Derivatives of Imidazo[5,1-*c*][1,4]benzoxazin-1-ones and Related Analogs. Part I.

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The bicyclic 2,3,3a,4-tetrahydro-1*H*-imidazo[5,1-*c*][1,4]benzoxazin-1-one system and the related 1,4-benzothiazine and 4,1]benzoxazepine analogs were synthesized. They were easily obtained by melting a suitable diamine derivative with urea. Some of them displayed very good reversible MAO-I activity selective for type A. The preparation of the intermediate amines is also given.

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During research for drugs active on CNS, starting from intermediates **1a-g** (see Table I), compounds **2a-g** (R^3 = H), (see Table II) (1) were synthesized.

In Table III derivatives of **2a-g** with $R^3 \neq H$ are reported. Compounds **19** and **22** in particular showed good activity as MAO inhibitors, reversible and selective for type A (2), with low toxicity.

Synthesis of **1a-d**.

The chemical problem was to find a good method for the preparation of compounds **1**. Benoit and Bovet (3) first

Scheme I

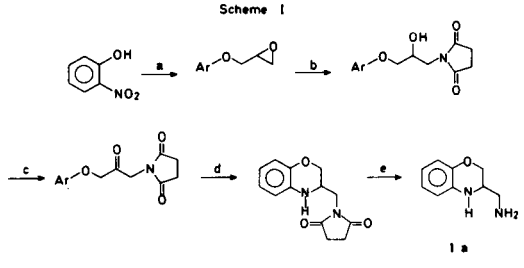
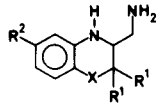


Table I



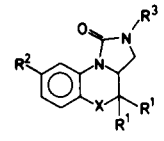
1a - g

	a	b	c	d	e	f	g
X	O	O	O	O	O	S	CH_2O
R^1	H	H	H	H	CH_3	H	H
R^2	H	CH_3	OCH_3	Cl	H	H	H

No.	X	R^1	R^2	Mp °C (a)	Analyses Calcd./Found C	H	N	Cl
1a	O	H	H	78-81 (b)	65.82	7.31	17.06	
					65.98	7.36	17.03	
1b	O	H	CH_3	oil	67.38	7.91	15.72	
					67.58	7.93	15.41	
1c	O	H	OCH_3	245-250 (c) dec	44.95	6.04	10.49	26.57
					44.76	5.95	10.10	26.35
1d	O	H	Cl	46-47	54.40	5.48	14.10	17.84
					54.29	5.60	13.98	17.65
1e	O	CH_3	H	245-250 (d)	57.76	7.49	12.25	15.50
					57.77	7.54	12.16	15.76
1f	S	H	H	250 (c) dec	42.35	5.52	10.97	22.64
					42.21	5.68	10.75	22.62
1g	CH_2O	H	H	oil	67.38	7.91	15.72	
					67.71	8.13	15.88	

(a) Melting points are uncorrected. (b) Lit 81-83° (7). (c) Dihydrochloride. (d) Hydrochloride.

Table II



2 a-g and 14-29

	a	b	c	d	e	f	g
X	O	O	O	O	O	S	CH_2O
R^1	H	H	H	H	CH_3	H	H
R^2	H	CH_3	OCH_3	Cl	H	H	H
R^3	see table III						

No.	X	R^1	R^2	Mp °C (a)	% Yield	Analyses Calcd./Found C	H	N	Cl	S
2a	O	H	H	168-170	65	63.14	5.29	14.73		
						63.30	5.29	14.80		
2b	O	H	CH_3	190-193	57	64.68	5.92	13.72		
						64.77	5.97	13.64		
2c	O	H	OCH_3	141-144	73	59.99	5.49	12.72		
						59.77	5.49	12.66		
2d	O	H	Cl	201-203	76	53.48	4.04	15.79	12.48	
						53.33	4.11	15.35	12.39	
2e	O	CH_3	H	235-240	75	66.03	6.46	12.83		
						65.78	6.49	12.77		
2f	S	H	H	173-175	78	58.23	4.88	13.58		15.54
						58.22	4.90	13.69		15.39
2g	CH_2O	H	H	250-252	54	64.68	5.92	13.72		
						64.43	6.01	13.59		

(a) Melting points are uncorrected.

