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SYNTHESIS OF ISOCYANATO- AND CARBODIIMIDOPIPERIDINOXYLS FROM 4-AMINO-2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL

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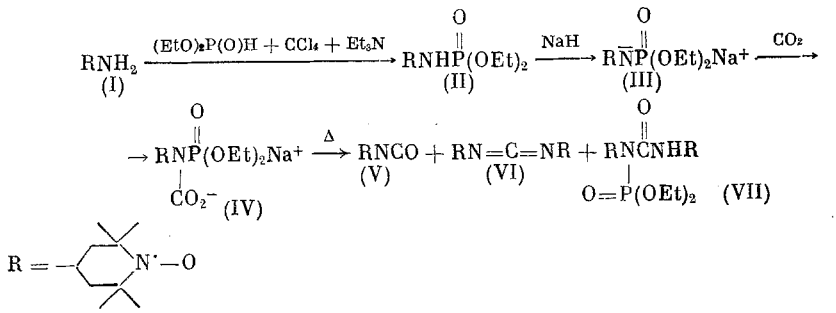
UDC 542.91:547.823

The Curtius rearrangement is used to prepare isocyanates of nitroxyl radicals [1]. However, carboxy-derivatives of nitroxyls are not always readily available and thus we used the thermal decomposition of N-carboxyphosphamide salts [2].

In the present work, we synthesized isocyanato- and carbodiimidopiperidinoxyls (V) and (VI) from aminopiperidinoxyl (I) by the following scheme



Amino radical (I) was converted to amide (II) by the Atherton–Todd reaction [3]. This reaction proceeds readily at about 20°C although the complete conversion of (I) cannot be achieved upon prolonged reaction even using a 1.5-fold excess of $(EtO)_2P(O)H$. Unreacted (I) may be removed from the product by chromatography on silica gel or by washing the ethereal solution with dilute acid. The latter method is simplest although it involves considerable losses of amide (II). In addition, the monohydrate (II)$\cdot H_2O$ may precipitate from the moist

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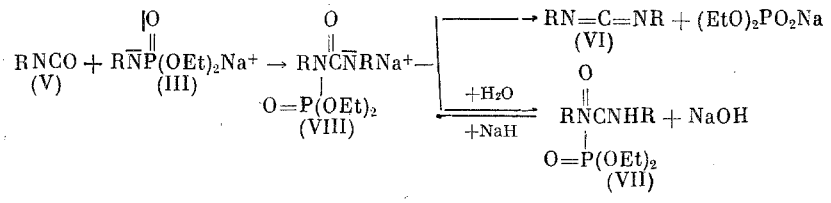
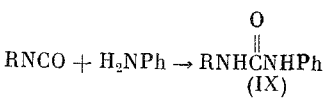
ethereal solution. The deuterohydrate of the deuteroamide (II-D)•D_2O crystallizes upon washing of the reaction solution with a deuteroacid. The hydrates of amide (II) are stable in the air and are dehydrated only with difficulty. Upon drying in vacuum, they melt as a result of the partial loss of water. The crystallization of (II)•H_2O may be avoided by rapid drying with Na_2SO_4 and molecular sieves after acid washing of the reaction solution. Subsequent treatment of (II) with sodium hydride, CO_2, and heating led to the formation of a mixture of products: isocyanate (V), carbodiimide (VI), and trisubstituted urea (VII). The ratio of these products depends on the reaction conditions.

The reaction of (II) with NaH in dimethoxyethane (DME) proceeds smoothly at about 20°C with the liberation of an equivalent amount of H_2 and the formation of amidate (III). In a separate experiment using 2,2,6,6-tetramethylpiperidine-1-oxyl, we found that the $>N^{\cdot}-O$ group does not react with NaH under these conditions as indicated by ESR and spectrophotometric control. The addition of CO_2 to the anion of (III) leads to salt (IV). This salt is rather stable at about 20°C. It remains as a red oil after removal of the solvent from the reaction mixture in vacuum and its IR spectrum in the region from 1500 to 2800 cm^{-1} has only the CO_2^- group band at 1650 cm^{-1}.

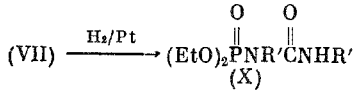
The heating of (IV) gives decomposition to RNCO (V) and $(EtO)_2PO_2Na$, as well as partial decarboxylation to starting (III) accompanied by gas liberation. An enhanced CO_2 pressure hinders the decarboxylation of (IV) and the yield of (V) increases from 10% at atmospheric pressure to 63% at about 100 atm. Then, isocyanate (V) reacts with (III) to form urea salt (VIII). The thermal decomposition of this salt leads to carbodiimide (VI), while hydrolysis, probably by the action of traces of moisture, leads to urea (VII). Heating of (VII) with NaH leads to carbodiimide (VI), which supports the hypothesis that (VIII) is a precursor of (VI)

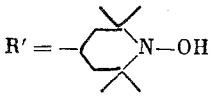


Isocyanate (V) crystallizes as long red prisms which sublimate readily, and has a specific odor. It reacts with aniline to form a high-melting urea (IX), which readily crystallizes.



