

A NEW METHOD FOR THE SYNTHESIS OF N-ALKYL-4-PIPERIDONES

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Translated from *Izvestiya Akademii Nauk SSSR, Otd. Khimicheskikh*

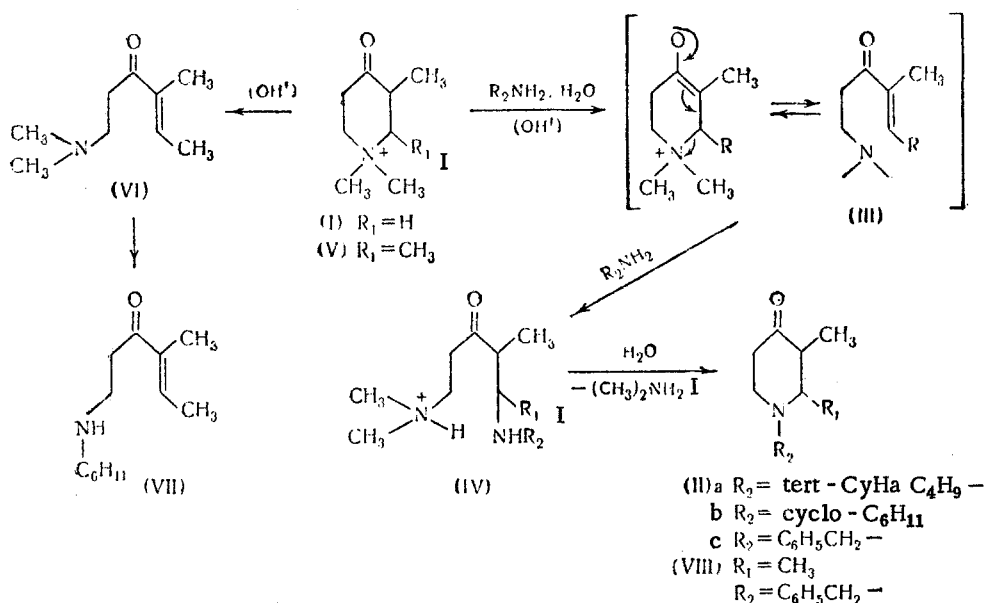
Nauk, 1961, No. 5,

pp. 932-933, May, 1961

Original article submitted October 28, 1960

In a previous paper we described the synthesis of some 4-piperidones with a methyl group or without a substituent on the nitrogen [1]. In order to study the influence of the nature of the substituent on the nitrogen in the esterification of 4-phenyl-4-piperidols [2] it was necessary to synthesize some N-alkyl-4-piperidones with alkyl substituents heavier than methyl. It was found that the readily available N-methyl-4-piperidones [1, 3] could be used as the starting products to obtain the N-alkyl-4-piperidones. The synthesis of the N-alkyl-4-piperidones was accomplished by reacting the methiodides of the 1-methyl-4-piperidones with primary amines (see the analogous reaction of 4-piperidone methiodides with H_2S [4]). The reaction goes with exceeding ease at room temperature and leads to the formation of the corresponding N-alkyl-4-piperidones in excellent yields.

In the case of the substituted 4-piperidones this method proves to be more convenient than the earlier used methods [1, 5]. It is interesting to mention that the methiodide of 1,3-dimethyl-4-piperidone reacts easily even with sterically hindered amines (for example, with *tert*- $C_4H_9NH_2$).



In this way we obtained 3-methyl-4-piperidones with substituents on the nitrogen, namely *tert*-butyl (IIa), cyclohexyl (IIb), and benzyl (IIc). Since we had previously shown [1] that unsaturated aminoketones (type III) are easily cyclized to piperidones using methylamine or ammonia, through the intermediate formation of diaminoketone (IV), then in the present case it is obviously also possible to assume the formation of (IV), either through the addition of the amine to the intermediate unsaturated aminoketone (III) or directly from the methiodide (I) by nucleophilic substitution on the β -carbon atom (see scheme).

From the obtained results it can be seen that an alkyl substituent on C_3 (or C_5) of the piperidine ring exerts little steric effect on the reaction of opening and recyclization of the piperidine ring. Substitution on the β -carbon atom (C_2 or C_6) possesses much greater importance in this respect. Thus, the methiodide of 1, 2, 3-trimethyl-4-piper-

idone gives cyclic products only with unhindered amines (for example, benzylamine). In the case of reaction with hindered amines, for example, tert-butylamine or cyclohexylamine, only opening of the piperidine ring of the methiodide (V) occurs and the reaction products are respectively 3-methyl-6-(dimethylamino)-2-hexen-4-one (VI) or the product of further amino exchange—aminoketone (VII). The noncyclic nature of compound (VII) was shown by the ultraviolet absorption spectrum: aminoketone (VII) absorbs in the region ($\lambda_{\max}$ 226 m μ , in alcohol) characteristic for α , β -unsaturated ketones. In order to compare the present method of synthesizing N-alkyl-4-piperidones with the McElvain method [5], we attempted to synthesize 1-tert-butyl-3-methyl-4-piperidone (IIa) via the Dieckmann condensation of the corresponding diester. However, it proved that tert-butylamine does not add to methyl methacrylate under the conditions where other amines (see [3]) give the corresponding addition products.

