REACTION OF 2-SUBSTITUTED 5,5-DIMETHYL-4-OXO-1-PYRROLINE-1-OXIDES WITH NUCLEOPHILIC REAGENTS AND SYNTHESIS OF NITROXYL RADICALS – DERIVATIVES OF PYRROLIDINE

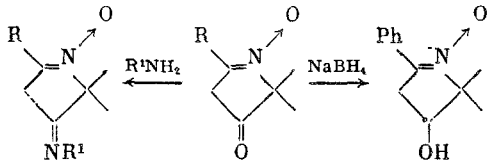
V. A. Reznikov and L. B. Volodarskii

UDC 542.91:541.515:547.743.1

The reaction of β-oxonitrones, derivatives of pyrroline, with nitrogeneous nucleophiles and $NaBH_4$ proceeds at the carbonyl group with the retention of the nitrone group. The reaction with organomagnesium and organolithium compounds takes place at the nitrone group with the retention of the carbonyl group, while the oxidation of the products formed proceeds to form nitroxyl radicals – derivatives of pyrrolidin-4-one, which were used in the synthesis of spin-labeled dioximes.

From the study of the reaction of pyrrolines (I) – cyclic β-oxonitrones – with electrophilic reagents, we showed that the reactions may proceed at the carbon atom between the carbonyl and the nitrone groups [1]. Considering that compounds (I) can exist in both the oxonitrone and in the enhydroxylamino-ketone tautomeric forms, we can note a definite similarity with respect to the reactivity of these compounds and the enaminoketones, in reactions with electrophilic reagents. It could be expected that also in reactions with nucleophilic reagents, pyrrolines (I) will behave similarly to enaminoketones, i.e., the attack of the nucleophile will occur at the carbon atom bound to the nitrogen atom. However, we also should not exclude the possibility of the occurrence of this reaction at the carbonyl group. Data on the reaction of β-oxonitrones with nucleophilic reagents are not to be found in the literature. The aim of the present work was to examine the reaction of cyclic β-oxonitrones, derivatives of pyrroline (I), with nucleophilic reagents.

The reaction of compounds (I) with hydrazine, hydroxylamine O-methylhydroxylamine and sodium borohydride proceeds exclusively at the carbonyl group with the retention of the nitrone group, as indicated by the UV spectra of the compounds obtained, in which an absorption characteristic for the nitrone group is observed. As a result of the reaction, hydrazones (II), oximes (III), and alcohol (IV), respectively, are formed.



(II), (III) (I) (IV)

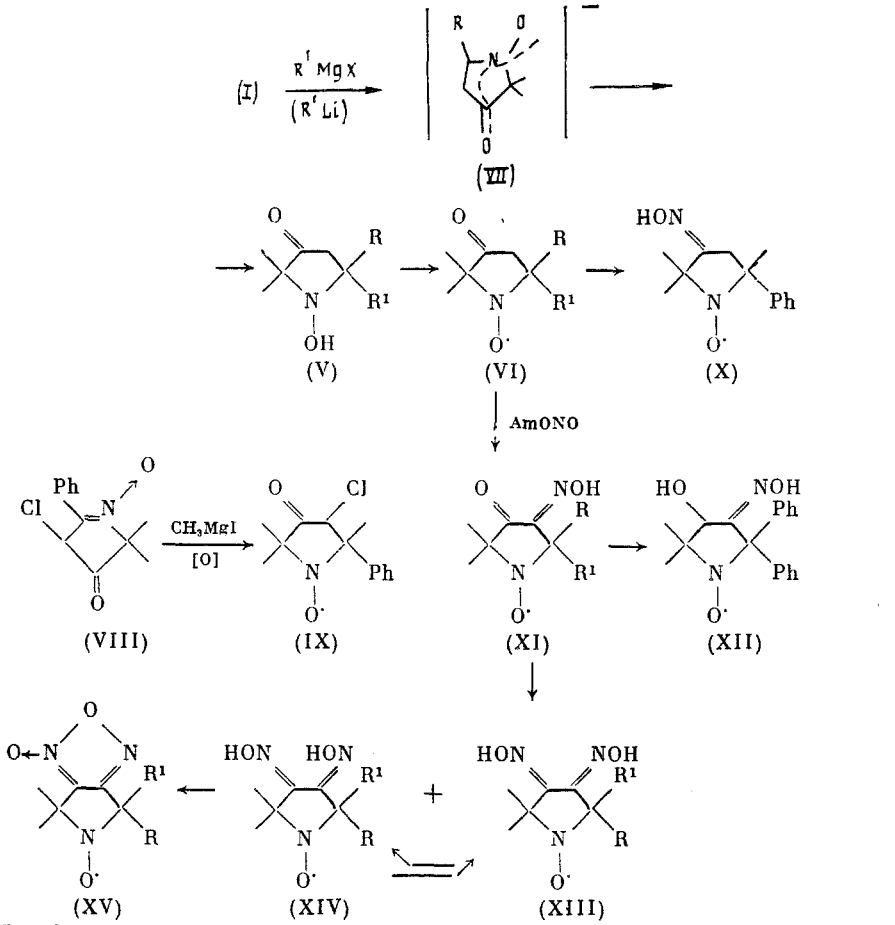
R = C_6H_5 (IIa), (IIIa), CF_3 (IIb), (IIIb,c); R^1 = NH_2 (IIa,b) OH (IIIa,b), OCH_3 (IIIc)

