SYNTHESIS OF 4,5'-DIHYDRO DERIVATIVES OF BENZODIFURAZAN, BENZODIFUROXAN, AND BENZOFURAZANOFUROXAN

V. A. Samsonov and L. B. Volodarskii

UDC 547.793.288.4

Starting with 2,6-diisonitrosocyclohexanone, we have synthesized the 4,5'-dihydro derivatives of benzodifurazan, benzodifuroxan, and benzofurazanofuroxan. The synthesis and the properties of the products are described.

Derivatives of benzodifurazan and benzodifuroxan are of interest to investigators as a new class of efficient vasodilators, benzodifuroxan being in addition a powerful monoamide oxidase inhibitor [1]. We thus undertook to synthesize the hydrogenated analogs of these compounds.

The purpose of this study was to synthesize the hydrogenated analogs of benzodifurazan, benzodifuroxan, and benzofurazanofuroxan and investigate their properties.

We used as starting material for these syntheses the readily available monosodium salt of 2,6-diisonitrosocyclohexanone (I), obtained by nitrosylation of cyclohexanone [2]. The action of an excess of

TABLE 1. Characteristics of Synthesized Compounds

Compound	Elemental formula	Mp, °C*	UV spectrum (ethanol), λ, nm (log ε)	IR spectrum, ν, cm^{-1}			Yield, %
				C-NO$_2$	C=O	C=N	
IIa	$C_6H_7N_3O_2$	172...175	260 (3,83)				56
IIb	$C_6H_7N_3O_2$	154...157	260 (3,61)				
III	$C_6H_6N_2O_2$	Oil**	210 (3,65), 230 (3,60)		1720	1580	87,5
IV	$C_6H_5N_3O_3$	178...180 (decomp.)	275 (3,83)		1710	1580	66
Va	$C_6H_6N_4O_3$	193...195	235 (4,00)			1650	70
Vb	$C_6H_6N_4O_3$	206...208	235 (4,00)			1650	
VIa,b	$C_6H_4N_4O_3$	126...128	208 (3,78), 240 (3,73), 288 (3,75)			1680	38,5
VII	$C_6H_4N_4O_2$	116...118	252 (3,90)				70
IX	$C_6H_7N_3O_3$	229...231 (decomp.)	226 (4,30), 284 (3,86)			1620	78
XI	$C_6H_5N_3O_4$	156 (decomp.)	232 (3,90), 277 (3,81)		1710	1630	76
XII	$C_6H_6N_4O_4$	129...132 (decomp)	268 (3,74)	1350, 1560			54
XIII	$C_6H_5N_3O_4$	82...85	270 (3,40)	1370, 1570	1720		65
XVI	$C_6H_5N_3O_4$	192 (decomp.)	230 (2,80), 300 (2,86)		1720		64
XVII	$C_6H_6N_4O_4$	198...200 (decomp.)	214 (4,34), 254 (4,09), 300 (3,64)			1620	44,5
XVIII	$C_6H_6N_4O_4$	155...158 (decomp.)	213 (4,20), 292 (3,83)			1650	65

*Recrystallization: IIa, Va, VIa, b, XI, and XVI-XVIII from ethanol; IIb and IV from ethyl acetate; Vb from ethyl acetate—hexane, 1:1; VII from hexane; IX from methanol; XII from ethyl acetate—hexane, 3:1; XIII from ether—hexane, 1:1.
**Bp 120-122°C (1 mm Hg).

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1408-1413, October, 1991. Original article submitted June 28, 1990.

0009-3122/91/2710-1135$12.50

TABLE 2. PMR Spectra of Synthesized Compounds

Compound	PMR spectrum, δ, ppm
IIa	1,80...2,10 (m, 2H, CH_2); 2,70...3,10 (m, 4H, $2CH_2$); 11,7 (s, 1H, OH)
IIb	1,70...2,12 (m, 2H CH_2); 2,67...3,13 (m, 4H, $2CH_2$); 12,1 (s, 1H, OH)
III	1,95...2,45 (m, 2H, CH_2); 2,45...2,83 (m, 2H, CH_2); 2,83...3,22 (m, 2H, CH_2)
IV	2,70...3,30 (m, 4H, $2CH_2$)
Va,b	2,75...3,22 (m, 4H, $2CH_2$)
VIa,b	3,27 (br.s, 4H, $2CH_2$)
VII	3,22 (s, 4H, $2CH_2$)
IX	1,37...1,95 (m, 2H, CH_2); 2,33...3,00 (m, 4H, $2CH_2$); 6,20 (br.s, 1H, OH)
XI	2,50...3,30 (m, 4H, $2CH_2$)
XII	2,37...3,68 (m, 4H, $2CH_2$); 6,47 (t, 1H, CH)
XIII	2,67...3,17 (m, 4H, $2CH_2$); 6,42...6,67 (m, 1H, CH)
XVI	2,77...3,42 (m, 4H, $2CH_2$)
XVII	2,63...3,17 (m, 4H, $2CH_2$)
XVIII	2,93...3,53 (m, 4H, $2CH_2$)

