ACYL CHLORIDES OF 2,2,5,5-TETRAMETHYL-3-IMIDAZOLIN-1-OXYL-4-O-ACYLHYDROXIMIC ACIDS

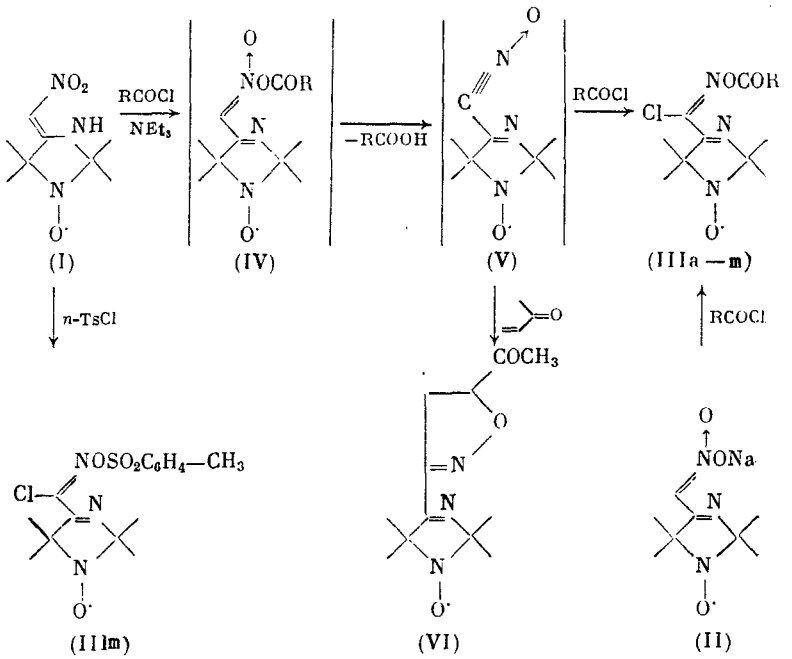
V. A. Reznikov, L. A. Vishnivetskaya, and L. B. Volodarskii

UDC 542.951.1:547.781.3-31:547.582.1

Acylation of nitroenamine derivatives of imidazolidin-1-oxyl with carboxylic acid chlorides leads to O-acylhydroximic acid chloride derivatives of 3-imidazolin-1-oxyl. The reaction proceeds apparently through a nitrile oxide. It was shown for the O-benzoyl derivative that reaction of the obtained acyl chlorides with nucleophilic reagents usually gives products of chlorine atom substitution with simultaneous cleavage of the acyl group.

It was shown by us earlier that the reaction of nitroenamine (I) with electrophilic reagents can proceed at two reaction centers – the enamine carbon atom and the N^3 nitrogen atom in the imidazolidine ring [1, 2]. Continuing the study of nitroenamine (I) we have examined its reaction with carboxylic acid chlorides. One could assume that products will be formed either of C-acylation analogously to enaminoketones of similar structure [3], or O-acylation to give mixed anhydrides of nitronic and carboxylic acid [4].

Upon reaction of nitroenamine (I) in chloroform or its Na-salt (II) in THF with benzoyl chloride in the presence of triethylamine a compound (IIIa) is formed which, according to elemental analysis is a product of addition of benzoyl chloride to the starting nitroenamine with elimination of water. In the IR spectrum of compound (IIIa) absorption bands are found at 1760 cm^{-1} due to the ester carbonyl group and at 1600 and 1580 cm^{-1} from the two conjugated C=N bonds (see [5]). In the UV spectrum absorption is observed with λ_{max} of 264 nm, close to the absorption of α-amino oximes [5]. On the basis of these data compound (IIIa)



R = C_6H_5 (a), 2-$CH_3OC_6H_4$ (b), 3-$NO_2C_6H_4$ (c), 4-ClC_6H_4 (d), 3-NO_2-4-ClC_6H_3 (e), 2-furyl (f), 5-NO_2-furyl (g), 4-FC_6H_4 (h), 4-pyridyl (i), CH_3 (j), $(CH_3)_2CH$ (k), C_2H_5O (ℓ).

