Heterocycles from Nitrile Oxides. II [1]. 1,2,4-Oxadiazin-6-ones

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Condensation of arylnitrile oxides with α-amino acid esters, other than those of glycine and analine, has been found to constitute a synthetic route to the hitherto unknown 1,2,4-oxadiazin-6-ones **7**. α-Amino alcohols yield with nitrile oxides the corresponding acyclic *N*-(arylhydroxamoyl)amino alcohols, which are also accessible by borohydride reduction of compounds **7**. In contrast, the adducts formed from nitrile oxides and α-amino acids are unstable; they decompose readily into the aldehyde, derived from the amino acid, together with the aldoxime, derived from the nitrile oxide. Both decomposition products are also formed when compounds **7** are subjected to mild hydrolysis.

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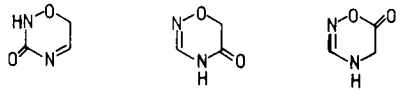
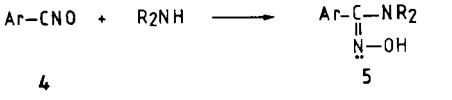
Whereas 1,2,4-oxadiazin-3-ones **1** [2] and 1,2,4-oxadiazin-5-ones **2** are known [3], the isomeric 1,2,4-oxadiazin-6-ones **3** are not described in the literature. As part of our program [1] directed towards syntheses of new heterocycles from nitrile oxides **4**, we now report on the preparation of 3,5-disubstituted-5*H*-1,2,4-oxadiazin-6(4*H*)-ones *via* interaction of **4** with α-amino esters.



1 **2** **3**

Although addition reactions of nitrile oxides to various nucleophiles have been extensively studied [4], work on their condensation with α-amino acids and α-amino esters is limited to that of Hegarty, *et al.* [5], who studied the kinetics of the reaction of nitrile oxides with glycine and ethyl glycinate, but with no mention of the reaction products.

Scheme I

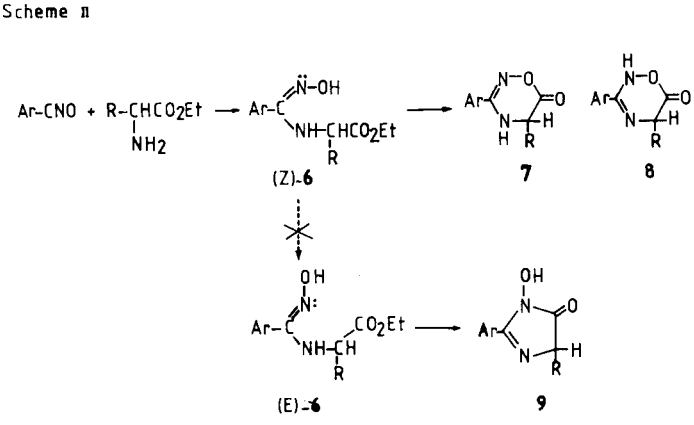


4 **5**

(/)- Amidoxime

Primary and secondary amines are known to add readily to nitrile oxides and yield initially the corresponding *(Z)*-amidoximes **5** as the kinetically controlled products [6] (Scheme I). In these nucleophilic 1,3-dipolar addition reactions, the entering nucleophile and the developing lone pair are mutually trans, leading to a stereospecific addition [7]. α-Amino esters should add similarly to nitrile oxides and the resulting *(Z)*-amidoxime esters **6** are likely to undergo intramolecular cyclization (through oxygen) in an allowed '6-Exo-Trig' process [8] to the corresponding oxadiazinones **7**. Cyclization (through nitrogen) to **9**, on the other hand, would require initial isomerization of *(Z)*-**6** to the *(E)*-form, in which the lone pair at the oximino nitrogen is properly situated for nucleophilic attack at the carbonyl carbon (Scheme II). Related intramolecular cyclizations of suitably functionalized oxime derivatives, both through the oximino oxygen [9] and nitrogen [10] have been reported.

