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cis-trans EQUILIBRIA IN 1-SUBSTITUTED-3,5-DIMETHYL-4-PIPERIDONES WITH DIFFERENT HYBRIDISATIONS OF NITROGEN[1]

M. D. BROWN, M. J. COOK, G. DESIMONI AND A. R. KATRITZKY

School of Chemical Sciences, University of East Anglia, Norwich, England.

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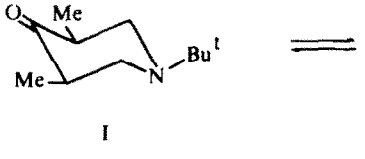
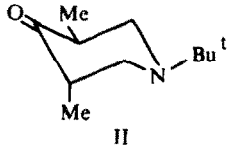
Abstract— A series of 1-substituted-3,5-dimethyl-4-piperidones has been prepared and the positions of *cis-trans* equilibria determined by NMR. The equilibrium constants for the 1-(*p*-substituted phenyl) compounds do not vary significantly with the *para* substituent and are similar to the equilibrium constant for the 1-t-butyl analogue.

STUDY of the configurational equilibrium I⇌II has allowed deductions regarding the steric requirements of the nitrogen lone pair; as the equilibrium favours the *trans* isomer II more than does the corresponding equilibrium for 2,6-dimethylcyclohexanone, the nitrogen lone pair steric requirements are, in this system, less than those of a CH-group.[2] We wished to determine whether modification of the hybridisation of the nitrogen lone pair from sp^3 in I, II towards sp^2 would affect its steric requirements. This paper describes the preparation of a series of *para*-substituted N-phenyl analogues and the determination of the corresponding equilibria III ⇌ IV.



I



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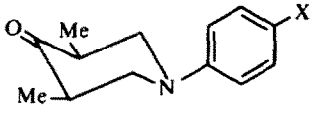

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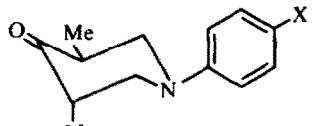
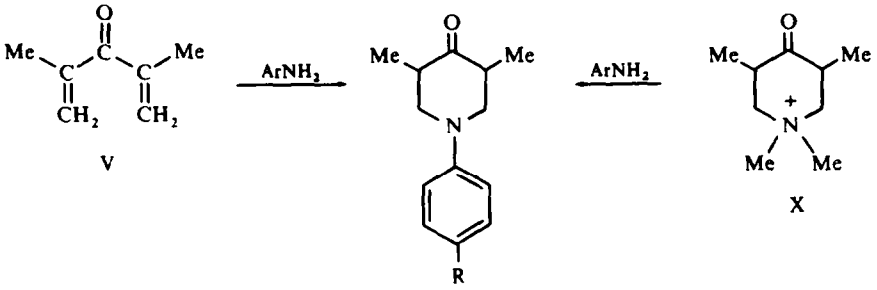


IV

Preparation of compounds. 1-Phenyl-3,5-dimethyl-4-piperidone together with its *p*-methyl and *p*-methoxy analogues, and the corresponding β-naphthyl derivative, were all prepared by reaction of the corresponding aromatic amines with the dimethylpentadienone[3] (V → VI, VII, VIII). The *p*-chloro derivative was prepared by the sequence X → IX, cf. refs 4, 5. Difficulty was experienced in the preparation of the *p*-nitro compound XI: attempts from V and X both failed, presumably due to the weak nucleophilicity of *p*-nitro aniline. Nitration of VI under most conditions gave mixtures of products. Although the *p*-nitroso derivative XIII was readily prepared, attempted oxidation of the nitroso group to nitro with periodic acid failed,[6] and treatment of XIII with nitric acid yielded the nitro-nitroso compound XIV. Eventually,

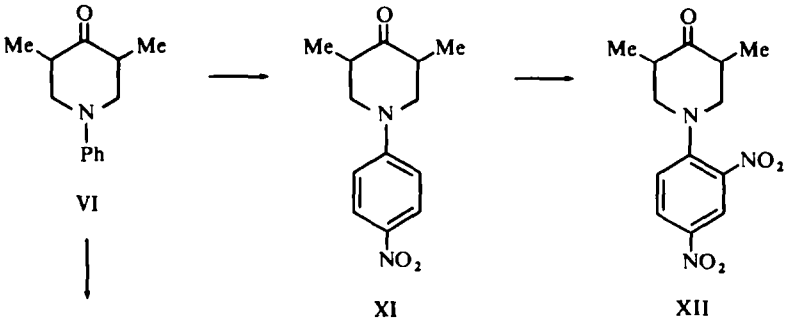
conditions for the controlled nitration VI → XI were found, and subsequently the dinitro-compound XII was easily obtained.



