CONDENSATION PRODUCTS OF 4-AMINO-2,2,6,6-TETRAMETHYLPIPERIDINE AND AMINOPIPERIDINOXYL RADICALS WITH ALDEHYDES

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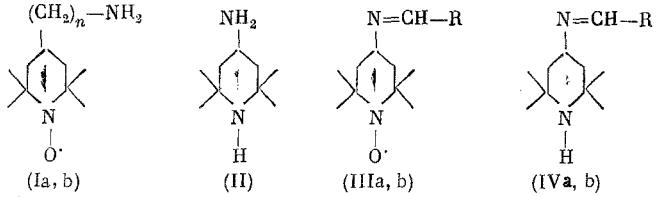
Aromatic and aliphatic aldehydes form Schiff's bases with primary amines, the bases being widely used for the synthesis of various compounds [1]. Paramagnetic Schiff's bases are of interest as intermediates for the synthesis of spin labels and probes, and also as ligands for the preparation of metal nitroxyl complexes [2, 3].

In the present work, we have studied the interaction of aminopiperidinoxyl radicals (Ia) and (Ib) and aminopiperidine (II) with formaldehyde, acetaldehyde, and benzaldehyde:



(Ia, b) (II) (IIIa, b) (IVa, b)

$n = 0$ (a), 1 (b);
R = CH_3 (a), C_6H_5 (b)

Like aromatic hydroxyaldehydes [2], benzaldehyde reacts with (Ia) and (II) to form stable azomethines (IIIb) and (IVb), respectively. This reaction proceeds rapidly and quantitatively in a variety of media. The most convenient solvent for preparing (IIIb) is methanol, since (IIIb) crystallizes immediately in analytically pure form from the reaction mixture. Since (IVb) is readily soluble in all organic solvents, it is best prepared in an aqueous medium. If freshly distilled benzaldehyde is not used, a benzoate salt of (IVb) is formed together with (IVb).

The condensation of acetaldhyde with (Ia), (Ib), and (II) is complicated by side reactions which result in the formation of a complex mixture of resinous products. If the reaction is performed at 0°C, however, (IIIa) and (IVa) are formed in 80-90% yield and crystallize in hydrate form irrespective of the character of the medium (H_2O or hexane). In contrast to the aromatic compounds, (IIIa) and (IVa) are unstable compounds which decompose back to the starting materials at room temperature.

The structure of azomethines (III)-(IV) is confirmed unequivocally by their elementary analyses and IR spectra (Table 1). The IR spectra of these substances contain strong C=N stretching bands in the 1640-1670 cm^{-1} range. The benzene ring shows up in the IR spectra of (IIIb) and (IVb) as two ring-stretching bands at 1490 and 1580 cm^{-1} and as three C–H stretching vibrations in the 3030-3080 cm^{-1} region. The amino group in (IVb) shows up as a weak band at 3310 cm^{-1}. In the hydrate of (IVa) the N–H vibration bands are masked by the strong absorption of the hydrate H_2O. Analogous H_2O bands are also present in the IR spectrum of the hydrate of (IIIa). The ESR spectra of (IIIa) and (IIIb) consist of three lines, which are characteristic of nitroxyl radicals. The azomethine group has little influence on the distribution of spin density in the radicals. Compounds (IIIa) and (IIIb) and the unsubstituted 2,2,6,6-tetramethylpiperidinoxyl radical have practically the same hyperfine coupling constants a_N and g factors.

The electronic spectra of radicals (IIIa) and (IIIb) have two nitroxyl bands with $\nu_{max} = 22{,}300$ and 41,300 cm^{-1}. In (IIIb), the second $>N\text{–}O$ band is masked by the stronger absorption of the Ph–CH=N group. This group produces bands at 36,000 and 40,300 cm^{-1} in the spectra of (IIIb) and (IVb). The first of these has a weak vibrational fine structure and partially overlaps with the second, more intense, band.

