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Synthesis of 2,3-Disubstituted-1,3-oxazolidines

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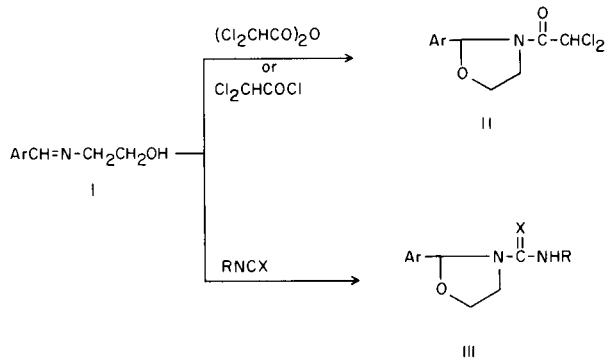
A series of 2-aryl-3-alkyl or aryl carbamoyl- and thiocarbamoyl-1,3-oxazolidines was prepared by the reactions of alkyl and aryl isocyanates and isothiocyanates with *N*-(2-hydroxyethyl)-benzalamines. The nuclear magnetic resonance spectra of these compounds are discussed.

The reactions of Schiff bases derived from ethanolamine and aromatic aldehydes (I) with dichloroacetic anhydride (1) and dichloroacetyl chloride (2) have been reported to yield the corresponding 3-haloacetyl-1,3-oxazolidines (II).



The unexpected results of these studies prompted us to investigate the reactions of I with isocyanates and isothiocyanates.

We have found that when a *N*-(2-hydroxyethyl)-benzalamine (I) was allowed to react with an alkyl or aryl isocyanate in boiling ether solution in the presence of pyridine, the product obtained was the corresponding 2-aryl-3-substituted carbamoyl-1,3-oxazolidine (III, X=O). The same product was obtained when the reaction was conducted without a catalyst. The infrared spectra of these compounds have absorption maxima at 2.95-3.05 μ (NH), 6.05-6.10 μ (C=O) and 6.45-6.55 μ (NH). If the product were the carbamate of I, ArCH=N-$CH_2CH_2O_2CNHR$, the carbonyl absorption band would have been at 5.8 μ (3).

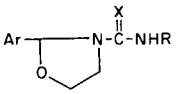
The reactions of I with alkyl and aryl isothiocyanates in boiling ethanol solution in the presence or absence of pyridine yielded the corresponding 2-aryl-3-substituted thiocarbamoyl-1,3-oxazolidines (III, X=S). These compounds exhibit infrared absorption bands at 3.0-3.1 μ, 6.4-6.5 μ (NH) and 7.5 μ (C=S).

The physical properties of III are summarized in Table I. Compound **1** was previously reported by Henry and Dehn (4) who prepared it by the reaction of 2-phenyl-1,3-oxazolidine with phenyl isocyanate.

In order to confirm our results, we have examined the nuclear magnetic resonance spectra of *N*-(2-hydroxyethyl)-4-chlorobenzalamine (I, Ar = 4-ClC_6H_4-) and of its reaction products with phenyl isocyanate (Compound **9**) and phenyl isothiocyanate (Compound **13**). The spectra were observed at 60 MHz in deuteriochloroform solution using tetramethylsilane as an internal standard.

One of the most important features of the spectrum of *N*-(2-hydroxyethyl)-4-chlorobenzalamine is the observation of the -CH=N- resonance at 8.16 ppm which is consistent with the chemical shift reported for this grouping (5,6,7). This assignment is supported by the C=N absorption at 6.1 μ in its infrared spectrum. The

