Chemistry of Heterocyclic Compounds, Vol. 32, No. 8, 1996

FORMATION OF THE PYRROLINE-N-OXIDE RING BY THE REACTION OF ISONITROSOKETONES WITH ENAMINES AND SOME CONVERSIONS OF THE PYRROLINE-N-OXIDES OBTAINED

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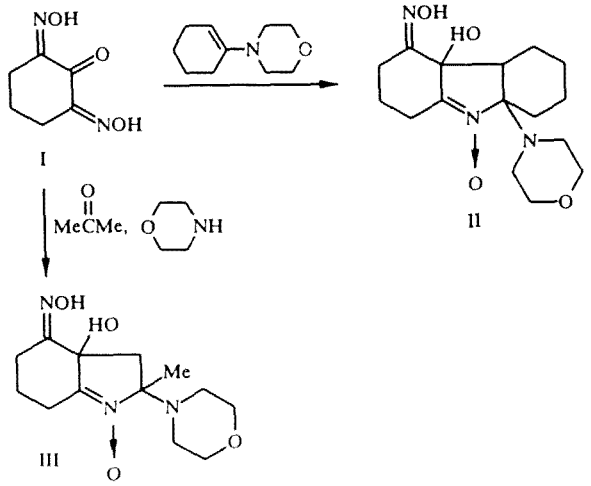
Compounds containing the pyrroline-N-oxide ring are obtained when isonitrosoketones — 2,6-dihydroxyiminocyclohexanone and ω-isonitrosoacetophenone — react with enamines. The compounds obtained behave as synthetic equivalents of 1,4-dicarbonyl compounds when undergoing reaction with amines, hydrazine, and hydroxylamine.

It was shown previously that isonitrosoketones — derivatives of tetrahydrobenzofurazan and tetrahydrobenzofuroxan — react readily both with enamines and with ketones and amines giving derivatives of pyrroline-N-oxide [1]. It could be proposed that the conversions found are general, and allow the synthesis of derivatives of pyrroline-N-oxide starting from isonitrosoketones and carbonyl compounds. In order to confirm this proposal, the reaction of a readily available alicyclic isonitrosoketone — 2,6-dihydroximinocyclohexanone (I) [2] — with an enamine — 1-(N-morpholinyl)cyclohex-1-ene, which led to a high yield of 4-hydroximino-4*a*-hydroxy-8*a*-(N-morpholinyl)-1,2,3,4,4b,5,6,7,8,8*a*-decahydro-4H-carbazole-9-oxide (II), was accomplished. Since the PMR and ^{13}C NMR spectra of the indicated product (see Table 1) only show one set of signals, whereas there are three asymmetric centers and an oxime group in its molecule, it is probable that one diastereomer is formed preferentially. As the result of the reaction of compound (I) with acetone and morpholine, the product (III) was obtained. On the basis of analytical and spectral data, (III) was assigned the structure 3a-hydroxy-2-methyl-2-(N-morpholinyl)-4-hydroximino-2,3,4,5,6,7-hexahydro-3*a*H-indole-1-oxide. The PMR and ^{13}C NMR spectra of compound (III) show a double set of signals, indicating that it is a mixture of diastereomers.



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0009-3122/96/3208-0907$15.00

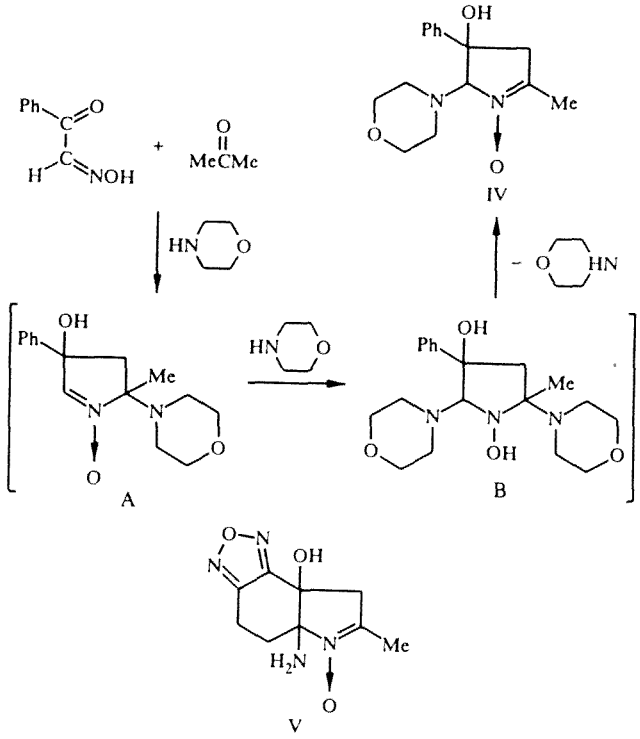
TABLE 1. PMR and ^{13}C NMR Spectral Data of the Compounds Synthesized

