THE CHEMISTRY OF AMIDOXIMES AND RELATED COMPOUNDS

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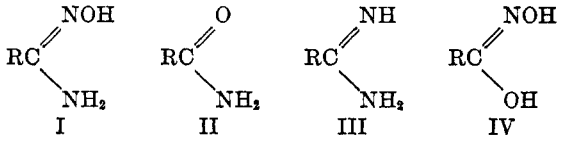
CONTENTS

AMIDOXIMES AND RELATED COMPOUNDS

I. INTRODUCTION

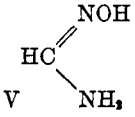
A. NOMENCLATURE

The amidoxime function (I) can be considered either as an amide (II) in which the oxygen atom of the carbonyl group has been replaced by an isonitroso group, or as an amidine (III) whose hydrogen atom of the imido group has been exchanged for a hydroxy radical. For this reason amidoximes are sometimes named oxamidines. They are also related to the hydroxamic acids (IV).



I II III IV

The lowest homolog (*i.e.*, R = H) was named "isuretin" (V) by Lossen and Schifferdecker (91).



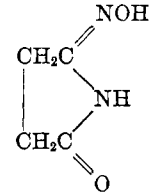
V

The name "amidoxime" was first used by Tiemann (175), who elucidated the structure of this class of compounds in 1884.

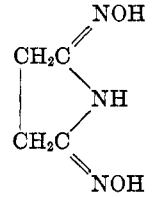
In the German papers published at the end of the nineteenth century, the name of the amidoximes is formed by adding "amidoxime" to the (obsolete) name of the corresponding trivalent radical. In the French literature, the suffix "oxime" is added to the name of the corresponding amide. According to Rule 32 of the International Union of Pure and Applied Chemistry, amidoximes should be named by adding "amidoxime" to the name of the corresponding hydrocarbon or by using the ending "carbonamidoxime." *Chemical Abstracts* considers the monoderivatives as amides of hydroxamic acids, *i.e.*, hydroxamamides, and the polyderivatives as oximes of the amides.

Examples for some simple compounds are summarized in Table 1.

Imidoximes can be considered as imides of organic dicarboxylic acids in which the oxygen atom of one or both carbonyl groups has been replaced by an isonitroso group. For example:



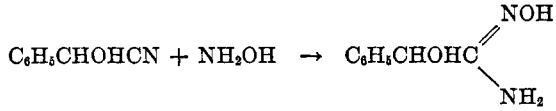
Succinimidoxime



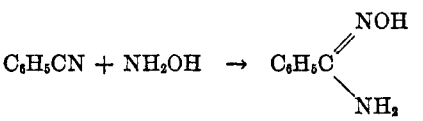
Succinimidedioxime

B. MOLECULAR STRUCTURE

Although the first amidoxime was prepared in 1873 by Lossen and Schifferdecker (91) from hydrogen cyanide and hydroxylamine, these authors did not establish the structure of this compound, which they called "isuretin." It was Tiemann (175) who assigned a structural formula to the novel functional group, naming it "amidoxime." He prepared two related compounds (VI and VII) by the addition reaction of hydroxylamine to benzaldehyde cyanohydrin and to benzonitrile.

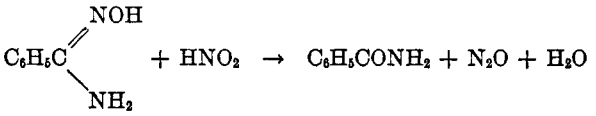


VI, Mandelamidoxime

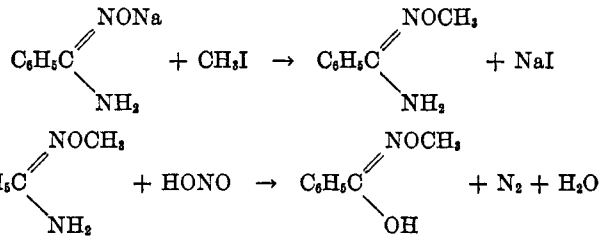


VII, Benzamidoxime

Tiemann proved the structure of the amidoxime function by showing the simultaneous presence of NH_2 and NOH groups (193): benzamidoxime forms salts with metals and with mineral acids just as would oximes and amines, respectively. The isonitroso group is identified by its acidic character and its reaction with nitrous acid with evolution of nitrous oxide.



When the sodium salt of benzamidoxime is alkylated with methyl iodide the resulting alkylated compound reacts with nitrous acid to yield nitrogen, thus proving the presence of the amino group.



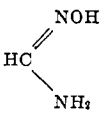
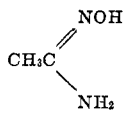
Tiemann recognized that the amidoximes may be present in two tautomeric forms (VIIIa and VIIIb), with VIIIa predominant.

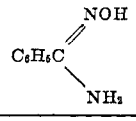
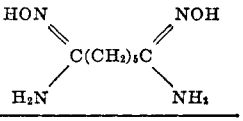
VIIIa VIIIb

The problem of tautomerism has been investigated more recently in the case of aminoglyoximes by Ponzio

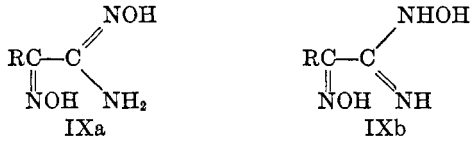
TABLE 1

Nomenclature

Nomenclature		
German	Methenylamidoxime	Ethenylamidoxime
French	Formamidoxime	Acetamidoxime
I.U.P.A.C.	Methanamidoxime	Ethanamidoxime
C.A.	Formhydroxamamide	Acetohydroxamamide

Nomenclature		
German	Benzenylamidoxime	
French	Benzamidoxime	Pimelamidoxime
I.U.P.A.C.	Benzamidoxime	Heptanediamidoxime
C.A.	Benzohydroxamamide	Pimelamide dioxime

and his collaborators (132). Several aminoglyoximes are known under two forms with distinct physical properties. According to Ponzio they should be mere tautomers IXa and IXb.

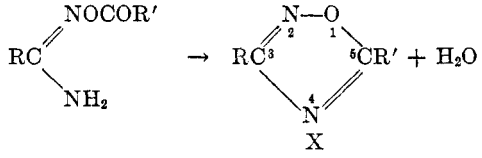


IXa IXb

The latter compounds can be transformed irreversibly into the former. However, the evidence given cannot be considered conclusive and only the more modern methods such as spectroscopy may finally settle the question of tautomerism in aminoglyoximes.

C. SCOPE OF THE REVIEW

This report deals with the chemistry of amidoximes. General and particular methods of their preparation, and their physical and chemical properties will be reviewed. The different classes of substitution products on both NOH and NH_2 groups and their derivatives will be examined, with the notable exception of the 1,2,4-oxadiazoles (X) formed by the cyclization of acylated amidoximes.



X

The greatest part of the work in the field of amidoximes was done by Tiemann and his co-workers (175–195) at the University of Berlin. They prepared most of the amidoximes and related compounds known at present. The more recent papers describe several new substances, but only a few new properties have been discovered.

II. SYNTHESIS OF AMIDOXIMES

1. Monoamidoximes

Most of the monoamidoximes which can be found in the literature since 1873 are listed in Table 2. The details of the different methods of preparation (A through L) are given in the following paragraphs.

Method A: Action of Hydroxylamine on Nitriles

$$RCN + NH_2OH \rightarrow RC(=NOH)NH_2$$

This is the most used process for the preparation of amidoximes. The experimental procedure recommended by Tiemann and Krüger (175) consists in liberating hydroxylamine from its hydrochloride using sodium carbonate, adding an equivalent amount of nitrile and enough alcohol to obtain a clear solution, and keeping the mixture at 60–80° during a few hours (method A1).

Instead of sodium carbonate, sodium or potassium hydroxide or sodium ethoxide also have been used. In the case of high-molecular-weight amidoximes Eitner and Weitz (35) used twice the theoretical amount of hydroxylamine and kept the reaction mixture for 25 hr. at 80°.

Yields rarely are given. Aromatic amidoximes generally are obtained with better yields than are aliphatic. As far as the lower members are concerned, their very high solubility in water and ethanol renders their isolation tedious.

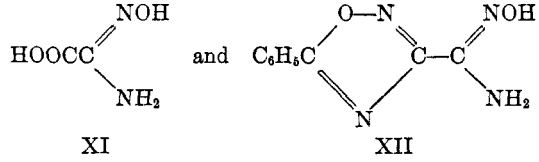
To avoid the separation of amidoximes from potassium chloride or sodium chloride some authors (3, 12, 48, 61, 93, 148, 169, 173, 201) used a solution of free hydroxylamine in absolute methanol or ethanol (method A2).

Highest yields are obtained when a 15% excess of a solution of hydroxylamine in butanol is used (81a). A solution of the nitrile in the same solvent is introduced and the mixture is left for 48 hr. at 60°. The amidoxime separates as a practically pure crystalline compound.

A procedure described by Schiff (157) and related to the classical method of Tiemann consists in forming hydroxylamine *in situ* by the oxidation of ammonia with an alkaline hypochlorite solution (method A3). This method of forming hydroxylamine gives very poor yields and has never been used since.

Method B: Action of Hydroxylamine on Amides or Thioamides

Hydroxylamine, as a rule, does not react with amides. This method has only been reported (32, 157) for the preparation of the two amidoximes.



XI XII

Some aromatic amidoximes have been prepared by the action of hydroxylamine on thioamides (45, 54a, 168, 179).

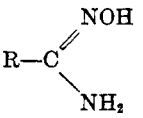
$$RCSNH_2 + NH_2OH \rightarrow RC(=NOH)NH_2 + H_2S$$

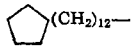
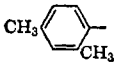
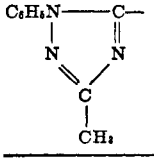
Hydroxylamine is liberated from its hydrochloride by an equivalent amount of aqueous sodium carbonate. The thioamide is then introduced and ethanol is added until the mixture is clear. The solution is refluxed for a few hours and the amidoxime isolated. This procedure is used when the thioamide is more easily available than the corresponding nitrile.

Method C: Reduction of Nitrosolic and Nitrolic Acids

Amidoximes can be obtained by reduction of nitro-

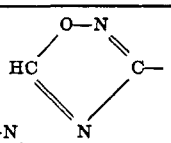
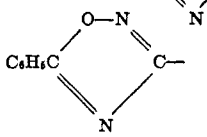
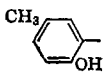
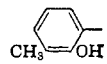
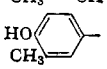
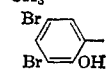
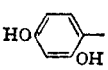
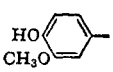
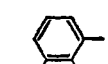
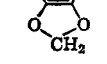
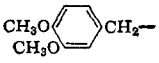
TABLE 2

Monoamidoximes 

R	Melting point, °C.	Method	Reaction medium	Reaction temp., °C.	Reaction time, hr.	Crystallized from:	Yield, %	Ref.
			R = Hydrocarbon radical					
H—	104–105	A1	Ethanol	40	48	Ethanol	60	91
	114–115	A1	Water	0–5	48	Ethyl acetate	80	110
CH_3—	135	A1	Ethanol–water	30–40	60–80	Ethanol–ether	20–25	112, 121, 194
	135–135.5	A2	Butanol	40	48	Butyl ether	90	36c
CH_3CH_2—		A1						112
$(CH_3)_2CH$—	55–58	A2	Butanol	60	36		75	36a
$(CH_3)_2CHCH_2CH_2$—	58	A1	Ethanol	Reflux	30	Benzene		55
$CH_3(CH_2)_{10}$—	92–92.5	A1	Ethanol–water	75	13–25	Benzene		35
$CH_3(CH_2)_{12}$—	97	A1	Ethanol–water	75	13–25	Benzene		35
$CH_3(CH_2)_{14}$—	101.5–102	A1	Ethanol–water	75	13–25	Benzene		35
$CH_3(CH_2)_{16}$—	106–106.5	A1	Ethanol–water	75	13–25	Benzene		35
	89	A1	Ethanol–water	Reflux	24	Ethanol		19
$CH_2=CH(CH_2)_8$—	69	A2	Ethanol			Benzene		61
C_9H_{15}—	101	A2	Ethanol	Reflux	Days			48
C_6H_5—	79–80	A1	Ethanol–water	60–80	Hours	Water	100	175, 193
C_6H_5—	79–80	A1	Ethanol–water	80	18			63
		B	Ethanol–water	Reflux	15–18			179
		C	Water	Cold				212
		D	Ether					207
		E	Ethanol	0		Ether		82
	76–77	F						88
	80	G	Water	20	Days	Ethanol–water		119
	77–78	H	Ethanol	175	8			89
o-$CH_3C_6H_4$—	149.5	A1	Ethanol–water	Reflux	6	Water		162
p-$CH_3C_6H_4$	147	A1	Ethanol–water	80	1.5	Ethanol	75–90	22
	145–146	A1	Ethanol–water	80–90	6	Water		161
$C_6H_5CH_2$—	67	A1	Ethanol–water	40–50	36–48	Ethanol–water	40–50	57
	178	A1	Ethanol–water	Reflux	5–6	Ethanol		114
$C_6H_5CH=CH$—	93	A1	Ethanol–water	60–70	Days	Ethanol	25	217
	93	A2	Methanol	0	72	Water		148
α-Naphthyl	148–149	A1	Ethanol–water	Reflux	10–12	Water		36, 151
	149	A1	Ethanol–water	80–90 (pressure)				150
β-Naphthyl	150	A1	Ethanol–water	80–90	10–12	Ethanol–water		36, 151
	150	A1	Ethanol–water	80–90 (pressure)				150
			R = Heterocyclic radical					
2-Furyl	Liq.	A1	Ethanol–water	70	21			79
2-Benzofuryl	190–191	A1[a]	Ethanol	70	24	Benzene		79
3-Benzofuryl	106–107	A1[a]	Ethanol	70	30	Benzene		79
2-Pyridyl	116–117	A1	Ethanol	70	5	Benzene		79
	116	A1	Ethanol–water	70	5	Water	80	27
3-Pyridyl	134	A1	Ethanol–water	Reflux	1.5	Benzene	75–90	22
	128	A1	Ethanol–water	70	8	Chloroform	57	27
	128	A1	Water	70	8	Chloroform		99
4-Pyridyl	197–198	A1	Ethanol	70	5	Water	38	79
	199	A1	Ethanol–water	70	5	Water		27
2-Quinolyl	162–163	A1	Ethanol–water	Reflux	24	Ethanol		79
3-Quinolyl	202–203	A1[a]	Ethanol–water	Reflux	36	Ethanol		79
4-Quinolyl	195	A1[a]	Ethanol	70	24	Benz. ethanol		79
6-Quinolyl	105	A1	Ethanol–water	Reflux		Alcohol		13
2-Thienyl	91–92	A1[a]	Ethanol–water	Reflux	30	Benzene		79, 98
3-Thienyl	91–92	A1				Benz. pet. ether		98
	208–210	A1	Ethanol–water	50–70	Hours	Ethanol		15

[a] Excess of NH_2OH used.