V

VI : R = H
VII ; R = Me
VIII; R = OMe
IX ; R = Cl

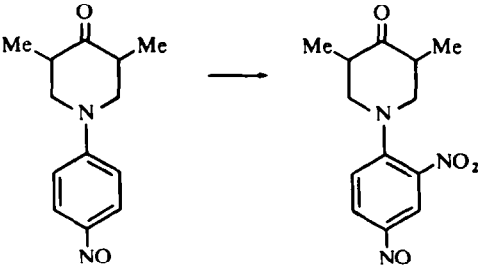
X



VI

XI

XII



XIII

XIV

The structures of all the compounds were confirmed by analysis and IR (a strong piperiodone carbonyl band at 1715 cm^{-1}) and NMR spectra (Table 1). Other details are given in Table 2.

TABLE 1. NMR CHEMICAL SHIFTS (PPM ON τ SCALE) OF 1-(4'-SUBSTITUTED-PHENYL)-3,5-DIMETHYL-4-PIPERIDONES[a]

Formulae Number	4'-Substituent	Aryl ring 2'	Aryl ring 3'	*J*(Hz)	Ring-CH_2[b]	Piperidone-CH_3[c] aryl Me	*cis*	*trans*
VI	H	2·88 – 3·21[d]		?	6·0 – 7·8	--	9·04	8·90
VII	Me	3·10	3·28	9·0	5·9 – 7·4	7·70	8·96	8·82
VIII	MeO	3·22	3·34	9·2	5·9 – 7·7	6·25	9·02	8·84
IX	Cl	3·12	2·80	8·5	5·9 – 7·4	--	9·00	8·86
XI	NO_2	3·00	1·78	9·5	5·5 – 7·6	--	?	8·87
XII	NO_2, NO_2[e]	2·82	1·28	2·6	6·1 – 7·4	-	?	9·01
XIII	NO	2·97	2·07	8·5	5·5 – 7·5	--	?	8·86
XIV	NO,NO_2[f]	2·77	1·27	2·6	6·1 – 7·4	--	?	8·92
			1·69	9·3				
	(β-naphthyl)[g]	2·2 – 3·1[d]		?	5·9 – 7·4	--	8·98	8·83

[a] Spectra refer to *ca* 35% w/v solutions in $CDCl_3$ with TMS as internal standard, and were determined at 60 MHz and at 34°.

[b] All complex multiplets

[c] All signals were doublets with J = 7Hz

[d] Complex multiplet

[e] 1-(2',4'-dinitrophenyl) derivative

[f] 1-(2'-nitro-4'-nitrosophenyl) derivative

RESULTS AND DISCUSSION

As before[2] equilibration was accomplished simultaneously with deuteriation at the position α to the carbonyl group, which resulted in simplification of the NMR spectra, by shaking carbon tetrachloride solutions with sodium deuteroxide in deuterium oxide. In some cases the addition of 1,4-dioxan was necessary to bring about equilibration within a reasonable time. Even so we found that considerably longer times were required to reach equilibration than the 7 days previously[2] used. The results are given in Table 3; at the times shown equilibration was complete as judged by successive measurements.

We were unable to equilibrate satisfactorily the four compounds containing nitro or nitroso groups or the β-naphthyl compound. Under the conditions previously used, the nitroso underwent extensive decomposition, turning dark brown. The *p*-nitro derivative has too low a solubility for convenience: it also developed a yellow colour on prolonged treatment with alkali possibly due to nucleophilic displacement. The β-naphthyl derivative was incompletely deuteriated even after treatment for 90 days.

The individual AB patterns in the *cis* and *trans* dideuterio derivatives were visible only in the absence of 1,4-dioxan. Their assignments followed precisely from the criteria developed in the earlier work;[2] (i) the AB chemical shift difference for the methylene protons is larger for *cis* derivatives, (ii) the lines of the inner AB system have similar half widths but the higher field lines of the outer AB are broader (half width: 4·8 Hz) than the low field lines (3·5 Hz). Only dideuteriated VI and IX were examinable by this approach and the *cis* isomers predominated as expected. The chemical shift of the Me groups of the *cis* isomers were to higher field than the time averaged signal for the Me groups of the *trans* isomers. This phenomenon has also been observed in