TABLE I



Compound No.	Ar	R	X	M.P. (a) °C	Yield (b) %	Molecular Formula	Analytical Data: Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found	Nitrogen, % Calc.	Nitrogen, % Found
1	C_6H_5	C_6H_5	O	111-113	77	$C_{16}H_{16}N_2O_2$	71.62	71.50	6.01	5.96	10.44	10.27
2	2-Cl-C_6H_4	CH_3	O	120-123	67	$C_{11}H_{13}ClN_2O_2$	54.89	54.62	5.44	5.27	11.64	11.61
3	2-Cl-C_6H_4	4-Cl-C_6H_4	O	150-152	72	$C_{16}H_{14}Cl_2N_2O_2$	56.99	57.09	4.18	3.87	8.31	8.40
4	2-Cl-C_6H_4	CH_3	S	179.5-180	68	$C_{11}H_{13}ClN_2OS$					10.91	11.00
5	2-Cl-C_6H_4	C_2H_5	S	136-138	51	$C_{12}H_{15}ClN_2OS$	53.23	53.40	5.58	5.44	10.35	10.11
6	2-Cl-C_6H_4	allyl	S	108-110	42	$C_{13}H_{15}ClN_2OS$					9.90	10.04
7	2-Cl-C_6H_4	cyclohexyl	S	122-124	16	$C_{16}H_{21}ClN_2OS$					8.62	8.90
8	4-Cl-C_6H_4	CH_3	O	118-120	21	$C_{11}H_{13}ClN_2O_2$	54.89	54.72	5.44	5.27	11.64	11.64
9	4-Cl-C_6H_4	C_6H_5	O	126-129	83	$C_{16}H_{15}ClN_2O_2$	11.7 (c)	11.7 (c)			9.25	9.30
10	4-Cl-C_6H_4	3,4-$Cl_2C_6H_3$	O	93-95	71	$C_{16}H_{13}Cl_3N_2O_2$	28.6 (c)	28.4 (c)			7.54	7.52
11	4-Cl-C_6H_4	C_2H_5	S	136-138	67	$C_{12}H_{15}ClN_2OS$	53.23	53.23	5.58	5.37	10.35	10.35
12	4-Cl-C_6H_4	allyl	S	96-98	94	$C_{13}H_{15}ClN_2OS$	55.21	54.98	5.35	5.55	9.91	9.97
13	4-Cl-C_6H_4	C_6H_5	S	129-131	86	$C_{16}H_{15}ClN_2OS$	60.27	60.06	4.74	4.87	8.79	8.61
14	2,4-$Cl_2C_6H_3$	C_6H_5	O	155-157	43	$C_{16}H_{14}Cl_2N_2O_2$	20.9 (c)	20.7 (c)			8.28	8.31
15	2,4-$Cl_2C_6H_3$	2-Cl-C_6H_4	O	108-110	40	$C_{16}H_{13}Cl_3N_2O_2$	28.5 (c)	28.3 (c)			7.52	7.58
16	2,4-$Cl_2C_6H_3$	4-Cl-C_6H_4	O	123-126	80	$C_{16}H_{13}Cl_3N_2O_2$	28.5 (c)	28.6 (c)			7.52	7.47
17	2,4-$Cl_2C_6H_3$	3-CH_3-C_6H_4	O	166-168	90	$C_{17}H_{16}Cl_2N_2O_2$	20.1 (c)	20.0 (c)			7.95	8.04

