POLYSUBSTITUTED 4-PIPERIDONES AND 4-PIPERIDOLS: SYNTHESIS AND SPATIAL CONFIGURATION

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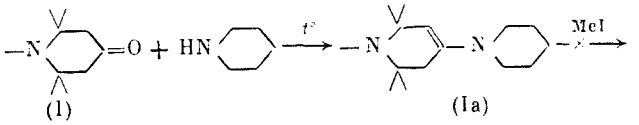
Triacetonamine was used to synthesize a series of highly substituted 4-piperidones and 4-piperidols. The spatial configuration of these compounds was determined. The anionoid addition to the carbonyl group of these piperidones proceeds through highly stereoselective equatorial attack. The position of the chair–chair–twist conformational equilibrium was determined for the polysubstituted 4-piperidols.

The few studies on piperidines [1-3] correlating the effects of steric strain with specific structure of the saturated six-membered rings do not indicate any conclusions concerning the effect of polysubstitution of the ring on the reactivity and conformational behavior of these compounds. Furthermore, piperidines with more than six substituents are completely unknown [4-6]. Thus, we undertook a study involving the synthesis of highly alkylated functional piperidine derivatives starting with 2,2,6,6-tetramethyl-4-piperidone (triacetonamine, TAA), which is a key reagent in the chemistry of polysubstituted piperidones [4], and established the spatial configuration of these compounds.

We used 1,2,2,6,6-pentamethyl-4-piperidone (I), obtained from TAA according to Lutz et al. [7], in order to obtain maximally methyl-substituted 4-piperidones. Attempts to effect the direct exhaustive alkylation of this ketone using methyl iodide in the presence of NaH led to a complex mixture of products with various extents of alkylation. PMR spectroscopy indicated the formation of both C- and O-alkylation products. An attempt to achieve monomethylation of the previously unreported enamine (Ia) of this ketone also proved unsuccessful. Piperedeine (Ia) does not react with MeI at 25°C, while tar formation occurs at 100°C.



(I) (Ia)

Hence, a new approach for 4-piperidones was tested for the stepwise replacement of the hydrogen atoms of the piperidine ring by methyl groups, entailing the reduction or reductive alkylation of the C=C bonds of conjugated enones [8]. In this case, each C=C bond in enones (IIa) and (IIb) [9] is a precursor for either a methyl or gem-dimethyl group. This permits the stepwise introduction of methyl groups at C^3 and C^5 of the starting TAA derivative. Enone (IIb) was obtained using successive Mannich reactions, methylation of the base formed, and Hofmann decomposition without the isolation of the intermediates.

The reduction of the C=C bond of enone (IIa) by lithium in liquid ammonia leads to hexamethylpiperidone (III), while alkylation of the intermediate enolate with MeI leads to asymmetrical heptamethylpiperidone (IV) along with a small amount of ketone (III). The analogous reduction of both C=C bonds of dienone (II) gives a virtually pure 1:1 mixture of the cis and trans isomers of symmetrical heptamethylpiperidone (Va) and (Vb). The stereoisomers were separated by chromatography on silica gel but the yield drops significantly due to decomposition on the adsorbent, which takes place upon the purification of all the piperidones obtained from TAA. Alkylation of the intermediate enolate from dienone (II) leads to a mixture of the C-methylation product – enone (VI), O-methylation product – vinyl ether (VII), and products of the reductive side reaction, namely, stereoisomers (Va) and (Vb). The only product upon the reduction of enone (VI) is octamethylpiperidone (VIII). Complete-

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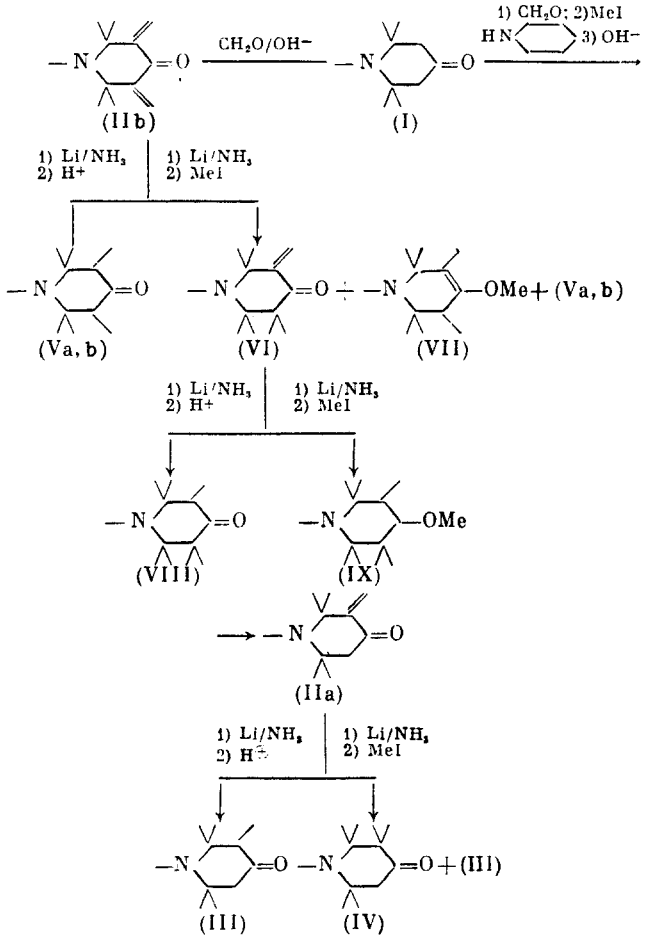
TABLE 1. TAA Derivatives (Ia)-(XX)

