Oxazepines and Thiazepines, XXIII[1]:

An Efficient Synthesis of 2,3-Dihydro-1,5-benzoxazepin-4(5H)-ones

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2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5H)-ones **5a-c** have been prepared by ring closure of 3-(2-aminophenoxy)butyric acids **4a-c** obtained by the reduction of 3-(2-nitrophenoxy)butyric acids **3a-c**.

Oxazepine und Thiazepine, 23. Mitt.[1]:
Eine leistungsfähige Synthesemethode für 2,3-Dihydro-1,5-benzoxazepin-4(5H)-one

Die 2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5H)-one **5a-c** wurden durch Ringschluß der 3-(2-Aminophenoxy)-buttersäuren **4a-c** hergestellt. Letztere wurden durch Reduktion der 3-(2-Nitrophenoxy)-buttersäuren **3a-c** erhalten.

2,3-Dihydro-1,4-benzoxazepin-5(4H)-ones can easily be prepared either by *Schmidt* reaction of 4-chromanones[2-6] or by *Beckmann* rearrangement of 4-chromanone oximes[7]. In some cases their 1,5-isomers were also obtained as by-products in these reactions. 2,3-Dihydro-1,5-benzoxazepin-4(5H)-one was synthesized by *Huckle* et al.[2] by ring closure of 3-(2-aminophenoxy)propionic acid. Recently 2,3-dihydro-1,5-benzoxazepin-4(5H)-one derivatives became important substances in drug research since they showed e.g. angiotensin converting enzyme (ACE) inhibitory activity[8] and vasodilating effect[9]. In the course of our work on benzothiazepines and benzoxazepines we are going to synthesize 1,5-benzoxazepine derivatives of biological and pharmacological interest. In our present paper a convenient procedure for the preparation of 2,3-dihydro-1,5-benzoxazepin-4(5H)-ones is reported.

Starting materials were 3-(2-nitrophenoxy)butyric acids **3a-c** prepared by the reaction of appropriately substituted 2-nitrophenols **1a-c** and β-butyrolactone (**2**) under alkaline conditions. Owing to various side reactions the yields were generally less then 30%, but the nitrocarboxylic acids **3a-c** proved to be very convenient intermediates for further chemical transformations. Hydrogenation of **3a-c** gave the 3-(2-aminophenoxy)butyric acids **4a-c** in almost quantita-

Table 1 - Physical Constants and Analytical Data

Compound	Yield (%)	M.p. (°C)	Formula (Mol. Weight)	Analysis (%):	Found Calcd.
				C	H
3a	28	78-79	$C_{10}H_{11}NO_5$	53.2	4.98
			(225.2)	53.3	4.92
3b	28	101-102	$C_{11}H_{13}NO_5$	55.5	5.53
			(239.2)	55.2	5.47
3c	21	114-115	$C_{11}H_{13}NO_5$	55.4	5.43
			(239.2)	55.2	5.47
4a	95	103	$C_{10}H_{13}NO_3$	61.6	6.74
			(195.2)	61.5	6.71
4b	92	95-96	$C_{11}H_{15}NO_3$	63.1	7.16
			(209.2)	63.2	7.22
4c	96	140-141	$C_{11}H_{15}NO_3$	63.1	7.08
			(209.2)	63.1	7.22
5a	72[a]	115	$C_{10}H_{11}NO_2$	68.1	6.26
	87[b]		(177.2)	67.8	6.21
5b	70[a]	131-132	$C_{11}H_{13}NO_2$	69.3	6.96
	84[b]		(191.2)	69.1	6.82
5c	78[a]	161-162	$C_{11}H_{13}NO_2$	69.3	6.89
	80[b]		(191.2)	69.1	6.82

[a] Method A
[b] Method B

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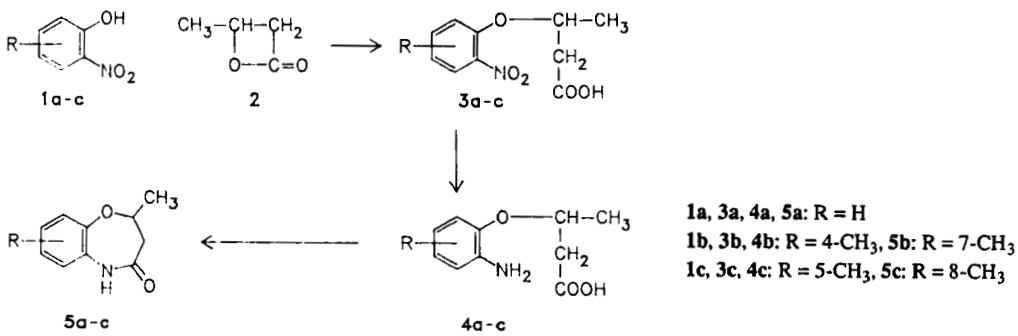
Table 2 - Spectral Data