Compound*		NMR spectra, δ, ppm (J, Hz)
II	^1H	1,20...3,50 (23H,m, CH, 11CH_2), 5,71 (1H, s, OH), 10,86 (1H, s, -NOH)
	^{13}C	18,7, 20,0, 20,3, 20,5, 20,8, 21,3, 27,8 (CH_2), 38,2 (CH), 45,3 (CH_2—N), 66,8 (CH_2—O—), 76,0 (—C—OH), 92,4 (N—C—N), 142,0 (C-N—O), 156,7 (C-NOH)
III	^1H	1,20...3,50 (19H,m, 8CH_2, CH_3), 5,95, 6,05 (1H, s. s, OH), 10,86, 10,91 (1H, s. s, -NOH)
	^{13}C	20,5, 20,6, 20,8, 20,9, 21,5 (CH_2), 23,5 (CH_3), 45,5, 46,1 (CH_2—N), 66,7 (CH_2—O—), 74,1, 74,7 (—C—OH), 91,7, 91,9 (N—C—N), 142,9, 143,0 (C-N—O), 156,0, 156,8 (C-NOH)
IV	^1H	1,98, 2,00 (3H, s, CH_3), 2,30...3,30 (6H,m, 3CH_2), 3,40...3,60 (4H, m, 2CH_2), 4,35, 4,52 (1H, s. s, CH), 5,40, 5,81 (1H, s. s, OH), 7,20...7,60 (5H,m, H_{Ph})
	^{13}C	12,0 (CH_3), 43,7, 48,0 (CH_2), 48,5, 49,8 (CH_2—N—), 66,0, 66,4 (CH_2—O—), 72,5, 75,0 (—C—OH), 97,4, 100,2 (CH), 123,9, 126,9, 127,1, 127,2, 128,2, 140,3, 140,8 (C_{Ph}), 141,2, 147,5 (C-N)
VI	^1H	2,47 (3H, s, CH_3), 8,96 (1H, d, J_{46} = 2 Hz, H_{Het}), 7,33 (1H, d, J_{46} = 2 Hz, H_{Het}), 7,15...7,25 (3H,m, H_{Ph}), 7,35...7,40 (2H, m, H_{Ph})
	^{13}C	22,2 (CH_3), 123,9 ($C_{(4)}$), 127,9, 130,2, 130,6 (CH_{Ph}), 135,7 (C_{Ph}), 138,4 ($C_{(5)}$), 148,1 ($C_{(6)}$), 160,7 ($C_{(3)}$)
VII	^1H	1,62 (3H, s, CH_3), 2,83 (2H, s, CH_2), 5,75 (1H, s, OH), 7,20...7,40 (5H, m, H_{Ph}), 7,41 (1H, s, CH-N), 10,28 (1H, s, -NOH), 10,78 (1H, s, -NOH)
	^{13}C	15,0 (CH_3), 45,4 (CH_2), 74,8 (C—OH), 125,7, 126,8, 127,8 (CH_{Ph}), 143,6 (C_{Ph}), 153,5 (C-NOH), 153,9 (CH-NOH)
VIII	^1H	2,19 (3H, s, CH_3), 3,56 (3H, s, OCH_3), 6,27 (1H, s, CH), 7,20...7,30 (1H, m, H_{Ph}), 7,45...7,60 (7H,m, H_{Ph}), 7,78...7,83 (2H,m, H_{Ph})
	^{13}C	12,7 (CH_3), 61,2 (OCH_3), 103,4 ($C_{(3)}$), 106,1 ($C_{(2)}$), 122,6 ($C_{(4)}$), 124,6, 125,5, 127,3, 127,6, 128,3, 128,8 (CH_{Ph}), 134,8, 136,6 (C_{Ph}), 142,9 ($C_{(5)}$)
IX	^1H	2,23 (3H, s, CH_3), 3,42 (3H, s, N—CH_3), 3,78 (3H, s, OCH_3), 6,05 (1H, s, CH), 7,15 (1H,m, H_{Ph}), 7,37 (2H,m, H_{Ph}), 7,64 (2H,m, H_{Ph})
	^{13}C	12,0 (CH_3, 27,8 (N—CH_3), 61,2 (OCH_3), 102,0 ($C_{(3)}$), 105,0 ($C_{(2)}$), 121,6 ($C_{(4)}$), 124,3, 125,4, 128,2 (CH_{Ph}), 135,4 (C_{Ph}), 142,7 ($C_{(5)}$)
X	^1H	2,30 (3H, s, CH_3), 6,00 (1H, s, CH), 7,25...7,50 (3H,m, H_{Ph}), 7,80...7,90 (2H,m, H_{Ph}), 8,60 (1H, d, CH-N), 12,3 (1H, s, -NOH)
	^{13}C	20,3 (CH_3), 101,3 (CH), 127,4, 128,2, 132,2 (CH_{Ph}), 138,0 (C_{Ph}), 152,9 (-C), 160,5 (CH-N), 190,9 (C-O)
XI	^1H	2,51 (3H, s, CH_3), 1,79, 2,59, 2,94 (6H,m, 3CH_2), 7,61 (1H, s, CH), 11,90 (1H, s, -NOH)
	^{13}C	21,6 (CH_3, 21,0, 23,8, 30,3 (CH_2), 122,0 (CH), 151,6 (C-NOH), 132,8, 158,9, 160,2 (-C)
XII	^1H	0,50...1,00 (6H,m, 3CH_2), 1,70...2,20 (8H,m, 4CH_2)
	^{13}C	20,5, 21,6, 22,2, 25,0, 28,8, 29,7, 30,6 (CH_2), 132,6, 135,6 (-C), 154,0 (C-NOH), 158,2, 159,3 (C-N)
XIII	^1H	1,91 (3H, s, CH_3), 2,45...2,52 (6H,m, 3CH_2), 3,45...3,55 (2H,m, CH_2), 11,07 (2H, s, 2 -NOH)
	^{13}C	12,7 (CH_3), 18,0, 23,0, 36,9 (CH_2), 86,9 (C—O—), 153,9, 156,8 (C-NOH)

