Synthesis of 4-Acyl-2,3-dihydro-4*H*-1,4-oxazines

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The synthesis of 4-acyl-2,3-dihydro-4*H*-1,4-oxazines (**6a-h**) *via* acid dehydration of 4-acyl 2- and 3-morpholinols is described. During dehydration of 2-morpholinols **3d,e**, *N*-alkylisoquinolones **7a-e** were also isolated.

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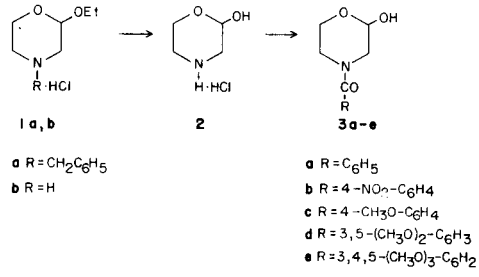
Nitrogen acylated 2,3-dihydro-4*H*-1,4-oxazines (**6**) can be regarded both as enamides and enolethers. In spite of their chemical interest (1,2), they received little attention (3) because of the lack of suitable synthetic procedures.

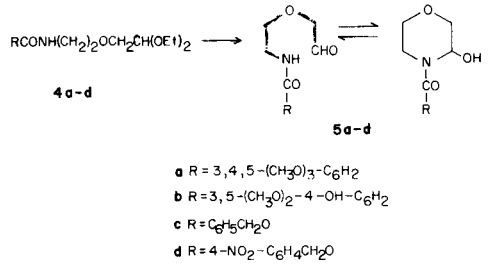
Recently, we reported the preparation of some *N*-alkoxybenzoyl 2- and 3-morpholinols as potential metabolites of trithiozine (4,5). We thought that, in a general way, 4-acyl 2- and 3-morpholinols could be dehydrated to the corresponding 4-acyl-2,3-dihydro-4*H*-1,4-oxazines.

Morpholinol **2** was prepared by cyclization in acidic medium of *N*-benzyl-*N*-(2-hydroxyethyl)-2-aminoacetaldehyde diethyl acetal (6) to **1a** in analogy to Shibata's



method (7); then catalytic hydrogenolysis of **1a** gave **1b**, which was subsequently hydrolyzed to **2**. A pyridine solution of morpholinol **2** was treated with the adequate acid chloride to afford the key intermediates **3a-e**.

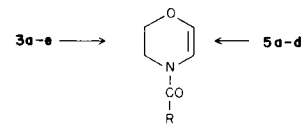
Compounds **4a,b** and **5a,b** were prepared as previously described (5). In analogy, **4c,d** were obtained by condensation of 2-(2-aminoethoxy)acetaldehyde diethyl acetal (5)



with the corresponding benzyloxycarbonyl chloride. Mild hydrolysis of **4c,d** with oxalic acid afforded 3-morpholinols **5c,d**.

3-Morpholinols generally exhibit ring chain tautomerism, however compounds **5c,d** are almost completely in the cyclic form (infrared OH stretching at 3300-3500 cm^{-1} and absence of aldehydic carbonyl stretching).

Dehydration of morpholinols **3** and **5** to 4-acyl-2,3-dihydro-4*H*-1,4-oxazines (**6a-h**) was performed in acid conditions (see Table 1). Reaction on 2-morpholinols **3a-c,e** was catalyzed by hydrochloric acid in hot acetone (Method



A); with compounds **3d,e** this method was unsatisfactory (see below), thus *p*-toluenesulfonic acid in boiling toluene (Method B) was preferred. Dehydration of 3-morpholinols **5a-d** required milder conditions such as hydrochloric acid in acetone at room temperature (Method C) and gave better yields. Obviously, treatment of compounds **4** in the conditions of method C led directly to the corresponding dihydrooxazines as shown for **6e** (see Experimental). The different reactivity may be rationalized by the relative stability of the possible intermediates after protonation and loss of water in 2-morpholinols (intermediate A) and in 3-morpholinols (intermediate B).