TABLE 2 (*Continued*)

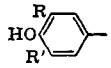
R	Melting point °C.	Method	Reaction medium	Reaction temp., °C.	Reaction time, hr.	Crystallized from:	Yield, %	Ref.
	115	[b]						81a
	158	B	Methanol	65		Ethanol		32
			R = substituted hydrocarbon radical					
$ClCH_2$—	91–92	A1	Water	30	0.25	Benzene	70	169, 171
Cl_2CH—	103–104	A1	Water	0	Min.	Benzene	60	169, 171
Cl_3C—	128–129	A1	Water	0	Min.	Benzene		169, 171
$BrCH_2$—	95–96	A2	Methanol	−8–0		Methanol		169, 173
Br_2CH—	120	A2	Methanol	0		Toluene		169, 173
Br_3C—	126	A2	Methanol	0	Hours	Ethanol		169, 173
ICH_2—	123–124	A2	Methanol	20	24	Ethanol	37.5	169, 171
o-ClC_6H_4—	117	D	Ethanol			Water		206
p-ClC_6H_4—	134–135	A1	Ethanol–water	Reflux	20	Ethanol	61	3
p-BrC_6H_4—	146–147	A1	Ethanol–water	Reflux	1.5	Ethanol	75–90	22
	144–145	A1	Ethanol–water	Reflux	20		72	3
$CH_3CH(OH)$—	115–116	A1	Water			Ethyl acetate	50	157
$(CH_3)_2C(OH)$—	52	A2	Ethanol	Reflux	2	Ether	60–70	70
	55–60	A3	Water			Ether	33	157
$(CH_3)_2CHCH_2CH(OH)$—	176.5	A1	Water			Ethanol–water	90–95	157
$C_6H_{11}CH(OH)$—	141	A1	Water	75	72	Ethanol–water	90–95	157
$C_6H_5CH(OH)$—	140	A1	Ethanol–water	20	Days			175
	158–159	A1	Ethanol–water	25–30	Days	Ethanol	25	50, 51
	163–164	K		0		Ethanol–chlorof.		24
$C_6H_5CH{=}CHCH(OH)$—	136	A1	Ethanol–water	7	12		50	17
$Cl_3CCH(OH)$—	156–157	A1	Water	20	Hours	Water	90–95	152, 157
o-HOC_6H_4—	98–99	B	Ethanol–water	Reflux	4	Water		100, 168
m-HOC_6H_4—	71	A1	Ethanol–water	Reflux	6	Water		23
				Cold	5–6 days			23
p-HOC_6H_4—	153	A1	Ethanol–water	70	10	Water	80	62
	123–124	B	Ethanol–water	Reflux	3–4	Benzene		45
	126.5	A1	Ethanol–water	60	15			116
	152	A1	Ethanol–water	Reflux	15			116
 [c]	180	B	Ethanol–water			Ethanol–water		168
	166	A2	Ethanol	20	6–8 days	Ethanol–water		93
o-$CH_3OC_6H_4$—	123	A1	Ethanol–water	Reflux	1.5	Benzene	75–90	22
	123	A1	Ethanol–water	90	6–8	Benzene	100	100
p-$CH_3OC_6H_4$—	122–123	A1	Ethanol–water	90	6–8	Benzene	81	100
	100	A2	Ethanol	80	15	Water		93
p-$CH_3(CH_2)_5OC_6H_4$—	110	A1	Ethanol–water	70	24	Ethanol–water	50	115
	151	A2	Ethanol	60				93
	164–165	A1	Ethanol–water	Reflux	24	Ethanol	55	3
	137	A1	Ethanol–water	Reflux	8	Ethanol		69

[b] Formed by the action of formic acid on oxamidedioxime. [c] These amidoximes have been prepared by the method A1 but no data are given (20a):

R =	R′ =
H	Cl
Cl	Cl
H	Br

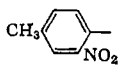
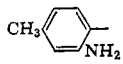
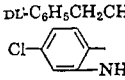
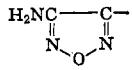
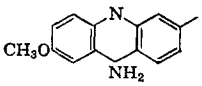
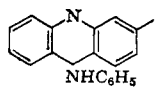
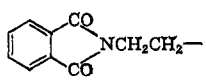
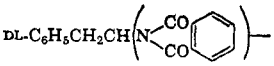
R = Br, R′ = Br; H, I; I, I

and



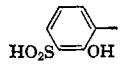
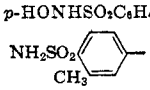
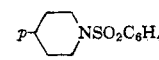
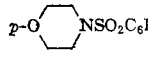
R =	R′ =
Cl	Cl
H	Br
Br	Br
I	I

TABLE 2 (*Continued*)

R	Melting point, °C.	Method	Reaction medium	Reaction temp., °C.	Reaction time, hr.	Crystallized from:	Yield, %	Ref.
$C_6H_5CH[O(C_{12}H_{21}O_{10})]$—	135–140	A1	Ethanol–water	20	72	Ethanol–water		156
C_6H_5CO—	129–131	D	Ether	20			56	76
HOOC—	158	[d]					50	52, 53
$HOOCCH_2$	144	[e]						103
$HOOC(CH_2)_4$—	156–158	C	Acetic acid	25		Methanol	83	44
m-$HOOCC_6H_4$—	200	A1	Ethanol–water	80–100	12			107
p-$HOOC_6H_4$—	330	A1	Ethanol–water	20	18	Ethanol–water		107
m-$C_2H_5OCOC_6H_4$—	118	A1	Ethanol–water	80–100	Hours	Water		107
p-$C_2H_5OCOC_6H_4$—	135	A1	Ethanol–water	60–100	8			106
NO_2CH_2—	108	A1	Water	20	24	Water		172
m-$NO_2C_6H_4$—	174	A1	Water	100	5			159
p-$NO_2C_6H_4$	169	A1	Ethanol–water	90	4–5	Water		201
	170	A1	Ethanol–water	Reflux	1.5	Water	75–90	22
	180	A2	Methanol	Reflux	1	Ethanol	66	12
$C_6H_5CH(NO_2)$—	125	A1	Water	20		Ether–pet. eth.		170
	161	A2	Ethanol					201
o-$NH_2C_6H_4$—	84–85	A1	Ethanol–water	Reflux	8	Benzene	65	121a
m-$NH_2C_6H_4$—		[f]						160
p-$NH_2C_6H_4$—	160–174	[f]				Water		201
	166	[f]					Poor	201
DL-$C_6H_5CH_2CHNH_2$—	117–118	A2	Methanol			Water	52	118
	128–130	A1	Ethanol–water	Reflux	8	Benzene	60	20b
	189–190	[g]				Water		83
	292–294	A1	Pyr. water–ethanol	100	1		54	47
		A1	Pyr. water–ethanol	100	2			47
NH_2COCH_2—	149	A2	Ethanol	80		Ethanol		74
$NH_2CO(CH_2)_{11}$—	157–158	A1	Ethanol	60	20	Ethyl acetate		75
DL-$C_6H_5CH_2CH(NHCOCH_3)$—	156–158	[h]				Water	66	118
L-	167–169	[h]				Water	74	118
DL-$C_6H_5CH_2CH(NHCOC_6H_5)$—	200–202	[h]				Methanol–water	62	118
L-	200–203	[h]				Methanol–water	44	118
	185	A1	Dimethylformamide–water	60	24	butanol	40	36a
DL- 	198–204	A1	Methanol	Reflux	3	Methanol	71	118
L-	164–171	A1	Methanol	Reflux	3	Methanol–water	73	118
$C_6H_5CONHCH_2$—	123–126							31
$CNCH_2$—	124–127	A1	Ethanol–water	20	Hours	Ethanol		158
$CN(CH_2)_3$—	103	A1	Ethanol–water	60–70	10	Water		14, 42
$CN(CH_2)_4$—	89–91	A2	Butanol	50	18		76	219a
$CN(CH_2)_8$—	71	A2	Butanol	50	18			219a
$CN(CH_2)_{11}$—	87–88	A1	Ethanol	60	20	Methanol		75
$CN(CH_2)_{15}$—	98	A1	Ethanol	60	20	Ethanol		75
p-$CNC_6H_4CH_2$—	168	A1	Ethanol–water					154
$HONHCOCH_2$—	152	A1[i]	Ethanol–water	40	3–4			102, 103
CH(:NOH)—	148–152	A1[j]	Water	60		Water		144, 169, 171
	152	D	Ethanol			Benzene		142
CCl(:NOH)—	109	A1[k]	Water	65	Min.	Eth. petr. ether	19	169, 171
$CH_3C(:NOH)$—	183–184	D	Water	20				146
	183–184	L	Water	20	Hours	Ether		145
$CH_3C(:NOCH_3)$—	99	D	Methanol	20		Pet. ether		6
$CH(:NOCOC_6H_5)$—	157–158	D	Ether–water	20		Ethanol–water		142, 144
β CH(:NOH)C(:NOH)—	147–148	A2	Methanol	20				85
$C_6H_5C(:NOH)$—	α 154	L						140, 141
	β 195	D	Ethanol	20	Hours	Ethanol		130, 138, 140

[d] Formed by partial hydrolysis of the diamidoxime $NH_2C(:NOH)C(:NOH)NH_2$. [e] Formed by partial hydrolysis of the hydroxamic acid $HONHCOCH_2C(:NOH)NH_2$. [f] Prepared by reduction of the corresponding nitro compound. [g] Formed by hydrolysis of the acetyl derivative. [h] Formed by partial hydrolysis of the diacylated aminoamidoximes. [i] From two moles of NH_2OH on $C_2H_5OCOCH_2CN$. [j] From a large excess of hydroxylamine on Cl_2CHCN. [k] From two moles of NH_2OH on Cl_2CCN.

TABLE 2 (*Continued*)

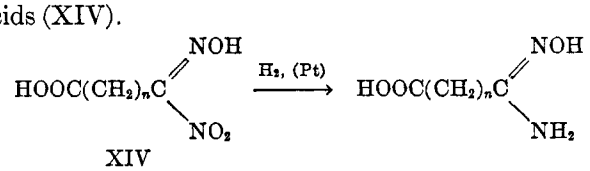
R	Melting point, °C.	Method	Reaction medium	Reaction temp., °C.	Reaction time, hr.	Crystallized from:	Yield, %	Ref.
$C_6H_5COC(:NOH)$—	α 127	L	Water	20	24			143
	β 187	[l]						143
p-$CH_3C_6H_4COC(:NOH)$—	α 114	L	Water	0				143
$C_6H_5C(:NOCOC_6H_5)$—	171–172	D	Ether–water	20		Ethanol		129, 131
	171–172	L	Ether–water	20		Ethanol		131
p-$CH_3C_6H_4C(:NOCOC_6H_5)$—	α 178–179	L	Ether–water	20		Ethanol		131
$C_6H_5NHC(:NOH)$—	180	A1	Ethanol	75–80		Water		180, 221
p-$CH_3C_6H_4NHC(:NOH)$—	175	A1	Ethanol	75–80		Water		199
p-$CH_3C_6H_4NHC(:NH)$—	147–148	A1	Ethanol	75–80		Benzene		199
C_6H_5—N=N—	125–126	A1	Water	20		Water		86
p-$CH_3C_6H_4$—N=N—	164–165	A1	Water	20		Water		86
p-$CH_3SC_6H_4$—	130	A1	Ethanol–water	Reflux	12	Water	100	20
p-$C_2H_5SC_6H_4$—	120	A1	Ethanol–water	Reflux	12	Water		20
p-$C_6H_5SC_6H_4$—	125	A1	Ethanol–water	Reflux	40	Ethanol		78, 79
p,p'-$ClC_6H_4SC_6H_4$—	159–161	A1	Ethanol–water	Reflux	40	Ethanol		78, 79
p,p'-$NO_2C_6H_4SC_6H_4$—	162–164	A1	Ethanol–water	Reflux	40	Benzene		78, 79
p-$HO_3SC_6H_5$—	236	A1	Ethanol–water	Reflux	3		25	3
	250	[m]						168
p-$CH_3SO_2C_6H_4$—	177	A1	Ethanol–water	Reflux	12	Ethanol–water		20
	188	A1	Ethanol–water	Reflux	1.75	Water	96	3
p-$C_6H_5SO_2C_6H_4$—	175–176	A1	Ethanol–water	Reflux	40	Ethanol		78, 79
p,p'-$ClC_6H_4SO_2C_6H_4$—	201–202	A1	Ethanol–water	Reflux	40	Ethanol		78, 79
p,p'-$NO_2C_6H_4SO_2C_6H_4$—	201–202	A1	Ethanol–water	Reflux	40	Ethanol		78, 79
p-$NH_2SO_2C_6H_4$—		A2	Methanol	Reflux	2	Water	80	12
		A1	Ethanol–water	Reflux	1.5		70–82	3
p-$HONHSO_2C_6H_4$—	152–153	A1	Ethanol	20		Water	51	3
	183–184	A1	Ethanol–water	Reflux	3	Water		3
p-$(C_2H_4)_2NSO_2C_6H_4$—	123–124	A1	Ethanol–water	Reflux	16		55	3
p-$(HOC_2H_4)_2NSO_2C_6H_4$—	183–184	A1	Ethanol–water	Reflux	16	Ethanol	40	3
p-$CH_3ONHSO_2C_6H_4$—	198[n]	A1	Ethanol–water	Reflux	16	Dil. HCl	56	3
p-$C_2H_5ONHSO_2C_6H_4$—	151–152[n]	A1	Ethanol–water	Reflux	16	Dil. HCl	57	3
p-$C_4H_7ONHSO_2C_6H_4$—	145–150[n]	A1	Ethanol–water	Reflux	16	Dil. HCl	55	3
p-$C_6H_9ONHSO_2C_6H_4$—	130–140[n]	A1	Ethanol–water	Reflux	16	Dil. HCl	76	3
	196–197	A2	Ethanol			Ethanol	93.5	3
	158–159	A1	Ethanol–water	Reflux	16	Ethanol	92.5	3
p,p'-$(CH_3)_2NSO_2C_6H_4NHSO_2C_6H_4$—	130	A2	Ethanol	Reflux	16	Water		3

[l] Formed by heating the α form in dilute acetic acid. [m] Formed by sulfonation of *o*-$OHC_6H_4C(:NOH)NH_2$. [n] Isolated as hydrochloride.

solic acids (XIII) with hydrogen sulfide. Wieland and Bauer (212) prepared benzamidoxime by this method.

$$C_6H_5C(=NOH)NO + 2H_2S \rightarrow C_6H_5C(=NOH)NH_2 + H_2O + 2S$$
XIII

Recently, an apparently general method was described (44) for the preparation of the monoamidoximes of dicarboxylic acids, by catalytic reduction of nitrolic acids (XIV).

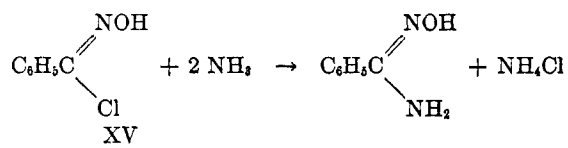


XIV

For example, adipomonoamidoxime was prepared by the reduction of adipomononitrolic acid; the latter was obtained from cyclohexanol and cold nitric acid.

Method D: Action of Ammonia on Hydroximic Acid Chlorides (Chloroximes)

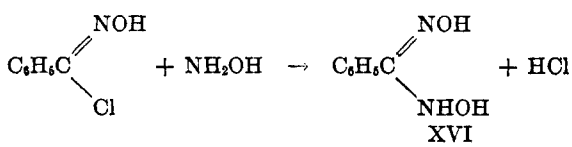
Hydroximic acid chlorides (XV) are formed by direct chlorination of aldoximes. These compounds react easily with ammonia to yield amidoximes. This procedure was used by Werner (206, 207) to prepare benzamidoxime, *o*-chlorobenzamidoxime (206, 207), and terephthalamidoxime (36a).



XV

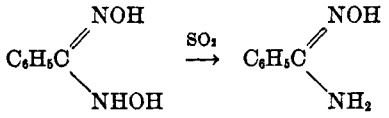
Method E: Reduction of Oxyamidoximes

Hydroximic acid chlorides also react with hydroxylamine to form oxyamidoximes (XVI). This reaction was used by Ley and Ulrich (82) to prepare benzoxyamidoxime.



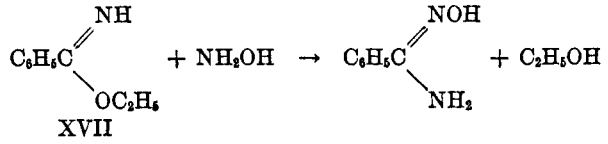
XVI

This compound then is reduced with sulfur dioxide to the corresponding amidoxime.



Method F: Action of Hydroxylamine on Iminoethers

This reaction was reported by Pinner (119) and Lossen (88), who obtained benzamidoxime by treating ethyl iminobenzoate (XVII) with hydroxylamine.

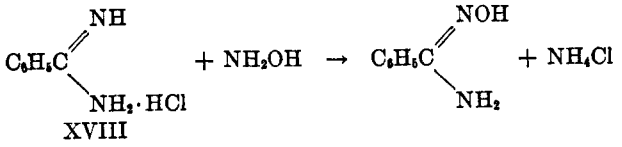


XVII

Since benzonitrile is the starting material for the synthesis of the iminoether, this reaction is not a practical method for the synthesis of amidoximes (compare with the more direct method A).

Method G: Action of Hydroxylamine on Amidine Hydrochlorides

Pinner (119) prepared benzamidoxime by treating benzamidine hydrochloride (XVIII) with hydroxylamine.

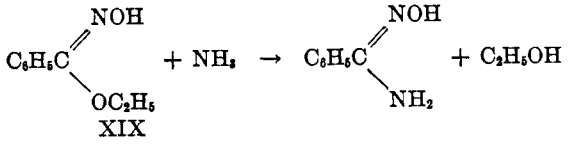


XVIII

This reaction has no practical interest, since amidines generally are obtained from nitriles, thioamides, or iminoethers (compare with methods A, B, and F).

Method H: Action of Ammonia on Oximinoethers

When heated in a pressure bottle for 8 hr. at 175°, an alcoholic solution of ammonia and ethyl benzhydroxamic acid (XIX) yields benzamidoxime (89).

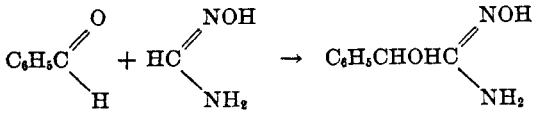


XIX

This reaction has not found general application.

Method K: Action of Formamidoxime on Aromatic Aldehydes

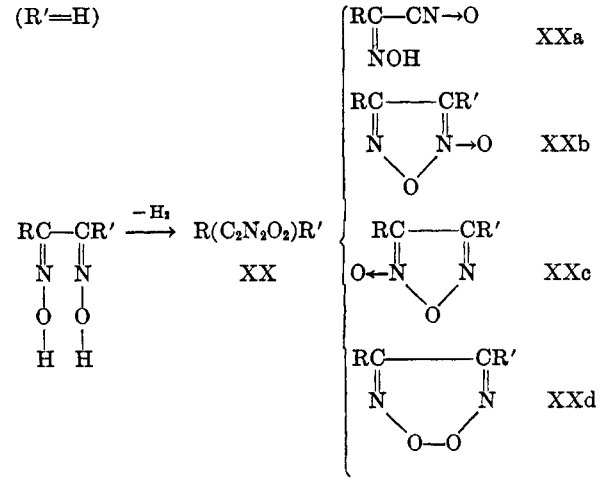
According to Conduché (24) formamidoxime reacts with aromatic aldehydes, leading to an aldol condensation



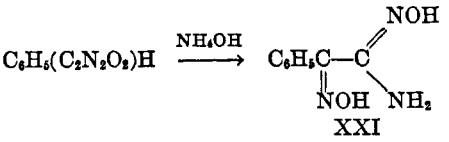
Mandelamidoxime is the only compound that has been prepared by this method.

