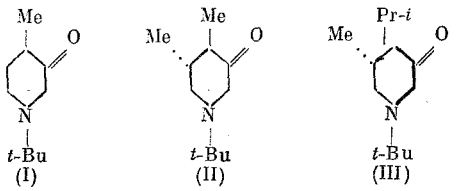
7. W. A. Smit, N. S. Zefirov, and I. Bodrikov, in: Organic Sulfur Chemistry, R. Kh. Freidlina and A. E. Skorova (eds.), Pergamon Press, Oxford–New York (1981), p. 159.
8. I. V. Bodrikov, A. V. Borisov, L. V. Chumakov, N. S. Zefirov, and W. A. Smit, Tetrahedron Lett., 115 (1980).
9. Syntheses of Organic Preparations [Russian translation], Coll. 4, Inostr. Lit., Moscow (1953), p. 540.
10. Syntheses of Organic Preparations [Russian translation], Coll. 5, Inostr. Lit., Moscow (1954), p. 51.
11. Weygand and Hilgetag, Preparative Organic Chemistry, Wiley (1972).
12. H. C. Brown, C. G. Scouten, and R. Liotta, J. Am. Chem. Soc., 101, 96 (1979).
13. J. E. Baldwin and J. A. Kapecki, J. Am. Chem. Soc., 92, 4874 (1970).

INFLUENCE OF AN EQUATORIAL SUBSTITUENT AT C^4 IN 3-KETOPIPERIDINES ON THE STEREOCHEMISTRY OF THE REDUCTION OF THE KETO FUNCTIONAL GROUP

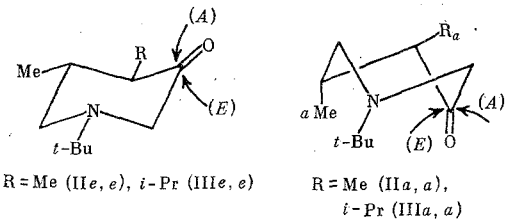
G. T. Katvalyan and É. A. Mistryukov

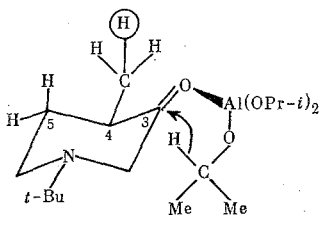
UDC 541.63:542.941.7:547.824

In the investigation of the stereochemistry of the reduction of 3-ketopiperidines it has been shown that the main reaction product is generally the equatorial alcohol, which appears as a result of the attack of the carbonyl function from the axial region [1, 2]. In the case of the appearance of a methyl group on the C^4 atom adjacent to the carbonyl, as in (I), the axial attack of some reagents is hindered, and the axial alcohol may be the predominant reaction product {for example, (I) with $(i\text{-PrO})_3Al$ affords 72% axial alcohol [3]}. However, in view of the conformational lability of ketone (I), it did not seem possible to demarcate the stereochemical details of the reagent and the substrate. In this context, in the present work we studied the reduction of the disubstituted ketones 1-tert-butyl-trans-4,5-dimethyl- (II) and 4-isopropyl-5-methyl-3-piperidone (III), which have equatorial substituents at C^4 and C^5.