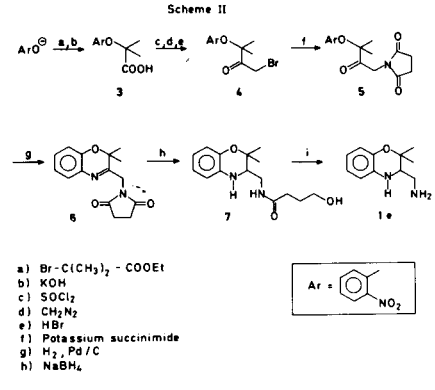
reported the synthesis of 3,4-dihydro-3-bromomethyl-2*H*-1,4-benzoxazines. Tozaburo *et al.* (4) synthesized some 3,4-dihydro-3-aminomethyl-2*H*-1,4-benzoxazines but their method worked only for tertiary amines. Potter and Monro (5) reported the preparation of the 3,4-dihydro-3-hydroxymethyl-1,4-benzoxazines but the yield was low. At the same time Chodnekar *et al.* (6) described a very short way to obtain 3,4-dihydro-3-ethoxycarbonyl-4-tosyl-1,4-benzoxazines but they were not able to detosylate them. Finally, Gupta *et al.* (7) synthesized **1a** in good yield following a pathway reported in Scheme I.

Gupta's method is also useful for synthesizing dihydrobenzoxazines substituted in the aromatic ring, and we used it for preparing **1b-d** with the sole difference that Adam's catalyst was used instead of Pd/C in the case of **1d** to avoid the hydrogenolysis of the aromatic chlorine. For the synthesis of 3,4-dihydro-3-aminomethyl-1,4-benzoxazines substituted in positions 2, 3 and α (see also Part II) we had to change methods.

Synthesis of **1e**.

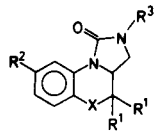
Compound **1e** was synthesized according to Scheme II.

Scheme II



When sodium 2-nitrophenoxide was reacted with ethyl 2-bromo-2-methylpropionate, the possible formation of side products derived from a dehydrohalogenation of the bromopropionate and possibly a Michael reaction of the nitrophenoxide with the resulting unsaturated ester was feared. However, only **3** was isolated after hydrolysis, as confirmed by ^1H nmr of the product. Reductive cyclisation of the nitroketone **5** stopped at the cyclic imine **6** even after reaction in ethanol at 80° for 24 hours. Usually in this kind of cyclisation the imine double bond is reduced

