REACTION OF MANNICH BASES WITH 2,2,6,6-TETRAMETHYLPIPERIDONE ENAMINES

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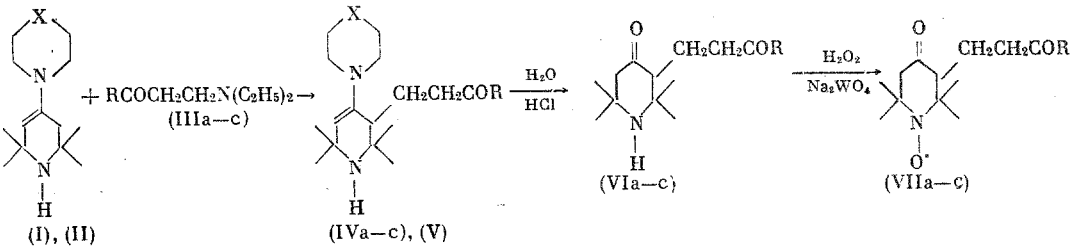
A large number of nitroxyl radicals of the piperidine series has been synthesized at the present time [1, 2], but up to now the insertion of functional substituents in the 3 position of their piperidine ring is a difficult task.

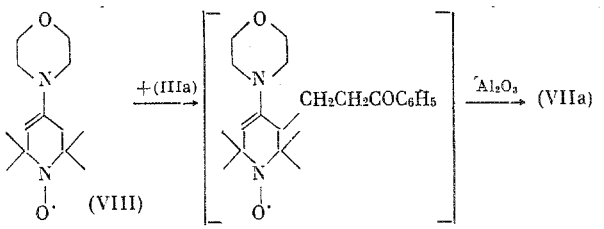
In the present paper we studied a possible route for the synthesis of 3-substituted triacetoneamine derivatives and the nitroxyl radicals corresponding to them, which is based on the condensation of enamines (I) and (II) with Mannich bases (III) and the subsequent hydrolysis of the condensation products (IV) and (V) by treatment with HCl. The oxidation of the thus obtained 3-substituted triacetoneamines (VI) with the H_2O_2–Na_2WO_4 system leads to the paramagnetic 1,5-diketones (VII), which have both theoretical and practical interest.



X = O (I), (IV), CH_2 (II), (V); R = C_6H_5 (a), *n*-$CH_3OC_6H_4$ (b), $C_6H_5CH{=}CH$ (c)

The starting enamines (I) and (II) were obtained in 75–80% yields by the reaction of 2,2,6,6-tetramethyl-4-oxopiperidine with morpholine and piperidine [3]. The yields of the products exceed 80% in the condensation and acid cleavage steps and are 50–95% in the oxidation step.

Nitroxyl radical (VIIa) was obtained by the direct alkylation of the 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl morpholine enamine (VIII) with the Mannich base (IIIa) and subsequent chromatographing of the condensation product (without isolating it from the reaction mixture) on Al_2O_3, during which process this product is converted to (VIIa).



The reaction of enamines with Mannich bases apparently proceeds by the cleavage–addition mechanism [4]. The α,β-unsaturated ketone Mannich bases that are formed during decomposition add to the enamines by the usual mechanism [5]. As was established by us, acrylonitrile, benzylideneacetone, and ethyl acrylate do not react with enamines (I) and (II) under the conditions of the condensation reaction (100°, dioxane).

The structure of the obtained compounds was confirmed by the IR, NMR, and mass spectra (Table 1). The IR spectra of (IVa, b) and (V) have bands in the 1680–1690 (ArC = O) and 1660–1670 cm^{-1} (C = C = –N <)

