EFFECT OF THE CHARACTER OF THE SUBSTITUTION ON THE REVERSIBLE CYCLIZATION OF 1-ALKENYL 2-ALKYLAMINOETHYL KETONES INTO 4-PIPERIDONES

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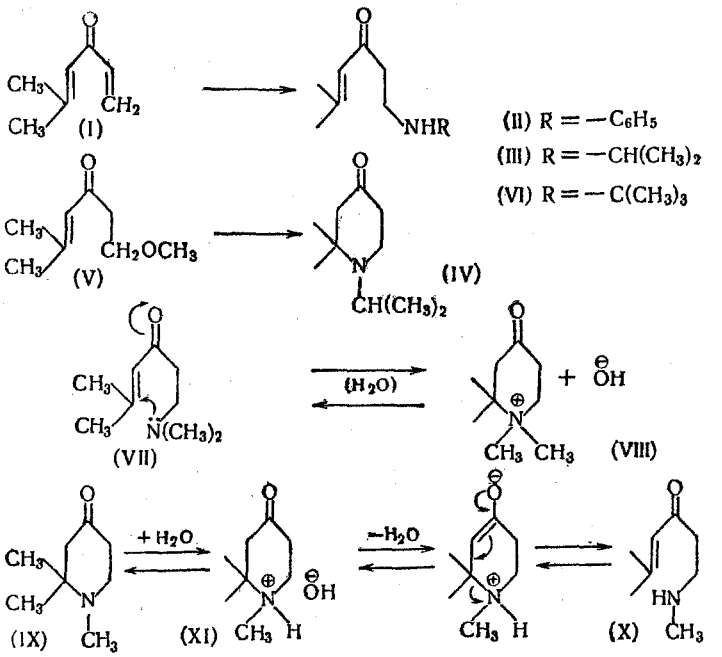
In a previous communication we described the synthesis of some 1-alkyl-4-piperidones having a bulky alkyl group on the nitrogen [1]. In the present paper we report the continuation of investigations on the effect of steric factors on the cyclization of α,β-unsaturated 2-alkylaminoethyl ketones into 4-piperidones and we describe also a new method of synthesizing 4-piperidones having a bulky alkyl on the nitrogen. Earlier, by the reaction of 5-methyl-1,4-hexadien-3-one (I) with aniline [2] and with isopropylamine [3] Nazarov and co-workers prepared unsaturated β-amino ketones [(II) and (III), respectively]. However, in the last case [3] it is stated that the unsaturated amino ketone (III) may be obtained in the cyclic form (IV) if instead of the divinyl ketone (I) the corresponding methoxy ketone (V) is brought into reaction with isopropylamine.



As the reaction was carried out under comparable conditions in the two cases it did not seem very probable that different products would be formed. In the investigation of these reactions it was indeed found that with either of the starting compounds [(I) or (V)] an equilibrium mixture is formed on the noncyclic amino ketone (III) and the 4-piperidone (IV) containing about 80% of (III) and 20% of (IV) (λ_{max} 238.5 mμ and ε 10180). The content of isomeric products in the equilibrium mixture was determined with the aid of ultraviolet spectra and the method of thin-layer chromatography on unbound alumina [4]. The fact that equilibrium occurs under the given conditions was established by isolation of the pure amino ketone (III) with the aid of preparative thin-layer chromatography (see Experimental), and this after extraction from alkaline aqueous solutions again gave two spots on the chromatograms, corresponding (in R_f and intensity) to the original mixture of (III) and the 4-piperidone (IV) (Fig. 1).

As a standard compound for the determination of the concentration of unsaturated β -amino ketones with the aid of ultraviolet absorption we took 1-t-butylamino-5-methyl-4-hexen-3-one (VI) (λ_{max} 238.5 mμ, ε 12570), which exists in the noncyclic form (in any case to an extent of more than 95% according to chromatographic data). The corresponding dimethylamino ketone (VII) gives somewhat weaker absorption (ε 11630 at 237.5 mμ), probably as a result of the disappearance of part of the unsaturated ketone (VII) with probably reversible cyclization (VII) ⇌ (VIII) [content of the form (VIII) is about 8% calculated on the basis of the identity of the chromophore C=C−C=O in (VI) and (VII)]. In piperidones of type (IV) the geminal methyls on C_2 show considerable steric hindrance to the formation of the cyclic form. As a result, even 1,2,2-trimethyl-4-piperidone (IX), which has a relatively small substituent on the nitrogen, in a water-dioxane-alcohol medium (see Experimental) contains about 20% of the noncyclic form (X) (λ_{max} 235 mμ, ε 2460).