Table III



No.	X	R^1	R^2	R^3	Mp °C (a)	% Yield	Obtained from	Alkylating agent	Analyses Calcd./Found C	H	N	Cl
14	O	H	H	CH_3	135-136	76	**2a**	MeI	64.68 64.57	5.92 5.89	13.72 13.61	
15	O	H	H	$CH_2C{\equiv}CH$	113-115	55	**2a**	$BrCH_2C{\equiv}CH$	68.40 68.19	5.30 5.26	12.28 12.11	
16	O	H	H	$(CH_2)_2N(CH_3)_2$	218-221 (c)	45	**2a**	$Cl(CH_2)_2N(CH_3)_2$	56.46 56.16	6.77 6.78	14.11 13.98	11.90 12.11
17	O	H	H	$(CH_2)_2N$ N-PhCl(p)	190-210 (d) dec	70	**2a**	$Cl(CH_2)_2N$ N-PhCl(p)	55.26 54.96	5.85 5.79	11.21 10.81	
18	O	H	H	$CONH_2$	243-246	53	**1a** (e)	——	56.65 56.75	4.75 4.76	18.02 18.01	
19	O	H	H	CH_2CONH_2	244-250	56	**2a**	$ClCH_2CONH_2$	58.29 58.25	5.29 5.30	16.99 16.89	
20	O	H	CH_3	CH_2CONH_2	235-237	51	**2b**	$ClCH_2CONH_2$	59.76 59.41	5.78 5.71	16.08 15.97	
21	O	H	OCH_3	CH_2CONH_2	180-183	79	**2c**	$ClCH_2CONH_2$	56.31 56.41	5.45 5.49	15.15 15.07	
22	O	H	Cl	CH_2CONH_2	214-216	56	**2d**	$ClCH_2CONH_2$	51.16 51.09	4.29 4.38	14.92 14.70	12.59 12.43
23	O	CH_3	H	CH_2CONH_2	185-188	80	**2e**	$ClCH_2CONH_2$	61.07 61.04	6.22 6.12	15.26 15.40	
24	S	H	H	CH_2CONH_2	255-260	85	**2f**	$ClCH_2CONH_2$	54.73 54.42	4.97 5.05	15.96 16.13	
25	CH_2O	H	H	CH_2CONH_2	218-220	62	**2g**	$ClCH_2CONH_2$	59.76 59.59	5.78 5.85	16.08 15.95	
26	O	H	H	CH_2COOH	207-210	84 (f)	**2a** (g)	——	58.03 58.07	4.88 4.89	11.28 11.37	
27	O	H	H	CH_2CO-$NHCH_3$	216-218	57 (f)	**26** (h)	——	59.76 59.55	5.79 5.79	16.08 15.99	
28	O	H	H	$(CH_2)_2CONH_2$	171-172	30 (f)	**2a** (i)	——	59.76 59.41	5.78 5.83	16.08 15.90	
29	O	H	H	$CH(CH_3)CONH_2$	203-205	35 (f)	**2a** (j)	——	59.76 59.82	5.79 5.73	16.08 16.20	
30					235 dec	26	**1a** (k)	——	59.76 59.72	5.79 5.85	16.08 15.93	
31					222-224	46	(l)	$ClCH_2CONH_2$	63.65 63.49	6.16 6.09	17.13 17.02	
32					97-102	30	(m)	——	57.82 57.52	6.06 6.05	16.85 16.87	
33					129-130	32	**1a**	$ClCH_2CONH_2$	59.50 59.50	6.83 6.92	18.99 18.92	

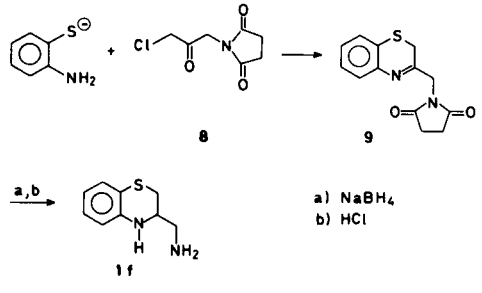
(a) Melting points are uncorrected. (b) Isolated product. (c) Hydrochloride. (d) Dihydrochloride. (e) Obtained melting **1a** with 2.5 equivalents of urea. (f) Overall yield. (g) Prepared by reaction of **2a** with ethyl chloroacetate and hydrolysis of the ester with potassium hydroxide in methanol. (h) Prepared through the acid chloride of **26**. (i) Prepared with the sequence (g) + (h): the starting ethyl ester was synthesized through a Michael reaction of **2a** and ethyl acrylate. (j) Prepared similarly to (i): the starting ester was prepared alkylating the ethyl ester of **26** with methyl iodide in DMF. (k) Prepared by reaction of **1a** with chloroacetyl chloride followed by cyclization with potassium carbonate in DMF and alkylation of the 3,4,4a,5-tetrahydro-1*H*-pyrazino[2,1-*c*][1,4]benzoxazin-2-one obtained. (*l*) 3,3a,4,5-Tetrahydro-2*H*-imidazo[4,3-*a*]quinazolin-1-one (10). (m) 1-(2-Methoxyphenyl)imidazolidin-2-one (mp 151-153°).

and 3,4-dihydrobenzoxazines are obtained (8). Probably in this case the two methyl groups prevent compound **6** from being absorbed on the catalyst. However, when **6** was treated with sodium borohydride both the succinimido group (9) and the double bond were reduced to give **7** from which **1e** could be easily obtained by hydrolysis in concentrated hydrochloric acid. In our experience the acid hydrolysis of hydroxy amides like **7** (see also **1g**) works better than hydrolysis of the corresponding succinimido derivatives, giving purer products in high yields.