Compound	Yield, %	Mp, °C Bp, °C (p, mm Hg)	Found, %			Chemical formula	Calculated, %		
			C	H	N		C	H	N
(Ia)	92	113–115(2)	76,2	11,9	12,0	$C_{15}H_{28}N_2$	76,3	11,9	11,9
(IIa)	35	74–78(0.5)	72,7	10.6	7,7	$C_{11}H_{19}NO$	72,9	10,5	7,7
(III)	65	Oil	72,6	11,8	7.6	$C_{11}H_{21}NO$	73,0	11,6	7,7
(IV)	30	»	73,3	11,6	6,8	$C_{12}H_{23}NO$	73,1	11,7	7,1
(Va)	50	»	73,2	11,6	7,2	$C_{12}H_{23}NO$	73,1	11,7	7,1
(Vb)	50	»	73,3	11,3	7,2	$C_{12}H_{23}NO$	73,1	11,7	7,1
(VI)	36	35–36	74,5	11,2	6,5	$C_{13}H_{23}NO$	74,6	11,1	6,7
(VII)	33	Oil	74,2	11,0	6,9	$C_{13}H_{23}NO$	74,6	11,1	6,7
(VIII)	75	»	–	–	–	$C_{13}H_{25}NO$	–	–	–
(IX)	93	»	74,3	11,8	6,0	$C_{14}H_{27}NO$	74,7	12,0	6,2
(X)	96	87–88	71,6	12,6	7,9	$C_{11}H_{23}NO$	71,4	12,4	7,6
(XI)	95	Oil	72,0	12,8	7,3	$C_{12}H_{25}NO$	72,4	12,6	7,0
(XII)	92	»	72,3	12,9	7,1	$C_{12}H_{25}NO$	72,4	12,6	7,0
(XIII)	97	»	72,2	12,8	6,8	$C_{12}H_{25}NO$	72,4	12,6	7,0
(XIV)	80	32	72,9	12,9	6,3	$C_{13}H_{27}NO$	73,2	12,7	6,6
(XV)	92	50(subl.)	71,3	12,2	7,4	$C_{11}H_{23}NO$	71,4	12,4	7,6
(XVI)	72	63–64	71,9	12,9	7,4	$C_{12}H_{25}NO$	72,4	12,6	7,0
(XVII)	65	Oil	72,9	13,0	6,3	$C_{13}H_{27}NO$	73,2	12,7	6,6
(XVIII)	60	»	73,1	12,8	6,4	$C_{13}H_{27}NO$	73,2	12,7	6,6
(XIX)	56	43–45	74,3	12,6	6,3	$C_{14}H_{29}NO$	74,0	12,8	6,2
(XX)	100	43–45	72,0	12,3	5,4	$C_{17}H_{34}N_2O$	72,3	12,1	5,0



ly methylated-4-piperidone could not be obtained since the reduction alkylation of enone (VI) converts this compound exclusively to O-alkylation product (IX) (Tables 1-3).

Thus, an increase in steric strain in the vicinity of the carbonyl group complicates synthesis of the ketones. In the series of enone (IIa), dienone (IIb), and enone (VI), we observe a transition from the formation of only the C-alkylation product (ketone) to formation of a mixture of products of C- and O-alkylation and then to formation of only the O-alkylation product (vinyl ether).