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TABLE 1. Characteristics of IR, Electronic, and ESR Spectra of Azomethines (III) and (IV) and Hexahydrotriazines (V)

Compound	IR spectrum*		Electronic spectrum†		ESR spectrum‡				
	ν, cm^{-1}	group	ν, cm^{-1}	ε, liter/mole · cm	medium	line number	apmplitude ratio	a_N, μT	g
(Va)	2665 m, 2709 w, 2734 m 2755 m, 2824 s, 2864 s 2904 s, 2937 s, 2975 s, 2993 s	C–H	22200	29,6±0,4	Heptane	9	100 : 24 : 3 : 29 : 102 : 25 : 2 : 22 : 94	1516±5	2,00627
			41000	$(6,3±0,3)\cdot10^3$	Toluene	3	100 : 99 : 94	1547±5	2,00608
(Vb)	2643 w, 2814 m, 2857 m, 2931 s, 2977 s, 2996 m	C–H	22200	31,8±0,5	Heptane	7	100 : 115 : 127 : 146 : 123 : 107 : 90	1518±1	2,00629
			41300	$(6,3±0,4)\cdot10^3$	Toluene	7	100 : 31 : 34 : 114 : 33 : 28	1548±3	2,00624
(Vc)	3323 w	N–H	–	–	–	–	–	–	–
	2660 m, 2720 w, 2750 w, 2821 m, 2846 m, 2867 m, 2889 m, 2928 s, 2959 s, 2973 s, 2997 m	C–H							
(IIIb)	1644 s, 3272 w	CH=N	22200	11,6±0,3	Heptane	3	100 : 97 : 95	1530±3	2,00619
(IVb)	3310 w	N–H	34800 sh	$(1,11±0,03)\cdot10^3$	–	–	–	–	–
	3028 m, 3065 w, 3084 w	C–H(Ph)	36000 sh	$(1,88+0,06)\cdot10^3$					
	1638 s, 3265 w	CH=N	40300	$(1,92±0,02)\cdot10^4$					
	1493 m, 1580 m	cyclic C_6							
(IIIa)	1666 s	CH=N	22400	11,2±0,2	Heptane	3	100 : 97 : 97	1526±3	2,00619
			41300	$(2,0±0,1)\cdot10^3$					
(IVa)·H_2O	1665 s	CH=N	–	–	–	–	–	–	–
	1622 m, 2194 w, 3195 s, 3412 s, 3515 s	H_2O							

* Compounds (Va-c) in CCl_4, the rest in mineral oil. Accuracy ±2 cm^{-1}.

† Recorded in 96% EtOH; accuracy ± cm^{-1} for ν; sh = shoulder.

‡ Recorded at 25°C.

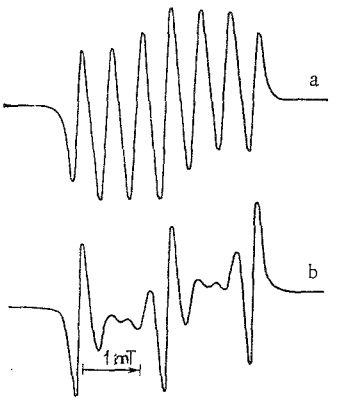


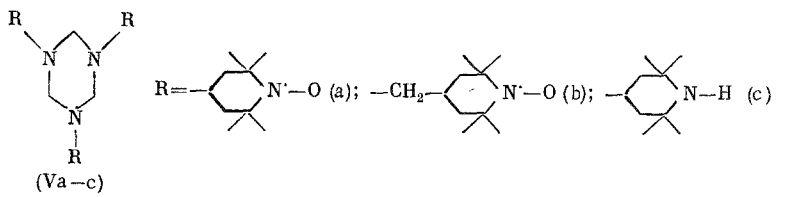
Fig. 1. ESR spectra of triradicals (V) in deaerated heptane (25°C, $5 \cdot 10^{-4}$ mole/liter): a) (Vb); b) (Va).

