

H. T. Katvalyan, A. S. Shashkov and E. A. Mistryukov\*

Institute of Organic Chemistry, USSR Academy of Sciences,  
Leninsky Prospect 47, Moscow, USSR

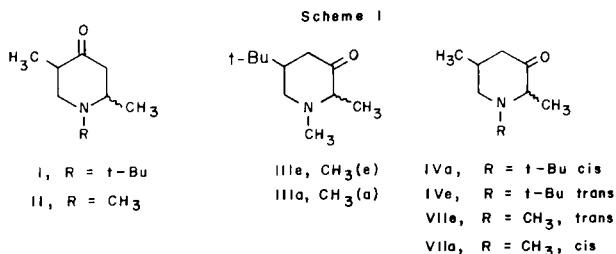
Received April 16, 1984

Chemical equilibration and <sup>1</sup>H-nmr spectroscopic studies on 1,2,5-substituted 3-ketopiperidines have been carried out. With the bulky *t*-butyl group on nitrogen the C<sub>(2)</sub>-methyl substituent is highly favored in the axial configuration. This phenomenon constitutes the basis of an efficient method of controlling diastereomer stabilities by varying the nitrogen substituent in the 3-keto- and 4-ketopiperidine series.

*J. Heterocyclic Chem.*, **22**, 53 (1985).

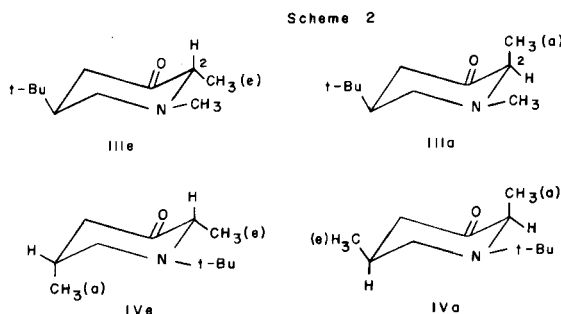
Earlier it was shown that the interaction of vicinal substituents on nitrogen and carbon in 4-ketopiperidines has a pronounced effect on the conformational energy of the C<sub>(2)</sub> substituent [1]. This interaction becomes especially strong when the substituent on nitrogen is a bulky group such as a *t*-butyl group. Thus, for ketones I and II relative stabilities of *cis*- and *trans*-forms change from the prevailing *cis*- for I (~82%) to the *trans*- for *N*-methylketone II [2]. This is true only for equilibrations in basic solutions (e.g., *t*-butylamine-water, 2:1). Surprisingly, the relative stabilities of the *cis*- and *trans*-forms of I and only of I, under acidic conditions (dry hydrogen chloride-ethyl acetate) change again drastically in favor of the *trans*-form. This unprecedented property of piperidone I was interconnected with the chair ⇌ twist boat conversion of the ring system. For *N*-methyl analog II stabilities of both *trans*- and *cis*-isomers in acidic or basic conditions are similar. This unique property of I is very useful in its synthetic aspects and permits preparation of both the *cis*- and *trans*-series of derivatives.

Therefore, it was of interest to try to extend this investigation to the class of 3-ketopiperidines which are important synthetic precursors of biologically active compounds.



In the present paper we report the results of stereochemical studies of 1,2-dimethyl-5-*t*-butyl- (III) and 2,5-dimethyl-1-*t*-butyl-3-ketopiperidines (IV). The *t*-butyl substituent on C<sub>(5)</sub> of III serves the function of an anchor group to fix the chair conformation of piperidine ring. The structures IIIe and IIIa to the individual isomers of ketone III

were tentatively assigned on chemical grounds (see experimental) respectively to the stable isomer and the kinetic product. An independent confirmation of this assignment was obtained by nmr spectroscopy.



The <sup>1</sup>H-nmr spectral evidence on individual isomers of III shows that there are negligible shift differences between C<sub>(2)</sub>-CH<sub>3</sub> signals in the axial or equatorial positions ( $\Delta\delta$  0.05 ppm). More salient is the difference in the coupling constants ( $J = 6.5$  and  $7.0$ , respectively) of CH-CH<sub>3</sub> system. The diagnostic feature of greater reliability is the chemical shift of the C<sub>(2)</sub>-H proton. Thus, spin-decoupling experiments gave resonances for C<sub>(2)</sub>-equatorial and C<sub>(2)</sub>-axial hydrogens at  $\delta$  2.92 and 2.57 respectively. The *t*-butyl group in both isomers IIIa and IIIe is the most likely to be equatorial since the changes in the nmr spectra occur only in the region of C<sub>(2)</sub>-H and C<sub>(2)</sub>-CH<sub>3</sub> resonance.