Synthesis of **1f**.

Compound **1f** was synthesized following a procedure requiring only three steps, as shown in Scheme III. This simple method could not be applied to the preparation of **1a** because the reaction between 2-aminophenol and **8** gave a complex mixture of products.

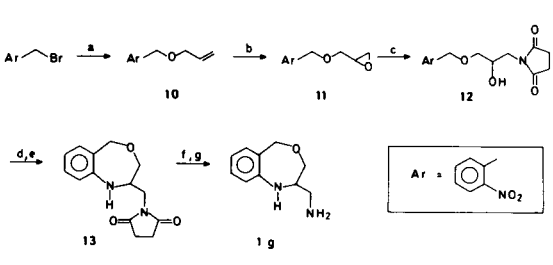
Scheme III



Synthesis of **1g**.

The last intermediate **1g** was prepared according to the method shown in Scheme IV, similar to that of Scheme I, with the exception of the synthesis of the oxirane **11**. This compound could not be obtained directly from 2-nitrobenzyl alcohol and epichlorhydrin but was prepared by oxidizing compound **10**, which was in turn prepared by reacting sodium allylate and 2-nitrobenzyl bromide.

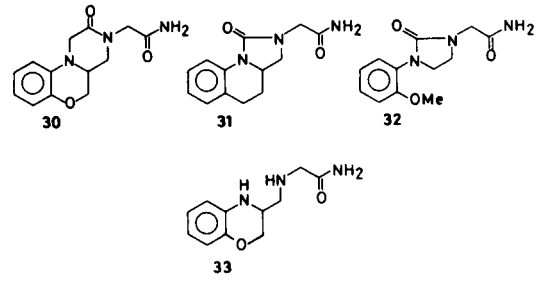
Scheme IV



a) Sodium allilate; b) MCPBA; c) Potassium succinimide; d) Jones reagent; e) H_2/Pd/C f) $NaBH_4$; g) HCl

Synthesis of **2a-g**.

Compounds **1a-g** were easily cyclized to **2a-g** by melting them with urea with a general method described in the experimental part (Table II). The compounds in Table III were obtained from the suitable compounds in Table II by alkylating them with known methods or with $R^3 \rightarrow R^3$ type transformations. When the R^3 carbamoylmethyl group was recognized, among those tried, as the best substituent for the MAO-I activity, the importance of the imidazo-benzoxazine structure was tested by synthesizing three close analogs of compound **19**, that is **30, 31, 32** and **33**. Some details of their preparation are given in the experimental part. All these four products were inactive as MAO-inhibitors.



EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 297 spectrophotometer. Some of nmr spectra were measured on a Brüker-90 MHz spectrometer (indicated as nmr*) and others on a Hitachi-Perkin Elmer R24B and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on a CH-7 Varian MAT spectrometer. Purity was estimated on the basis of differential scanning calorimetry. Analyses are reported in detail in Tables I, II and III and in the Experimental.

2-Methyl-2-(2-nitrophenoxy)propanoic Acid (**3**).

To a stirred solution of 43.1 g (0.27 mole) of sodium 2-nitrophenoxide in DMA (700 ml) 83.5 g (0.43 mole) of ethyl 2-bromo-2-methylpropanoate was added at room temperature and the mixture was heated at 100° for 20 hours. The solution was then cooled and filtered, and the solvent was concentrated *in vacuo*. After dilution with water the mixture was extracted with diethyl ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 51.0 g (75%) of crude propanoate, which was treated with 200 g of potassium hydroxide in 500 ml of methanol. After 20 hours at room temperature, the precipitate was collected by filtration and thoroughly washed with diethyl ether. The solid was then dissolved in water and the aqueous solution was made acid with 37% hydrochloric acid. The precipitate was collected by filtration, washed with water and dried *in vacuo* at 70°, giving 37 g (82%) of **3** as a colourless solid, mp 105-108°; nmr (deuteriochloroform): δ 1.7 (s, 6H, $C(CH_3)_2$), 10.9 (s, 1H, COOH).

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.30; H, 4.92; N, 6.22. Found: C, 53.64; H, 5.00; N, 6.19.

