Tetramethylhexahydropyridazine*-3,6-*dione* (12).—2,2-Dimethylsuccinic anhydride [21] (4·82 g) and commercial *NN'*-dimethylhydrazine dihydrochloride (5·00 g) according to the procedure of ref. 13 gave a viscous yellow oil, crystallisation of which from ether gave the *pyridazinedione* (1·09 g, 17%), as needles m.p. 93—96°, raised by sublimation to 95—96° (Found: C, 56·7; H, 8·1; N, 16·1. $C_8H_{14}N_2O_2$ requires C, 56·45; H, 8·3; N, 16·5%); $\nu_{max.}$ (Nujol) 1670 and 1650 cm^{-1} (C=O); τ ($CDCl_3$) 6·67 (s, 6H, CH_3N), 7·55 (s, 2H), and 8·84 (s, 6H).

Column chromatography (ether) on silica gel of the oily residue from the initial crystallisation gave 2,2-*dimethyl*-N-*dimethylaminosuccinimide* (18) (0·80 g, 13%) as prisms, m.p. 70—72° (from cyclohexane), followed by additional pyridazinedione (0·34 g, 5%), m.p. 93—96° (from ether). The m.p. of the succinimide was raised to 71—72·5° by sublimation (Found: C, 56·3; H, 8·6; N, 16·6. $C_8H_{14}N_2O_2$ requires C, 56·45; H, 8·3; N, 16·5%); $\nu_{max.}$ (Nujol) 1770 m and 1720 s cm^{-1} (C=O); τ ($CDCl_3$) 7·08 (s, 6H, CH_3–N), 7·7 (s, 2H), and 8·70 (s, 6H).

The pyridazinedione was preferably synthesised by adaptation of the general method of ref. 14, to include removal of water in the cyclisation step. The semicrystalline crude product from 2,2-dimethylsuccinic anhydride (11·90 g) and *NN'*-dimethylhydrazine [22] (5·75 g) was recrystallised from ether to give 1,2,4,4-tetramethylhexahydropyridazine-3,6-dione (10·18 g, 64·3%), m.p. 95—96°; the last two crops (0·78 g, 4·9%) were a mixture (t.l.c.) of the dione and 2,2-dimethyl-*N*-dimethylaminosuccinimide.

1,2,4,4-*Tetramethylhexahydropyridazine* (15).—Powdered 1,2,4,4-tetramethylhexahydropyridazine-3,6-dione (8·00 g) was added slowly to a stirred suspension of lithium aluminium hydride (3·57 g) in tetrahydrofuran (250 ml) under nitrogen. The mixture was stirred under reflux for three days, cooled to 0°, and worked up by the method of Mićović and Michailović.[18] Evaporation of the dried solution left a yellow oil which was dried overnight over sodium wire. Fractionation gave the pyridazine (3·45 g, 52%), b.p. 62—68°/23 mm, 99% by g.l.c.; $\nu_{max.}$ (liquid film) 2920, 2810, 1460, 1450, and 1080 cm^{-1}. Using borane as the reducing agent gave an increased yield. The solution containing diborane and 1,2,4,4-tetramethylhexahydropyridazine-3,6-dione (5·10 g) was refluxed for 7 h. Normal work-up gave the reduced *pyridazine* (3·54 g, 83·0%) as an oil, b.p. 59—60°/20 mm (Found: C, 67·9; H, 12·3. $C_8H_{18}N_2$ requires C, 67·55; H, 12·8%); τ (neat, 60 MHz) 7·38 (t, 2H, 6-CH_2), 7·71 (s, 6H, CH_3–N), 7·84 (s, 2H, 3-CH_2), 8·72 (t, 2H, C–CH_2–C), and 9·07 (s, 6H). The *monopicrate* had m.p. 199—200° (decomp.) (Found: C, 45·6; H, 6·0; N, 18·6. $C_{14}H_{21}N_5O_7$ requires C, 45·3; H, 5·7; N, 18·9%). The *monomethiodide* had m.p. 220—221° (decomp.) (Found: C, 38·1; H, 8·2; N, 9·5. $C_9H_{21}IN_2$ requires C, 38·0; H, 7·5; N, 9·9%).