Method L: Action of Ammonia on Glyoxime Peroxides

Dehydrogenation of substituted glyoximes yields "oxides" (XX), the structure of which has not yet been established with certainty. Depending on the relative configuration of the NOH groups (*syn*, *anti*, or *amphi*) and on the nature of the substituents, the "oxides" are considered as nitrile oxides (XXa), furazane oxides (XXb,c), or peroxides (XXd).

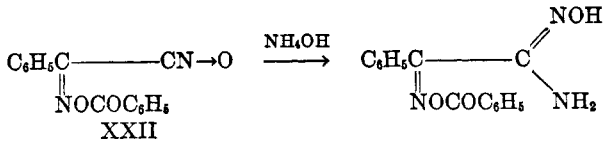


On treatment with ammonium hydroxide phenylglyoxime peroxide yields an oxime containing amidoxime (XXI) (140, 141, 215).



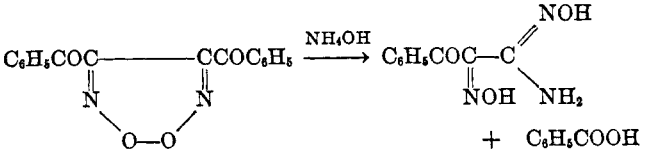
XXI

The reaction is analogous to that of the *O*-benzoylated nitrile-oxide XXII (131).



XXII

Another example is the reaction of dibenzoylglyoxime peroxide with ammonium hydroxide (143).

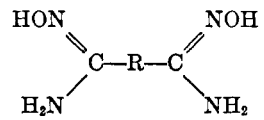


2. Diamidoximes

Diamidoximes, *i.e.*, compounds containing two amidoxime groups simultaneously can be prepared by reactions analogous to those described in section 1. The diamidoximes heretofore prepared and their methods of preparation are summarized in Table 3.

TABLE 3

Diamidoximes

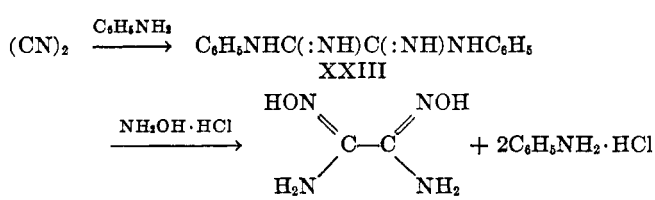


R	Melting point, °C.	Method	Reaction medium	Reaction temp., °C.	Reaction time, hours	Crystallized from:	Yield, %	Ref.
—(oxamidedioxime)	196–200	A1	Water	0		Water	40	40
	195	A1	Ethanol	20				180
	196–200	A1	Ethanol	Reflux		Water		199, 221
	212	A1	Water	0–5		Water	53	36a
	198	B	Ethanol	Reflux		Ethanol		37
	200	D	Ethyl acetate	20		Water		54
—CH_2—	163–167	A1	Ethanol–water	20	24	Ethanol–water	80	158
—CH_2CH_2—	188	A1	Ethanol–water	20	4 days	Water		52, 166
	188	A1	No solvent	60–65				81c
	188	A1	Ethanol	70	8	Water		42
—$CH_2CH_2CH_2$—	233	A1	Ethanol–water	60–70	10	Water		14, 42
—$(CH_2)_4$—	226	A2	Butanol	50	48	Butanol	100	36a, 81a
	168–170	A2	Butanol	70			47	219a
—$(CH_2)_5$—	142–144	A1[a]	Ethanol	60	20–30	Ethanol		75
—$(CH_2)_6$—		A2	Butanol	50	40			36a, 81a
—$(CH_2)_7$—	156	A1[a]	Ethanol	60	20–30	Ethanol		75
—$(CH_2)_8$—	152	A2	Butanol	70				219a
—$(CH_2)_9$—	167	A1[a]	Ethanol	60	20–30	Methanol		75
—$(CH_2)_{10}$—	184–186	A1[a]	Ethanol	60	20–30	Ethanol		75
—$(CH_2)_{11}$—	166	A1[a]	Ethanol	60	20–30	Methanol		75
—$(CH_2)_{12}$—	170	A1[a]	Ethanol	60	20–30	Ethanol		75
—CH=CH—	212	A1	Water	20	15	Water	16	92
—C(:NOH)—	154	A2	Ethanol	50–60	36	Water	100	83
—C(:NOH)C(:NOH)—	181–182	A1	Water	50–60				83
—$CC(CH_3)_2N{=}NC(CH_3)_2C$—	154	A1	Ethanol–water	20	24	Ethanol–pet. ether	82	174a
m-C_6H_4—	193	A2	Ethanol	Reflux		Ethanol		46
p-C_6H_4—	180	D					100	36a, 81a
p-$CH_2C_6H_4$—	192	A1	Ethanol–water	20	24	Water		154
p,p'-C_6H_4—C_6H_4—	245	A1[b]	Ethanol	60	20–30	Ethanol		75
	290[c]	A2	Butanol	45	48	Acetone–water	100	36a, 81a
p,p'-$C_6H_4CH_2C_6H_4$—	245	A1[b]	Ethanol	60	20–30	Ethanol		75
p,p'-$C_6H_4CH_2CH_2C_6H_4$—	243	A1[b]	Ethanol	60	20–30	Ethanol		75
p,p'-$C_6H_4CH{=}CHC_6H_4$—	>320	A1[b]	Ethanol	60	20–30	Ethanol		75
p-$CH_2C_6H_4CH_2$—	250	A2	Butanol	45	48	Butanol	85	36a, 81a
p,p'-$C_6H_4O(CH_2)_3OC_6H_4$—								7
p,p'-$C_6H_4O(CH_2)_5OC_6H_4$—	190	A2	Butanol	45	48		100	36a, 81a
p,p'-$C_6H_4SC_6H_4$—	200	A1	Ethanol–water	Reflux	40	Dioxane–water		78, 79
p,p'-$C_6H_4SO_2C_6H_4$—	214–220	A1	Ethanol–water	Reflux	40	Dioxane–water		78, 79
p,p'-(—$C_6H_4CH_2S$)$_2$	195	A2	Butanol	45	72	Dimethylformamide–water	85	36a, 81a

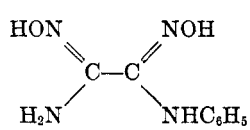
[a] Twice the theoretical amount of hydroxylamine used. [b] Excess of hydroxylamine used. [c] Analyzed as the dihydrochloride.

The most usual synthesis is still the Tiemann method (dinitrile + hydroxylamine). Highest yields are obtained if free hydroxylamine in butanol is used (81a). This procedure also facilitates the isolation of the product. With high molecular weight dinitriles an excess of hydroxylamine is needed to obtain good yields.

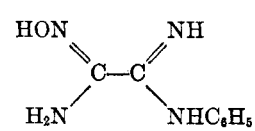
In the case of oxamidedioxime a variant of method A1 has been described (180, 199, 221). Instead of cyanogen, its addition compound with aniline, diphenyloxamidine (XXIII) is treated with hydroxylamine hydrochloride.



Two by-products also are formed during the reaction



and



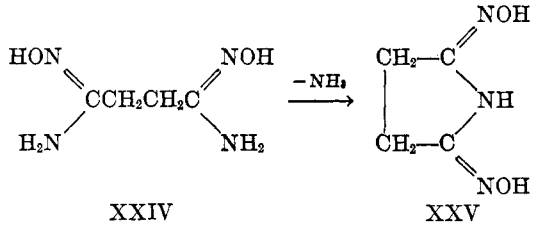
Other amines such as benzylamine and *p*-toluidine can be used.

It appears that best yields and the purest product are obtained if gaseous cyanogen is led directly into an aqueous hydroxylamine solution at 0° (36a).

3. Imidoximes

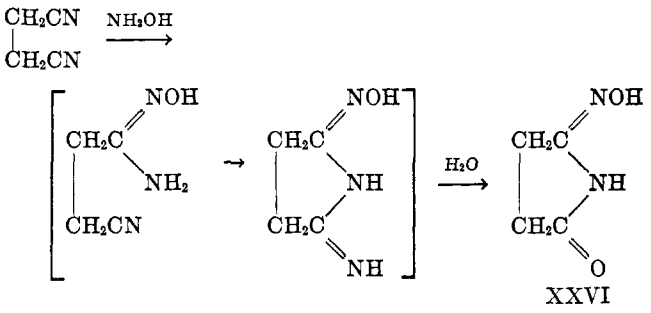
The formation of diamidoximes often is accompanied by side reactions which are influenced by such factors as the proportion of reagents, temperature, and the choice of solvents. When intramolecular cyclization can occur, mono and dioximes of the corresponding imides are formed. These reactions take place, for instance, with the dinitriles of succinic, glutaric, and *o*-phthalic acids and with *o*-cyanomethylbenzonitrile.

When one mole of succinonitrile reacts with two moles of hydroxylamine in aqueous ethanol at room temperature, a small amount of succinimidedioxime (XXV) accompanies the major product, succinamidedioxime (XXIV). At 60–70° the yield in XXV increases (166). The latter is formed by splitting off ammonia from XXIV.



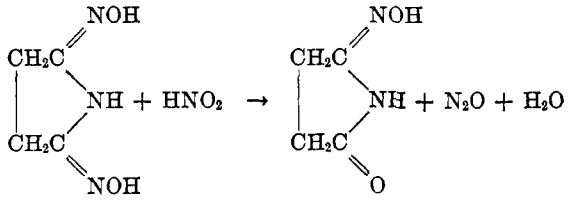
XXIV XXV

If the molar ratio of reactants is one, either an open chain diamidoxime or a cyclic imidoxime is formed (XXVI), depending on the reaction conditions: in absolute ethanol, at room temperature, the former is the main reaction product, while at 60–70° or in the presence of water the cyclic compound (XXVI) is formed (42). Probably an intermediate monoamidoxime first cyclizes into an imide which then hydrolyzes readily into an imidoxime.

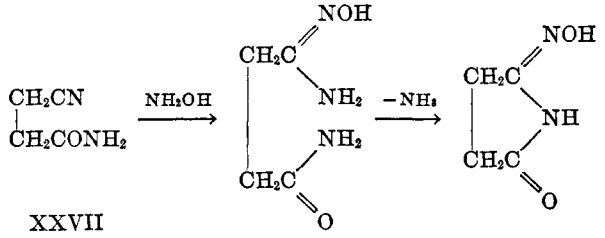


XXVI

The same end product XXVI can be obtained through two other distinct methods. The first consists in treating succinimidedioxime (XXV) with an equivalent amount of nitrous acid.



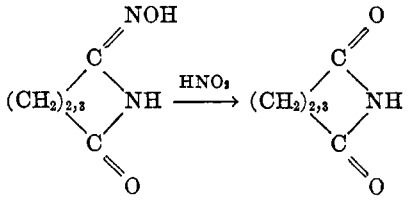
In the second, β-cyanopropionamide (XXVII) reacts with hydroxylamine.



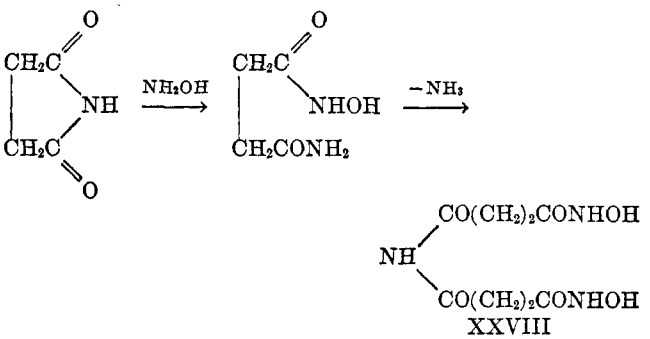
XXVII

The behavior of glutaronitrile is very similar (14).

Imidoximes are still able to react with nitrous acid, yielding the corresponding imides.

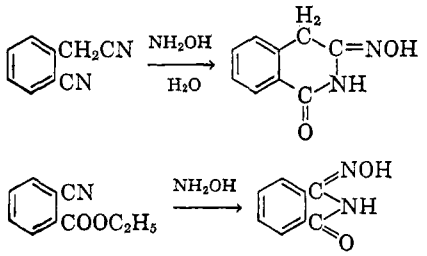


However, these cyclic imides cannot be converted into the oximes by hydroxylamine; while glutarimide fails to react, succinimide yields disuccinimide-dihydroxamic acid (XXVIII) (42).



XXVIII

Imidoximes also were prepared from certain aromatic nitriles with hydroxylamine. For instance, *o*-cyanomethylbenzonitrile and ethyl *o*-cyanobenzoate, respectively, yield the imidoximes (34, 188, 107).



The latter compound is hydrolyzed easily to phthalimide, which does not react further with hydroxylamine.

Phthalonitrile yields phthalimidedioxime (22).

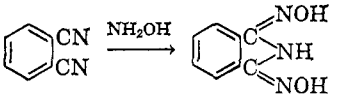


Table 4 lists all imidoximes and imidedioximes described in the literature.

4. Polyamidoximes

Alkylenediaminetetraacetamidoximes recently have been synthesized and used as fungicides (11a)

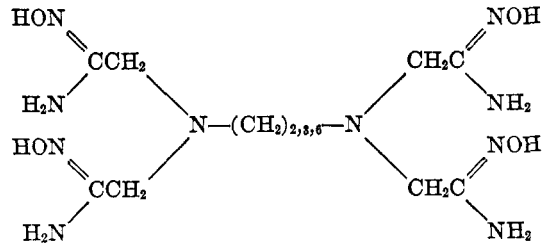
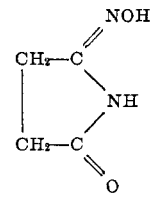
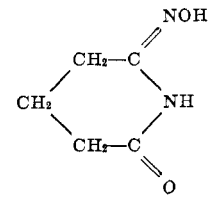
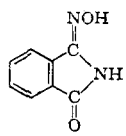
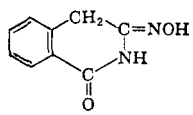
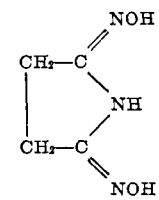
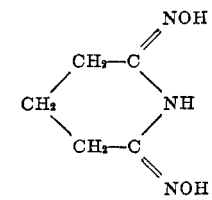
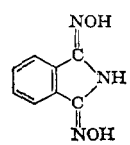
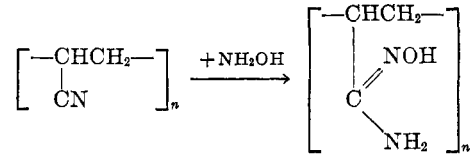


TABLE 4

Imidoximes and Imidedioximes

Compound	Melting point, °C.	Ref.
	197	42
	196	42
	250	107
	158	34, 188
	198	42, 166
	193	14, 42
	271	22

Polymers containing the amidoxime function have been obtained by Schouteden (160a, b and c) by treating a polyacrylonitrile of low molecular weight with a slight excess of hydroxylamine. The reaction was carried out in dimethylformamide as solvent, and its kinetics have been studied.



III. PROPERTIES AND REACTIONS OF AMIDOXIMES

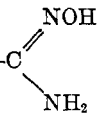
1. Physical Properties

The amidoximes are crystalline, colorless compounds which generally decompose when heated over their melting point. The melting points of amidoximes are listed in Tables 2, 3, and 4. Aryl amidoximes are more stable than the aliphatic amidoximes (193).

The first members of the aliphatic series are soluble in water but their solubility decreases with increasing molecular weight. Aryl amidoximes are less or not soluble in water but soluble in alcohol and in most organic solvents.

The infrared spectra of the amidoximes show two well defined absorption bands (36a): The first is a doublet at 2.87–2.93 μ and 2.96–3.03 μ, assigned to the two NH_2 stretching modes; the second between 5.95 and 6.08 μ to the C=N stretching (see Table 5). The OH stretching band of the NOH group is very broad and has its maximum at approximately 3.2 μ.

TABLE 5

Characteristic Absorption of the  *Group*

	—NH_2 stretching, μ		C=N stretching, μ
Formamidoxime	2.93	3.03	5.95
Acetamidoxime	2.87	2.98	6.03
Benzamidoxime	2.87	2.96	6.08
Oxamidedioxime	2.88	2.98	6.05
Adipodiamidoxime	2.88	2.98	6.05

Crystallographic data about amidoximes are very scarce: only those of benzamidoxime (178) and succinamidedioxime (166) have been published.

2. Chemical Properties

(a) Salt Formation

The amidoximes are amphoteric substances, soluble in dilute mineral acids as well as in aqueous alkaline solutions (193).

The amino group in the molecule confers basic properties to the amidoximes. Salts of amidoximes with mineral or organic acids are known; they are crystallized easily and have well defined melting points.

On the other hand, the hydrogen atom of the NOH group can be substituted, as in the case of oximes, by a metal. Many sodium and silver salts have been described.

Amidoximes form colored crystalline compounds with the salts of some metals (176). Werner (204) prepared a great number of such compounds with different amidoximes and proved that they are internal complexes in which the metal atom is linked to the oxime group as well as to the amino group.

These amidoximes have been used as analytical reagents for various cations (197, 198): formamidoxime (68), hydroxyisobutyramidoxime (70), benzamidoxime (30, 117), hippuramidoxime (31), phenylacetamidoxime (71, 117), *o*- and *p*-toluamidoxime (117), homoveratramidoxime (69), 2- and 4-pyridinamidoxime (117), oxamidoxime (74), oxalhydroxamamidoxime (72), oxamidedioxime (30, 113, 117), malonamidedioxime (73, 117), and succinamidedioxime (117).