Scheme II



(Z)-**6** **7** **8**

(E)-**6** **9**

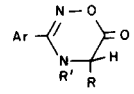
In the present study, α-amino esters are indeed found to react with hydroxamoyl chlorides (precursors of nitrile oxides) in the presence of triethyl amine at low temperatures to give directly the desired 1,2,4-oxadiazin-6-ones **7** (Table I). Apparently, under such mild reaction conditions, intramolecular cyclization of the intermediate acyclic *(Z)*-amidoxime ester **6** is faster than its *(Z)* → *(E)* isomerization. Except for glycine and alanine esters, cyclization to **7** occurs so readily that attempts to isolate the acyclic adduct **6** from the reaction mixture were unsuccessful.

The new heterocycles **7** exhibit infrared absorptions at about 3250, 1750 and 1600 cm^{-1} attributable, respectively, to N-H, C=O and C=N bond stretching modes.

The contribution (if any) of tautomeric structure **8** is insignificant as evidenced by pmr spectroscopy. The chiral C(5)-H proton appears as one doublet for the phenylglyc-

Table I

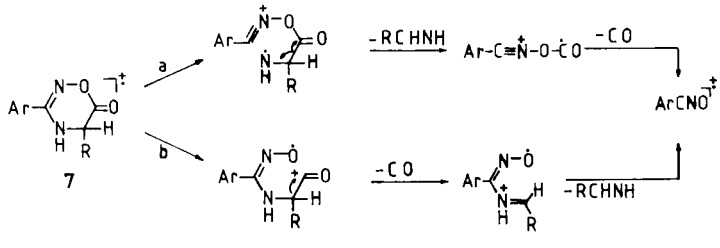
Physical Data for Compounds **7**



No.	Ar	R	R'	Yield (%)	Mp °C	$[\alpha]_D^{20}$ [c]	PMR [d] H-5	Analyses (%) Calcd./Found C	H	N
7a	*p*-ClC_6H_4	$CHMe_2$	H	55	178-179	+28.0	3.86, d	57.04	5.19	11.09
					[a]		3.97, d	56.88	5.22	11.04
7b	*m*-ClC_6H_4	$CHMe_2$	H	32	125-126	+18.2	3.88, d	57.04	5.19	11.09
					[b]		3.95, d	56.81	5.19	11.11
7c	o-ClC_6H_4	$CHMe_2$	H	12	151-152	+36.7	3.91, d	57.04	5.19	11.09
					[b]		3.98, d	56.86	5.29	10.92
7d	*p*-$NO_2C_6H_4$	$CHMe_2$	H	30	180-181	+27.2	3.91, d	54.75	4.98	15.96
					[a]		4.00, d	54.23	5.09	16.02
7e	*m*-$NO_2C_6H_4$	$CHMe_2$	H	45	154-155	+23.2	4.07, d	54.75	4.98	15.96
					[b]		4.18, d	54.28	4.98	15.89
7f	*p*-BrC_6H_4	$CHMe_2$	H	50	193-194	+23.7	3.88, d	48.50	4.41	9.43
					[a]		3.97, d	48.73	4.38	9.68
7g	*p*-MeC_6H_4	$CHMe_2$	H	66	173-174	+39.7	3.85, d	67.22	6.94	12.06
					[b]		3.95, d	66.99	6.88	12.19
7h	C_6H_5	$CHMe_2$	H	50	130-131	+27.7	3.93, d	66.04	6.46	12.84
					[b]		4,00, d	65.65	6.38	12.84
7i	*p*-ClC_6H_4	$CHMe_2$	Me	23	120-121	+155.1	3.66, d	58.54	5.67	10.50
					[b]			58.43	5.70	10.45
7j	*p*-ClC_6H_4	CHMeEt	H	57	181-182	+38.7	3.60, d	58.54	5.67	10.50
					[a]		3.68, d	58.30	5.66	10.48
7k	C_6H_5	CHMeEt	H	55	134-135	+39.7	3.98, d	67.22	6.94	12.06
					[a]		4.05, d	66.85	6.94	12.02
7l	*p*-ClC_6H_4	CH_2CHMe_2	H	55	179-180	+42.5	4.07, m	58.54	5.67	10.50
					[a]			58.19	5.65	10.43
7m	*p*-ClC_6H_4	$CH_2C_6H_5$	H	73	187-188	+88.0	4.38, m	63.90	4.36	9.31
					[a]			63.68	4.39	9.37
7n	C_6H_5	$CH_2C_6H_5$	H	63	154-155	+79.2	4.33, m	72.16	5.30	10.52
					[a]			71.68	5.37	10.68
7o	*p*-ClC_6H_4	C_6H_5	H	60	168-169	+159.5	5.17, d	62.84	3.87	9.77
					[a]			62.70	3.89	9.87
7p	C_6H_5	C_6H_5	H	60	160-161	+162.0	5.20, d	71.42	4.79	11.10
					[a]			70.84	4.78	11.21
7q	*p*-ClC_6H_4	$-CH_2CH_2CH_2-$		20	124-126	+47.4	3.87, d	57.49	4.42	11.17
					[b]		4.01, d	57.40	4.61	11.02

