Synthesis of 2-(α-Hydroxyalkyl)-1,3-heterocyclic Alcohols and Aryl Carbamates

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Several *N*-(substituted phenyl)carbamoyloxylalkyl-1,3-heterocycles of the structure **3** were prepared from their respective α-hydroxyalkyl-1,3-heterocyclic alcohols **1**. Efficient syntheses of the prerequisite novel 1,3-heterocyclic alcohols, such as 2-(α-hydroxyalkyl)-2-oxazolines, -5,6-dihydro-1*H*-1,3-oxazines, -1,4,5,6-tetrahydropyrimidines, -imidazolines, and 4,5,6,7-tetrahydro-1*H*-1,3-diazepines were developed. Stannous octoate was found to effectively catalyze the formation of the carbamate **3** from heterocyclic alcohol **1** and arylisocyanate **2**.

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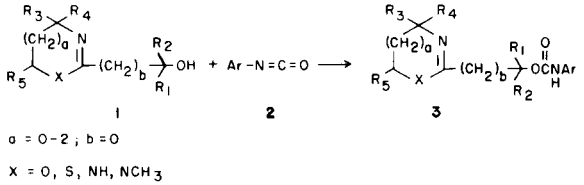
Several *N*-(substituted phenyl)carbamoyloxyalkyl-1,3-heterocycles **3** were found by us to have useful activity against certain fungicidal pathogens. The most obvious route for the preparation of **3** is from 1,3-heterocyclic alcohols **1** (Scheme I). Wherein the synthesis of carbamates **3** followed standard methods, the syntheses of the starting 1,3-heterocyclic alcohols **1** required developing new procedures.

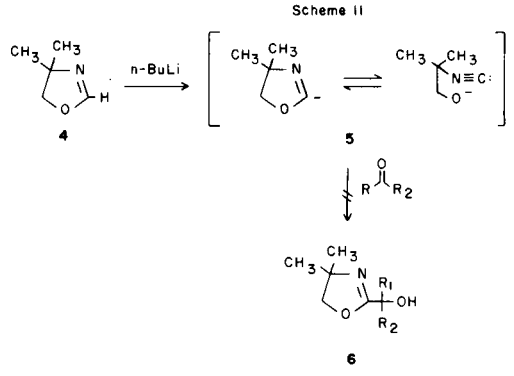
Scheme I



Most previously reported examples of heterocyclic alcohols such as **1** are of the type where b ≥ 1 [2-4,7]. Although, there are literature reported examples where b = 0, such as 2-(α-hydroxyalkyl)-1,3-heterocycles, they are primarily diazo compounds (a = 0-2, X = N), for example imidazolines, 1,4,5,6-tetrahydropyrimidines, and 4,5,6,7-1*H*-diazapines [5-6]. This laboratory was particularly interested in the synthesis of 2-(α-hydroxyalkyl)-2-oxazolines **1** (X = O, b = a = o) and homologous oxazines (b = o, a = 1). The only example of a direct synthesis [4c] of 2-(α-hydroxyalkyl)-2-oxazolines was reported by Levy and Litt [4b] who obtained in low yields (17%) the desired material by thermal condensation of an α-hydroxycarboxylic acid with ethanolamine at 280°.

One method considered as a potential general route to 2-oxazolines **6** or **1** (a = b = o, X = O) involved hydroxyalkylation of 2-lithio-4,4-dimethyl-2-oxazoline (**5**) which has previously been proposed as an intermediate by Meyers [8a] (Scheme II). A similar intermediate, obtained by addition of lithiomethylisonitriles to aromatic aldehydes, was proposed by Schöllkopf [9a,b] and Saegusa [9c]. The starting material, 4,4-dimethyl-2-oxazoline (**4**) was prepared in 80% yield [8b], but the inability to isolate cleanly carbonyl addition products **6** precluded the use of **4** as an intermediate in a general synthesis of 2-(α-hydroxyalkyl)-2-oxazolines **6**.

Scheme II



We now report our results in preparing in one step and in good yields some heretofore unreported 2-(α-hydroxyalkyl)-2-oxazolines **6** and other 2-(α-hydroxyalkyl)-1,3-heterocycles by thermal condensation of the appropriate α-hydroxy carboxylic acid or ester with an aminoalcohol [10]. In addition, results in preparing still other 2-(α-hydroxyalkyl)-1,3-heterocycles by different methods will be discussed.

Results and Discussion.