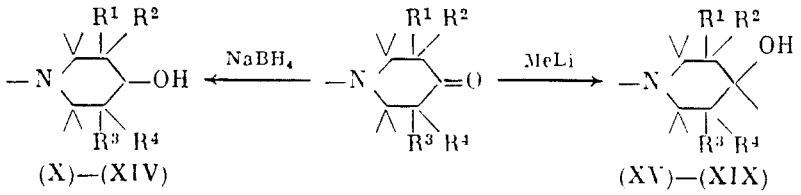
TABLE 2. IR, Mass, and PMR Spectral Indices for TAA Derivatives (IIa)-(XX)

Compound	IR spectrum, ν, cm⁻¹		M⁺, m/z	PMR spectrum δ, ppm (J, Hz)*				Other groups
	C=C	C=O		1-Me	3-, 5-, and 4-Me	H³, H⁵	H⁴	
(Ia)	–	–		2,32	0,99, 0,99, 1,00, 1,00	1,86, 4,25	–	$(CH_2)_3$: 1,45–1,60 m NCH_2: 2,65
(IIa)	1620	1690		2,37	1,09, 1,09, 1,13, 1,13	2,44	–	$C=CH_2$: 5,34 d (0,7), 5,85 d (0,7)
(III)	–	1715	183	2,28	0,81, 0,96, 0,98 d (7,0), 1,17, 1,18	2,4–2,5 *	–	–
(IV)	–	1710	197	2,26	0,93, 0,93, 1,05, 1,05, 1,08, 1,08	2,42	–	–
(Va)	–	1720	197	2,22	0,95, 0,95, 1,00 d (7,0), 1,05, 1,05	2,34 q (7,0)	–	–
(Vb)	–	1720	197	2,31	0,69, 0,69, 0,79 d (6,8), 1,26, 1,26	2,50 q (6,8)	–	–
(VI)	1600	1690	209	2,35	0,99, 0,99, 1,05, 1,05, 1,28, 1,28	–	–	$C=CH_2$: 5,23 d (1,2), 6,01 d (1,2)
(VII)	1615 1690		209	2,32	1,12, 1,12, 1,17, 1,17, 1,75	–	–	OMe: 3,46, $C=CH_2$: 4,75, 5,02
(VIII)		–	211	2,23	0,68, 0,74, 0,88 d (7,0), 0,90, 1,07, 1,20, 1,25	2,82 q (7,0)	–	–
(IX)	1670	–	225	2,25	0,90, 0,90, 0,95, 0,95, 1,05, 1,05, 1,60	–	–	OMe: 3,56
(X)	–	–	185	2,16	0,90 d (6,7), 0,98, 1,03, 1,03, 1,11	1,6 *	4,10 d.t (10,5; 4,0)	–
(XI)	–	–	199	2,13	0,81, 0,86, 0,87, 0,94, 1,10, 1,21	1,4 *	3,6 d.d (11,8; 4,9)	
(XII)			199	2,22	0,83, 0,93 d (6,9), 0,94 d (7,0), 1,04, 1,12, 1,22	1,6 *	3,76 d.d (11,0; 4,4)	–
(XIII)			199	2,32	1,02 d (7,0), 1,04, 1,04, 1,10, 1,10	1,53 q.d (7,0; 3,0)	3,51 t (3,0)	
(XIV)			213	2,21	0,97, 0,98, 1,00, 1,00, 1,02 d (7,0), 1,09, 1,12	1,86 q.d (7,0; 3,3)	3,32 d (3,3)	–
(XV)	–	–		2,22	1,03, 1,03, 1,08, 1,18, 1,18	1,45 d (12,2), 1,59 d (12,2)	–	–
(XVI)	–	–		2,27	0,96 d (7,0), 1,07, 1,11, 1,12, 1,17, 1,19	1,52 d (7,0) 1,6 *	–	–
(XVII)			213	2,26	0,94, 0,96, 1,02, 1,09, 1,12, 1,17, 1,21	1,40 d (14,0), 1,86 d (14,0)	–	–
(XVIII)	–	–	213	2,25	0,81 d (7,5), 0,88 d (7,2), 0,93, 0,93, 1,00, 1,07, 1,13	1,61 q (7,2) 1,75 q (7,5)	–	–
(XIX)	–	–	227	2,24	0,86, 0,89 d (7,0), 0,91, 0,97, 0,98, 1,01, 1,09, 1,11	1,75 q (7,0)	–	–
(XX)	–	–		2,30	0,70, 0,75, 0,93, 1,10, 1,25, 1,32	2,18 m	–	NCH_2: 2,85 m *t*-Bu: 1,05

*Signal overlapping.

Borohydride reduction and organometallic synthesis were employed in order to obtain polysubstituted 4-piperidones. The stereochemistry of this reaction was studied thoroughly by Mistryukov [10].

