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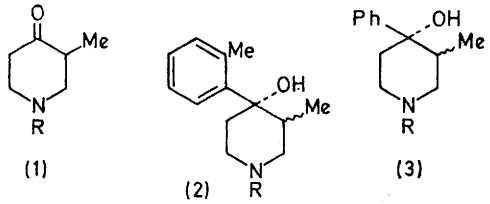
Synthesis, Configuration, and Dehydration of some 1-Alkyl- and Aralkyl-3-methyl-4-*o*-tolylpiperidin-4-ols

By **M. A. Iorio**, Laboratories of Therapeutical Chemistry, Istituto Superiore di Sanità, Rome, Italy
A. F. Casy,* Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Diastereoisomeric 3-methyl-4-*o*-tolylpiperidin-4-ols, derived from 4-piperidones, have been separated and their configurations have been established on the basis of ^{1}H n.m.r. data and their behaviour towards dilute hydrochloric acid. The isomeric dehydration products of these alcohols have been separated and their slow rates of equilibration, in comparison with those of 4-phenyl analogues, have been demonstrated. The ratios of the 3- and 5-methyltetrahydropyridines derived by treatment of the 4-*o*-tolylpiperidin-4-ols and related tertiary alcohols with acid are reported and discussed.

THIS work is an extension of previous configurational and elimination studies of 4-aryl-3-methylpiperidin-4-ols.[1-3] Treatment of the 4-piperidones (1) with *o*-tolyllithium gave diastereoisomeric mixtures of piperidin-4-ols (2), which were separated into major (α) and minor (β) components by fractional crystallization of the



(1) (2) (3)

a; R = Me
b; R = Et
c; R = CH_2Ph

hydrochlorides or by column chromatography. The assignment of the configurations *trans*-4-Ar/3-Me for α- and *cis*-4-Ar/3-Me for β-isomers follows from consideration of their ^{1}H n.m.r. characteristics and their behaviour towards dilute hydrochloric acid. Isomeric 4-phenylpiperidin-4-ols (3) are distinguished by the 3-methyl chemical shifts of the bases and hydrochlorides in deuteriochloroform; that of the α-base is close to that of the α-salt whereas the β-hydrochloride signal is 0·23—0·3 p.p.m. downfield of the base signal.[1,3] These differences are interpreted in terms of the preferred conformations (4) and (5) for α- and β-isomers respectively. In (5), the 3-methyl group is closer to the deshielding $\overset{+}{N}H$ function. The Δ value (the 3-methyl chemical shift of the salt minus that of the base, expressed in p.p.m.) of β-(3a) also exceeds that of the α-isomer in [$^2H_6$]dimethyl sulphoxide but the difference is less pronounced (Table 1, nos. 1 and 2), probably owing to (5) being less favoured in polar solvents;[4] hence

[1] A. F. Casy, *Tetrahedron*, 1966, **22**, 2711.
[2] A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, 1967, **23**, 1405.
[3] A. F. Casy, M. A. Iorio, and P. Pocha, *J. Chem. Soc.* (*C*), 1967, 942.
[4] A. F. Casy, *J. Medicin. Chem.*, 1968, **11**, 188; A. F. Casy and A. P. Parulkar, *Canad. J. Chem.*, 1969, **47**, 3623.

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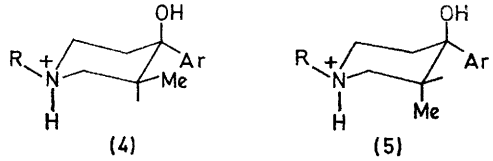
deuteriochloroform is the solvent of choice for detecting these shifts. This solvent could not be used to study the αβ-pairs (2a) and (2b) [only α-(2b) hydrochloride was



soluble] but data for [$^2H_6$]dimethyl sulphoxide solutions showed Δ values of 0·16 p.p.m. for β-(2b) and 0·02 p.p.m. for the α-isomer, supporting *cis*- and *trans*-4-Ar/3-Me configurations respectively for these isomers (Table 1, nos. 3 and 4). The aromatic signals of α- and

