3-(N-3'-Aminocarbonyl-2'-hydroxy-1'-phenylethyl)-aminochinolin **(20)**

5 g (0,034 mol) 3-Aminochinolin und 5,6 g (0,034 mol) *trans*-3-Phenylglycidsäureamid werden in 30 ml n-Butanol gelöst und 4 h unter Rückfluß gekocht. Dabei fällt eine farblose Substanz aus, die aus Ethanol umkristallisiert wird. Schmp.: 229°, Ausb.: 6 g (56 % d.Th.).

Sämtliche Elementaranalysen und spektroskopische Daten bestätigen die angegebenen Strukturen.

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Synthesis and Biological Evaluation of Sydnone-4-sulfonamides

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Some 3-arylsydnones have been chlorosulfonated. The resulting sydnone-4-sulfonyl chlorides have been condensed with aromatic and aliphatic amines. The sulfonamides have been evaluated for their antiinflammatory and antimicrobial activities.

Synthese und biologische Prüfung von Sydnon-4-Sulfonamiden

Einige 3-Arylsydnone wurden sulfochloriert. Die erhaltenen Sydnon-4-sulfonyl-chloride wurden mit aromatischen und aliphatischen Aminen zu Sulfonamiden kondensiert. Die Sulfonamide wurden auf ihre entzündungshemmende und antimikrobielle Wirkung geprüft.

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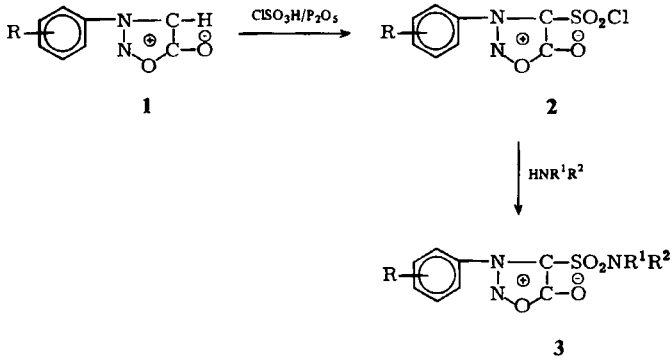
Sydnone derivatives have been extensively studied for their varied biological properties[1]. Aryl sydnones are proven to be less toxic and more active over alkyl sydnones[2]. The presence of chloro and methyl substituents in the phenyl ring of the sydnone was found to enhance the biological activity[3].

Recently we have reported[4] the chlorosulfonation of 3-phenylsydnone in position-4, which serves as an intermediate to synthesise many biologically active sydnone derivatives. The 3-phenyl sydnone-4-sulfonamides have shown weak antiinflammatory and diuretic activity[4].

Now, this chlorosulfonation has been extended to other biologically active arylsydnones with a view to screen their sulfonamides for antimicrobial activity. However these derivatives can also be tested for antiinflammatory activity since some sulfonamides have been found to be good antiinflammatory agents[5].

The sydnones were prepared according to the literature methods[6]. They were chlorosulfonated by adding chlorosulfonic acid in refluxing chloroform in presence of phosphorous pentoxide. The resulting sulphonyl chlorides were condensed with aromatic amines in acetone containing traces of pyridine. The secondary amines were condensed only in pyridine.



1 2 3

Some selected sydnone-4-sulfonamides have been screened for their antibacterial, antifungal and antiinflammatory activities. The compounds have been studied for their acute toxicity test and were found to be nontoxic even at a dose of 300 mg/kg body weight.

Out of eight sydnone-4-sulfonamides tested, six compounds showed weak antiinflammatory activity. The chlorine atom in the phenyl ring of 3-phenyl sydnone enhances the activity.

Out of twelve sydnone-4-sulfonamides **(3a, 3d, 3e, 3f, 3i, 3j, 3m, 3n, 3o, 3r, 3s, 3v)**, tested for antibacterial activity, all have shown activity better than the standard compounds employed. Compounds **3r** and **3s** did not show any activity against S. aureus and B. subtilis. The sulfonamides of primary amines are more active than those of secondary amines. The substitution on the phenyl ring seems to have not much influence on the antibacterial activity.

Out of ten sydnone-4-sulfonamides **(3e, 3r, 3i, 3j, 3m, 3n, 3o, 3r, 3s, 3v)**, screened for antifungal activity only the two compounds. **3e** and **3n** have shown complete inhibition against C. albicans and A. niger. This certainly shows that substitution in the amide group decreases the activity.

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Experimental Section

1) 3-p-Tolylsydnone-4-sulphonylchloride **(2e)**

8.8 g (5 mmole) of 3-p-tolyl sydnone were dissolved in 200 ml of dry chloroform, taken in a three necked flask, provided with a condenser, guard tube, mechanical stirrer and a dropping funnel, 30.0 g phosphorous pentoxide were added and the solution was heated on a water bath. 10.0 ml chlorosulfonic acid were added dropwise during 30 min to the well stirred solution. The reaction mixture was refluxed for 6–7 h. The hot chloroform layer was decanted and the residue was rinsed with hot chloroform. The combined chloroform solution was washed with 10 % sodium hydrogen carbonate solution, followed by water and dried over anhydrous calcium chloride. Chloroform was removed under reduced pressure to leave the residue of **2e** which was crystallised from benzene. Yield 9.8 g (70 %), m. p. 122–124°. $C_9N_7N_2O_4SCl$, Cald. C 39.4 H 2.55 N 10.2 Found: C 39.2 H 2.45 N 10.0.