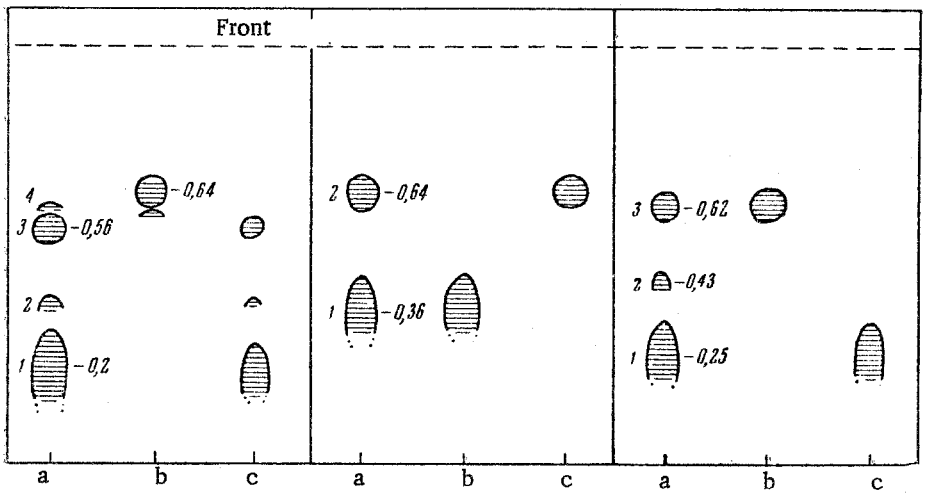


Fig. 1. Fig. 2. Fig. 3.

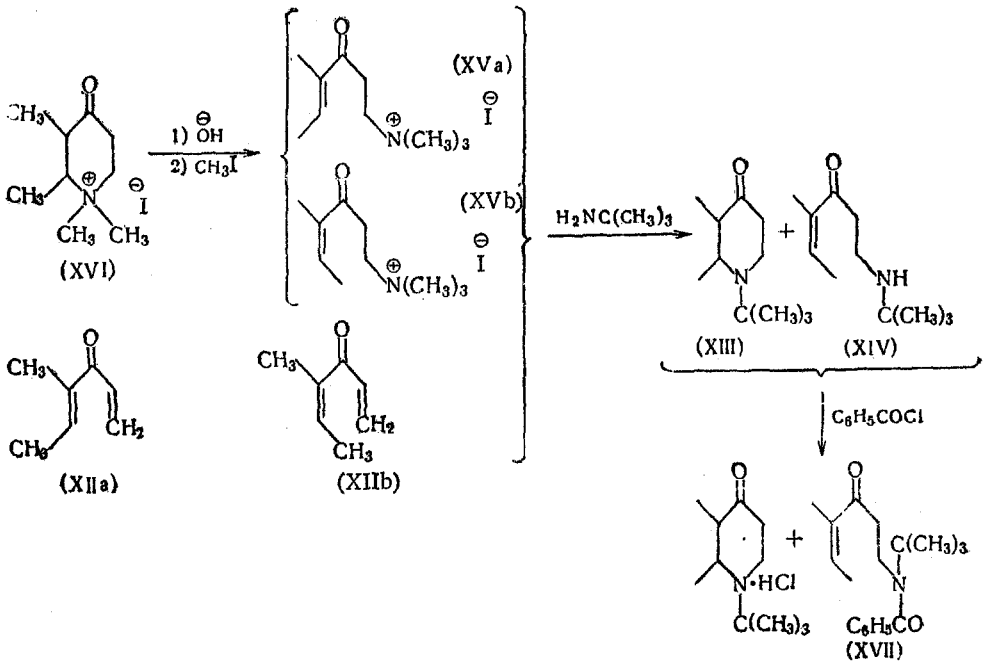
Figures 1-3. Thin-layer chromatograms on unbound alumina of activity II in the system acetone-heptane (1 : 3).