1-Bromo-3-methyl-3-(2-nitrophenoxy)butan-2-one (**4**).

A solution of 27 g (0.12 mole) of **3** in 150 ml of thionyl chloride, was refluxed for 90 minutes. The crude acid chloride obtained as a red oil after evaporation of thionyl chloride *in vacuo* was dissolved in diethyl ether (500 ml) and added to a solution of 14.8 g (0.35 mole) of diazomethane in dry ether (800 ml) at 0°. After being stirred for 20 hours the mixture was cooled at 0° and hydrogen bromide was bubbled in for 40 minutes. The ether was then washed with water, with 10% sodium carbonate and three times with water again. After being dried over anhydrous sodium sulfate, the solution was evaporated *in vacuo* to dryness to give a pale red oil. Crystallization from diethyl ether/petroleum ether (1:1) gave 27.7 g (78%) of **4** as white solid, mp 32°; ir (nujol): ν max 1730 cm^{-1} (CO),

1520 and 1360 ($ArNO_2$).

Anal. Calcd. for $C_{11}H_{12}BrNO_4$: C, 43.72; H, 4.00; N, 4.64. Found: C, 43.86; H, 4.08; N, 4.57.

1-Succinimido-3-methyl-3-(2-nitrophenoxy)butan-2-one (**5**).

To a stirred suspension of 3 g (0.062 mole) of 50% sodium hydride/mineral oil in anhydrous DMA (40 ml), 6.11 g (0.062 mole) of succinimide was added and the mixture was cooled at 0°. A solution of 18.8 g (0.062 mole) of **4** in DMA (40 ml) was added dropwise and the mixture was stirred at 0° for 3 hours, then poured into water. The precipitate was filtered and washed with water. Crystallization from diethyl ether gave 14.7 g (74%) of **5**, mp 92-93°; nmr* (deuteriochloroform): δ 1.60 (s, 6H, $C(CH_3)_2$), 2.82 (s, 4H, $COCH_2CH_2CO$), 4.76 (s, 2H, $COCH_2N$).

Anal. Calcd. for $C_{15}H_{16}N_2O_6$: C, 56.24; H, 5.03; N, 8.74. Found: C, 55.85; H, 5.06; N, 8.64.

2,2-Dimethyl-3-(*N*-succinimidomethyl)-2*H*-1,4-benzoxazine (**6**).

A solution of 14.7 (0.046 mole) of **5** in 300 ml of ethanol was hydrogenated at 4 atm and 60° in the presence of 10% Pd/C as a catalyst. The warm solution was filtered and cooled. The precipitate was collected by filtration and washed twice with cold ethanol yielding 8.8 g (70%) of **6** as white solid, mp 176-178°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 66.00; H, 6.28; N, 10.09.

3,4-Dihydro-2,2-dimethyl-3-[(4-hydroxybutanoyl)aminomethyl]-2*H*-1,4-benzoxazine (**7**).

Eight g (0.20 mole) of sodium borohydride was added in small portions to a warm solution of 19 g (0.07 mole) of **6** in ethanol (600 ml). The solution was stirred for 1 hour at 60° and the ethanol was removed *in vacuo*; water was added and the mixture was extracted with diethyl ether. The ether extracts were wahed with water, dried, and evaporated to yield an oil which was crystallized from *n*-pentane giving 18 g (92%) of **7**, mp 78-80°; ir (nujol): ν max 3450 and 3400 cm^{-1} (NH and OH), 1660 (C=O), 1525 and 1365 ($ArNO_2$); nmr* (DMSO-d_6): δ 1.17 (s, 3H, CH_3), 1.73 (m, 2H, CH_2CH_2OH), 2.21 (m, 2H, CH_2CO), 2.70-3.20 (m, 2H, CH_2N), 3.44 (m, 3H, CH_2OH + CHN), 4.54 (bs, 1H, OH), 5.69 (bs, 1H, ArNH), 7.91 (s, 1H, CONH).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.72; H, 7.96; H, 10.06. Found: C, 64.76; H, 8.06; N, 9.99.

2,2-Dimethyl-3-aminomethyl-2*H*-1,4-benzoxazine (**1e**).