Initial attempts to effect the thermal condensation of α-hydroxy carboxylic acid or ester **7** with 2-amino-2-methyl-1-propanol **8** (Scheme III) failed when toluene (bp 111°) was used as solvent [11]. It was determined that although

Scheme III

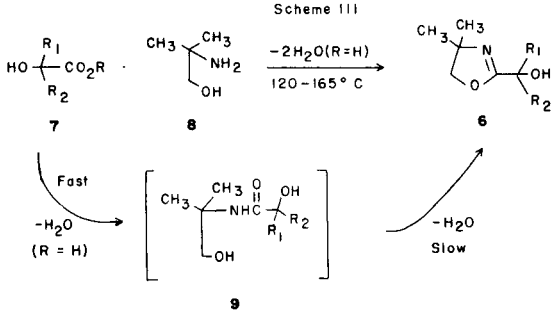
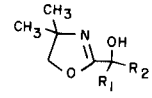


Table I

2-(α-Hydroxyalkyl)-2-oxazolines **6**

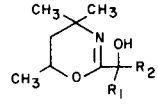


Compound No.	R_1	R_2	Method [a] [d]	Yield, %	Bp, °C (torr)
17	CH_3-	CH_3-	A (B)	59 (64)	82 (20)
18	CH_3-	H	C	70	100 (20)
19	H	H	B	60	105 (20)
20	H	n-C_8H_{17}	B	67	115 (20)
21	-$(CH_2)_6$-		B	23	93 (0.25)
22	Ph	H	A [b]	~83 [c]	—
23	CH_3CH_2-	H	C	70	105 (25)
24	CH_3CH_2-	CH_3-	B	12	170 (25)
25	n-C_3H_7-	H	A	53	150 (20)
26	n-C_4H_9-	H	B	37	103 (0.5)
27	CH_3	CH_2=CH-	A	40	170 (15)
28	Ph	CH_2=CH-CH_2-	D	~83 [c]	—
29	Ph	CH_3-C≡C-	D	~82 [c]	—

[a] Isolated yields unless otherwise noted. All entries were satisfactorily characterized as their carbamates (see Tables IV-VI). [b] Ethyl mandelate was used as starting material since we found that mandelic acid yielded only the oxidative decarboxylation product benzaldehyde. [c] Used as crude material in the next step. [d] 2-(2-Hydroxyprop-2-yl)-thiazoline was prepared in 15% yield using method A: bp, °C (torr); 123-125° (20).

Table II

2-(α-Hydroxyalkyl)-1,3-oxazines **12**



Compound No.	R_1	R_3	Method	Yield, %	Bp, °C (torr)
14	H	H	E (F)	~16 (57) [a]	—
30	CH_3	CH_3	E	26	43 (0.5)

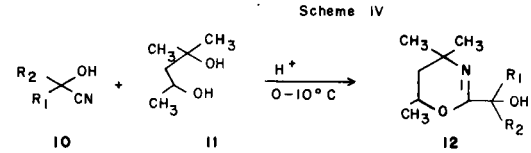
[a] Used as crude material.

the reaction had stopped (or proceeded slowly) at the amide stage [4a], it would proceed at a moderate rate if the reaction vessel was maintained within the 120-165° range. The 2-oxazoline **6** distilled as it formed as a clear viscous oil. In some cases distillation was not attempted, rather the reaction was monitored by gc until complete (Table I).

Synthesis of 2-oxazolines **6** *via* intermediate *N*-(2-hydroxyalkyl)amide **9** requires elimination of one equivalent of water. To facilitate this elimination, a Lewis acid catalyst may be employed. However, to reduce the potential for side reactions involving the α-hydroxy moiety and because of the known ability of acidic catalytst to enhance polymerization of 2-oxazolines [7], highly acidic catalysts were avoided. Interestingly, we found stannous octoate or oleate and *p*-toluenesulfonic acid to be effective in catalyzing the cyclization of the amide **9** to **6** [18,19] (Experimental, Method C).

The homologous compounds, 2-(α-hydroxyalkyl)-5,6-dihydro-1*H*-1,3-oxazines **12**, were prepared using the Pinner reaction procedure utilized by Meyers [12] to synthesize the 2-alkyl derivatives of **12**. In our case, in order to prepare **12** (Scheme IV), the cyanohydrin **10** was used as starting material, yielding inefficiently (*ca.* 30%) the desired oxazine. The only previously reported synthesis of

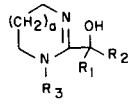
Scheme IV



10 11 12

Table III

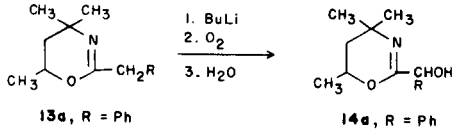
2-(α-Hydroxyalkyl)-1,3-diazines



Compound No.	R_1	R_2	R_3	a	Method	Yield, %	Bp, °C (torr)
15	H	H	CH_3	0	B	54	99 (0.4)
16	Ph	H	H	2	G	34	129 (mp)

