2,3-Dimethyl-5-methoxy-1,4-naphthochinon **(2):** Gelbe Nadeln aus Methanol. $C_{13}H_{12}O_3$ (216,2) Ber. C 72,2 H 5,60 Gef. C 72,3 H 5.59. – IR (KBr): 1640, 1660 (C=O) cm^{-1}. – MS (70 eV): m/z = 216 (100 % M^+), 201 (36 %), 187 (32 % M–CO^+), 173 (43 %), 159 (23 %), 145 (37 %). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2,12; 2,14 (2d: 2 CH_3, J = 1Hz), 3,99 (s: OCH_3), 7,24 (q: H-6, J_1 = 7,4 Hz J_2 = 1Hz), 7,62 (t: H-7, J = 7,9 Hz), 7,74 (q: H-8, J_1 = 7,6 Hz J_2 = 1,2 Hz).

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Antiinflammatory Activities of Compounds Derived From Salicylic and Benzoic Acids[+)]

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Eighteen new compounds were prepared from salicylic and benzoic acids. All compounds were studied for antiinflammatory and ulcerogenic activities and for acute LD_{50}. Compound **4h** (table 1) was found to be a potent antiinflammatory agent and to be less ulcerogenic than salicylic acid.

Die entzündungshemmende Aktivität von Verbindungen, die sich von Salicylsäure und Benzoesäure ableiten

18 neue Verbindungen wurden aus Salicylsäure und Benzoesäure synthetisiert. Alle Verbindungen wurden auf ihre entzündungshemmende Wirkung untersucht. Ferner wurde ihre ulcerogene Wirkung

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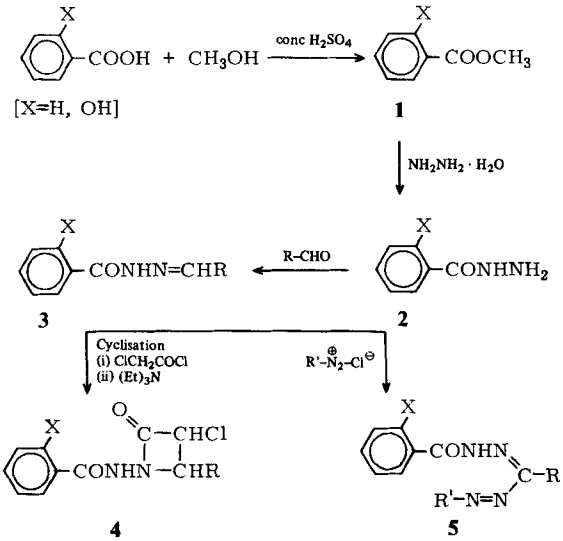
untersucht sowie die LD_{50} and UD_{50} bestimmt. Verbindung **4h** (Tab. 1) zeigte eine starke entzündungshemmende und im Vergleich zu Salicylsäure geringere ulcerogene Wirkung.

Most of the present day nonsteroidal antiinflammatory agents possess ulcerogenic liability which is a limiting factor in the therapy. With the objective of developing better antiinflammatory agents we have synthesized two series of compounds: 3-Chloro-4-substituted(phenyl/indol-3-yl)-1-benzamido/-2-hydroxy-benzamido)-2-azetidinones **4** and 3-substituted(phenyl/indol-3-yl)-1-(benzoyl/2-hydroxy benzoyl)-4-substituted phenylformazans **5** derived from salicylic and benzoic acid. These compounds were evaluated for antiinflammatory activity against carrageenin induced rat paw oedema and also for ulcerogenic potency in rats.



Experimental Part

The compounds were synthesized as shown in the scheme. *MP*: in open capillary tube uncorr. The compounds were routinely checked by TLC on silica gel G.

Benzoyl and 2-hydroxybenzoyl hydrazones

A mixture of 0.01 mole benzoic or salicylic acid hydrazide[1,2] and 0.01 mole of appropriate aromatic aldehyde, and few drops of glacial acetic acid was refluxed for 2 h. The reaction mixture on cooling yielded the corresponding benzoylhydrazone, which was recrystallized.

3-Chloro-4-(2-methoxyphenyl)-1-benzamido-2-azetidinone **(4a)**

To a mixture of 0.01 mole 2-methoxybenzaldehyde benzoylhydrazone and 0.02 mole triethylamine in 20 ml dry D.M.F 0.02 mole chloroacetyl chloride was added dropwise during 30 min, and the reaction

mixture was refluxed for 3 h. The separated solid was filtered off, the filtrate was concentrated and then poured into ice cold water. The solid which separated out was recrystallized from methanol/water. Compounds **4b–4k** were synthesized in the same way.