TABLE 1

3-Methyl ^{1}H n.m.r. characteristics of some 1-substituted 3-methyl-4-*o*-tolylpiperidin-4-ols

No.	Structure	Isomer	Form	Solvent	3-Me signal [a]	Δ [b]
1	(3a)	α	Base	$(CD_3)_2SO$	9·53	
		α	HCl		9·42	0·11
2	(3a)	β	Base		9·37	
		β	HCl		9·18	0·19
3	(2b)	α	Base		9·42	
		α	HCl		9·40	0·02
4	(2b)	β	Base		9·34	
		β	HCl		9·18	0·16
5	(2c)	α	Base	$CDCl_3$	9·32	
		α	HCl		9·32	0
6	(2a) propionate ester [c]	α	Base		9·22	
		α	HCl		9·20	0·02
		β	Base		9·24	
		β	HCl		8·93	0·31

[a] Doublet, *J ca.* 7 Hz, chemical shifts in τ units with tetramethylsilane as internal standard. [b] Protonation shift of 3-Me signal [ν(HCl) − ν(base)] in p.p.m. [c] O·CO·CH_2*Me* signals (t, *J ca.* 7 Hz): α, τ 8·77; β, τ 8·87.

β-(2b) are readily distinguishable (Figure 1); that of the α-isomer is the more complex, showing a broad hump downfield of one weak and two more intense singlets. The *N*-methyl pair (2a) have aromatic signals which differ

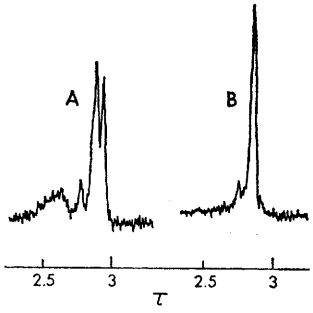
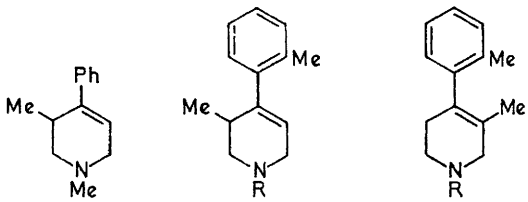


FIGURE 1 Aromatic ^{1}H n.m.r. signals of α-(2b) (A) and β-(2b) (B) in $CDCl_3$ (60 MHz)

in the same way and configurations are assigned accordingly. The *o*-tolyl proton signals of the *N*-benzyl pair (2c) are partly obscured by the *Ph*CH_2·N signal but *trans*- (two singlets, τ 2·82 and 2·87) and *cis*-patterns (one singlet, τ 2·81) are clear in α- and β-aromatic signals respectively. The *trans*-configuration of α-(2c) is further supported by the identical 3-methyl chemical shift of the base and hydrochloride in deuteriochloroform (Table 1, no. 5). Hydrochlorides of the diastereoisomeric propionate esters of (2a) were both soluble in deuteriochloroform and their 3-methyl Δ values (α 0·02, β 0·31 p.p.m.) and the higher field position of the β-O·CO·CH_2*Me* signal [1] were in accord with assigned configurations (Table 1, nos. 6 and 7).

Further evidence of configuration was obtained from the action of dilute hydrochloric acid (24 hr. at 50°) on isomeric pairs. It has been shown that the *cis*-3-Me/4-Ph piperidinol (3a) is extensively dehydrated, giving the 5-methyltetrahydropyridine (6) exclusively, whereas the



a; R = Me b; R = Et c; R = CH_2Ph

trans-isomer is recovered unchanged after this treatment.[2] The same difference in reactivity was found for the αβ-pairs (2a, b, and c) [β-isomers likewise gave the 5-methyl isomers (7) as the sole or major elimination product], confirming configurational assignments based on ^{1}H n.m.r. data (Table 2, nos. 1—3).