A solution of 3 g (11 mmole) of **7** in 37% hydrochloric acid (100 ml) was refluxed for 10 minutes. After cooling, the precipitate was filtered, washed with little cold water and dried; 1.5 g (65% of **1e** hydrochloride, was obtained, mp >250°.

1-Chloro-3-(*N*-succinimido)propan-2-one (**8**).

To a solution 2.7 g (0.050 mole) of sodium methylate in methanol (250 ml), 50 g (0.050 mole) of succinimide and 43 g (0.45 mole) of epichlorhydrine were added. After standing in the dark at room temperature for 2 days, the solvent was removed *in vacuo* to yield a colourless oil. Crystallization from isopropyl alcohol gave 61.3 g (70%) of 1-chloro-3-(*N*-succinimido)-2-propanol, which was oxidized with Jones solution (225 ml) in 300 ml of acetone at 0°. The solution was then poured into water, extracted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to yield **8** as crude solid, which, after crystallization from ethanol weighed 35.6 g (64%), mp 92-96°.

Anal. Calcd. for $C_7H_8ClNO_3$: C, 44.35; H, 4.25; N, 7.39; Cl, 18.70. Found: C, 44.38; H, 4.29; N, 7.42; Cl, 18.67.

3-(*N*-Succinimidomethyl)-2*H*-1,4-benzothiazine (**9**).

To a stirred solution of 25 g (0.020 mole) of 2-aminothiophenol in dry THF, 12.5 g (0.020 mole) of 50% sodium hydride/mineral oil was added under nitrogen and the mixture was cooled to 0°. A solution of 45 g (0.20 mole) of **8** in dry THF was then added and the mixture was stirred for 1 hour at 0°, then poured into water and extracted with ethyl acetate. After washing with water and drying over anhydrous sodium sulfate, the solvent was evaporated to yield a red oil. Crystallization from ethanol/*n*-pentane (10:1) gave 34 g (65%) of **9**. The product was recrystallized from isopropanol: mp 118-121°; ir (nujol): ν max 1780, 1700 cm^{-1} (cyclic imide), 1640 (C=N); nmr* (deuteriochloroform): δ 2.78 (s, 4H, $COCH_2CH_2CO$), 3.12 (s, 2H, SCH_2), 4.50 (s, 2H, CH_2N).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.29. Found: C, 59.78; H, 4.64; N, 10.42; S, 12.02.

3,4-Dihydro-3-aminomethyl-2*H*-1,4-benzothiazine (**1f**).

Forty g (1.15 moles) of sodium borohydride was added in small portions under nitrogen to a solution of 30 g (0.12 mole) of **9** in ethanol (500 ml) at room temperature. The mixture was stirred for 1 hour at room temperature, the ethanol was removed, water was added and the mixture was extracted with diethyl ether. The ether extracts were washed with water, dried and evaporated to yield 26.5 g (85%) of 3,4-dihydro-2,2-dimethyl-3[(4-hydroxybutanoyl)aminomethyl]-2*H*-1,4-benzothiazine as pale yellow solid, mp 80-82°.

Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 58.62; H, 6.81; N, 10.51. Found: C, 58.61; H, 7.17; N, 10.06.

Twenty-six g (0.10 mole) of this intermediate were treated with 37% hydrochloric acid (200 ml) for 5 minutes and the solution evaporated to one tenth of its volume. The mixture was then diluted with ethanol/isopropyl alcohol (1:1). The precipitate was filtered, washed thoroughly with ethanol and diethyl ether to give 18 g (70%) of **1f**, dihydrochloride, mp 250°.

Allyl 2-Nitrobenzyl Ether (**10**).

Sodium (2.3 g, 0.10 mole) was added to allyl alcohol (100 ml) under nitrogen and the mixture was stirred at room temperature for 1 hour. A solution of 21.6 g (0.10 mole) of 2-nitrobenzyl bromide in allyl alcohol (50 ml) was then added dropwise at 35°. The mixture was stirred at this temperature for 1 hour then poured into water and extracted with diethyl ether. The solution was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was distilled (bp 90-93°/0.2 mm Hg) to give 17.2 g (89%) of **10** as a colourless oil.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.77; H, 5.69; N, 7.01.

