5-Amino-4,5-dihydroisoxazoles. Part II (1). Reactions of 5-Amino-3-aryl-4-methylene-4,5-dihydroisoxazoles with Nucleophiles

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Several 5-amino-3-aryl-4-methylene-4,5-dihydroisoxazoles were reacted with methoxide, benzenethiolate, benzenethiol, carboxylic acids and secondary amines. Addition and/or addition-elimination products were obtained. Reaction mechanisms are discussed.

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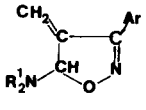
In the preceeding paper (Part I) (1) we described the preparation of 5-amino-3-aryl-4-aminomethyl-4,5-dihydroisoxazoles **1a-g** through base-catalyzed deamination of 5-amino-4-ammoniomethyl-3-aryl-4,5-dihydroisoxazoles.

As a part of our program concerning the reactivity of 5-amino-4-methylene-4,5-dihydroazoles (2) we now report the results we have obtained by reacting the above isoxazole derivatives with nucleophiles. According to their reaction mode, the nucleophiles employed in the present work can be divided in three groups: (i) anionic reagents (methoxide, benzenethiolate); (ii) acidic reagents (carboxylic acids, benzenethiol, methanol/hydrochloric acid); and (iii) secondary amines.



(**1a**): R^1_2N = morpholino; Ar = $C_6H_4NO_2$-4
(**1b**): R^1_2N = pyrrolidino; Ar = $C_6H_4NO_2$-4
(**1c**): R^1_2N = morpholino; Ar = C_6H_4Br-4
(**1d**): R^1_2N = morpholino; Ar = C_6H_4Cl-4
(**1e**): R^1_2N = morpholino; Ar = C_6H_3-Cl_2-2,6
(**1f**): R^1_2N = pyrrolidino; Ar = $C_6H_2(CH_3)_3$-2,4,6
(**1g**): R^1_2N = piperidino; Ar = $C_6H_3Cl_2$-2,6

Reactions with Methoxide and Benzenethiolate.

Compounds **1a-c** reacted slowly at room temperature with sodium methoxide in methanol solution, yielding a mixture of the 4-methoxymethyl-dihydroisoxazole derivatives **3a-c** and of the corresponding aromatized compounds **4a-b** (Scheme 1) (3). The products could be easily separated by column chromatography and were identified by analytical and ^{1}H-nmr criteria.

The *trans* configuration was assigned to compounds **3a-c** on the basis of the H_4-H_5 coupling constant (1-2 Hz) (4). The isolated 4,5-dihydroisoxazole derivative **3a** could be deaminated by reaction with sodium methoxide in methanol, thus correlating compounds **3a** and **4a**.

Compounds **1a-b** reacted with sodium benzenethiolate in ethanol affording mainly the 4-phenylthiomethyl-3-(4-nitrophenyl)isoxazole **4c**. In the crude reaction mixture from **1a**, a small amount of the *trans*-4,5-dihydroisoxazole derivative **3d** was identified both by tlc and ^{1}H-nmr. The identity of this compound was confirmed by its independent synthesis from 1-morpholino-3-phenylthiopropene and 4-nitrobenzohydroxamoyl chloride in the presence of triethylamine. On reaction with sodium hydroxide in

Table 1

Reactions of **1** with Secondary Amines

Starting Compound	Amine	Reaction Temperature °C	Reaction Time (hours)	Dihydroisoxazole (Yield %) (a)		Isoxazole (Yield %) (a)	
1a	pyrrolidine	25	1	**9a**	(100)		
1a	piperidine	25	100	**10a**	(70) (b)		
1a	morpholine	25	5			**7a**	(100) (c)
1c	pyrrolidine	25	5 (d)	**9b**	(55)	**7b**	(45)
1d	dimethylamine	30	75	**9c** (e), **10b**	(60)	**7c**	(40)
1d	pyrrolidine	25	1 (f)	**9d**	(85)	**7d**	(15)
1d	morpholine	50	100			**7e**	(100) (c)
1e	piperidine	50	100			**7f**	(100)
1f	dimethylamine	30	100 (g)			**7g**	(100)
1f	pyrrolidine	50	70			**7h**	(100)
1g	dimethylamine	30	100			**7i**	(100)
1g	pyrrolidine	25	2			**7j**	(100)

(a) Yields determined on the crude reaction mixture. Yields of isolated products in Tables 2 and 3. (b) By-products present. (c) Not isolated; identified by comparison with an authentical sample (1). (d) No change after 100 hours. (e) ^{1}H-nmr: δ H-5 = 5.15; J = 9 Hz. Isomerized to **10b** during isolation by column chromatography. (f) After 100 hours, ratio **9d**:**7d** = 2:1. (g) Conversion 70%.