TABLE 2. PREPARATION OF 1-(4'-SUBSTITUTED PHENYL)-3,5-DIMETHYL-4-PIPERIDONES

Formulae Number	*para*-Substituents	Method[a]	Yield %	m.p. (bp/mm)	Solvent for crystallisation	Cryst. form	Molec. formula	Found % C	Found % H	Found % N	Required % C	Required % H	Required % N
VI	H	A	45	(110–112°/0·3 mm)	--	--	$C_{13}H_{17}NO$	76·9	8·2	7·2	76·8	8·4	6·9
VII	Me	A	46	(156–158°/3 mm)	--	--	$C_{14}H_{19}NO$	77·4	8·8	6·4	77·4	8·8	6·4
VIII	MeO	A	68	(125–127°/1 mm	--	--	$C_{14}H_{19}NO_2$	72·3	8·4	6·1	72·1	8·2	6·0
IX	Cl	B	42	47–49°	hexane/benzene	needles	$C_{13}H_{16}NOCl$	66·2	6·9	6·0	65·7	6·8	5·9
XI	NO_2	C	63	196–197°	MeOH	yellow needles	$C_{13}H_{16}N_2O_3$	62·8	6·7	11·4	62·9	6·5	11·3
XII	$(NO_2)_2$[b]	C	85	139–140°	MeOH	yellow prisms	$C_{13}H_{15}N_3O_5$	53·6	5·2	14·3	53·2	5·2	14·3
XIII	NO	C	85	138–139°	EtOH	green prisms	$C_{13}H_{16}N_2O_2$	67·0	7·1	11·7	67·2	6·9	12·1
XIV	NO, NO_2[c]	C	84	132–133°	MeOH	yellow needles	$C_{13}H_{15}N_3O_4$	55·8	5·4	14·9	56·3	5·5	15·2
	[d]	A	11	128–129°	MeOH	needles	$C_{17}H_{19}NO$	80·8	7·5	5·5	80·6	7·6	5·5

[a] See experimental
[b] 2',4'-dinitro derivative
[c] 1-(2'-nitro-4'-nitrosophenyl) derivative
[d] 1-β-naphthyl-3,5-dimethyl-4-piperidone

2,6-dimethylcyclohexanone, 3,5-dimethyltetrahydrothiapyran-4-one and its 1,1-dioxide.[7] The signals for the Me groups in the remaining equilibrated *cis* and *trans* dideuteriated aryl piperidone mixture were assigned accordingly.

Equilibrium constants were calculated (Table 3) from the Me group signal areas

TABLE 3. *Cis-trans* EQUILIBRATION OF 1-(4'-SUBSTITUTED-PHENYL)-3,5-DIMETHYL-4-PIPERIDONE AT 20°

4' Substituent	Solvent	Time (days)	A[a] *cis*	A[a] *trans*	K[b]	ΔG°[c] (Kcal Mole)	ΔH°
H	CCl_4	10	0·825 ± 0·015	0·175 ± 0·015	4·71	0·90	1·30
	CCl_4 + dioxan	10	0·835 ± 0·020	0·165 ± 0·020	5·07	0·95	1·35
Me	CCl_4 + dioxan	29	0·869 ± 0·010	0·131 ± 0·010	6·64	1·10	1·50
OMe	CCl_4 + dioxan	10	0·864 ± 0·005	0·136 ± 0·005	6·41	1·08	1·48
Cl	CCl_4	45	0·847 ± 0·02	0·153 ± 0·020	5·54	1·00	1·40
(4-t-Butyl)[d]	CCl_4	7	0·829	0·171	4·85	0·93	1·33

[a] Integrated areas within the peak due to the methyl protons

[b] K = [cis]/[trans]

[c] Calculated on values of K: a positive value indicates the equilibrium favours the *cis* form

[d] Taken from ref 2: the temperature in this case was 25°

as measured with the LORENTDECOMP computer program[8] which fits the observed curves to theoretical lorenzian curves, no estimation of base line being needed. The error in the measurement of the areas is believed to be small and within the limits quoted (Table 3). Equilibrium constants afforded ΔG° values and, assuming that the entropy difference between the isomers is the entropy of mixing of the *trans* isomer (which exists in two equivalent conformations), gives the ΔH° values of Table 3. Results for 1-phenyl-3,5-dimethyl-4-piperidone (VI) show to within the limits of experimental error that the addition of 1,4-dioxan to the equilibrating mixture does not affect the equilibrium constant. The ΔH° values for all four 1-aryl-3,5-dimethyl-4-piperidones (VI–IX) closely resemble ΔH° for the 1-t-butyl analogue (I ⇌ II) and are considerably different from the ΔH° for 2,6-dimethylcyclohexanone which has been reported as 2·18 ± 0·11[9] or 1·95 ± 0·26 kcals.[10]

The substituent on the N atom is expected to adopt the equatorial position and the *cis-trans* equilibrium constant is therefore a function of the axial lone pair-axial Me interaction. The ΔH° values obtained are almost the same within experimental error and the variations do not follow a particular trend. A recent microwave study[11] has shown that the out of plane HNH angle in aniline is 37°39′ which rises to 46°22′ in *p*-fluoroaniline. Our results suggest that the present method using a conformational probe (the axial Me group) is insufficiently sensitive to detect small changes in the geometry about a piperidone ring nitrogen caused by small changes in hybridisation which result from the alteration of *p*-substituents in an aryl group or even from the change of an alkyl to an aryl substituent at the nitrogen atom.