[a] Crystallized from chloroform. [b] Crystallized from chloroform + petroleum ether (bp 40-60°). [c] Solvent, dimethylformamide. [d] Solvent, deuteriochloroform + DMSO-d_6.

Scheme II



ine derivatives **7o,p** and as two doublets for the valine **7a-h** and isoleucine **7j,k** derivatives. Upon deuterium oxide exchange, these collapse, respectively, to a singlet and a sharp doublet.

In addition to the molecular ion peaks, the mass spectra of compounds **7** are dominated by intense peaks, base peaks in several cases, corresponding to the nitrile oxide ions, formed from $[M]^+$ by successive elimination of CO and RCH=NH (Scheme III, Table II). Except for the proline and phenylglycine derivatives, the aldimine is lost, *via* bond rupture at C(3)-N(4) and C(5)-C(6), prior to CO as indicated by the occurrance of intense [M-(RCH=NH)] ions.

Table II

m/z Values (relative abundance in parentheses) [a] of the Principle Fragments for Compounds **7**

Compound No.	$[M]^+$	$[M-(RCHNH)]^+$	$[M-CO]^+$	$[ArCNO]^+$	$[ArCN]^+$
7a	252/254 (26)	181/183 (52)	—	153/155 (100)	137/139 (32)
7b	252/254 (52)	181/183 (68)	—	153/155 (100)	137/139 (35)
7c	252/254 (23)	181/183 (63)	—	153/155 (100)	137/139 (50)
7d	263 (26)	192 (100)	—	164 (68)	148 (29)
7e	263 (16)	192 (100)	—	164 (69)	148 (35)
7f	296/298 (24)	225/227 (73)	—	197/199 (100)	181/183 (50)
7g	232 (32)	161 (46)	—	133 (100)	117 (39)
7h	218 (26)	147 (56)	—	119 (100)	103 (46)
7j	266/268 (26)	181/183 (52)	—	153/155 (100)	137/139 (32)
7k	232 (8)	147 (45)	—	119 (87)	103 (78)
7l	266/268 (5)	181/183 (45)	—	153/155 (100)	137/139 (47)
7m	300/302 (6)	181/183 (3)	—	153/155 (7)	137/139 (16)
7n	266 (10)	147 (5)	—	119 (29)	103 (21)
7o	286/288 (40)	181/183 (26)	258/260 (24)	153/155 (42)	137/139 (28)
7p	252 (34)	147 (25)	224 (23)	119 (39)	103 (23)
7q	250/252 (35)	—	222/224 (17)	153/155 (16)	137/139 (100)

[a] (%) Ion abundance belongs to the light halogen isotope.