Scheme 1





(I) · $Al(OPr\text{-}i)_3$

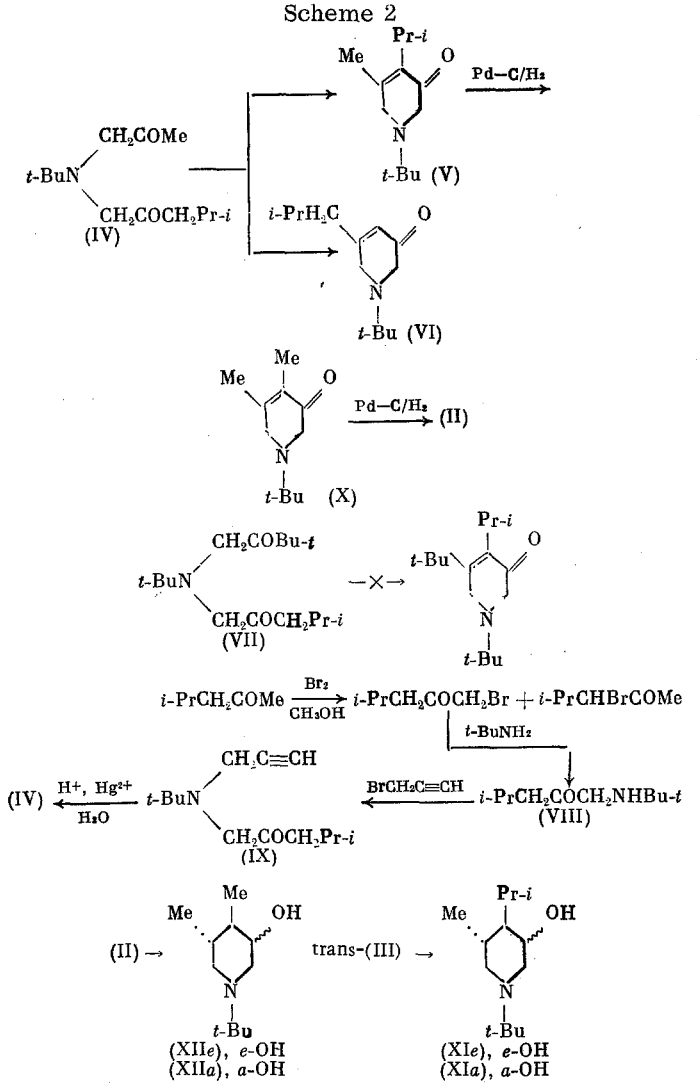
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2352-2356, October, 1983. Original article submitted November 24, 1982.

0568-5230/83/3210-2119$07.50

Owing to such diequatorial substitution, we may expect greater stabilization of the chair configuration of the original ketone in comparison to (I) and, in addition, stabilization of the chair configurations of the transition states and the final reduction products. In fact, the alternative trans-diaxial conformation [(IIa, a) or (IIIa,a)] has a strongly hindered E coordinate reaction due to the syn-axial substituent on C^5 (Scheme 1). In the (IIa,a) and (IIIa,a) conformation there are also additional steric hindrances to the attack of the reagent along the A coordinate on the side of the substituent on C^4, which has a similar direction. Therefore, it may be assumed that the principal reacting conformation is the diequatorial conformation [(IIe, e) or (IIIe, e)], which results in the formation of epimeric alcohols upon the attack of the carbonyl by a reagent along the A or E coordinate.

The synthesis of piperidones II and III was carried out as indicated in Scheme 2. The cyclization of azadiketone IV is of special interest in this scheme. It was previously shown in other azadiketones of type IV that cyclization with the participation of the acetonyl carbonyl as the electrophile [i.e., (IV) → (V)] is the exclusive reaction path, regardless of the cyclization conditions [4]. In the case of diketone (IV), the accumulation of the steric hindrances on the C^7 atom adjacent to the methylene group results in an appreciable loss of regioselectivity in the cyclization and the formation of appreciable amounts (10%) of isomeric ketone (VI). The further accumulation of methyl substituents significantly hampers the reaction, and under standard conditions ketone (VII) is resistant to cyclization. Compound (III) was obtained from unsaturated ketone (V) by hydrogenation over Pd/C. The presence of an appreciable steric interaction between the adjacent isopropyl and methyl substituents in (III) follows from the fairly high content of cis-(III) in the equilibrium mixture of epimeric ketones (35% cis and 65% trans at equilibrium in 2:1 t-$BuNH_2-H_2O$ at 50°C). A kinetic mixture of 41% cis-(III) and 59% trans-(III) forms directly upon the hydrogenation of (V). When the hydrochlorides of the mixture of