Independent from these structural identifications are the data on solvent effect. Really, whereas in carbon tetrachloride both isomers IIIa and IIIe gave practically superimposable resonances of the C<sub>(2)</sub>-CH<sub>3</sub> doublets centered at  $\delta$  1.11, benzene solutions of IIIa gave the upfield shift of 0.09 ppm for the same signal ( $\delta = 1.02$ ). This upfield solvent induced shift is characteristic of the axial methyl substituent. Of special interest is the similar shift for the equatorial C<sub>(2)</sub>-methyl in IIIe but here downfield (0.13 ppm) ( $\delta = 1.11$  and  $1.24$  for carbon tetrachloride and benzene respectively).

If either pure isomer IIIa or IIIe or a mixture of isomers were subjected to chemical equilibration in acidic or basic

solution the equilibrium mixture was obtained with a IIIe, IIIa ratio *ca* 4:1 (80% and 20% for *t*-butylamine-water and 78-22% for dry hydrogen chloride-ethyl acetate). This gives for  $C_{(2)}\text{-CH}_3$  (e)  $\rightarrow$  (a) inversion  $-\Delta G^\circ$  value of 0.91 for acid and 0.81 kcal/mol for basic equilibrations. Therefore conformational energy of the  $C_{(2)}$ -methyl group in *N*-methyl-3-ketopiperidines does not differ much from that in the *N*-methyl-4-keto series [1].

In the 4-ketopiperidine series drastic changes in the conformational stabilities of the  $C_{(2)}$ -methyl take place with the substitution of the *N*-methyl for *N*-*t*-butyl group. Therefore, the *N*-*t*-butylketone IV is of special interest. Here, the complicating factor is the conformational ambiguity of its structure, *i.e.* the *cis*-ketone IV may give a mixture of two conformers IVa and IVe as it has no anchoring group (*cf.* ketone III).

Synthesis of IV is outlined in Scheme 3. At the catalytic hydrogenation of the dehydro derivative V (R = *t*-Bu) one isomer of IV was obtained as the prevailing product. This product is also the most stable. In acidic equilibration no other isomer was detected (glc) in basic equilibration this isomer constitutes 95% of the mixture. Chemical correlation (see Scheme 2 VII  $\rightarrow$  VIII + IX and IV  $\rightarrow$  VI  $\rightarrow$  IX) shows that the most stable isomer of IV corresponds to the less stable isomer of the *N*-methyl series VII, *i.e.* it is of the *cis*-configuration IVa. Here is the similarity with the 4-keto series (ketone I) with the exception that the *cis*-isomer IV is also the most stable isomer both in acidic and basic solutions.