Table III

Physical Data for Compounds **11**

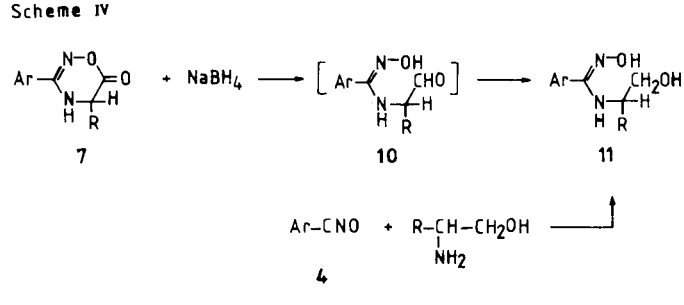
No.	Ar	R	Yield (%)	Mp °C	$[\alpha]_D^{20}$ [d]	Analyses (%) Calcd./Found C	H	N
11a	*m*-$NO_2C_6H_4$	$CHMe_2$	76	110-112 [c] [a]	−35.2	53.92 54.08	6.41 6.53	15.72 15.38
11b	*p*-BrC_6H_4	$CHMe_2$	86	129-130 [a]	−59.8	47.85 47.90	5.69 5.63	9.30 9.60
11c	*p*-ClC_6H_4	$CHMe_2$	90	125-126 [a]	−68.7	56.14 55.85	6.67 6.73	10.91 10.87
11d	*p*-ClC_6H_4	C_6H_5	78	119-120 [b]	−90.1	61.97 62.03	5.20 5.16	9.64 9.64
11e	C_6H_5	C_6H_5	83	130-131 [a]	−13.2	70.29 70.20	6.29 6.32	10.93 10.84

[a] Crystallized from chloroform + petroleum ether (bp 40-60°). [b] Crystallized from chloroform. [c] Hygroscopic. [d] Measured in DMF.

For the proline derivative **7q**, the loss of CO preceeds the elimination of the aldimine, as evidenced by the presence of an [M-CO], but no [M-(RCH=NH)], fragment ion in its mass spectrum implying that $[M]^+$ suffers ring opening at the C(6)-O bond in this case. Both modes of heteroring opening are operative for the phenylglycine derivatives **7o,p** since their mass spectra exhibit peaks corresponding to both [M-(RCH=NH)] and [M-CO] ions.

The 1,2,4-oxadiazin-6-ones **7** are reduced readily with sodium borohydride at room temperature to the corresponding acyclic *N*-(arylhydroxamoyl)amino alcohols **11** (Scheme IV, Table III), presumably *via* the aldehyde **10**. Structure **11** is confirmed by elemental analysis and spectral data. In the pmr spectra, the methylene protons appear at δ 3.55-3.70 (2H, unresolved doublet), the OH and NH protons at around δ 5.2 (3H, broad, exchangeable). Their infrared spectra exhibit absorptions in the region 3350-3150 cm^{-1}, attributable to O-H and N-H bond stretching.

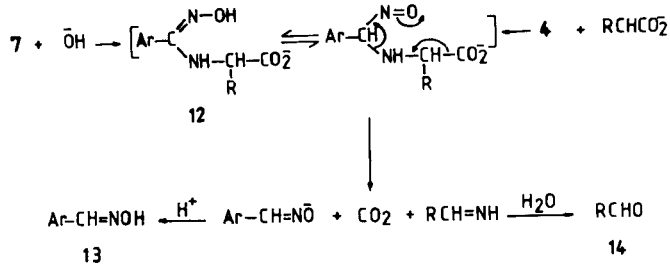
Scheme IV



The amino alcohol derivatives **11** are also accessible by direct interaction of nitrile oxides and α-amino alcohols. This lends further support to the assigned structure.