3-(2-hydroxyphenyl)-1-(2-hydroxybenzoyl)-4-(4-chlorophenyl)formazan **(5a)**

2 g 4-chloroaniline was dissolved in 4 ml glacial acetic acid and 3 ml of conc. HCl was added at 0–5 °C. A solution of $NaNO_2$ (1 g in 5 ml of water) was added dropwise. The diazonium salt solution thus prepared was added with stirring to 2.4 g of 2-hydroxybenzaldehyde-2-hydroxy-benzoyl-hydrazone in 50 ml pyridine. During the addition the temp. was maintained below 12 °C. The reaction mixture thus obtained was left at room temp. for several h and then poured into 250 ml of cold water. The dark red solid which separated out was washed with water and recrystallized from methanol/water. Compounds **5b–5g** were prepared in the same way.

Biological studies

Methods – The animals used in this study were adult albino rats of either sex.

Antiinflammatory activity – A freshly prepared suspension of carrageenin, 0.05 ml (1.0 % in 0.9 % saline) was injected under the planter-aponeurosis of the right paw of the rats by the method of *Winter* et al[3]. One group of ten rats was kept as control and the animals of the other groups of ten each were pretreated with the test drugs given orally 1 h before the carrageenin injection. The vol. of the foot was measured before and 3 h after carrageenin treatment by the micropippette method described by *Buttle* et al[4]. The mean increase in the vol. of paw in each group was calculated and percent antiinflammatory activity was calculated.

Table 1: *3-Chloro-4-substituted(phenyl/indol-3-yl)-1-benzamido/2-hydroxybenzamido)-2-azetidinones* **4** *and their antiinflammatory activity*

Compound No. 4	X	R	M.P. °C	Yield %	Molecular formula	Antiinflammatory activity % inhibition 50 mg/kg p.o.
a	H	2-methoxy phenyl	160	50	$C_{17}H_{15}ClN_2O_3$	33.6
b	OH	2-hydroxy phenyl	140	62	$C_{16}H_{13}ClN_2O_4$	32.1
c	OH	2-fluoro phenyl	224	45	$C_{16}H_{12}ClFN_2O_3$	33.1
d	OH	m-chloro phenyl	235	55	$C_{16}H_{12}Cl_2N_2O_3$	36.0
e	OH	phenyl	152	68	$C_{16}H_{13}ClN_2O_3$	41.0
f	H	m-chloro phenyl	228	48	$C_{16}H_{12}Cl_2N_2O_2$	20.9
g	OH	indolyl	106	70	$C_{18}H_{14}ClN_3O_3$	28.0
h	OH	2-methoxy phenyl	95	52	$C_{17}H_{15}ClN_2O_4$	43.6
i	H	indolyl	122	65	$C_{18}H_{14}ClN_3O_2$	26.7
j	H	phenyl	148	60	$C_{16}H_{13}ClN_2O_2$	30.2
k	H	p-methoxy phenyl	186	56	$C_{17}H_{15}ClN_2O_3$	39.1

All compounds were analysed for N, analysis were found within limits

Table 2: *3-substituted(phenyl/indol-3-yl)-1-(benzoyl/2-hydroxybenzoyl) 4-substituted phenylformazans* **5** *and their antiinflammatory activity*

Compound No. 5	X	R	R′	M.P °C	Yield %	Molecular formula	Antiinflammatory activity % inhibition 50 mg/kg p.o
a	OH	2-hydroxy-phenyl	p-chlorophenyl	185	55	$C_{20}H_{15}N_4ClO_3$	9.0
b	OH	2-hydroxy-phenyl	o-methylphenyl	226	62	$C_{21}H_{18}N_4O_3$	22.1
c	OH	2-hydroxy-phenyl	p-anisyl	270	53	$C_{21}H_{18}N_4O_4$	21.2
d	OH	phenyl	p-anisyl	116	50	$C_{21}H_{18}N_4O_3$	23.4
e	OH	o-tolyl	o-tolyl	190	65	$C_{21}H_{18}N_4O_2$	16.5
f	OH	3-indolyl	p-chlorophenyl	112	48	$C_{22}H_{16}ClN_5O$	35.4
g	H	m-chloro-phenyl	o-chlorophenyl	128	60	$C_{20}H_{14}Cl_2N_4O$	27.0

All the compounds were analysed for N, analysis were found within limits.