α-hydroxyoxazines was by Wasserman [13a] who was able to lithiate 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1*H*-1,3-oxazine (**13a**) forming the α-carbanion that underwent reaction with molecular oxygen to give 2-(α-hydroxymethylphenyl)-5,6-dihydro-1*H*-1,3-oxazine (**14a**) (Scheme V). This oxygenation procedure [13] using the 2-methyl analog **13b** yielded 2-(α-hydroxymethylphenyl)-5,6-dihydro-1*H*-1,3-oxazine (**14b**) in 57% yield (Table II). However, oxygenation of 2-benzyl-4,4-dimethyl-2-oxazoline gave only the autoxidation product 2-benzoyl-4,4-dimethyl-2-oxazoline. This observation was also reported recently by two other research groups [14,15,16].

Scheme V



13a, R = Ph
13b, R = H

14a, R = Ph
14b, R = H

Imidazoline **15** (Table III) was prepared using the thermal condensation (method B) in good yield (54%) while 2-(α-hydroxymethylphenyl)-1,4,5,6-tetrahydro-1,3-diazepine (**16**) could only be prepared in low yield (34%) by condensing 1,4-diaminobutane with ethyl mandelimidate hydrochloride [5,6].

All of the *N*-(substituted-phenyl)carbamates **3** were obtained by reaction of rigorously dried heterocyclic alcohol **1** with the *N*-(substituted-phenyl)isocyanate in an inert solvent using stannous octoate as catalyst in a similar manner to that described by Francis [17,18]. This catalyst, or alternatively stannous oleate or dibutyltin dilaurate, gave 10-20% higher yields over the more commonly used catalyst triethylamine. See Tables IV-VI for the analytical data for the carbamates.

EXPERIMENTAL

All melting points were taken in glass capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137-B. The nmr spectra were obtained in DMSO-d_6 or deuteriochloroform with TMS as internal standard on a Varian T-60 spectrometer. Gas chromatography was done on a Hewlett-Packard 5710A using a 6 ft × 1/8 inch glass column of 5% OV-101 on Anakrom ABS 90/100 mesh.

General Procedure for the Preparation of 2-(α-Hydroxylakyl)-2-oxazolines: 2-(2-Hydroxyprop-2-yl)-4,4-dimethyl-2-oxazoline (**17**). Method A.

To a 100 ml single-necked flask was added 2-hydroxyisobutyric acid (26.0 g, 0.25 mole) and 2-amino-2-methyl-1-propanol (**8**) (22.5 g, 0.25 mole). The flask was then heated under reflux 1 hour at 170° (oil bath temperature). The oil bath was then removed and distilling head was attached to the flask (a 6 cm vigreux column was initially used to more efficiently remove volatile materials but was subsequently removed). Electric heating tape was wrapped around the neck of the distilling head and azeotropic distillation conducted over 4-6 hours. The clear viscous distillate was dissolved in hexane and dried over magnesium sulfate. Concentration of the organic layer and distillation produced the α-hydroxyoxazoline **17** (23.0 g, 0.146 mole, 59%), bp 82-85° (~20 torr); ir (film): 3300 (OH), 1650 cm^{-1} (C=N); nmr (DMSO-d_6): δ 4.9 (s, 1, O-H), 3.85 (s, 2, CH_2-O), 1.1 (s, 6, CH_3-), 1.3 (s, 6, CH_3-).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 57.80; H, 9.73; N, 8.42. Found: C, 58.31; H, 9.54; N, 8.32.

Method B.

2-Hydroxyisobutyric acid (26.0 g, 0.25 mole) and 2-amino-2-methyl-1-propanol (**8**) (22.5 g, 0.25 mole) were heated together in xylene until 10 ml of aqueous solution had been collected in a Dean-Stark trap (~16 hours). At the end of this time the reaction flask was cooled and the solvent removed under vacuum. The residue obtained was slowly distilled to yield the oxazoline **17**; 25.0 g (0.16 mole, 64%); bp 95° (~25 torr).

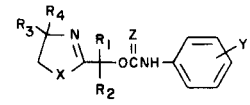
2-(1-Hydroxyethyl)-4,4-dimethyl-2-oxazoline (**18**). Method C.

Ethyl lactate (166.0 g, 1.4 moles) was combined with the 2-amino-2-methyl-1-propanol (**8**) (120.5 g, 1.35 moles) in a 500 ml single-necked flask and the solution heated under reflux (135°). Due to ethanol formation the reaction temperature fell to 105° during the initial 0.5 hour of reflux. At this time the ethanol slowly distilled allowing the pot temperature to increase to 160°. The reaction was then cooled and stannous octoate (5.0 g, 0.012 mole) in 225 ml of xylenes was added. The resulting solution was heated under reflux (130°) and the water that formed was azeotropically removed (10 ml) until the reaction temperature reached 140°. The xylenes was distilled away and 173 g of mesitylene added. The reaction was again heated to reflux (160°) and water continued to azeotrope as it formed.