According to the literature data, when isolated oxo- and nitrone functions are present in the molecule, the reaction with organometallic compounds proceeds primarily at the carbonyl group [2, 3]. Contrary to this, in the reaction of pyrroline (Ib) with methylmagnesium iodide, an addition product (V) is formed at the nitrone group, the oxidation of which leads smoothly to a nitroxyl radical (VI). As known, β-oxonitrones are strong CH-acids [3], and therefore the reaction with one equivalent of the organometallic compound leads to the formation of an anion (VII), which on reacting with the second equivalent of the organometallic compound forms an addition product at the nitrone group. In the adduct formed, the carbonyl group is enolized and further addition does not take place. The reaction of other pyrrolines (I) with organomagnesium or organolithium compounds proceeds in a similar way. In no case was an addition product at the carbonyl group observed. The above scheme of preparation of

Novosibirsk Institute of Organic Chemistry, Siberian Branch of Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 390-395, February, 1990. Original article submitted December 15, 1988.

0568-5230/90/3902-0329$12.50

the nitroxyl radicals, derivatives of pyrrolidin-3-one, makes it possible to vary the substituents within wide limits in the immediate vicinity of the nitroxyl group (cf. [4]). It should be noted that the reaction of the monochloro derivative (VIII) with methylmagnesium iodide also proceeds by addition at the nitrone group, and after the oxidation, a nitroxyl radical (IX) is formed.



R = CH_3, R^1 = CH_3 (a), C_6H_5 (b), CF_3 (c), 2-pyridyl (d); R = C_6H_5, R^1 = CF_3 (e), C_6H_5 (f), 2-pyridyl (g), $(CH_3)_3C$ (h); R = C_4H_9, R^1 = CF_3 (i).

In the reaction of compound (VI) with hydroxylamine and subsequent oxidation, oxime (X) is formed. Nitrosation of pyrrolidine-1-oxyls (VI) with amyl nitrite in an alkaline medium leads to a mixture of E- and Z-isomers of oximes (XI). In the reduction of compounds (XIf) by sodium borohydride, α-hydroxyoxime (XII) is obtained, forming complex compounds with several metals. A series of chelate-forming spin-labeled compounds, dioximes (XIII), was obtained by oximation of compounds (XI) by the action of hydroxylamine, followed by oxidation with MnO_2. Thus, not only is an anti-isomer (XIII) formed, but also a certain amount of an amphi-isomer (XIV), the proportion of which increases with increase in the volume of substituents R and R^1, which makes it possible to ascribe the configuration shown in the scheme to the amphi-isomer. When the solutions of compounds (XIII) and (XIV) in alcohol are allowed to stand, their mixture is formed. On oxidation under mild conditions of compounds (XIII) and (XIV) with MnO_2, furoxanopyrrolidines (XV) are unexpectedly formed.