*Spectra of the compounds (II)-(IV), (VI), (VII), and (XIII) were recorded in DMSO-D_6. Spectra of (VIII)-(X) were recorded in $CDCl_3$. Spectrum of compound (XII) was recorded in the 2% solution of NaOH in D_2O.

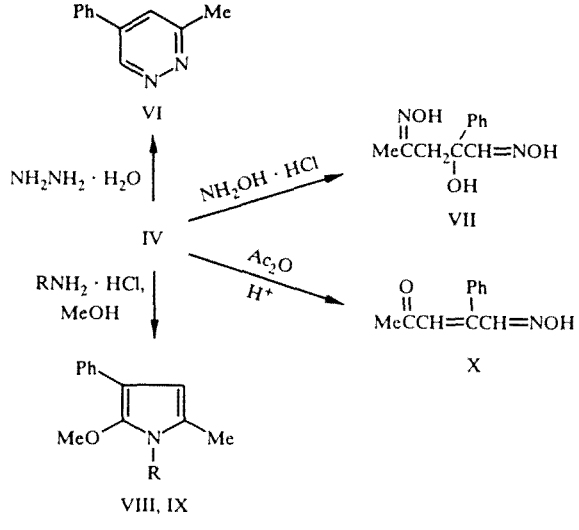
In an analogous way, the reaction of the readily available ω-isonitrosoacetophenone with acetone and morpholine results in the formation of the colorless product (IV), for which a double set of signals is observed in the PMR and ^{13}C NMR spectra. Since it is difficult to make a conclusion concerning the structure of the compound obtained on the basis of analytical and spectral data, the structure was established from x-ray structure analysis (see Table 2 and Fig. 1). The bond lengths of the five-membered ring are close to the corresponding values for the previously synthesized compound (V) [1]. The given ring has the shape of an envelope with an axial hydroxyl group, whereby the deviation of the $C_{(4)}$ atom from the plane of the double bond equals 0.385(4) Å. For compound (V), the analogous deviation comprises 0.479(5) and 0.481(5) Å (two independent