After 3 hours, the pot temperature had reached 165° and a total of 26 ml of water had been collected. By gc analyses, the reaction was shown to be nearly complete. At this time a slow distillation of the 2-oxazoline product in mesitylene was initiated, and after 1.5 hours a nitrogen sweep was employed to complete the distillation. By this procedure, 352.3 g of a 38.4% mesitylene solution of the 2-(1-hydroxyethyl)-4,4-dimethyl-2-oxazoline (**18**) was collected (percent yield of product determined by titrating the mesitylene solution with 0.1 *M* perchloric acid in glacial acetic acid

Table IV

Physical and Spectral Properties of 2-[Alkyl(thio)carbamoyloxy]-1,3-heterocycles **3**



Compound No.	R_1	R_2	R_3	R_4	X	Y	Z	Mp, °C	C=Z cm^{-1}	C=N cm^{-1}	NMR (DMSO-d_6)	Elemental Analysis % Calcd./(Found) C	H	N
31	CH_3	CH_3	CH_3	CH_3	O	3,5-Cl_2	O	186-188	1725	1665	9.8 (s, 1, N-H), 7.55 (d, 2, aromatic), 7.2 (m, 1, aromatic), 3.9 (s, 2, CH_2-O), 1.6 [s, 6, $(CH_3)_2$-C-O], 1.2 [s, 6, $(CH_3)_2$-C]	52.19 (52.14)	5.26 (5.36)	8.11 (8.03)
32	CH_3	CH_3	CH_3	CH_3	O	3,5-Cl_2	S	114-116	1470	1590	7.8 (s, 1, aromatic), 7.5 [d, 2, aromatic), 4.4 (s, 1, N-H), 3.4 (q, 2, CH_2-O), 1.6 [s, 6, $(CH_3)_2$-C-O], 1.2 (s, 3, CH_3-C), 0.6 (s, 3, CH_3-C)	49.87 (49.79)	5.02 (5.17)	7.75 (7.78)
33	CH_3	H	CH_3	CH_3	O	3,5-Cl_2	O	107-110	1725	1665	8.6 (s, 1, N-H), 7.25 (d, 2, aromatic), [a] 6.9 (m, 1, aromatic), 5.45 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 1.5 (d, 3, CH_3-C), 1.2 [s, 6, $(CH_3)_2$-C]	50.77 (50.76)	4.87 (4.87)	8.46 (8.61)
34	H	H	CH_3	CH_3	O	3,5-Cl_2	O	125	1725	1680	8.5 (s, 1, N-H), 7.6 (d, 2, aromatic), 7.2 (m, 1, aromatic), 4.8 (s, 2, CH_2-O), 4.0 (s, 2, CH_2-O), 1.2 [s, 6, $(CH_3)_2$-C]	49.23 (49.00)	4.45 (4.43)	8.83 (8.87)
35	H	CH_3	CH_3	CH_3	O	2,4,5-Cl_3	O	120-122	1725	1660	7.65 (d, 2, aromatic), 5.2 (q, 1, CH-C), 3.95 (s, 2, CH_2-O), 1.4 (d, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	45.88 (46.02)	4.37 (4.26)	7.64 (7.24)
36	CH_3	CH_3	H	H	S	3,5-Cl_2	O	148	1730	1600	8.36 (s, 1, N-H), 7.4 (d, 2, aromatic), 7.2 (m, 1, aromatic), 4.2 (t, 2, CH_2-S), 3.3 (m, 2, CH_2-N), 1.7 [s, 3, $(CH_3)_2$-C]	46.86 (46.44)	4.23 (4.29)	8.41 (8.57)
37	-$(CH_2)_6$-		CH_3	CH_3	O	3,5-Cl_2	O	84	1730	1655	8.13 (s, 1, N-H), 7.4 (d, 2, aromatic), 7.1 (m, 1, aromatic), 3.8 (s, 2, CH_2-O), 2.2 (m, 4, -CH_2-), 1.5 (m, 8, -CH_2-), 1.2 [s, 6, $(CH_3)_2$-C]	57.15 (56.80)	6.06 (6.20)	7.02 (7.42)
38	Ph	H	CH_3	CH_3	O	3,5-Cl_2	O	200	1730	1665	7.6 (m, 8, aromatic), 6.35 (s, 1, CH-Ph), [a] 4.1 (s, 2, CH_2-O), 1.31 [s, 6, $(CH_3)_3$-C]	58.03 (57.99)	4.61 (4.54)	7.12 (6.72)
39	Ph	-CH_2-CH=CH_2	CH_3	CH_3	O	3,5-Cl_2	O	184-186	1735	1645	7.5 (m, 8, aromatic), 5.8-4.8 (m, 3, CH_2=-CH), 3.9 (s, 2, CH_2-O), 3.4 (m, 2, CH_2-C=), 1.3 [2s, 6, $(CH_3)_2$]	60.98 (61.25)	5.11 (5.28)	6.46 (6.81)
40	Ph	-C≡C-CH_3	CH_3	CH_3	O	3,5-Cl_2	O	198-199	1725 2247 (-C≡C-)	1655	7.6 (m, 8, aromatic), 4.0 (s, 2, CH_2-O), 2.0 (s, 3, CH_3-C≡), 1.3 [2s, 6, $(CH_3)_2$-]	61.26 (60.75)	4.67 (4.64)	6.49 (6.75)