As known, in the reaction of enaminoketones with the Lawson reagent enaminothiones are formed [5]. In contrast to this, under similar conditions, or by the action of P_2S_5 in benzene on pyrrolines (I), the carbonyl group is replaced by a thiocarbonyl group with simultaneous deoxygenation, leading to enaminothiones (XVI) (see scheme on page 332).

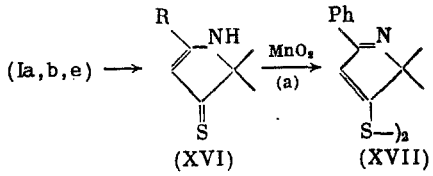
TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	Mp, °C	Found/Calculated, %			Empirical formula	IR spectrum (KBr), ν, cm^{-1}	UV spectrum (ethanol)
			C	H	N			
(IIa)	80	152–154	65,7 65,9	6,9 6,9	19,0 19,3	$C_{12}H_{15}N_3O$	1565 (C=N), 1575 (C=N), 3220, 3340 (NH_2)	227 (4,33) 296 (4,41)
(IIb)	90	98–100	40,0 40,2	5,0 4,8	19,8 20,1	$C_7H_{10}F_3N_3O$	1610 (C=N)	242 (3,43)
(IIIa)	100	168–170	65,4 65,1	6,4 6,4	12,5 12,8	$C_{12}H_{14}N_2O_2$	1560 (C=N), 1580 (C=C), 3285, 3385 (NOH)	227 (3,90) 286 (4,18)
(IIIb)	90	100–101	36,8 36,8	4,8 4,8	12,5 12,5	$C_7H_9F_3N_2O\cdot H_2O$	1640 (C=N)	–
(IIIc)	80	57–58	43,0 42,8	4,8 4,9	12,6 12,5	$C_8H_{11}F_3N_2O_2$	1660 (C=N)	–
(IV)	95	157–158	70,3 70,3	7,5 7,3	6,7 6,8	$C_{12}H_{15}NO_2$	1570, 1585 (C=C, C=N) 3610 (OH, in CCl_4)	227 (3,90) 293 (4,23)
(IVd)	70	42–43	65,4 65,8	6,9 6,9	12,8 12,8	$C_{12}H_{15}N_2O_2$	1770 (C=O), 1600 (C=N)	–
(VIf)	95	84–85	77,3 77,2	6,4 6,4	5,0 5,0	$C_{18}H_{18}NO_2$	1765 (C=O)	–
(VIg)	40	Oil	72,3 72,6	5,6 5,8	10,0 10,0	$C_{17}H_{17}N_2O_2$	1770 (C=O), 1660 (C=C, C=N)	–
(VIh)	60	112–114	73,6 73,8	8,3 8,5	5,7 5,4	$C_{16}H_{22}NO_2$	1760 (C=O)	–
(IX)	40	81–83	61,6 61,8	6,0 6,0	5,3 5,6	$C_{13}H_{15}ClNO_2$	1780 (C=O)	–
(X)	85	145–147	67,0 67,0	7,5 7,3	11,8 12,0	$C_{13}H_{17}N_2O_2$	1605 (C=N)	–
(XIb)	80	172–173	62,5 62,2	6,0 6,1	11,4 11,3	$C_{13}H_{15}N_2O_3$	1755 (C=O), 1625 (C=N)	245 (4,04)
(XIc)	65	141–142	40,3 40,2	4,2 4,2	11,8 11,7	$C_8H_{10}F_3N_2O_3$	1740 (C=O), 1620 (C=N)	238 (3,95)
(XId)	75	184–186	58,0 58,1	5,6 5,6	16,8 16,9	$C_{12}H_{14}N_3O_3$	1740, 1750 (C=O), 1640, 1595 (C=N)	255 (4,07)
(XIf)	60	160–162	69,0 69,0	5,6 5,5	8,9 9,1	$C_{18}H_{17}N_2O_3$	1740 (C=O), 1620 (C=N)	244 (3,91)
(XII)	70	180–182	69,3 69,5	6,3 6,1	9,0 9,0	$C_{18}H_{19}N_2O_3$	1600 (C=N)	–
(XIIIa)	50	205–209	47,6 48,0	7,2 7,0	20,9 21,0	$C_8H_{14}N_3O_3$	1640 (C=N)	238 (3,92)
(XIIIb)	30	193–196	59,2 59,6	6,1 6,1	15,8 16,0	$C_{13}H_{16}N_3O_3$	1640 (C=N)	238 (3,99)
(XIIIc)	70	204–206	37,8 37,8	4,2 4,3	16,5 16,5	$C_8H_{11}F_3N_3O_3$	1620 (C=N)	232 (4,01)
(XIIId)	35	210–211	54,4 54,8	5,7 5,7	21,0 21,3	$C_{12}H_{15}N_4O_3$	1595 (C=N)	250 (3,97)
(XIIIf)	30	194–196	67,1 66,8	5,8 5,6	12,8 13,0	$C_{18}H_{18}N_3O_3$	1600 (C=N)	236 (3,99)
(XIIIg)	15	186–188	62,7 62,8	5,4 5,2	16,8 17,2	$C_{17}H_{17}N_4O_3$	1595 (C=N)	253 (3,92)
(XIVb)	15	217–218	59,3 59,6	6,3 6,1	15,8 16,0	$C_{13}H_{16}N_3O_3$	1620 (C=N)	246 (4,0)
(XIVd)	25	220–222	54,5 54,8	5,6 5,7	21,0 21,3	$C_{12}H_{15}N_4O_3$	1600 (C=N)	254 (3,99)
(XIVg)	30	205–206	62,7 62,8	5,3 5,2	17,1 17,2	$C_{17}H_{17}N_4O_3$	1595 (C=N)	257 (4,03)
(XVa)	15	98–100	48,4 48,4	6,1 6,1	21,2 21,2	$C_8H_{12}N_3O_2$	1680 (C=N)	270 (3,62)
(XVb)	20	64–65	60,0 60,0	5,6 5,7	16,4 16,2	$C_{13}H_{14}N_3O_3$	1680 (C=N)	270 (3,60)