Ethyl 1-*Phenylethylidenecyanoacetate*.— Acetophenone (60·0 g), ethyl cyanoacetate (57·0 g), acetic acid (24·0 g), and ammonium acetate (7·7 g) in benzene (120 ml) were refluxed for 30 h with water removal (Dean–Stark). Normal work-up and subsequent fractional distillation gave the unsaturated cyano-ester (61·7 g, 57·4%), b.p. 123—131°/0·25 mm.

Ethyl 1-p-*Nitrophenylethylidenecyanoacetate*.—This compound was prepared by the method of Le Moal *et al.*[23] The product was crystallised from 95% ethanol as a mixture of the two geometrical isomers (15·1 g, 58·1%), m.p. 80—130° (lit.,[23] 93—94 and 144°); $\nu_{max.}$ (Nujol) 3080, 2210 (C≡N), 1730 (C=O), 1600, 1520 (NO_2), 1500, 1380, and 1340 (NO_2) cm^{-1}; τ ($CDCl_3$, 60 MHz): *p*-nitrophenyl and ethoxycarbonyl *trans* (m.p. 93—94°) 1·60, 1·75, 2·31, 2·46 (A_2B_2, 4H, *J* 9 Hz), 5·66 (q, 2H, *J* 7 Hz), 7·30 (s, 3H), 8·62 (t, 3H, *J* 7 Hz); *p*-nitrophenyl and ethoxycarbonyl *cis* (m.p. 144°) 1·66, 1·81, 2·57, 2·72 (A_2B_2, 4H, *J* 9 Hz), 5·90 (q, 2H, *J* 7 Hz), 7·45 (s, 3H), and 8·85 (t, 3H, *J* 7 Hz). According to n.m.r. the crude product contained *ca.* 53% of the *cis*-isomer.

2-*Methyl*-2-p-*nitrophenylsuccinic Acid*.—Ethyl 1-*p*-nitrophenylethylidenecyanoacetate (30·4 g) was converted [24] into the substituted succinic acid (26·2 g, 88·9%), m.p. 163—164° (lit.,[25] m.p. 168°).

2-*Methyl*-2-p-*nitrophenylsuccinic Anhydride* (10b).—Acetic anhydride (34·6 g, redistilled) and 2-methyl-2-*p*-nitrophenylsuccinic acid (25·0 g) [24] were refluxed for 24 h. Solvent was then distilled off at 75° under reduced pressure

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[25] H. Le Moal, A. Foucaud, R. Carrié, J. Hamelin, and C. Sévellec, *Bull. Soc. chim. France*, 1964, 579.

(to 10 mm). The residue crystallised from benzene yielding the anhydride (22·7 g, 97·7%), m.p. 120—121° (lit.,[26] m.p. 123—124°).

1,2,4-*Trimethyl*-4-p-*nitrophenylhexahydropyridazine*-3,6-*dione* (13b).—The method of Feuer, Rosenquist, and Brown,[14] adapted to include removal of water in the cyclisation step, gave a viscous red-brown oil from 2-methyl-2-*p*-nitrophenylsuccinic anhydride (18·76 g) and *NN'*-dimethylhydrazine (4·85 g). Fractional crystallisation from benzene–ether gave the *pyridazinedione* (8·30 g, 37·6%) as pale yellow prisms, m.p. 140—141·5° after sublimation and recrystallisation from 95% ethanol (Found: C, 55·9; H, 5·7; N, 15·1. $C_{13}H_{15}N_3O_4$ requires C, 56·3; H, 5·5; N, 15·1%) together with 2-*methyl*-2-p-*nitrophenyl*-N-*dimethylaminosuccinimide* (4·60 g, 20·9%), which crystallised from methanol as faintly yellow needles, m.p. 148—149° (Found: C, 56·3; H, 5·6; N, 15·0. $C_{13}H_{15}N_3O_4$ requires C, 56·3; H, 5·5; N, 15·1%). In general the two products were obtained as alternate crops, although in two instances, crystals were separated mechanically. The pyridazinedione had $\nu_{max.}$ (Nujol) 3060, 3040, 1685, and 1660 (C=O), 1600, 1530, and 1350 (NO_2), and 855 cm^{-1}; τ ($CDCl_3$, 60 MHz) 1·65, 1·80, 2·35, 2·50 (A_2B_2, 4H, *J*, 9 Hz), 6·65 (s, 3H, CH_3–N), 6·80 (d, 1H, *J* 16 Hz), 7·02 (d, 1H, *J* 16 Hz), 7·13 (s, 3H, CH_3–N), 8·46 (s, 3H). The succinimide had $\nu_{max.}$ (Nujol) 1780 and 1715 (C=O), 1600, 1520 (NO_2), 1500, 1355 (NO_2), and 855 cm^{-1}; τ ($CDCl_3$, 60 MHz) 1·63, 1·78, 2·29, 2·44 (A_2B_2, 4H, *J* 9 Hz), 6·94 (d, 1H, *J* 14 Hz), 7·06 (s, 6H, CH_3–N), 7·14 (d, 1H, *J* 14 Hz), and 8·25 (s, 3H).