Carbodiimide (VI) forms pink crystals which are stable in the air. IR spectroscopy indicates that heating a solution of (VI) in moist benzene for 3 h gives less than 5% hydrolysis to the symmetrical urea. Urea (VII) forms red crystals which melt without marked decomposition. In solution, (VII) slowly decomposes to (VI) even at 80°C. At atmospheric hydrogen pressure in the presence of platinum black at almost 20°C, (VII) is readily hydrogenated at the nitroxyl group to give (X)





The structures of the radicals obtained were indicated by elemental analysis and spectral methods. The characteristic IR bands are given in Table 1. The mass spectra display molecular ion peaks M^+ as well as fragment ions for piperidine nitroxyls $[M - Me^+]$, $[M - CH_2O]^+$, $[M - NO]^+$, $[M - CH_2{=}CMe_2]^+$, $[M - Me_2CH - NO]^+$, and $[M - CH_2{=}CMe_2 - NO]^+$. For (VII), the M^+ ion is found only for rapid heating of the sample in the ionization chamber (100 deg/min). In the case of slower heating, the ion with largest mass in the mass spectrum is found at m/z 350. The formation of this ion is apparently the result of the thermolysis of (VII) to (VI) (M^+, m/z 350).

TABLE 1. IR, UV, and ESR Spectra of Derivatives of 2,2,6,6-Tetramethylpiperidine-1-oxyl

Compound	IR spectrum*		UV spectrum			ESR spectrum †	
	ν, cm^{-1}	group	solvent	λ_{max}, nm	E, liters/mole·cm	a_N, mT (±0,002)	g-factor (±0,00001)
(II)	965, 1031, 1058 1230 3210, 3437,	P–O P=O N–H	EtOH	242 452	2080 10,6	1,552	2,00588
(V)	2193, 2262, 2280	N=C=O	MeCN	241 465	1970 10,1	1,548	2,00591
(VI)	2057, 2115	N=C=N	MeCN	241 464	4250 20,3	1,548	2,00590
(VII)	982, 1015, 1045 1537 1678 3287	P–O CONH C=O N–H	EtOH	243 453	4470 21,3	1,551	2,00587
(IX)	1516, 1597 1731, 1792, 1863, 1955 3030, 3038, 3083 3135, 3198, 3292, 3337, 3372 1545 1695	C=C(Ph) Ph CH(Ph) N–H $CO(NH)_2$ C=O	EtOH	241 268 пл 274 пл 452	24700 2400 2060 10,6	1,551	2,00590

*The spectrum of the liquid is given for (II) while the spectra of vaseline mulls are given for the other compounds.
†In benzene at about 20°C and concentration of $5 \cdot 10^{-4}$ mole/liter.

The ESR spectra of dilute solutions of monoradicals (II), (V), and (IX) show three lines while the spectra of biradicals (VI) and (VII) display a greater number of lines. The hyperfine coupling constants a_N and g factors of the radicals obtained are given in Table 1. These characteristics are approximately identical for all the piperidine radicals. Thus, $a_N = 1.563 \pm 0.002$ mT and $g = 2.00585 \pm 2 \cdot 10^{-5}$ for a benzene solution of 2,2,6,6-tetramethylpiperidine-1-oxyl.

The spectra of biradicals (VI) and (VII) change depending on the temperature and solvent. The spectra of benzene solutions of (VI) and (VII) at 25°C consist of 11 and 13 lines with amplitude ratio 4:100:39:6:48:97:42:8:41:95:4 and 0.3:1:20:100:73:57:95:45:73:86:17:0.8:0.25. Both spectra are symmetrical relative to the central line while the distances of the sidebands to the central line in a_N units are 0.33, 0.56, 0.68, 1, 1.82 for (VI) and 0.29, 0.68, 1, 1.58, 1.95, 2.11 for (VII).

The UV spectra of the radicals obtained have two bands for the $\rangle N^{\cdot}-O$ group with maxima at ~240 and 450-470 nm. The molar absorption coefficients ε for the biradicals are twice as great as for the monoradicals (Table 1). The short-wavelength band for the $\rangle N^{\cdot}-O$ group in the spectrum of (IX) is superposed by the stronger absorption of the benzene chromophore (see Table 1).