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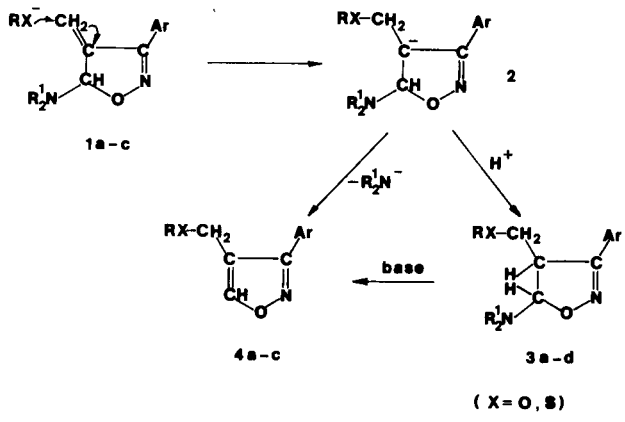
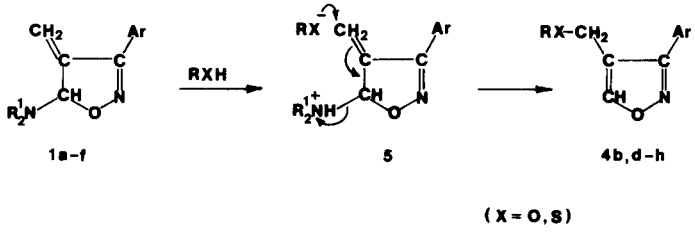


Scheme 1



Scheme 2

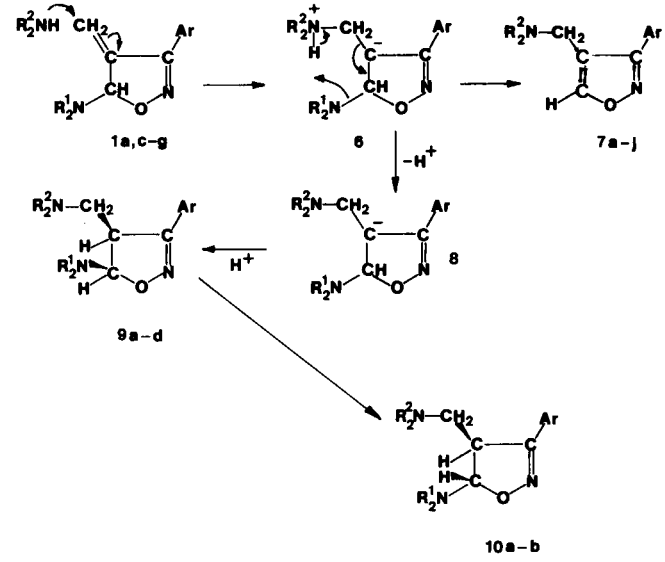
ethanol compound **3d** was deaminated to **4c**. Compounds **1e,f** failed to react under the above conditions both with methoxide and benzenethiolate.

As shown in Scheme 1, the above reactions can be explained through the formation of a carbanionic intermediate **2** (5), which can undergo elimination to the isoxazole derivative **4** or protonation from the solvent to **3**. Compounds **3** can be ruled out as the precursors of the isoxazoles **4** since their base-catalyzed deamination was found to be significantly slower than the formation of **4** from **1**.

Reactions with Methanol/Hydrochloric Acid, Benzenethiole and Carboxylic Acids.

These reactions are represented in Scheme 2. The addition of methanol to **1c** could also be obtained in acidic medium. By refluxing **1c** with methanol containing hydrochoric acid, compound **4c** was formed. Compound **1c** reacted also rapidly with an excess of benzenethiol at room temperature yielding **4d**.