1,2,4-*Trimethyl*-4-p-*nitrophenylhexahydropyridazine* (16b).—Reduction of the dione (13b) (5·54 g) with borane, was according to Brown and Heim [27] for sterically hindered tertiary amides, and with a reflux period of 8 h gave a viscous orange oil (4·90 g) by concentration of the final ethereal solution. Fractional distillation yielded the *hexahydropyridazine* (4·35 g, 87·5%) as an orange oil, b.p. 137—140°/0·05 mm, which solidified when set aside, and crystallised from light petroleum (b.p. 60—80°)–ether as orange cubelets, m.p. 46—49° (Found: C, 62·5; H, 7·3; N, 17·2. $C_{13}H_{19}N_3O_2$ requires C, 62·6; H, 7·7; N, 16·9%); $\nu_{max.}$ (liquid film) 3070, 1600, 1515 (NO_2), 1500, 1350 (NO_2), and 855 cm^{-1}; τ (CCl_4, 60 MHz), 1·77, 1·92, 2·36, 2·51 (A_2B_2, 4H, *J* 9 Hz), 7·25 (m, 4H, CH_2–N), 7·60 (s, 3H, CH_3–N), 7·67 (s, 3H, CH_3–N), 8·10 (m, 2H, C–CH_2–C), and 8·71 (s, 3H). The *monopicrate* (from acetone) had m.p. 198—199° (decomp.) (Found: C, 48·2; H, 4·6; N, 17·1. $C_{19}H_{22}N_6O_9$ requires C, 47·7; H, 4·6; N, 17·6%).

1,2,4-*Trimethyl*-4-*phenylhexahydropyridazine*-3,6-*dione* (13).—This *pyridazinedione*, prepared as for the *p*-nitro-compound, after sublimation (135°, 0·15 mm) had m.p. 95—96° (Found: C, 67·5; H, 6·6; N, 12·1. $C_{13}H_{16}N_2O_2$ requires C, 67·2; H, 6·9; N, 12·1%). The *methiodide* (from 95% ethanol) had m.p. 216—217° (decomp.) (Found: C, 48·6; H, 6·9; N, 7·9. $C_{14}H_{23}IN_2$ requires C, 48·6; H, 6·7; N, 8·1%).

Deuteriated Compounds.—All the following deuteriated compounds (17) were obtained by the action of hexadeuteriodiborane on the corresponding hexahydropyridazine-3,6-diones. Experimental conditions followed those used by Brown and Heim [27] with sterically hindered tertiary amides. The B_2D_6 was generated from boron trifluoride etherate and lithium borodeuteride. Compounds were characterised by their n.m.r. spectra.

[26] A. Foucaud, *Bull. Soc. sci. Bretagne*, 1960 **35**, 88 (*Chem. Abs.*, 1961, **55**, 3516*e*).

3,3,6,6-*Tetradeuterio*-1,2,4,4-*tetramethylhexahydropyridazine*.—The solution containing B_2D_6 (from 1·95 g $LiBD_4$) and 1,2,4,4-tetramethylhexahydropyridazine-3,6-dione (5·10 g) was heated under reflux for 6 h. Normal work-up afforded the *tetradeuteriohexahydropyridazine* (3·17 g, 72·3%), as an oil, b.p. 60°/21 mm; $\nu_{max.}$ (liquid film) 2200—2060 cm^{-1} (seven bands, C–D); τ (CCl_4, 60 MHz), 7·68 (s, 6H, N–CH_3), 8·71 (s, 2H, C–CH_2–C), and 9·06 (s, 6H, CH_3C).