*Spectra of IIa, b, VIa, b, XI, XII, XVI, and XVII were recorded in DMSO-d_6; III in CCl_4; IV, Va, b, and XVIII in acetone-d_6; VII and XIII in $CDCl_3$; IX in pyridine-d_5.

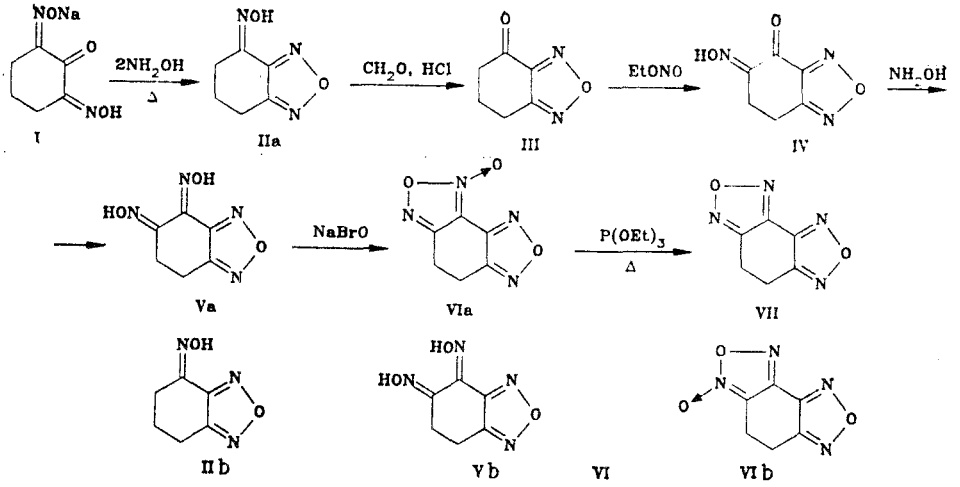
TABLE 3. Mass Spectra of Synthesized Compounds

Compound	Mass spectrum, m/z (I_{rel}, %)*
IIa	153 (100) M^+, 136 (20), 123 (50), 105 (46), 96 (30), 78 (40), 66 (30), 53 (50)
IIb	153 (100) M^+, 136 (20), 123 (50), 105 (46), 96 (30), 78 (40), 66 (30), 53 (50)
III	138 (40) M^+, 80 (80), 53 (100)
IV	167 (90) M^+, 150 (30), 82 (20), 70 (100), 54 (40)
Va,b	182 (100) M^+, 165 (20), 122 (20), 105 (20), 78 (20), 66 (20), 54 (30), 44 (15)
VIa,b	180 (100) M^+, 150 (30), 80 (20), 70 (15), 64 (20)
VII	164 (100) M^+, 134 (60), 84 (60)
IX	169 (100) M^+, 149 (15), 111 (10), 92 (10), 77 (15), 65 (20)
XI	183 (30) M^+, 153 (100), 125 (30), 82 (40), 78 (20), 66 (25), 52 (30), 45 (20)
XII	198 (10) M^+, 152 (80), 134 (100), 121 (20), 104 (30), 82 (25), 78 (20), 66 (25), 52 (30)
XIII	183 (100) M^+, 137 (60)
XVI	183 (20) M^+, 153 (100), 125 (35), 82 (50), 78 (20), 66 (30), 52 (20)
XVII	198 (15) M^+, 169 (100), 77 (10), 64 (15), 54 (15)
XVIII	196 (100) M^+, 80 (15), 66 (25), 50 (20)

*Ion peaks of $I_{rel} > 10\%$ are given.