Similarly, compounds **1a,b,d-f** were easily transformed by an excess of lower carboxylic acids into the corresponding 4-acyloxymethylisoxazoles **4e-h** in good yields. As indicated in the above reactions with acidic reagents, only isoxazole products were obtained. This agrees with the mechanism indicated in Scheme 2 in which the nucleophile adds to the double bond of the protonated substrate **5**. Owing to this protonation the elimination step is easy.



Scheme 3

Secondary Amine Addition.

Compounds **1a,c-g** were reacted with secondary amines by allowing the methylene derivative to react with an excess of the amine (both as the reactant and the solvent). In Table 1 all the pertinent data are reported. As indicated in Scheme 3, 4-aminomethyl-3-aryl-isoxazoles **7a-j** and/or 5-amino-4-aminomethyl-3-aryl-4,5-dihydroisoxazoles **9a-d** were obtained. These latter were formed always with the

Table 2

4,5-Dihydroisoxazoles **3**, **9** and **10**

Compound No.	RX or R^2_2N	R^1_2N	Ar	Recrystallization Solvent	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	^{1}H-Nmr (Deuteriochloroform) (a) δ H-4	δ H-5	J 4-5	Other Signals
3a	MeO	morpholino	$C_6H_4NO_2$-4	methanol	144-148	20	56.2	6.2	12.8	$C_{13}H_{14}N_2O_5$	56.0	6.0	13.1	3.6	5.20	2	3.33 (MeO)
3b	MeO	pyrrolidino	$C_6H_4NO_2$-4	methanol	143-147	48	58.8	6.3	13.6	$C_{13}H_{15}N_3O_4$	59.0	6.3	13.8	3.5	5.55	2	3.25 (MeO)
3c	MeO	morpholino	C_6H_4Br-4	*n*-pentane/ isopropyl ether	117-118	33	51.0	5.3	7.8	$C_{13}H_{16}BrNO_3$	50.7	5.4	7.9	3.5	5.27	~1	3.25 (MeO)
3d	PhS	morpholino	$C_6H_4NO_2$-4	ethanol	141	25	60.0	5.3	10.4	$C_{20}H_{21}N_3O_5S$	60.2	5.3	10.5	3.2	5.33	3	
9a	pyrrolidino	morpholino	$C_6H_4NO_2$-4	ethanol	143-145	55	60.3	7.0	15.3	$C_{15}H_{24}N_4O_4$	60.0	6.7	15.6	3.8	5.49	10	2.87, J = 5 (CH_2)
9b	pyrrolidino	morpholino	C_6H_4Br-4	*n*-pentane	120-122	35	54.5	6.1	10.3	$C_{19}H_{24}BrN_3O_3$	54.9	6.2	10.6	3.7	5.35	9.5	2.84 (CH_2)
9d	pyrrolidino	morpholino	C_6H_4Cl-4	*n*-pentane	113-114	60	61.4	6.8	11.7	$C_{19}H_{24}ClN_3O_3$	61.8	6.9	12.0	3.7	5.35	9.5	2.83 (CH_2)
10a	piperidino	morpholino	$C_6H_4NO_2$-4	ethanol	167-168	20	60.6	7.0	14.8	$C_{19}H_{26}N_4O_4$	61.0	7.0	15.0	3.7	5.42	2.5	
10b	Me_2N	morpholino	C_6H_4Cl-4	*n*-pentane	137-139	30	59.0	6.6	12.7	$C_{16}H_{22}ClN_3O_3$	59.4	6.9	13.0	3.6	5.32	~1	

(a) Only approximate values owing to overlapping with the amine signals.

less stable *cis* configuration. The *cis* configuration of products **9** was established on the basis of the H_4-H_5 coupling constant of 9.5-10 Hz (4) in the ^{1}H-nmr spectrum. In some cases, compounds **9** could be identified in the crude reaction mixture, but isomerization to the *trans* isomers **10** occurred during elaboration.