3,3,6,6-*Tetradeuterio*-1,2,4-*trimethyl*-4-*phenylhexahydropyridazine*.—The reflux period for the reaction between B_2D_6 (from 1·00 g $LiBD_4$) and 1,2,4-trimethyl-4-phenylhexahydropyridazine-3,6-dione (2·80 g) was 16 h. The *tetradeuterio-compound* was isolated as an oil (1·96 g, 77·7%), b.p. 109—110°/0·30 mm; $\nu_{max.}$ (liquid film) 2210—2060 cm^{-1} (C–D); τ (CCl_4, 60 MHz) 2·63 (m, 5H), 7·60 (s, 3H, CH_3N), 7·65 (s, 3H, CH_3N), 8·1 (m, 2H, C–CH_2–C), and 8·70 (s, 3H, CH_3C).

3,3,6,6-*Tetradeuterio*-1,2,4-*trimethyl*-4-p-*nitrophenylhexahydropyridazine*.—Reaction conditions and reagent quantities for the reduction of 1,2,4-trimethyl-4-*p*-nitrophenylhexahydropyridazine-3,6-dione (3·55 g) duplicated those of the preceding experiment. Fractional distillation afforded the *tetradeuterio-compound* (2·79 g, 86%) as a viscous orange oil, b.p. 156—158°/0·07 mm. After being set aside overnight in a refrigerator the sample had solidified completely; $\nu_{max.}$ (liquid film) 2210—2060 cm^{-1} (C–D); τ (CCl_4, 60 MHz), 1·74, 1·89, 2·31, 2·46 (A_2B_2, 4H, *J* 9 Hz), 7·58 (s, 3H, CH_3N), 7·65 (s, 3H, CH_3N), 8·13 (q, 2H, C–CH_2–C), and 8·69 (s, 3H, CH_3C).

Physical Measurements.—Dipole moments were measured by the method previously described; [28] results are recorded in Tables 1 and 2. I.r. spectra were obtained using a Perkin-Elmer 237 spectrometer. N.m.r. spectra were recorded at 60 MHz on a Perkin-Elmer R10 spectrometer, with probe temperature 35° or at 100 MHz on a Varian HA 100 spectrometer using a variable-temperature probe.

METHOD AND RESULTS

1,2-Dimethylhexahydropyridazine exists in four conformations (Scheme 4), of which (20) and (21) are equivalent. Elucidation of its conformational equilibria requires the study of additional compounds in which some

TABLE 1

Dielectric constant and specific volume measurements * in cyclohexane at 25°

10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$	10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$
1,2-Dimethylhexahydropyridazine			1,2,4,4-Tetramethylhexahydropyridazine		
2120	4026	7	4305	2775	82
3059	5806	10	5803	3740	110
4041	7657	12	6420	4140	122
4792	9095	16	7735	4986	147
1,2,4-Trimethyl-4-*p*-nitrophenylhexahydropyridazine			1-Methyl-1-*p*-nitrophenylcyclohexane		
1664	16,060	340	891	9792	239
2541	24,147	660	1033	11,360	277
3175	30,956	790	1642	18,057	450
4227	40,050	1133	2176	23,923	594

* w = Weight fraction of solute, ε = dielectric constant, v = specific volume. The suffixes 1 and 12 refer to solvent and solution respectively.

[27] H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 1964, **86**, 3566.

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of the possibilities are absent. We chose first the 1,2,4,4-tetramethyl analogues (Scheme 5) in which, because of unfavourable *syn*-axial interactions, the conformers analogous to (19) and (20) with the 2-methyl group axial, are unlikely to be present to any significant extent. (In the corresponding carbocyclic system the potential energy due to the *syn*-axial interactions of two methyl groups and one hydrogen atom [29,30] is 3·7 + 2 × 0·85 = 5·4 kcal mol^{-1}; whilst easier angle deformation at nitrogen will reduce this repulsion in the present system, it should still be large enough for the preceding assumption to be valid.) As a check on the results obtained from Scheme 5, we also studied 1,2,4-trimethyl-4-*p*-nitrophenylhexahydropyridazine (Scheme 6) together with the model compound 1,3-dimethyl-3-phenylpiperidine [(29) ⇌ (30)]. The results are summarised in Tables 3 and 4.