Ketones (III)-(Va), (Vb), and (VIII) were reduced by $NaBH_4$ to secondary alcohols (X)-(XIV), while treatment of these ketones (except for (Vb)) and (I) with MeLi gave the corresponding tertiary alcohols (XV)-(XIX).

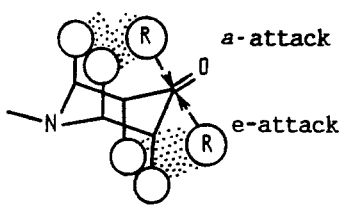


(X)—(XIV) (XV)—(XIX)

	(XV)	(X), (XVI)	(XI), (XVII)	(XII), (XVIII)	(XIII)	(XIV), (XIX)
R^1	H	H	H	H	H	H
R^2	H	H	H	Me	Me	Me
R^3	H	H	Me	H	Me	Me
R^4	H	Me	Me	Me	H	Me

PMR spectroscopy showed that products (X)-(XIX) are formed virtually as a single isomer. The stereospecific or, at least, highly stereoselective conversion of ketones (III), (Vb), and (VIII), which, in principle, are capable of giving epimeric alcohols, is an interesting property of the 1,2,2,6,6-pentasubstituted piperidone system. Previously studied reactions at the carbonyl group of various 4-piperidones, including derivatives with diaxial substitution at C^2 and C^6 [10], were not highly stereoselective.

Of the reported features of the steric control in the reactions at the carbonyl group of 4-piperidones [10], we note the special role of axial substitution at any ring position. An axial substituent at C^2 or C^6 in the ring hinders axial attack (i.e., formation of the e-alcohol) in the borohydride reduction and organolithium synthesis, while an axial substituent at C^3 or C^5 hinders equatorial attack (i.e., formation of the *a*-alcohol). However,



the operation of these effects do not extend to substrates with axial substituents at both the α and β piperidone ring positions. Thus, these results may be divided into results for systems for which these rules are valid (Group I), and results for systems, for which the existing steric control rules are not suitable (Group II). The reactions of ketones (III) and (Vb) fall into the Group I, while the reactions of (IV), (Va), and (VIII), whose configurations will be discussed below, fall into Group II.

The finding of a cis configuration of piperidols (X), (XIII), (XIV), (XVII), and (XVIII), on one hand, and the assumption of a predominance of the chair conformation with least number of syn–axial methyl–methyl interactions for the starting piperidones for the starting piperidones, on the other, permits us to consider that there is stereospecific

TABLE 3. ^{13}C NMR Spectral Data for Piperidones (I), (Va), and (Vb) and Piperidols (XII) and (XIII) (δ, ppm)

Compound	1-Me	2-, 3-, 5- and 6-Me	C^2		C^6		C^3		C^5		C^4
			calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.	
(I)	28,27	26,91, 26,91, 26,91, 26,91	55,05	58.43	55,05	58.43	54.76	55,37	54.76	55,37	209,40
(Va)	29,09	11,92, 11.92, 13,07, 13.07, 22,41, 22,41	57.42	60,93	57,42	60,93	54,04	52,58	54,04	52,58	215.72
(Vb)	29.37	9,79, 9,79, 15,94, 15.94, 30,64, 30,64	63,13	63.91	63,13	63,91	58.50	54,58	58,50	54,58	212,71
(XII)	28,57 *	8,01, 13,33, 15,95, 18,23, 21,26. 29,52 *	–	58,11	–	58,11	–	41,54 *	–	44,97 *	71,02
(XIII)	30,16	14,45, 17.08, 17.08, 14.45, 29,55, 29,55	–	58,30	–	58,30	–	44,34	–	44,34	75,94

*Tentative assignment.

TABLE 4. IR Spectra and Conformation of Piperidols (X)-(XIX)

Compound	IR spectrum ν, cm^{-1}		C/T conformer ratio, %	Substitutent orientation	
	free OH	H-bonded OH		β-Me	OH
(X)	3624	3396	65/35	3*a*	*e*
(XI)	3636	3380	89/11	3*e*3*a*	*e*
(XII)	3640	3380	82/18	3*e*5*a*	*e*
(XIII)	3640	–	100/0	3*e*5*e*	*a*
(XIV)	3644	3344	76/24	3*e*3*a*5*e*	*a*
(XV)	3612	3416	74/26	–	*a*
(XVI)	3620	3416	49/51	3*e*	*a*
(XVII)	3624	3396	34/66	3*e*3*a*	*a*
(XVIII)	3620	3402	10/90	3*e*5*a*	*a*
(XIX)	3632	3332	60/40	3*e*3*a*5*e*	*a*

equatorial attack of the reagent at the carbonyl group (with initial formation of the axial alcohol) in these anionoid additions to piperidones (III), (Vb), and (VIII). Since the set of substituents with various orientations at C^3 and C^5 of these piperidones is rather broad (from one e-substituent in the case of piperidone (III) to one *a*- and two e-substituents in the case of piperidone (VIII)), the hypothesis of stereospecific equatorial attack and initial formation of the *a*-alcohol may be extended to piperidones (IV) and (Va).

