SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 5-BENZYL-2-OXAZOLIDONE DERIVATIVES

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A number of 5-benzyl-2-oxazolidone derivatives were synthesized and tested for pharmacological activity.

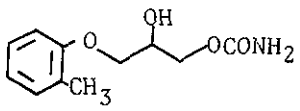
They were found to have muscular relaxing, analgesic and anti-inflammatory activities.

It is well known that some skeletal muscular relaxants contain a carbamate moiety. For example, 2-hydroxy-3-(o-methylphenoxy)propylcarbamate (mephenesincarbamate) (1) and 3-phenylpropylcarbamate (phenprobamate) (2) have the linear carbamate group. 5-Chloro-2-benzoxazolidone (chlorzoxazone) (3) and 5-(o-methoxyphenoxymethyl)-2-oxazolidone (mephenoxalon) (4) contain the cyclic carbamate group. Furthermore, it is interesting that the derivatives of 1,3-benzoxazine (5) have been found to possess an effect on central nervous system[1].

We have prepared the cyclic carbamates such as 3-methyl-

2,3,4,5-tetrahydro[1,3]benzoxazepin-2-one (6)[2], 4-benzyl-oxazolidone (7)[3] which was derived from (2) and 5-benzyl-2-oxazolidone (8), and screened the muscular relaxing activity.

The result showed (6) and (7) did not have the muscular relaxing activity, but (8) had the activity.



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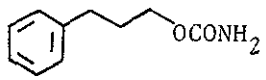

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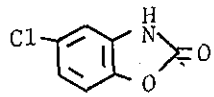

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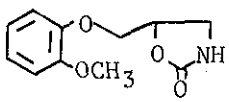

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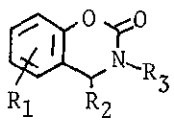

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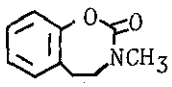

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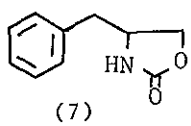

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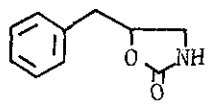
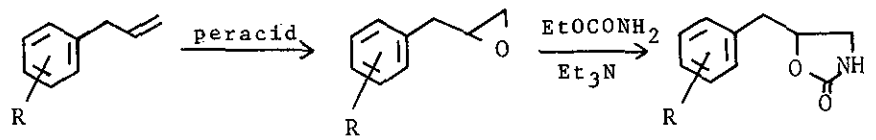


(8)

In an attempt to find the scope of the activity and the effect on the activity with changes in structure of the 5-benzyl-2-oxazolidone derivatives many substituted 5-benzyl-2-oxazolidone derivatives have been synthesized. The present paper deals with the synthesis and pharmacological evaluation of the 5-benzyl-2-oxazolidone derivatives.

The synthesis of the substituted 5-benzyl-2-oxazolidones was accomplished, in general, by heating the appropriate allyl-benzene oxide with ethyl carbamate and triethylamine at 100-150°

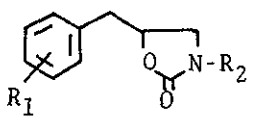
for several hours[4]. Allylbenzene oxide derivatives to be used as starting materials were easily prepared by the reaction of the allylbenzene derivatives with peracids in chloroform (Scheme 1). These new 5-benzyl-2-oxazolidones are listed in Table 1.



(9) (10) (11)

Scheme 1

Table 1 5-Benzyl-2-oxazolidone Derivatives

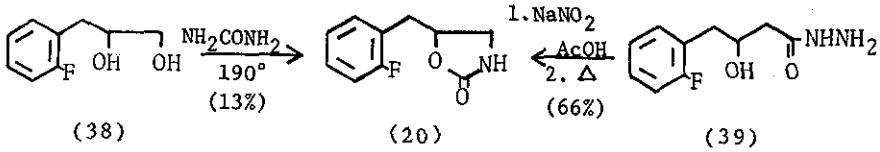


Compd. No.	R_1	R_2	Yield %	Recrystn[a] solvent	Mp.(°C)
8	H	H	34	A	104-105
12	2-Me	H	46	B	121-122
13	3-Me	H	22	A	89- 90
14	4-Me	H	43	B	144-146
15	2-MeO	H	40	C	60- 64
16	4-MeO	H	51	D	121-123
17	2-Cl	H	35	A	114-115
18	3-Cl	H	26	A	113-114
19	4-Cl	H	69[b]	B	125-126
20	2-F	H	—	A	113-114
21	3-F	H	41[b]	A	78- 80
22	4-F	H	37	A	120-121
23	2-Br	H	25	A	130-131