Table IV, continued

Compound No.	R_1	R_2	R_3	R_4	X	Y	Z	Mp, °C	C=Z cm^{-1}	C=N cm^{-1}	NMR (DMSO-d_6)	Elemental Analysis % Calcd./(Found) C	H	N
41	CH_3	H	CH_3	CH_3	O	3,4-Cl_2	O	135-137	1745	1665	7.75 (m, 1, aromatic), 7.45 (m, 2, aromatic), 5.4 (q, 1, CH_3-CH), 4.0 (s, 2, CH_2-O), 1.45 (d, 3, CH_3-CH), 1.2 [s, 6, $(CH_3)_2$]	50.77 (51.15)	4.87 (4.97)	8.46 (8.94)
42	CH_3	H	CH_3	CH_3	O	3-Cl	O	78-81	1745	1675	7.6-7.8 (m, 4, aromatic), 5.25 (q, 1, C-CH_3), 3.9 (s, 2, CH_2-O), 1.4 (d, 3, CH_3-C), 1.1 [s, 3, $(CH_3)_2$]	56.66 (57.05)	5.77 (5.85)	9.44 (9.70)
43	CH_3	H	CH_3	CH_3	O	2-Cl, 3-CF_3	O	105-107	1745	1670	8.1-7.3 (m, 3, aromatic), 5.4 (q, 1, CH-C), 4.0 (CH_2-O), 1.5 (d, 3, CH_3-C), 1.2 [s, 6, $(CH_3)_2$]	49.39 (49.50)	4.42 (4.50)	7.68 (8.17)
44	CH_3CH_2	H	CH_3	CH_3	O	3,5-Cl_2	O	105-106	1745	1665	7.45 (d, 2, aromatic), 7.1 (m, 1, aromatic), 5.2 (t, 1, CH-C), 3.9 (s, 2, CH_2-O), 1.8 (qt, 2, C-CH_2-C), 1.2 [s, 6, $(CH_3)_2$], 0.9 (t, 3, C-CH_3)	52.19 (52.24)	5.26 (5.41)	8.11 (8.01)
45	CH_3	-CH_2CH_3	CH_3	CH_3	O	3,5-Cl_2	O	198-200	1740	1665	7.6 (d, 2, aromatic), 7.2 (m, 1, aromatic), 4.0 (s, 2, CH_2-O), 2.0 (q, 2, CH_2-C), 1.6 (s, 3, CH_3), 1.3 [s, 6, $(CH_3)_2$], 1.0 (t, CH-CH_3)	53.49 (53.59)	5.61 (5.72)	7.86 (7.75)
46	H	-C_3H_7	CH_3	CH_3	O	3,5-Cl_2	O	110	1750	1670	7.5 (d, 2, aromatic), 7.2 (m, 1, aromatic), 5.2 (q, 1, -CH-O), 4.0 (s, 2, CH_2-O), 2.0-0.8 (m, 5, CH_2-CH_3), 1.2 [s, 6, $(CH_3)_2$-]	53.49 (53.59)	5.60 (5.71)	7.80 (7.64)
47	H	-C_4H_9	CH_3	CH_3	O	3,5-Cl_2	O	110-111	1750	1665	7.6 (d, 2, aromatic), 7.2 (m, 1, aromatic), 5.3 (t, 1, -CH-O), 4.0 (s, 2, CH_2-O), 2.1-0.6 (m, 9, C_4H_9), 1.2 [s, 3, $(CH_3)_2$]	54.70 (54.81)	5.94 (6.10)	7.50 (7.48)
48	H	CH_3	CH_3	CH_3	O	3-SCH_3	O	107-108	1730	1665	7.6-7.8 (m, 4, aromatic), 5.4 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 2.3 (s, 3, S-CH_3), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	58.43 (58.42)	6.54 (6.68)	9.09 (9.41)
49	H	CH_3	CH_3	CH_3	O	3,5-$(CF_3)_2$	O	138-140	1745	1675	8.1 (s, 2, aromatic), 7.6 (s, 1, aromatic), 5.45 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 2, $(CH_3)_2$]	48.25 (48.05)	4.08 (4.09)	7.03 (6.89)
50	H	CH_3	CH_3	CH_3	O	3-NO_2	O	124-125	1725	1665	8.45 (m, 1, aromatic), 7.9-7.3 (m, 3, aromatic), 5.4 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	54.72 (54.50)	5.58 (5.70)	13.67 (13.61)
51	H	CH_3	CH_3	CH_3	O	3-CF_3	O	105-107	1730	1665	8.0-7.4 (m, 4, aromatic), 5.4 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	54.54 (54.58)	5.19 (5.36)	8.48 (8.45)