The stereochemical results of the $NaBH_4$ reduction and MeLi treatment for Group I ketones conformed to our predictions. The orientation rule for Group II ketones establishes the same stereochemical result. The effect of the methyl groups at C^2 and C^6 completely predominates in the steric control of the attack on the carbonyl group of 4-piperidones when there are both axial positions at the α and β positions.

Such "nonadditivity" of the opposite orientation rules (effect of only one rule) suggests that the geometrical parameters of the polysubstituted system are somewhat altered as a result of the steric interaction of the substituents and one of the controlling factors disappears. Apparently, the interaction of the 1,2,2,6,6-pentamethyl system with a 3-axial (or 5-axial) substituent causes flexure of the ring fragment from the carbonyl group toward the 2,6-diaxial region. In this case, the hindrance to equatorial attack due to axial substitution in the β position decreases and the role of shielding of the carbonyl group by the α-axial substituents upon axial attack is enhanced. This accounts for the transition from the previously reported stereoselectivity to the stereospecificity observed for TAA piperidones observed in the present work.

Enones (Va), (Vb), and (VI) are also capable of undergoing reduction by $NaBH_4$ to saturated alcohols. Dienone (IIb) gives a mixture of piperidols (XII) and (XIII) [9], while enones (IIb) and (VI) give almost quantitative formation of alcohols (X) and (XIV), respectively. The high stereoselectivity of these reactions relative to the carbonyl group is a

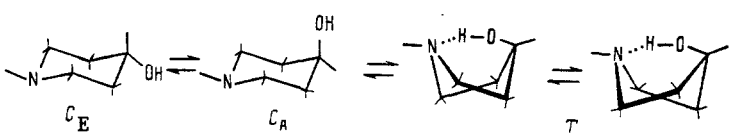
function of the stereoselectivity for the reduction of these saturated ketones because the C=C bond is initially reduced upon the complete reduction of the double bonds in these enols.

The direct determination of the geometrical configuration of piperidones (Va) and (Vb) appears very difficult and their configuration was determined by correlation with the configuration of the 3,5-substituents of corresponding piperidols (XII) and (XIII). The alcohol formed upon the reduction of cis-3,5-disubstituted piperidone taking account of time-averaging of the individual conformations, belongs to the C_s point group, while the alcohol formed from the trans-ketone belongs to the C_1 point group. Thus, the finding of half the number of signals for ring carbon atoms C^2, C^3, C^5, and C^6 and of the signals of the attached groups in the ^{13}C NMR spectrum of (XIII) in comparison with the number of signals for these atoms in the spectrum of (XII) permits us to assign a cis configuration for ketone (Vb) and trans configuration for ketone (Va) and, correspondingly, 3,5-cis configuration for alcohol (XIII) and 3,5-trans configuration for alcohols (XII) and (XVIII).

In this regard, we should indicate the erroneousness of the initial assignment of the isomers of previously obtained 3,5-disubstituted TAA derivatives to the cis and trans series [9,11,12] based on an incremental scheme for calculating the chemical shifts of the ring ^{13}C nuclei in piperidines [11]. Such a scheme, developed specially for 4-piperidones [13] upon the correlation of ^{13}C NMR spectral data for piperidones (Va), (Vb), and (I), proves useful for assigning the ring ^{13}C nuclei in these compounds. However, deviation of the calculated chemical shifts from the experimental values, which may reach 3-3.5 ppm, does not permit us to make a reliable selection between cis and trans structures for (V) using the ^{13}C NMR spectral data. Thus, the proposed criterion for assignment of the cis and trans isomers of 3,5-dialkyl derivatives of TAA using PMR spectroscopy [11] should be replaced by the opposite criterion as well and the proposed steric configuration of the corresponding rings [9,11,12] should also be reversed.

