REACTION OF CARBAMOYL DERIVATIVES OF 4- AND 5-HYDROXYLAMINOTHIAZOLIDINE-2-THIONES AND 4-HYDROXYLAMINOIMIDAZOLIDIN-2-ONE WITH METHYL CHLOROFORMATE. PROPERTIES OF SUBSTITUTED 1,2,4-OXADIAZOLIDINE-3,5-DIONES

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Acylation with methyl chloroformate of N-monocarbamoyl derivatives of 4- and 5-hydroxylaminothiazolidin-2-thione and 4-hydroxylaminoimidazolidin-2-one, depending on their structure and the reaction conditions, leads either to N,O-bisacylhydroxylamines or to their intramolecular cyclization products, the substituted 1,2,4-oxadiazolidine-3,5-diones which, on decarboxylation, may convert into the corresponding 4- and 5-carbamoyliminothiazolidine-2-thiones.

It was previously shown [1, 2] that in the reaction of thiazolidine-2-thiones and imidazolidin-2-ones containing an exocyclic hydroxylamino group with isocyanates, N-monocarbamoyl derivatives, the hydroxyureas I-III, are formed.

It was found that the acylation of these compounds by methyl chloroformate leads to various products, according to their structure and the reaction conditions. Thus, by treatment of methylhydroxyureas Ia, IIa, and IIIa (R^1 = H), with an equimolar amount of methyl chloroformate in a solvent in the presence of triethylamine (TEA) (method A), the corresponding 4- and 5-[(N-methylcarbamoyl-O-methoxycarbonyl)hydroxylamino]thiazolidine-2-thiones IV, VI and -imidazolidin-2-one V are formed. At the same time, acylation of arylhydroxyureas Ib, IIb, IIIb, (R^1 = H) under these conditions results in the formation of compounds VIIb, VIIIb, IXb, which, according to spectral data and known analogies [2-4], were identified as substituted 1,2,4-oxadiazolidine-3,5-diones.

In the case of hydroxyureas IIIc, d ($R^1 = CH_3$), the presence of the methyl group in the 5-position of the heterocyclic ring hinders acylation and an excess of methyl chloroformate is required to carry it out (method B). Thus, both methyl- (IIIc) and arylhydroxyurea (IIId) give oxadiazolidine-3,5-diones IXc, d. However, methylhydroxyurea Ic ($R^1 = CH_3$) could not be acylated. In solution, the reaction nearly does not proceed, while during acylation by method B the formation (TLC data) of the known 3,5,5-trimethyl-4-methylidenethiazolidine-2-thione is observed [5], which is probably due to the great steric strain of the molecule.

The possibility of formation of various oxadiazolidinediones [3, 4] as a result of intramolecular cyclization of N,O-bisacylhydroxylamines during heating of their solutions or on treatment by alkalies, is confirmed by the example of compound VI, which on heating in the presence of TEA gives oxadiazolidine-3,5-dione VIIa (method C). It should be noted that not in all cases during the acylation of hydroxyureas could the bisacyl derivatives IV-VI be isolated; this is explained by the fact that during the acylation of hydroxyureas IIIc, d by method B, rigorous conditions (increase in temperature) of carrying out the reaction promote the cyclization, while in the case of arylhydroxyureas Ib, IIb, IIIb ($R^3 = 3,4\text{-}Cl_2C_6H_3$), the cyclization is promoted by the high acidity of the ArNH proton, compared with the CH_3NH proton of compounds Ia, IIa. According to the TLC data, in the latter case an initial formation of an intermediate compound is observed (most probably, an N,O-bisacylhydroxylamine), which then converts into the reaction product.

However, unlike in the case of compound IV, a similar cyclization of the N,O-bisacylhydroxylamine based on imidazolidin-2-one V could not be carried out. On heating in the presence of TEA or an alkali, it undergoes hydrolysis to the initial hydroxyurea IIa. The corresponding oxadiazolidine-3,5-dione IXa could not be obtained, including from the N,O-bisacylhydroxylamine VIa, but, in this case, even the formation of the starting hydroxyurea could not be observed, as in the case of the imidazolidin-2-one derivative V.