Fig. 1. a) 1) (III); 2) impurities; 3) (IV); 4) impurities in the divinyl ketone; b) unchanged 5-methyl-1,4-hexadien-3-one; c) the amino ketone (III) after dissolution in water.

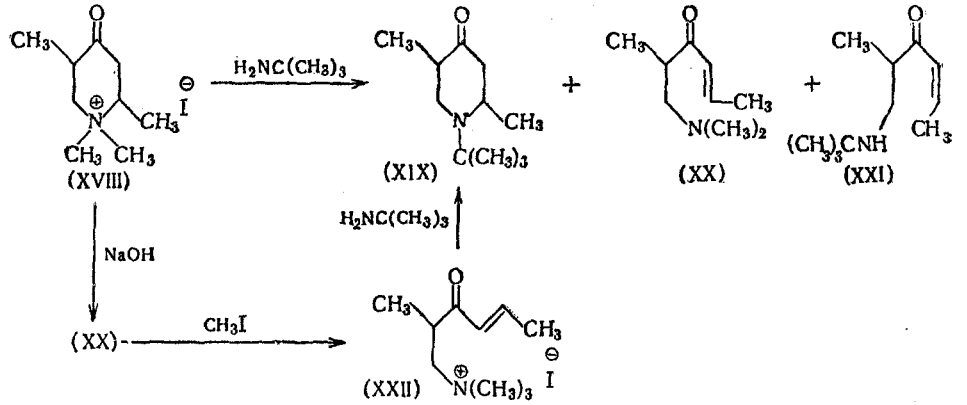
Fig. 2. a) 1) the amino ketone (XIV); 2) (XIII); b) (XIV) after dissolution in water; c) (XIII) after dissolution in water.

Fig. 3. a) 1) the amino ketone (XX); 2) (XXI) (?); 3) (XIX); b) (XIX); c) (XX).

The probable role of water in these processes of decyclization-cyclization consists in a considerable facilitation of the enolization of the ammonium form (XI) of the piperidone (see scheme). This view is supported by the extraordinary ease with which 4-piperidone methiodides give noncyclic amino ketones under the action of bases. To determine the effect on the cyclization of two methyl groups on neighboring carbon atoms we investigated the reaction of 4-methyl-1,4-hexadien-3-one (probably consisting of a mixture of cis (XIIa) and trans(XIIb) isomers with respect to the methyl groups) with t-butylamine. There was formed a mixture of (1 : 1) of 2,3-dimethyl-1-t-butyl-4-piperidone (XIII) and the noncyclic amino ketone (XIV). However, in this case, when the chromatography of (XIII) or (XIV), isolated from aqueous alkaline solutions, was repeated (Fig. 2), the chromatograms showed only one spot, corresponding to the starting compound, i.e., the change (XIII) ⇌ (XIV) does not occur. Hence, if equilibrium between the cyclic and open forms exists in this case, then it is displaced strongly to the side of the 4-piperidone (XIII) or noncyclic amino ketone (XIV). Hence, certain factors hinder the change of the amino ketone (XIV) into the cyclic form. From an examination of models it may be concluded that the trans position of the methyls at the double bond greatly hinders cyclization, so that it is extremely probable that the amino ketone (XIV) has the trans configuration.