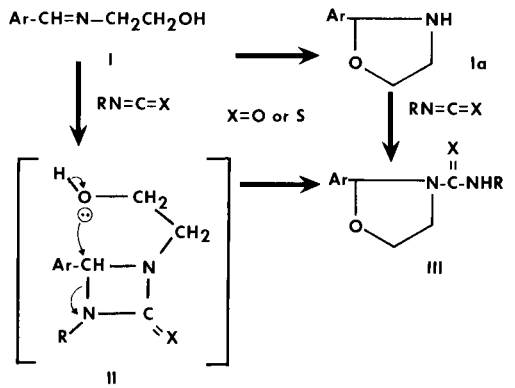
18	2,6-$Cl_2C_6H_3$	CH_3	O	149-152	59	$C_{11}H_{12}Cl_2N_2O_2$	48.02	47.88	4.40	4.46	10.18	10.15
19	2,6-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3$	O	145-148	69	$C_{16}H_{12}Cl_4N_2O_2$	47.32	47.23	2.98	2.98	6.90	6.92
20	2,6-$Cl_2C_6H_3$	CH_3	S	196-198	69	$C_{11}H_{12}Cl_2N_2OS$	45.37	45.40	4.15	4.20	9.62	9.79
21	2,6-$Cl_2C_6H_3$	C_2H_5	S	185-186	56	$C_{12}H_{14}Cl_2N_2OS$	47.22	47.24	4.62	4.60	9.18	7.17
22	2,6-$Cl_2C_6H_3$	2-ClC_6H_4	S	149-152	46	$C_{16}H_{13}Cl_3N_2OS$	49.56	49.32	3.38	3.28	7.23	7.17
23	3,4-$Cl_2C_6H_3$	2-$CH_3C_6H_4$	O	131-134	92	$C_{17}H_{16}Cl_2N_2O_2$	20.2 (c)	20.0 (c)			7.98	8.00
24	3,4-$Cl_2C_6H_3$	CH_3	S	167-169	74	$C_{11}H_{12}Cl_2N_2OS$	45.47	45.32	4.15	4.30	9.62	9.56
25	3,4-$Cl_2C_6H_3$	C_2H_5	S	161-163	59	$C_{12}H_{14}Cl_2N_2OS$	47.22	47.33	4.62	4.74	9.18	9.09
26	3,4-$Cl_2C_6H_3$	allyl	S	105-107	55	$C_{13}H_{14}Cl_2N_2OS$	49.22	49.13	4.45	4.37	8.83	8.82
27	3,4-$Cl_2C_6H_3$	cyclohexyl	S	122-124	56	$C_{16}H_{20}Cl_2N_2OS$	53.48	53.63	5.61	5.54	8.92(d)	8.94 (d)
28	3,4-$Cl_2C_6H_3$	2-ClC_6H_4	S	126-127	53	$C_{16}H_{13}Cl_3N_2OS$	49.50	49.37	3.38	3.30	7.23	7.24
29	3-$NO_2C_6H_4$	CH_3	O	156-158	71	$C_{11}H_{13}N_3O_4$	52.59	52.49	5.22	5.08	16.73	16.86
30	3-$NO_2C_6H_4$	C_6H_5	O	129-131	91	$C_{16}H_{15}N_3O_4$	61.34	61.31	4.83	4.74	13.41	13.39
31	3-$NO_2C_6H_4$	2-ClC_6H_5	O	108-110	87	$C_{16}H_{14}ClN_3O_4$	55.26	55.28	4.06	3.96	12.08	12.01
32	3-$NO_2C_6H_4$	CH_3	S	190-191	94	$C_{11}H_{13}N_3O_3S$	49.43	49.50	4.90	5.20	15.72	8.12
33	4-$CH_3OC_6H_4$	4-ClC_6H_4	O	125-127	64	$C_{17}H_{17}ClN_2O_3$	61.35	61.07	5.15	4.97	8.42	8.12
34	2,5-$(CH_3O)_2C_6H_3$	CH_3	S	139-142	35	$C_{13}H_{18}N_2O_3S$	55.30	55.32	6.42	6.34	9.92	10.11
35	3,4-$(CH_3O)_2C_6H_3$	CH_3	O	70-72	52	$C_{13}H_{18}N_2O_4$	61.89	61.70	7.19	7.23	5.55	5.30
36	3,4-$(CH_3O)_2C_6H_3$	4-ClC_6H_4	O	157-159	20	$C_{18}H_{19}ClN_2O_4$	59.57	59.85	5.28	5.33	7.72	7.81
37	3,4-$(CH_3O)_2C_6H_3$	3,4-$Cl_2C_6H_3$	O	135-137	25	$C_{18}H_{18}Cl_2N_2O_4$	54.42	54.20	4.56	4.31	7.05	7.06
38	3,4-$(CH_2O_2)C_6H_3$	C_6H_5	O	145-147	46	$C_{17}H_{16}N_2O_4$	65.38	65.36	5.16	5.17	8.97	8.89
39	3-Pyridyl	C_6H_5	O	130-131	80	$C_{15}H_{15}N_3O_2$	66.90	66.96	5.61	5.69	15.60	15.64
40	3-Pyridyl	CH_3	S	180-182	82	$C_{10}H_{13}N_3OS$	53.79	53.92	5.87	6.08	18.82	18.77
41	3-Pyridyl	allyl	S	113-115	54	$C_{12}H_{15}N_3OS$	57.80	57.64	6.06	6.09	16.85	17.00
42	3-Pyridyl	cyclohexyl	S	149-150	68	$C_{15}H_{21}N_3OS$	61.82	61.90	7.26	7.56	14.42	14.58
43	3-Pyridyl	C_6H_5	S	148-149	62	$C_{15}H_{15}N_3OS$	63.13	63.10	5.34	5.30	14.73	14.80

(a) Melting points are for analytical samples (b) Yields are for once or twice recrystallized material. (c) Chlorine analysis. (d) Sulfur analysis.