TABLE 2

Integral data for products of dehydration and alkene-equilibration experiments [a]

No.	Substrate	Solvent, heating period and temperature	^{1}H n.m.r. integrals: Vinylic [b]	sec-Me [c]	t-Me [d]	Ratio [e] 3-Me(8) : 5-Me(7)
1	β-(2a)	*i*	8	25		(7a) sole product
2	β-(2b)	*i*	8	24		(7a) sole product
3	β-(2c)	*i*	9	27	5	1 : 5·4
4	(7a)	*j*	8	23	5	1 : 4·6
5	(8a)	*j*			26	(8a) sole product
6	(2a) [f]	*k*	5	15	7	1 : 2·1
7	(2b) [f]	*k*	3·5	12	6	1 : 2
8	(2c) [f]	*k*	3	10	5	1 : 2
9	(9)	*k*	5	13		5-Methylalkene sole product
10	(10)	*i*	7	23	5	1 : 4·5 [g]
11	*h*	*k*		2	28	14 : 1
12	(10)	*k*		2	30	15 : 1

[a] General procedure: a mixture of the substrate (60—70 mg.), conc. HCl (0·3 ml.), and glacial acetic acid (0·6 ml.) or conc. HCl (2 ml.) and water (2 ml.) is heated for the stated period, made alkaline with aqueous ammonia and extracted with ether. The dried extract is evaporated under vacuum and the residue is examined by ^{1}H n.m.r. spectroscopy ($CDCl_3$). [b] Triplet near τ 4·5. [c] Doublet near τ 9·15. [d] Broad singlet near τ 8·63. [e] Calculations based upon integrals of methyl signals. [f] Isomeric mixture, α-form in excess. [g] Ratio 2-*o*-tolyl-1-methylcyclohexene : isomer (11). [h] Alkene mixture derived from no. 10. [i] HCl–H_2O, 24 hr., 50°. [j] HCl–H_2O, 12 hr., reflux. [k] HCl–AcOH, 12 hr., reflux.

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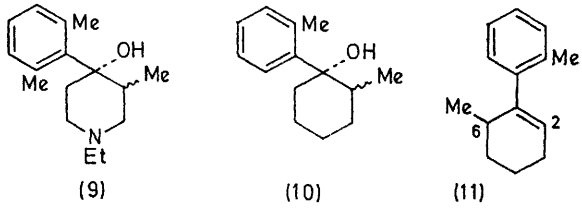
Treatment of the α-isomers (2a, b, and c) with a mixture of acetic and hydrochloric acids at reflux temperature gave binary mixtures of the isomeric tetrahydropyridines (7) and (8) containing the 5- and 3-methylalkenes in about a 2 : 1 ratio (Table 2, nos. 6—8). This ratio must represent closely that of the initial dehydration products, because equilibration of pure samples of the isomeric alkenes (separated by column chromatography) was not observed after heating under reflux (6 and 72 hr.) with the same mixture of acids. These results are in contrast with the behaviour of 4-phenyl analogues of (7) and (8) (b and c), which give binary mixtures of tetrahydropyridines after acid treatment, with the 3-methyl isomer preponderant when equilibrium is reached.[2] In aqueous hydrochloric acid (12 hr. reflux) the 5-methyltetrahydropyridine (7a) was 20% isomerised, while the 3-methyl isomer (8a) was unaffected (Table 2, nos. 4 and 5). Conformations with coplanar aromatic and double bond planes are less favoured in 4-*o*-tolyltetrahydropyridines (7) and (8) than in the corresponding 4-phenyl derivatives, as is evident from u.v. (absence of absorption peaks near 235 mμ in the *o*-tolyl derivatives)[5] and ^{1}H n.m.r. spectral differences (in 4-*o*-tolyl derivatives, vinylic or 3-methyl signals are at higher field than those of the corresponding 4-phenyl analogues).[6] This fact, together with evidence that protonated nitrogen retards acid-catalysed elimination–equilibration processes in 4-arylpiperidin-4-ols and tetrahydropyridines,[2] may account for the slow isomerisation rates of the 4-*o*-tolyl derivatives (7) and (8); it is likely that their equilibration proceeds *via* planar carbonium ion intermediates. Both carbonium ion intermediate and tetrahydropyridine will be planar about C-4 and equilibration of (7) and (8) is likely to proceed through a *common* carbonium ion intermediate. The importance of having the aryl group in plane with the original double bond lies in the easier protonation at C-3 or C-5 due to the stabilisation of the incipient carbonium ion by ' empty ' *p*–π overlap.*