Ulcerogenic activity[5] – Albino rats of either sex were divided into groups of 10 animals each. Pregnancy was excluded in the female rats and they were fasted for 24 h prior to the administration of drugs. Water was allowed ad libitum to the animals. Three doses of the most active compound and salicylic acid (control) were given orally. The animals were sacrificed 8 h after drug treatment. The stomach duodenum and jejunum were removed and examined with a hand lens for any evidence of (a) shedding of epithelium (b) petechial and frank haemorrhages and (c) erosion or discrete ulceration with or without the presence of haemorrhage. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.

Results and Discussion

Antiinflammatory activity

All eighteen compounds showed varying degree of antiinflammatory activity. Nine compounds viz. **4a, 4b, 4c, 4d, 4e, 4h, 4j, 4k** and **5f**, exhibited protection of 30 % and above in the dose of 50 mg/kg (oral). Compound **4h** was found to be the most potent showing 43.6 % protection against the carrageenin induced rat paw oedema. This compound was therefore studied in detail at three doses of 25,50 and 100 mg/kg. In these doses, it exhibited a dose related antiinflammatory effect. The ED_{50} for antiinflammatory activity

of compound **4h** was found to be 75.8 mg/kg which was much lower than the ED_{50} (251.5 mg/kg) of salicylic acid (table 3).

Table 3: *Antiinflammatory activity of compound* **4h** *and salicylic acid*

Compound	Dose mg/kg p.o.	% protection	ED_{50}
4h	25	15	
	50	43.6	75.8
	100	53.2	
Salicylic acid	100	17.5	
	200	42.5	251.5
	300	57.5	

Ulcerogenic activity

The compound **4h** was also tested for ulcerogenic activity at three doses viz. 100, 200 and 300 mg/kg (orally) and compared with the ulcerogenic activity of the same doses of salicyclic acid. Interestingly enough the new compound was found to be less ulcerogenic than salicyclic acid (UD_{50} of compound **4h** = 200 mg/kg as compared to UD_{50} of salicylic acid = 158.5 mg/kg) (table 4).

Table 4: *Ulcerogenic activity of* **4h** *and salicylic acid*

Compound	Dose mg/kg p.c.	% ulcer	UD_{50}
4h	100	20	
	200	50	200
	300	70	
Salicylic acid	100	30	
	200	60	158.5
	300	80	

Acute toxicity

The approximate 50 % lethal dose (LD_{50})[6] of compound **4h** given orally was found to be more than 2000 mg/kg the maximum dose tested.

The results of the present study revealed that all compounds (11-azetidinones and 7-formazans) possess antiinflammatory activity of varying degree. The compound **4h** was 3.3 times more potent than salicyclic acid in antiinflammatory activity (table 3) and had lesser ulcerogenic liability (table 4).

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Piperidinediones, III[1)]

Structure-Activity Relationships of the Enantiomers of a Series of 2,6-Piperidinedione Derivatives

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Among the racemic 2,6-piperidinediones **1–6**, compound **6** has the highest anesthetic activity. The enantiomers of **1, 2, 4** and **5** possess different anesthetic potencies depending on the nature of the aliphatic side chain. The S(–)-enantiomers of the piperidinediones **2, 3** and **5** cause initial CNS stimulation with convulsive symptoms followed by anesthesia.

Piperidindione, 3. Mitt.: Struktur-Aktivitätsbeziehungen der Enantiomere einer Reihe systematisch abgewandelter 2.6-Piperidindione

Von den racem. 2.6-Piperidindionen **1–6** ist die Verbindung **6** die narkotisch wirksamste Verbindung. Die Enantiomere von **1, 2, 4** und **5** besitzen in Abhängigkeit von der aliphatischen Seitenkette eine unterschiedliche narkotische Wirkungsstärke. Die S(–)-Enantiomere der Piperidindione **2, 3** und **5** verursachen initial ZNS-Stimulation mit konvulsiven Symptomen, gefolgt von Narkose.

The racemates and the enantiomers of the 2.6-piperidinediones **1–6** (tab. 1), structurally related to the sedative-hypnotic glutethimide (Doriden®), were synthesized[2)] and their absolute configuration was deduced[1)] (tab. 1).

Earlier investigations showed that the enantiomers of N-methylated barbituric acids stereoselectively produce manifold different pharmacodynamic and pharmacokinetic effects[3–7)].

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