TABLE 2

Dipole moments

Compound	dε/d*w*	d*v*/d*w*	$_{T}P_{2\infty}$	$_{E}P$	μ(D)
1,2-Dimethylhexahydropyridazine	1·898 ± 0·002	−0·0033 ± 0·0001	79·56	34·46	1·49 ± 0·01
1,2,4,4-Tetramethylhexahydropyridazine	0·645 ± 0·0002	−0·019 ± 0·002	66·58	43·55	1·06 ± 0·01
1,2,4-Trimethyl-4-*p*-nitrophenylhexahydropyridazine	9·52 ± 0·13	−0·25 ± 0·03	512·12	68·067	4·66 ± 0·04
1-Methyl-1-*p*-nitrophenylcyclohexane	10·994 ± 0·004	−0·270 ± 0·002	510·33	60·71	4·69 ± 0·01

TABLE 3

Chemical shifts (p.p.m. on δ scale) of *C*-methyl and *N*-methyl resonances for compounds studied at various temperatures

	T (K)	δ-(*N*-Methyl) *	δ-(*C*-Methyl) *
1,2,4,4-Tetramethylhexahydropyridazine	293	2·29, 2·27	0·97
	183	2·32, 2·26 2·24, 2·16	1·00, 0·87
1,2,4-Trimethyl-4-*p*-nitrophenylhexahydropyridazine	330	2·34, 2·27	1·25
	223	2·37, 2·23 †	1·41, 1·18
1,3-Dimethyl-3-phenylpiperidine	308	2·18	1·24
	183	2·16	1·09, 1·34

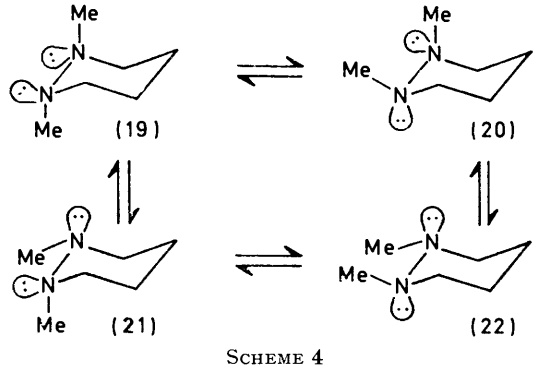
* Measured at 100 MHz. † Major peaks.

TABLE 4

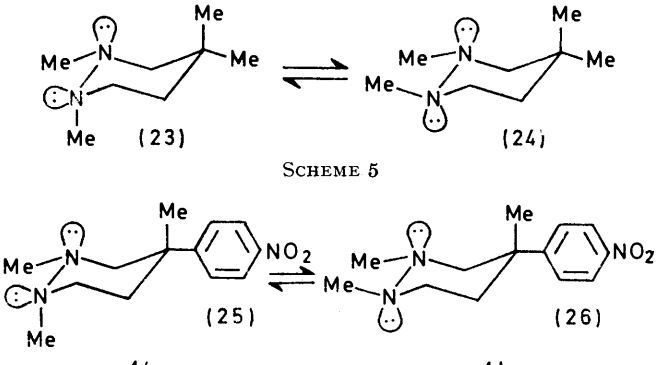
Populations and relative enthalpies of conformers of 1,2-dimethylhexahydropyridazine and derivatives at 298 K

4-Substituents	Conformer	%	Δ*H*° (kcal mol^{-1})
H,H	(19)	36	0
	(22)	30	0·11
	(20) + (21)	34	0·47 [a]
Me,Me	(24)	64	0
	(23)	36	0·36
Me, *p*-$C_6H_4NO_2$	(26)	38	0
	(28)	26	0·22
	(25)	21	0·35
	(27)	15	0·55

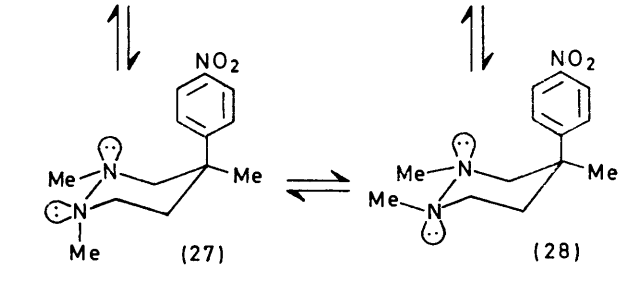
[a] Allowing for 2-fold degeneracy.