Scheme 2



isomers is crystallized, only the more stable (thermodynamically) hydrochloride of trans-(III) is recovered in the crystalline phase (the equilibrium is shifted). Ketone (II) was synthesized in a similar manner (from the dehydro analog (X) [4]). In this case, the mixture contains 21% cis- and 79% trans-(II) after hydrogenation.* The equilibrium mixture (2:1 t-$BuNH_2-H_2O$ at 50°C) contains 13% and 87%, respectively. The acid equilibrium (absolute ethyl acetate–dry HCl) corresponds to 8% cis- and 92% trans-(II).

From these equilibrium data there follows a somewhat larger value for the energy of vicinal repulsion of the e,e-isopropyl and methyl substituents in comparison to the analogous interaction of two methyl groups. In addition, from these data it follows that the value for the vicinal repulsion of the two alkyl substituents on C^4 and C^5 in piperidine is comparable to the analogous interaction of the substituents in the cyclohexane series [5], and the two e,e-methyls may, therefore, be considered sufficiently reliable stabilizers of the chair conformation of trans-ketone (II). The same applies to trans-ketone (III).

The results of the reduction of these ketones are given in Table 1, from which it is seen that ketones (II) and (III) are practically equivalent with respect to $NaBH_4$ and $(i\text{-}PrO)_3Al$. At the same time, the ratio of the epimeric alcohols obtained is close to the analogous data for C^4-monomethyl ketone (I) [3]. Therefore, a conformation with an equatorial C^4 substituent should be assumed to be the reacting conformation for ketones (I), (II), and (III). The differences between (II) and (III) in the case of reduction by other reagents (Li/NH_3 and Pt/H_2) are apparently caused by the participation of rotamers with different shielding of the carbonyl function in the case of isopropyl ketone (III). Thus, the specific influence of the C^4-e-methyl group on the stereospecificity of the reduction of the 3-keto function in piperidines is displayed exclusively with respect to $(i\text{-}PrO)_3Al$. In this case, the axial region of the carbonyl is almost completely shielded. It is interesting that the equatorial alcohol always predominates in the case of reduction by an isopropoxide when the other ring carbon atoms have a substituent (i.e., the reagent attacks from the axial region) [1, 2]. Such a specific influence of the C^4 substituent on the stereochemistry of the reduction of 3-keto-piperidines is apparently attributable to the predominance of the anti configuration of the ketone–isopropoxide complex (the C^3-C^4 and O–Al bonds are trans) due to the steric hindrances on the part of the C^4-methyl and to the additional hindrances to axial hydride transfer on the part of the syn-axial hydrogen in the methyl substituent (which is circled in Scheme I)

EXPERIMENTAL

Bromination of Methyl Isobutyl Ketone. a) The addition of bromine to a mixture of the ketone, water and $KBrO_3$ produced a mixture of 85% 3-bromo and 15% 1-bromo ketones (GLC).

b) The reaction carried out in a similar manner, but without $KBrO_3$, gave 55% 3-bromo and 45% 1-bromo ketones.

c) Bromine was added to a solution of the ketone in methanol. This produced a mixture of 70% 1-bromo ketone, bp 48-50°C (8-9 mm Hg), and 30% 3-bromo ketone, bp 43-44°C (8-9 mm Hg). The structure of the bromo ketones was proved by the PMR spectrum. The amination step does not require the isolation of the isomeric bromo ketones in a pure form owing to the significant difference between the reaction rates of the 1- and 3-isomers.

1-(N-tert-Butyl)amino-4-methyl-2-pentanone (VIII). tert-Butylamine (2 molar equivalents) was added with cooling to an acetone solution of 1-bromo-4-methyl-2-pentanone (or a mixture of the isomeric bromo ketones), the mixture was left to stand at 20°C for 12 h, ether was added, and the hydrochloride of amino ketone (VIII) was obtained from the filtrate under the action of 1:1 HCl. The yield was 58%, and the mp 205-206°C. Found: C, 57.58; H 10.75; N, 6.75; Cl, 17.24%. Calculated for $C_{10}H_{22}NOCl$: C, 58.0; H, 10.62; N, 6.75; Cl, 17.15%. IR spectrum: 1735 cm^{-1} (C=O).