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 444-450, February, 1991. Original article submitted April 27, 1990.

 0568-5230/91/4002-0382$12.50

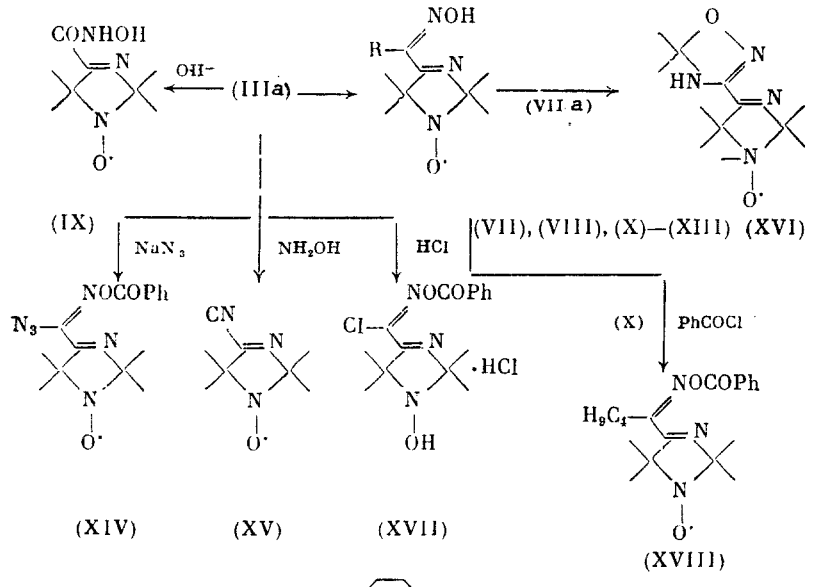
was assigned the structure of O-benzoylhydroximic acid chloride. A similar reaction occurs with acylnitrophenylmethane upon acylation with benzoyl chloride [6].

Formation of compound (IIIa) can be explained by a scheme which involves benzoylation at the nitro group oxygen atom with formation of a mixed anhydride (IV) followed by elimination of a benzoic acid molecule with formation of nitrile oxide (V). Further addition of a benzoyl chloride molecule leads to compound (IIIa). It should be noted that for complete reaction 2.5 equivalents of acid chloride is necessary. Intermediate formation of nitrile oxide (V) is confirmed by the fact that upon benzoylation in the presence of methylvinylketone a cycloadduct (VI) was isolated.

In order to determine the limits of applicability for this reaction, the reaction was studied of nitroenamine (I) with a series of acyl chlorides of aromatic as well as aliphatic carboxylic acids. It was established that in all cases the corresponding O-acylhydroximic acid chlorides (IIIb-k) are formed with 35-80% yield. It should be noted that upon reaction with acetyl and isobutyryl chlorides, the corresponding compounds (IIIj, k) are formed only in small yield. Reaction with ethyl chloroformate and p-toluenesulfonyl chloride also leads to the corresponding acyl chlorides (IIIℓ, m). Nitroenamine (I) under these conditions does not react with trimethylchlorosilane, N,N-dimethylthiocarbaminic acid chloride, or benzoyl fluoride.

It could be expected (see [7]) that acyl chlorides (III) would react easily with nucleophilic reagents. In fact, upon reaction of compound (IIIa) with ammonia, tert-butylamine, and morpholine substitution of the chlorine atom by the amino group takes place with cleavage of benzoic acid and formation of amidoximes (VIIa-c), respectively. Analogously, reaction of (IIIa) proceeds with other nucleophilic reagents; sodium methoxide, aqueous alcohol solution of NaOH, butylmercaptan, and KCN. Upon action of compound (IIIa) on imidazole and triazole there are formed respectively imidazo (XII) and triazo derivatives (XIII). Unexpectedly, upon reaction of sodium azide on (IIIa) substitution of the chlorine atom by the azido group takes place with preservation of the O-benzoyl group. This direction of the reaction can be associated with the lower basicity and high nucleophilicity of sodium azide. Upon reaction of (IIIa) with hydroxylamine nitrile (XV) is formed (see [7]).