Elimination of water from the 4-(2,6-dimethylphenyl)-piperidinol (9) (configuration is probably *trans*-4-Ar/3-Me) by an acetic–hydrochloric acid mixture gave chiefly the corresponding 5-methyl-1,2,5,6-tetrahydropyridine (Table 2, no. 9). Treatment of 2-methylcyclohexanone with *o*-tolyl-lithium gave the tertiary alcohol (10), which appeared to be substantially a single isomer (t.l.c.); its aromatic ^{1}H n.m.r. signal was typical of the α-piperidin-4-ols (2) (details in Experimental section) and it is thus assigned a *trans*-1-Ar/2-Me configuration.† Under mild conditions (dilute hydrochloric acid at 50°) it gave the alkene (11) as main dehydration product; treatment of this material with a mixture of acetic and hydrochloric acids under reflux, or dehydration of the alcohol (10) under more vigorous conditions, gave chiefly the isomeric alkene, 1-methyl-2-*o*-tolylcyclohexene (Table 2, nos. 10—12). The *o*-tolylcycloalkene (11), therefore, isomerizes in acid far more readily than do the ring-nitrogen-containing analogues (7), and this result



further illustrates the retarding influence of charged nitrogen upon the equilibration of cyclic alkenes.

Hydrochlorides of the 5-methyltetrahydropyridines (7) exist in epimeric ($^+$NH) forms in deuteriochloroform as is evident from their ^{1}H n.m.r. spectra. Thus the spectrum of (7a) hydrochloride displays duplicate HN*Me*, Ar*Me*, and 5-Me signals (Figure 2); signals of

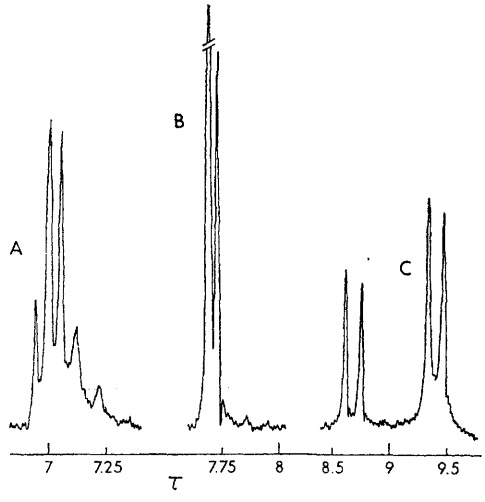
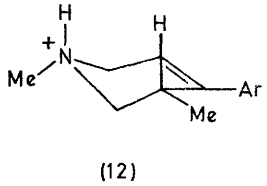


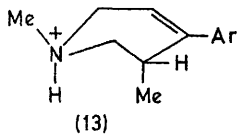
FIGURE 2 Part of ^{1}H n.m.r. spectrum of (7a) hydrochloride in $CDCl_3$ (100 MHz): A, NMe (the three lower-field singlets of this signal collapse to a singlet when D_2O is added; B, ArMe; C, 5-Me (NMe signal exhibits coupling with $^+$NH proton)

greater intensity are attributed to the *cis*-1-Me/3-Me isomer, preferred conformation (12), and less intense signals to the *trans*-isomer of preferred conformation



(12)

Higher field 1-Me and 5-Me
Lower field Ar-Me



(13)

Lower field 1-Me and 5-Me
Higher field Ar-Me

(13).[6] The *cis–trans* ratio is almost 2 : 1 from integrals of the 5-methyl signals. The relative chemical shifts of

* We thank a referee for this amplification.