TABLE 2. Compositions of Adducts Formed by Triradical (Va) and Characteristic Frequencies of the Included Compounds

Included compound (IC)	IC : (Va) molar ratio	IR spectrum (ν, cm^{-1})
H_2O	0,93±0,03	1668 s, 2155 m, 3248 m, 3352 m, 3524 s
D_2O	–	1575 w, 2399 m, 2464 m, 2609 s
CH_3COCH_3	1,99±0,03	1721 m
C_2H_5OH	2,48±0,02	3251 m, 2291 w
C_6H_6	0,86±0,1	675 s, 3036 m, 3073 w, 3094 w
$Cl(CH_2)_2Cl$	2,00±0,02	652 m, 678 m, 718 m
CH_3CN	0,91±0,09	2251 m, 2291 w

The mass spectra of (III)-(IV) have peaks corresponding to the molecular ions M^+. The spectra of (IIIa) and (IIIb) have peaks corresponding to the fragment ions $[M - CH_3]^+$, $[M - CH_2O]^+$, and $[M - C_nH_{2n-1}NO]^+$, which are characteristic of piperidinoxyls [4]. The spectra of (IVa) and (IVb) have intense $[M - CH_3]^+$ peaks.

In contrast to acetaldehyde and aromatic aldehydes, the end products of the condensation of amino nitroxyls (Ia) and (Ib) and aminopiperidine (II) with formaldehyde are hexahydrotriazines (Va-c):



In aqueous media with initial reactant concentrations of ~1 mole/liter, the reaction takes place as the reactants are mixed, the hydrates of (Va) and (Vc) and anhydrous (Vb) crystallizing out in practically quantitative yield. The intermediates in this reaction are evidently the methylol derivatives of the amines (I) and (II) and the corresponding azomethines, which trimerize to the end products. Triazines (Va) and (Vb) are high-melting crystalline compounds. In contrast to the azomethines (IIIa) and (IVa), they are thermally stable and do not decompose right up to their melting points.

The IR spectra of the triradicals (Va) and (Vb) contain only a group of aliphatic CH stretching bands in the 1500-4000 cm^{-1} region (see Table 1), while the spectrum of (Vc) also contains a weak band (3315 cm^{-1} in solid, 3323 cm^{-1} in CCl_4 solution) due to N–H absorption. The electronic spectra of (Va) and (Vb) have two absorption bands characteristic of the $>N-O$ group. As would be expected, the intensity of these bands is three times that in the monoradicals.

The mass spectra of (Va-c) have weak molecular ion peaks and strong peaks corresponding to $[RNCH_2]^+$ and $[RNCH_2 - CH_3]^+$. Compounds (Va-c) are also characterized by $[M - CH_3]^+$, $[M - R]^+$, $[M - R - HCN]^+$, and $[M - 2R]^+$ ions, and (Va-b) also by $[M - CH_2O]^+$ and $[M - C_nH_{2n-1}NO]^+$ ions.

The ESR spectra of solutions of (Vb) consist of seven lines (see Table 1 and Fig. 1). The width (H) and amplitude (I) of the intermediate components depend on the temperature and the solvent, while the width of the end lines is constant and equal to the width of the corresponding lines of the initial radical (Ib). The ratio of the integral intensities of the lines, as calculated from IH^2, is 1 : 0.6 : 0.7 : 1.6 : 0.7 : 0.6 : 1 in toluene and 1 : 2 : 2.6 : 2.6 : 2.6 : 2 : 1 in heptane at 25°C. This intensity distribution is quite different from the ratio of 1 : 3 : 6 : 7 : 6 : 3 : 1 observed for triradicals with strong and rapid exchange interactions [5]. The spectrum of (Vb) evidently represents the superposition of the spectra of several conformers with exchange interactions ranging from $J \ll a_N$ to $J \gg a_N$.