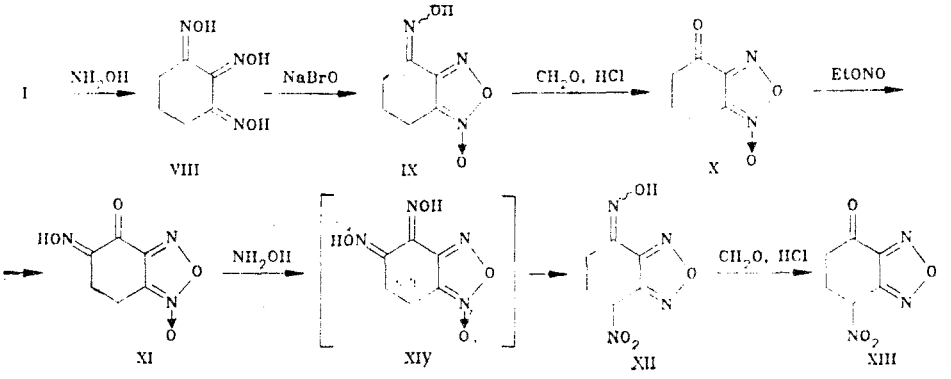
hydroxylamine on compound I gave on heating a 1:8 mixture of two isomeric 4-hydroxyimino-4,5,6,7-tetrahydrobenzofurazan (IIa and IIb), differing in the configuration of the oxime group. Tetrahydrobenzofurazan has been synthesized previously under analogous conditions and characterized as a single compound with mp 172-175°C [3]. On reproducing the method of [3] we found that a mixture of two isomers is formed. Both isomers, IIa and IIb, were separated chromatographically and characterized (see Table 1); the configurations of the oxime groups were established from the ^{13}C NMR spectra and the data in [4]. The E-configuration IIa was assigned to the major isomer in the mixture and the Z-configuration IIb to the minor. The data presented in [3] refer to the IIa isomer (see below).

Treatment of isomeric oximes IIa, IIb with a mixture of sulfuric acid and formaldehyde led to hydrolysis of the oxime groups to form 4-oxo-4,5,6,7-tetrahydrobenzofurazan (III), nitrosylation of which gave 4-oxo-5-hydroxyimino-4,5,6,7-tetrahydrobenzofurazan (IV). Reaction of isonitrosoketone IV with hydroxylamine afforded 4,5-dihydroxyimino-4,5,6,7-tetrahydrobenzofurazan (Va). Dioxime Va, synthesized by this method, probably has the oxime groups in the *anti* configuration since it forms a colored complex with nickel salts. Heating Va in water



gave a mixture of dioxime Va and its isomer Vb, which gave no colored complex with metal salts, probably indicating the *anti* and *syn* configurations of these groups. Heating in water or DMSO, or dissolution in an aqueous solution of alkali and then acidification, will convert any isomeric dioxime to a mixture of isomers. The ^{13}C NMR spectrum in DMSO shows a doubled number of carbon-atom signals corresponding to an isomeric mixture. Treatment of dioxime Va or Vb with sodium hypobromite in alkaline solution gave a product that the ^{13}C NMR spectrum showed to be a mixture of two isomers VIa and VIb, differing in the position of the N-oxide oxygen atom. The ready isomerization of benzofuroxan has often been noted in the literature [1]. An analogous mixture of VIa and VIb also forms on oxidation of dioximes Va or Vb with nitric acid. We were unable to separate isomers VIa and VIb. Reaction of 4,5′-dihydrobenzofurazanofuroxan VIa, VIb with triethyl phosphite gave 4,5′-dihydrobenzo[1,2-c: 3,4-c′]-bis[1,2,5]oxadiazole (VII).