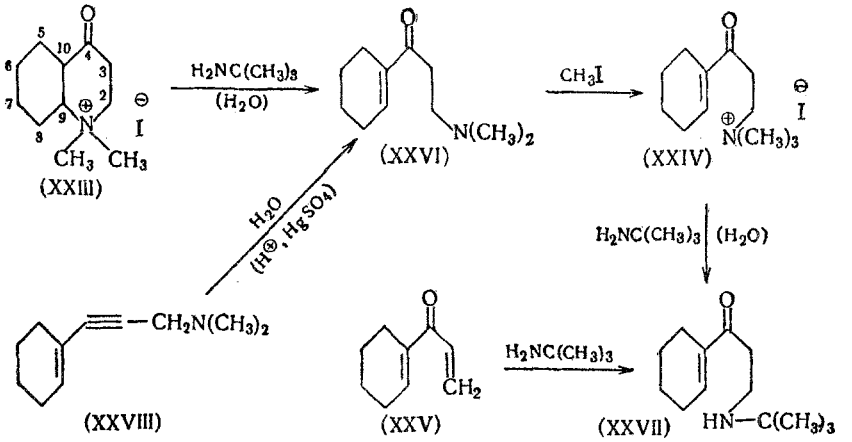
Analogous results were obtained on replacement of the divinyl ketone (XII) by the methiodide (XV), which is probably a mixture of cis (a) and trans (b) isomers. As 1,2,3-trimethyl-4-piperidone methiodide (XVI) is a completely homogeneous substance which does not change its melting point after repeated crystallization, it must be supposed that the formation of cis and trans amino ketones to which the methiodides (XVa) and (XVb) correspond proceeds on the opening of the ring of (XVI) with alkali. The formation of a mixture of (XIII) and (XIV) from one original divinyl ketone (XII) or amino ketone (XV) is not very probable because, as stated above, mutual conversion of the open and



cyclic forms is not observed. The mixtures of the 4-piperidone (XIII) and the amino ketone (XIV) obtained in this way were separated either by chromatography on alumina or by benzoylation of a chloroform solution of (XIII) and (XIV) with benzoyl chloride. The hydrochloride of the piperidone (XIII) then crystallizes out, and the benzamido ketone (XVII) can be isolated from the mother liquors. This method for the synthesis of 4-piperidones having a bulky alkyl on the nitrogen via methiodides of α,β-unsaturated 2-aminoethyl ketones was found to be more convenient in some cases than the method described earlier [1]. For example, in the reaction of 1,2,5-trimethyl-4-piperidone methiodide (XVIII) with t-butylamine there is formed a mixture of 2,5-dimethyl-1-t-butyl-4-piperidone (XIX), the dimethylamino ketone (XX),* and probably very small amounts of the noncyclic t-butylamino ketone (XXI) (Fig. 3).

*The direction in which the ring opened in the methiodide (XVIII) was not specially investigated.

On the other hand, from the methiodide (XXII) with $t\text{-}C_4H_9NH_2$ we obtained a 53% yield of the 4-piperidone (XIV), the ultraviolet spectrum of which did not show absorption in the region characteristic for α,β-conjugated ketones. Analogous reactions occurred with decahydro-1-methyl-4-quinolone methiodide (XXIII) and 1-cyclohexen-1-yl 2-dimethylaminoethyl ketone methiodide (XXIV) or 1-cyclohexen-1-yl vinyl ketone (XXV), which gave, respectively, 1-cyclohexen-1-yl 2-dimethylaminoethyl ketone (XXVI) and 1-cyclohexen-1-yl 2-t-butylaminoethyl ketone (XXVII). The amino ketone (XXVI) was obtained by the hydration [5] of the acetylenic amine (XXVIII).



The noncyclic nature of the product of the reaction of the amino ketone (XXVII) may be explained by the additional hindrance of the pseudoaxial hydrogens at C_7 and C_6 to cyclization, as compared with the analogous case of the cis ketones (XIIa) or (XVa). From what we have stated it follows that 4-piperidones (particularly "hindered" ones) form a labile system in aqueous solutions, consisting of cyclic and open forms. On the other hand the hydrochlorides of these 4-piperidones are quite stable and do not show absorption characteristic for α,β-unsaturated ketones. The same applies to the methiodides* of 4-piperidones in nuetral or acid media.

EXPERIMENTAL

The chromatography was carried out as described previously [4] or (for preparative separation) on 24 × 24 cm plates with an alumina layer (activity II) of thickness 1.5 or 3 mm. For preparative separation the samples were applied as a strip at 0.8-1.5 mm from the edge of the plate. Only a narrow strip (1-2 cm) was developed with the aid of a simple device (see Fig. 4a), and then the strip containing the required product was removed and extracted with the aid of a device (Fig. 4b) consisting of an ordinary glass filter fitted with a stopper carrying a tube.