It appears reasonable that the acyliminium salt B is less stable than the oxonium salt A in acid medium, thus its conversion to **6** will be faster.

Compounds **6** show carbonyl stretching at about 1640 cm^{-1}, with the exception of **6g,h** and the vinyl proton signals in the range of δ 5.8-6.5.

It is worthwhile to note that 2-morpholinol **3d**, in the conditions of Method A afforded the isoquinolones **7a,b**, while **3e** in halogenhydric acid gave small amounts of **6e** together with **7e-c**. The nmr spectra of isoquinolones in

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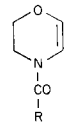
Table 1

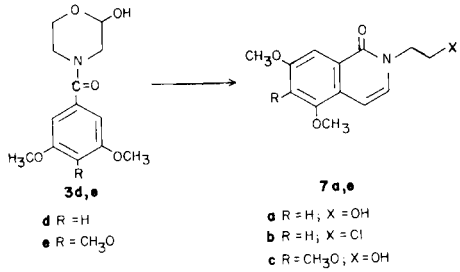


4-Acyl-2,3-dihydro-4*H*-1,4-oxazines (**6a-h**)

Compound No.	R	M.p. (solvent)	Method	Yield (%)	Molecular Formula	Analyses % Calcd./Found C	H	N
6a	C_6H_5	colourless oil	A	21	$C_{11}H_{11}NO_2$	69.82-69.66	5.86-5.98	7.40-7.52
6b	4-NO_2-C_6H_4	98° (benzene/hexane)	A	35	$C_{11}H_{10}N_2O_4$	56.41-56.60	4.30-4.18	11.96-12.08
6c	4-CH_3O-C_6H_4	colourless oil	A	30	$C_{12}H_{13}NO_3$	65.74-65.52	7.81-7.78	6.39-6.54
6d	3,5-$(CH_3O)_2$-C_6H_3	colourless oil	B	9 (a)	$C_{13}H_{15}NO_4$	62.64-62.80	6.06-6.11	5.62-5.48
6e	3,4,5-$(CH_3O)_3$-C_6H_2	85° (benzene/hexane)	A	17	$C_{14}H_{17}NO_5$	60.21-60.00	6.13-5.80	5.02-5.10
			B	37				
			C	89				
6f	3,5-$(CH_3O)_2$-4-OH-C_6H_2	128° (ethyl acetate)	C	91	$C_{13}H_{15}NO_5$	58.86-59.01	5.70-5.64	5.28-5.39
6g	$C_6H_5CH_2O$	colourless oil	C	96	$C_{12}H_{13}NO_3$	65.74-65.60	5.98-6.02	6.39-6.28
6h	4-NO_2-$C_6H_4CH_2O$	127° (ether)	C	94	$C_{12}H_{12}N_2O_5$	54.54-54.71	4.58-4.45	10.60-10.82

(a) The main product of the reaction was the isoquinolone **7a**.

deuterochloroform are characterized by the presence of two vinyl protons at δ 7.0-7.2 and δ 6.7-6.8 with a coupling constant of about 8 Hz. Their formation is well justified,



3d,e

d R = H
e R = CH_3O

7a,e

a R = H; X = OH
b R = H; X = Cl
c R = CH_3O; X = OH
d R = CH_3O; X = Cl
e R = CH_3O; X = Br

taking into account that the introduction of two methoxy groups in position 3 and 5 of the benzene ring strongly enhances the reactivity of carbon 2 and allows an electrophilic substitution to be operated by the protonated hemiacetal function according to a mechanism reminiscent of the Pomeranz-Fritsch reaction (8).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were taken with a Perkin-Elmer 157 spectrophotometer. Nuclear magnetic resonance spectra were taken with a Perkin Elmer R 12B spectrometer using TMS as internal standard and are expressed in δ. Mass spectra were taken with a Varian Mat 112 spectrometer. Column chromatographies were performed on silica gel (Merck 60). Standard drying agent was magnesium sulfate and all evaporations were carried out *in vacuo*. No attempt was made to optimize yields.