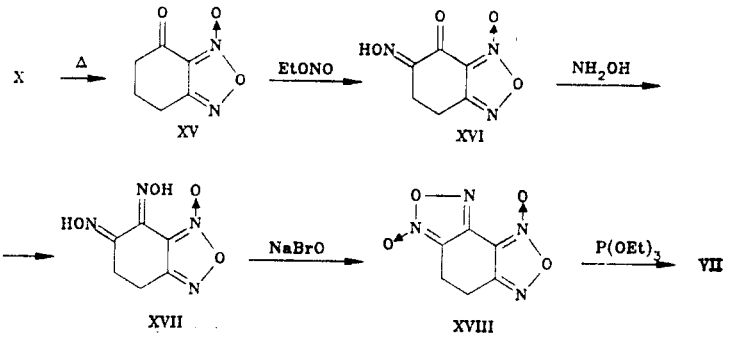
The synthesis of 4,5-dihydrobenzodifuroxan began with 1,2,3-trihydroxyiminocyclohexane (VIII) [2]. Oxidation of trioxime VIII with sodium hypobromite gave 4-hydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (IX). Hydrolysis of the oxime group of IX with a mixture of sulfuric acid and formaldehyde afforded 4-oxo-4,5,6,7-tetrahydrobenzofuroxan (X). This compound has been previously obtained from dihydroresorcinol in 3% yield [5]. Nitrosylation of X led smoothly to 4-oxo-5-hydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (XI). Treatment of XI with hydroxylamine afforded compounds XII, whose IR spectrum displays absorption bands at 1350 and 1560 cm^{-1} characteristic of nitro compounds. The spectral and elemental analysis data permitted assignment of this compound as 4-hydroxyimino-7-nitro-4,5,6,7-tetrahydrobenzofurazan (XII). Hydrolysis of the oxime group of XII gave 4-oxo-7-nitro-4,5,6,7-tetrahydrobenzofurazan (XIII). The formation of XII is explained by ready Boulton—Katritzky rearrangement of the initially forming 4,5-dihydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (XIV) (compare [1]).



A complication in the synthesis of 4,5-dihydrobenzodifuroxan was overcome by isomerization of ketone X to 7-oxo-4,5,6,7-tetrahydrobenzofuroxan (XV) as in [5]. Nitrosylation of ketone XV gave 7-oxo-6-hydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (XVI), further treatment of which with hydroxylamine gave 6,7-dihydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (XVII). The ^{13}C NMR spectrum of XVII shows a doubled set of carbon-atom signals corresponding to a mixture of two isomeric dioximes XVII. Acidification of dioximes XVII with sodium hypobromite or nitric acid yielded 4,5-dihydrobenzodifuroxan (XVIII).

TABLE 4. ^{13}C NMR Spectra of Synthesized Compounds

Compound	δ, ppm (in DMSO-d_6)			
	C=N	C=N→O	C=O	$-CH_2-$
IIa	146,02; 148,92; 154,32			20,24; 20,85; 23,42
IIb	141,57; 144,39; 154,27			20,80; 22,52; 29,43
III	148,27; 155,57		188,60	18,53; 20,46; 38,85
IV	141,52; 143,11; 146,33		165,16	7,26; 11,66
Va	127,58; 134,68; 139,31; 143,21			8,05; 10,77
Vb	129,65; 134,21; 134,45; 139,69			12,87; 17,05
VIa,b	156,25; 154,12; 153,17	112,49		17,29; 19,59
	141,23; 143,40; 145,50	105,34		16,86; 17,24
VII	145,51; 153,98			17,24
IX	134,79; 141,35	103,49		8,77; 9,13; 12,12
X	150,55	113,63	188,77	20,23; 39,10; 18,72
XI	142,46; 143,58	104,94	165,10	6,35; 10,58
XV	156,78	108,36	185,13	20,64; 21,40; 38,86
XVI	142,39; 147,66	101,53	162,23	9,31; 11,20
XVII	124,88; 139,19; 146,10	97,26		9,27; 10,67
	125,00; 138,90; 146,67	99,90		9,63; 11,80
XVIII	155,86; 143,69	105,20; 110,94		16,72; 18,73



The ^{13}C NMR spectrum of this compound shows six carbon signals, indicating the presence of a single isomer. Reaction of XVIII with triethyl phosphite gave 4,5-dihydrobenzodifurazan VII.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr disks, 0.25%; UV spectra on a Specord UV-vis in ethanol, and PMR spectra on a Varian A-56-60 A with internal standard of HMDS. Mass spectra were taken on a Finnigan MAT MS8200 at ionization potential 70 eV. ^{13}C NMR spectra were taken on a Bruker WP 200 spectrometer. The identities of compounds described previously were established by mp temperatures and comparison of IR and UV spectra.

Elemental analysis data for C, H, and N corresponded to those calculated.

4-Hydroxyimino-4,5,6,7-tetrahydrobenzofurazan (IIa, b). A mixture of 125 g (0.7 mole) of the monosodium salt of 2,6-diisonitrosocyclohexanone (I), 28 g (0.7 mole) NaOH, 97 g (1.4 mole) hydroxylamine sulfate, and 300 ml H_2O was refluxed 4 h. The mixture was cooled and the precipitate filtered off, washed with water, and dried to give 60 g (56%) of a mixture of isomers IIa and IIb.