Oxamidedioxime ("Niccolox"), which forms complex salts with Ni^{++}, Cu^{++}, Ag^{+}, Co^{++}, has been applied in quantitative analysis (21, 65, 66, 67).

Nicotinamidoxime can be used for the spectrophotometric determination of uranium (196).

Finally, analytical applications of amidoximes were studied recently by Pearse (117), who proposed a colorimetric method for the determination of cobalt based upon the benzamidoxime complex and a spectrophotometric method for the determination of cobalt and nickel using a single reagent, oxamidedioxime.

(b) Organic Complexes

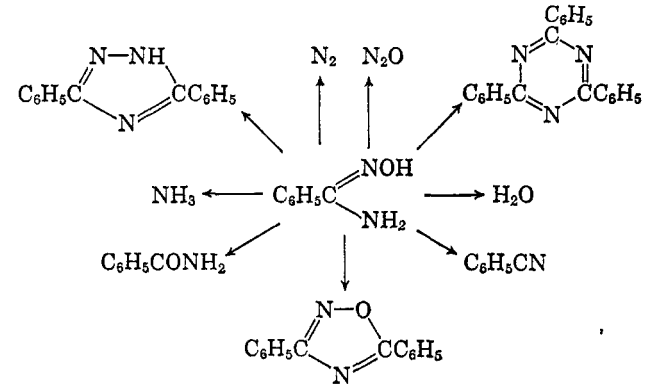
Amidoximes form with chloral bimolecular complexes, which are insoluble in water and soluble in organic solvents. They have sharp melting points and may be used for the identification of amidoximes (39, 55, 114, 175).

N-Phenylbenzamidoxime also forms a complex with chloral (109). However, oxamidedioxime is reported to react with chloral to give a product $C_8H_6N_4O_4Cl_2$ whose structure has not been elucidated (199).

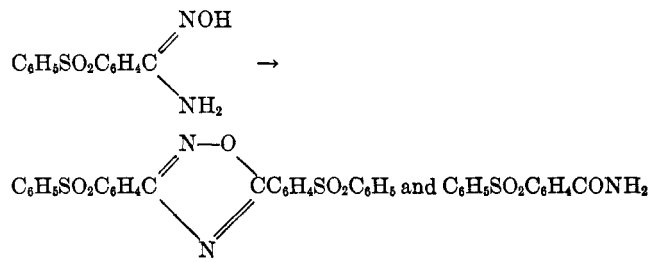
Trichloroacetic acid yields with an aqueous solution of adipamidedioxime a crystalline precipitate, soluble in alcohol. Its formula corresponds to the addition compound of 2 molecules of trichloroacetic acid to 1 molecule of adipamidedioxime (36a). It has not been established definitely whether this substance is a salt or a molecular complex.

(c) Thermal Decomposition

Generally, amidoximes are decomposed when heated in the neighborhood of their melting point. Benzamidoxime, melting at 80°, is stable up to 170°. At this temperature it decomposes, yielding several products which were identified (81) as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, diphenyl-1,2,4-oxadiazole, diphenyl-1,2,4-triazole and triphenyl-1,3,5-triazine.

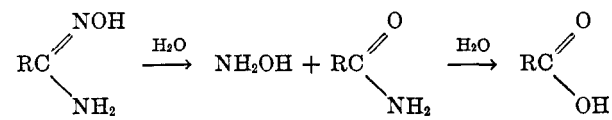


The thermal decomposition of *p*-phenylsulfonylbenzamidoxime yields *p*-phenylsulfonylbenzamide and 3,5-diphenylsulfone-1,2,4-oxadiazole.



(d) Hydrolysis

Many amidoximes, which at room temperature form soluble salts with dilute mineral acids and alkalies, are hydrolyzed completely when heated in the same media (176). Amides and hydroxylamine are formed, and under drastic conditions the amides are hydrolyzed into the corresponding acids:

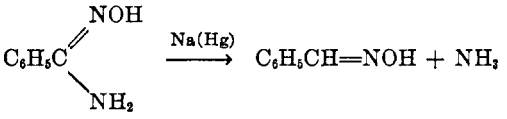


At 200°, a solution of ammonium hydroxide hydrolyzes benzamidoxime into benzamide and ammonium benzoate (90). Oxamidedioxime is hydrolyzed by concentrated hydrochloric acid into oxalic acid, ammonia, and hydroxylamine (52, 53).

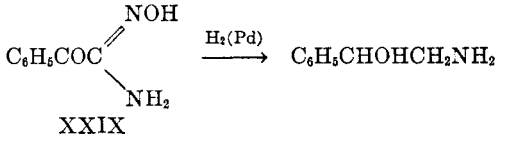
Polyacrylamidoximes of low molecular weight have been hydrolyzed in aqueous solution at different pH values (160c, 160d). The reaction can be limited at will to the NH_2 groups or extended to both NH_2 and NOH groups. A polymer finally is obtained which contains simultaneously hydroxamic acid, amide, and carboxylic groups.

(e) Reduction

The reduction of benzamidoxime with sodium amalgam (193, 195) produces ammonia and benzaldoxime with a yield of only 10 to 12%; most of the amidoxime remains unchanged.

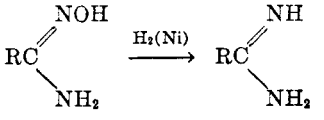


Phenylglyoxalamidoxime (XXIX) has been reduced to phenylethanolamine on a palladium charcoal catalyst under 10 to 20 atmospheres of hydrogen (76).



When N-substituted amidoximes are reduced under the same conditions only 3 moles of hydrogen are taken up; there is evidence that both nitrogen atoms are still present in the reaction product but the structure of these substances has not yet been established.

Amidines can be prepared by reduction of the corresponding amidoximes (7) (20a) in the presence of Raney nickel at 30 atm. and 60–80°.

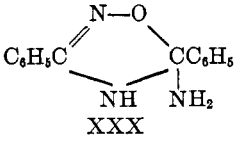


The electrolytic reduction of benzamidoxime in 3.3% HCl also yields benzamidine (7). The same compound is formed when benzamidoxime is acetylated with thioacetic acid. The hydrogen sulfide produced during the reaction reduces the amidoxime *in statu nascendi* into benzamidine (36a).

Zinc in hydrochloric acid does not reduce amidoximes. Therefore this reagent reduces *p*-nitrobenzamidoxime to *p*-aminobenzamidoxime (201).

(f) Oxidation

Oxidizing agents such as potassium ferricyanide, chlorine, or bromine in acetic acid, and iodine in aqueous bicarbonate react with benzamidoxime to yield a product $C_{14}H_{13}N_3O$ which corresponds to an aminodihydroöxadiazole XXX (64).



Compound XXX also is obtained together with nitrous oxide and aminodiazobenzene when benzenediazonium chloride or sulfonate reacts with benzamidoxime (174). The mechanism of formation of XXX is not known.

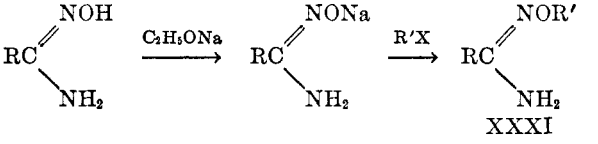
Iodine in sodium hydroxide yields benzonitrile with benzamidoxime.

The transformation of benzamidoxime into 3,5-diphenyl-1,2,4-oxadiazole when heated with a carboxylic acid also has been interpreted as an oxidation-reduction disproportionation to XXX with subsequent loss of ammonia (see page 175) (64, 164).

The oxidation of oxamidedioxime, studied by Holleman (52), failed to yield any definite product.

(g) O-Alkylation

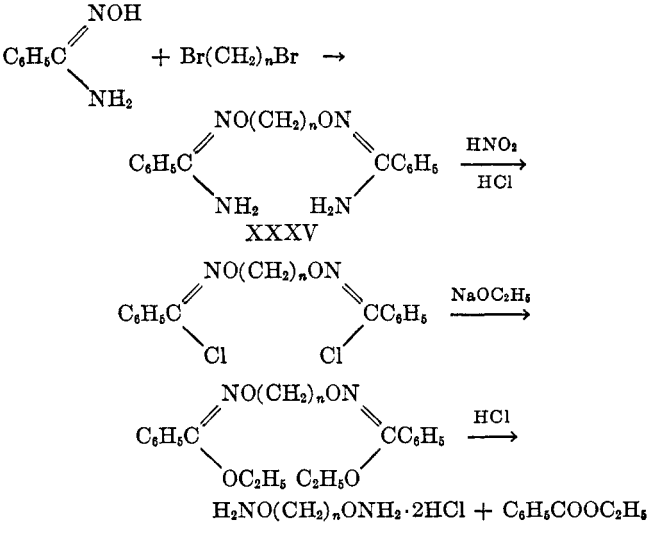
As mentioned before amidoximes and their N-substituted derivatives exhibit acidic properties and form salts with metals. Sodium salts, readily obtained from sodium alcoholate, yield O-alkyl ethers (XXXI) when treated with aliphatic halogen compounds (41a, 63, 108, 193, 208a)



Instead of sodium ethoxide, potassium or sodium hydroxide in aqueous alcoholic solution can be used (202). O-Methyl derivatives have been prepared from amidoximes and methyl sulfate (6, 18).

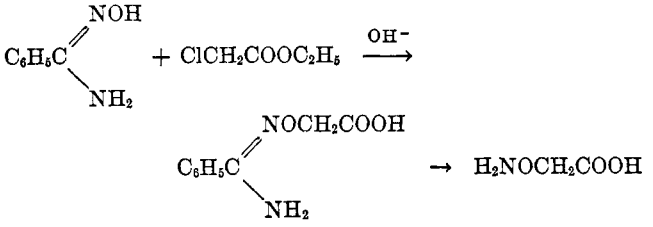
The O-alkyl derivatives of aliphatic amidoximes are oily unstable compounds which have not yet been obtained in a pure state. Those of aromatic amidoximes are low melting stable compounds, soluble in common organic solvents, and can be prepared in good yields (63, 112, 194).

The reaction of benzamidoxime with α,ω-dihalides yielded the expected O,O′-dialkylene derivatives (7, 8, 39). The ethylene di-O,O′-benzamidoxime (XXXV, $n = 2$) on treatment with nitrite in the presence of hydrochloric acid (see page 169) gave the corresponding chlorobenzaldoxime derivative. The latter with sodium ethoxide furnished the ethylene ester of an ethylbenzhydroxamic acid which was hydrolyzed to ethylenedioxydiamine (208a).



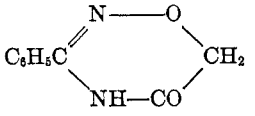
However this method could not be applied to the preparation of other alkylenedioxydiamines, since all attempts to convert hexamethylene and dodecamethylene di-O,O′-benzamidoxime (XXXV, $n = 6, 12$) into the chloride oximes failed completely (7).

The similar reaction of benzamidoxime with an α-halogenated carboxylic ester has been used for the synthesis of α-hydroxylaminocarboxylic acids (209).

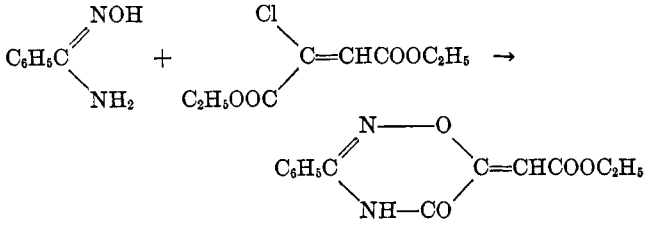


The α-hydroxylamine derivatives of acetic, propionic, butyric, and isobutyric acids have been prepared by this method (205, 208).

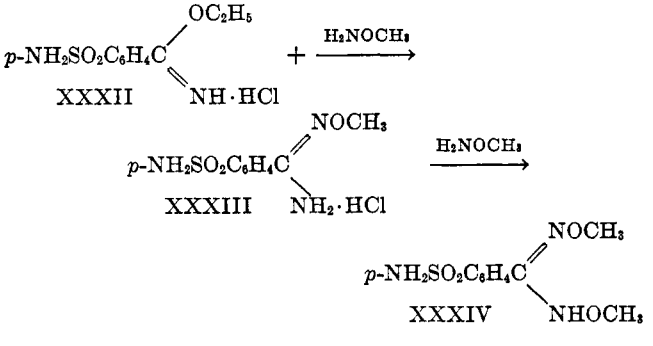
It should be mentioned that the acid formed in the first step is always accompanied by its corresponding lactam, 3-phenyl-5,6-dihydro-1,2,4-oxadiazine-5-one



The 6-substituted homologs also have been obtained (59, 205, 208) with ethyl chlorofumarate and benzamidoxime or α-phenylacetamidoxime; only the cyclic product is isolated (216).

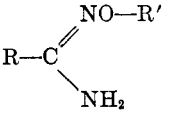


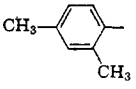
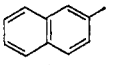
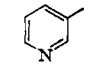
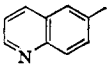
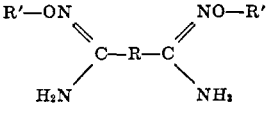
O-Alkyl substituted sulfamidobenzamidoximes have been obtained by an altogether different method (3). An alcoholic solution of sulfamidobenziminoethyl ether hydrochloride (XXXII) is treated with an O-alkylhydroxylamine, at 37° for a fortnight in a pressure bottle. NH_4Cl separates from the reaction mixture and two products can be isolated from the solution. The first, insoluble in dilute hydrochloric acid, is the dialkyl ether of sulfamidobenzoxyamidoxime (XXXIV). The second, soluble in diluted HCl, is the O-alkyl derivative of the amidoxime (XXXIII). For example, O-methyl hydroxylamine reacts



The O-alkyl amidoximes are listed in Table 6.

TABLE 6

O-Alkylated Amidoximes 

R	R′	M. p., °C.	Ref.
CH_3—	—CH_3	Unst. oil	112
CH_3—	—C_2H_5	Unst. oil	112
CH_3—	—$CH_2C_6H_5$	Unst. oil	112
$(CH_3)_2CHCH_2$—	—C_2H_5	35	55
$CH_3C(:NOCH_3)$—	—CH_3	B.p. 192	6
C_6H_5—	—CH_3	57 B.p. 230	63, 193
C_6H_5—	—C_2H_5	67	63, 194
C_6H_5—	—$(CH_2)_5CH_3$	49–50	41a
C_6H_5—	—CH_2CH_2—	155–156	39, 208a
C_6H_5—	—$(CH_2)_6$—	106	41a
C_6H_5—	—$(CH_2)_{12}$—	105	41a
C_6H_5—	—$CH_2C_6H_5$	90.5	63
C_6H_5—	—$CH_2C_6H_4NO_2$-*p*	105–106	202
C_6H_5—	—CH_2COOH	123–124	59
C_6H_5—	—$CH(CH_3)COOH$	168[a]	209
C_6H_5—	—$CH(C_2H_5)COOH$	81–82	208
C_6H_5—	—$CH(C_2H_5)COOC_2H_5$	57	208
C_6H_5—	—$C(CH_3)_2COOH$	182–185[a]	205
C_6H_5—	—$C(CH_3)_2COOC_2H_5$	37–38	205
o-$CH_3C_6H_4$—	—C_2H_5	140	162
p-$CH_3C_6H_4$—	—CH_3	85	161
p-$CH_3C_6H_4$—	—C_2H_5	64	161
$C_6H_5CH_2$—	—C_2H_5	58	57
$C_6H_5CH_2$—	—$CH_2C_6H_5$	55	57
	—C_2H_5	172	114
$C_6H_5CH{=}CH$—	—CH_3	98	217
$C_6H_5CH{=}CH$—	—C_2H_5	83	217
	—C_2H_5	74–75	150, 151
	—$CH_2C_6H_5$	80	99
	—C_2H_5	85	13
o-HOC_6H_4—	—C_2H_5	B.p. 220 (15 cm.)	168
C_6H_5CHOH—	—C_2H_5	89	50
C_6H_5CHOH—	—$CH_2C_6H_5$	102–103	50
p-$CH_3OC_6H_4$—	—C_2H_5	51–52	100
o-$C_2H_5OC_6H_4$—	—C_2H_5	B.p. 195 (18 cm.)	168
m-$C_2H_5OC_6H_4$—	—C_2H_5	109	23
p-$C_2H_5OC_6H_4$—	—C_2H_5	84	62
m-$NO_2C_6H_4$—	—CH_3	75	18
m-$NO_2C_6H_4$—	—C_2H_5	Oil	159
m-$NO_2C_6H_4$—	—$CH_2C_6H_5$	58	159
p-$NO_2C_6H_4$—	—C_2H_5	59–60	201
p-$NH_2SO_2C_6H_4$—	—CH_3	214–215[a]	3
p-$NH_2SO_2C_6H_4$—	—C_2H_5	221–222[a]	3
p-$NH_2SO_2C_6H_4$—	—$(CH_2)_3CH_3$	127–128	3
p-$NH_2SO_2C_6H_4$—	—$(CH_2)_4CH_3$	136–137[a]	3
p-$CH_3C_6H_4NHC(:NH)$—	—C_2H_5	132–133	199
p-$CH_3C_6H_4NHC(:NH)$—	—$CH_2C_6H_5$	165	199
			
— (oxamidedioxime)	—CH_3	144	6
— (oxamidedioxime)	—C_2H_5	114–115	221
—CH_2CH_2—	—C_2H_5	119	166

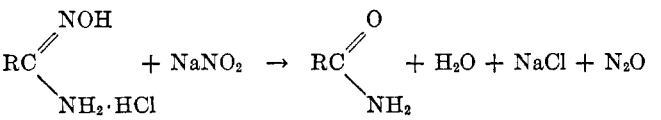
[a] Isolated as hydrochloride.