4-Benzyl-2-ethoxymorpholine Hydrochloride (**1a**).

To a stirred and ice-cold ether solution of *N*-benzyl-*N*-(2-hydroxyethyl)-2-aminoacetaldehyde diethyl acetal (6) (16.4 g., 60 mmoles), 3*N* hydrogen chloride in ether was added. The mixture was cooled and stirred overnight, then the precipitate was filtered and recrystallized from ethanol to give 14.4 g. of **1a** (93%), m.p. 192° dec.; ir (oil mull): 2450, 1080, 755, 710 cm^{-1}.

Anal. Calcd. for $C_{13}H_{19}NO_2$·HCl: Cl, 13.75; N, 5.43. Found: Cl, 13.92; N, 5.45.

2-Ethoxymorpholine Hydrochloride (**1b**).

A mixture of **1a** (72.4 g., 0.28 mole) in methanol (600 ml.) was hydrogenated at 3 atmospheres for 1 hour in the presence of palladium on charcoal 10% (5 g). The catalyst was filtered and the solvent removed to give **1b** (9) in almost quantitative yield, m.p. (picrate) 156-157° from ethanol.

2-Morpholinol Hydrochloride (**2**).

Crude **1b**, from the above reaction, was hydrolyzed in 10% hydrochloric acid at room temperature overnight. Water was removed and the residue was tritured with ethanol, to give 30.7 g. of **2** (78%), m.p. 140-142° dec. [lit. (7) m.p. 136-137° dec.].

4-(4-Nitrobenzoyl)-2-morpholinol (**3b**).

To a stirred cold mixture of **2** (2 g., 14.3 mmoles) and pyridine (20 ml.), 4-nitrobenzoyl chloride (14.3 mmoles) was added dropwise, while the temperature was kept at 5°. After 1 hour, the mixture was poured into ice, acidified with hydrochloric acid and extracted with chloroform. Column chromatography (chloroform/methanol 99:1) afforded 1 g. (28.3%) of **3b**, m.p. 149-150° (from isopropyl alcohol/isopropyl ether); ir (oil mull): 3350, 1625 cm^{-1}; nmr (deuterochloroform/DMSO-d_6): 8.29 (2H, ABq, J = 8.6 Hz, O_2N-ArH), 7.71 (2H, Abq, J = 8.6 Hz, OCOArH), 6.38 (1H, d, J = 5.3 Hz, OH), 4.95 (1H, m, CH), 4.40-3.1 (6H, m, $CH_2NCH_2CH_2$); ms: m/e 252 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 5.13; N, 11.10. Found: C, 52.43; H, 4.90; N, 10.94.

In the same way were also prepared:

4-Benzoyl-2-morpholinol (**3a**).

This compound was obtained as an oil (10) in a yield of 71%; ir (liquid

film): 3300, 1625 cm^{-1}.

4-(4-Methoxybenzoyl)-2-morpholinol (**3c**).

This compound was obtained in a yield of 30%, m.p. 121-122° from ethanol/ether.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.97; H, 6.29; N, 6.03.

4-(3,5-Dimethoxybenzoyl)-2-morpholinol (**3d**).

This compound was obtained in yield of 43.4%, m.p. 110-111° from ethanol/ether.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.50; H, 6.60; N, 5.29.

4-(3,4,5-Trimethoxybenzoyl)-2-morpholinol (**3e**).

This compound was obtained in a yield of 39%, m.p. 139-140° from ethyl acetate (lit. (5) 139-140°, (11) 137-138.5°).

2-[2-(Benzyloxycarbonylamino)ethoxy]-1,1-diethoxyethane (**4c**).

To a stirred and ice-cold solution of 2-(2-aminoethoxy)-1,1-diethoxyethane (5) (3 g., 17 mmoles) and triethylamine (3 ml.) in methylene chloride (20 ml.) benzyloxycarbonyl chloride (2,5 ml., 17 mmoles) in methylene chloride was added and the reaction mixture was stirred at room temperature overnight. The solution was washed with water, dried and the solvent removed to afford 4.5 g. of **4c** (85%) as a syrup; ir (liquid film): 3350, 1740 cm^{-1}; ms: m/e 311 (M^+).