Reaction of acyl chloride (IIIa) with nucleophilic reagents indicates that compounds (III) could be useful acylating spin labels. The compounds obtained from reaction of (IIIa) with nucleophilic reagents form complexes with a series of metals and therefore can be used as chelate-forming spin labels. It should be noted that upon reaction of amidoxime (VIIa) with acetone there was obtained imidazooxadiazole (XVI) which is also a chelate-forming reagent.



R = NH_2 (VII a), $(CH_3)_3CNH$ (VII b),  (VII c), CH_3O (VIII), C_4H_9S (X), CN (XI),

 (XII),  (XIII).

Thus, O-acylhydroximic acid chlorides in reactions with nucleophilic reagents are synthetic equivalents of nitrile oxide (V), since formation of products with nucleophilic reagents can be considered as the result of 1,3-dipolar addition of the C≡N → O group. In connection with this it was of interest to carry out also a reaction characteristic of nitrile oxides, such as 1,3-dipolar cycloaddition. However, it was not possible to carry out such a reaction, since it would be necessary to hydrolytically cleave the acylhydroxime group with preservation of the nucleofugic chlorine atom. Upon reaction with nucleophilic reagents not only cleavage of the acyl group takes place, but also substitution of the chlorine atom, which excludes further participation of compounds (III) in dipolar cycloaddition reactions. Compound (IIIa) does not react with weakly nucleophilic bases such as pyridine, triethylamine or sodium hydride. It was not possible to carry out the cycloaddition thermally. Thus, upon boiling acyl chloride (IIIa) in cyclohexene only the starting compound was isolated. It was not possible to cleave the ester group in acidic media. Upon reaction of (IIIa) with HCl solution in ether the ester group is preserved and reduction of the nitroxyl group to the hydroxylamino group proceeds with formation of compound (XVII). The reaction apparently proceeds through disproportionation of the nitroxyl group with formation of a hydroxylamino group and an oxyammonium salt which, being a strong oxidant, is reduced by traces of water (see [8]).

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr (concentration 0.25%) and in solutions of CCl_4 (concentration 5%). UV spectra were taken on a Specord UV-VIS instrument in ethanol and PMR spectra were recorded on a Varian A56/60 instrument (concentration 7%). Yields, melting points, data of elemental analysis, IR, and UV spectra of the synthesized compounds are shown in Table 1. Compounds (I) and (II) were obtained according to [1].

Acylation of Nitroenamine (I) (general method). a. To a suspension of Na salt (II) (0.1 mole) in 30 ml of dry THF 0.15 mole of triethylamine was added and a solution of 0.15 mole of acid chloride in 30 ml of THF was added dropwise with stirring and cooling to 0°C. Stirring was continued for 0.5 h at 20°C. The NaCl precipitate was filtered and solution evaporated. Compounds (III) were isolated by chromatography on a column with silica gel using chloroform as eluent. After elution of acid chloride (III) was eluted with a chloroform and methanol mixture (30:1). There was isolated 5-6 g of starting nitroenamine (I). Increasing the amount of acid chloride does not lead under these conditions to complete consumption of the starting nitroenamine.

b. To a solution of 0.1 mole of nitroenamine (I) and 0.25 mole of triethylamine in 300 ml of dry chloroform a solution of 0.25 mole acid chloride in 100 ml of chloroform was added dropwise with stirring and cooling to 0°C. Stirring was continued for 15 min, the solution evaporated, the residue diluted with 300 ml of dry ether, the precipitated triethylamine hydrochloride was filtered, and the solution evaporated. Acid chloride (III) was isolated by chromatography on a column of silica gel with chloroform as eluent. Under these conditions acid chlorides (IIIa-m) were obtained. Their yields are shown in Table 1 according to method b.