1-(N-tert-Butyl-N-propargyl)amino-4-methyl-2-pentanone (IX). A mixture of 20 g of K_2CO_3, 20 ml of water, and 30 ml of MeCN was given an addition of 12 g of amino ketone (VIII) and 11 g of propargyl bromide. The mixture was stirred at 20°C for 3 h, ether (150 ml) was added, the organic layer was filtered through Al_2O_3, and the base was recovered in the form of the hydrochloride. Crystallization from a n-butanol–ethyl acetate mixture yielded 15 g of the hydrochloride of (IX) with mp 105°C. Found: C, 62.88; H, 9.88; N, 5.71; Cl, 15.0%. Calculated for $C_{13}H_{24}NOCl$: C, 63.54; H, 9.78; N, 5.70; Cl, 14.46%.

* The configuration of ketones (II) and (III) was determined on the basis of the relative stability of the epimers. This assignment is adequately substantiated in view of the distance of the substituents from the bulky alkyl on the nitrogen.

TABLE 1. Reduction of Ketones (II) and (III)

Expt. No.	Reduction conditions	Ketone, trans-(III) hydrochloride		Ketone, trans-(II) hydrochloride	
		Proportion of epimeric alcohols			
		(XIa)	(XIe)	(XIIa)	(XIIe)
1	$NaBH_4 - H_2O$, 0°	9	91	10,5	89,5
2	$Li/NH_3 - C_2H_5OH$	14	86	3	97
3	$Al(OPr\text{-}i)_3$ – i-PrOH	86	14	85	15
4	$PtO_2/H_2 - H_2O$	74	26	47	53

4-Aza-8-methyl-4-tert-butyl-4,6-nonanedione (IV). A solution of 3 ml of H_2SO_4 in 7 ml of water was given an addition of 2 g of acetylenic amino ketone (IX) and ~ 0.2 g of $HgSO_4$. The mixture was stirred for 40 min, diluted with water and 30 ml of ether, and the acid was neutralized by K_2CO_3. The ethereal extract of the reaction products was filtered through Al_2O_3. After the usual treatment, the hydrochloride of diketone (IV) was obtained in a 90% yield with mp 144°C. Found: C, 59.25; H, 10.05; N, 5.28; Cl, 13.11%. Calculated for $C_{13}H_{26}NO_2Cl$: C, 59.20; H, 9.86; N, 5.68; Cl, 13.4%.

1-tert-Butyl-5-methyl-4-isopropyl-4,5-dihydro-3-piperidone (V). a) A 10-g portion of acetylenic ketone (IX) was stirred at 40°C with 25 ml of water, 10 ml of conc. H_2SO_4, and 0.8 g of $HgSO_4$ for 40 min. The mixture was heated to 75°C and subjected to a vacuum with a residual pressure of 20 mm Hg in a rotary evaporator. The removal of the water was accompanied by the simultaneous cyclization of the diketone formed (IV) to piperidone (V), which was completed after 2 h (GLC). The reaction product contained ~ 10% isomeric ketone (VI)* along with (V).

Base (V) was isolated after neutralization by 13 N NH_4OH and converted into the hydrochloride. The yield of the hydrochloride of (V) was 80%, and the mp was 172-173°C. Found: C, 63.28; H, 9.77; N, 5.81; Cl, 14.38%. Calculated for $C_{13}H_{24}NOCl$: C, 63.54; H, 9.77; N, 5.70; Cl, 14.46%. IR spectrum: 1683 cm^{-1} (C=C–C=O), 1645 cm^{-1} (C=C). UV spectrum: λ_{max} = 243 nm, ε = 12,900. PMR spectrum (δ, ppm): 1.08 (s, 9H, t-C_4H_9), 1.23 (s, 6H, i-C_3H_7), 1.9 (s, 3H, C=CCH_3), 3.10 (m, 2H, NCH_2CO), 3.20 (m, 2H, CH_2N), 2.28 [hept, 1H, $CH(CH_3)_2$].