From the above results it can be seen that compounds **9** are not formed starting from substrates bearing bulky aryl residues **1e-g** or employing morpholine as the amine. By following the reaction of **1g** with pyrrolidine and of **1d** with morpholine by ^{1}H-nmr, the absence of the corresponding compounds **9**, even as labile intermediates, could be confirmed through the lack of the expected signals.

This result agrees with the following mechanistic view (Scheme 3): upon addition of the amine to **1**, a zwitterionic intermediate **6** is formed, which can afford compound **7** through amine elimination. However, in strongly basic medium (pyrrolidine or piperidine), compound **6** is extensively deprotonated to **8**, which can undergo elimination to **7** or protonation from the less hindered side to **9**. When the aryl group hinders the carbanionic centre, protonation is difficult and the formation of **7** is preferred.

The reactivity of compounds **1** with nucleophiles can be generally ascribed to the conjugation of the exocyclic double bond with the dihydroisoxazole ring and is dependent on the nature of the aryl group, through its general effect on the heterocyclic system. Accordingly, compound **1a** was found to react generally faster than **1c**. Compounds **1e-g** showed a lower reactivity, which can be ascribed to direct steric hindrance and to a reduced interaction of the aryl group with the heterocyclic system owing to conformational arguments (1).

EXPERIMENTAL

^{1}H-nmr spectra were recorded on Varian A-60 and 360-A spectrometers operating at 60 MHz (TMS as internal standard); column chromatography was run on silica gel (Merck) and for tlc silica gel (GF 254, Merck) was used with benzene (10-60%)-ethyl acetate as eluent. Melting points are uncorrected.

The starting compounds **1a-g** were prepared as previously described (1).

The physical, analytical and spectroscopic data for compounds **3**, **9**, **10**, and **4** and **7** are summarized in Tables 2 and 3, respectively.

Reaction of **1a-c** with Methoxide.

The substrate **1a-c** (2.5 mmoles) was suspended in methanol (10-20 ml.) and 1% sodium methoxide in methanol (2.5 mmoles) was added. The reaction mixture was stirred at room temperature until complete conversion of the starting material (tlc). The solution obtained was evaporated under reduced pressure, water was added and the product filtered with suction or extracted with diethyl ether. The crude reaction mixture was chromatographed on a silica gel column with benzene-ethyl acetate (3:7) as eluent. The products **3a-c** were separated and purified by recrystallization.

Reaction of **1a,b** with Benzenethiolate.

The starting compound **1a,b** (2 mmoles) was reacted with a solution in ethanol of benzenethiol (3 mmoles) which had been neutralized with sodium hydroxide. The reaction solution was stirred until a white precipitate separated (about 0.5 hour). The product was filtered and recrystallized yielding **4c**. On the residue obtained after evaporation of the mother liquor from **1a**, compound **3d** was identified by its ^{1}H-nmr spectrum and by tlc.

Synthesis of **3d**.

3-Phenylthiopropanal (6) (25 mmoles) was dissolved in benzene (20 ml.)