Table IV, continued

Compound No.	R_1	R_2	R_3	R_4	X	Y	Z	Mp, °C	C=Z cm^{-1}	C=N cm^{-1}	NMR (DMSO-d_6)	Elemental Analysis % Calcd./(Found) C	H	N
52	H	CH_3	CH_3	CCH_3	O	3-Br	O	107-109	1750	1655	7.7-7.0 (m, 4, aromatic), 5.25 (q, 1, CH-C), 3.95 (q, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	49.28 (49.14)	5.02 (5.14)	8.21 (8.30)
53	H	CH_3	CH_3	CH_3	O	3-F	O	93-95	1730	1665	7.5-6.6 (m, 4, aromatic), 5.4 (q, 1, CH-C), 3.9 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	59.99 (60.34)	6.11 (6.34)	9.99 (9.98)
54	H	CH_3	CH_3	CH_3	O	2,6-Cl_2	O	112-114	1735	1665	7.6-7.2 (m, 3, aromatic), 5.4 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	50.77 (50.57)	4.87 (5.01)	8.46 (8.18)
55	H	CH_3	CH_3	CH_3	O	3-OPh	O	99-101	1730	1660	7.4-6.6 (m, 4, aromatic), 5.4 (q, 1, CH-C), 3.9 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	67.78 (67.90)	6.26 (6.39)	7.90 (7.87)
56	H	CH_3	CH_3	CH_3	O	2,3-Cl_2	O	88-90	1750	1680	7.6-7.3 (m, 3, aromatic), 5.4 (q, 1, CH-C), 4.0 (s, CH_2-O), 1.5 (d, 3, C-CH_3), 1.25 [s, 6, $(CH_3)_2$]	50.77 (50.77)	4.87 (4.79)	8.46 (8.24)
57	H	CH_3	CH_3	CH_3	O	—	O	81-83	1730	1660	7.6-6.9 (m, 5, aromatic), 5.4 (q, 1, CH-C), 3.95 (2, s, -CH_2O), 1.5 (d, 3, C-CH_3), 1.25 [s, 6, $(CH_3)_2$]	64.10 (64.20)	6.92 (6.90)	10.68 (10.48)
58	H	CH_3	CH_3	CH_3	O	2-Cl, 3-CH_3	O	94-96	1735	1675	7.2 (m, 3, aromatic), 5.3 (q, 1, CH-C), 3.95 (s, 2, -CH_2-O), 2.2 (s, 3, -CH_3), 1.5 (d, 3, -C-CH_3), 1.2 [s, 6, $(CH_3)_2$]	57.97 (58.14)	6.16 (6.25)	9.01 (9.11)
59	H	CH_3	CH_3	CH_3	O	2,4-Cl_2	O	101-103	1740	1670	7.7-7.1 (m, 3, aromatic), 5.4 (q, 1, CH-C), 4.0 (s, 2, CH_2-O), 1.5 (d, 3, C-CH_3), 1.25 [s, 6, $(CH_3)_2$]	50.77 (50.66)	4.87 (4.89)	8.46 (8.28)
60	CH_3	-CH=CH_2	CH_3	CH_3	O	3,5-Cl_2	O	168-170	1735	1655	10.0 (s, 1, N-H), 7.45-7.2 (m, 3, aromatic), 6.2-5.0 (m, 3, CH=CH_2), 3.9 (s, 2, CH_2-O), 1.7 (s, 3, -CH_3), 1.2 [s, 6, $(CH_3)_2$]	53.80 (53.99)	5.08 (4.79)	7.84 (8.29)

[a] Deuteriochloroform used as solvent.

using crystal violet as indicator) [11b]. This solution calculated to contain 137 g (0.945 mole, 70%) of product.

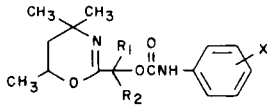
1-(4,4-Dimethyl-2-oxazoline-2-yl)-1-phenyl-4-buten-1-ol (**28**). Method D.