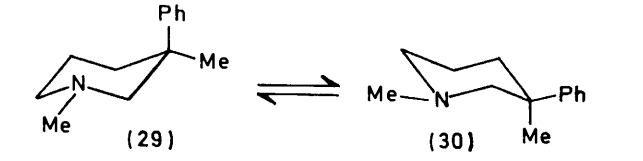
SCHEME 4



SCHEME 5



SCHEME 6



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1,2,4,4-*Tetramethylhexahydropyridazine* (Scheme 5).—The n.m.r. spectrum of the 3,3,6,6-tetradeuterio-compound (Figure 1a) shows at 0° a single line for the geminal *C*-methyl group protons and two singlets for the two *N*-methyl group protons; the spectrum is in accord with rapid ring and nitrogen inversion. As the temperature is lowered the *C*-methyl signals separate into a doublet and the *N*-methyl signals separate into four distinct peaks, two doublets of unequal area. We assign the more intense doublet, in which the peaks are separated by 0·064 p.p.m., to the conformer (24) with both *N*-methyl groups equatorial, and the weaker doublet (separation 0·106 p.p.m.) to the conformer (23) with one *N*-methyl group axial and one equatorial; it can be seen from Figure 1b that this assignment implies that the three equatorial *N*-methyl signals are close together and to low field of the single axial *N*-methyl signal. Direct area measurements and peak-height times width-at-half-height measurements both give a value for the equilibrium constant at 183 K of 2·7. In order to use this information in conjunction with dipole moment measurements we must extrapolate to 298 K; assuming that there is no entropy difference between the conformers, and that ΔH° is independent of temperature, then log K_{298} = (183/298) log K_{183}, and K_{298} = 1·8, corresponding to values of N_{23} and N_{24} [mole fractions of conformers (23) and (24) respectively] of 0·35 and 0·65 respectively.

The measured dipole moment of the conformational mixture of Scheme 5 (μ_v) will be given by the mean square relation (1). We assume that $\mu_{24} = 0$, because of

$$\mu_v^2 = N_{23}\mu_{23}^2 + N_{24}\mu_{24}^2 \quad (1)$$

$$\mu_v^2 = N_{23}\mu_g^2 \quad (2)$$

the pseudo-centrosymmetrical arrangement of bonds about the centre of the N–N bond. We further write $\mu_{23} = \mu_g$, the moment deriving from a molecule containing an N–N fragment with *gauche* lone-pairs. Thus equation (1) simplifies to (2), and by inserting the measured value of N_{23} we find that μ_g = 1·79D.

$$(N_{19} + 2N_{20})\mu_g^2 = \mu_{iv}^2 \quad (3)$$

$$N_{19} + 2N_{20} + N_{22} = 1 \quad (4)$$

$$N_{22} = 1.8N_{20} \quad (5)$$

1,2-*Dimethylhexahydropyridazine* (Scheme 4).—By noting the identity of conformers (20) and (21), and by assuming that $\mu_{22} = 0$ and that $\mu_{19} = \mu_{20} = \mu_{21} = \mu_g$, we may write equations (3) and (4). If we further assume that the equilibrium constant between the diequatorial conformer (22) and a *single* equatorial-axial conformer [(20) or (21)] is the same as that found for the 1,2,4,4-tetramethyl analogue (namely 1·8 at 298 K) we have a third simultaneous equation, (5). Solution of these three equations gives values for N_{19}, N_{20}, and N_{22} of 0·36, 0·17, and 0·30 respectively, corresponding to 30% of the diequatorial conformer, 34% of the doubly degenerate equatorial-axial conformer, and 36% of the diaxial conformer.