† The stereochemistry of (10) and related *o*-alkylphenyl-cyclohexanols has previously been discussed on the basis of OH chemical shift data.[7]

[5] A. H. Beckett, A. F. Casy, and M. A. Iorio, *Tetrahedron*, 1966, **22**, 2745.

[6] A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef, *Tetrahedron*, 1965, **21**, 3387.

[7] H. Timmerman, R. F. Rekker, and W. Th. Nauta, *Rec. Trav. chim.*, 1965, **84**, 1348.

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the 1-methyl groups in (12) and (13) are those to be anticipated from screening influences of a methyl substituent upon β-equatorial protons in cyclohexane derivatives (axial methyl has a deshielding influence while equatorial methyl has a negligible effect upon the resonance position of the β-equatorial group).[8]

EXPERIMENTAL

Chromatography was carried out with columns packed with silica gel (0·08 mm.) and on glass plates coated with thin layers (0·3 mm.) of silica gel G (Merck). The ^{1}H n.m.r. spectra were recorded with Varian A60 and HA100 spectrometers.

Diastereoisomeric 3-methyl-4-o-tolylpiperidin-4-ols (2).—These were prepared by the previously described general method[6] from 1,3-dimethyl-, 1-ethyl-3-methyl-, and 1-benzyl-3-methyl-4-piperidone and *o*-tolyl-lithium. The total products gave the pure α-isomers when recrystallized from hydrocarbon solvents. The residues from the mother liquors were distilled and acidified with ethereal hydrogen chloride, and the salts were fractionally crystallized to yield pure β-(2a) and β-(2b). The (2c) residue was chromatographed on silica gel with chloroform as solvent, the β-alcohol being the more readily eluted isomer (see also R_F values of Table 3). New compounds are as follows: α-(2a), m.p. 94—95° [from ether–light petroleum (b.p. 40°)] (Found: C, 76·7; H, 9·5; N, 6·4. $C_{14}H_{21}NO$ requires C, 76·7; H, 9·65; N, 6·4%); β-(2a) *hydrochloride*, m.p. 267—268° (from ethanol–ether) (Found: C, 65·9; H, 8·4; N, 5·35. $C_{14}H_{22}ClNO$ requires C, 65·7; H, 8·7; N, 5·5%); β-(2b) *hydrochloride*, m.p. 257° (from ethanol–ether) (Found: C, 66·65; H, 8·95; N, 5·2. $C_{15}H_{24}ClNO$ requires C, 66·8; H, 9·0; N, 5·2%); β-(2c), m.p. 101° (from cyclohexane) (Found: C, 81·35; H, 8·8; N, 4·7. $C_{20}H_{25}NO$ requires C, 81·3; H, 8·5; N, 4·7%); α-(9) (from 2,6-dimethylphenyl-lithium), m.p. 122—124° [from ether–light petroleum (b.p. 40°)] (Found: C, 77·7; H, 10·1; N, 5·6. $C_{16}H_{25}NO$ requires C, 77·7; H, 10·2; N, 5·7%); α-(2b) and α-(2c) have been previously reported.[6]

TABLE 3

T.l.c. R_F values on silica gel G (Merck) of some piperidinols and tetrahydropyridines

	Solvents [a]				
	I	II	III	IV	V
α-(2b)	0·02	0·00	0·03	0·06	0·11
β-(2b)	0·06	0·00	0·09	0·08	0·18
α-(2c)	0·43	0·15	0·80	0·51	0·60
β-(2c)	0·53	0·37	0·89	0·62	0·68
(7a)	0·13	0·10	0·18	0·11	0·27
(8a)	0·07	0·04	0·08	0·05	0·15
(7b)	0·18	0·28	0·41	0·19	0·35
(8b)	0·12	0·09	0·19	0·09	0·23
(7c)	0·77	1·00	1·00	0·67	0·74
(8c)	0·72	1·00	0·94	0·60	0·70