3-(2-Nitrobenzyloxy)-1-propene Oxide (**11**).

To a stirred solution of 83 g (0.43 mole) of **10** in dry dichloromethane (1450 ml) a solution of 130 g (0.65 mole) of 85% *m*-chloroperoxybenzoic acid in dry dichloromethane (750 ml) was added. The mixture was stirred at room temperature for 40 hours. The precipitate was filtered off and washed with dichloromethane. The organic layer was subsequently washed with solutions of sodium bisulfite, sodium bicarbonate and water. After drying over anhydrous sodium sulfate, the solvent was evaporated *in vacuo* and the crude oil was distilled at reduced pressure, to yield 78 g (87%) of **11**, bp 142-145°/0.5 mm Hg. A good elemental analysis could not be obtained and the product was used as such for the next step.

1-(2-Nitrobenzyloxy)-3-(*N*-succinimido)-2-propanol (**12**).

A solution of 77.5 g (0.37 mole) of **11** in absolute ethanol (1 *l*) was refluxed under nitrogen for 60 hours with 40.3 g (0.40 mole) of succinimide and 0.6 ml of pyridine. After evaporation of the solvent *in vacuo* and crystallization from methanol, 76.5 (67%) of **12** were obtained, mp 78-83°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.66; H, 5.39; N, 8.74.

1,2,3,5-Tetrahydro-2-(*N*-succinimidomethyl)4,1-benzoxazepine (**13**).

Jones reagent (75 ml) was added dropwise to a solution of 23 g (0.075 mole) of **12** in acetone (300 ml) at 0°. The mixture was stirred at 15° for 8 hours, then poured into water and extracted with ethyl acetate. The solution was washed with water and, after drying over anhydrous sodium

sulfate, the solvent was removed *in vacuo* to yield crude 1-(2-nitrobenzyloxy)-3-(*N*-succinimido)propan-2-one. Crystallization from methanol gave 14.5 g (63%) of a solid, mp 63-65°, which was hydrogenated for 7 hours in ethanol (300 ml) at 4 atmospheres and 60° with 5% Pd/C (3.4 g) as catalyst. The warm solution was filtered and the solvent was removed *in vacuo* to yield a colourless oil. Crystallization from methanol gave 10.15 g (82%) of **13**, mp 117-120°; nmr* (deuteriochloroform): δ 2.72 (s, 4H, $COCH_2CH_2CO$), 3.36 (d, 1H, CH_AH_BN), 3.6 (m, 1H, $NCHCH_2$), 3.96 (dd, 1H, CH_AH_B), 4.46 (d, 1H, $ArCH_AH_BO$), 4.66 (d, 1H, $ArCH_AH_BO$).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.23; H, 6.21; N, 10.56.

1,2,3,5-Tetrahydro-2-aminomethyl-4,1-benzoxazepine (**1g**).

Seven g (0.18 mole) of sodium borohydride were added in small portions to a solution of 8 g (0.030 mole) of **13** in absolute ethanol (450 ml). After stirring for 30 hours, ethanol was removed *in vacuo*, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a colourless oil (8 g) which was treated with 37% hydrochloric acid at 60° for 5 hours. After cooling, the mixture was made alkaline with 20% sodium hydroxide and extracted with diethyl ether. The solution was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated to give 5 g (95%) of the amine **1g** as a colourless oil.

General Method for Compounds **2a-g**.

Compounds **1a-g** (0.10 mole) and urea (0.115 mole) were melted together and heated at 160-180° for 3 hours. The cooled mixtures were ground with plenty of water. The resulting solids were filtered, washed with water and crystallized from a suitable solvent to give **2a-g**; ir (potassium bromide): 3460-3430 cm^{-1} (NH), 1715-1705 (imidazolidinone carbonyl).

General Alkylation Procedure.

To a mixture of the **2a-g** (10 mmole) in DMF, 50% sodium hydride (11 mmole) was added at room temperature. After cooling to 0°, a solution of the alkylating agent (11 mmole) in DMF was added dropwise. The mixture was stirred at 0° for 1 hour and at 25-50° for 3-20 hours, then poured into water and extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give the crude product.

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