(h) Action of Nitrous Acid

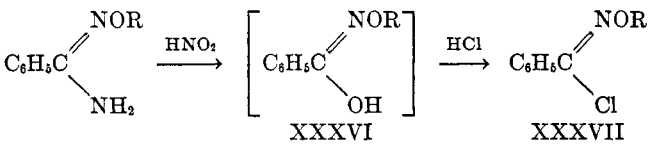
The reaction of nitrous acid on benzamidoxime has been one of the methods which helped to elucidate the structure of the amidoxime group.

Tiemann and Krüger (193) identified the presence of the NOH group by the fact that benzamidoxime, as hydroxylamine itself, evolves nitrous oxide when treated with an equivalent amount of nitrous acid. Under these conditions, benzamidoxime is transformed into benzamide. Acetamidoxime reacts similarly yielding acetamide and nitrous oxide (112).

$$NH_2OH + HNO_2 \rightarrow 2\,H_2O + N_2O$$



However, an O-alkylated benzamidoxime treated with nitrous acid evolves nitrogen, which proves that an amino group is present in the molecule (112). In this reaction the corresponding hydroximic acid (XXXVI) is not isolated, but in the presence of an excess hydrochloric acid, the hydroximic acid chloride (XXXVII) is formed in almost quantitative yields (18, 57, 63, 162, 168, 193, 194, 202, 218).

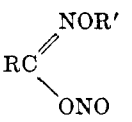


XXXVI XXXVII

O-Alkyl hydroximic acid chlorides are very stable oils which can be steam distilled without decomposition. They are soluble in most organic solvents.

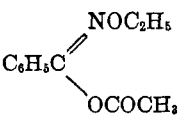
Hydroximic acid bromides and fluorides are prepared in a similar way if hydrobromic or hydrofluoric acid is used instead of hydrochloric acid in the preceding reaction (162, 189, 203).

Nitrites of the type



(189, 201, 203, 218) are formed when O-alkyl amidoximes are treated with nitrous acid in the presence of sulfuric acid. These very unstable substances explode on heating.

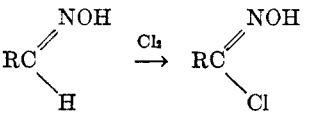
In the presence of acetic acid, the formation of the acetate



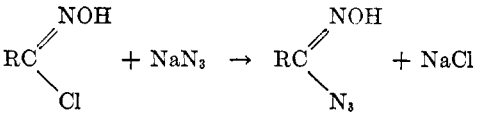
is reported by Tiemann (189) but it could not be isolated in a pure state.

When treated with an alcoholic solution of ammonia, 6 to 8 hours at 160–180°, O-alkylated hydroximic acid halides are converted back to the corresponding amidoximes (194).

Unsubstituted hydroximic acid chlorides generally are prepared by direct chlorination of of aldoximes

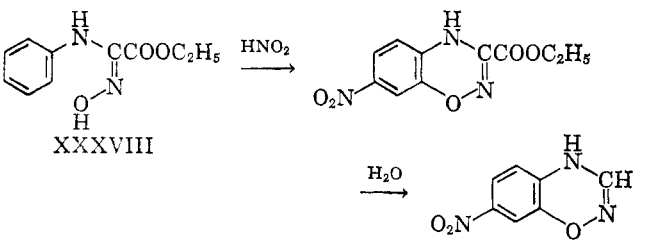


The action of ammonia on the latter compounds already has been mentioned (p. 161). With NaN_3, azidoximes (azides of hydroximic acids) are formed.



The azide structure of these compounds, heretofore erroneously formulated as hydroxytetrazoles, has been proved recently (36d).

The exceptional action of nitrous acid on the oxime of N-phenyloxamic acid ethyl ester XXXVIII was particularly studied by Jovitschitsch (56) and the structure of the oxidation product formed was proved twenty-five years later by Semper and Lichtenstadt (167) to be 6-nitro-4,1,3-benzoxadiazine.

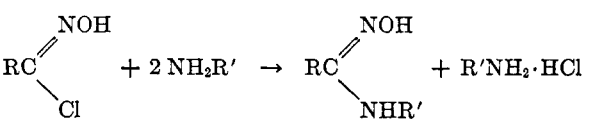


XXXVIII

(i) N-Substitution

One of the methods outlined below may be used to replace one or both hydrogens of the amino group by an alkyl or aryl radical.

a. Action of an amine on hydroximic acid halides is the usual way of preparing N-substituted amidoximes. Primary and secondary, aliphatic and aromatic amines have been used.



The reaction is carried out in absolute ethanol or in ether at room temperature and an excess of amine is used to neutralize the hydrochloric acid formed.

b. Action of hydroxylamine on N-substituted thioamides

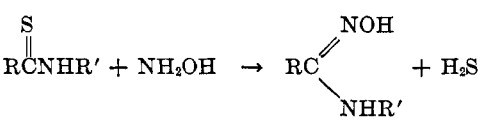
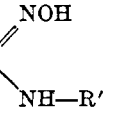
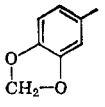
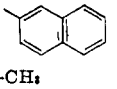


TABLE 7

N-Monoalkylated Amidoximes 

R	R′	M.p., °C.	Method	Yield, %	Ref.
H—	—C_6H_5	138	d	62	110
			b		109
			a		110
CH_3—	—C_6H_5	120–121	d		112
			b		109
C_2H_5OCO—	—C_6H_5	109	a		56
$CH_3C(:NOH)$—	—C_6H_5				139
C_6H_5—	—$CH(CH_3)_2$	Viscous oil	a	90	76
C_6H_5—	—$CH(CH_3)CH_2CH_2N(C_2H_5)_2$		a		7
C_6H_5—	—C_6H_5	136	b		108
C_6H_5—	—$C_6H_4CH_3$-*o*	147	b	Poor	174
C_6H_5—	—$C_6H_4CH_3$-*p*	176	b	Poor	109
		161–162	a		149
p-$CH_3C_6H_4$—	—$C_6H_4CH_3$-*p*	134–135	a		149
p-$(CH_3)_2CHC_6H_4$—	—C_6H_5	145–146	a		149
	—C_6H_5	126–127	a		149
o-ClC_6H_4—	—C_6H_5	140	a		206
o-ClC_6H_4—	—$C_6H_4CH_3$-*o*	173	a		206
p-ClC_6H_4—	—$C_6H_4CH_3$-*p*	169.5–170	a		149
	—$C_6H_4CH_3$-*p*	150–151	a		149
C_6H_5CO—	—CH_3	132–133[a]	a	80	76
C_6H_5CO—	—C_2H_5	Viscous oil	a	79	76
C_6H_5CO—	—$CH_2CH_2CH_3$	Viscous oil	a	68	76
C_6H_5CO—	—$(CH_2)_3CH_3$	120–125[a]	a	85	76
C_6H_5CO—	—$(CH_2)_4CH_3$	123–125[a]	a	70	76
C_6H_5CO—	—C_6H_5	142	a	62	76
C_6H_5CO—	—$CH_2C_6H_5$	Viscous oil	a	82	76
C_6H_5CO—		178–179	a	93	76
p-$CH_3C_6H_4CO$—	—CH_3	124	a	75	76
p-$CH_3C_6H_4CO$—	—C_6H_5	163–164	a	95	76
$C_6H_5C(:NOH)$—	—CH_3	α 178	c		87
		β 159–160	a		87
$C_6H_5C(:NOH)$—	—C_6H_5	α 187–188	c		139, 141
		β 124	c, a		139
		191–192	a		129
$C_6H_5C(:NOH)$—	—$CH_2C_6H_5$	α 174	c		87
		β 158–159	a		87
$C_6H_5C(:NOCOCH_3)$—	—CH_3	160	[b]		87
$C_6H_5NHC(:NOH)$—	—C_6H_5	218	a[c]		128

[a] Isolated as hydrochloride. [b] Formed by the action of acetic anhydride on $C_6H_5C(:NOH)C(:NOH)NH_2$. [c] Prepared from chlorobromoglyoxime.

The yields are less than in the case of unsubstituted thioamides (108, 109, 174).

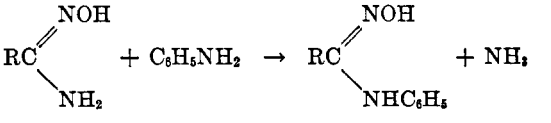
c. Action of amines on glyoxime peroxides yields N-substituted aminoglyoximes (XXXIX) (87, 139, 141) (see p. 162).

$$R(C_2N_2O_2)H + R'NH_2 \rightarrow \underset{\underset{NOH}{\|}}{RC}\!\!-\!\!\!-\!\!\underset{\underset{NOH}{\|}}{C}NHR'$$

(XXXIX)

Different isomers of aminodioximes (XXXIX) have been isolated but their configuration is not definitively established (87).

d. Action of Aniline on Amidoximes.—Aniline is reported to react directly on acetamidoxime and formamidoxime hydrochloride; at 80–90° ammonia is evolved with formation of the corresponding N-substituted amidoximes (110, 112).



No other examples of the direct action of an amine on an amidoxime are known.

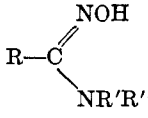
A series of N-substituted amidoximes with their melting points, methods of preparation, and references are listed in Tables 7 and 8.

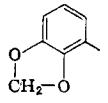
(j) Action of Isocyanates and Isothiocyanates

According to Tiemann (193) cyanic acid and phenyl isocyanate react with benzamidoxime to yield ureide or

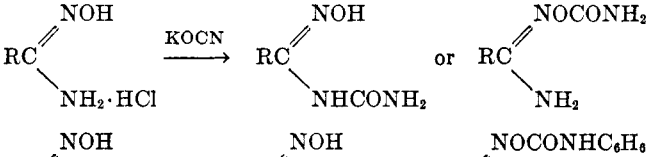
TABLE 8

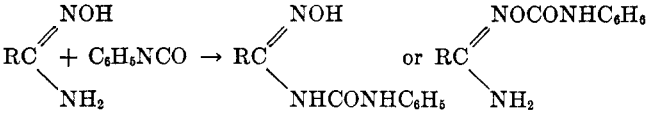
N-Dialkylated Amidoximes



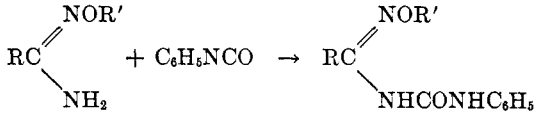
R	NR′R″	M.p., °C	Method	Yield	Ref.
C_6H_5—	Piperidyl		a		7
o-ClC_6H_4—	Piperidyl	165	a		206
	Piperidyl	181–182	a		149
m-$NO_2C_6H_4$—	—$N(CH_3)_2$	160	a	57	18
m-$NO_2C_6H_4$—	—$N(CH_3)(C_2H_5)$	123	a		18
C_6H_5CO—	Morpholinyl	98	a	2	76
$C_6H_5C(:NOH)$—	—$N(CH_2CH_2CH_3)_2$	62–66	a		207

phenylureide oximes. However, no proof was ever given for the structure of these compounds which could be as well the isomeric carbamates (176, 177)

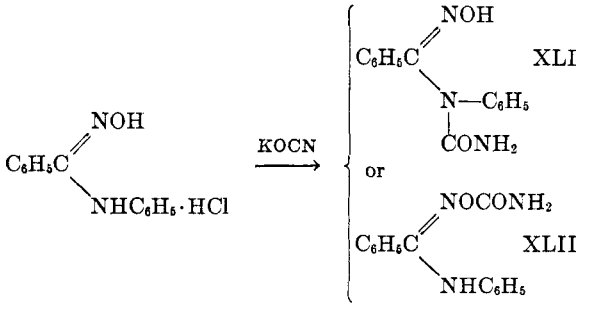




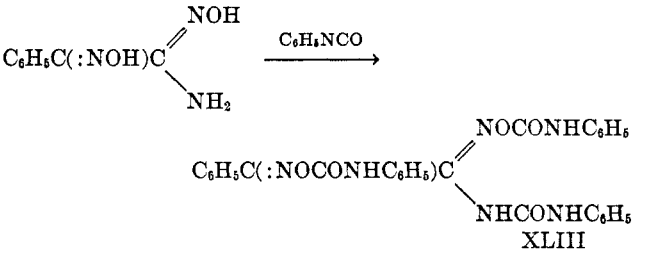
In the case of O-alkyl amidoximes, isocyanates can evidently yield only ureide oximes (51, 58, 218).



Benzanilidoxime hydrochloride is reported to react with potassium cyanate (108). The formula proposed for the reaction product is that of an ureide oxime (XLI) but the compound is completely insoluble in alkali and therefore it is more probable that the correct structure is that of a carbamate (XLII).

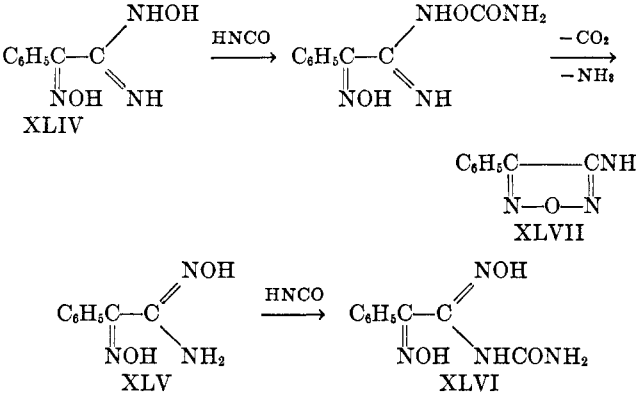


An example in which the isonitroso group is reported to form a carbamate when treated with phenyl isocyanate is given by Longo (84), who transformed phenylaminoglyoxime into a trisubstituted compound XLIII.

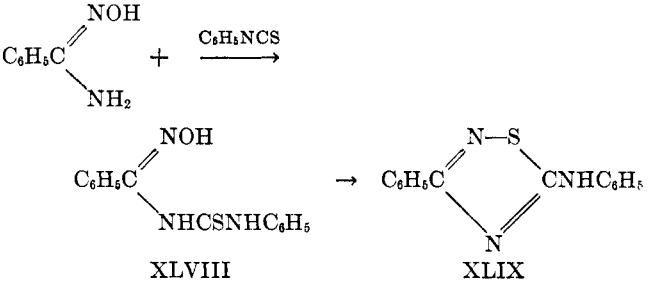


The formation of carbamates also was observed by Ponzio (132), who claimed that the α and β forms of the arylaminoglyoximes are structural isomers containing respectively the hydroxamino and the isonitroso groups. For example, α-phenylaminoglyoxime should have the structure XLIV and the β isomer the structure XLV (see pp. 156 and 176).

According to Ponzio, the β-form treated with cyanic acid gives a ureide oxime XLVI stable in boiling water and ethanol, while the α-form gives a carbamate which in boiling ethanol easily loses CO_2 and NH_3 to yield the phenylaminofurazan XLVII (132)

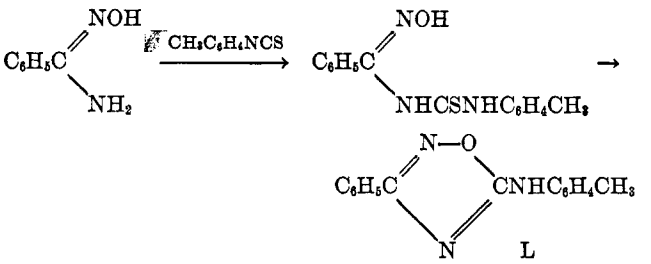


When phenyl isothiocyanate and benzamidoxime react in equimolecular amounts and the reaction is carried out at room temperature, benzoylphenylthiourea oxime (XLVIII) is formed (60, 63).

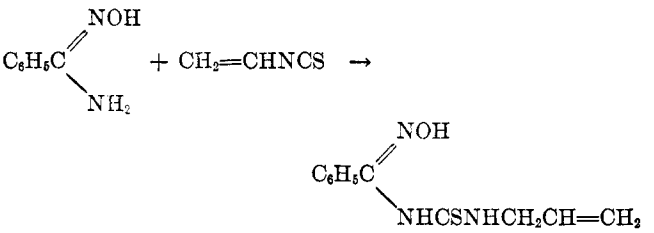


When two moles of isothiocyanate is used for one mole of benzamidoxime and the reaction is carried out in boiling chloroform hydrogen sulfide is evolved and 3-phenyl-5-anilino-1,2,4-*thia*diazole (XLIX) is formed.

On the contrary, under similar conditions, *p*-tolyl isothiocyanate forms the corresponding thiourea oxime, but by cyclization 3-phenyl-5-*p*-toluidino-1,2,4-*oxa*diazole (L) is produced (60).



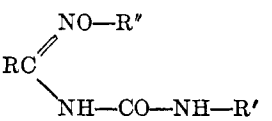
Finally, with allyl isothiocyanate the thiourea derivative is isolated but no cyclization occurs (60).