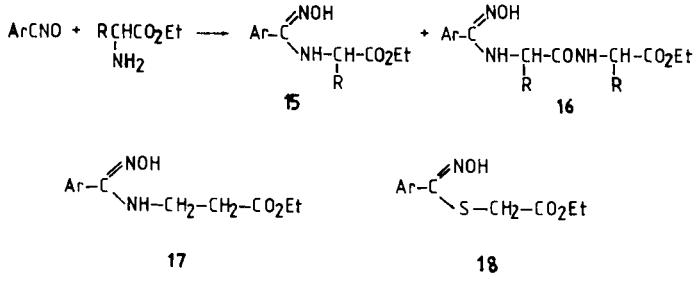
Facile ring opening of compounds **7** at the lactone site is also effected by base. Treatment of **7** with cold dilute alkali results in spontaneous evolution of carbon dioxide and leads to the formation of the aldoxime **13** (derived from nitrile oxide) together with the aldehyde **14** (derived from the amino acid residue). We believe that this reaction proceeds as postulated in (Scheme V), where **12** is an intermediate, since it has been found that both end products **13** and **14** are also obtained when nitrile oxides are reacted with amino acids at 0°. Thus, nitrile oxides repesent a new additional reagent to those [11] that can bring about oxidative decarboxylation of α-amino acids and ultimately lead to the next lower aldehyde drived thereof. Further study of this reaction is underway.

Scheme V



It is noteworthy that when the size of subsituent in the acyclic adduct **6** is small (R = H or CH_3), subsequent cyclization to **7** does not take place. Thus, glycine and alanine ethyl esters yield with nitrile oxides the acyclic addition products **15** and **16** (Scheme VI). Likewise, β-alanine and thioglycolic acid esters give the corresponding acyclic compounds **17** and **18**, respectively.

Scheme VI



EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 577 spectrometer. A Varian T-60 spectrometer was used for taking the pmr spectra. Mass spectra were obtained on a Varian CH-5 spectrometer by the direct inlet technique (70 eV). Microanalyses were performed at the Mikroanalytisches Labor Pascher (Bonn). Optical rotations were measured on a Pekin Elmer 141 Polarimeter.

Hydroxamoyl Chlorides.

These compounds were prepared according to previously published procedures [1].

3,5-Disubstituted-5*H*-1,2,4-oxadiazin-6(4*H*)-ones (**7**).

Triethyl amine (0.025 mole) in absolute ethanol (10 ml) was dropwise added to a stirred solution of the appropriate hydroxamoyl chloride (0.010 mole) and L-amino ester hydrochloride (0.012 mole) in absolute ethanol (40 ml) at −15°. The temperature of the reaction mixture was then allowed to rise slowly to room temperature and stirring was continued for 2 hours. The gelatinous precipitate of furoxan was removed by filtration, and the filtrate was concentrated *in vacuo* and then diluted with water (100 ml). In most cases, the product precipitated out as colorless solid, which was collected and crystallized from the appropriate solvent. If the product separated as oil, it was extracted with chloroform (3 × 20 ml). The combined organic extracts were dried and the solvent removed under reduced presure. The residue, which solidified upon trituration with petroleum ether, was finally crystallized.

N-(Arylhydroxamoyl)amino Alcohols (**11**).

(a) From **7** by Reduction.

To a stirred solution of **7** (0.01 mole) in methanol (40 ml) was added, in small portions, excess of sodium borohydride (0.04 mole) at room temperature. Stirring was continued for 30 minutes, the solvent was then removed under reduced pressure, water (50 ml) was added, and the precipitate was collected and crystallized from the appropriate solvent.

(b) From Hydroxamoyl Chlorides and Amino Alcohols.

An ethanolic solution (10 ml) of the amino alcohol [12] (0.012 mole) and triethyl amine (0.015 mole) was dropwise added to a stirred solution of the appropriate hydroxamoyl chloride (0.01 mole) in absolute ethanol (40 ml) at −15°. Stirring was continued for one hour at the temperature of the ice-bath and for another hour at room temperature. The mixture was then filtered, the filtrate was concentrated *in vacuo* and then diluted with water (100 ml). The product was collected by filtration, dried and crystallized.