The ESR spectrum of (Va) in solvents such as benzene, acetone, $CHCl_3$, nitrobenzene, and EtOH consists of three lines and remains unchanged right up to the boiling point of the solvent. The line widths for (Va) and the initial radical (Ia) are the same, the ratio of their amplitudes at the same concentration in acetone being $I_{(Va)}/I_{(Ia)} = 1.9 \pm 0.1$. This ratio is equal to 3 in the case of triradicals with $J \ll a_N$ and is equal to 1/3 in the case of triradicals with $J \gg a_N$. Consequently, (Va) has conformers with both weak and strong exchange coupling, and the additional lines are broadened by modulation of the exchange interaction. Such lines are also observed for (Va) in heptane solution, the spectrum of which consists of nine lines with approximately equal spacing between the components (see Fig. 1). In this spectrum, all the odd-numbered lines are of approximately equal width, and the width of the even lines is ~1.5 times that of the odd lines.

Triradical (Va) forms crystalline inclusion compounds with many organic substances, as shown in Table 2. Red-colored adducts with organic solvents are readily formed by recrystallization of (Va) from the solvents. The composition of these adducts corresponds to simple stoichiometric ratios, which are characteristic of clathrate compounds formed by inclusion of molecules in cage-type vacancies in the crystal lattice of the clathrate former [6]. As can be seen from the data in Table 2, 1-3 molecules of the included substance are added to one molecule of (Va). However, (Va) certainly does not form adducts with all substances. Thus, bulky tert-butanol evidently cannot enter the lattice vacancies of (Va) and does not form an adduct.

The stability of the adducts formed by (Va) varies widely. Thus, the adducts with benzene, acetone, and dichloroethane desolvate rapidly at room temperature, whereas the adducts with water and ethanol are stable under these conditions. The adduct with acetonitrile withstands prolonged heating at 56°C under vacuum. The stability of the adducts also depends on the size of the crystals. None of the adducts of (Va) prepared by us has a well-defined melting point. When heated, they gradually decompose into their components and the partially desolvated adduct then melts at a temperature 10-20° below the melting point of (Va). The adducts dissociate into their components in solution.

The x-ray powder diffraction patterns of the adducts differ strongly from one another and from that of free (Va), indicating that (Va) and its adducts have different crystal structures. The IR spectra of the solid adducts have different crystal structures. The IR spectra of the solid adducts represents the superposition of the spectra of free (Va) and the included substance. The characteristic frequencies of the latter are given in Table 2. The vibrations of the included substance interact weakly with the vibrations of (Va) and have little effect on the frequency and mode of its bands.

The ability of nitroxyl radicals to form clathrates has been discussed in [9], in which it is reported that 2,2,6,6-tetramethyl-4-oxopiperidin-1-oxyl forms adducts with hydrocarbons. As shown by x-ray structural investigation in [10, 11], however, the change in properties of the oxopiperidinoxyl observed in [9] as a function of the crystallization conditions is due not to clathrate formation but to the polymorphic transformation of the radical, which exists in three crystalline modifications.

EXPERIMENTAL

The IR spectra were obtained using a Specord 75-IR spectrometer, the electronic spectra using a Specord UV-VIS spectrometer, and the ESR spectra using an RÉ 1307 3-cm radiospectrometer. Melting points were determined using a RNMK apparatus (German Democratic Republic) and the mass spectra using an LKV-9000 instrument at an electron-ionization energy of 70 eV and an ionization-chamber temperature of 250-270°C. The aminopiperidinoxyls (Ia) and (Ib) were prepared as described in [7] and [8], respectively.

4-Amino-2,2,6,6-tetramethylpiperidine (II). A solution of 500 g triacetonamine in 1700 ml of NH_3-saturated methanol was hydrogenated in the presence of 30 g Raney nickel at 65°C and 9 MPa until H_2 absorption ceased

(~3 h). After removing the catalyst, the reaction mixture was evaporated in a rotary evaporator and the residue was distilled in a rectification column, the fraction with a bp of 77 ±0.5°C/1.33 kPa being collected. The yield of aminopiperidine was 390 g (78%).

4-Benzylidenamino-2,2,6,6-tetramethylpiperidin-1-oxyl (IIIb). A solution of 5.14 g (Ia) in 10 ml methanol was stirred while adding 3.34 ml benzaldehyde. Red crystals (6.17 g) were precipitated after 3 h, and a further 1.1 g of crystals was isolated by evaporating the solution. The overall yield of (IIIb) was 7.27 g (93.4%). Red prisms (from heptane) with a mp of 117-118°C. Found: C 74.29; H 9.04; N 10.93%; M^+ 259. $C_{16}H_{23}N_2O$. Calculated C 74.09; H 8.94; N 10.80%; M 259.3701.