Determination of the contents of cyclic and conjugated products in the reaction of 5-methyl-1,4-hexadien-3-one (I) with amines. a) To 0.96 ml of t-butylamine (5% excess) in 2.2 ml of water we added under ice cooling 1 ml (0.8788 g) of 5-methyl-1,4-hexadien-3-one (I) and then 4 ml of dioxane (for homogenization). The mixture was left at 20° for three hours and at 3-5° for 30 hours. The ultraviolet spectra were determined after dilution of the reaction mixture with alcohol: λ_{max} 238 mμ, ε 12570; R_f 0.31 (alumina of activity II, 1:3 acetone-hexane).

b) To 1.15 ml of a 7.3 N solution of $HN(CH_3)_2$ (5% excess) in 2.2 ml of water we added 1 ml of (I) and 4 ml of dioxane. The further procedure was analogous to that of the preceding experiment. Ultraviolet spectrum: λ_{max} 237.5 mμ, ε 11630; R_f 0.34 (alumina of activity II, 1:3 acetone-heptane).

c) To 7.20 ml of isopropylamine (5% excess) in 2.2 ml of water we added 1 ml of (I). In ultraviolet radiation the reaction mixture gave absorption with λ_{max} 238.5 mμ, ε 10180; R_f 0.2 (III) and 0.56 (IV) (alumina of activity II, 1:3 acetone-heptane).

d) To 0.81 ml of a 10.3 N solution of CH_3NH_2 in 2.2 ml of water we added 1 ml of (I). In ultraviolet radiation the reaction mixture gave absorption with λ_{max} 235 mμ, ε 2460.

2,5-Dimethyl-1-t-butyl-4-piperidone (XIX). a) 11 g of 1,2,5-trimethyl-4-piperidone methiodide [6], m. p. 194-195°, was dissolved in 10 ml of water, and 6 ml of t-butylamine was added to the resulting solution. After 24 hours at 20° the excess of t-butylamine was vacuum-distilled off; the reaction mixture was saturated with potassium carbonate and extracted with ether (for the chromatography of the ether extract see Fig. 3). After distillation we

*Methiodides give absorption with λ_{max} 226 mμ, characteristic for the iodide ion.

obtained 2.9 g of a mixture of amines, b. p. 96-98° (7 mm) and $n^{24}D$ 1.4580, which according to chromatographic data was identical to the mixture of amines before distillation.

b) Ether was added to a solution of 38 g of 1,2,5-trimethyl-4-piperidone methiodide (XVIII) in water, and with stirring and cooling the mixture was saturated with sodium hydroxide. After distillation we obtained 131 g of the amino ketone (XX), m. p. 79-82°. On chromatography (alumina of activity II; 1:3 acetone-heptane) the amino ketone (XX gave one spot, R_f 0.25. From (XX), by the usual method, we prepared the methiodide (XXII), m. p. 233-236° (decomp.). t-Butylamine (7 ml) was added with cooling to a solution of 20 g of the methiodide (XXII) in 25 ml of water. The mixture was left for one day at room temperature, excess of amine was vacuum-distilled off, and the reaction products were saturated with potassium carbonate and extracted with ether. After distillation we obtained 6.5 g (53%) of 2,5-dimethyl-1-t-butyl-4-piperidone (XIX); b. p. 64-65% (2 mm); $n^{19.5}D$ 1.4650; R_f 0.62 (alumina of activity II; 1:3 acetone-heptane); hydrochloride, m. p. 182-183°. Found: C 60.52; H 10.02; N 6.84; Cl 16.02%. $C_{11}H_{22}NOCl$. Calculated: C 60.11; H 10.08; N 6.37; Cl 16.13%.

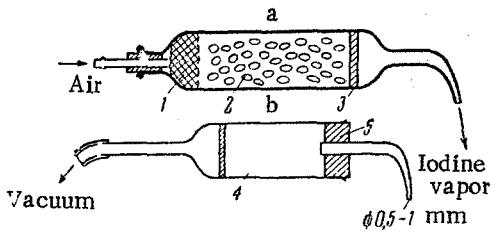


Fig. 4. Apparatus for chromatograph [a) for development; b) for removal and extraction]: 1) glass wool; 2) crystalline iodine; 3) porous glass; 4) glass filter, 30-40 mm in diameter (Nos. 2-3); 5) rubber stopper carrying tube.