[a] I chloroform–acetone (2 : 1 v/v), II ether, III ether–acetone (9 : 1 v/v), IV acetone, V acetone–methanol (9 : 1 v/v)

α-1,3-Dimethyl-4-propionyloxy-4-o-tolylpiperidine hydrochloride, m.p. 198° (Found: C, 65·6; H, 8·4; N, 4·3. $C_{17}H_{26}ClNO_2$ requires C, 65·5; H, 8·4; N, 4·5%), was prepared by heating α-(2a) with propionic anhydride and pyridine.[9] The corresponding *β-ester hydrochloride*, m.p. 203° (Found: C, 65·2; H, 8·4; N, 4·5%) was similarly prepared.

Dehydration of the Piperidin-4-ols (2) *and* (9).—The piperidinols were treated with a mixture of acetic and hydrochloric acids, as previously described,[6] and the total products (samples analysed by ^{1}H n.m.r. spectroscopy; Table 2) were chromatographed on silica gel and eluted successively with ether and ether–acetone (9 : 1); chloroform was the eluant in the case of the *N*-benzyl derivatives. Column effluent fractions were checked by t.l.c. in several solvent systems and spots were detected by spraying with Dragendorff's reagent (Table 3). In every case, the tetrahydropyridines (7) were the more readily eluted isomers. The separated bases were converted into hydrochlorides and further purified by crystallization. New *hydrochlorides* were as follows: (7a), m.p. 178—179° (from ethanol–ether) (Found: C, 70·5; H, 8·4; N, 5·8. $C_{14}H_{20}ClN$ requires C, 70·7; H, 8·5; N, 5·9%), τ (base in $CDCl_3$) 4·46 (t, vinylic) and 9·15 (d, 5-Me); (8a), m.p. 198—199° (from ethanol–acetone) (Found: C, 70·6; H, 8·5; N, 5·7%), τ (base in $CDCl_3$) 8·62 (s, 3-Me); (8b), m.p. 218—219° (from ethanol–ether) (Found: C, 71·5; H, 8·7; N, 5·4. $C_{15}H_{22}ClN$ requires C, 71·6; H, 8·8; N, 5·6%), τ (base in $CDCl_3$) 8·63 (s, 3-Me); (8c), m.p. 209—211° (from propan-2-ol–ether) (Found: C, 76·5; H, 7·6; N, 4·3. $C_{20}H_{24}ClN$ requires C, 76·5; H, 7·7; N, 4·5%), τ (base in $CDCl_3$) 8·65 (s, 3-Me); *4-(2,6-dimethylphenyl)-1-ethyl-5-methyl-1,2,5,6-tetrahydropyridine*, m.p. 263—264° (from ethanol) (Found: C, 72·2; H, 9·2; N, 5·2. $C_{16}H_{24}ClN$ requires C, 72·3; H, 9·1; N, 5·3%), τ (base in $CDCl_3$) 4·53 (t, vinylic) and 9·13 (d, 5-Me).

2-Methyl-1-o-tolylcyclohexanol (10), b.p. 80—85°/0·2 mm. n_D^{22} 1·5478 (lit.,[7] b.p. 121—122°/1 mm., n_D^{20} 1·5426), τ ($CDCl_3$) 2·50, 2·83, and 2·87 (main peaks of aromatic m), 7·43 (s, Ar*Me*), 8·33 (s, OH), and 9·3 (d, *J* 6·7 Hz, 2-Me), was prepared from 2-methylcyclohexanone and *o*-tolyl-lithium; t.l.c. single spot (R_F 0·77) on silica gel G with acetone–chloroform (1 : 2) as developing solvent and iodine vapour as detecting agent.

[9/1036 *Received, June 17th*, 1969]

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[9] A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, 1957, **9**, 939.