EXPERIMENTAL

All m.ps. are uncorrected. IR spectra were determined as liquid films or nujol mulls on a Perkin-Elmer 257 spectrophotometer. NMR spectra were obtained using Perkin-Elmer R10 60MHz and Varian HA100 100MHz spectrophotometers.

1-Aryl-3,5-dimethyl-4-piperidones

Method a. Freshly prepared 2,4-dimethylpentadien-3-one[12] (7·0g, 0·064 mole), arylamine (0·1 mole). 1,4-dioxan (25 ml) and water (6 ml) were heated under reflux for 48 hr. Aqueous HCl 1:1 (40 ml) was added and the soln concentrated by distillation under reduced pressure. Water (30 ml) was added and the soln was washed with ether (2 × 15 ml), made basic with 30% NaOH aq, and extracted with ether (3 × 100 ml). The ether extract was washed with water (2 × 5 ml), dried ($MgSO_4$), and the ether removed by distillation under reduced pressure. The residue was fractionally distilled under reduced pressure, and the higher boiling fraction collected. The product was further purified by chromatography on silica gel using chloroform as eluant.

Method b. 1,3,5-Trimethyl-4-piperidone-N-methyliodide[13] (12·83 g, 0·01 mole), arylamine (0·011 mole), acetone (10 ml) and water (15 ml) were refluxed for 48 hr. The solvent was distilled off under vacuum and the residue dissolved in 2N HCl. The acidic soln was worked up as in Method a.

1-p-*Nitrosophenyl-3,5-dimethyl-4-piperidone*

1-Phenyl-3,5-dimethyl-4-piperidone (0·8 g) conc HCl (3 ml) and ice (5 g) were stirred and a soln of $NaNO_2$ (0·3 g) in water (2 ml) was added dropwise at 0° over 15 min. The mixture was stirred for 15 min more at 0° and an additional 15 min at 20°. The suspension was slowly basified with $NaHCO_3$ aq and the green-yellow ppt (0·77 g) crystallized to give pure 1-*p*-nitrosophenyl-3,5-dimethyl-4-piperidone (Table 2).

1-p-*Nitrophenyl-3,5-dimethyl-4-piperidone*

Fuming HNO_3 (*d* 1·53; 0·08 ml) in $AcOH/Ac_2O$, 1:1 (1·0 ml) was added dropwise to a stirred soln of 1-phenyl-3,5-dimethyl-4-piperidone (0·40 g) in $AcOH/Ac_2O$ (1:1, 2·0 ml), keeping the temp below −10°. After an additional 2 hr at −10°, the mixture was kept for 12 hr at 20°. The yellow ppt was filtered off (0·13 g) and crystallized from MeOH with charcoal, giving pure 1-*p*-nitrophenyl-3,5-dimethyl-4-piperidone (Table 2). Further product (0·18 g − total 0·31 g) was obtained from the acetic acid mother liquors after dilution with water and purification.

1-(2'-*Nitro-4'-nitrosophenyl-*)-3,5-*dimethyl-4-piperidone*

1-*p*-Nitrosophenyl-3,5-dimethyl-4-piperidone (0·30 g) was added to stirred 22% HNO_3 (20 ml) and the mixture warmed up to 45°. The green-yellow solid dissolved and after a few min a yellow-brown crystalline product began to separate. After 30 min the solid was filtered off (0·25 g) and crystallized. An additional 0·05 g of the same 1-(2'-nitro-4'-nitrosophenyl)-3,5-dimethyl-4-piperidone was obtained from the nitric acid mother liquors after basification and extraction with ether (Table 2).

1-(2',4'-*Dinitrophenyl*)-3,5-*dimethyl-4-piperidone*

1-*p*-Nitrophenyl-3,5-dimethyl-4-piperidone (0·20 g), suspended in HNO_3 (30%, 3 ml), was warmed 3 min at 40°. The mixture became clear and after standing overnight at 20°, basification with $NaHCO_3$ aq precipitated a yellow solid which was recrystallized (Table 2).

Equilibration of 1-*aryl-3,5-dimethyl-4-piperidones*

The 1-aryl-3,5-dimethyl-4-piperidone (1 M mole) either in CCl_4 (0·4 ml) or in a mixture of CCl_4:1,4-dioxane, 1:1 (0·7 ml), was added to a freshly prepared 10% soln of NaOD in D_2O (3 ml) (obtained by dissolving the required amount of Na in D_2O) and the mixture was stirred at 20° for the required period. The organic layer was separated and the NMR spectrum registered at 100 MHz immediately after addition of a trace of TMS as internal standard.

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