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TABLE 1

Compound	Yield, %	mp*, °C	Empirical formula	Found / Calculated, % C	H	N	M+	Infrared spectra (ν, cm⁻¹)	NMR spectrum (δ, ppm)
(I)	80	120—123(3) n_D^{20} 1,4970	$C_{13}H_{24}N_2O$	69,12 / 69,60	10,60 / 10,78	12,51 / 12,49			
(II)	76	112—115(3) n_D^{20} 1,4980	$C_{14}H_{26}N_2$	75,23 / 75,67	11,52 / 11,71	12,48 / 12,61			
(IVa)	89	118	$C_{22}H_{32}N_2O_2$	73,50 / 74,11	9,28 / 9,05	7,43 / 7,86	356	1690 1660	1,24 s (CH_3); 1,30 s ($3CH_3$; 1,85 m (HC); 2,3—3,4 m ($4CH_2$); 3,5 m ($O(CH_2)_2$); 4,76 s (HC≡C), 7,6—8,24 m (C_6H_5)
(IVb)	82	114—115	$C_{23}H_{34}N_2O_3$	71,06 / 71,47	8,95 / 8,87	7,10 / 7,25	386	1670 1650	1,26 s (CH_3); 1,30 s ($3CH_3$); 1,8 m (HC); 2,25—3,4 m ($4CH_2$); 3,6 d.t ($O(CH_2)_2$); 4,04 s (CH_3O); 4,76 s (HC≡C); 7,1—8,2 m (C_6H_4)
(IVc)	83	106—107	$C_{24}H_{34}N_2O_3$	74,98 / 75,35	9,13 / 8,96	7,23 / 7,96	382	1670 1620	1,24 s (CH_3); 1,30 s ($3CH_3$); 1,77 m (HC); 2,3—3,2 m ($4CH_2$); 3,73 t (J = 6 Hz) ($O(CH_2)_2$); 4,74 s (HC≡C); 6,85 d and 7,72 d (J = 16 Hz) (trans-HC=CH); 7,46—7,92 m (C_6H_5)
(V)	90	89	$C_{23}H_{34}N_2O$	78,02 / 77,92	9,82 / 9,66	8,11 / 7,90	354	1720 1650	
(VIa)	95	106	$C_{18}H_{35}NO_2$	75,20 / 75,20	8,62 / 8,77	4,61 / 4,61		3360 1700 1680	1,02, 1,12, 1,20 and 1,28 s ($4CH_3$); 1,8 m (HC); 2,2 s (ring CH_2); 2,25—3,2 m ($2CH_2$); 7,2—7,95 m (C_6H_5)
(VIb)	95	90,5	$C_{19}H_{37}NO_3$	71,40 / 71,89	8,41 / 8,57	4,12 / 4,41		3370 1700 1670	1,0, 1,1, 1,18 and 1,28 s ($4CH_3$); 1,8 m (HC), 2,2 s (ring CH_2); 2,3—3,1 m ($2CH_2$); 3,8 s (OCH_3); 6,8—8,0 m (C_6H_4)
(VIc)	75	98	$C_{20}H_{37}NO_2$	76,70 / 76,40	8,60 / 8,68	4,20 / 4,47		3360 1695 1615	0,95, 1,06, 1,15 and 1,21 s ($4CH_3$); 1,7 m (HC); 2,16 s (ring CH_2); 2,2—2,8 m ($2CH_2$); 6,5 d and 7,4 d (J = 16 Hz) (trans-HC=CH); 7,1—7,45 m (C_6H_5)
(VIIa)	95	104	$C_{18}H_{34}NO_3$	71,76 / 71,49	7,92 / 8,00	4,61 / 4,63	302	1720 1690	
(VIIb)	69,5	78	$C_{19}H_{36}NO_4$	68,41 / 68,65	7,72 / 7,98	4,19 / 4,21	332	1700 1670	
(VIIc)	51,5	86	$C_{20}H_{36}NO_3$	73,01 / 73,14	8,20 / 7,98	4,14 / 4,20	328	1700 1645	
(VIII)	80	106,5	$C_{13}H_{23}N_2O_2$			11,96 / 11,70	239	1645	

*For (I) and (II), bp, °C (p, mm of Hg).

regions, while the latter disappear in the spectra of (VIa, b) and (VIIa), and bands appear in the 1700-1710 cm^{-1} region (C = O). The IR spectrum of (IVc) has a band at 1670 cm^{-1} (at 1695 cm^{-1} after hydrolysis).