A cis configuration of the hydroxyl group and adjacent methyl group in secondary piperidines (X), (XIII), and (XIV) was established using the vicinal coupling constants in the PMR spectra of the chairlike six-membered rings (the contribution of nonchairlike conformations to the coupling constants may be neglected for these compounds as discussed below). The vicinal coupling constants of H^3 (H^5) and H^4, which do not exceed 4.5 Hz ((Table 2), indicate *a*,e-orientation of these protons and, thus, a cis configuration of the hydroxyl and methyl groups in these positions. In the case of piperidol (X), this conclusion is also based on the nature of the decoupling of the signal for H^4. The observed doublet of triplets of this proton may be obtained only in the case of equatorial orientation of the hydroxyl group and axial orientation of the 3-methyl group and thus indicates not only cis arrangement of these substituents in piperidol (X) but also predominance of a chairlike conformation (of the two possible conformations). Analogously, predominance was determined for configurations with an equatorial OH group for piperidols (XII) and (XIII) and axial OH group for piperidol (XIV).

Both a narrow free hydroxyl group band and broad band for an OH group in an intramolecular hydrogen bond are found in the IR spectra for most of these piperidols in dilute CCl_4 solutions. This indicates participation of chairlike and twist forms in equilibrium [14], where the C_E chair conformation (with an equatorial OH) group is favored for secondary piperidones (X)-(XII), while the C_A chair (with an axial OH group) is favored for secondary piperidols (XIII) and (XIV) and tertiary piperidols (XV)-(XIX). Such a selection of the orientation of the hydroxyl group for various piperidols is based on an approximate evaluation of the energy difference between the structures with axial and equatorial positions of the more bulky 4-substituent in each of these alcohols. This difference in piperidols derived from TAA is extremely large due to three syn-axial interactions involving this substituent and the methyl groups at C^2 and C^6 of the ring.



The fractions of conformers C_E and T for piperidols (X)-(XII) and the fractions of conformers C_A and T for piperidols (XIII)-(XIX) were determined by calculating the peak intensities [15] of the free OH group band in the IR spectra of these piperidols (Table 3). We assumed that the peak molar extinction coefficients of the chairlike conformers C_E and C_A

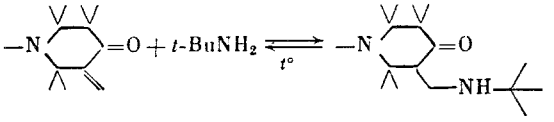
of all the piperidols examined were equal and that the same coefficients of the T conformers of these piperidols are also equal. The peak molar extinction coefficient for C conformers (ε 46) was obtained from the spectrum of 1,2,2,6,6-pentamethyl-4-piperidol, which exists virtually only in the C conformation.

The spatial configuration of piperidols (XIV) and (XIX) was established by comparing common stereochemical behavior in saturated six-membered rings with the IR spectral data. In the $C_A \rightleftarrows T$ equilibrium, the fraction of the T form for piperidol (XVIII) should be comparable with that for piperidol (XVI) with trans configuration of the hydroxyl and methyl groups (both trans-piperidol (XVI) and piperidol (XVIII) have an axial 3-methyl group in conformation C_A). However, the fraction of the T form should be much greater for piperidol (XVIII) than for piperidol (XVI) with cis configuration of these groups (with an equatorial 3-methyl group in conformer C_A). This hypothesis is based on the assumption that an axial substituent destabilizes the chair conformation, while a pseudoaxial substituent destabilizes the twist conformation in piperidol derivatives of TAA (due to 1,3-diaxial or 1,4-dipseudoaxial methyl–methyl interactions). In the case of trans configuration of piperidol (XVI), it has one 3-axial substituent in the C_A conformer similar to piperidol (XVIII) and both piperidols may exist in a conformation of the T family without 3-pseudoaxial substituents. In another case, piperidol (XVIII), in contrast to piperidol (XVI) with cis configuration, has a 3-axial substituent in the C_A conformer, and, analogously to the former case, both piperidols may exist in a twist conformation without pseudoaxial substituents at C^3. The IR spectra of these compounds correspond to the latter case: the fraction of the twist form for piperidol (XVIII) is much greater than the fraction of this form for piperidol (XVI) (Table 4).

By analogy to the above, the cis and trans configuration of the 4-hydroxy and 5-methyl groups of piperidol (XIX) should give different ratios of the C_A and T forms. In the case of the cis configuration, the fraction of form C_A in piperidol (XIX) should be significantly less than the fraction of this form in piperidol (XVII). Realization of the former case as indicated by IR spectroscopy (Table 4) implies cis configuration of the hydroxyl and adjacent methyl groups in piperidol (XIX).