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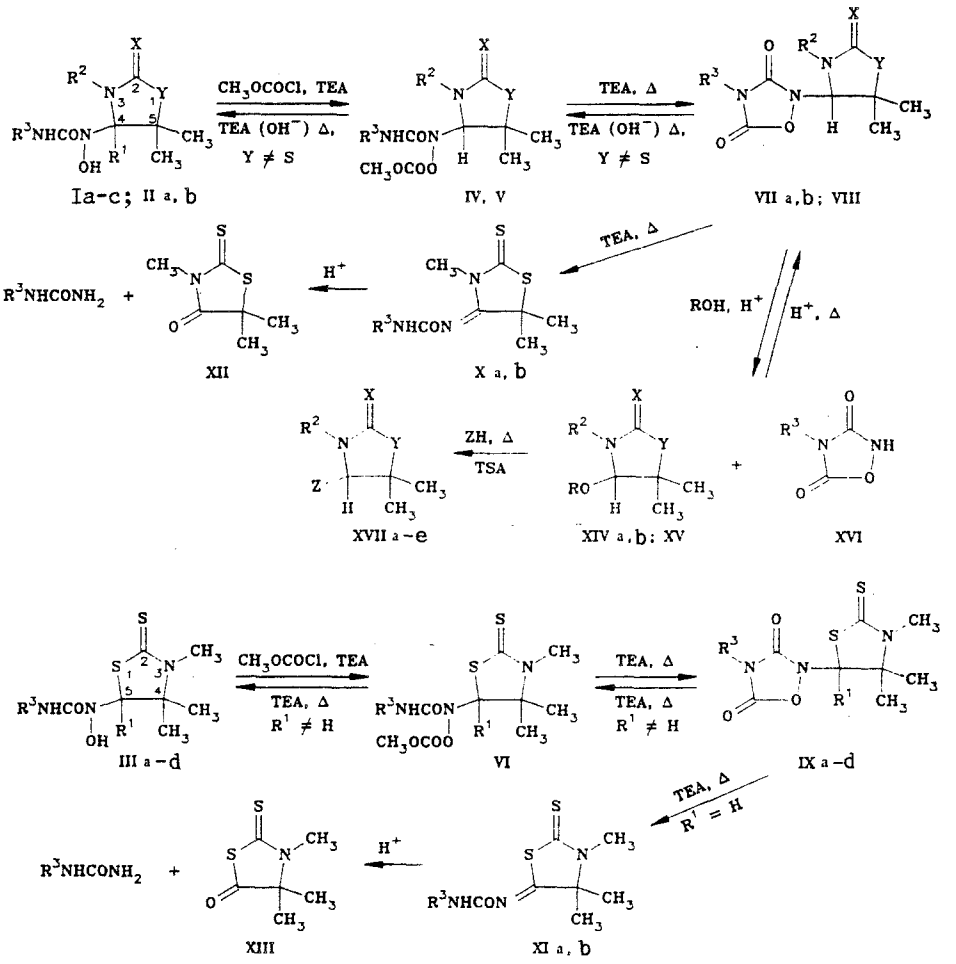

Ia, b, IIa, b R^1 = H; Ic R^1 = R^2 = CH_3; Ia, b IV, VIIa, b, XIVa, b, XVIIa–c, R^2 = CH_3; IIa, b, V, VIIa, b, XV, XVIId, e R^2 = C_6H_5; Ia, c, IIa, IV, V, VIIa, Xa R^3 = CH_3; Ib, IIb, VIIb, VIII, Xb, XVI R^3 = 3,4-$Cl_2C_6H_3$; XIVa, XV R = H; XIVb R = CH_3; Ia, b, IV, VIIa, b, XIVa, b, XVIIa–c X = Y = S; IIa, b, V, VIII, XVIId, e X = O, Y = NCH_3; XVIIa Z = 3,4-$Cl_2C_6H_3NHCONH$, b Z = CH_2=$C(CH_3)CH$=NO, c, d Z = 1,2,4-triazol-1-yl, d Z = $NHCONH_2$; IIIa, b, VI, IXa, b, R^1 = H; IIIc, d, IXc, d R^1 = CH_3; IIa, c, VI, IXa, c, XIa R^3 = CH_3; IIIb, d, IXb, d, XIb R^3 = 3,4-$Cl_2C_6H_3$.