Upon acylating nitroenamine (I) by method b in the presence of an equimolar amount of methylvinylketone, followed by chromatography on silica gel using chloroform as eluent, together with acid chloride (IIIa) also 4-(5-acetyl-4,5-dihydroisoxazolyl-3)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (VI) was obtained.

Amidoxime of 2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-carboxylic Acid (VIIa). A solution of 0.3 g of compound (IIIa) in a mixture of 1.5 ml 20% ammonia and 2 ml of methanol was kept for 1 h at 20°C. The precipitated deposit of amidoxime (VIIa) was filtered, washed with water, and dried. The yield was 0.12 g (65%), mp 193-195°C (ethanol) (193-195°C, [9]).

Tert-butylamidoxime of 2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-carboxylic Acid (VIIb). A solution of 2 g (6.1 mmoles) of compound (IIIa) and 3 ml (36.5 mmoles) of tert-butylamine in 20 ml of methanol was kept for 48 h at 20°C and then evaporated. Compound (VIIb) was isolated by chromatography on a column with silica gel using chloroform as eluent.

Under the same conditions upon reaction of (IIIa) with morpholine over 0.5 h the morpholinoamidoxime of 2,2,5,5-tetramethyl-3-imidazolin-1-oxyl-4-carboxylic acid (VIIc) was obtained.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	Mp,* °C	Empirical formula	Found/Calculated, %				IR spectrum, KBr, ν, cm^{-1}	UV (ethanol) λ_{max} (log ε)
				C	H	N	Cl		
(IIIa)	80	134–135	$C_{15}H_{17}ClN_3O_3$	55,5 55,8	5,3 5,3	12,8 13,0	11,2 11,0	1760 (C=O), 1600, 1580 (C=N)	246(4,21)
(IIIb)	60	90–91	$C_{16}H_{19}ClN_3O_4$	54,6 54,5	5,4 5,4	11,9 11,9	10,4 10,1	1790 (C=O), 1605, 1595 (C=N)	245(4,33) 307(3,77)
(IIIc)	60	175–176	$C_{15}H_{16}ClN_4O_5$	48,9 49,0	4,3 4,4	14,9 15,2	10,4 10,0	1785 (C=O), 1620, 1595 (C=N) 1545, 1360 (NO_2)	233(4,60)
(IIId)	80	171–172	$C_{15}H_{16}Cl_2N_3O_3$	50,3 50,4	4,4 4,5	12,0 11,8	19,9 19,9	1770 (C=O), 1610, 1595 (C=N)	257(4,30)
(IIIe)	70	167–168	$C_{15}H_{15}Cl_2N_3O_5$	44,5 44,8	3,6 3,7	14,0 13,9	17,4 17,7	1775 (C=O), 1610, 1595 (C=N) 1555, 1360 (NO_2)	243(4,56)
(IIIf)	60	125–126	$C_{13}H_{15}ClN_3O_4$	49,6 49,9	4,8 4,8	13,1 13,4	11,1 11,4	1785 (C=O), 1610, 1580 (C=N) 3120, 3160 (CH-furyl)	227(4,11) 272(4,44)
(IIIg)	35	162–163	$C_{13}H_{14}ClN_4O_6$	43,7 43,6	4,0 3,9	15,5 15,7	9,8 9,9	1795 (C=O), 1610, 1595, 1560 (C=N, C=C), 3140 (CH-furyl)	237(4,33) 299(4,21)
(IIIh) †	70	153–154	$C_{15}H_{16}ClN_3FO_3$	52,9 52,9	4,7 4,7	12,3 12,3	10,4 10,4	1765 (C=O), 1605, 1590 (C=N)	248(4,41)
(IIIi)	40	158–160	$C_{14}H_{16}ClN_4O_3$	51,8 52,0	5,1 5,0	17,1 17,3	10,8 11,0	1770 (C=O), 1605, 1590 (C=N)	237(4,45)
(IIIj)	20	74–75	$C_{10}H_{15}ClN_3O_3$	46,1 46,2	5,6 5,8	16,6 16,1	13,9 13,6	1785 (C=O), 1605, 1575 (C=N)	227(4,24)
(IIIk)	5	103–104	$C_{12}H_{19}ClN_3O_3$	49,5 49,9	6,6 6,6	14,3 14,6	12,7 12,3	1800 (C=O), 1610, 1595 (C=N)	228(4,35)
(IIIℓ)	75	114–115	$C_{11}H_{17}ClN_3O_4$	45,4 45,4	5,9 5,9	14,6 14,5	12,2 12,2	1780 (C=O), 1610, 1590 (C=N)	225(4,26)
(IIIm)‡	20	108–109	$C_{15}H_{19}ClN_3O_4S$	48,8 48,4	5,3 5,1	11,0 11,2	9,4 9,5	1610 (C=N), 1595 (C=N)	231(4,18)