1-tert-Butyl-5-methyl-4-isopropyl-3-piperidone Hydrochloride (III). A solution of 4.9 g of the hydrochloride of unsaturated ketone (V) in 20 ml of water was hydrogenated over Pd/C to saturation. The GLC analysis showed that the ratio between the trans and cis isomers of ketone (III) is 65:35. However, only the trans isomer was recovered in the solid phase upon crystallization of the hydrochloride from a butanol–ethyl acetate mixture (owing to the displacement of the equilibrium). The yield of pure trans-(III) was 3.9 g, and the mp 204-205°C. Found: C, 63.10; H, 10.42; N, 5.68; Cl, 14.32%. Calculated for $C_{13}H_{26}NOCl$: C, 63.03; H, 10.50; N, 5.65; Cl, 14.34%. Only additional amounts of trans-(III) are recovered upon crystallization of the mother solutions.

a-Epimer of trans-N-tert-Butyl-5-methyl-4-isopropyl-3-piperidone. Hydrochloride (III) was boiled in i-PrOH for 35 min in the presence of $(i\text{-}PrO)_3Al$, and a mixture of isomeric alcohols with a 86:14 composition was obtained (see Table 1). After the usual treatment, the hydrochlorides were crystallized from a methanol–acetone mixture. This gave the pure (GLC) hydrochloride of the a-alcohol, a-(IX), mp 245°C. Found: C, 62.34; H, 11.27; N, 5.51; Cl, 14.27%. Calculated for $C_{13}H_{28}NOCl$: C, 62.50; H, 11.38; N, 5.61; Cl, 14.20%. IR spectrum (base in CCl_4): 3500 cm^{-1} (bound OH).

e-Epimer of trans-N-tert-Butyl-5-methyl-4-isopropyl-3-piperidone (e-(XI). The hydrochloride of pure trans-(III) was reduced in water by $NaBH_4$ at 0°C. The composition of the reaction products is given in Table 1. Crystallization from a methanol–acetone mixture gave the pure hydrochloride (GLC), mp 255°C. Found: C, 62.32; H, 11.27; N, 5.52; Cl, 14.43%. Calculated for $C_{13}H_{28}NOCl$: C, 62.5; H, 11.38; N, 5.61; Cl, 14.20%. IR spectrum (base in CCl_4, 0.005 M): 3595 cm^{-1} (free OH).

trans-N-tert-Butyl-4,5-dimethyl-3-piperidone (II). The hydrobromide of unsaturated ketone (X) [4] was hydrogenated over Pd/C, as described above, and a 21:79 mixture of the hydrobromides of the cis and trans ketones was obtained. A single crystallization from an MeOH–ethyl acetate mixture give the pure (GLC) hydrobromide of (II), mp 208°C. Found: C, 49.42; H, 8.29; N, 5.39; Br, 30.45%. Calculated for $C_{11}H_{22}NOBr$: C, 50.0; H, 8.36; N, 5.30; Br, 30.30%.

Isomerization of Ketone (II). a) The hydrobromide of (II) in a 2:1 t-$C_4H_9NH_2$–H_2O solution was heated at 50°C for 5 h. GLC analysis: 13% cis-(II) and 87% trans-(II) (glass capillary, 0.25 mm × 25 m, PEG 40 M, 130°C, N_2, 0.5 atm).

b) A suspension of the hydrobromide of (II) in ethyl acetate was saturated with dry HCl until the precipitate dissolved completely, and it was heated for 3 h at 50°C. The composition of the mixture after neutralization by saturated K_2CO_3 was: 8% cis-(II) and 92% trans-(II) (GLC data).