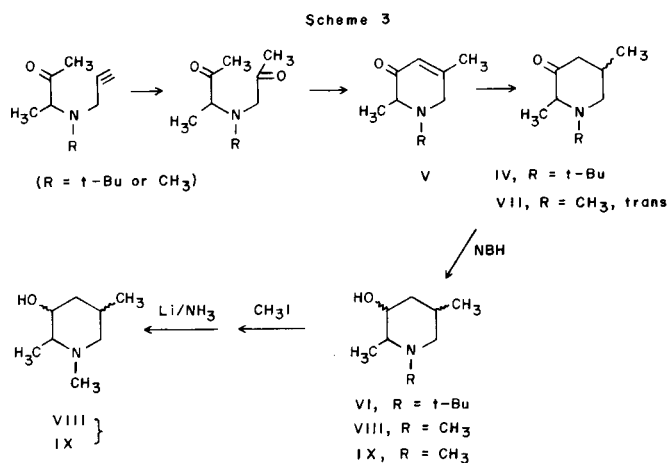
The structural assignments for ketone IV in favor of conformation IVa were again supported by  $^1\text{H}$  nmr data in combination with the relevant data for the rigid structure of III. The  $^1\text{H}$  nmr spectrum of IV consists of signals for  $C_{(5)}\text{-CH}_3$  ( $\delta$  0.93,  $\alpha$ , J = 6 Hz),  $C_{(2)}\text{-CH}_3$  ( $\delta$  1.16,  $\alpha$ , J = 7 Hz),  $t\text{-C}_4\text{H}_9$  ( $\delta$  1.10, s),  $C_{(2)}\text{-H}$  ( $\delta$  3.73, q) and the region of overlapping multiplets ( $\delta$  1.5-3.2 (from the rest of protons). By the addition of the shift reagent  $\text{Eu}(\text{dpm})_3$  the spectrum of IV was reduced to a first order spectrum. With the maximal concentration of the shift reagent (50 mg)  $-\text{COCH}_2-$  protons separated as AB, part of an ABX system. Analysis of this AB portion gave J = 4.5 Hz for AX and J = 10.5 Hz for BX, *i.e.*, one of these two constants corresponds to the axial-axial interaction. Therefore, from the equation  $J_{\text{obs}} = J(\text{a,a}) N^{\text{a}} (\text{mol fraction of IVa}) + J(\text{a,a}) N^{\text{e}} (\text{mol fraction of IVe})$ , where  $N^{\text{a}} + N^{\text{e}} = 1$ , the molar fraction of the conformer IVa is almost 100%, if the  $J(\text{a,a})$  is the same as in cyclohexane [3]. Values of J for  $\text{CH}_3\text{-C}_{(5)}\text{H}$  (J = 6 Hz) confirms this conclusion. The nmr signals of the substituents at  $C_{(2)}$  for the quantitative evaluation of conformational equilibrium IVa  $\rightleftharpoons$  IVe is less reliable because of the small difference in the chemical shifts of e- and a-methyls at  $C_{(2)}$  (see above). Nevertheless the magnitude of the shift for  $C_{(2)}\text{-H}$  is not in the defiance with the

axial  $C_{(2)}\text{-CH}_3$  bond orientation.

Another (qualitative) confirmation of the prevailing conformation (IVa) is the solvent-dependence of the nmr spectra. Here, the protons at  $C_{(2)}$  shift 0.25 ppm upfield in benzene (in comparison with carbon tetrachloride) [4].

From these data it follows that for the 3-keto series there is strong interaction of the vicinal *N*- $\text{C}_4\text{H}_9$  group with the (e)-methyl group at  $C_{(2)}$ . As a result the total energy of the system is reduced when this equatorial methyl group assumes axial configuration. Presumably this phenomenon reflects the flattening of the piperidine ring by the bulky *t*-butyl group on a nitrogen atom.

Therefore, the similarity of the *N*-*t*-butyl-3- and 4-ketopiperidines (III and I) lies in the stabilization of the *cis*-isomers in which conformers with the axial  $C_{(2)}$ -methyl group predominate. But the difference between these series is also evident and constitutes the further destabilization of the *trans*-form for the 3-ketopiperidines by additional torsional strain imposed by the shift of the carbonyl function from the  $C_{(4)}$  to the  $C_{(3)}$ -position.



## EXPERIMENTAL

The  $^1\text{H}$  nmr spectra were recorded as deuteriochloroform solutions at 60 MHz on a Varian DA-60IL spectrometer using TMS as the internal standard. Experiments with the shift reagent  $\text{Eu}(\text{dpm})_3$  were conducted with a fixed concentration of substrate. Shift reagent (purified by sublimation) was added in 10 mg portions (the maximum quantity was 30 mg). On the graphs the  $\delta_i$  vs shift concentrations indicated that all points fit well on straight lines. The lowest angle was used as a unit for the rest of the lines.

### 1-*t*-Butyl-2,5-dimethyl-3-piperidone (IVa).

To a mixture of 40 g of potassium carbonate 20 ml of water, 50 ml of acetonitrile, 28.6 g of 3-*t*-butylamino-2-butanone and 30 g of sodium iodide was added slowly 15 g of propargyl chloride and the mixture stirred at 45° for 6 hours. The organic phase was filtered through alumina and fractionally distilled. The 3-(*t*-butylpropargyl)amino-2-butanone was obtained, bp 56-57° at 8-9 mm, yield 30 g; hydrochloride, mp 156°. To a solution of 4.9 g of this product in aqueous sulfuric acid (5 ml concentrated sulfuric acid and 12 ml of water) was added *ca* 0.1 g of mercuric sulfate. The reaction proceeds with evolution of heat (*ca* 50°) with the formation