TABLE 1 (continued)

Compound	Yield, %	Mp,* °C	Empirical formula	Found/Calculated, %				IR spectrum, KBr, ν, cm^{-1}	UV (ethanol) λ_{max}(log ε)
				C	H	N	Cl		
(VI)	15	108–110	$C_{12}H_{17}N_3O_3$	57,4 57,4	7,0 6,8	16,4 16,7		1730 (C=O), 1605 (C=N)	246(3,79) 344(3,83)
(VIIb)	80	153–155	$C_{12}H_{23}N_4O_2$	56.5 56.5	9,1 9,0	21,7 21,9		1605, 1660 (C=N)	280(3,66)
(VIIc)	60	133–135	$C_{12}H_{21}N_4O_3$	53,5 53,5	8,0 7,8	20,8 20,8		1610, 1620 (C=N)	215(4,10) 303(3,45)
(VIII)	15	119–121	$C_9H_{16}N_3O_3 \cdot H_2O$	46,9 46,6	7.5 7,2	18,1 18,1		1660, 1690 (C=N), 3460 (OH)	237(3,90)
(IX)	60	163–165	$C_8H_{14}N_3O_3$	47,8 48,0	7,0 7,0	20,7 21.0		1620, 1675, 1680 (O=C–C=N), 3160 (NH), 2870, 3415, 3490, 3560 (OH)	242(3,86)
(XI)	96	178–179	$C_9H_{13}N_3O_2$	52,1 51,8	6,4 6,2	27,6 27,8		1605, 1610, 1640 (C=N), 2245 (C≡N)	243(4,20)
(XII)	67	220–221	$C_{11}H_{16}N_5O_2$	52,8 52,8	6,6 6,4	28,1 28,0		1610, 1635 (C=N), 3130, 3160 (CH imidazolyl)	215(4,19) 237(4,16)
(XIII)	50	210–211	$C_{10}H_{15}N_6O_2$	47,7 47,8	6,0 6,0	33,6 33,5		1610 (C=N), 3155 (CH–triazolyl)	238(4,22)
(XIV)	40	90–91	$C_{14}H_{17}N_6O_3$	54,9 54,7	5,2 5,2	25,8 25,5		1585, 1620 (C=N), 1770 (C=O) 2150, 2195 (N_3)	242(4,07) 260(4,07)
(XVI)	40	205–206	$C_{11}H_{19}N_4O_2$	55,2 55,3	7,8 8,0	23,2 23,5		1580, 1620 (C=N), 3180 (NH)	308(3,38)
(XVII)	60	150–152	$C_{15}H_{18}ClN_3O_3 \cdot HCl$	50,2 50,0	5,3 5,3	11,8 11,7	19,6 19,7	1590, 1605, 1645 (C=N), 1785 (C=O)	244(4,27)
(XVIII) ‡	75	Oil	$C_{19}H_{26}N_3O_3S$	60,4 60,7	6,7 6,9	11,4 11,5		1605 (C=N), 1770 (C=O)	240(4,33) 276(3,86)

*Compounds (IIIa-i, k, ℓ, m), (VI), (VIIc), (VIII) and (XI) were recrystallized from a mixture of ethyl acetate and hexane, (IIIj), (VIIb), and (IX) from aqueous methanol, (XII) and (XIII) from methanol, (XIV) from hexane, (XVI) from ethyl acetate, (XVII) from ethanol, and compound (XVIII) was chromatographed.