molecules). We will note the $C_{(5)}-N_{(2)}$ bond, which is reduced to 1.420(3) Å by comparison with the expected value of 1.469(14) Å for $C_{sp3}-N_{sp3}$ [3]. It is possible that this reduction is determined by the neighboring nitrone grouping, since the C-NH_2 bond in compound (V) is also short — 1.415(4) and 1.426(4) Å. The molecules of (IV) in the crystal are connected in chains by the hydrogen bonds $O_{(2)}-H...O_{(1)}$ [$O_{(2)}-H$ 0.95(4) Å, $H...O_{(1)}$ 1.75(4) Å, $O_{(1)}...O_{(2)}$ 2.668(3) Å, and $O_{(2)}-H...O_{(1)}$ 161(4)°]. It is obvious from these data that compound (IV) is 2-methyl-4-hydroxy-4-phenyl-5-(N-morpholinyl)-1-pyrroline-1-oxide. It is probably the result of the conversion of the initially formed condensation product A (see [1]). The last undergoes addition of morpholine at the aldonitrone group, and is converted to the intermediate compound B, from which the further cleavage of morpholine leads to the formation of the oxide (IV).



Therefore, the reaction of isonitrosoketones with enamines leads to compounds containing the pyrroline-N-oxide ring.

We also studied some chemical conversions of the products (II)-(IV) obtained. Thus, the treatment of compound (IV) with hydrazine hydrate leads to a high yield of 3-methyl-5-phenylpyridazine (VI), and treatment with hydroxylamine hydrochloride leads to the dioxime (VII). Reaction of the oxide (IV) with methylamine hydrochloride and aniline in methanol leads to the formation of the corresponding pyrroles — (VIII) and (IX). The reaction of compound (IV) with acetic anhydride in the presence of acid gives 1-hydroximino-2-phenyl-4-oxopent-2-ene (X).



VIII R = Ph, IX R = Me

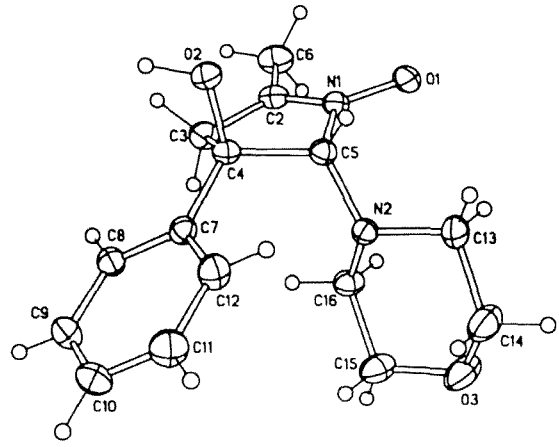
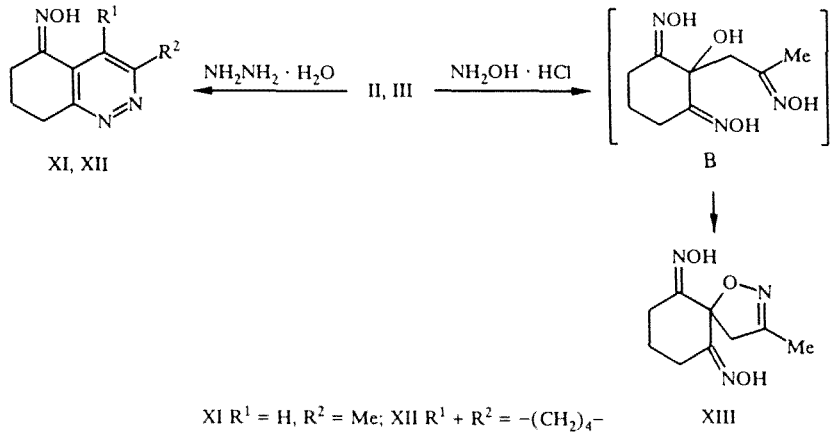