EXPERIMENTAL

The IR spectra were taken on a Specord 75-IR spectrophotometer. The electronic spectra were taken on a Specord UV-VIS spectrometer. The ESR spectra were taken on an RE-1307 radiospectrometer. The mass spectra were taken on a Finnigan chromatomass spectrometer at electron ionization energy 16-70 eV and ionization chamber temperature 200-250°C with rapid heating of 100 deg/min for heat-sensitive compounds. The melting points were taken on a PHMK heating block manufactured in East Germany.

4-(Diethylphosphorylamino)-2,2,6,6-tetramethylpiperidine-1-oxyl (II). A sample of 4.3 ml triethylamine was added with stirring to a solution of 4.25 g diethyl phosphite and 5 ml CCl_4 in 50 ml dry ether cooled to 0°C and then, a solution of 5.27 g 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl in 20 ml ether was added. The mixture was stirred for an additional 2 h without cooling and left to stand overnight. The triethylamine hydrochloride precipitate

was filtered off and the filtrate was washed with 1 N H_2SO_4 at 0-5°C until the wash water was neutral. Depending on the means of drying, either the monohydrate (II)•H_2O or anhydrous (II) was obtained.

Drying over molten $CaCl_2$ gives crystallization of 5.2 g (52%) (II)•H_2O from ethereal solution as pink needles with mp 75-78°C (from DME). Found: N 8.6 ± 0.1, H_2O 5.3 ± 0.2%. $C_{13}H_{28}N_2O_4P•H_2O$. Calculated, %: N 8.61; H_2O 5.53. IR spectrum (Vaseline oil, ν, cm^{-1}): 1625, 3352, 3545 (H_2O), 3215 (NH). Washing with 1 N H_2SO_4 in D_2O gives (II-D)•D_2O. IR spectrum (Vaseline oil, ν, cm^{-1}): 2480, 2616 (D_2O), 2405 (ND).

Thorough drying of the washed ethereal solution over roasted Na_2SO_4 and then 5 Å molecular sieving with subsequent removal of the solvent in vacuum gave 7.46 g (79%) anhydrous (II) as hygroscopic red plates with mp 38-47°C which distill with partial decomposition at 180-190°C (1.2 Pa). Found, %: C 50.5 ± 0.3; H 9.3 ± 0.1; N 9.0 ± 0.1; m/z 307 (M^+). $C_{13}H_{28}N_2O_4P$. Calculated, %: C 50.80; H 9.18; N 9.11. M 307.35. The yield of (II) could be enhanced to 91% if the reaction mixture was subjected to chromatography on a silica gel column with acetone eluent without washing.

4-Isocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl (V), Di-(2,2,6,6-tetramethyl-1-oxyl-piperidin-4-yl)carbodiimide (VI), and N,N'-Di-(2,2,6,6-tetramethyl-1-oxyl-piperidin-4-yl)-N-diethylphosphorylurea (VII). A solution of 4.89 g anhydrous (II) in 8 ml DME was added in an argon atmosphere with stirring to a suspension of 420 mg NaH in 7 ml DME (freshly distilled over $LiAlH_4$). After liberation of the calculated hydrogen volume over about 4 h, the reaction mixture was cooled with ice and saturated for 1 h with dry CO_2 and then heated in a reflux for 1 h. The solution was separated from the tarry precipitate and the precipitate was washed twice with 1 ml hot DME. Cooling of the combined solution gave 0.89 g (32%) (VI) as pink needles with mp 175-178°C (from benzene). Found, %: C 65.2 ± 0.1; H 9.72 ± 0.06; N 15.9 ± 0.1; m/z 350 (M^+). $C_{19}H_{34}N_4O_2$. Calculated, %: C 65.11; H 9.78; N 15.98. M 350.50. Removal of the solvent from the remaining mother liquor in vacuum gives red crystals. Sublimation of these crystals at 80-100°C (5 Pa) gave 315 mg (10%) (V) as red rods with mp 102-103°C. Found, %: C 60.85 ± 0.05; H 8.80 ± 0.2; N 14.2 ± 0.2; m/z 197.1 (M^+). $C_{10}H_{17}N_2O_2$. Calculated, %: C 60.89; H 8.69; N 14.20. M 197.26. After sublimation, chromatography of the residue on silica gel with chloroform eluent gave 0.84 (21%) (VII) as pink rods with mp 157-159°C (from DME). Found, %: C 55.0 ± 0.2; H 8.95 ± 0.05; N 11.0 ± 0.1; m/z 504.6 (M^+). $C_{23}H_{45}N_4O_6P$. Calculated, %: C 54.75; H 8.99; N 11.10; M 504.61. If the reaction mixture is heated after saturation with CO_2 in an autoclave under CO_2 pressure of about 100 atm, the yield of (V) is raised to 63%.