†Found/calculated, %: F 5.6/5.9.

‡Found/calculated, %: (S) 8.6/8.9 (IIIm), 8.9/8.5 (XVIII).

Methyl Ester of 2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-carbohydroximic Acid (VIII). A solution of 0.5 g (1.54 mmoles) of compound (IIIa) and 0.5 g (11 mmoles) of sodium methoxide in 30 ml of methanol was kept for 0.5 h at 20°C, then evaporated. The residue was diluted with 10 ml of water, neutralized with 5% HCl, and extracted with chloroform. The extract was dried with $MgSO_4$, the solution evaporated, and compound (VIII) was isolated by chromatography on a column with silica gel using chloroform as eluent.

Under the same conditions reacting hydroxylamine with (IIIa) gave nitrile (XV) in 35% yield, identified from its IR spectrum by comparison with a known sample [10].

2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-carbohydroximic Acid (IX). A solution of 0.3 g of compound (IIIa) in a mixture of 6 ml of 5% NaOH solution and 3 ml of THF was kept for 15 min at 20°C and then acidified to pH with 4.5% HCl, and extracted with chloroform. The extract was dried with $MgSO_4$, the solution evaporated, and compound (IX) was isolated by chromatography on a column with silica gel using a mixture of chloroform and methanol (25:1) as eluent.

S-Butyl Ester of 2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-thiohydroximic Acid (X). A solution of 1 g (3.1 moles) of compound (IIIa), 0.7 ml (6.5 mmoles) of butylmercaptan, and 0.4 g (7.7 mmoles) of sodium methoxide in 20 ml of methanol was kept for 2 h at 20°C, and evaporated. Compound (X) was isolated by chromatography on a column with silica gel and chloroform as eluent. Thioester (X) was characterized in the form of its benzoyl derivative (XVIII) which was obtained by benzoylation of 0.2 g (0.74 mmole) of (X) with 0.25 ml of benzoyl chloride in 5 ml of 5% NaOH and isolated by chromatography on a column with silica gel using ethyl acetate–hexane (1:4) as eluent.

4-Cyanohydroximinomethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XI). A solution of 3.23 g (10 mmoles) of compound (IIIa) and 1.7 g (25 mmoles) of KCN in 40 ml of methanol was kept for 1 h at 20°C and then evaporated. The residue was dissolved in water, acidified with 5% HCl to pH of 3, and extracted with chloroform. The extract was dried with $MgSO_4$, the solution evaporated, and the residue diluted with hexane. The precipitate was filtered and washed with a mixture of ether and hexane (1:2) (3 × 5 ml).

4-Imidazohydroximinomethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XII). A mixture of 4.8 g (15 mmoles) of (IIIa) and 3.12 g (45 mmoles) of imidazole in 30 ml of methanol was heated until dissolved and kept for 3 h at 20°C. The precipitate of compound (XII) was filtered off. Additional product was isolated by evaporation of the filtrate. The residue after evaporation was washed with 5 ml of cold ethanol and compound (XII) was filtered off.

4-(1,2,4-Triazolohydroximinomethyl)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XIII). A mixture of 4.8 g (15 mmoles) of (IIIa) and 3.12 g (45 mmoles) of 1,2,4-triazole in 30 ml of ethanol was boiled for 8 h. Triazole derivative (XIII) precipitated upon cooling and was filtered and washed with cold ethanol (2 × 5 ml).

Azide of 2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-O-benzoylhydroximic Acid (XIV). A mixture of 0.65 g (2 mmoles) of compound (IIIa) and 0.2 g (3 mmoles) of sodium azide in 10 ml of acetonitrile was stirred for 1 h at 20°C and the solution was evaporated. By chromatography on silica gel using a mixture of $CHCl_3$ and CCl_4 (1:1) as eluent, there were isolated 0.4 g of starting compound (IIIa) and 0.1 g of azide (XIV).