Compound	MS (m/z)	IR ν (cm^{-1})	^{1}H-NMR δ (ppm)	^{13}C-NMR δ (ppm)
3a[a]	225	1720, 1525, 1360	1.41 (d, 3H, CH_3), 2.64 (dd, 1H, CH_2), 2.88 (dd, 1H, CH_2), 4.93 (m, 1H, $OCH(CH_3)$), 7.00-7.73 (m, 4 aromatic protons)	19.4 (CH_3), 40.9 (CH_2), 72.7 (CH), 116.3 (CH), 120.8 (CH), 125.2 (CH), 133.7 (CH), 140.9 (C), 150.5 (C), 176.6 (C=O)
3b[a]	239	1720, 1530, 1355	1.40 (d, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.63 (dd, 1H, CH_2), 2.87 (dd, 1H, CH_2), 4.87 (m, 1H, $OCH(CH_3)$), 7.03-7.55 (m, 3 aromatic protons)	19.6 (CH_3), 20.1 (CH_3), 41.0 (CH_2), 73.0 (CH), 116.7 (CH), 125.4 (CH), 131.1 (C), 134.4 (CH), 140.9 (C), 148.4 (C), 176.6 (C=O)
3c[a]	239	1720, 1520, 1350	1.40 (d, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.65 (dd, 1H, CH_2), 2.88 1H, CH_2), 4.92 (m, 1H, $OCH(CH_3)$), 6.80-7.70 (m, 3 aromatic protons)	19.6 (CH_3), 21.8 (CH_3), 41.0 (CH_2), 72.7 (CH), 116.8 (CH), 121.7(CH), 125.6 (CH), 138.6 (C), 145.4 (C), 150.8(C), 176.4 (C=O)
4a[b]	195	3300-2000, 1650, 1600	1.23 (d, 3H, CH_3), 2.58 (m, 2H, CH_2), 4.58 (m, 1H, $OCH(CH_3)$), 6.47-6.89 (m, 4 aromatic protons)	19.5 (CH_3), 41.2 (CH_2), 71.4 (CH), 114.4 (CH), 115.8 (CH), 116.0 (CH), 121.9 (CH), 139.4 (C), 143.5 (C), 172.4 (C=O)
4b[b]	209	3370, 3300 2500, 1700	1.20 (d, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.55 (m, 2H, CH_2), 4.49 (m, 1H, $OCH(CH_3)$), 6.27-6.67 (m, 3 aromatic protons)	19.5 (CH_3), 20.6 (CH_3), 41.3 (CH_2), 71.7 (CH), 115.2 (CH), 116.5 (CH), 116.6 (CH), 130.9 (C), 139.4 (C), 141.4 (C), 172.5 (C=O)
4c[b]	209	3300-2600 1680, 1600	1.22 (d, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.56 (m, 2H, CH_2), 4.57 (m, 1H, $OCH(CH_3)$), 6.51-6.63 (m, 3 aromatic protons)	19.5 (CH_3), 20.4 (CH_3), 41.3 (CH_2), 71.4 (CH), 114.5 (CH), 116.5 (CH), 122.2 (CH), 124.8 (C), 136.7 (C), 143.5 (C), 172.4 (C=O)
5a[a]	177	3190, 3130 1685	1.42 (d, 3H, CH_3), 2.57 (dd, 1H, CH_2), 2.72 (dd, 1H, CH_2), 4.79 (m, 1H, $OCH(CH_3)$), 7.03 (m, 4 aromatic protons)	21.2 (CH_3), 41.9 (CH_2), 78.3 (CH), 122.0 (CH), 123.2 (CH), 124.1 (CH), 125.7 (CH), 130.7 (C), 147.8 (C), 172.5 (C=O)
5b[a]	191	3180, 3120 1680	1.40 (d, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.52 (dd, 1H, CH_2), 2.69 (dd, 1H, CH_2), 4.78 (m, 1H, $OCH(CH_3)$), 6.79-6.93 (m, 3 aromatic protons)	20.6 (CH_3), 21.1 (CH_3), 41.7 (CH_2), 78.7 (CH), 122.4 (CH), 123.0 (CH), 126.4 (CH), 130.6 (C), 134.1 (C), 145.5 (C), 172.4 (C=O)
5c[a]	191	3190, 3120, 1685	1.41 (d, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.55 (dd, 1H, CH_2), 2.69 (dd, 1H, CH_2), 4.77 (m, 1H, $OCH(CH_3)$), 6.85 (m, 3 aromatic protons)	20.7 (CH_3), 21.2 (CH_3), 41.8 (CH_2), 78.3 (CH), 121.7 (CH), 123.7 (CH), 124.8 (CH), 127.9 (C), 135.9 (C), 147.5 (C), 172.1 (C=O)

