Analgesic Activity of Some 3-(Arylpiperidinomethyl)-2-benzoxazolinone Derivatives

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In our previous study[1,2], the antimicrobial activities of 16 new compounds synthetized by reacting 2-benzoxazolinones with derivatives of piperidine were determined. In this study, the analgesic activities of these compounds, using modified *Koster's* test[3] is investigated. The analgesic activities of these compounds are higher than that of O-acetyl salicilic acid.

Analgetische Effekte einiger 3-(Arylpiperidinomethyl)-2-benzoxazolinone

In unseren früheren Mitteilungen[1,2] wurden die antimikrobiellen Aktivitäten von 16 neuen Substanzen, die durch Kondensation von 2-Benzoxazolinonen mit Piperidin-Derivaten dargestellt wurden, bestimmt. In dieser Arbeit wird die analgetische Aktivität dieser Substanzen nach einem modifizierten Test von *Koster*[3] untersucht: die analgetischen Aktivitäten sind höher als die von O-Acetylsalicylsäure.

After the report on 2-benzoxazolinones as potent hypnotics[4] the biological activities of 2-benzoxazolinone derivatives were widely investigated. They were found to be potent analgesic[5-12], antipyretic[7,8], and antiinflammatory[8] agents.

2-Benzoxazolinones which were modified structurally at the position 3 and systematically at the positions 5 and 6 were screened for their biological activities and aminoalkyl substition at position 3 was found to pronounce the analgesic activity.

Bonte[6] and *Renard*[9] synthesized 6-acyl-2-benzoxazolinone derivatives with analgesic activities more potent than those of aspirin[6,9,13].

In this study, several new 3-(piperidine-1-yl)methyl-2-benzoxazolinone derivatives (Table 1) have been prepared, and their analgesic activity and toxicities at single high dose levels have been examined.

Results and Discussion

16 compounds with 3-(4-arylpiperidine-1-yl)methyl-2-benzoxazolinone structure were synthesized by Mannich reaction using 2-benzoxazolinone, 5-chloro-2-benzoxazolinone, their 6-acyl derivatives and piperidine increments[1,2] (Table 1).

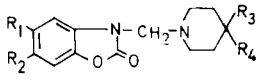
6-Acyl derivatives of 2-benzoxazolinone and 5-chloro-2-benzoxazolinone were prepared by *Friedel-Crafts*-acylation of 2-benzoxazolinone or 5-chloro-2-benzoxazolinone with aromatic acids (Scheme 1).

The compounds were screened for their analgesic activities by a modified *Koster's* method.

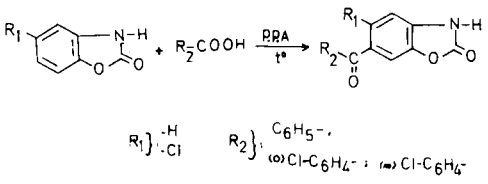
Since all the 2-benzoxazolinone derivatives have analgesic activities, further experiments are carried out to elucidate their antiinflammatory activities and their inhibition of prostaglandin synthesis.

The title compounds were prepared by *Mannich* reaction. 2-Benzoxazolinone derivatives as active hydrogene compounds and piperidine derivatives as amines were used (Scheme 2).

Table 1: 3-Arylpiperidinomethyl-2-Benzoxazolinones



Comp.No:	R^1	R^2	R^3	R^4
1	H	H	-OH	C_6H_5-
2	H	H	-H	C_6H_5-CH_2-
3	H	C_6H_5-CO-	-OH	C_6H_5-
4	H	C_6H_5-CO-	-H	C_6H_5-
5	h	C_6H_5-CO-	-H	C_6H_5-CH_2-
6	H	(o)Cl-C_6H_4-CO-	-OH	C_6H_5-
7	H	(o)Cl-C_6H_4-CO-	-H	C_6H_5-CH_2
8	H	(o)Cl-C_6H_4-CO-	-H	C_6H_5-
9	Cl	H	-OH	C_6H_5-
10	Cl	(o)Cl-C_6H_4-CO-	-OH	C_6H_5-
11	Cl	H	-H	C_6H_5-CH_2-
12	Cl	(o)Cl-C_6H_4-CO-	-H	C_6H_5-
13	Cl	C_6H_5-CO-	-OH	C_6H_5-
14	Cl	C_6H_5-CO-	-H	C_6H_5-
15	Cl	(m)Cl-C_6H_4-CO-	-OH	C_6H_5-
16	Cl	(m)Cl-C_6H_4-CO-	-H	C_6H_5-



Scheme 1

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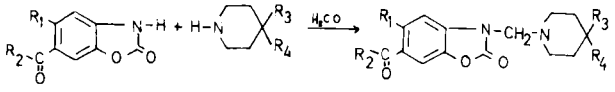

Scheme 2

IR- and ^{1}H-NMR-spectra are in accordance with the anticipated structures.

Experimental Part

Material and Methods

1. Chemistry

2-Benzoxazolinone, 5-chloro-2-benzoxazolinone, 4-hydroxy-4-phenylpiperidine, 4-benzylpiperidine and 4-phenylpiperidine were purchased from Merck and Aldrich.

Melting points: Buchi SMP-20, uncorrected. – UV spectra: Hitachi 2205 Spectrophotometer, methanol $6\cdot10^{-4}$ M concentration. – IR spectra: Perkin Elmer 457 IR Grating Spectrophotometer, KBr pellets. – ^{1}H-NMR spectra: Brucker 200 MHz, [D_6]DMSO, tetramethylsilane as int. standard. – Elemental analysis: Beller Mikroanalytisches Laboratorium, D-3400 Göttingen, Theaterstraße 23, West Germany.