4-Benzylidenamino-2,2,6,6-tetramethylpiperidine (IVb). A solution of 4.74 g (III) in 10 ml of water was treated with 3.34 ml benzaldehyde. The resulting emulsion was stirred for 6 h until it crystallized completely. The colorless precipitate (6.69 g) was filtered off, washed with water, dried in air, and extracted with 25 ml of hot hexane. The hexane-insoluble impurity (0.7 g), i.e., the benzoate salt of (IVb), was filtered off and the solution was evaporated, resulting in the crystallization of colorless crystals of (IVb), mp 70°C. Yield 5.8 g (78%). Found: C 78.68; H 9.88; N 11.48%; M^+ 244. $C_{16}H_{24}N_2$. Calculated: C 78.64; H 9.90; N 11.46%; M^+ 244.388, 244.379.

Benzoate Salt of (IVb). This was prepared by mixing ether solutions of (IVb) and benzoic acid. Colorless needles (from EtOH), mp 161-164°C. Found: N 7.58%. $C_{23}H_{30}N_2O_2$. Calculated: N 7.64%. IR spectrum (in mineral oil, ν, cm^{-1}): 1380 and 1539 (CO_2^-), 1577 and 1631 (Ph), 1639 (C=N), 1589, 2134, 2172, 2375, 2440, 2600, 2657, and 2736 ($\overset{+}{N}H_2$), 3021, 3062 and 3082 (CH, Ph).

4-Ethylidenamino-2,2,6,6-tetramethylpiperidin-1-oxyl (IIIa). A solution of 3.42 g (Ia) in 10 ml H_2O was stirred and ice-cooled while adding 1.35 ml acetaldehyde. After 1 h, the precipitated yellow-orange platelets of the hydrate of (IIIa) were filtered off, washed with cold water, and dried in air. Yield 3.35 g (78%), mp 59-60°C. Found: C 61.25; H 10.68; N 13.34%. $C_{11}H_{23}N_2O_2$. Calculated: C 61.36; H 10.77; N 13.01%. IR spectrum (in mineral oil, ν, cm^{-1}): 1668 (C=N), 1644, 2169, 3235, 3336, and 3516 (H_2O). Upon drying over a zeolite under vacuum (6 Pa, 20°C, 20 h), the hydrate is converted to anhydrous (IIIa) Red platelets (from hexane), mp 55-57°C. Found: M^+ 197. $C_{11}H_{21}N_2O$. Calculated: M 197.300.

4-Ethylidenamino-2,2,6,6-tetramethylpiperidine (IVa). A solution of 3.25 g (II) in 10 ml hexane was stirred and ice-cooled while adding 1.41 ml acetaldehyde. After 1 h, the precipitated colorless crystals of the hydrate were filtered off, washed with cold hexane, and dried in air for 10 min. Yield 3.5 g (88%). Colorless prisms (from hexane), mp 55°C. Found: N 13.81%. $C_{11}H_{24}N_2O$. Calculated: N 13.98%. On drying under vacuum, the substance volatilizes and decomposes into the starting materials.

1,3,5-Tris(2,2,6,6-tetramethyl-1-oxylpiperidin-4-yl)hexahydro-1,3,5-triazine (Va). A solution of 5.14 g (Ia) in 30 ml water was stirred while adding 4 ml of 10.5 M formalin, resulting in immediate precipitation of rose-colored fine crystals of the hydrate of (Va), which were filtered off, washed with cold water, and dried in air. Yield 5.61 g (99%).