Products (IV) and (V) do not contain the possible isomers at the double bond. The NMR spectra of these compounds have a singlet (δ 4.76 ppm) (1H) that belongs to the vinyl proton of the piperidine ring in the 5 position and a multiplet (1H) (δ 1.8 ppm) that belongs to the proton of the piperidine ring in the 3 position.

The EPR spectra of (VIIa-c) as crystals represent a single signal. Solutions of the radicals in benzene give triplet spectra with a splitting of 15.6 Oe between the components.

EXPERIMENTAL

The NMR spectra were obtained on a Varian H-100 instrument in $(CD_3)_2CO$ solution for (IVa-c), and in CCl_4 solution for (VIa-c) (TMS was the internal standard). The IR spectra were obtained on a Specord instrument, while the mass spectra were taken on an RMU-6D instrument at an ionizing voltage of 70 eV.

4-Morpholino-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine (I). A solution of 77.6 g (0.5 mole) of 2,2,6,6-tetramethyl-4-oxopiperidine, 52.5 g (0.6 mole) of morpholine, and 0.5 g of benzoic acid in 300 ml of toluene was refluxed in a flask, equipped with a Dean–Stark trap, until the liberation of water ceased (6-8 h), after which the toluene was distilled off. Vacuum distillation of the residue gave 89.5 g of (I). Compounds (II) and (VIII) were obtained in a similar manner.

2,2,6,6-Tetramethyl-3-(2-benzoylethyl)-4-morpholino-1,2,3,6-tetrahydropyridine (IVa). A solution of 22.4 g (0.1 mole) of (I) and 24.1 g (0.12 mole) of 1-phenyl-3-diethylamino-1-propanol (IIIa) in 75 ml of dioxane was refluxed until the liberation of diethylamine ceased (20-24 h), after which the solvent was distilled off. The residue, which changed to a solid on standing, was recrystallized from isopropanol to give 31.4 g of (IVa). Compounds (IVb, c) and (V) were obtained in a similar manner.

2,2,6,6-Tetramethyl-3-(2-benzoylethyl)-4-oxopiperidine (VIa). A solution of 3.6 g of crude (IVa) in 10% HCl solution was treated with active carbon and left to stand for 24 h. The solution was filtered, made alkaline with 40% NaOH solution, and the obtained crystals were separated, washed with water, and recrystallized from isopropanol. We obtained 2.75 g of (IVa). Compounds (VIb, c) were obtained in a similar manner.

2,2,6,6-Tetramethyl-3-(2-benzoylethyl)-4-oxopiperidine-1-oxyl (VIIa). To a solution of 1.8 g (0.063 mole) of (VIa), 0.1 g of Trilon B, and 0.1 g of Na_2WO_4 in 10 ml of methanol was added 1.6 ml of 30% H_2O_2 solution, and the mixture was left to stand in the dark for several days until the conversion of (VIa) was complete. The reaction course was checked chromatographically. At the end of reaction the mixture was treated with 10 ml of water, and the obtained crystals were separated and recrystallized from isopropanol. We obtained 1.8 g of (VIIa). Compounds (VIIb, c) were obtained in a similar manner.

We also obtained (VIIa) by the reaction of 1.2 g (0.005 mole) of (VIII) with 1.2 g (0.006 mole) of (IIIa) and subsequent chromatographing of the product on Al_2O_3, using $CHCl_3$ as the eluant. We obtained 0.9 g (60%) of (VIIa). The mixed melting point with the above described sample was not depressed. Both samples had identical IR spectra.

CONCLUSIONS

1. The alkylation of 2,2,6,6-tetramethyl-4-oxopiperidine enamines with Mannich bases gave 3-(2-acylethyl)-2,2,6,6-tetramethyl-4-oxopiperidines, which were converted to the corresponding nitroxyl radicals by oxidation with the H_2O_2–Na_2WO_4 system.

2. Analogous stable products can be obtained by the hydrolysis of the alkylation products of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl enamines with Mannich bases.

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