Anal. Calcd. for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.61; H, 8.18; N, 4.38.

2-[2-(4-Nitrobenzyloxycarbonylamino)ethoxy]-1,1-diethoxyethane (**4d**).

This compound was prepared from 2-(2-aminoethoxy)-1,1-diethoxyethane and 4-nitrobenzyloxycarbonyl chloride according to the procedure described for **4c**, yield 84.5% as a yellow oil; ir (liquid film): 3400, 1730, 1340 cm^{-1}; ms: m/e 356 (M^+).

Anal. Calcd. for $C_{16}H_{24}N_2O_7$: C, 53.92; H, 6.79; N, 7.86. Found: C, 54.08; H, 6.67; N, 7.81.

4-Benzyloxycarbonyl-3-morpholinol (**5c**).

A solution of **4c** (6 g., 19 mmoles) and oxalic acid (1 g.) in 10% aqueous acetone was refluxed for 4 days, the solvent was removed and the residue was taken up with ether and washed with sodium bicarbonate. Column chromatography (hexane/ethyl acetate 8:2) afforded 2.7 g. of **5c** (60%) as an oil; ir (liquid film): 3450, 1700 cm^{-1} nmr (DMSO-d_6): 7.50 (5H, s, ArH), 6.01 (1H, d, J = 5.3 Hz, OH), 5.40 (1H, m, CH), 5.22 (2H, s, $ArCH_2O$), 3.98-3.26 (6H, m, $CH_2CH_2OCH_2$); ms: m/e 237 (M^+).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37; N, 5.90. Found: C, 60.91; H, 6.40; N, 6.22.

4-(4-Nitrobenzyloxycarbonyl)-3-morpholinol (**5d**).

This compound was prepared from **4d** (19.8 g., 55 mmoles) according to the procedure described for **5c**, yield 42.8%, m.p. 123° (ethyl acetate).

Anal. Calcd. for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.92. Found: C, 51.11; H, 5.10; N, 9.73.

Synthesis of 4-Acyl-2,3-dihydro-4*H*-1,4-oxazines (**6a-h**).

Method A.

4-Benzoyl-2,3-dihydro-4*H*-1,4-oxazine (**6a**).

An acetone solution of **3a** (1 g., 4.8 mmoles) containing a catalytic amount of hydrochloric acid was refluxed for 3 days. The solvent was removed, the residue taken up with chloroform and washed with aqueous sodium bicarbonate. Column chromatography (hexane/ethyl acetate 8:2) afforded 0.19 g. of **6a** (21%) as an oil; ir (liquid film): 1650, 1120, 1080 cm^{-1}; nmr (deuterochloroform): 7.47 (5H, s, ArH), 5.87 (2H, m, OC*H*C*H*N), 4.35-3.54 (4H, m, OCH_2CH_2N); ms: m/e 189 (M^+).

Method B.

4-(3,5-Dimethoxybenzoyl)-2,3-dihydro-4*H*-1,4-oxazine (**6d**).

A toluene solution of **3d** (1 g., 3.7 mmoles) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed for 1 hour. The solvent was evaporated and the residue purified by column chromatography to afford 83 mg. of **6d** (9%) as an oil; ir (liquid film): 1645, 1600, 1155 cm^{-1}; nmr (deuterochloroform): 6.62 (3H, m, ArH), 5.90 (2H, m, OC*H*C*H*N), 3.78 (6H, s, OCH_3), 4.30-3.50 (4H, m, OCH_2CH_2N); ms: m/e 249 (M^+).

Method C.

4-(3,4,5-Trimethoxybenzoyl)-2,3-dihydro-4*H*-1,4-oxazine (**6e**).