Fig. 1. Structure of the molecule of 2-methyl-4-hydroxy-4-phenyl-5-(N-morpholinyl)-1-pyrroline-1-oxide (IV). The bond lengths (Å) and bond angles (deg) pertaining to the 1-pyrroline-1-oxide fragment are as follows: $N_{(1)}-C_{(2)}$ 1.291(4), $N_{(1)}-O_{(1)}$ 1.313(3), $N_{(1)}-C_{(5)}$ 1.506(3), $C_{(2)}-C_{(3)}$ 1.481(4), $C_{(3)}-C_{(4)}$ 1.543(4), $C_{(4)}-C_{(5)}$ 1.558(4), $C_{(5)}-N_{(2)}$ 1.420(3), $C_{(2)}-N_{(1)}-O_{(1)}$ 127.0(2), $C_{(5)}-N_{(1)}-O_{(1)}$ 118.8(2), $C_{(2)}-N_{(1)}-C_{(5)}$ 114.1(2), $N_{(1)}-C_{(2)}-C_{(3)}$ 111.3(2), $N_{(1)}-C_{(2)}-C_{(6)}$ 122.5(3), $C_{(3)}-C_{(2)}-C_{(6)}$ 126.2(3), $N_{(1)}-C_{(5)}-N_{(2)}$ 113.8(2), $N_{(2)}-C_{(5)}-C_{(4)}$ 117.8(2), $N_{(1)}-C_{(5)}-C_{(4)}$ 100.9(2).

The analogous conversions are characteristic for the compounds (II) and (III). When they are treated with hydrazine hydrate, the corresponding tetrahydrocinnolines — (XI) and (XII) — are obtained. The reaction of compound (III) with hydroxylamine hydrochloride results in the formation of 2',6'-dihydroximinospiro(3-methylisoxaline-5)-5,1'-cyclohexane (XIII), probably via the stage of the intermediate dioxime B.



XI R^1 = H, R^2 = Me; XII $R^1 + R^2 = -(CH_2)_4-$

Therefore, the synthesized derivatives of pyrroline-N-oxide (II)-(IV) behave as 1,4-dicarbonyl compounds, which allows them to be utilized as the basis for the ready synthesis of derivatives of cinnoline, pyridazine, and pyrrole. The characteristics of the compounds synthesized are presented in Table 3.

EXPERIMENTAL

The IR spectra were recorded on the UR-20 instrument using tablets of KBr; the concentration of the substance was 0.25%. The UV spectra were recorded on the Specord UV-vis instrument in ethanol. The PMR and ^{13}C NMR spectra were

TABLE 2. Coordinates($\times 10^4$) and Temperature Factors ($Å^2, \times 10^3$) of Non-hydrogen Atoms of Compound (IV)

Atom	x/a	y/b	z/c	U_{eq}
$N_{(1)}$	-2470(3)	3061(2)	2612(1)	36(1)
$C_{(2)}$	-2527(4)	3905(3)	2127(1)	38(1)
$C_{(3)}$	-2081(4)	5339(3)	2329(1)	39(1)
$C_{(4)}$	-1236(4)	5159(3)	3009(1)	31(1)
$C_{(5)}$	-1990(4)	3738(3)	3248(1)	32(1)
$C_{(6)}$	-3027(5)	3452(4)	1464(1)	53(1)
$C_{(7)}$	-1496(4)	6386(3)	3464(1)	32(1)
$C_{(8)}$	-1875(4)	7694(3)	3225(1)	36(1)
$C_{(9)}$	-2023(4)	8828(3)	3633(2)	46(1)
$C_{(10)}$	-1796(5)	8665(3)	4289(2)	54(1)
$C_{(11)}$	-1370(5)	7378(4)	4534(1)	55(1)
$C_{(12)}$	-1213(4)	6244(3)	4130(1)	43(1)
$C_{(13)}$	-3733(5)	2479(3)	4074(1)	45(1)
$C_{(14)}$	-4894(5)	2804(4)	4651(2)	62(1)
$C_{(15)}$	-6286(5)	4630(4)	4092(1)	52(1)
$C_{(16)}$	-5161(4)	4345(3)	3495(1)	39(1)
$N_{(2)}$	-3438(3)	3754(2)	3704(1)	32(1)
$O_{(1)}$	-2856(3)	1732(2)	2607(1)	48(1)
$O_{(2)}$	668(2)	4863(2)	2942(1)	38(1)
$O_{(3)}$	-6579(3)	3418(3)	4467(1)	66(1)

taken on the Bruker WP-200 SY and AC-200 spectrometers. The melting temperatures of the compounds were determined on a Kofler microheating stage. The yields, melting temperatures, and spectral characteristics of the compounds synthesized are presented in the Tables 2 and 3.