Establishment of the position of the chair–twist conformational equilibrium in a series of monotypic polysubstituted 4-piperidols permits us to make certain conclusions concerning the effect of the extent and nature of the substitution on this equilibrium. On the whole, the twist conformation for piperidol derivatives of TAA makes a larger contribution to the equilibrium than in less substituted analogs. Axial substitution of the chair conformation in secondary and tertiary polysubstituted piperidols leads to an increase in the fraction of the twist form if this substitution does not give rise to 1,4-dipseudoaxial orientation of the methyl substituents (i.e., the substituents at C^3 and C^6 of the piperidol ring) in all the conformers of the corresponding twist family. The appearance of such an orientation, which does not disappear upon twist–twist transitions within the twist family (as in piperidol derivatives of TAA with 3,3-gem-dimethyl substitution) again reduces the content of the twist form to a value close to its content in secondary and tertiary 4-piperidols without axial β-substituents.

Product (VI) is a useful model for examining the specific reactivity of polysubstituted methylenepiperidones [9,12,16] related to opening of the piperidine ring. This enone adds tert-butylamine, which is a "ring-opening reagent" [9], without opening of the piperidone ring. Gas-liquid chromatography indicated that the reverse reaction occurs upon heating rather than ring opening in the piperidone formed (XX).



(VI) (XX)

This supports our hypothesis [16] concerning the predominant role of the ring conformation in determining the direction of such Michael–retro-Michael reactions. Going from a chair-like form in (XX) to the strained compressed form in (VI) stabilizes the highly substituted ring (addition without subsequent ring opening). Retention of the compressed form of the six-membered saturated ring reduces the stability of this ring. Thus, we find opening of the ring in (IIb) after the addition of nucleophiles [9,12,16] even though this ring is less substituted than the ring in (VI).

EXPERIMENTAL

The NMR spectra were taken on a Bruker WP-200 spectrometer in CCl_4 or $CDCl_3$. The IR spectra were taken neat on a UR-10 spectrometer. The UV spectra were taken on a Specord UV-VIS spectrometer in heptane. The mass spectra were obtained on a VG-7070E spectrometer at 70 eV. The temperature of the ionization chamber was 50-100°C. Column chromatography was carried out on silica gel (50-100 μm) with a UV detector at λ 260 nm.

1,2,2,6,6-Pentamethyl-4-piperidino-3-piperideine (Ia). A sample of 20 mmoles hydrochloride (I) in 10 ml piperidine was heated at reflux for 15 min. Then, 10 ml hexane was added to the cooled solution. The mixture was filtered and evaporated. Distillation of the residue gave (Ia).

1,2,2,6,6-Pentamethyl-3-methylene-4-piperidone (IIa). A mixture of 50 mmoles piperidone (I), 35 ml water, 5.5 ml 38% formaldehyde and 50 mmoles piperidine was stirred for 8 h at 25°C and then extracted with three 50-ml chloroform portions. The combined extract was dried over K_2CO_3 and evaporated. A sample of 50 ml benzene and 20 ml MeI were added to the residue and maintained for 12 h. The mixture was decanted and the solid was dissolved in 80 ml 1 N KOH. After 6 h, this solution was extracted with two 60-ml hexane portions and dried over K_2CO_3. Evaporation and distillation of the residue gave 18 mmoles enone (IIa). UV spectrum (λ_{max}, nm (ε)): 223 (8700).

1,2,2,3,6,6-Hexamethyl-4-piperidone (III). A solution of 5 mmoles enone (IIa) and 10 mmoles t-BuOH in 25 ml ether was added over 15 min to a solution of 25 mmoles lithium in 150 ml liquid ammonium (previously distilled over sodium) at -50°C. After 10 min, ammonium chloride was added in small portions until the solution was decolored. The dry ice condenser was replaced with a water condenser and ammonia was distilled off. Then, 50 ml ether and 50 ml water were added. The organic layer was separated and dried over K_2CO_3. Chromatography with placement in hexane and elution by the same solvent gave 1.7 mmoles (III).

1,2,2,3,3,6,6-Heptamethyl-4-piperidone (IV). A solution of 5 mmoles enone (IIa) and 5 mmoles t-BuOH in 25 ml ether was added to a solution of 25 mmoles lithium in 150 ml liquid ammonia at -50°C. Then, a solution of 15 mmoles MeI in 25 ml ether was added over 3 min. The reaction mixture was treated by analogy to the above procedure. Elution by hexane gave 7.5 mmoles (25%) (IV) and 7.5 mmoles (25%) (III).

Trans- (Va) and cis-1,2,2,3,5,6,6-Heptamethyl-4-piperidone (Vb). An equimolar mixture of trans (Va) and cis isomers (Vb) was obtained, by analogy to the procedure for the preparation of ketone (III) from 30 mmoles lithium, 5 mmoles dienone (IIb), and 20 mmoles t-BuOH, in quantitative yield prior to the chromatography stage. After chromatography, with sequential elution with hexane and a 10:1 mixture of hexane–ether, the cis isomer (Vb) was obtained from the first fraction of the eluate and the trans isomer from the second fraction. The yields of each were 25-30%.