2-Benzoyl-4,4-dimethyl-2-oxazoline (1.0 g, 4.9 mmoles), prepared in 80% yield by manganese dioxide oxidation of the corresponding alcohol using the procedure of White [6a], was dissolved in 100 ml of dry ether at room temperature under a dry nitrogen atmosphere. To this solution at room temperature was slowly added an equimolar amount of allylmagnesium chloride (2.27 *M*, 2.2 ml). The resulting white suspension was allowed to stand at room temperature overnight then quenched with aqueous ammonium chloride. All organic materials were then removed by several ether extractions of the aqueous layer. The combined and dried (magnesium sulphate) organic solution was concentrated to yield 1.1 g of crude material. The desired product was characterized as its carbamate (see Table IV).

General Procedure for the Preparation of 2-(α-Hydroxyalkyl)-4,4,6-trimethyl-5,6-dihydro-1*H*-1,3-oxazines: 2-(2-Hydroxyprop-2-yl)-4,4,6-trimethyl-5,6-dihydro-1*H*-1,3-oxazine (**30**). Method E.

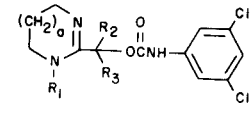
To a 250 ml three-necked flask with a thermometer, a mechanical stir-

Table V



Compound No.	R_1	R_2	X	Mp, °C	C=O cm^{-1}	C=N cm^{-1}	NMR (DMSO-d_6)	Elemental Analysis % Calcd./(Found) C	H	N
61	CH_3	CH_3	3,5-Cl_2	174-176	1725	1665	7.4 (d, 2, aromatic), 7.1 (s, 1, N-H), 7.0 (m, 1, aromatic), 4.2 (m, 1, CH-O), 2.0-0.8 (m, 11)	54.68 (54.94)	5.98 (6.06)	7.53 (7.62)
62	CH_3	CH_3	3,5-CH_3	159-161	1700	1665	9.2 (s, 1, N-H), 7.1 (d, 2, aromatic), 6.6 (m, 1, aromatic), 4.2 (m, 1, CH-O), 2.0-0.8 (m, 11)	68.65 (68.43)	8.49 (8.79)	8.43 (8.34)
63	CH_3	CH_3	3,5-OCH_3	137-140	1725	1660	9.3 (s, 1, N-H), 6.7 (d, 2, aromatic), 6.1 (m, 1, aromatic), 4.1 (m, 1, CH-O), 3.6 (s, 6, OCH_3), 2.0-0.7 (m, 11)	62.62 (62.43)	7.74 (8.00)	7.69 (7.86)
64	H	H	3,5-Cl_2	157-159	1750	1660	8.5 (s, 1, N-H), 7.5 (d, 2, aromatic), 7.08 (m, (m, 1, aromatic), 4.5 (s, 2, CH_2-O), 4.2 (m, 1, CH-O), 2.0-0.8 (m, 11)	52.19 (52.43)	5.26 (5.39)	8.11 (8.16)

Table VI



Compound No.	R_1	R_2	R_3	a	Mp, °C	C=O cm^{-1}	C=N cm^{-1}	NMR (DMSO-d_6)	Elemental Analysis % Calcd./(Found) C	H	N
65	H	Ph	H	2	185	1750	1665	7.5 (m, 8, aromatic), 6.3 (s, 1, CH-Ph), 3.6 (m, 4, -CH_2-), 1.9 (m, 4, -CH_2-)	53.12 (53.26)	4.89 (4.89)	9.78 (9.64)
66	CH_3	H	H	O	172-174	1725	1600	7.48 (d, 2, aromatic), 7.2 (m, 1, aromatic), 4.85 (s, 2, CH_2-O), 4.0-3.1 (m, 4, CH_2-CH_2), 2.8 (s, 3, CH_3-N)	47.70 (47.76)	4.34 (4.35)	13.91 (13.57)

rer, and a 100 ml addition funnel attached was added 200 ml of concentrated sulfuric acid. The acid was cooled to 0-5° with a dry ice-acetone bath while 51 g (0.6 mole) of the acetone cyanohydrin was added at such a rate so as to maintain the temperature in the −10 to 10° range (**Note - caution must be exercised in the initial stages of the addition since a vigorous exothermic reaction occurs**). After the addition of the cyanohydrin, 59.0 g (0.5 mole) of 2-methyl-2,4-pentanediol (**11**) was added again at a rate that kept the temperature in the −10 to 10° range (see the previous **Note**). The mixture was stirred for an additional 1 hour then poured into crushed ice (~5°). The acidic aqueous solution was then extracted twice with ether and the ether layers discarded. The acidic aqueous layer was then poured into a large beaker which contained 400 g of solid sodium bicarbonate and ether. The beaker was cooled with an ice-water bath and was not allowed to rise past 36° (basification with aqueous potassium hydroxide resulted in more extensive decomposition due to the higher temperature obtained). The ether layer was dried over potassium carbonate and concentrated. The residue obtained was distilled at 43° (0.5 torr) to yield 24 g (0.13 mole, 26%) of product; ir (film): 3305 (OH), 1640 cm^{-1} (C=N); nmr (deuteriochloroform): δ 4.6 (s, 1, O-H), 4.1 (m, 1, CH-O), 2.0-0.8 (m, 11, ring). See Table V for analysis of carbamate.