A mixture of 1 g of isomers IIa and IIb was chromatographed on silica gel with ether—hexane, 1:1 to yield 0.89 g of IIa and 0.11 g of IIb.

4-Oxo-4,5,6,7-tetrahydrobenzofurazan (III). To a mixture of 200 ml of 40% formaldehyde and 200 ml concentrated HCl was added 30.6 g (0.2 mole) of the isomeric mixture of IIa and IIb. The mixture was stirred at room temperature 20 min and extracted with chloroform (3 × 100 ml). The chloroform extract was washed with water and dried with $MgSO_4$. The solvent was distilled off and the residue redistilled under vacuum to give the main fraction with bp 120-121°C (1 mm Hg). Yield: 24.2 g (87.5%) of ketone III.

4-Oxo-4,5,6,7-tetrahydrobenzofuroxan (X) and 4-oxo-7-nitro-4,5,6,7-tetrahydrobenzofurazan (XIII) were obtained analogously to III. The spectral characteristics of X agreed fully with those described in [5]. Yield 78%.

4-Oxo-5-hydroxyimino-4,5,6,7-tetrahydrobenzofurazan (IV). To a solution of 7.7 g (0.05 mole) of ketone III in 50 ml EtOH was added 50 ml acetic acid and 4.0 g (0.058 mole) of sodium nitrite. The mixture was stirred 4 h with cooling by cold water and left overnight at room temperature. The precipitate was filtered off, washed with water, and dried. Yield 5.57 g of IV. Evaporation of the filtrate gave a further 1.04 g of IV. Overall yield 66%.

4,5-Dihydroxyimino-4,5,6,7-tetrahydrobenzofurazan (Va). Into a solution of 4.2 g (0.06 mole) of hydroxylamine sulfate in 60 ml MeOH cooled to 0°C was poured a solution of 8.15 g (0.06 mole) sodium acetate in 60 ml MeOH. The mixture was stirred 10 min and the solution filtered into a flask and 8.4 g (0.05 mole) of isonitrosoketone IV added. The resulting mixture was gently heated until a homogeneous solution formed, then left 24 h at room temperature. The methanol was distilled off. The residue was suspended in water and the precipitate filtered off and dried. Yield 7.65 g (70%) of dioxime Va.

Isomerization of Dioxime Va to Dioxime Va. A. To 1 g (0.0055 mole) of dioxime Va was added 20 ml H_2O and the mixture was refluxed for 1 h and cooled, then extracted with ethyl acetate (4 × 50 ml) and the extract dried with $MgSO_4$. After evaporation of the solvent the residue was chromatographed on silica gel with ether—hexane, 4:1. Yield 0.4 g of Vb and 0.5 of the starting dioxime Va.

B. To 1 g (0.0055 mole) of dioxime Va was added 20 ml of a 5% solution of NaOH. The mixture was held at room temperature for 30 min and neutralized with 10% sulfuric acid. The product was extracted with ethyl acetate (4 × 50 ml) and the extract dried with $MgSO_4$. After evaporation of the solvent the residue was chromatographed on silica gel with ether—hexane, 4:1. Yield 0.35 g of dioxime Vb and 0.52 of the starting dioxime Va.

4,5-Dihydrobenzo[1,2-c:3,4-c']*bis*[1,2,5]oxadiazol-1-oxide (VIa) and 4,5-Dihydrobenzo[1,2-c:3,4-c']*bis*[1,2,5]oxadiazol-3-oxide (VIb). To a solution of 0.5 g (0.0025 mole) of dioxime Va in 5 ml H_2O and 0.1 g (0.0025 mole) of NaOH was added, maintaining the temperature at 0-5°C, a solution of sodium hypobromite obtained from 0.1 g (0.0025 mole) of NaOH, 0.2 g (0.00125 mole) bromine, and 5 ml H_2O. The mixture was stirred 30 min at room temperature and extracted with ethyl acetate (3 × 20 ml). The extract was washed with saturated NaCl solution and dried with $MgSO_4$. The solvent was evaporated and the residue suspended in hexane. Yield, about 0.35 g of a mixture of VIa and VIb.