TABLE 1 (continued)

Compound	Yield, %	Mp, °C	Found/Calculated, % C	H	N	Empirical formula	IR spectrum (KBr), ν, cm^{-1}	UV spectrum (ethanol)
(XVd)	15	102–103	55,0 55,2	4,9 5,0	21,2 21,5	$C_{12}H_{13}N_4O_3$	1675 (C=N)	258 (3,86)
(XVf)	20	113–115	67,2 67,1	5,1 5,0	12,8 13,1	$C_{18}H_{16}N_3O_3$	1665 (C=N)	244 (3,73) 277 (3,62)
(XVIa)	70	170–172	70,6 70,9	6,4 6,4	6,3 6,9	$C_{12}H_{13}NS$	1605, 1570 (C=C), 3440 (NH in CCl_4)	272 (4,26) 413 (4,33)
(XVIb)	80	130–132	43,5 43,2	4,2 4,1	7,1 7,2	$C_7H_8F_3NS$	1520, 1670 (C=C), 3440 (NH in CCl_4)	308 (3,85) 394 (4,32)
(XVIc)	30	176–178	64,3 64,6	5,9 5,9	13,4 13,7	$C_{11}H_{12}N_2S$	1545 (C=C), 3430 (NH in CCl_4)	242 (3,98) 273 (4,06)
(XVII)	95	126–129	71,6 71,6	6,2 6,0	6,8 7,0	$C_{24}H_{24}N_2S_2$	1590, 1605 (C=N, C=C)	418 (4,49) 262 (4,49)