4-(4,5-Dihydro-5,5-dimethyl-1,2,4-oxadiazolyl-3)-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (XVI). A solution of 0.25 g of amidoxime (VIIa) in 10 ml of acetone was boiled with a catalytic amount of p-toluenesulfonic acid for 20 h and evaporated. Compound (XVI) was isolated by chromatography on a column of silica gel using chloroform as eluent.

Hydrochloride of 2,2,5,5-Tetramethyl-3-imidazolin-1-oxyl-4-O-benzoylhydroximic Acid Chloride (XVII). A solution of 0.5 g of compound (IIIa) in dry ether was saturated with hydrogen chloride and kept for 24 h at 20°C. The precipitated deposit of (XVII) was filtered and washed with dry ether. PMR spectrum (CD_3OD, δ, ppm): 1.72 s (6H), 1.88 s {6H, 2,5-$(CH_3)_2$}, 7.8 m (5H, C_6H_5).

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SYNTHESIS OF CYANAMIDES CONTAINING THE PHENOTHIAZINE FRAGMENT AND THEIR REACTIONS WITH DIALKYLDITHIOPHOSPHORIC ACIDS

R. M. Kamalov, G. M. Makarov, I. A. Litvinov, O. N. Kataeva, M. A. Pudovik, and R. A. Cherkasov

UDC 542.91:547.869.2:547.26'118

Reaction of phenothiazine with dialkoxyphosphoryl or chlorosulfenyl isocyanide dichlorides has given 10-cyanophenothiazine, which adds dialkyldithiophosphoric acids at the C≡N bond. The addition products rearrange to 10-[N'-(dialkoxythiophosphoryl)thiocarbamoyl]phenothiazines, which are prone to decompose to dialkoxythiophosphoryl isothiocyanates and phenothiazine, or on treatment with alkyl halides in the presence of base afford stable S-alkyl-N-dialkoxythiophosphoryl-(10-phenothiazinyl)isothioformamides. The reaction between 10-cyanophenothiazine and an excess of dithiophosphoric acids also affords 10-thiocarbamoylphenothiazine and tetraalkyl trithiopyrophosphates. An x-ray diffraction examination of the molecular structure of S-methyl-N-diisopropoxythiophosphoryl-(10-phenothiazinyl)isothioformamide has shown it to possess the Z-configuration. The dihedral angle formed by the benzene rings of the phenothiazine fragment is 125.7°. The products of the addition of dithiophosphoric acids to the C≡N bond of N,N-bis[2'-(10-phenothiazinyl)-2'-oxoethyl]cyanamide, obtained from 10-(chloroacetyl)phenothiazine and NaNHCN, also isomerize by 1,3S → N migration of the thiophosphoryl group. Subsequent heterocyclization, with elimination of phenothiazine, affords 2-(dialkoxythiophosphorylimino)-3-[2'-(10-phenothiazinyl)-2'-oxoethyl]thiazolidin-5-ones.

The considerable and diverse biological activity of 10-substituted phenothiazines [1], above all their therapeutic properties [2], makes it necessary to develop novel methods of synthesis of compounds of this type. It has been shown that phenothiazine reacts with phenyl isocyanide dichloride to give 10-(N'-phenylchloroformimidoyl)phenothiazine. This compound, and some of its derivatives, react with dialkyl (di)thiophosphates at the C=N bond, providing a convenient method for the preparation of 10-(thio)carbamoylphenothiazines [3]. We have now examined various possible methods for the attachment of a cyano group or a group containing it to the nitrogen atom of phenothiazine with a view to its subsequent reaction with dialkyl dithiophosphoric acids. The latter readily undergo addition at the C≡N bond to give a wide range of products, depending on the reaction partners selected and on the reaction conditions [4].

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Branch, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 451-460, February, 1991. Original article submitted December 15, 1989.

 0568-5230/91/4002-0388$12.50