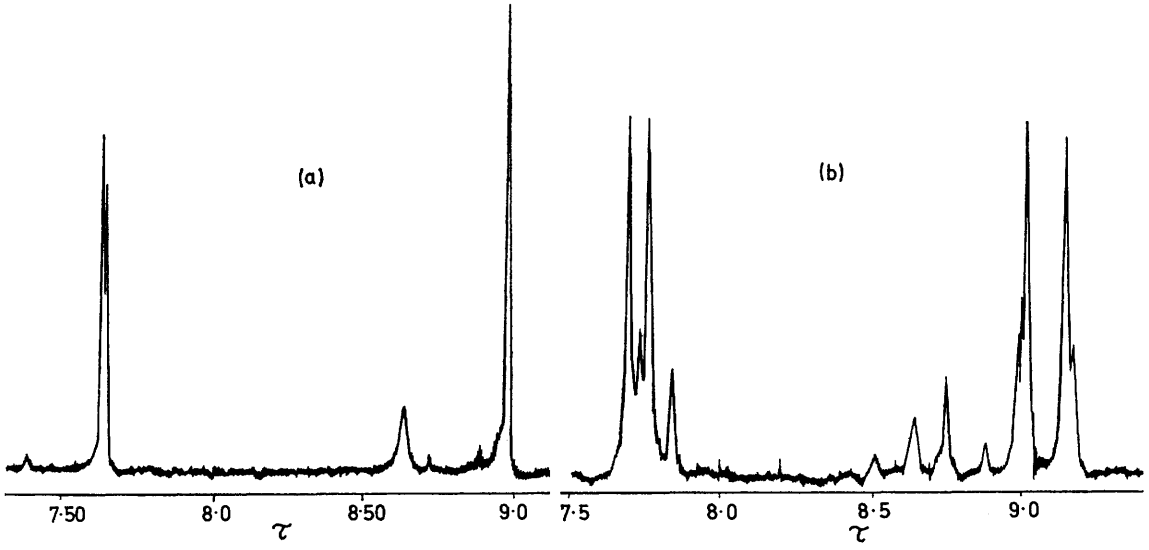

FIGURE 1 N.m.r. spectrum of 1,2,4,4-tetramethyl-3,3,6,6-tetradeuteriohexahydropyridazine (a) at 0°; (b) at −90°

1,2,4-*Trimethyl*-4-p-*nitrophenylhexahydropyridazine* (Scheme 6).—Because we have not been able to measure the equilibrium constant of Scheme 5 directly at room temperature we have studied another system to check on the consistency of our method. The n.m.r. spectrum of the 3,3,6,6-tetradeuterio-compound of Scheme 6 (Figure 2a) shows at +57° the expected singlet for the *C*-methyl group protons and doublet for the *N*-methyl group protons. At −70° the *C*-methyl signal appears as a doublet (Figure 2b); we assign the two signals to the pairs of conformers [(25) ⇌ (26)] and [(27) ⇌ (28)], assuming that the inversion at N-1 is not causing resolvable separation of the C-4 methyl signals. We thus determine the equilibrium constant between the axial-methyl/equatorial-aryl and axial-aryl/equatorial-methyl conformers to be 0·674 at 203 K and by analogy with

carbocyclic systems we presume that the equatorial-aryl conformers [(25) ⇌ (26)] predominate. (Direct area measurements were, in this case, judged to be less reliable than peak height × half-width because of slight overlap of the C-5 methylene protons.) As a further check we also measured the spectra of 1,3-dimethyl-3-phenylpiperidine, in which the equilibrium [(29) ⇌ (30)] should be closely similar to [(27) + (28)] ⇌ [(25) + (26)]. The equilibrium constant at 203 K, determined from the relative areas of the 3-methyl group doublet peaks, was 0·67, in excellent agreement with the preceding results. Extrapolation, as before, to 298 K gives an equilibrium constant at that temperature of 0·76 for both these systems.