Oxygenation of 2,4,4,6-Tetramethyl-5,6-dihydro-1*H*-1,3-oxazine (**13b**). Method F [13].

The oxazine **13b** (5.0 g, 0.035 mole) was dissolved in 20 ml of dry tetrahydrofuran and the solution then cooled to −60°. To this cooled solution under a dry nitrogen atmosphere was added 29 ml of *n*-butyllithium (1.6 *M*) in hexane. The temperature was not allowed to rise above −50°. After 1 hour, a voluminous yellow precipitate was produced and the suspension was allowed to stir an additional hour. The addition funnel was removed (**Caution! If the funnel is left in place, residual *n*-butyllithium may cause detonation during introduction of oxygen** [14]) and replaced by a gas dispersion tube extending below the surface of the mixture. Dry oxygen was bubbled into the solution with the temperature of the reaction vessel being maintained near −60°. A brown coloration initially developed but the solution turned to a bright yellow after ~45 minutes. The addition of oxygen was continued for 1 hour then stopped and the solution was allowed to stand 2 hours. The solution was then poured into a saturated aqueous solution of sodium sulfite to decompose any peroxides present. All of the organic materials were then removed by several ether extractions of the aqueous layer. The combined and dried (magnesium sulfate) organic solution was concentrated to yield a mixture (30/70) of **13b** and the product 2-hydroxymethyl-4,4,5-trimethyl-5,6-dihydro-1*H*-1,3-oxazine (**14b**); ir (film): 3400 (OH) and 1672 cm^{-1} (C=N); nmr (deuteriochloroform): δ 4.1 (m, 1, CH-O), 3.8 (s, 2, CH_2O), 3.2 (bs, 1, OH), 1.9-1.0 (m, 11, ring). The desired product **14b** was characterized as its carbamate (see Table V).

General Procedure for the Preparation of 2-(α-Hydroxyalkyl)cyclic Amidines: 2-(α-Hydroxymethylphenyl)-4,5,6,7-tetrahydro-1*H*-1,3-diazepine Hydrochloride (**16**). Method G.

To 200 ml of absolute ethanol was added 1,4-diaminobutane at 0° with continuous stirring. To this solution was added an equal molar amount of ethyl mandelimidate hydrochloride. After stirring at 0-5° for 2 hours, the suspension was heated under reflux for 12 hours then cooled and concentrated to remove any traces of ammonia. The concentrated solution was acidified by dropwise addition of ethanolic hydrogen chloride into the suspension which was then concentrated to dryness and the residue recrystallized several times from acetonitrile/ether to a 34% yield of product **16**, mp 179-181° (HCl), 129° (base); ir of base (potassium bromide): 1625 cm^{-1} (C=N); nmr of base (deuteriochloroform): δ 7.4 (m, 5, Ph), 5.6 (bs, 2, O-H and N-H), 4.9 (s, 1, CH-Ph), 3.35 [m, 4, $(-CH_2-)_2$], 1.8 [m, 4, $(CH_2-N)_2$]. See Table VI for analysis of the carbamate of **16**.

General Procedure for the Preparation of Carbamates **3**, 2-[*N*-(3,5-Ditrifluoromethylphenyl)carbamoyloxyethyl]-4,4-dimethyl-2-oxazoline (**49**).

The 2-oxazoline **18** (2.5 g, 17.3 mmoles) was added to a 250 ml flask containing 100 ml of methylene chloride along with 0.1 g of stannous octoate catalyst [18]. The solution was heated under reflux 0.5 hour then allowed to cool to room temperature. The 3,5-ditrifluoromethylphenylisocyanate (4.0 g, 17.3 mmoles) in 50 ml of methylene chloride was then added to the reaction vessel. The reaction solution was then heated under reflux 6 hours then cooled to room temperature and vacuum filtered to remove any methylene chloride insoluble material. The filtrate was then concentrated to ~50 ml and hexanes was added to the point of cloudiness. On standing 6.0 g (16 mmoles, 93%) of product crystallized from the solution, mp 138-140°. See Tables IV-VI for analytical data.

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