24	3-Br	H	77[c]	A	126-127
25	4-Br	H	24	A	115-117
26	2-CF_3	H	26	A	112-113
27	2-$PhCH_2O$	H	39	A	121-122
28	2-HO	H	88	G	93- 95
29	2-AcO	H	71	A	98- 99
30	2-CH_2=CH-CH_2O	H	88	–	oil
31	2-$(CH_2O)_2CMe$	H	36	A	109-110
32	2-Ac	H	86[e]	A	85- 86
33	H	Me	84	H	80- 82
34	H	n-Pr	59	–	bp_2 169-172
35	H	Ac	74	A	90
36	H	PhCO	88	F	109-111
37	H	$Me_2NCH_2CH_2$	53	–	$bp_{1.5}$ 176

[a] A, C_6H_6-n-C_6H_{14}; B, AcOEt; C, Et_2O-Pet.ether; D, C_6H_6; E, Et_2O; F, EtOH; G, $CHCl_3$-C_6H_6; H, n-C_6H_{14}; I, i-PrOH. [b] Crude. [c] From 4-(m-bromophenyl)-3-hydroxybutyric acid hydrazide. [d] From 41.

5-(o-Fluorobenzyl)-2-oxazolidone (20) was obtained by the reaction of 3-(o-fluorophenyl)propane-1,2-diol[5] (38) with urea at 190° for 5 hours[6]. (20) was also prepared from 4-(o-fluorophenyl)-3-hydroxybutyric acid hydrazide[5] (39) by the Curtius reaction[7] (Scheme 2).



Scheme 2

Hydrogenolysis of 5-(o-benzyloxybenzyl)-2-oxazolidone (27) over palladium on carbon afforded the 5-(o-hydroxybenzyl)-2-

oxazolidone (28), which was treated with acetyl chloride or allyl bromide in the presence of sodium carbonate in acetone under reflux to give (29) or (30). N-Substituted compounds (33)-(37) were prepared by the reaction of (8) with sodium in benzene and then with alkyl halides or acyl halides under reflux.

Pharmacological experiments were performed on mice (ddY, male) or rats (Wistar, male): animals were always treated orally with the test sample suspended in 0.2% carboxymethylcellulose (CMC) solution.

The muscular relaxing action was evaluated by the rotarod method, the traction test and the inclined plane test. The analgesic and anti-inflammatory activities were demonstrated by the acetic-induced writhing method and by the carrageenin-induced edema in the rat hind paw, respectively.

The effects of the typical compounds are shown in Table 2, 3 and 4.

Table 2. ED_{50} values (mg/kg) of the central muscular relaxing effect in mice

Method / Compd	Rotarod method	Traction test	Inclined plane test
8	460	660	940
15	175	350	380
17	210	390	330
19	240	380	520
20	220	315	330
22	295	350	370
23	183	253	270
33	340	500	500
mephenesin	268	460	470

Table 3. Analgesic activities on acetic acid-induced writhing Syndrome in mice

Compd	Ratio of $\frac{\text{Aminopyrine } ED_{50}}{\text{Sample } ED_{50}}$
8	1.23
15	1.64
17	4.39
19	0.78
20	1.18
22	1.30
23	4.05
33	0.83

Table 4. Anti-inflammatory activities on carrageenin-induced edema in rats

Compd	Dosage (mg/kg)	Inhibition (%)[a] 3 hrs	6 hrs	Compd	Dosage (mg/kg)	Inhibition (%)[a] 3 hrs	6 hrs
8	200	49.5	13.0	22	200	52.0	21.3
15	200	32.3	23.3	23	100	64.0	31.1
17	200	16.8	15.9	33	200	33.3	19.7
19	200	30.6	22.8	Phenyl-butazone	200	76.6	45.1
20	200	58.6	21.7				

a Calculated based on the Swelling in the control

These results show the halogeno-substituted compounds have particularly, a strong muscular relaxing activity together with an analgesic and anti-inflammatory activity.

REFERENCES AND NOTES

1 (a) L. Bermardi, S. Code and G.K. Suchowsky, Experientia, 24, 774(1968); (b) Brit.Patent, 1,180,337(1967).

2 (6) was prepared by the cyclization of o-hydroxy-N-methyl-phenethylamine with N,N'-carbonyldiimidazole in tetrahydrofuran. (mp58-59°, 47%).

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5 (38) and (39) were obtained from o-fluorobenzyl bromide as starting material via several steps [(38), oil; (39),mp124-126°].

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