Table 2: 3-Piperidinemethyl-2-Benzoxazolinone Derivatives. Melting points, % yield and elemental analyses.

Comp.No.	m.p °C	Recrys.	%Yield		Elemental Analyses %C	%H	%N
1	195-6	Acetonit.	65	Calcd.	70.4	6.2	8.6
				Found	70.5	6.3	8.7
2	142-3	EtOH	60		74.5	6.9	8.7
					74.6	6.9	8.7
3	144-5	Acetonit.	74		72.9	5.6	6.5
					73.0	5.8	6.5
4	153-4	EtOH	75		75.7	5.9	6.9
					75.5	5.8	6.8
5	159-60	Iso-PrOH	93		76.0	6.1	6.6
					76.0	6.2	6.5
6	175-6	Iso-PrOH	51		67.5	5.0	6.5
					67.6	5.0	6.1
7	172-3	EtOH	65		70.4	5.5	6.1
					70.4	5.4	6.0
8	158-9	EtOH	59		69.9	5.2	6.3
					69.7	5.3	6.3
9	184-5	Acetonit.	81		63.6	5.3	7.8
					63.8	5.4	7.9
10	185-6	Acetonit.	76		62.8	4.5	5.6
					62.8	4.6	6.0
11	101-2	Acetonit.	74		67.3	5.9	7.9
					67.5	5.9	7.8
12	159-60	Iso-PrOH	79		64.9	4.6	5.8
					64.8	4.8	5.8
13	186-7	Iso-ProH	90		67.5	5.0	6.1
					67.5	5.2	6.0
14	177-8	Iso-PrOH	89		69.8	5.2	6.3
					69.8	5.3	6.3
15	160-1	Iso-ProH	85		62.8	4.5	5.6
					62.9	4.6	5.8
16	114-5	Iso-PrOH	72		64.9	4.6	5.8
					65.1	4.7	5.8

a) 6-Acyl-2-benzoxazolinones[13]

200 g polyphosphoric acid were added to 0.1 M benzoxazolinone and 0.1 M aromatic acid (acylating agent) were added in small portions. This mixture was heated and stirred at 150 °C until a dark brown colour was reached, than poured into 900 ml ice water and stirred for a further 7 h. The precipitate so formed was washed, dried and crystallized from appropriate solvents.

b)3-(4-Arylpiperidine-1-yl)methyl-2-benzoxazolinones

A solution of 0.01 M 5-chloro-2-benzoxazolinone (chlorzoxazone) and 0.01 M 1-arylpiperidine in 30 ml methanol was heated to reflux and 1 ml (0.01 M) 37% formaldehyde(w/v) was added dropwise. After stirring a few min the precipitate so formed was crystallized by appropriate solvents (Table 2).

2. *Pharmacology*

Local breed, female albino mice, weighing 22±2g were used. The animals were housed in groups of 6, with food and water ad libitum and were allowed to get accustomed to their environment for at least 2 days before the experiments.

Drugs and routes of administration

The synthesized compounds and aspirin were suspended in 5% gum arabic syrup and were administered orally. 3% acetic acid solution was administered intraperitoneally.

All results were statistically analysed by Student's-T test for paired observations.

Analgesic activity test

Modified Koster's Test was employed. Aspirin was used as reference, pain was induced by i.p. acetic acid (300 mg/kg) injection. – 1 h prior to this injection, the compounds were administered orally to mice grouped in 6, at dose levels given in Table 3. – 2 control groups (n = 6) received gum arabic syrup 1 h before injecting acetic acid. – Animals were placed in glass cages 5 min after acetic acid administration and the number of "streching" per animal was recorded during the following 10 min; % analgesic activity was calculated:

$$\% \text{ Analgesic activity} = \frac{n-n'}{n} x100$$

n = average number of "streching" of control group
n'= average number of "streching" of test group

Toxicity Tests

Compounds with high analgesic activity were employed in toxicity tests: 22 2g mice were grouped in 3. Compounds were administered orally at 1000 mg/kg dose level. Mortality rates and behavioral activity of animals were determined within the following 7 days. When compounds were lethal at 1000 mg/kg, the same procedure was undertaken at 500 mg/kg. Results are given in Table 4.

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Table 3: Analgesic activity test results.

Comp.No.	Dose mg/kg (oral)	% Analgesic activity	Statistical results
1	100	60	$p<0.01$
2	100	55	$p<0.05$
3	100	53	$p<0.05$
4	100	62	$p<0.01$
5	100	60	$p<0.01$
6	100	57	$p<0.05$
7	100	64	$p<0.01$
8	100	61	$p<0.01$
9	100	67	$p<0.01$
10	100	69	$p<0.01$
11	100	66	$p<0.01$
12	100	77	$p<0.01$
13	100	61	$p<0.01$
14	100	68	$p<0.01$
15	100	71	$p<0.01$
16	100	69	$p<0.01$
aspirin	100	48	$p<0.05$

Table 4: Toxicity test results

Comp.no.	Dose (mg/kg) oral	Mortality rate	Observed Toxicity
1	1000	0/3	-
2	1000	0/3	-
3	1000	0/3	-
4	1000	0/3	-
5	1000	0/3	-
6	1000	0/3	-
7	1000	0/3	-
8	1000	0/3	-
9	1000	1/3	muscular hypotony
	500	0/3	-
10	1000	0/3	-
11	1000	0/3	-
12	1000	1/3	muscular hypotony
	500	0/3	-
13	1000	0/3	-
14	1000	1/3	muscular hypotony
	500	0/3	-
15	1000	1/3	muscular hypotony
	500	0/3	-
16	1000	1/3	mild muscular atony
	500	0/3	-

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