THE MANNICH REACTION WITH HETEROCYCLIC γ-KETONES

II. The Aminomethylation of 1,2,3-Trimethyl-4-piperiodine*

E. T. Golovin and A. P. Nikiforova

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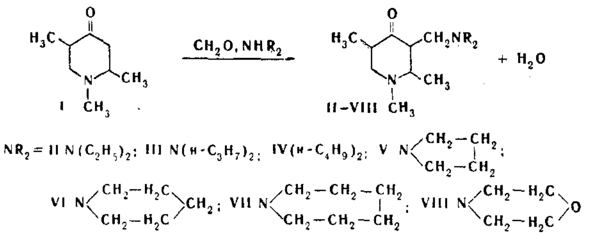
A number of β-aminomethyl-γ-piperidones have been obtained by the aminomethylation of 1, 2, 5-trimethyl-4-piperidone with formaldehyde and various secondary amines.

Continuing previous work [1], we have carried out the aminomethylation of 1,2,5-trimethyl-4-piperidone (I) [2] with formaldehyde and various secondary amines: diethylamine, di-n-propylamine, di-n-butylamine, pyrrolidine, piperidine, hexamethyleneimine, and morpholine. The corresponding 1,2,5-trimethyl-3(5)-aminomethyl-4-piperidones (II–VIII) were obtained with yields of 40–75% (see table).

The aminomethylation reactions were carried out with the hydrochlorides of the seconary amines and 30% aqueous formaldehyde solution in a ratio of 1 mole of I to 1.1 mole of amine to 1.5 mole of formaldehyde. The Mannich reaction with I took place vigorously and was accompanied by the evolution of heat. In view of this, the mixing of the initial reactants had to be carried out gradually with efficient cooling. Performing the reaction without cooling led to the spontaneous heating of the reaction mixture and, consequently, to resinification and a reduction in the yield of product.



The β-aminoketones II–VIII consist of colorless liquids with an amine-like smell. Their crystalline derivatives in the form of the dipicrates and dihydrochlorides melt with decomposition. The dihydrochlorides are strongly hygroscopic substances, which complicates their crystallization and purification.

The β-aminomethyl-γ-piperidones obtained are intended for further use in the synthesis of the corresponding piperidine γ-amino alcohols and esters in order to study their physiological effects.

EXPERIMENTAL

1, 2, 5-Trimethyl-3(5)-diethylaminomethyl-4-piperidone (II). With stirring and ice-water cooling, a solution of 12 g (0.11 mole) of diethylamine hydrochloride in 15 ml (0.15 mole) of 30% formalin was added in drops to 14.1 g (0.1 mole) of 1, 2, 5-trimethyl-4-piperidone (I) at such a rate that the temperature of the mixture did not rise above 10° C. The mixture was stirred at room temperature for 2 hr and was then made alkaline with 40% sodium hydroxide solution and extracted with ether. The ethereal extracts were dried with magnesium sulfate, the ether was driven off, and the residue was distilled in vacuum to give 13.2 g of compound II (58.4%) and 2.4 g of the initial piperidone I. After distillation, 4 g of a resinous residue was left. A change in the order of addition of the reactants, the use of ethanol and methanol as solvents, and the addition of a few drops of concentrated hydrochloric acid did not increase the yield of reaction products.

All the other β-aminomethyl-γ-piperidones (III–VIII) were obtained similarly.

REFERENCES

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2. I. N. Nazarov and V. A. Rudenko, Izv. AN SSSR, OKhN, 610, 1948.

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Lomonosov Moscow Institute
of Fine Chemical Technology

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*For communication I, see [1].

Aminomethylpiperidones and Their Derivatives

Compound	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %	Dipicrate*, mp, °C (decomp.)	Dihydrochloride**, mp, °C (decomp.)
				found	calculated		C	H	N	C	H	N			
II	114—115 (5)	0.9377	1.4736	67.79	67.65	$C_{13}H_{26}N_2O$	68.96 69.08	11.20 11.27	11.98 12.06	68.97	11.58	12.38	58.4	73—74	58—60
III	134—135 (6)	0.9222	1.4712	77.12	76.98	$C_{15}H_{30}N_2O$	70.64 70.33	12.46 12.16	11.30 11.60	70.81	11.89	11.01	56.3	106—108	61—62
IV	143—145 (6)	0.9127	1.4692	86.22	86.22	$C_{17}H_{34}N_2O$	72.81 72.63	12.68 12.57	9.94 10.10	72.28	12.13	9.92	59.5	137—139	74—76
V	106—107 (4)	0.9930	1.4910	65.43	65.45	$C_{13}H_{24}N_2O$	—	—	12.39 12.50	—	—	12.49	37.5	152—154	48—49
VI	132—133 (6)	0.9902	1.4952	70.21	70.13	$C_{14}H_{26}N_2O$	70.48 70.17	10.77 10.69	12.10 12.20	70.54	10.99	11.76	67.8	96—98	72—73
VII	136—137 (6)	0.9849	1.4970	74.96	74.93	$C_{15}H_{28}N_2O$	71.99 72.31	11.25 11.30	11.10 11.00	71.40	11.18	11.09	41.6	77—78	58—59
VIII	133—134 (5)	1.0383	1.4920	67.16	67.25	$C_{13}H_{24}N_2O_2$	64.82 64.76	9.98 9.87	11.60 11.60	64.96	10.06	11.66	75.6	110—112	77—79

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*The dipicrates of compounds **II**-VI were recrystallized from 50% ethanol, that of **VII** from ethanol, and that of VIII from 50% acetone.

**The compositions of the dipicrates and dihydrochlorides were confirmed by analyses for nitrogen and chlorine, respectively.