When the initial reactant concentrations are $[Ia] = (5-7)\cdot 10^{-2}$ and $[CH_2=O] = 0.1$ mole/liter, well-defined red needles of the monohydrate of (Va), mp 130-181°C (decomp.), crystallize slowly from the aqueous solution. Found: C 63.85; H 10.55; N 14.65%. $C_{30}H_{59}N_6O_4$. Calculated: C 63.35; H 10.47; N 14.80. On drying under vacuum (1 Pa, 56°C, 1 h), the hydrate is converted to anhydrous (Va), mp 175-185°C. Found: M^+ 549. Calculated: M 549.82.

Molecular Compounds of Triradical (Va). Anhydrous (Va) was dissolved by boiling in the minimum amount of organic solvent. On cooling the solutions, the adducts crystallize as red crystals, which were filtered off, washed with the solvent, and dried in air. The composition of the adduct with MeCN was determined spectrophotometrically on the basis of the 2257 cm^{-1} band in the IR spectrum of its solution in CCl_4. The composition of the other adducts were determined by drying the substance under vacuum (~1 Pa) at room temperature.

1,3,5-Tris(2,2,6,6-tetramethylpiperidin-4-yl)hexahydrotriazine (Vc). A solution of 7.8 g (II) in 40 ml H_2O was stirred while adding 9.52 ml of 10.5 M formalin. The colorless hydrate of (Vc) precipitated immediately, mp 130-155°C. IR spectrum (in mineral oil, ν, cm^{-1}): 3275 (NH), 1515, 1660, 2185, and 3385 (H_2O). On drying under vacuum (20°C, 1 Pa), the hydrate is converted to anhydrous (Vc). Yield 7.2 g (86%) of colorless needles (from MeCN), mp 180-182°C. Found: C 71.74; H 12.04; N 16.68%; M^+ 504. $C_{30}H_{60}N_6$. Calculated: C 71.37; H 11.98; N 16.65%; M 504.844.

1,3,5-Tris(2,2,6,6-tetramethyl-1-oxylpiperidin-4-ylmethyl)hexahydrotriazine (Vb). A suspension of 339 ml (Ib) in 6 ml H_2O was stirred while adding 0.35 ml of 10.5 M formalin. After 1 h, the precipitated crystals of (Vb) were filtered off, washed with water, and dried under vacuum. Yield 328 mg (91%) of red prisms (from

heptane), mp 170-172°C. Found: C 66.91; H 10.73; N 14.43%; M^+ 591. $C_{33}H_{63}N_6O_3$. Calculated: C 66.97; H 10.73; N 14.20%; M 591.898.

The authors wish to thank B. V. Rozynov for recording the mass spectra.

CONCLUSIONS

1. Aminopiperidine oxyl and the corresponding aminopiperidine react with acetaldehyde to form thermally unstable azomethines, which readily decompose back to the starting materials.

2. Aminopiperidine oxyls and aminopiperidines react quantitatively with formaldehyde to form the corresponding hexahydrotriazines.

3. A paramagnetic clathrate former which forms crystalline inclusion compounds with organic substances has been prepared for the first time.

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REDUCTION OF ALIPHATIC NITRO COMPOUNDS. 4. REGIOSELECTIVE REDUCTION OF THE NITRO GROUP IN INDOLYLNITROACRYLATES AND THE SYNTHESIS AND STRUCTURE OF α,β-DEHYDROTRYPTOPHAN DERIVATIVES

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The regioselective reduction of the nitro group in α-nitroacrylates to give α,β-dehydrotryptophan derivatives has acquired importance in recent years in light of advances in the asymmetric synthesis of α-amino acids using these derivatives.

In earlier work [1, 2], we showed that one of the most important amino acids, tryptophan, may be obtained by the stepwise reduction of the equilibrium mixture of Z- and E-isomers [3] of methyl α-nitro-β-(indol-3-yl)acrylate (I) initially over Pd black and then in an autoclave over Raney nickel. In a later study of the first reduction step, we found that the hydrogenation of (I) at atmospheric pressure over palladium leads to the formation of methyl α-amino-β-(indol-3-yl)acrylate (II) and methyl α-nitro-β-(indol-3-yl)propionate (III) in 34 and 52% yield, respectively [4].

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