Unexpected results were obtained during the acylation of methylhydroxyurea IIIa and arylhydroxyureas Ib, IIIb (R^1 = H) by an excess of methyl chloroformate (method B). In these cases compounds X, XI were obtained, in the IR spectra (KBr) of which only an absorption band of the carbonyl group in the 1665-1680 cm^{-1} region and an "amide II" band at 1510-1545 cm^{-1} are present. In the PMR spectra of the compounds obtained, the signal of the gem-dimethyl grouping appears in the form of a singlet, and the proton signal at the $C_{(4)}$ or $C_{(5)}$ atom is absent. There are also signals of the carbamoyl fragment. These data indicate that compounds X, XI have the structure of 4- and 5-carbamoyliminothiazolidine-2-thiones, respectively. Hydrolysis of compounds Xb and XIb to 3,4-dichlorophenylureas and the known 3,5,5-trimethylthiazolidin-4-one-2-thione (XII) [6] or 3,4,4-trimethylthiazolidin-5-one-2-thione (XIII) [7] confirms the proposed structure.

It should be noted that heating of hydroxyureas with TEA is not accompanied by any changes; hence the formation of imines X, XI is not due to their dehydration. On the other hand, on heating of N,O-bisacylhydroxylamine VI, an almost instantaneous formation of two compounds was observed, one of which then rapidly converts into the other (the TLC data). Thus, transformation of compound VI into imine XIa proceeds via an intermediate product, which most likely is the corresponding oxadiazolidinedione IXa. In fact, on short-term heating of oxadiazolidinedione IXb in acetone in the presence of catalytic amounts of TEA, imine XIb is formed (method C). In a similar way, 4-imino derivatives were obtained from compounds VII but, in this case, prolonged boiling was required in the presence of an equimolar amount of TEA.

Clearly, the fact that an attempt to cyclize N,O-bisacylhydroxylamine VI, unlike for the isomeric compound VI, gave the imine XIa, and not oxadiazolidinedione, is in particular explainable by the ease of formation of 5-imino derivatives XI.

It is clear that the formation of imines is possible only in the presence of a hydrogen atom in the 4- or 5-position of the heterocyclic ring. In the case of oxadiazolidine-3,5-diones IXc, d (R^1 = CH_3) in the presence of TEA, a slow hydrolysis was observed to the corresponding hydroxyurea. However, oxadiazolidinedione VIII, a derivative of imidazolidinone, although it

TABLE 1. Characteristics of Compounds IIa, IV-XI, XIVb, XV-XVII

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1} (KBr)		Yield, %
			C=O	"amide II"	
IIa	$C_{14}H_{20}N_4O_3$	207...208	1670	1510	96
IV	$C_{10}H_{17}N_3O_4S_2$	114...115	1780, 1700, 1675	1530	50
V	$C_{16}H_{22}N_4O_5$	150...152	1790, 1685	1510	68
VI	$C_{10}H_{17}N_3O_4S_2$	115...117	1790, 1670	1545	60
VIIa	$C_9H_{13}N_3O_3S_2$	145...147	1840, 1740	—	52
VIIb	$C_{14}H_{13}Cl_2N_3O_3S_2$	83...84	1825, 1745	—	80
VIII	$C_{20}H_{18}Cl_2N_4O_4$	138	1820, 1755, 1700	—	60
IXb	$C_{14}H_{13}Cl_2N_3O_3S_2$	175...177	1820, 1745	—	50
IXc	$C_{10}H_{15}N_3O_3S_2$	173...174	1825, 1740	—	48
IXd	$C_{15}H_{15}Cl_2N_3O_3S_2$	131...132	1810, 1745	—	50
Xb	$C_8H_{13}N_3OS_2$	105...107	1680 (3470)*	1545	55
Xa	$C_{13}H_{13}Cl_2N_3OS_2$	135...136	1650 (3430)*	1525	66
XIa	$C_8H_{13}N_3OS_2$	163...164	1665 (3470)*	1510	43
XIb	$C_{13}H_{13}Cl_2N_3OS_2$	210...212	1670 (3430)*	1500	85
XIVb	$C_7H_{13}NOS_2$	32...34	—	—	52
XV	$C_{12}H_{17}N_2O_2$	162	—	—	80
XVI	$C_8H_4Cl_2N_2O_3$	181...182	1720, 1810	—	70
XVIIa	$C_{13}H_{15}Cl_2N_3OS_2$	215...217	1710	1530	56
XVIIb	$C_{12}H_{20}N_2OS_2$	Oil	—	—	90
XVIIc	$C_8H_{12}N_4S_2$	150...152	—	—	80
XVIId	$C_{14}H_{17}N_5O$	150	1690	—	86
XVIIe	$C_{13}H_{18}N_4O_3$	220	1670**	—	72

*The NH band (in CCl_4).