Reaction of Hydroxamoyl Chlorides with α-Amino Acids.

A solution of the hydroxamoyl chloride (0.01 mole) in ethanol (30 ml) was dropwise added to a stirred solution of the appropriate amino acid (0.01 mole) in 10% aqueous sodium hydroxide (10 ml) at 0°. The mixture was stirred for 30 minutes and then filtered and extracted with ether (2 × 20 ml). The combined organic extracts were dried (magnesium sulfate) and the solvent evaporated to give the aldehyde **14**, which was identified from its ir and pmr spectra, and by conversion to its 2,4-dinitrophenylhydrazone. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether (3 × 20 ml). The residue left after evaporation of ether was the aldoxime **13**, which was identified from its mp and spectral data.

In a typical experiment, *p*-bromobenzhydroxamoyl chloride and phenyl glycine gave *p*-bromobenzaldoxime (60%) and benzaldehyde (50%).

Hydrolysis of **7**.

Aqueous 5% sodium hydroxide (5 ml) was added to a cooled (ice-bath) solution of **7o** (0.005 mole) in ethanol (20 ml). The mixture was stirred for 30 minutes and then concentrated *in vacuo*. It was then extracted with ether (2 × 10 ml). Evaporation of ether gave benzaldehyde (40%). The residue left after extraction was acidified with 10% HCl and extracted with ether (2 × 20 ml). Evaporation of ether gave *p*-chlorobenzaldoxime (50%).

N-Benzhydroxamoylglycine Ethyl Ester (**15**).

This compound was obtained from benzhydroxamoyl chloride and glycine ethyl ester hydrochloride following the procedure described above for the preparation of compounds **7**. The red gummy product thus obtained was chromatographed on preparative silica gel plates using chloroform-petroleum ether (3:2) as the eluent to give the title compound (20%), mp 109-110°; ms: m/e (%), 222 (47), 176 (2), 149 (53), 119 (69), 103 (69).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C,

59.19; H, 6.28; N, 12.58.

N-(p-Chlorobenzhydroxamoyl)alanylalanine Ethyl Ester (**16**).

This compound was obtained from *p*-chlorobenzhydroxamoyl chloride and L-alanine ethyl ester hydrochloride in 15% yield, mp 89-90°; ms: m/e (%), 343/341 (1), 326/324 (4), 227/225 (4), 199/197 (43), 155/153 (44).

Anal. Calcd. for $C_{15}H_{20}ClN_3O_4$: C, 52.71; H, 5.90; N, 12.29. Found: C, 52.50; H, 6.17; N, 12.14.

N-(m-Nitrobenzhydroxamoyl)-β-alanine Ethyl Ester (**17**).

This compound was prepared from *m*-nitrobenzhydroxamoyl chloride and β-alanine ethyl ester hydrochloride in a manner analogous to the preparation of compounds **7**. Crystallization from chloroform/petroleum ether gave the product (63%), mp 69-70°; ms: m/e (%), 281 (29), 264 (1), 235 (2), 194 (10), 164 (22), 149 (39), 116 (100).

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 50.83; H, 5.40; N, 14.86.

Ethyl *S-(p*-Chlorobenzhydroxamoyl)thioglycolate (**18**).

Triethyl amine (0.015 mole) in ether (10 ml) was dropwise added to a stirred solution of *p*-chlorobenzhydroxamoyl chloride (0.01 mole) and ethyl thioglycolate (0.01 mole) in ether (40 ml) at −15°. The mixture was left for one hour in the ice-bath and for another hour at room temperature. After washing with water (30 ml), the organic layer was dried and evaporated. The residue was crystallized from ether/petroleum ether to give the title compound in 73% yield, mp 79-80°; ms: m/e (%), 275/273 (26), 258/256 (22), 229/227 (4), 184/182 (24), 157/155 (62), 155/153 (100) 139/137 (59).

Anal. Calcd. for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.42; N, 5.12. Found: C, 48.38; H, 4.40; N, 5.14.

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