X-Ray Structural Investigation of Compound (IV). This was performed on the SYNTEX-P21 diffractometer. Crystals were of the rhombic system: a = 7.355(2) Å, b = 9.644(3) Å, c = 20.609(5) Å, V = 1461.8(7) $Å^3$, the space group $P2_12_12_1$, $C_{15}H_{20}N_2O_3$, Z = 4, d_{calc} = 1.256 g/cm^3, and the λ CuKα (graphite monochromator). The intensities of 1282 independent reflections with the $2\theta < 120°$ were measured by the method of $\theta/2\theta$-scanning. Corrections for absorption (corrections 0.89-1.11) were introduced by the DIFABS program. The structure was interpreted by the direct method using the SHELXS-86 program, and was specified using the SHELXL-93 program by the method of least squares with the full-matrix anisotropic–isotropic approximation up to wR_2 = 0.0944 and S = 1.122 for all reflections (R = 0.0342 for $1210F_0 > 4\delta$). The positions of the H atoms were calculated geometrically, and parameters of the hydroxyl H atom were specified. The coordinates obtained for the non-hydrogen atoms are presented in Table 1.

4*a*-Hydroxy-4-hydroximino-8*a*-(N-morpholinyl)-1,2,3,4,4b,5,6,7,8,8*a*-decahydro-4aH-carbazole-9-oxide (II). To the solution of 1.56 g (10 mmole) of the isonitrosoketone (I) in 50 ml of methanol are added 1.67 g (10 mmole) of 1-(N-morpholinyl)cyclohex-1-ene. The mixture is stirred at room temperature for 48 h. The solvent is distilled off *in vacuo*, and the residue is triturated with ether. Compound (II) is obtained with the yield of 2.40 g.

2-Methyl-2-(N-morpholinyl)-3*a*-hydroxy-4-hydroximino-2,3,4,5,6,7-hexahydro-3*a*H-indole-1-oxide (III). To the solution of 7.8 g (50 mmole) of the isonitrosoketone (I) in 200 ml of acetone are added 6 g (70 mmole) of morpholine, and the mixture is stirred at room temperature for 70 h. The residue is filtered off, washed with ether, and dried. Compound (III) is obtained with the yield of 10.7 g.

2-Methyl-4-hydroxy-4-phenyl-5-(N-morpholinyl)-1-pyrroline-1-oxide (IV). To the solution of 1.49 g (10 mmole) of α-isonitrosoacetophenone in 20 ml of acetone is added 1.0 g (11 mmole) of morpholine, and the mixture is left at room temperature for 8 days. The residue is filtered off, washed with methanol, and dried. Compound (IV) is obtained with the yield of 1.56 g.

TABLE 3. Characteristics of the Compounds Synthesized

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C	UV spectrum (ethanol), λ, nm (log ε)	Yield, %
		C	H	N			
II	$C_{16}H_{25}N_3O_4$	59,3 59,4	7,9 7,8	13,0 13,0	168 (decomp.)	244 (4,12)	74
III	$C_{13}H_{21}N_3O_4$	55,1 55,1	7,4 7,5	14,8 14,8	167...169	244 (4,04)	80
IV	$C_{15}H_{20}N_2O_3$	65,2 65,2	7,3 7,3	10,1 10,1	196...198	232 (3,96)	55
VI	$C_{11}H_{10}N_2$	77,6 77,6	6,0 5,9	16,4 16,5	102...104	265 (4,14)	91
VII	$C_{11}H_{14}N_2O_3$	59,4 59,5	6,4 6,4	12,6 12,6	133...135	—	85
VIII	$C_{18}H_{17}NO$	82,1 82,1	6,6 6,5	5,4 5,3	81...83	247 (4,08)	27
IX	$C_{13}H_{15}NO \cdot H_2O$	71,1 71,2	7,8 7,8	6,4 6,4	51...53	238 (3,75), 283 (3,75)	32
X	$C_{11}H_{11}NO_2$	69,8 69,8	5,9 5,9	7,4 7,4	98...100	315 (4,45)	65
XI	$C_9H_{11}N_3O \cdot H_2O$	55,4 55,4	6,7 6,7	21,5 21,5	219...221	270 (4,28), 292 (4,34)	85
XII	$C_{12}H_{15}N_3O$	66,4 66,4	6,9 6,9	19,5 19,4	269...271	270 (3,92)	72
XIII	$C_9H_{13}N_3O_3$	51,1 51,2	6,2 6,2	19,9 19,9	229...231	—	75