**A broad band.

TABLE 2. PMR Spectra of Compounds VII, IX-XI, XIV, XVII*

Compound	Chemical shift s, ppm (SSCC, Hz)				
	$C(CH_3)_2$	CH or CCH_3	R^2 (CH_3 of Ar)	R^3 (CH_3 or Ar)	NH*** (CH=N of the triazole ring)
VIIa	1,48; 1,69	5,86 s	3,2 s	3,06 s	—
VIIb	1,50; 1,65	6,06 s	3,25 s	7,46...7,99 m	—
IXb	1,43; 1,56	6,06 s	3,15 s	7,35...7,99 m	—
IXc	1,46; 1,58	1,99 s	3,26 s	3,08 s	—
IXd	1,44; 1,57	2,0 s	3,24 s	7,50...8,10 m	—
Xa	1,72 s	—	3,30 s	2,7 d (4,5)	5,81
Xb	1,84 s	—	3,38 s	7,38...8,03 m	9,3
XIa	1,61 s	—	3,38 s	2,85 d (4,5)	7,34
XIb	1,65 s	—	3,34 s	7,35...8,33 m	10,13
XIVb	1,38; 1,47	4,98 s	3,24 s	3,58 s (OCH_3)	—
XVIIa	1,43; 1,63	5,7 d (10)	3,26 s	7,20...8,10 m	7,35 and 8,73
XVIIc	1,05; 1,76	6,34 s	3,11 s	—	(7,95 and 8,46)
XVIIe***	1,12; 1,20	5,47 d (9)	6,86...7,62 m	5,55 (NH_2CO)	6,76 d (9)

*The spectra of compounds VIIa, Xb, XIVb were obtained in CD_3CN; VIIb, IXb, d, XVIIe in DMSO-D_6; IXc, Xa, XIa, b, XVIIc in $(CD_3)_2CO$; XVIIa in $(CD_3)_2CO$ + DMSO-D_6.

**A broadened signal.

***An NCH_3 group signal – at 2.61 ppm.

contains a hydrogen atom at $C_{(4)}$, does not rearrange into an imine in the presence of a base, but gives the initial hydroxyurea. The presence of a sulfur atom in the molecule of oxadiazolidinediones VII, IX, during their rearrangement into imines X, XI possibly results in that at the first stage the N–O bond is cleaved, which is facilitated by electron pairs of the sulfur atom, which interact with the σ*-antibonding orbital of the N–O bond. Further transfer of the proton and splitting off of carbon dioxide lead to the imine. In the 4-derivatives VII, because of the distance of the sulfur atom, this reaction is less effective than in compounds IX, and, as a result, the rearrangement into the imine proceeds with greater difficulty. However, in the

case of the imidazolidinone derivative VIII, no such cooperative effect takes place and, therefore, the decarboxylation with the formation of the corresponding imine is not observed.

The formation of the corresponding imines also takes place on heating the oxadiazolidinediones VIIb and IXb to 90°C in DMSO-D_6 directly in the sensor of the spectrometer. Thus, in the PMR spectra, together with decrease in intensity of the $C(CH_3)_2$, NCH_3, and CH group signals of the starting compounds, the proton signals appear of the $C(CH_3)_2$ and NCH_3 groups with chemical shifts characteristic for the corresponding imines. However, when a mixture of DMSO-D_6 and D_2O is used as the solvent, heating of both the oxadiazolidinedione VIIb and compound VIII is accompanied by the appearance of signals characteristic for the corresponding 4-hydroxythiazolidine-2-thione XIVa [5] and 4-hydroxyimidazolidin-2-one XV.