EXPERIMENTAL

1, 3-Dimethyl-4-piperidone methiodide (I). 1, 3-Dimethyl-4-piperidone methiodide was obtained in quantitative yield by treating an acetone solution of 1, 3-dimethyl-4-piperidone with CH_3J . The synthesis of 1, 3-dimethyl-4-piperidone was accomplished either from isopropenylacetylene [1] or by a modification of the Howton method [3]: 326 g of methyl-(2'-carbomethoxyethyl) (2'-carbomethoxypropyl) amine was added rapidly to a solution of 36.3 g of metallic sodium in 1200 ml of liquid ammonia; the reaction mixture was stirred for 30 min and then allowed to stand overnight to evaporate the ammonia. The obtained semiliquid mass was treated with 700 ml of ether, and any residual ammonia was removed by heating under reflux (about 1 hr). Then the mixture was acidified with 525 ml of concd. hydrochloric acid in 300 ml of water, the ether was distilled off, and the aqueous solution was boiled until the evolution of CO_2 ceased (1 hr). The excess acid and water were removed by vacuum-distillation, and the dry residue was treated with ether (500 ml), 150 g of solid NaOH, and then gradually with 75 ml of water. From the ether layer we obtained 171.5 g (90%) of 1, 3-dimethyl-4-piperidone with b.p. 62–64° (12 mm); n_D^{20} 1.4572.

Reaction of methiodides of 1-methyl-4-piperidones with primary amines. A mixture of 13.4 g of methiodide (I), 6 ml of cyclohexylamine and 6 ml of water was allowed to stand overnight at room temperature. The free base was isolated from the obtained homogeneous solution by saturation with ammonium sulfate (or potassium carbonate) and extraction with ether. We obtained 7.0 g of 3-methyl-1-cyclohexyl-4-piperidone (IIb); b.p. 106–108° (1 mm); n_D^{21} 1.4907. Found: C 74.24; H 10.80; N 7.50%. $\text{C}_{12}\text{H}_{21}\text{NO}$. Calculated: C 73.79; H 10.84; N 7.17%. Hydrochloride, m.p. 189–190° (from CH_3COOH —ethyl acetate); picrate, m.p. 172–174° (from CH_3COOH). If the crude piperidone (IIb) is purified through the picrate (without distillation), then the yield of the picrate is 66%.

In a similar manner: from 6.5 g of (I) and 6 ml of tert-butylamine in 3 ml of water we obtained 2.3 g of 3-methyl-1-tert-butyl-4-piperidone (IIa), b.p. 104–105° (23 mm); n_D^{20} 1.4558; hydrochloride, m.p. 180–182° (from CH_3COOH —ethyl acetate); picrate, m.p. 182–184° (from CH_3COOH). Found: C 48.21; H 5.48; N 13.74%. $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_8$. Calculated: C 48.20; H 5.55; N 14.07%; from 13.4 g of (I) and 5.5 ml of benzylamine in 6 ml of water we obtained 4.13 g of 3-methyl-1-benzyl-4-piperidone (IIc), b.p. 112–117° (1 mm); n_D^{23} 1.5313. Found: C 76.30; H 8.51; N 7.42%. $\text{C}_{13}\text{H}_{17}\text{O}$. Calculated: C 76.81; H 8.43; N 6.89%; picrate, m.p. 160–162°, from alcohol (when purified through the picrate the yield of (IIc) was 66%); from 28.3 g of (V) (m.p. 150–153°, from CH_3COOH) and 10.7 g of benzylamine in 10 ml of water we obtained 11.2 g of 2,3-dimethyl-1-benzyl-4-piperidone, b.p. 124–125° (1 mm); $n_D^{21.5}$ 1.5355; hydrochloride, m.p. 166–167° (from CH_3COOH —ethyl acetate). Found: C 65.99; H 8.12; N 5.54; Cl 13.90%. $\text{C}_{14}\text{H}_{20}\text{NOCl}$. Calculated: C 66.40; H 7.95; N 5.52; Cl 13.97%; from 14.2 g of (V) and 5.3 ml of tert-butylamine in 5 ml of water we obtained 4.7 g of 3-methyl-6-(dimethylamino)-2-hexen-4-one (VI), b.p. 93–95° (25 mm); n_D^{22} 1.4680; $\lambda_{\max}$ 231 m μ (in alcohol); hydrochloride, m.p. 165–166° (from CH_3COOH —ethyl acetate). Found: C 56.07; H 9.79; Cl 18.60; N 7.99%. $\text{C}_9\text{H}_{18}\text{NOCl}$. Calculated: C 56.38; H 9.46; Cl 18.49; N 7.30% (VI) was also obtained from (V) and aqueous NaOH solution; and from 14.2 g of (V) and 6.5 ml of cyclohexylamine in 5 ml of water we obtained 3.8 g of 3-methyl-6-cyclohexylamino-2-hexen-4-one (VII), b.p. 119–122° (2 mm); n_D^{22} 1.4900; $\lambda_{\max}$ 226 m μ (in alcohol); picrate, m.p. 172–173.5° (from alcohol). Found: C 51.89; H 6.18; N 12.91%. $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_8$. Calculated: C 52.05; H 5.98; N 12.78%.

SUMMARY

A new method, based on the reaction of the methiodides of N-methyl-4-piperidones with primary amines, was proposed for the synthesis of N-alkyl-substituted 4-piperidones.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