*Compounds (II), (III), (VI), and (X) were recrystallized from alcohol. Compound (IV) was recrystallized from dimethylsulfoxide. Compounds (VII) and (XI)-(XIII) were recrystallized from water. Compounds (VIII) and (IX) were recrystallized from hexane.

3-Methyl-5-phenylpyridazine (VI). To the solution of 2.86 g (10 mmole) of compound (IV) in 50 ml of water are added 2 ml of acetic acid and 1.0 g (20 mmole) of hydrazine hydrate. The mixture is boiled for 15 min. The mixture is cooled, and the residue is filtered off, washed with water, and dried. Compound (VI) is obtained with the yield of 1.55 g.

2,5-Dihydroximino-4-hydroxy-4-phenylpentane (VII). To the solution of 2.86 g (10 mmole) of compound (IV) in 30 ml of water is added 1.0 g (14 mmole) of hydroxylamine hydrochloride, and the mixture is stirred for 24 h at room temperature. The residue is filtered off, washed with water, and dried. Compound (VII) is obtained with the yield of 1.9 g.

2-Methyl-1,4-diphenyl-5-methoxypyrrole (VIII). To the solution of 2.86 g (10 mmole) of compound (IV) in 50 ml of methanol are added 1.30 g (10 mmole) of aniline hydrochloride, and the mixture is boiled using a reflux condenser for 3 h. The solvent is distilled off *in vacuo*, and the residue is chromatographed on aluminum oxide; the eluent is carbon tetrachloride. Compound (VIII) is isolated with the yield of 0.72 g.

Under analogous conditions, compound (IV) and methylamine hydrochloride afford 1,2-dimethyl-4-phenyl-5-methoxypyrrole (IX).

1-Hydroximino-2-phenyl-4-oxopent-2-ene (X). To 15 ml of acetic anhydride at the temperature of 5-10°C are added 2.86 g (10 mmole) of the pyrroline-N-oxide (IV). To the resulting solution is added a drop of concentrated sulfuric acid, and the mixture is stirred at 5-10°C for 1.5 h. The reaction mass is poured into 200 ml of ice water, and the residue is filtered off after 2 h, washed with water, and dried. Compound (X) is obtained with the yield of 1.26 g.

3-Methyl-5-hydroximino-5,6,7,8-tetrahydrocinnoline (XI). To the solution of 2.67 g (10 mmole) of compound (III) in 20 ml of water are added 6.0 ml of acetic acid and 3 g (15 mmole) of hydrazine hydrate. The mixture is boiled for 15 min and cooled. The residue is filtered off, washed with water, and dried. Compound (XI) is obtained with the yield of 1.50 g.

Under analogous conditions, compound (II) and hydrazine hydrate afford 10-hydroximino-1,2,3,4,7,8,9,10-octahydrobenzo[c]cinnoline (XII).

2′,6′-Dihydroximinospiro(3-methylisoxaline-5)-5,1′-cyclohexane (XIII). To the solution of 2.67 g (10 mmole) of compound (III) in 80 ml of water are added 2.0 g (29 mmole) of hydroxylamine hydrochloride, and the mixture is boiled for 20 min. The mixture is cooled, and the residue is filtered off, washed with water, and dried. Compound (XIII) is obtained with the yield of 1.72 g.

REFERENCES

1. V. A. Samsonov, L. B. Volodarskii, I. Yu. Bagryanskaya, Yu. V. Gatilov, and K. É. Lakman, Khim. Geterotsikl. Soedin., No. 2, 199 (1994).
2. Methods for the Isolation of Chemical Reagents and Preparations, No. 25, Research Institute of Chemical Reagents and Specially Pure Chemical Substances (IREA), Moscow (1973), p. 224.
3. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, J. Chem. Soc. Perkin II, No. 12, S1 (1987).