2,3-Dimethyl-1-t-butyl-4-piperidone (XIII). a) Sodium hydroxide (50 g) was added with cooling to a solution of 32 g of 1,2,3-trimethyl-4-piperidone (XVI) [7], m. p. 182-184° (from acetic acid), in 50 ml of water. The organic base was extracted with ether and distilled. We obtained 14.8 g (84%) of the amino ketone, b. p. 90° (8 mm); it gave one spot on chromatography (R_f 0.47 on alumina on activity II; 1:3 acetone-hexane); methiodide (XV), m. p. 191-193°. To a solution of 18.8 g of the methiodide (XV) in 25 ml of water we added 7 ml of t-butylamine. We obtained 6.7 g of a mixture of the amino ketone (XIV) and the piperidone (XIII); b. p. 74-76° (1 mm); $n^{18}D$ 1.4670, λ_{max} 231 mμ, ε 6600. The chromatogram is shown in Fig. 2.

Benzoyl chloride (2.5 ml) in dry chloroform was added with cooling to 4.9 g of this mixture. Solvent was distilled off, and dry ether was added. The hydrochloride that was then precipitated was washed with ether and crystallized from methanol – ethyl acetate. We obtained 2.47 g of 2,3-dimethyl-1-t-butyl-4-piperidone, m. p. 149-150°. Found: C 59.92; H 10.14; N 6.58; Cl 16.03%. $C_{11}H_{22}NOCl$. Calculated: C 60.11; H 10.08; N 6.37; Cl 16.13%. On chromatography, the base (XIII), obtained from the hydrochloride by the action of aqueous potassium carbonate, gave one spot of R_f 0.64 (alumina of activity II; 1:3 acetone-heptane). The mother solutions remaining after the separation of the hydrochloride were evaporated down, and the residue was dissolved in benzene; the solution was washed with dilute (1:10) hydrochloric acid and with a solution of sodium bicarbonate; it was then filtered through a little alumina and evaporated to dryness; the residue was crystallized from heptane. We obtained 1.54 g of the benzamido ketone (XIV), m. p. 75-76°; R_f 0.43 (alumina of activity II; 1:3 acetone-heptane). Found: C 74.9; H 8.60; N 5.03%. $C_{18}H_{25}NO$. Calculated: C 75.22; H 8.79; N 4.87%. When the bulk of the hydrochloride had been separated, the mother solutions, which contained mainly (XVII), gave a further about 0.5 g of the hydrochloride of the base (XIV) on addition of heptane; m. p. 154-155°; λ_{max} 232 mμ, ε 12830, R_f 0.27 (base obtained by the action of potassium carbonate). Found: C 60.11; H 9.87; N 6.28%. $C_{11}H_{22}NOCl$. Calculated: C 60.11; H 10.08; N 6.37; Cl 16.13%.

b) A twofold excess of t-butylamine was added to an aqueous solution of noncrystalline 1-diethylamino-4-methyl-4-hexen-3-one [8], and the further procedure was as in the experiment with the methiodide (XV). The chromatograms of the reaction product did not differ from those of the above-described mixtures.

c) With cooling and stirring a solution of 8.7 g of 4-methyl-1,4-hexadien-3-one (XII) [8] in ether was added to an aqueous solution of 10 ml of t-butylamine. The chromatograms obtained did not differ from those obtained previously in experiments (a) and (b). The relative amounts of (XIII) and (XIV) did not change even after long standing (one month).

3-(1-Cyclohexen-1-yl)-N,N-dimethyl-2-propynylamine (XXVIII). A mixture of 164 g of 1-ethynylcyclohexene, 55.5 g of paraform, and 200 ml of dioxane containing a little (about 0.3 g) of $FeCl_3$ [9] was cooled to −4°, and 123 ml of dimethylamine was added rapidly. This temperature was maintained for 30 minutes, and the mixture

was then warmed (cold water) to 10° and left overnight. The mixture was boiled for 30-35 hours, and dioxane was vacuum-distilled off. An ethereal solution of the reaction products was washed with a solution of ammonium sulfate in aqueous ammonia and distilled. We obtained 220.5 g of 3-(1-cyclohexen-1-yl)-N,N-dimethyl-2-propynylamine (XXVIII), b. p. 105-107° (7 mm); $n^{20}D$ 1.5040. Found: C 80.44; H 10.44; N 8.68%. $C_{11}H_{17}N$. Calculated: C 80.92; H 10.50; N 8.58%.