An attempt to isolate the products of splitting of compound VIII from DMSO by dilution with water leads to the precipitation of the starting oxadiazolidinedione in an almost quantitative yield. This is possibly due to the reversibility of the hydrolysis, i.e., a rapid reaction of 4-hydroxyimidazolidin-2-one XV formed with the second splitting product – 4-(3,4-dichlorophenyl)-1,2,4-oxadiazolidine-3,5-dione (XVI), as confirmed by the reaction between authentic samples of these compounds. When the same reaction was carried out with compound VIIb in methanol, the splitting products, 4-methoxythiazolidine-2-thione XIVb and compound XVI, could be separated.

It should be noted that the reverse synthesis of oxadiazolidinedione VI could be accomplished by boiling the corresponding hydroxythiazolidine-2-thione XIVa and compound XVI in benzene in the presence of 4-toluenesulfonic acid (TSA).

The observed differences in the behavior of the isomeric oxadiazolidinediones VII and IX, and also of compound VIII are most probably due to the fact that, similarly to the transformations of 4-hydroxylamino derivatives in acid media [5, 8], compounds VII, VIII undergo an intermediate ring opening. However, for compound IXb (similarly to 5-hydroxylaminothiazolidine-2-thiones), this process is not very likely and, therefore, rearrangement into an imine results in all cases.

The above-noted mobility of the OH group at the 4-position of thiazolidine-2-thiones and imidazolidin-2-one makes it possible to exchange it for various nitrogen-containing fragments. For example, by reaction of 4-hydroxy derivatives XIVa, XV with urea, 1,2,4-triazole, 2-methylpropenaldoxime (i.e., with reagents having fair nucleophilicity, but which are not strong bases), compounds XVII were obtained. It is clear that, as in the case of the hydrolysis of 4-hydroxylaminothiazolidine-2-thiones [5] and 4-hydroxyaminoimidazolidin-2-ones [8] and oxadiazolidinediones VII, VIII based on them, these reactions proceed with an intermediate ring opening, which is catalyzed by an acid. The catalytic action of the acid is also confirmed by the fact that, in the case of imidazole or any aliphatic amine, which are strong bases, the exchange of the OH group in compounds XIVa, XV does not take place.

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer 457 spectrophotometer in KBr tablets and in CCl_4 solutions. The PMR spectra were run on Bruker HX-90E (90 MHz) and Varian FT-80A (80 MHz) spectrometers. The course of the reaction was monitored on Silufol UV-254 plates in a benzene–acetone (3:1) system of solvents.

The melting points, yields, and spectral characteristics are given in Tables 1 and 2. The results of the elemental analysis of compounds II, IV-XVII for C, H, N correspond to the calculated data.

The hydroxyureas used in the investigation were obtained by the method in [1], while 4-hydroxyimidazolidin-2-one XV was obtained by a method analogous to that described in [8].

4(or 5)-[(N-Methylcarbamoyl-O-methoxycarbonyl)hydroxylamino]thiazolidine-2-thiones (IV, VI) and -imidazolidin-2-one (V). A solution of 10 mmoles of methyl chloroformate in 10 ml of acetone and a solution of 10 mmoles of TEA in 10 ml of acetone were added simultaneously, with stirring, to a solution of 10 mmoles of methylhydroxyurea Ia, IIa, or IIIa in 30 ml of acetone. At the end of the reaction (TLC control), the TEA hydrochloride was filtered off and acetone was evaporated. The residue was dissolved in 30 ml of benzene and the solution was filtered. The filtrate was evaporated, and the oil obtained was treated with 10 ml of ether. Compounds IV-VI were filtered off.

2-[Thiazolidine-2-thion-4(or 5)-yl or -imidazolidin-2-on-4-yl]-4-[3,4-dichlorophenyl(or methyl)-1,2,4-oxadiazolidine-3,5-diones (VIII, IX). A. A solution of 10 mmoles of methyl chloroformate in 10 ml of acetone and a solution of 10 mmoles of TEA in 10 ml of acetone were added dropwise simultaneously, with stirring, to a solution of 10 mmoles of arylhydroxyurea Ib, IIb, or IIIb in 30 ml of acetone. At the end of the reaction (TLC control) the TEA hydrochloride was filtered off, the solution was evaporated, and the residue was treated with petroleum ether. Compounds VIIb, VIII, IXb were obtained.