Table 3

Isoxazoles **4** and **2**

Compound No.	RX or R_3^1N	Ar	M.p. (°C) (b.p./torr)	Crystallization Solvent	Starting Compound	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	^{1}H-Nmr (Deuteriochloroform) δ H-5	δ CH_2	Other Signals
4a	MeO	$C_6H_4NO_2$-4	127-128	methanol	**1a**	30	56.5	4.3	12.0	$C_{11}H_{10}N_2O_4$	56.4	4.3	12.0	8.40	4.37	3.40 (MeO)
					1b	20										
					3a	60										
4b	MeO	C_6H_4Br-4	64-66	*n*-pentane/ isopropyl ether	**1c**	13	49.5	3.9	5.3	$C_{11}H_{10}BrNO_3$	49.3	3.75	5.2	8.50	4.37	3.40 (MeO)
					1c (a)	50										
4c	PhS	$C_6H_4NO_2$-4	89-91	ethanol	**1a**	65	61.9	4.0	8.9	$C_{16}H_{12}N_2O_2S$	61.6	3.9	9.0	8.80	4.07	
					1b	60										
					3d	30										
4d	PhS	C_6H_4Br-4	42-44 (200-205/0.5)	(b)	**1c**	80	55.2	3.3	4.0	$C_{16}H_{12}BrNOS$	55.5	3.5	4.1	8.12	3.90	
4e	HCOO	C_6H_4Cl-4	84	ethanol	**1d**	67	55.4	3.5	6.1	$C_{11}H_8ClNO_3$	55.6	3.4	5.9	8.08	5.12	8.55 (HCO)
4f	MeCOO	$C_6H_4NO_2$-4	133-135	methanol	**1a**	51	55.2	3.8	10.7	$C_{12}H_{10}N_2O_5$	55.0	3.9	10.7	7.20	5.10	2.10 (Ac)
					1b	40										
4g	MeCOO	$C_6H_3Cl_2$-2,6	64-67	ethanol	**1e**	36	50.4	3.2	4.9	$C_{12}H_9Cl_2NO_3$	50.4	3.2	4.9	8.82	4.96	1.97 (Ac)
4h	EtCOO	$C_6H_2Me_3$-2,4,6	oil (c)		**1f**	35	70.2	6.7	5.2	$C_{16}H_{19}NO_3$	70.3	7.0	5.1	8.58	4.75	1.05, 2.06 (Et)
7b	pyrrolidino	C_6H_4Br-4	114-117	isopropyl ether	**1c**	10	53.0	4.3	9.7	$C_{13}H_{13}BrN_2O$	53.3	4.5	9.6	8.38	3.37	
7c	Me_2N	C_6H_4Cl-4	(135/0.3)		**1d**	25	61.2	5.4	12.2	$C_{12}H_{13}ClN_2O$	60.9	5.6	11.9	8.42	3.31	
7d	pyrrolidino	C_6H_4Cl-4	50-51 (170-180/0.3)	(b)	**1d**	10	63.8	5.5	10.6	$C_{14}H_{15}ClN_2O$	64.0	5.8	10.7	8.35	3.50	
7f	piperidino	$C_6H_3Cl_2$-2,6	86-88	cyclohexane	**1e**	65	57.6	5.4	8.7	$C_{15}H_{16}Cl_2N_2O$	57.9	5.2	9.0	8.58	3.27	
7g	Me_2N	$C_6H_2Me_3$-2,4,6	(130/0.3)		**1f**	30	74.1	7.9	11.4	$C_{15}H_{20}N_2O$	73.8	8.3	11.5	8.49	3.05	
7h	pyrrolidino	$C_6H_2Me_3$-2,4,6	(150/0.3)		**1f**	80	75.6	8.5	10.3	$C_{17}H_{22}N_2O$	75.5	8.2	10.4	8.30	3.00	
7i	Me_2N	$C_6H_3Cl_2$-2,6	57-58	(b)	**1g**	60	53.5	4.5	10.5	$C_{12}H_{12}Cl_2N_2O$	53.2	4.5	10.4	8.57	3.19	
7j	pyrrolidino	$C_6H_3Cl_2$-2,6	82-83	*n*-pentane/ isopropyl ether	**1g**	70	56.9	4.8	9.6	$C_{14}H_{14}Cl_2O$	56.6	4.8	9.5	8.53	3.35	

(a) Reaction with methanol/hydrochloric acid. (b) Pure product obtained by distillation. (c) Purified by column chromatography.

and anhydrous sodium sulfate was added (50 mmoles). Under stirring, morpholine (27 mmoles) was dropped in and stirring was continued for 3 hours. The solution was evaporated and distilled in a bulb tube yielding a somewhat impure 1-morpholino-3-phenylthiopropene (20 mmoles). The enamine (3 mmoles) was reacted with a benzene solution of 4-nitrobenzonitrile oxide (3 mmoles) obtained by treating with sodium hydroxide a solution of 4-nitrobenzohydroxamoyl chloride (3.3 mmoles) in chloroform (10 ml.) and separating and drying over sodium sulfate the organic layer. After 5 hours the reaction solution was evaporated to dryness and the residue crystallized yielding **3d**.

Reaction of **3d** with Sodium Hydroxide/Ethanol.

Compound **3d** (1 mmole) was reacted with 1% sodium hydroxide in ethanol (10 ml.). The reaction mixture was stirred at 40° until complete conversion of **3d** (tlc). The reaction mixture was evaporated, taken up with water and the product **4c** filtered and recrystallized.