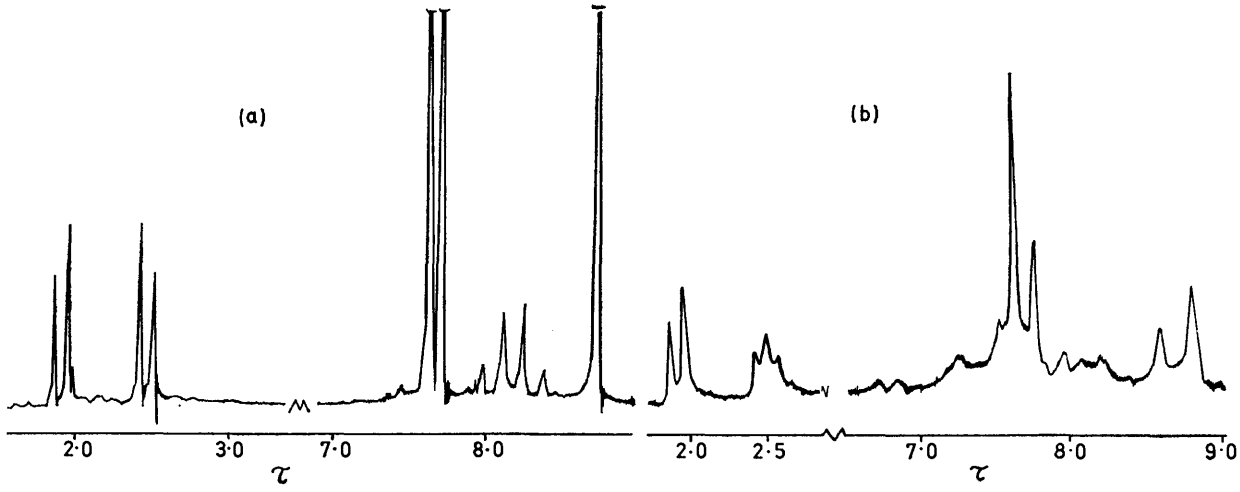

FIGURE 2 (a) N.m.r. spectrum at 57° of 1,2,4-trimethyl-4-*p*-nitrophenyl-3,3,6,6-tetradeuteriohexahydropyridazine; (b) N.m.r. spectrum at −70° of 1,2,4-trimethyl-4-*p*-nitrophenylhexahydropyridazine

We must now make assumptions about the dipole moments of the four conformers of Scheme 6. First we suppose that the pseudocentrosymmetric hydrazine moiety of conformers (26) and (28) contributes nothing to the overall moments of these species each of which we therefore equate with the measured moment, μ_1, of 1-methyl-1-*p*-nitrophenyl cyclohexane (1). Next we calculate the moments of conformers (25) and (27) by supposing that they can be derived from two components μ_1 and μ_g deriving from the aryl and hydrazine portions respectively. The angles between the two constituent vectors were calculated [31] to be 150·5 and 43·3° respectively, by assuming the hydrazine group moment to act along the pseudo-C_2 axis bisecting the N–N bond, and using the following bond lengths and angles: CC, 154 pm; CN, 147 pm; NN, 148 pm; CCC, 111·5°; CNN and CCN, 110°. These calculations lead to values for μ_{25} and μ_{27} of 3·26 and 6·11D respectively.

We may now write equations (6) and (7), in which K is the equilibrium constant $N_{28}/N_{27} = N_{26}/N_{25}$ at 298 K. Solving these equations simultaneously gives $N_{25} = 0{\cdot}21$ (and consequently, $N_{26} = 0{\cdot}38$, $N_{27} = 0{\cdot}15$, and $N_{28} = 0{\cdot}26$), and $K = 1{\cdot}8$. This value is identical to that derived (by extrapolation to 298°) from the low-temperature n.m.r. data on 1,2,4,4-tetramethylhexahydropyridazine (Scheme 5), and gives us considerable confidence in the reliability of our results.

$$\mu_{VI}^2 = N_{25}\mu^2_{25} + KN_{25}\mu_{26}^2 + 0{\cdot}76N_{25}\mu^2_{27} + 0{\cdot}76KN_{25}\mu_{28}^2 \quad (6)$$

$$N_{25}(1 + K + 0{\cdot}76 + 0{\cdot}76K) = 1 \quad (7)$$

The relative proportions of the conformers that were found were unexpected, particularly the large amount of conformer (19) with two axial *N*-methyl groups. We believe that the energy of this conformer is considerably reduced by distortions at the nitrogen atom by bending the axial *N*-methyl group away from the β-axial hydrogen atoms on the same side of the ring. Examination of models shows that in (19), such distortion moves the two *gauche* lone pairs away from each other, whereas in (20) and (21) similar distortions bring the *gauche* lone pairs closer together. We have previously presented evidence for such distortions in the *N*-methyl axial conformer of *N*-methyl-piperidine.[32]

Conclusions.—All three non-equivalent conformations of 1,2-dimethylhexahydropyridazine are populated to an approximately equal extent. This conclusion differs from that of Anderson [33] who interpreted his n.m.r. results in terms of the overwhelming preponderance of the diequatorial conformer (22). This conformer is expected to have a dipole moment close to zero; the measured value for 1,2-dimethylhexahydropyridazine of 1·48D is not consistent with Anderson's conclusions. The reasons for the discrepancies are under investigation.

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