Gheorghiu and Barbos (43) observed that when benzamidoxime reacts with an excess of phenyl isothiocyanate, free sulfur readily is produced, which shows that autoxidative phenomena probably take place.

Most of the known ureidoximes and thioureidoximes are listed in Tables 9 and 10.

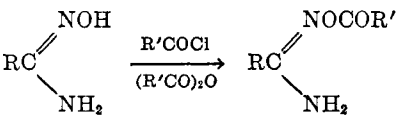
TABLE 9

O-Alkyl Derivatives of Ureide Oximes 

R	R′	R″	M.p., °C.	Ref.
$C_6H_5CH_2$—	—C_6H_5	—C_2H_5	148	58
C_6H_5CH=CH—	—C_6H_5	—C_2H_5	155-156	218
C_6H_5CHOH—	—C_6H_5	—C_2H_5	119	51

(k) Acylation

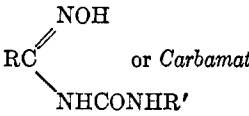
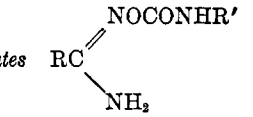
O-Acylated Amidoximes.—Amidoximes can be acylated readily at room temperature by acid chlorides or anhydrides.

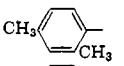
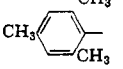
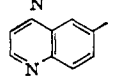
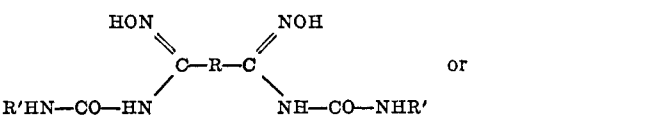


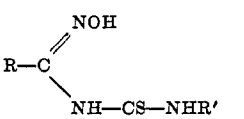
That the reaction occurs on the isonitroso group is proved by the fact that the acyl derivatives still show basic properties whereas the acidic behavior of the amidoximes has disappeared completely (175). Also the infrared spectra of the acyl derivatives show the presence of the NH_2 and —O—CO-groups and the absence of the broad OH-absorption band at about 3.2 μ (36c).

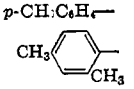
Tables 11, 12, 13, 14 list most of the O-acylated amidoximes, diamidoximes, and imidoximes described in current literature. The methods of acylation are all

TABLE 10

Ureide Oximes  or *Carbamates* 

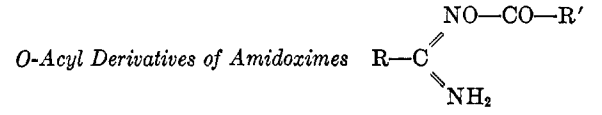
R	R′	M.p., °C.	Ref.
HC(:NOH)—	—H	157	144
HC(:NOCONHC$_6$H$_5$)—	—C_6H_5	172	84
CH_3C(:NOCONHC$_6$H$_5$)—	—C_6H_5	191-192	84
C_6H_5—	—H	115	39
C_6H_5—	—C_6H_5	115	63
p-$CH_3C_6H_4$—	—H	170	162
p-$CH_3C_6H_4$—	—C_6H_5	155	162
	—H	155	114
	—C_6H_5	138	114
$C_6H_5CH_2$—	—C_6H_5	123	57
C_6H_5CH=CH—	—H	158-159	218
C_6H_5CH=CH—	—C_6H_5	158-159	218
C_6H_5CHOH—	—H	127	51
C_6H_5CHOH—	—C_6H_5	155	51
o-HOC_6H_4—	—H	148	168
o-HOC_6H_4—	—C_6H_5	119	168
p-$NH_2SO_2C_6H_4$—	—H	202	3
C_6H_5C(:NOH)—	—H	185	132
p-$CH_3C_6H_4C$(:NOH)—	—H	195-196	132
C_6H_5C(:NOCONHC$_6$H$_5$)—	—C_6H_5	190	84
	—C_6H_5	167	99
	—H	164.5	13
			
— (oxamidedioxime)	—H	191-192	221
—CH_2CH_2—	—H	163.5	166

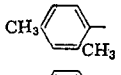
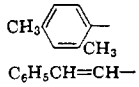
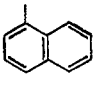
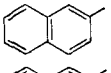
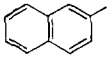
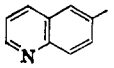
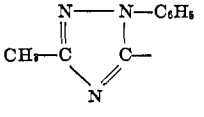
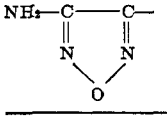
Thioureide Oximes 

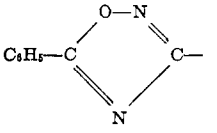
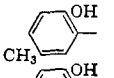
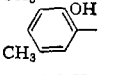
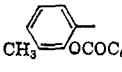
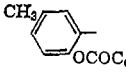
C_6H_5—	—CH_2CH=CH_2	71	60
C_6H_5—	—C_6H_5	172	60, 63
C_6H_5—	—$C_6H_5CH_2$-p	67	60
p-$CH_3C_6H_4$—	—C_6H_5	190	162
	—C_6H_5	150	114

based on well-known classical procedures using either an acid chloride, or an anhydride. However, it is noteworthy that formamidoxime yields only dibenzhydroxamic acid when treated with benzoyl chloride (91). The expected O-benzoyl derivative is obtained when benzoic anhydride is used as an acylating agent (36c).

Instead of acid anhydrides and chlorides, other reagents have been used, such as ketene, mixed carbox-

O-Acyl Derivatives of Amidoximes 

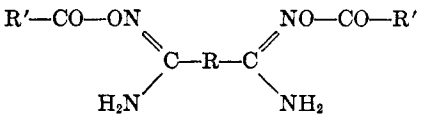
R	R′	M.p., °C.	Ref.
R = hydrocarbon radical			
H—	—H	Viscous oil	103a
H—	—CH_3	77.5	36c
H—	—C_6H_5	115–120	36c
H—	—C_6H_4Br-*p*	120	36c
CH_3—	—H	29	36a
CH_3—	—CH_3	96	81a
CH_3—	—C_6H_5	108	36a
$(CH_3)_2CHCH_2CH_2$—	—CH_3	87	55
$(CH_3)_2CHCH_2CH_2$—	—$CH_2CH_2CH(CH_3)_2$	115	55
$(CH_3)_2CHCH_2CH_2$—	—C_6H_5	105–106	55
C_6H_5—	—H		36a
C_6H_5—	—CH_3	96	164
C_6H_5—	—C_2H_5	93	164
C_6H_5—	—C_3H_7	94	164
C_6H_5—	—C_6H_5	140–148	22, 193
C_6H_5—	—COCOOH	159[a]	219
C_6H_5—	—$COCOOC_2H_5$	118	219
o-$CH_3C_6H_4$—	—C_6H_5	145	162
o-$CH_3C_6H_4$—	—$C_6H_4CH_3$-*o*	117–118	174
p-$CH_3C_6H_4$—	—CH_3	132	22
p-$CH_3C_6H_4$—	—CH_2Br		94
p-$CH_3C_6H_4$—	—CH_2CN		94
p-$CH_3C_6H_4$—	—CH_2—	188–189	96
p-$CH_3C_6H_4$—	—C_6H_5	173	161, 22
p-$CH_3C_6H_4$—	—$CH_2C_6H_5$	146–147	96
p-$CH_3C_6H_4$—	—$CH_2C_6H_4NO_2$-*p*	160–161	96
$C_6H_5CH_2$—	—CH_3	124	57
$C_6H_5CH_2$—	—C_6H_5	144	57
	—CH_3	189	114
	—C_6H_5	158	114
C_6H_5CH=CH—	—C_6H_5	160	217
	—CH_3	129	150, 151
		228	36
	—CH_3	154	150, 151
	—C_6H_5	179	150, 151
R = heterocyclic radical			
	—CH_3	143–147	22, 99
	—C_6H_5	194	22, 99
	—CH_3	115	13
	—CH_3	148	15
	—CH_3	193–194	83

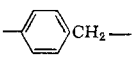
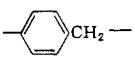
R	R′	M.p., °C.	Ref.
	—C_6H_5	206	32
R = substituted hydrocarbon radical			
o-ClC_6H_4—	—C_6H_5	162	206
p-BrC_6H_4—	—CH_3	145	22
p-BrC_6H_4—	—C_6H_5	161	22
CH_3CHOH—	—C_6H_5	188–189	157
C_6H_5CHOH—	—CH_3	140	50, 175
C_6H_5CHOH—	—C_6H_5	149	50, 175
o-HOC_6H_4—	—CH_3	117	168
o-HOC_6H_4	—C_6H_5	173	168
m-HOC_6H_4—	—CH_3	90	23
m-HOC_6H_4—	—C_6H_5	166	62
p-HOC_6H_4—	—CH_3	122.5	62
	—CH_3	148–149	45
	—C_6H_5	181–182	45
o-$CH_3OC_6H_4$—	—CH_3	130	22
p-$CH_3OC_6H_4$—	—CH_3	106	100
p-$CH_3OC_6H_4$—	—C_6H_5	148	100
$HOCOCH_2$—	—C_6H_5	135	103
$C_6H_{13}CH(OCOC_6H_5)$—	—C_6H_5	143	157
o-$CH_3OCOC_6H_4$—	—CH_3		168
$C_6H_5CH(OCOCH_3)$—	—CH_3	113	50
$C_6H_5CH(OCOCH_3)$—	—C_6H_5	165	50
o-$C_6H_5OCOC_6H_4$—	—C_6H_5	127	168
m-$C_6H_5OCOC_6H_4$—	—C_6H_5	152.5	23
p-$C_6H_5OCOC_6H_4$—	—C_6H_5	185	62
	—C_6H_5	164	116
	—C_6H_5	143	45
p-$NO_2C_6H_4CH_2$—	—CH_3	145	22
p-$NO_2C_6H_4CH_2$—	—C_6H_5	148	22
$C_6H_5CH_2CH(NHCOCH_3)$—	—CH_3	DL 160–162	118
$C_6H_5CH_2CH(NHCOC_6H_5)$—	—C_6H_5	DL 206–207	118
		L 204–211	118
$CNCH_2$—	—CH_3	142	158
$CNCH_2$—	—C_6H_5	184–182	158
p-$CNC_6H_4CH_2$—	—C_6H_5	172	154
CH(:NOH)—	—C_6H_5	146–147	144
CH_3C(:NOH)—	—C_6H_5	158	130
C_6H_5C(:NOH)—	—C_6H_5	β 168–169	130
CH_3C(:$NOCH_3$)—	—C_6H_5	134–135	6
CH(:$NOCOCH_3$)—	—CH_3	82	54, 144
CH(:$NOCOCH_3$)—	—C_6H_5	166–167	144
CH_3C(:$NOCOCH_3$)—	—CH_3	123	146
CH_3C(:$NOCOCH_3$)—	—C_6H_5	143	130
C_6H_5C(:$NOCOCH_3$)—	—CH_3	β 133–138	132, 140
C_6H_5C(:$NOCOCH_3$)—	—C_6H_5	β 139–140	130
CH(:$NOCOC_6H_5$)—	—CH_3	145–146	142
CH(:$NOCOC_6H_5$)—	—C_6H_5	186–187	144
CH_3C(:$NOCOC_6H_5$)—	—C_6H_5	206	130
C_6H_5C(:$NOCOC_6H_5$)—	—C_6H_5	α 190	140
		β 185–186	130, 132, 140
C_6H_5COC(:$NOCOC_6H_5$)—	—C_6H_5	158–159	143
$C_6H_5COONHCOCH_2$—	—C_6H_5	165	103
C_6H_5—N=N—	—CH_3	168	86
C_6H_5—N=N—	—C_6H_5	191–192	86
p-$CH_3C_6H_4$—N=N—	—CH_3	193–194	86
p-$CH_3C_6H_4$—N=N—	—C_6H_5	192–193	86
p-$CH_3SC_6H_4$—	—C_6H_5		20
p-$NH_2SO_2C_6H_5$—	—CH_2Cl	210	12

[a] Prepared by saponification of the ethyl ester.

TABLE 12

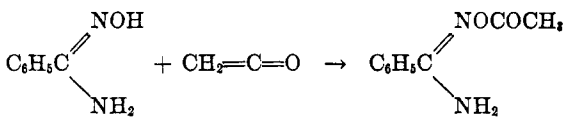
O-Diacyl Derivatives of Diamidoximes



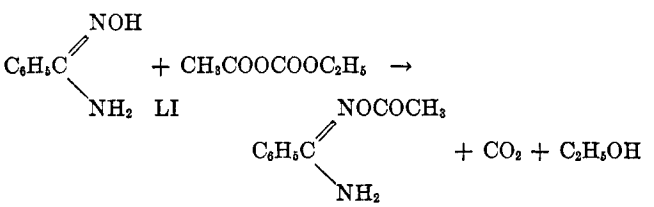
R	R'	M.p., °C.	Ref.
— (oxamidedioxime)	—H	175–176	36a
	—CH_3	184–187	40, 128, 221
		206–212	54
	—$COOC_2H_5$	168–169	36a
	—C_6H_5	217–222	52, 221
—CH_2—	—CH_3	153–159	158
—CH_2—	—C_6H_5	183–185	158
—CH_2CH_2—	—CH_3	167–168	166
—CH_2CH_2—	—C_6H_5		166
—$CH_2CH_2CH_2$—	—CH_3	115	14
—$(CH_2)_{10}$—	—CH_3	129	75
	—CH_3	161.5–162	154
	—C_6H_5	184	154

ylic–carbonic anhydrides, carboxylic acid azides, and thioacetic acid (36a, c).

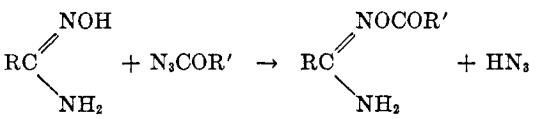
Ketene reacts instantaneously with benzamidoxime in an inert solvent to give the O-acetylbenzamidoxime in quantitative yields



Benzamidoxime and acetamidoxime give the corresponding O-acetyl derivative quantitatively when treated at room temperature with an ethereal solution of acetic–ethylcarbonic anhydride (LI).



Also carboxylic acid azides are very efficient acylation agents which react readily at room temperature with amidoximes.



In particular, formamidoxime, which cannot be benzoylated with benzoyl chloride, formed the expected derivative with benzoyl azide (36c).

With thioacetic acid, benzamidoxime is acetylated at room temperature with evolution of hydrogen sulfide. The reaction can be conducted in water. However, sulfur appears during the reaction showing that simultaneously a reduction occurs. A by-product of the formula $C_9H_{12}O_2N_2$ can be isolated, which could be identified as a salt of benzamidine with acetic acid (36a).

Acylation with a carboxylic acid is reported to occur

TABLE 13

O-Acyl Derivatives of Imidoximes and Imidedioximes

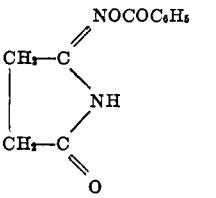
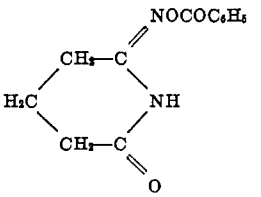
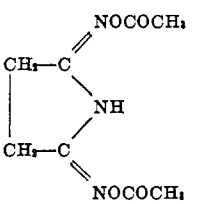
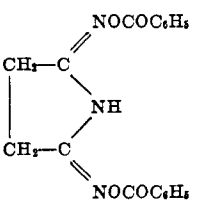
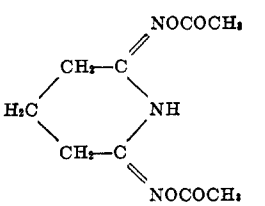
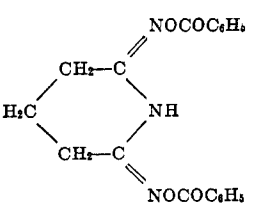
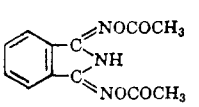
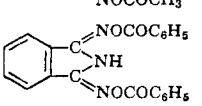
Compound	M.p., °C.	Ref.
	184	42
	160	42
	170–171	166
	187–188	166
	127	14
	179–180	14
	192	22
	248	22

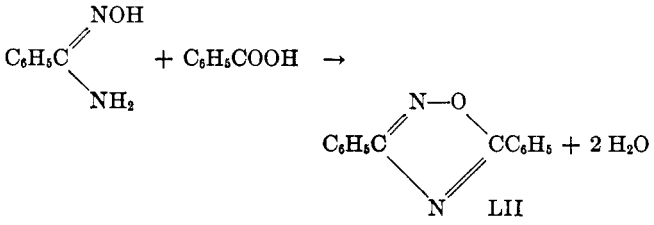
TABLE 14

O-Acylated N-Substituted Amidoximes R—C(=NOCO—R″)—NH—R′

R	R′	R″	M.p., °C	Ref.
H—	—C_6H_5	—C_6H_5	144–145	109
CH_3—	—C_6H_5	—C_6H_5	110	109
C_6H_5—	—C_6H_5	—C_6H_5	116	108
$C_6H_5C(:NOCOCH_3)$—	—C_6H_5	—CH_3	α 179	139
			β 150	139
$C_6H_5C(:NOCOCH_3)$—	—$CH_2C_6H_5$	—CH_3	β 122–123	87
$C_6H_5C(:NOCOC_6H_5)$—	—CH_3	—C_6H_5	β 155	87
$C_6H_5C(:NOCOC_6H_5)$—	—C_6H_5	—C_6H_5	α 201	139
$C_6H_5C(:NOCOC_6H_5)$—	—$CH_2C_6H_5$	—C_6H_5	β 162	87

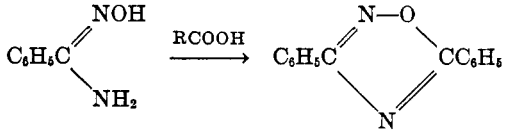
in a few cases. *p*-Nitrobenzamidoxime reportedly was acylated with boiling glacial acetic acid and *p*-sulfaminobenzamidoxime reacted on heating with chloracetic acid to give the chloroacetyl derivative (12).