Note. Compounds (VI), (IX), (XVa, b, d) were purified by recrystallization from hexane, (IIa, b), (IIIb), (X), (XIf), (XII), (XIIIc) – from an ethyl acetate–hexane mixture: (XIIId), (XIVb, g) – from alcohol; (IIIa), (IV), (XId), (XIIIb, f) – from ethyl acetate, (XIb) – from a CCl_4–ethanol mixture, (XIIIa) – from aqueous alcohol, (XIIIg) – from a heptane–ethyl acetate mixture, (XIVd) – from methanol, (XVf) – from cyclohexane, (XVII) – from pentane. Compounds (VId, g), (XIVa-c) were purified chromatographically, (IIIc), (VIh), (XIc) – by sublimation. Found/Calculated (Cl, %): 14.1/14.1 (IX). Found/Calculated (F, %): 26.8/27.3 (IIb), 24.9/25.0 (IIIb), 25.2/25.4 (IIIc), 23.6/23.9 (XIc), 22.4/22.4 (XIIIc), 28.9/29.2 (XVIb). Found/Calculated (S, %): 15.6/15.8 (XVIa), 16.7/16.4 (XVIb), 15.4/15.7 (XVIc), 15.5/15.9 (XVII).



R = C_6H_5 (a), CF_3 (b), 2-pyridyl (c).

It should be noted that compound (XVI) is readily oxidized even during its separation, and by the action of MnO_2, disulfide (XVII) is readily formed (cf. [6]).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets (concentration 0.25%) and in CCl_4 solutions (concentration 5%) and the UV spectra on a "UV-VIS" spectrophotometer in alcohol. The PMR spectra were run on a "Varian A-56-60A" spectrometer in DMSO-d_6, CCl_4, and $CDCl_3$ solutions (concentration 7-10%). The data of the elemental analysis, melting points, yields, IR and UV spectra of the synthesized compounds are given in Table 1. Compounds (XIa, g) were used in the synthesis of the corresponding dioximes without isolation in a pure state. The synthesis and properties of compounds (Vb), (VIb, c, e, i) are described in [7].

5,5-Dimethyl-4-oxo-2-phenyl-1-pyrroline-1-oxide Hydrazone (IIa). A solution of 0.2 g (1 mmole) of pyrroline (Ib) and 0.4 ml (8 mmoles) of hydrazine hydrate in 10 ml of ethanol was allowed to stand for 4 days at 20°C, and then evaporated. The residue was diluted with 10 ml of a saturated solution of NaCl in water and extracted with $CHCl_3$ (3 × 15 ml). The extract was dried over $MgSO_4$, the solution was evaporated, the residue was washed with an ether–hexane 1:2 mixture, and the precipitate of hydrazone (IIa) was filtered off.

5,5-Dimethyl-4-oxo-2-trifluoromethyl-1-pyrroline-1-oxide Hydrazone (IIb) was obtained in a similar manner from pyrroline (Ic).

4-Hydroximino-5,5-dimethyl-4-oxo-2-phenyl-1-pyrroline-1-oxide (IIIa). A solution of 0.17 g (3 mmoles) of CH_3ONa in 5 ml of methanol was added to a solution of 0.35 g (5 mmoles) of hydroxylamine hydrochloride in 10 ml of methanol. The NaCl precipitate that separated out was filtered off, and 0.2 g (1 mmole) of pyrroline (Ib) was added to the solution, which was allowed to stand for 24 h at 20°C. The solution was evaporated, the residue was diluted with 10 ml of water saturated with NaCl, the oxime (IIIa) precipitate was filtered off, and dried. PMR spectrum (DMSO-d_6, δ, ppm): 1.57 (6H, 5-$(CH_3)_2$), 3.88 (2H, CH_2), 7.8 m (5H, C_6H_5), 9.24 (1H, NOH). 4-Hydroximino-5,5-dimethyl-2-trifluoromethyl-1-pyrroline-1-oxide (IIIb) was obtained under similar conditions by oximation of pyrroline (Ic) with hydroxylamine, while 5,5-dimethyl-4-methoximino-2-trifluoromethyl-1-pyrroline-1-oxide (IIIc) was obtained by the action of O-methylhydroxylamine. PMR spectrum of compound (IIIc) (DMSO-d_6, δ, ppm): 1.53 (6H, 5-$(CH_3)_2$), 3.62 d (1H, J = 1.5 Hz), 3.68 d (1H, 3-CH_2, J = 1.5 Hz), 3.89 (3H, OCH_3).