Hydrobromide of the e-Epimer of trans-N-tert-Butyl-4,5-dimethyl-3-piperidone (e-XII). A solution of 0.1 g of the hydrobromide of (II) in 25 ml of liquid NH_3 was given an addition of 1.5 ml of absolute ethanol and an excess of Li. The usual treatment gave a 3:97 mixture of the epimeric alcohols, which, were converted into the hydrobromides and crystallized from an MeOH–ethyl acetate mixture. The hydrobromide of pure (GLC) e-(XII) with mp 262-263°C was obtained. Found: C, 49.40; H, 9.12; H, 5.38; Br, 31.36%. Calculated for $C_{11}H_{24}NOBr$: C, 49.62; H, 9.02; N, 5.20; Br, 30.01%. IR spectrum (base, CCl_4, 0.005 M): 3610 cm^{-1} (free OH).

CONCLUSIONS

In 3-ketopiperidines an e-methyl at C^4 specifically shields the axial region of the carbonyl only with respect to reduction by aluminum isopropoxide and, to a lesser degree, to reduction over platinum.

LITERATURE CITED

1. É. A. Mistryukov and G. T. Katvalyan, Izv. Akad. Nauk SSSR, Ser. Khim., 702 (1969).
2. G. T. Katvalyan, N. A. Semenova, and É. A. Mistryukov, Izv. Akad. Nauk SSSR, Ser. Khim., 129 (1976).
3. G. T. Katvalyan, N. A. Semenova, and É. A. Mistryukov, Izv. Akad. Nauk SSSR, Ser. Khim., 1806 (1976).
4. G. T. Katvalyan, N. A. Semenova, A. S. Shashkov, and É. A. Mistryukov, Izv. Akad. Nauk SSSR, Ser. Khim., 468 (1976).
5. W. Cocker, T. B. H. McMurry, and E. R. Simmons, J. Chem. Soc., 3022 (1965).

CONVENIENT MEANS OF CONVERTING NITROXYL RADICALS INTO O-METHYLHYDROXYLAMINES

G. I. Shchukin, I. A. Grigor'ev, and L. B. Volodarskii

UDC 541.515:542.91:547.238

Sterically hindered O-methylhydroxylamines (O-MHA) are convenient diamagnetic analogs of nitroxyl radicals particularly in the study of the influence of the nitroxyl group on the chemical and spectral properties of other functional groups available in structurally similar paramagnetic and diamagnetic compounds. In comparison with the usually used hydroxylamines they possess the advantage that for them the possibility of ready regeneration of the initial nitroxyl radicals (NR) is absent. However, until the present there has been no convenient and universal means of synthesizing O-MHA. Sterically hindered O-MHA are formed on alkylating the corresponding hydroxylamines with methyl iodide in the presence of strong bases [1], however in many cases the synthesis of the initial hydroxylamines has specific difficulties as a result of their instability and ready oxidation to NR [2]. Another method is the alkylation of the hydroxylamine anion with methyl iodide or dimethyl sulfate, the anion is generated directly from NR by reduction of the latter with organometallic compounds or with metallic sodium [3]. The O-MHA are formed from NR on interaction with methylmagnesium iodide [4] but for this there must be no functional groups in the molecule which react with Grignard reagent [5]. The formation of O-MHA is also known by the interaction of NR with acetyl benzoyl peroxide [6] and methyltrichlorotitanium [7]. The NR of piperidine form O-phenylhydroxylamines in addition to hydroxylamines on interaction with phenylhydrazine [8]. It might have been expected that the interaction of NR with methylhydrazine also led to O-MHA. In addition it seemed of interest to consider this reaction for NR of 3-imidazoline-3-oxide since on interaction of the latter with hydrazine deoxygenation of the nitrone group occurs [9].

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR.

Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2357-2360, October, 1983. Original article submitted January 10, 1983.

0568-5230/83/3210-2123$07.50