B. Ten to twelve drops of TEA were added slowly dropwise to a mixture of 1 mmole of hydroxyurea IIIc or IIId and 3 ml of methyl chloroformate. A strong heating up was observed, the reaction mixture liquefied, and then crystallized. The mass formed was treated with 10 ml of water, and the precipitate was filtered off and dried in air. Compounds IXc, d were obtained.

C. A solution of 1 mmole of the N,O-bisacylhydroxylamine IV in 10 ml of acetone was boiled for 15 min in the presence of catalytic amounts of TEA. The acetone was evaporated and the residue was treated with ether. The precipitate was filtered off and compound VIIa was obtained.

Compounds VII-IX was recrystallized from benzene or CCl_4.

4- and 5-[N-(3,4-Dichlorophenyl(or methyl)carbamoylimino]thiazolidine-2-thiones (X, XI). A solution of 1 mmole of compound VIIa, b and 1 mmole of TEA in 10 ml of acetone was boiled for 10 h. At the end of the reaction (TLC control), the acetone was evaporated, the residue was treated with ether, and compound X was obtained.

Compounds Xb and XIa, b were also obtained from hydroxyureas Ib and IIIa, b by treating them with an excess of methyl chloroformate by method B.

Compounds XIa, b were obtained from N,O-bisacyl derivative VI and oxadiazolidine-3,5-dione IXb, respectively, by method B.

Compounds X and XI were recrystallized from benzene or CCl_4.

Hydrolysis of 4- and 5-Carbamoyliminothiazolidine-2-thiones Xb and XIb. A 6-ml portion of concentrated HCl was added to a mixture of 0.5 mmole of compound Xb or XIb, 3 ml of alcohol and 3 ml of water, and the mixture was boiled to the complete dissolution of the starting compounds. The solution was evaporated to dryness. The residue was treated with hot benzene, from which 3,4-dichlorophenylurea precipitated on cooling (the IR spectrum was identical with that of an authentic sample). The filtrate was evaporated, the residue was treated with boiling pentane and decanted. The precipitate that separated out on cooling (dry ice + acetone) was filtered off. Compounds 3,5,5-trimethylthiazolidin-4-one-2-thione (XII), mp 91-93°C (according to the data in [6], mp 96°C), yield 57%, or 3,4,4-trimethylthiazolidin-5-one-2-thione (XIII), mp 76-78°C (according to the data in [7], mp 87-88°C) were obtained. The IR spectrum of the latter compound was identical with that of a compound obtained during the hydrolysis of 3,5,5-trimethyl-4-methyliminothiazolidine-2-thione [7].

Methanolysis of a Substituted 1,2,4-Oxadiazolidine-3,5-dione VIIb. A 0.5 portion of water and 1 ml of DMSO were added to a solution of 1 mmole of compound VIIb in 30 ml of methanol, and the mixture was boiled for 1.5 h. The reaction mixture was evaporated to dryness. The residue was treated with boiling benzene and filtered off. On cooling, a precipitate separated out from the mother liquor. Compound XVI was obtained, mp 180-181°C. The IR spectrum was identical to that of an authentic sample. The filtrate obtained after the separation of compound XVI was evaporated, and the residue was treated with boiling hexane and decanted. The precipitate that separated out on cooling was filtered off. Compound XIVb was obtained.

4-(3,4-Dichlorophenyl)-1,2,4-oxadiazolidine-3,5-dione (XVI) was obtained by a method analogous to that described in [3].

Condensation of 4-Hydroxyimidazolidin-2-one XV with Oxadiazolidine-3,5-dione XVI. Equimolar amounts of compounds XV and XVI were dissolved in DMSO and the solution was heated to 40°C. The reaction mixture was diluted with water (1:10), the precipitate was filtered off, and a compound was obtained whose IR spectrum was identical with the spectrum of a substituted oxadiazolidinedione VIII.

Reaction of 4-Hydroxy Derivatives XIV and XV with Nucleophilic Reagents. Equimolar amounts of compound XIVa or XV and 3,4-dichlorophenylurea, 1,2,4-triazole, 2-methylpropanal oxime, or urea were boiled in toluene or in benzene with a Dean–Stark adapter in the presence of catalytic amounts of TSA. At the end of the reaction (a TLC control), the reaction mixture was filtered and evaporated. The residue was treated with hexane or ether, and compounds XVII were obtained.

Imidazole and aliphatic amines do not react with compounds XIVa, XV under these conditions.

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