4-Hydroximino-2,5,5-trimethyl-2-phenylpyrrolidine-1-oxyl (X) was obtained under similar conditions by oximation and subsequent oxidation of pyrrolidine (VIb).

4-Hydroxy-4,5-dimethyl-2-phenyl-1-pyrroline-1-oxide (IV). Sodium borohydride (0.3 g, 8 mmoles) was added in portions with stirring and cooling to 0°C to a solution of 0.3 g (1.5 mmoles) of pyrroline (Ib) in 20 ml of ethanol. Stirring was continued for 1 h, the solution was evaporated, the residue was diluted with 10 ml of water, and extracted with chloroform. The extract was dried over $MgSO_4$, the solution was evaporated, the residue was washed with hexane, and the precipitate comprising compound (IV) was filtered off.

Reaction of Pyrrolines (I) with Organometallic Compounds (general procedure). A solution of 2 mmoles of pyrroline (I) in 10 ml of dry THF was added dropwise, with vigorous stirring, to a solution of 10 mmoles of organomagnesium or organolithium compound in 30 ml of absolute ether. In the case of organolithium derivatives, the reaction was carried out in an argon atmosphere. Stirring was continued for 12 h, then 10 ml of water was added, the organic layer was separated, and the aqueous layer was extracted with ether (4 × 15 ml). The combined ether extract was dried over $MgSO_4$, the drying agent was filtered off, 3 g of MnO_2 was added to the solution, and the mixture was stirred for 3 h at 20°C. The excess of the oxidizing agent was filtered off, the filtrate was evaporated, and compound (VI) was separated by chromatography on silica gel, using an ether–hexane 1:3 mixture as eluent. Action of methylmagnesium iodide on pyrroline (Ia) gave pyrrolidine (VIa), action of methylmagnesium iodide or methyllithium on pyrroline (Ib) gave pyrrolidine (VIb) and by phenyllithium gave compound (VIf), action of methylmagnesium iodide on pyrroline (Ic) gave compound (VIc), with phenyllithium gave (VIe), and with butylmagnesium bromide – (VIi), action of phenyllithium on pyrroline (Id) gave (VIh), action of methyllithium on pyrroline (Ie) gave (VId) and of phenyllithium gave (VIg).

4-Oxo-2,5,5-trimethyl-2-phenyl-3-chloropyrrolidine-1-oxyl (IX) was obtained under similar conditions by the action of methylmagnesium iodide on pyrroline (VIII).

Nitrosation of Pyrrolidines (VI) (general procedure). A solution of 1 mmole of pyrrolidine (VI), 0.23 g (4 mmoles) of CH_3ONa and 0.27 ml (2 mmoles) of amyl nitrite in methanol was allowed to stand for 24 h at 20°C, and then evaporated. The residue was diluted with 10 ml of water, the solution was washed with ether (3 × 15 ml), neutralized with 5% HCl and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the solution was evaporated. The residue was washed with a small amount of hexane, and the precipitate of a mixture of E- and Z-isomers of oximes (XI) was filtered off. Compounds (XI) can be purified by chromatography on a column with silica gel, using $CHCl_3$ as eluent.

4-Hydroxy-3-hydroximino-2,2-diphenylpyrrolidine-1-oxyl (XII). A 0.3 g portion (8 mmoles) of $NaBH_4$ was added with stirring to a solution of 0.5 g (1.6 mmoles) of compound (XIf) in 15 ml of ethanol. The stirring was continued for 5 min, and the solution was evaporated. The residue was dissolved in 10 ml of water, and extracted with $CHCl_3$. The extract was washed with 1% HCl, dried, the solution was evaporated, the residue was washed with an ethyl acetate–hexane 1:3 mixture, and the precipitate of compound (II) was filtered off.