1,2,2,5,5,6,6-Heptamethyl-3-methylene-4-piperidone (VI) and 1,2,2,3,6,6-Hexamethyl-4-methoxy-5-methylene-3-piperidene(VII). By analogy to the procedure for preparation of ketone (IV) from 30 mmoles lithium, 5 mmoles dienone (IIb), 10 mmoles t-BuOH, and 50 mmoles MeI, chromatography with pentane elution gave two fractions. Chromatography of the first fraction on neutral alumina with placement in hexane and elution with 3:1 hexane–ether gave 1.7 mmoles vinyl ether (VII). Chromatography of the second fraction on silica gel was carried out with elution first by hexane and then 10:1 hexane–ether. The hexane eluate gave, in order of elution, enone (VI) in 36% yield and a 1:10 mixture of ketone (Vb) and vinyl ether (VII) in 25% overall yield. The mixed eluate gave (Va) in 6% yield. UV spectrum of enone (VI) (λ_{max}, nm (ε)): 225 (6200).

1,2,2,3,3,5,6,6-Octamethyl-4-piperidone (VIII). By analogy to the procedure for the preparation of ketone (III) excluding the chromatography, 30 mmoles lithium, 5 mmoles enone (VI), and 10 mmoles t-BuOH gave 3.8 mmoles (VIII).

1,2,2,3,5,5,6,6-Octamethyl-4-methoxy-3-piperidine (IX). By analogy to the procedure for the preparation of ketone (IV), 30 mmoles lithium, 5 mmoles enone (VI), 5 mmoles t-BuOH, and 50 mmoles MeI gave 4.4 mmoles (IX) after chromatography with pentane eluent and chromatography on neutral alumina with elution by 3:1 hexane–ether.

r-1,2,2,c-3,6,6-Heptamethyl-c-4-Piperidol (X), 1,2,2,3,3,6,6-Heptamethyl-4-piperidol (XI), r-1,2,2,c-3,t-5,6,6-Heptamethyl-4-piperidol (XIII), r-1,2,2,c-3,c-5,6,6-Heptamethyl-c-4-piperidol (XII), and r-1,2,2,3,3,c-5,6,6-Octamethyl-c-4-piperidol (XIV) (general method). A solution of 2 mmoles $NaBH_4$ in 5 ml 1:1 ethanol–water was added over 5 min to a solution of 0.5 mmole piperidone (III)-(Va), (Vb), or (VIII) in 5 ml 1:1 ethanol–water at 0-5°C. After 12 h, dilute acetic acid was added with cooling. Ethanol was distilled off and aq. KOH was

added to pH 10. The mixture was extracted with three 20-ml chloroform portions. The extracts were dried over K_2CO_3, concentrated, and subjected to chromatography with elution by chloroform and then 5:1 chloroform—ethanol. Piperidols (X)-(XIV) were obtained from fractions of the latter eluent.

A solution of 2-4 mmoles $NaBH_4$ in 5 ml 1:1 ethanol—water was added to a solution of 1 mmole (IIa) or (VI) in 5 ml 1:1 ethanol—water. Treatment by analogy to the above gave piperidols (X) and (XIX), respectively.

1,2,2,4,6,6-Hexamethyl-4-piperidol (XV), r-1,2,2,c-3,c-4,6,6-Heptamethyl-4-piperidol (XVI), 1,2,2,3,3,4,6,6-Octamethyl-4-piperidol (XVII), r-1,2,2,c-3,c-4,t-5,6,6-Octamethyl-4-piperidol (XVIII), and r-1,2,2,3,3,c-4,c-5,6,6-Nonamethyl-4-piperidol (XIX). A sample of 5 ml ethereal MeLi obtained from 5 mmoles lithium and 5.2 mmoles MeI was added over 2-3 min to a solution of 0.5 mmole piperidones (I), (III)-(Va) or (VIII) in 5 ml ether at 20°C. After 4 h, 10 ml water and then 2 ml acetic acid were added. The aqueous layer was separated. Aqueous KOH was added to pH 10 and the mixture was extracted with three 15-ml chloroform portions. Chromatographic purification by analogy to the above procedure gave piperidols (XV)-(XIX), respectively.

1,2,2,3,3,6,6-Heptamethyl-5-tert-butylaminomethyl-4-piperidone (XX). A solution of 5 mmoles enone (VI) and 6 mmoles t-$BuNH_2$ in 3 ml ethanol was maintained at 25°C for seven days. Evaporation at 30°C gave (XX).

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