Benzamidoxime reacts on heating with benzoic acid (193). The acylated amidoxime cannot be isolated but its dehydration product 3,5-diphenyl-1,2,4-oxadiazole (LII) is formed.



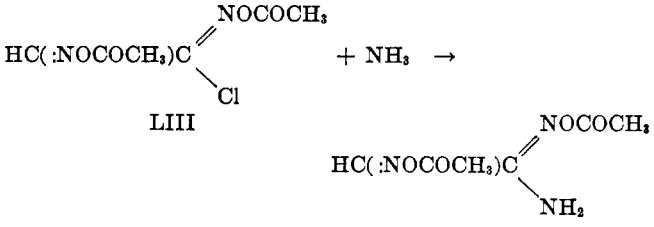
LII

This compound is formed in all media where benzamidoxime and benzoic acid are present (193). However, no definite proof ever has been given that a normal acylation occurs. Indeed, when treated with acetic, propionic or butyric acid, benzamidoxime also is transformed into 3,5-diphenyl-1,2,4-oxadiazole and no trace of a 5-alkyl cyclic derivative can be isolated (162, 164)



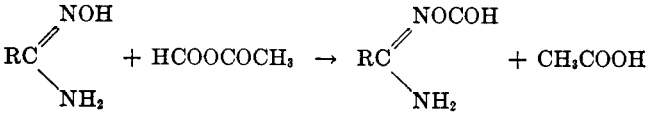
This reaction has been interpreted as an autoxidation of benzamidoxime (64) (see p. 167).

O-Acylated amidoximes also have been prepared from acylated hydroximic acid chlorides (LIII) and ammonia. This reaction was applied to some derivatives of glyoxime (54, 144).

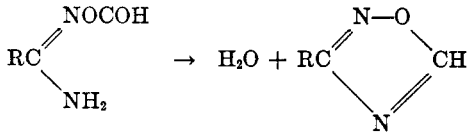


LIII

The formylation of amidoximes recently has been performed with the mixed anhydride of formic and acetic acids

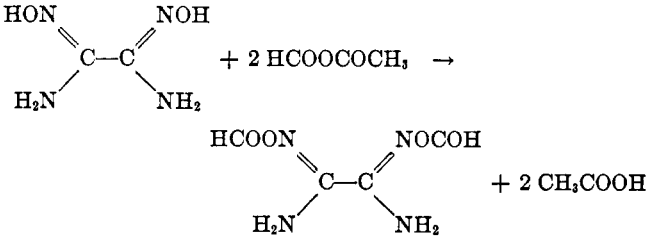


The formyl esters of formamidoxime, acetamidoxime, and benzamidoxime have been synthesized but have not been isolated in a pure state: they were immediately dehydrated into the corresponding 3-monosubstituted oxadiazoles (LIV) (36b, 81a).



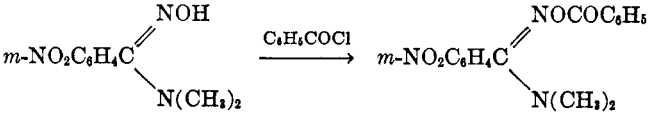
LIV

The diformyl ester of oxamidedioxime could be prepared in good yields using this mixed anhydride (81a).



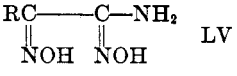
N-Monosubstituted amidoximes also give O-acylated derivatives (87, 108, 109, 139). These compounds are listed in Table 14.

Only one N-disubstituted amidoxime, N,N-dimethyl *m*-nitrobenzamidoxime, is reported to yield a benzoylated compound (18).



The most important chemical properties of O-acylated amidoximes are the readiness with which they are hydrolyzed into the parent amidoximes and their ability to cyclize into the corresponding 1,2,4-oxadiazoles (see p. 177).

N-Acylated Amidoximes.–N-Acyl derivatives of amidoximes have been described by Ponzio and his collaborators who have published a great number of papers concerning the stereochemistry of α-dioximes. Part of the glyoximes studied were amino glyoximes which can be considered as α-oximino-amidoximes (LV).

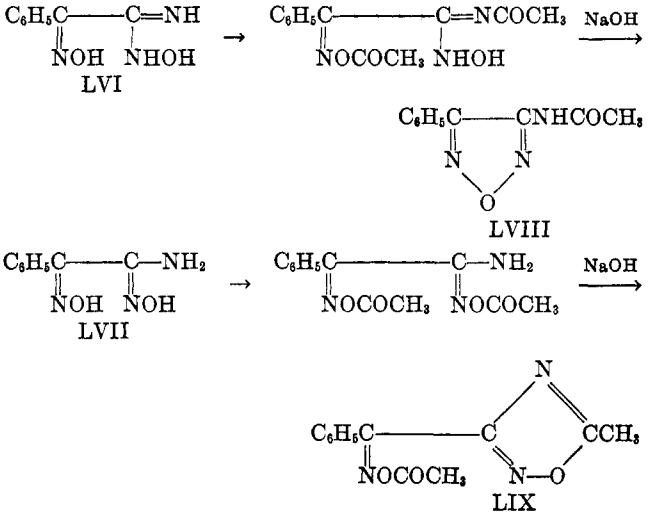


LV

Ponzio's conclusions must be included into this report

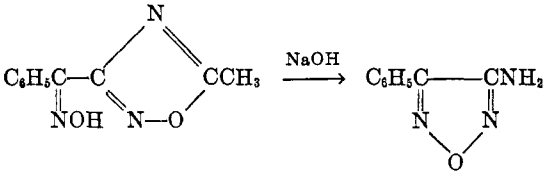
because they raise important questions about the tautomerism of amidoximes (see pp. 156 and 171).

Ponzio has claimed (132) that the two isomers α and β of 1-phenyl-2-aminoglyoxime correspond to the structures LVI and LVII, respectively, and that on acylation, the amidoxime group of the former is N-acylated, while the latter undergoes O-acylation. In order to prove this point, cyclization with aqueous alkali is performed, which leads to a furazan LVIII in the first case and to an oxadiazole ring (LIX) in the second (129, 144).



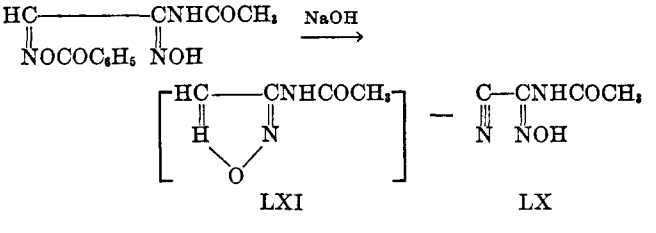
This dissimilar behavior in cyclization is Ponzio's main argument to prove the existence of forms LVI and LVII.

On the other hand he established (140) the possibility of transformation of the oxadiazole derivative into the corresponding furazan by treatment with alkali



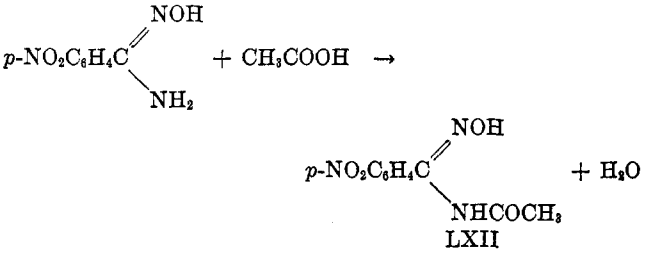
so that the above proof of the structure appears to be less convincing.

Another N-acyl amidoxime, N-acetylcyanoformamidoxime (LX), was claimed to have been isolated by Ponzio when he tried to prepare a monosubstituted furazan (LXI), which he did not obtain; for this reason he considered the latter structure too unstable to exist in alkaline medium (135).



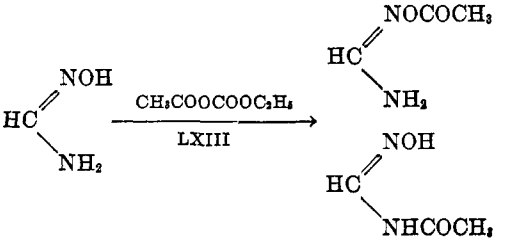
Steinkopf (169, 171), who studied the halogenated acetamidoximes, claimed that their acylation occurs on the amino nitrogen, but no proof was given.

p-Nitrobenzamidoxime has been reported (12) to give an N-acetyl derivative (LXII) when treated with boiling acetic acid



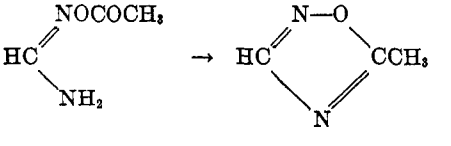
The proposed structure has been based on the interpretation of the infrared spectrum, but the arguments are not wholly convincing.

Recently, both N- and O-acetylated formamidoximes have been synthesized (36c). When the acylation of formamidoxime is carried out with mixed acetic-ethylcarbonic anhydride (LXIII), the two isomers are present in almost equal quantities.



The infrared spectra of both isomers are quite distinct: the NH_2 doublet at 3295 and 3420 cm.$^{-1}$ and the —OC=O band at 1735 cm.$^{-1}$ characterize the O-acetyl formamidoxime molecule, whereas the N-acetylated compound shows only a simple band at 3335 cm.$^{-1}$ as well as a broad absorption region between 3300 and 2900 cm.$^{-1}$, while the carbonyl absorption band of the amide function is visible at 1730 cm.$^{-1}$.

Solubility and chemical behavior of the two isomers also are dissimilar: for example, the O-derivative can be dehydrated into the 5-methyl-1,2,4-oxadiazole, whereas the N-derivative cannot.



If the acylation is carried out with acetic anhydride, the same isomers are obtained but in addition a small amount of acetyl urea is formed. A Lossen transformation may explain the presence of this product (see p. 180).

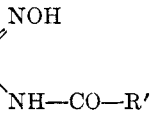
The formylation of formamidoxime also yields both O and N-formylated isomers. Only the latter has been isolated and identified by its infrared spectrum,

while the former has been dehydrated immediately into unsubstituted 1,2,4-oxadiazole (36b, 103a).

Derivatives of amidoximes reported in the literature as having the N-acyl structure are listed in Table 15.

TABLE 15

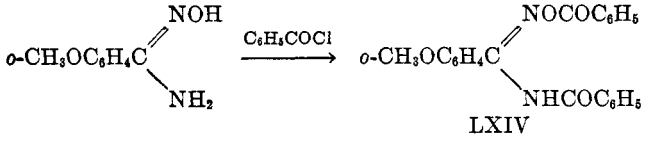
N-Acyl Derivatives of Amidoximes



R	R′	M.p., °C.	Ref.
H—	—H	146–147	103a
H—	—CH_3	175	36c
$CHCl_2$—	—CH_3[a]	114–115	169, 171
CH_2I—	—CH_3[a]	103–105	169, 171
CN—	—CH_3[a]	186	144
p-$NO_2C_6H_4$—	—CH_3[a]	226	12
CH(:NOCOCH$_3$)—	—CH_3[a]	154	144, 169, 171
C_6H_5C(:NOCOCH$_3$)—	—CH_3[a]	α 150–151	132, 140
p-$CH_2C_6H_4C$(:NOCOCH$_3$)—	—CH_3[a]	168	132
C_6H_5C(:NOCOC$_6$H$_5$)—	—CH_3[a]	190–191	129
C_6H_5C(:NOCOC$_6$H$_5$)—	—C_6H_5[a]	α 189	132
p-$CH_3C_6H_4C$(:NOCOCOC$_6$H$_5$)—	—C_6H_5[a]	199–200	132

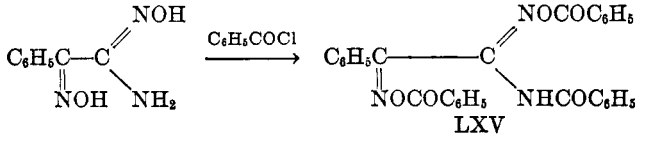
[a] No proof of the structure is given.

Diacyl Derivatives of Amidoximes.—The benzoylation of *o*-methoxybenzamidoxime gives the N,O-dibenzoyl derivative (LXIV), even at room temperature, when treated with an equivalent amount of benzoyl chloride (22).



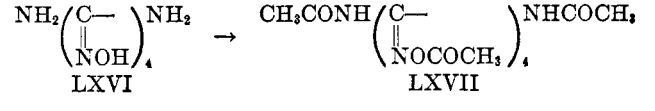
LXIV

When treated with benzoyl chloride at 100°, phenylaminoglyoxime is reported to yield a tribenzoyl derivative (LXV) (132).



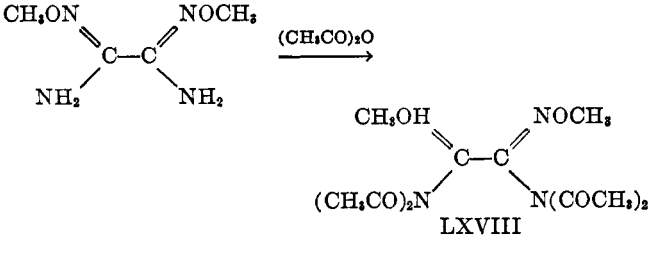
LXV

A hexaacetyl compound (LXVII) is formed when the diaminotetraoxime LXVI is treated with hot acetic anhydride (83).



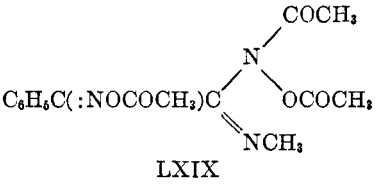
LXVI LXVII

O,O′-dimethyloxamidedioxime is reported to form a tetraacetyl derivative (LXVIII) (6).

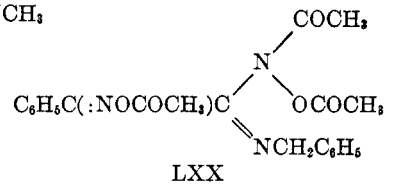


LXVIII

Finally, although the structure of the compounds is not well elucidated, it is worth mentioning that Longo (87) reported the formation of diacetyl amidoximes LXIX and LXX in which the two acetyl radicals are linked to the hydroxamino group NHOH.

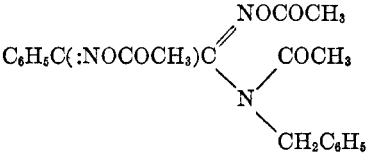


LXIX

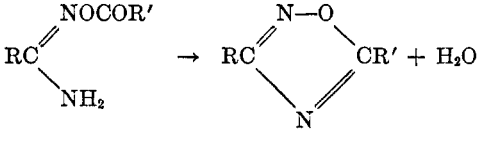


LXX

The β-form of LXX has been formulated by Longo as



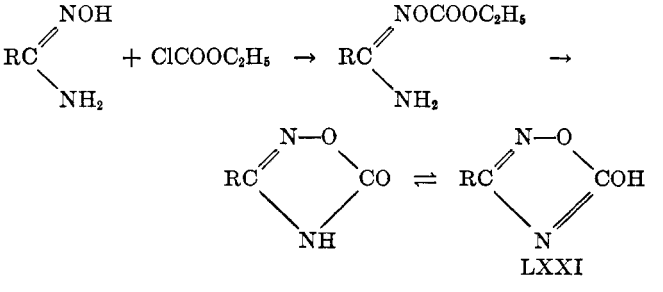
Formation of 1,2,4-Oxadiazoles.—Acyl derivatives of the amidoximes are in most cases dehydrated easily into the corresponding 3,5-disubstituted 1,2,4-oxadiazole



The dehydration of the acyl amidoximes generally is accomplished by heating these compounds either in the dry state or in solution in glacial acetic acid, acetic anhydride, water, dilute NaOH, or H_2SO_4. If the acylation of amidoximes is carried out at 100° or above, spontaneous cyclization occurs.

(l) Carbonic Acid Derivatives of Amidoximes

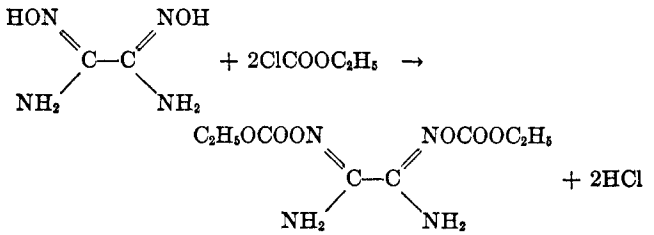
Ethyl chloroformate reacts with the isonitroso group of the amidoximes to give carbonic acid derivatives (38, 177).