Oximation of Compounds (XI) (general procedure). A solution of 0.8 g (15 mmoles) of CH_3ONa in 10 ml of methanol was added to a solution of 1.68 g (25 mmoles) hydroxylamine hydrochloride in 20 ml of methanol. The NaCl precipitate was filtered off, 5 mmoles of oxime (XI) (mixture of isomers) was added to the solution, and the mixture was allowed to stand for 24 h at 20°C. The solution was evaporated and the residue was diluted with 10 ml of

water. The precipitate that separated out was filtered off or the solution was extracted with ethyl acetate or chloroform, the extract was dried over $MgSO_4$, and the drying agent was filtered off. The solution was stirred with 5 g of MnO_2, the excess of the oxidant was filtered, and the solution was evaporated. The residue was chromatographed on a column with silica gel, using $CHCl_3$ as eluent. Furoxane (XV) was first eluted, then the anti-isomer (XIII), and amphi-isomer (XIV) was eluted last.

Furoxanes (XV) can be obtained by oxidation of dioximes (XIII, XIV) or their mixture with MnO_2 in $CHCl_3$ or ethanol in the course of one week in a yield of 80-90%.

5,5-Dimethyl-2-phenyl-2-pyrroline-4-thione (XVIa). A suspension of 0.4 g (2 mmoles) of pyrroline (Ib) and 0.6 g (1.5 mmoles) of 2,4-bis(p-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide in 20 ml of a dry CH_2Cl_2 was stirred for 24 h at 20°C, and then evaporated. Compound (XVIa) was separated by successive chromatography on a column with silica gel, using a 50:1 mixture of chloroform with methanol as eluent and with aluminum oxide, using $CHCl_3$ as eluent.

5,5-Dimethyl-2-trifluoromethyl-2-pyrroline-4-thione (XVIb) and 5,5-dimethyl-2-(2-pyridyl)-2-pyrroline-4-thione (XVIc) were obtained in a similar manner from pyrrolines (Ic, e). PMR spectrum of (XVIb), ($CDCl_3$, δ, ppm): 1.39 (6H, 5-$(CH_3)_2$), 6.28 (1H, –CH=); (XVIc): 1.30 (6H, 5-$(CH_3)_2$), 6.71 (1H, –CH=), 7.8 br. s (1H, NH), 8.1-9.4 m (4H, 2-pyridyl).

Bis(2,2-dimethyl-5-phenyl-2H-pyrrol-3-yl) Disulfide (XVII). A mixture of 0.2 g of pyrroline (XVIa) and 1 g of MnO_2 in $CHCl_3$ was stirred for 24 h at 20°C. The excess of the oxidant was filtered off, and the solution was evaporated. Compound (XVII) was separated by chromatography on a column with silica gel, using $CHCl_3$ as eluent. PMR spectrum (CCl_4, δ, ppm): 1.28 (6H, 5-$(CH_3)_2$), 6.18 (1H, –CH=), 7.5 m (5H, C_6H_5).

LITERATURE CITED

1. V. A. Reznikov, L. A. Vishnivetskaya, and L. B. Volodarskii, Izv. Akad. Nauk SSSR, Ser. Khim., 395 (1990).
2. C. Berti, M. Colonna, L. Greci, and L. Marchetti, Tetrahedron, 35, 1745 (1975).
3. D. StC. Black, N. A. Blackman, and L. M. Johnstone, Aust. J. Chem., 32, 2025 (1979).
4. E. G. Rozantsev and L. A. Krinitskaya, Tetrahedron, 25, 491 (1965).
5. W. Walter and T. Proll, Synthesis, 941 (1979).
6. D. Murnietse and Ya. F. Freimanis, Zh. Org. Khim., 5, 941 (1969).
7. V. A. Reznikov and L. B. Volodarskii, Inventor's Certificate No. 1,244,145 (USSR); Byull. Izobret., No. 26 (1986).