of a hydration product. The same compound was prepared by a similar procedure from bromoacetone. The reaction mixture from a sulfuric acid-mercuric sulfate preparation was subjected to distillation on a rotary evaporator with heating up to 70° under reduced pressure. The reaction was controlled by glc. At the completion of the reaction the mixture was made basic with concentrated potassium hydroxide, the organic matter was taken into ether, filtered over alumina and converted into the hydrochloride. After crystallisation from 1-butanol-ethyl acetate the yield of the unsaturated piperidone V was 3.7 g, mp 163-164°; uv (ethanol):  $\lambda$  max nm ( $\epsilon$ ) 242 (12050); ir (carbon tetrachloride): 1675 (C=C=O), 1640  $\text{cm}^{-1}$  (C=C);  $^1\text{H}$  nmr:  $\delta$  ppm 1.13 (d,  $J = 7$  Hz, 3H), 1.14 (s, 9H, *N-t*-Bu), 1.94 (m,  $\text{CH}_2\text{-C}_4=\text{CH}$ ), 3.44 (m, 2H,  $\text{CH}_2\text{N}$ ), 5.83 (m, 1H, C=CH).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{20}\text{ClNO}$ : C, 60.60; H, 9.25; N, 6.40; Cl, 16.13. Found: C, 60.15; H, 9.36; N, 6.21; Cl, 16.15.

The solution of 3 g of V hydrochloride in 20 ml of water was hydrogenated over Pd/C at atmospheric pressure. After filtration and evaporation there was obtained 2.9 g of the hydrochloride of IV, composed of 95% IVa and 5% IVe. A single crystallisation from 1-butanol-ether acetate gave pure IVa hydrochloride, mp 170-171°; ir: (carbon tetrachloride): 1720  $\text{cm}^{-1}$  (C=O). Compound IV methiodide had mp 148-149°. For analysis the chloride of IVa was hydrogenated into the hydroxy derivative VI. The same 3-hydroxypiperidine VI was obtained when compound V was hydrogenated over platinum oxide, mp 87-88° (free base from hexane).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{23}\text{NO}$ : C, 69.34; H, 12.43; N, 7.02. Found: C, 69.96; H, 12.46; N, 6.64.

#### 1,2-Dimethyl-5-*t*-butyl-3-piperidone (IIIe and IIIa).

To a mixture of 70 ml of 25% aqueous methylamine and 40 ml of THF were added 17.9 g of 1-bromo-3,3-dimethyl-2-butanone with cooling (10°). After 30 minutes of stirring were added 30 ml of diethyl ether and 20 g of potassium carbonate. The organic products were filtered over alumina, dried (potassium carbonate) and distilled. The yield of 1-methylamino-3,3-dimethyl-2-butanone was 11.7 g (90%), bp 42° (7-8 mm). The hydrobromide had mp 208-209°.

*Anal.* Calcd. for  $\text{C}_7\text{H}_{16}\text{BrNO}$ : C, 40.19; H, 7.65; N, 6.59; Br, 38.27. Found: C, 40.23; H, 7.47; N, 6.65; Br, 38.32.

To a mixture of 11.7 g (0.02 mole) of this aminoketone, 15 g of potassium carbonate, 10 ml of water and 30 ml of benzene were slowly added 15 g (0.1 mole) of bromo-2-butanone. After 30 minutes of stirring the benzene solution was separated, filtered over alumina and extracted with aqueous hydrochloric acid (1:1). The acid washings were evaporated to dryness with 1-butanol and the solid was crystallised from 1-butanol-acetone. The yield of 4-aza-3,4,7,7-tetramethyl-2,6-heptadione was 15 g as the hydrochloride, mp 193-194°. The crude hydrochloride was cyclized with potassium hydroxide-*n*-tetrabutylammonium bromide [5]. The yield of 1,2-dimethyl-5-*t*-butyl-1,2,3,5-tetrahydro-3-pyridone was 12 g as the hydrobromide, mp 213-214°. This hydrobromide is only sparingly soluble in water.