Measured in [a] $CDCl_3$, [b] DMSO-d_6



1a, 3a, 4a, 5a: R = H
1b, 3b, 4b: R = 4-CH_3, **5b:** R = 7-CH_3
1c, 3c, 4c: R = 5-CH_3, **5c:** R = 8-CH_3

tive yield. Ring closure of substances **4a-c** has been performed under two different reaction conditions. The amino acids **4a-c** were allowed to react with dicyclohexylcarbodiimide in anhydrous CH_2Cl_2[10] and the 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5H)-ones **5a-c** were obtained in good yields. Conversion of compounds **4a-c** has also been achieved in hot toluene in the presence of Kieselgel 60 affording **5a-c** with comparable results (Table 1).

Structures of compounds synthesized have been elucidated by IR-, MS-, ^{1}H-, and ^{13}C-NMR-spectroscopic methods; spectral data are summarized in Table 2. On the basis of our experimental results it can be stated that we developed an efficient method for the preparation of 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5H)-ones which can probably be extended for the synthesis of 2,3-dihydro-1,5-benzoxazepin-4(5H)-ones possessing other substituents in position 2.

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Experimental Part

IR-spectra: Perkin-Elmer 221, KBr discs.- Mass spectra: Varian MAT CH-5 or CH-7.- ^{1}H- and ^{13}C-NMR spectra: Bruker AM 400, solutions indicated in Table 2.

3-(2-Nitrophenoxy)butyric acids **3a-c**

β-Butyrolactone (**2**; 0.2 mol) was added to a stirred mixture of **1a-c** (0.1 mol), KOH (0.1 mol), water (50 ml), and N,N-dimethylformamide (50 ml) at 70°C. The solution was stirred and kept at this temp. for 7 h, then poured into water, acidified with dilute HCl and extracted with ether (3 x 40 ml). The ethereal solution was extracted with saturated $NaHCO_3$ solution (3 x 60 ml) and the aqueous phase acidified with dilute HCl, then extracted with ether (3 x 40 ml). The solvent was evaporated and the residue treated with 2 molequiv. KOH dissolved in water (100 ml) at 70°C for 2.5 h, then acidified with dilute HCl, and the residue filtered off. The crude product was crystallized from a mixture of benzene and hexane to afford compounds **3a-c** (Table 1).

3-(2-Aminophenoxy)butyric acids **4a-c**

Compounds **3a-c** (10 mmol) dissolved in ethanol (100 ml) were allowed to react with H_2 in the presence of 50 mg Pd/C (10%) until the end of the H_2-consumption. The catalyst was filtered off, the solvent evaporated and the residue crystallized from a mixture of ethyl acetate and hexane to yield **4a-c** (Table 1).

2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5H)-ones **5a-c**

Method A

A mixture of compounds **4a-c** (10 mmol), anhydrous CH_2Cl_2 (100 ml), and dicyclohexylcarbodiimide (10 mmol) was stirred overnight at room temp. A small amount of acetic acid and ethanol was then added and stirring was continued for another 4 h. The precipitate was filtered off, the solvent evaporated, and the residue crystallized from benzene/hexane to obtain compounds **5a-c**.

Method B

A mixture of compounds **4a-c** (10 mmol), Kieselgel 60 (Merck) (6.0 g), and toluene (60 ml) was refluxed in an apparatus equipped with a water separator for 3 h, then cooled down, the solid material filtered off, and washed with CH_2Cl_2. The solvent was evaporated and the residue crystallized from benzene/hexane to afford **5a-c** (Table 1).

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