1-Cyclohexen-1-yl 2-dimethylaminoethyl ketone (XXVI). With cooling (temperature not above 30°) 49 g of 3-(1-cyclohexen-1-yl)-N,N-dimethyl-2-propynylamine (XXVIII) was added gradually to a solution of 1.5 g of mercuric sulfate in 70 ml of water and 16 ml of concentrated sulfuric acid. The mixture was heated at 92° for 90 minutes. Chromatography of the reaction mixture showed complete disappearance of the of the original acetylenic amine. After neutralization with 13 N ammonia under cooling and extraction with ether we obtained 46.3 g of 1-cyclohexen-1-yl 2-dimethylaminoethyl ketone (XXVI), which was investigated further without additional purification. Methiodide (XXIV), m. p. 218-220°.

Decahydro-1-methyl-4-quinolone methiodide (XXIII). A mixture of the amino ketone (XXVI) and excess of an aqueous solution of methylamine (cf. [7]) was left for two hours and than heated at 90° with simultaneous removal of dimethylamine and excess methylamine by distillation. After the distillation we obtained decahydro-1-methyl-4-quinolone [7] in 60% yield, and from this and CH_3I in acetone we prepared the methiodide (XXIII), m. p. 199-200°.

1-Cyclohexen-1-yl 2-dimethylaminoethyl ketone (XXVI). With cooling 4 ml of t-butylamine was added to a solution of 10 g of the methiodide (XXIII) in 10 ml of water, and the reaction mixture was left for two days. After extraction with chloroform with simultaneous saturation with potassium carbonate and distillation we obtained 3.7 g of the amino ketone (XXVI); b. p. 95-100° (1 mm); λ_{max} 234.5 mμ, ε 11730, R_f 0.44 (alumina of activity II; 1:3 acetone-hexane). Hydrochloride, m. p. 167-168° (from methanol – ethyl acetate). Found: C 59.96; H 9.07; N 6.66; Cl 16.92%. $C_{11}H_{20}NOCl$. Calculated: C 60.69; H 9.12; N 6.43; Cl 16.30%.

1-Cyclohexen-1-yl 2-t-butylaminoethyl ketone (XXVII). a) t-Butylamine was added to a solution of 1-cyclohexen-1-yl 2-dimethylaminoethyl ketone methiodide (XXIV) as in the preceding experiment. Chromatography of the reaction mixture on alumina showed that it contained mainly the amino ketone (XXVII), R_f 0.38 (λ_{max} 235.5 mμ, ε 2850). The substance giving a spot with R_f 0.7 (alumina of activity II; 1:3 acetone-hexane) was not cyclic because it gave absorption in ultraviolet radiation characteristic for α,β-unsaturated ketones (λ_{max} 237 mμ).

b) A reaction mixture of analogous composition was obtained when 1-cyclohexen-1-yl vinyl ketone (XXV) [8] was used: from 5.2 g of (XXV) we obtained 5.9 g (77%) of the hydrochloride of 1-cyclohexen-1-yl 2-t-butylaminoethyl ketone; m. p. 166-167°, λ_{max} 236 mμ, ε 8430. Found: C 63.32; H 9.78; Cl 14.28; N 6.21%. $C_{13}H_{24}NOCl$. Calculated: C 63.59; H 9.80; Cl 14.44; N 5.71%.

The spectrographic part of the investigation was carried out by T. M. Fadeeva, to whom the authors express their thanks.

SUMMARY

In aqueous solutions 4-piperidones form labile systems consisting of a cyclic and an open-chain form. In the case of 4-piperidones having a bulky alkyl on the nitrogen and a substituent on C_2 or a medium-sized alkyl on the nitrogen and two 2-substituents ("hindered piperidones") equilibrium is displaced toward the open-chain form.

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