Reaction of (VII) with NaH. A solution of 0.43 g (VII) in 1.5 ml DME was added in an argon atmosphere to a suspension of 24 mg NaH in 1 ml DME. The mixture was heated at reflux for 1.5 h and the hot solution was filtered. Cooling gave crystallization of 150 mg (50%) (VI).

N,N'-Di-(1-hydroxy-2,2,6,6-tetramethylpiperidin-4-yl)-N-diethylphosphorylurea (X). A sample of 504 mg (VII) was hydrogenated in the presence of 95 mg PtO_2 in 10 ml ethanol at 30°C. After absorption of the calculated amount of hydrogen in about 10 min, the solution was filtered and evaporated to one-half of the original volume. Cooling gave 300 mg (59%) (X) as colorless prisms with mp 196-202° (decomp., from ethanol). IR spectrum (Vaseline oil, ν, cm^{-1}): 3422, 3388 (OH), 3328 (NH), 1678 (C=O), 1525 (CONH), 1050, 1020, 968 (P–O).

N-(2,2,6,6-Tetramethyl-1-oxylpiperidin-4-yl)-N'-phenylurea (IX). A solution of 0.193 g aniline in 2 ml ether was added with stirring to a solution of 0.41 g (V) in 5 ml dry ether. The mixture was let stand for 24 h to yield a crystalline precipitate of 0.47 g (78%) (IX) as orange rods with mp 160-161°C (from DME). Found, %: C 66.3 ± 0.1; H 8.3 ± 0.05; N 14.3 ± 0.1; m/z 290.3 (M^+). $C_{16}H_{24}N_3O_2$. Calculated, %: C 66.18; H 8.33; N 14.47; M 290.38.

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CONCLUSIONS

The reaction of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl with diethyl phosphite yields 4-(diethylphosphorylamino)-2,2,6,6-tetramethylpiperidine-1-oxyl. Subsequent treatment with NaH, CO_2, and heating gives 4-isocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl and di(2,2,6,6-tetramethyl-1-oxylpiperidin-4-yl)carbodiimide.

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REACTION OF ALKYLTHIOLCHLOROPHOSPHONITES AND DIALKYLCHLORODITHIOPHOSPHITES WITH CARBONYL COMPOUNDS

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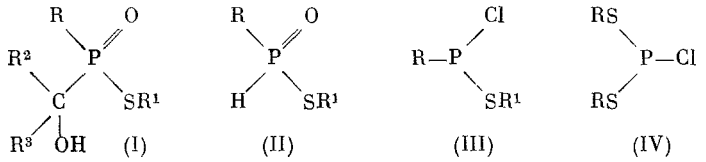
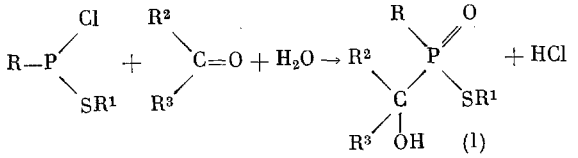
Thiol esters of α-hydroxyalkylthiophosphinic acids (I), which have not yet been described, hold interest as potentially physiologically active compounds. A possible pathway for the synthesis of (I) may be the addition of acid S-alkylthiophosphonites (II) to carbonyl compounds



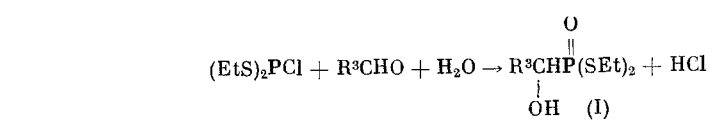
However, we were unable to find information indicating the existence of (II) as a free compound. On the other hand, several reactions of S-alkylchlorothiophosphonites (III) which yield the products of the addition of thiolphosphonites (II) to unsaturated ketones indicate that thiophosphonites (II) are formed as intermediates from acid chlorides (III) by hydrolysis [1, 2].

Hence, as continuation of work on the synthesis of α-hydroxyalkylphosphoryl compounds [3-5], we studied the reaction of S-alkylchlorothiophosphonites (III) for R = Et and Ph and S,S-dialkylchlorodithiophosphites (IV) with aldehydes and ketones in the presence of hydroxyl-containing compounds.

The reaction of acid chlorides (III) with aldehydes or ketones and water in equimolar amounts at 10-15°C in ether yields S-alkyl esters of alkyl- and aryl-α-hydroxyalkylthiophosphinic acids (I) in 60-90% yield



The reaction of diethylchlorodithiophosphite (IV) (R = Et) with carbonyl compounds and water proceeds analogously to give S,S-diethyl-α-hydroxyalkyldithiophosphonates (I) with R = EtS



$R^3 = Cl_3C$, $o\text{-}O_2NC_6H_4$.

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2114-2121, September, 1983. Original article submitted December 15, 1982.

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