Reaction of **3a** with Sodium Methoxide.

The dihydroisoxazole **3a** (0.1 mmole) was suspended in 1% sodium methoxide in methanol (5 ml.). The reaction solution was kept at 50° for 24 hours. The product **4a** was identified by comparison with an authentical sample (tlc).

Reaction of **1c** with Methanol/Hydrochloric Acid.

Compound **1c** (1 mmole) was dissolved in methanol and to the solution 35% hydrochloric acid (1.5 mmoles) was dropped in. The reaction mixture was refluxed for 3 hours and evaporated. The residue was partitioned between water and ethyl ether and the ethereal layer was evaporated. The product **4b** was identified by comparison with an authentical sample (tlc and ^{1}H-nmr).

Reaction of **1c** with Benzenethiol.

Compound **1c** (1 mmole) was reacted with benzenethiol (3 ml.) at room temperature. After 2 hours the reaction suspension was evaporated under reduced pressure, water was added, the product was extracted with ether and the organic layer was washed with 5% sodium hydroxide and with water until neutral. After evaporation the residue was chromatographed on silica gel with benzene as eluent. The fractions containing the product were evaporated and the residue distilled in a bulb tube yielding the pure **4d**. The viscous oil solidified slowly.

Reactions of **1a,b,d-f** with Carboxylic Acids.

The methylene substrate (2 mmoles) was dissolved in pure formic, acetic or propionic acid (5 ml.) and reacted at room temperature or at 40° until complete reaction (tlc). The reaction mixture was evaporated and the residue taken up with water and ethyl ether. The organic layer was separated, dried over sodium sulfate and evaporated. The residue was crystallized yielding **4e-g**. Compound **4h** solidified only at very low temperature.

Reactions of **1a,c-g** with Secondary Amines.

The 4-methylene-4,5-dihydroisoxazole (**1a,c-g**; 2 mmoles) was reacted with the secondary amine (50 mmoles) at the temperature and for the time indicated in Table 1. Thereafter the excess amine was evaporated under reduced pressure and the crude residue was analyzed by tlc and ^{1}H-nmr to determine its composition. The products were isolated as follows:

(a) Compounds **7a** and **7e** were recrystallized and the identity was confirmed by comparison with an authentical sample (1).

(b) Products **7f, 7j** and **9a** were recrystallized from the solvent indicated in Tables 1 and 2.

(c) The crude products **7g, 7h** and **7i** were purified by vacuum distillation in a bulb tube and in case the distillate was brought to crystallization by cooling to −20° and scratching.

(d) Compound **10a** was taken up with *n*-pentane yielding a highly impure solid which was chromatographed on a silica gel column with diethyl ether as eluent.

(e) The crude mixture of **7b** and **9b** was diluted with diisopropyl ether yielding a solid product containing both compounds which was isolated by filtration. This solid was recystallized from diisopropyl ether yielding essentially pure **9b** which was recrystallized once more from *n*-pentane. The mother liquor from the first crystallization was evaporated to dryness and then recrystallized from diisopropyl ether affording pure **7b**.

(f) The crude mixture containing **7c** and **9c** was chromatographed on a silica gel column using chloroform as the eluent. The first fraction containing **7c** was evaporated and distilled in a bulb tube at reduced pressure. The second fraction contained **10b** and was evaporated and recrystallized.

(g) The mixture of the crude **7d** and **9d** was dissolved in *n*-pentane and the solution was chilled to −50°. The oily precipitate solidified slowly. The solid was filtered and recrystallized yielding pure **9d**. The mother liquor of the first precipitation and of the recrystallization was evaporated and the residue distilled in a bulb tube yielding **7d**.

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(3) A similar result was obtained by reacting under the same conditions the 4-(*N*-methylmorpholinio)-5-morpholino-3-(4-nitrophenyl)-4,5-dihydroisoxazole iodide (1): **1a** was formed as the main product accompanied by **2a** and **3a**, the amount of which was increased by prolonging the reaction time.

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(5) For the sake of simplicity the resonance possibilities of this intermediate are not considered in Scheme 5.

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