LXXI

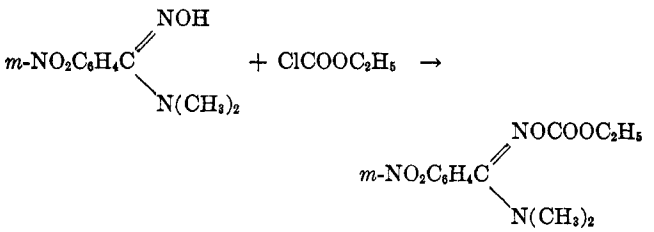
On heating ethanol is eliminated and a 5-hydroxy-1,2,4-oxadiazole LXXI is formed (38, 39, 178).

Similarly oxamidedioxime forms a disubstituted derivative (221).

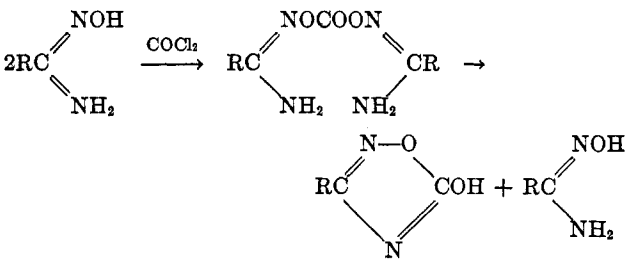


This compound could not by cyclized.

N-Substituted amidoximes also react in the same way (18). For example, N-dimethyl *m*-nitrobenzamidoxime treated with ethyl chloroformate yields a carbonic ester.



Phosgene reacts with amidoximes to give derivatives of carbonic acid; on cyclization one molecule of amidoxime is regenerated (194).

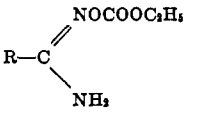


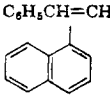
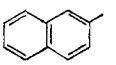
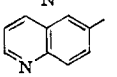
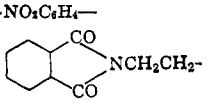
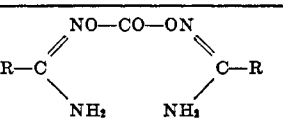
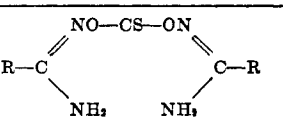
Thiophosgene and amidoximes yield derivatives of thiocarbonic acid, which on cyclization give 5-mercapto-1,2,4-oxadiazoles (64).

Table 16 contains the list of the carbonic acid derivatives of amidoximes.

TABLE 16

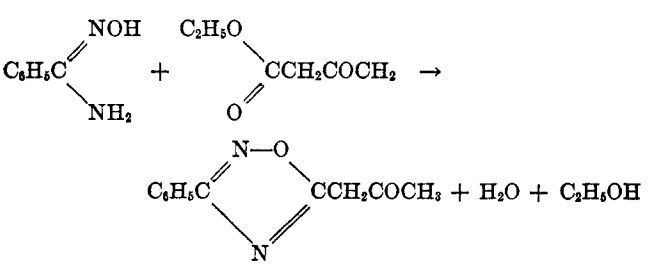
Carbonic Acid Derivatives of Amidoximes



R	M.p., °C.	Ref.
C_6H_5—	127	1, 38, 39
p-$CH_3C_6H_4$—	130	162
	142	114
$C_6H_5CH{=}CH$—	101	218
	111	151
	121	151
	136	99
	97	13
o-HOC_6H_4—	96	100
C_6H_5CHOH—	106–107	51
p-$CH_3OC_6H_4$—	119–120	100
m-$NO_2C_6H_4$—	152–153	159, 160
p-$NO_2C_6H_4$—	169	201
	142	36a
		
$(CH_3)_2CHCH_2CH_2$—	114	55
C_6H_5—	128–129	38, 39
C_6H_5CHOH—	131	51
p-$NO_2C_6H_4$—	232	201
		
C_6H_5—	96	64
p-$CH_3C_6H_4$—	115	64

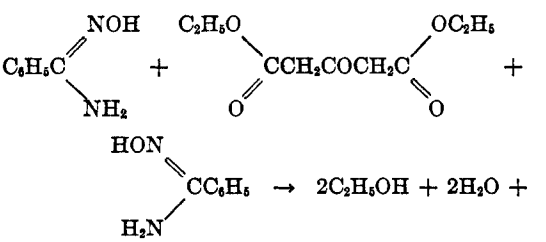
(m) Reaction with β-Ketocarboxylic Esters

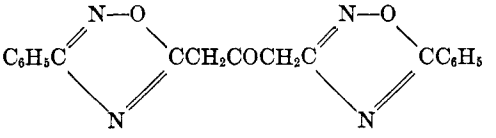
Although amidoximes are indifferent toward nonactivated esters, they react on heating with an excess of ethyl acetoacetate. Water and ethanol are eliminated and 5-aryl-3-acetonyl-1,2,4-oxadiazoles are formed (151, 162, 182, 201).



Highest yields are obtained when the reaction is carried out in boiling toluene until all water and ethanol are eliminated by distillation (95).

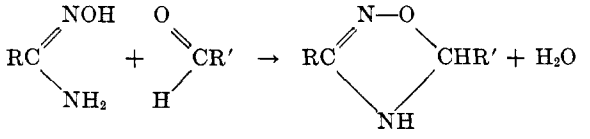
Other β-ketocarboxylic esters such as ethyl benzoylacetate, *o*-methoxybenzoylacetate, and acetonedicarboxylate react similarly with aromatic amidoximes; *e.g.* (95).





(n) Reaction with Aldehydes

The aliphatic aldehydes react with amidoximes yielding 3,5-disubstituted 4,5-dihydro-1,2,4-oxadiazoles (182, 220).

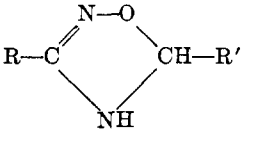


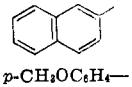
The reaction occurs when a solution of the reagents in water or aqueous ethanol is left for a few hours at room temperature or on a water-bath. Aromatic aldehydes do not react with amidoximes with the exception of *o*-hydroxybenzaldehyde which yields the expected product with benzamidoxime after several weeks of standing (220).

The dihydro-oxadiazoles are crystalline products with basic properties, forming salts with mineral acids. They are hydrolyzed with diluted acids and bases into the corresponding aldehydes and amidoximes and are easily oxidized by potassium permanganate into the corresponding oxadiazoles (182, 220). Analogous dicyclic compounds are obtained from oxamidedioxime (199). The 3,5-disubstituted 4,5-dihydro-1,2,4-oxadiazoles reported in literature are listed in Table 17.

TABLE 17

4,5-Dihydro-1,2,4-oxadiazoles



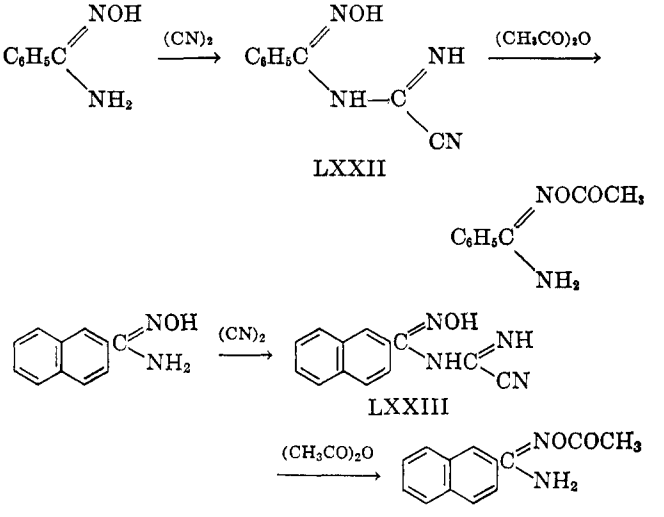
R	R'	M.p., °C.	Ref.
C_6H_5—	—CH_3	82	182
C_6H_5—	—C_2H_5	64	220
C_6H_5—	—$CH(CH_3)_2$	96	220
C_6H_5—	—$CH_2CH(CH_3)_2$	83	220
C_6H_5—	—$CH_2C_6H_5$	136	220
C_6H_5—	—C_6H_4OH-*o*	155	220
p-$CH_3C_6H_4$—	—CH_3	127.5	162
	—CH_3	121	151
p-$CH_3OC_6H_4$—	—CH_3	127.5	100
p-$NO_2C_6H_4$—	—CH_3	153	201
p-$NO_2C_6H_4$—	—CH_2Cl	176	201

The exceptional complex forming reaction of chloral with amidoximes has been mentioned already (page 166).

Acetone and acetone dimethyl acetal also are reported to give 5-dimethyl-4,5-dihydroöxadiazoles (20b, 36a).

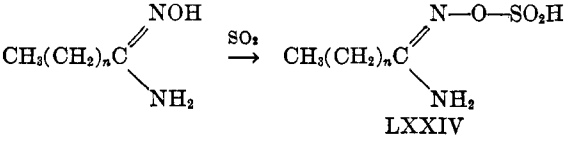
(o) Action of Cyanogen

Cyanogen and benzamidoxime or β-naphthamidoxime yields addition products (111) formulated as LXXII and LXXIII. They are rather unstable and hydrolyze readily into the original amidoximes. The same compounds treated with acetic anhydride give the corresponding O-acetylamidoximes:



(p) Action of Sulfur Dioxide

Sulfur dioxide gives with amidoximes derived from long chain fatty acids unstable addition compounds (LXXIV) (35).

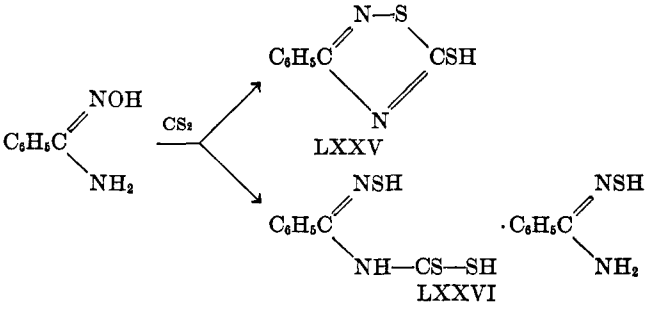


The structure of these substances is not well established.

(q) Action of Carbon Disulfide

The reaction of carbon disulfide with amidoximes in alkaline alcoholic solution produces cyclic compounds known as 5-mercapto-1,2,4-thiadiazoles (25) (LXXV).

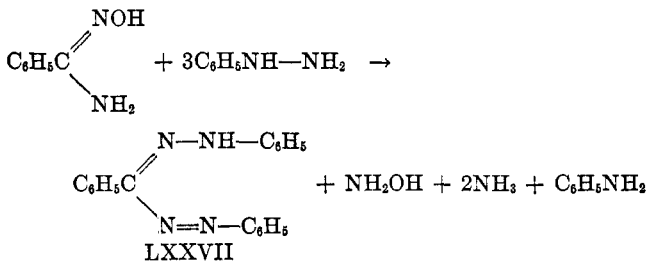
In boiling ethanol, benzamidoxime gives with an excess of CS_2 the thiobenzamidoxime salt of the thioloxime of benzoyldithiocarbamic acid (LXXVI). Dilute hydrochloric acid hydrolyzes this compound into benzamidine hydrochloride.



Methylbenzamidoxime shows a similar behavior (25).

(r) Action of Phenylhydrazine

Phenyl formazyl (LXXVII) is formed when benzamidoxime is refluxed with phenylhydrazine in dilute acetic acid (8).

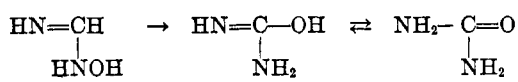


LXXVII

Other reactions of an amidoxime with a hydrazine derivative have not been reported.

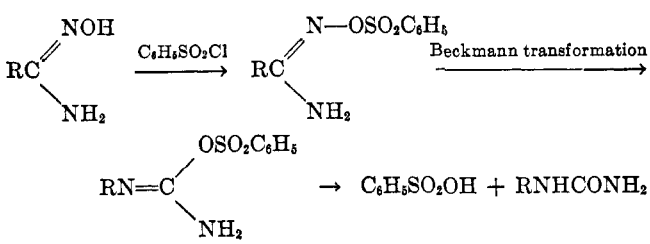
(s) Beckmann Transformation

The presence of urea among the decomposition products of formamidoxime (91) has been explained tentatively by a Lossen rearrangement, related to the Beckmann transformation (41).



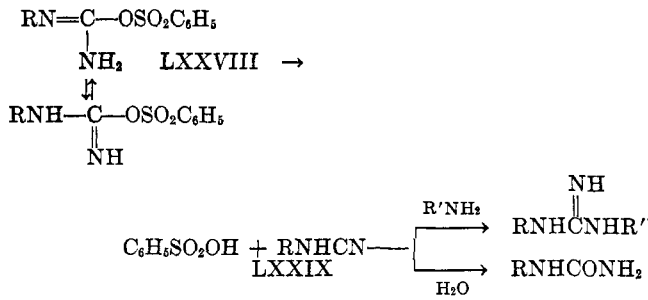
The formation of acetylurea when formamidoxime is acetylated with acetic anhydride also could be interpreted by a Lossen–Beckmann transformation (36c) (see page 176).

Amidoximes have been converted into unsymmetrical ureas when treated first with benzenesulfonyl chloride and then with water. The mechanism postulated by Tiemann (191) involves the conversion of the amidoxime into its O-benzene-sulfonyl derivative which then undergoes a Beckmann transformation into an O-benzenesulfonylisourea. Subsequent hydrolysis yields the asymmetrical urea.



In support of this reaction mechanism it was found (120, 121) that certain amidoximes yielded isolable O-benzenesulfonyl derivatives which on heating with water gave the expected ureas (or their decomposition products) and benzenesulfonic acid.

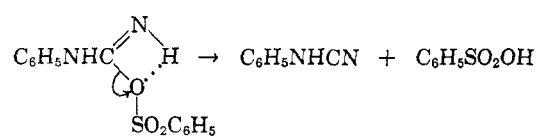
Nevertheless, Partridge and Turner (115) claimed in 1953 that the isourea derivative (LXXVIII) decomposes spontaneously into benzenesulfonic acid and a substituted cyanamide (LXXVIX). Hydrolysis of this cyanamide would then yield a urea, whereas its reaction with an amine yielded a guanidine derivative. The urea is therefore to be considered as a secondary reaction product and the isolable primary products should be benzenesulfonic acid and a substituted cyanamide.



The formation of the O-benzenesulfonyl derivative of the amidoxime is demonstrated readily in the case of phenylacetamidoxime, since the derivative is stable and can be purified without decomposition, whereas O-benzenesulfonylbenzamidoxime is too unstable to be isolated. On heating in an inert solvent, O-benzenesulfonylphenylacetamidoxime readily undergoes a Beckmann transformation into benzyl cyanamide and benzenesulfonic acid. When the transformation is carried out in pyridine with the sulfonyl derivative of the amidoxime formed *in situ*, the yield of benzylcyanamide is 61%. The benzenesulfonyl ester of benzamidoxime prepared in pyridine similarly affords phenylcyanamide and its trimer.

When the products of the transformation are heated with an amine, a N,N′-disubstituted guanidine is obtained in good yield.

The mechanism may be represented as an intramolecular process in which the hydrogen bond controls the subsequent electronic displacements.



When the amino group is substituted by two methyl radicals, no transformation occurs and the O-benzenesulfonyl derivative can be isolated easily (18).

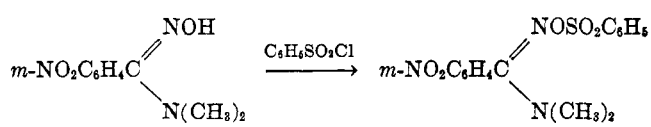


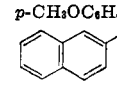
Table 18 summarizes the results obtained in this field.

3. Chemotherapeutic Properties of Amidoximes

Several papers have been published concerning the anti-bacterial activity of amidoximes, compared with amidines. *p*-Sulfamidobenzamidoxime for example has a slightly superior activity over the corresponding

TABLE 18

Beckmann Transformation of Amidoximes

	Tiemann reaction				Partridge reaction				
	$NOSO_2C_6H_5$ // RC \ NH_2		$RNHCONH_2$		$RNHCH$		$RNHCNHR'$ (NH)		
R	M.p., °C.	Yield, %	M.p., °C.	Yield, %	M.p., °C.	Yield, %	R'	M.p., °C.	Yield, %
CH_3—	130	68							
C_6H_5—			147	43–44	40.5	15	C_6H_5—	141–142	71
						60 (trimer)	*p*-BrC_6H_4—	167–168	66
							p-$CH_3C_6H_4$—	123–124	77
p-$CH_3C_6H_4$—			180	43–44					
$C_6H_5CH_2$—	128	73	148	8	42.5	50–61	C_6H_5—	122–123	46–64
							p-$CH_3OC_6H_4$—	122–123	76
								172	51
p-$CH_3(CH_2)_3OC_6H_4$—							C_6H_5—	94	87

amidine on experimental typhus infections in mice (3, 200). However, in most cases, the introduction of the oxygen atom decreases the anti-bacterial power of the amidines, together with their toxicity (20).

Lamb and White (75) have studied the trypanocide activity of several diamidoximes.

2-Methoxy-9-aminoacridine-6-amidoxime and 9-anilacridine-3-amidoxime are patented as products having pharmacological properties and useful in therapeutics (47).

Some halogenated phenols carrying an amidoxime group are active against *Mycobacterium tuberculosis, in vitro* (20a).

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