A solution of **5a** (2 g., 6.7 mmoles) in acetone was stirred with a catalytic amound of hydrochloric acid at room temperature overnight. The solvent was removed and the residue crystallized from benzene/hexane to afford 1.65 g. of **6e** (89%), m.p. 85°; ir (oil mull): 1655, 1600, 1135 cm^{-1}; nmr (deuterochloroform): 6.80 (2H, s, ArH), 5.96 (2H, m, OC*H*C*H*N), 3.86 (9H, s, OCH_3), 4.40-3.70 (4H, m, OCH_2CH_2N); ms: m/e 279 (M^+).

Compound **6e** was also directly prepared by stirring a solution of **4a** (3.7 g., 10 mmoles) in acetone (200 ml.) with a catalytic amount of hydrochloric acid at room temperature for 3 days. The solvent was removed and the residue crystallized (benzene/hexane) to afford **6e** (78%), m.p. 85°.

The properties of dihydrooxazines **6a-h** are listed in Table 1.

2-(2-Hydroxyethyl)-5,7-dimethoxy-1-isoquinolone (**7a**).

An acetone solution of **3d** (1.5 g., 5.6 mmoles) with hydrochloric acid 37% (1 ml.) was heated at 40° for 2 days. After cooling the white precipitate was filtered and crystallized from 2-propanol to yield 0.75 g. of **7a** (53.5%), m.p. 188°; ir (oil mull): 3400, 1650, 1620 cm^{-1}; nmr (deuterochloroform): 7.47 (1H, d, J = 2.2 Hz, ArH); 7.04 (1H, ABq, J = 7.6 Hz, NCH), 6.85 (1H, ABq, J = 7.6 Hz, ArCH), 6.73 (1H, d, J = 2.2 Hz, ArH), 3.92 (6H, s, OCH_3), 4.50-3.78 (4H, m, CH_2CH_2); ms: m/e 249 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.35; H, 5.99; N, 5.92.

2-(2-Chloroethyl)-5,7-dimethoxy-1-isoquinolone (**7b**).

Column chromatography (hexane/ethyl acetate 80:20) of the mother liquors of the above reaction gave 0.15 g. of **7b** (10%), m.p. 181° from ethyl acetate.

Anal. Calcd. for $C_{13}H_{14}ClNO_3$: Cl, 13.24; N, 5.23. Found: Cl, 13.12; N, 5.41.

2-(2-Hydroxyethyl)-5,6,7-trimethoxy-1-isoquinolone (**7c**).

An acetone solution of **3e** (4 g., 14.3 mmoles) and hydrochloric acid 37% (1 ml.) was refluxed for 24 hours. The solvent was evaporated and the residue purified by column chromatography (hexane/ethyl acetate 8:2) to afford a small amount of **7c**, ir (chloroform): 1650, 1600 cm^{-1}; ms: m/e 279 (M^+).

2-(2-Chloroethyl)-5,6,7-trimethoxy-1-isoquinolone (**7d**).

From the above column chromatography two other products were also isolated: **6d** (0.7 g., 17%) identical with the product already obtained and **7d** (0.4 g., 9.4%), m.p. 112° from ethyl acetate; ir (oil mull): 1655, 1600 cm^{-1}; nmr (deuterochloroform): 7.76 (1H, s, ArH), 7.14 (1H, ABq, J = 8.0 Hz, NCH), 6.82 (1H, ABq, J = 8.0 Hz, ArCH), 3.90 (9H, s, OCH_3), 4.50-3.10 (4H, m, CH_2CH_2); ms: m/e 297 (M^+).

Anal. Calcd. for $C_{14}H_{16}ClNO_4$: Cl, 11.91; N, 4.70. Found: Cl, 12.02; N, 4.58.

2-(2-Bromoethyl)-5,6,7-trimethoxy-1-isoquinolone (**7e**).

An acetone solution of **3e** (1 g., 3.4 mmoles) with hydrobromic acid (0.5 ml.) was refluxed for 24 hours. After evaporation of the solvent, column chromatography (hexane 80, ethyl acetate 20) gave **7e**, yield 8.6% as a yellow syrup; ir (liquid film): 1650, 1600 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}BrNO_4$: Br, 23.35; N, 4.09. Found: Br, 23.61; N, 4.19.

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