AA'BB' pattern arising from the *p*-disubstituted aromatic ring protons in this compound are quite similar to the spectrum of *p*-chlorobenzaldehyde (8). The chemical shift of AA' protons is 7.59 ppm, while that of the BB' protons is 7.24 ppm. This is compatible with the Schiff base structure since oxazolidine formation would obviate the paramagnetic effect of the C=N linkage, thereby shifting the AA' protons to higher field. The >C=N-CH_2CH_2OH grouping gives rise to a broad complex absorption at 3.5-4.0 ppm with one of the five protons in this region being readily exchanged with deuterium oxide.

The ^1H nmr spectrum of Compound **9** (III, X = O, Ar = 4-ClC_6H_4-, R = C_6H_5) showed the absence of the -CH=N- grouping at 8.16 ppm, a change in the aromatic AA'BB' pattern and no expected paramagnetic effect on the -CH_2O- chemical shift due to carbamate formation. The aromatic region due to nine protons at 6.9-7.35 ppm did not have the symmetrical pattern of the starting material, indicating a high field shift due to the saturation of the C,N double bond because of oxazolidine ring formation. A single proton resonance occurred at 6.14 ppm, and a slightly broadened NH absorption was noted at 6.63 ppm. In the 3.4-4.15 ppm region, 4 protons due to -N(-)-CH_2CH_2O- were observed. These data are compatible with the structure of 2-(4-chlorophenyl)-3-phenylcarbamoyl-1,3-oxazolidine rather than the phenyl carbamate of the Schiff base.

The ^1H nmr spectrum of Compound **13** (III, X = S, Ar = 4-ClC_6H_4, R = C_6H_5) was similar to that of Compound **9**. The aromatic region due to nine protons and the NH proton appeared at 7.0-7.5 ppm and had the same pattern as Compound **9**. Changing to DMSO-D_6 solvent caused the NH proton to shift to lower field, 9.38 ppm. The -N(-)-CH_2-CH_2-O- protons appeared as a complex 4 proton absorption at 3.7-4.2 ppm, while the methine proton of the 1,3-oxazolidine ring appeared as a single resonance at 6.50 ppm.



Formation of 2,3-disubstituted-1,3-oxazolidines (III) by the reactions of *N*-(2-hydroxyethyl)benzalamines (I) with isocyanates and isothiocyanates could proceed by two possible mechanisms. Cyclization of I to the oxazolidine I_a prior to reaction with the isocyanate or isothiocyanate would yield III. Alternatively, 1,2-cycloaddition of the isocyanate or isothiocyanate to the C,N double bond of I (9) would yield the intermediate II which can be attacked by the hydroxyl function, suitably disposed for oxazolidine ring formation to give III.

EXPERIMENTAL

The ^1H nmr spectra were obtained at 60 MHz in deuteriochloroform solution using a Varian Model A-60 N.M.R. Spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 137 Spectrometer. All melting points were obtained using a MelTemp capillary melting point apparatus.

N-(2-Hydroxyethyl)benzalamines were prepared according to published procedures (10, 11).

2-Aryl-3-Substituted Carbamoyl-1,3-Oxazolidines.

To a well-stirred boiling ether solution of a *N*-(2-hydroxyethyl)-benzalamine (0.10 mole) containing 1 ml. of pyridine (optional), an aryl or alkyl isocyanate (0.10 mole) was added dropwise. Boiling under reflux was continued for 4-6 hours. The solid products usually separated on cooling or were obtained by evaporation of the solvent. These products were recrystallized from ethanol or methanol.

2-Aryl-3-Substituted Thocarbamoyl-1,3-Oxazolidines.

A solution of 80 ml. ethanol, a *N*-(2-hydroxyethyl)benzalamine (0.10 mole), an alkyl or aryl isothiocyanate (0.10 mole) and 1 ml. of pyridine (optional) was boiled under reflux for 3-6 hours. The solid products separated on cooling and were recrystallized from ethanol.

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