To 0.5 g (0.0025 mole) dioxime Va suspended in 50 ml chloroform was added 3 g (0.042 mole) conc. HNO_3 (density 1.50). The mixture was stirred 2 h at room temperature, washed with water and dried with $MgSO_4$. The solvent was evaporated, and the residue suspended in hexane. Yield, about 0.35 g (56%) of a mixture of VIa and VIb.

4,5-Dihydrobenzo[1,2-c:3,4-c']*bis*[1,2,5]oxadiazol-1,6-di-N-oxide (XVIII) was obtained analogously to isomers VIa from dioxime XVII in 65% yield.

4,5-Dihydrobenzo[1,2-c:3,4-c']*bis*[1,2,5]oxadiazole (VII). To 0.1 g of compounds VIa, b or dihydrobenzodifuroxan XVIII was added 0.5 ml triethylphosphite and the mixture stirred to the boiling point, then refluxed 5 min and cooled. Sulfuric acid (5 ml of 5%) was added and after 30 min dihydrobenzodifurazan VII was filtered out. Yield 70%.

4-Hydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (IX). To a solution of 51.3 (0.3 mole) of trioxime VIII in 180 ml of 10% NaOH was added at reaction temperature 10-15°C a solution of sodium hypobromite prepared from 24 g (0.6 mole) of NaOH, 225 ml H_2O, and 15.4 ml (0.3 mole) of bromine. The mixture was stirred 1 h at room temperature and 40 ml (0.465 mole) concentrated HCl was added dropwise. The precipitate was filtered off, washed with water, and dried to yield 40 g (78%) of compound IX.

4-Hydroxyimino-7-nitro-4,5,6,7-tetrahydrobenzofurazan (XII). To a solution of 3.68 g (0.02 mole) of isonitrosoketone XI in 70 ml MeOH was added 1.75 g (0.025 mole) of hydroxylamine sulfate. The mixture was heated until a homogeneous solution formed and left 4 days at room temperature. To the mixture was added a solution of 2.1 g (0.02 mole) of Na_2CO_3 in 10 ml H_2O and it was stirred 3 h at room temperature and evaporated. The residue was chromatographed on silica gel with ether—hexane, 1:1. Separated yield: 2.15 g (54%) of nitrooxime XII.

6,7-Dihydroxyimino-4,5,6,7-tetrahydrobenzofuroxan (XVII). To a solution of 1 g (0.00565 mole) of isonitrosoketone XVI in 50 ml EtOH was added 0.5 g (0.00725 mole) of hydroxylamine sulfate. The mixture was heated until full dissolution of the precipitate and left 6 days at room temperature. The solvent was distilled off and the residue suspended in H_2O and filtered off, washed with water, and dried. Yield 0.48 g (44.5%) of dioxime XVII.

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INVESTIGATIONS OF 2-SUBSTITUTED IMIDAZOLES. 2.* SYNTHESIS AND ELECTROPHILIC SUBSTITUTION OF 1-METHYL-2-(THIENYL-2)IMIDAZOLE. A CONVENIENT METHOD OF METHYLATION OF 2-R-IMIDAZOLES

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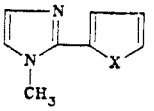
UDC 547.785.5

We have synthesized 2-(thienyl-2)imidazole and its N-methyl derivative. The latter product was obtained by nitration, bromination, acylation, and formylation, occurring as a rule on the thiophene ring. A general method for methylating 2-R-imidazoles with methyl iodide KOH—dimethoxy ethane is proposed.

We have previously studied electrophilic substitution reactions of 1-methyl-2-(furyl-2)imidazole (I) [1]. Here we report the synthesis and investigation of the hitherto undescribed 1-methyl-2(thienyl-2)imidazole (II).



I, II

I X=O; II X=S

Reaction of aqueous ethylenediamine with thiophene-2-carboxylic acid as in [2] gave in 84% yield 2-(thienyl-2)imidazoline (III). On reflux in diphenyl oxide in the presence of 2% palladium on carbon, the product rapidly dehydrogenated to give 2-(thienyl-2)imidazole (IV). However, the reaction did not go to conclusion, probably due to poisoning of the catalyst with sulfur-containing degradation products of the thiophene ring. The mixture of III and IV could not be separated by fractional crystallization or column chromatography. Their different reactions with silver nitrate afforded a separation. Imidazole IV formed an insoluble salt, while imidazoline III gave a complex soluble in DMF and partly soluble in other solvents.

*For Communication 1 see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1414-1418, October, 1991. Original article submitted November 14, 1990

0009-3122/91/2710-1140$12.50