Five g of the crude hydrobromide was hydrogenated over Pd/C in 20 ml of water. There were obtained 4.6 g of the hydrobromide of III which was insoluble in water. The composition (glc) was ca 85% III and 15% IIIe. After two crystallisations from methanol-ethyl acetate pure bromide of (IIIa) was prepared, mp 116-117° (with the isomerisation into IIIe).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{22}\text{BrNO}$ : C, 50.0; H, 8.36; N, 5.30; Br, 30.3. Found: C, 49.53; H, 8.31; N, 5.43; Br, 30.8.

Pure *trans*-ketone IIIe was prepared by saturation with dry hydrogen bromide solution and crystallisation of the residue from all acetone-1-butanol gave *trans*-IIIe, mp 220-221°.

#### (e)-Epimer of 1,2,5-Trimethyl-3-piperidol (VIII).

1,2,5-Trimethyl-1,2,3,5-tetrahydro-3-pyridone was synthesised by the procedure used for the preparation of V (amination with methylamine). The hydrochloride had mp 154-155°; ir (carbon tetrachloride): 1685 (C=C=O) and 1660  $\text{cm}^{-1}$  (C=C-H); uv (ethanol):  $\lambda$  max nm ( $\epsilon$ ) 231 (13700).

*Anal.* Calcd. for  $\text{C}_8\text{H}_{14}\text{ClNO}$ : C, 54.70; H, 7.94; N, 7.97; Cl, 20.22. Found: C, 54.33; H, 7.90; N, 7.94; Cl, 20.9.

Upon hydrogenation (Pd/C) this hydrochloride gave a 73:27 mixture of two saturated ketones VII. Crystallisation gave the pure hydrochloride, mp 170-171°. This is the more stable isomer (*trans*) and constitutes 77% of the equilibrium mixture. For analysis the pure hydrochloride VII was converted into the equatorial epimer of the corresponding alcohol VII by the reduction with lithium-ethanol-liquid ammonia. Compound VIII hydrochloride had mp 194°.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{18}\text{ClNO}$ : C, 53.40; H, 10.03; N, 7.37; Cl, 19.77. Found: C, 53.41; H, 10.40; N, 7.54; Cl, 19.67.

#### Correlations of the Structures of the *N-t*-Butyl- and *N*-Methyl Series.

These correlations were performed essentially according to the published procedure by quaternization-reductive dealkylation [6].

From the *N-t*-butylpiperidol VI by boiling with an excess of methyl iodide in acetone, VI methiodide was prepared. This salt was dissolved in liquid ammonia and treated with metallic lithium until the blue coloration persisted. Ammonia was evaporated and the organic products were extracted with ether.

On glc (glass capillary, PEG 40 m) this extract gave only one peak of the *N*-methylpiperidol IX; the same compound was prepared by sodium borohydride reduction of IVa followed by reaction with methyl iodide and lithium/ammonia.

This compound IX was compared with products of sodium borohydride reductions of pure *N*-methylketone VII the major piperidol VIII and the mixture of isomeric ketones after equilibration (80% of the major isomer VII and 20% of the minor isomer). From the reaction of this mixture with sodium borohydride a mixture of four isomeric *N*-methylpiperidols was obtained: two isomers from the major isomer (relative ratio 5:1) and two isomers from the minor isomer (relative ratio 4:1).

From the glc data it follows that the *N*-methylpiperidol prepared from *N-t*-butyl ketone IV does not coincide with any of the piperidols derived from the major isomer of VII but fits well with one of the piperidols from the minor isomer.

#### REFERENCES AND NOTES

- [1] E. A. Mistryukov and G. N. Smirnova, *Tetrahedron*, **27**, 375 (1971).
- [2] E. A. Mistryukov and G. N. Smirnova, *Izv. Akad. Nauk. USSR, Ser. Chim.*, 1622 (1970).
- [3] K. M. Wellman and F. G. Bordwell, *Tetrahedron Letters*, 1703 (1963).
- [4] J. D. Connolly and R. M. McGrindle, *Chem. Ind.*, 379 (1965).
- [5] H. T. Katvallyan and E. A. Mistryukov, *Izv. Akad. Nauk. USSR, Ser. Chim.*, 671 (1976).
- [6] H. T. Katvallyan and E. A. Mistryukov, *Izv. Akad. Nauk. USSR, Ser. Chim.*, 2575 (1968).