2) 3-p-Chlorophenylsydnone-4-sulfonylchloride **(2n)**

9.8 g (5 mmole) of 3-p-chlorophenylsydnone were similarly chlorosulfonated. Yield 11.2 g (75 %), m. p. 128–130°. $C_8H_4N_2O_4SCl_2$ Calcd.: C 32.9 H 1.35 N 9.5 Found: C 32.8 H 1.32 N 9.4.

3) 3-p-Tolylsydnone-4-sulfonamide **(3e)**

1.37 g (5 mmole) of **2e** were suspended in 30 ml aqueous ammonia and refluxed on a water bath till all the solid was dissolved. After refluxing for another 5 min the reaction mixture was cooled and diluted with water. Neutralisation with dilute sulphuric acid gave a solid which was washed with water and crystallised from ethanol. Sulfonamides prepared according to the procedure are set out in table 1.

4) 3-p-Tolylsydnone-4-(N-phenyl)sulfonamide **(3f)**

1.37 g (5 mmole) of **2e** were dissolved in 25 ml of dry acetone, containing traces of pyridine. The solution was cooled to 0–5°. Then 0.47 g (5 mmole) aniline were added and the reaction mixture was stirred for 2 h. The reaction mixture was poured into water. After acidification with hydrochloric acid, the solid was washed with water and crystallised from ethanol. Various sydnone-4-sulfonamides prepared in this way are set out in table 1.

5) 3-p-Tolylsydnone-4-(N-diethyl)sulfonamide **(3k)**

To a solution of 0.36 g (5 mmole) of diethylamine in 20 ml pyridine 1.37 g (5 mmole) of **2e** were added in a single lot. After stirring for 30 min, the reaction mixture was poured into water. The solid separated was collected, washed with water and crystallised from ethanol. Various sydnone-4-(N-substituted) sulfonamides prepared in this way are set out in table 1.

Table 1: *Compounds* **3**

3	R	-NR^1R^2	Yield %	M.P. °C	Formula	Calcd. Found C	Analysis H	N
a)	H	-NHphenyl	73	135–136	$C_{14}H_{11}N_3O_4S$	52.9 52.7	3.47 3.40	13.3 13.2
b)	H	-NH(p-chloro-phenyl)	75	175–176	$C_{14}H_{10}N_3O_4SCl$	47.8 47.7	2.84 2.70	12.0 11.8
c)	H	-NH(p-tolyl)	82	138–140	$C_{15}H_{13}N_3O_4S$	54.4 54.2	3.92 3.78	12.7 12.6
d)	H	-NH(2'-thia-zole)	68	205–206	$C_{11}H_8N_4O_4S_2$	40.7 40.6	2.47 2.32	17.3 17.2
e)	p-CH_3	-NH_2	87	148–149	$C_9H_9N_3O_4S$	42.3 42.1	3.52 3.45	16.5 16.2
f)	p-CH_3	-NHphenyl	72	154–155	$C_{15}H_{13}N_3O_4S$	54.4 54.2	3.92 3.78	12.7 12.5
g)	p-CH_3	-NH(p-chloro-phenyl)	75	172–173	$C_{15}H_{12}N_3O_4SCl$	49.2 49.1	3.28 3.15	11.5 11.3
h)	p-CH_3	-NH(p-tolyl)	75	160–162	$C_{16}H_{15}N_3O_4S$	55.6 55.4	4,35 4.21	12.2 12.2
i)	p-CH_3	-NH(2'-thia-zole)	68	208–210	$C_{12}H_{10}N_4O_4S_2$	42.6 42.4	2.96 2.71	16.6 16.3
j)	p-CH_3	-$N(CH_3)_2$	68	140–142	$C_{11}H_{13}N_3O_4S$	46.6 46.5	4.59 4.41	14.8 14.7
k)	p-CH_3	-$N(C_2H_5)_2$	73	171–173	$C_{13}H_{17}N_3O_4S$	50.2 50.2	5.46 5.23	13.5 13.4
l)	p-CH_3	Morpholine	70	162–163	$C_{13}H_{15}N_3O_5S$	48.0 47.8	4.61 4.55	12.9 12.8
m)	p-CH_3	Piperidine	70	151–152	$C_{14}H_{17}N_3O_4S$	52.0 51.9	5.26 5.18	13.0 12.8
n)	p-Cl	-NH_2	80	178–179	$C_8H_6N_3O_4SCl$	34.8 34.7	2.18 2.11	15.3 15.3
o)	p-Cl	-NHphenyl	75	188–190	$C_{14}H_{10}N_3O_4SCl$	47.8 47.6	2.84 2.90	12.0 11.9
p)	p-Cl	-NH(p-chloro-phenyl)	75	196–198	$C_{14}H_9N_3O_4SCl_2$	43.5 43.4	2.33 2.15	10.9 10,7
q)	p-Cl	-NH(p-tolyl)	72	178–180	$C_{15}H_{12}N_3O_4SCl$	49.2 49.1	3.28 3.30	11.5 11.3
r)	p-Cl	-NH(2'-thia-zole)	65	201–202	$C_{11}H_7N_4O_4S_2Cl$	36.8 36.7	1.95 1.75	15.6 15.5
s)	p-Cl	-$N(CH_3)_2$	68	144–145	$C_{10}H_{10}N_3O_4SCl$	39.6 39.4	3.29 3.27	13.8 13.7

Table 1: (Forts.)

3	R	-NR^1R^2	Yield %	M.P. °C	Formula	Calcd. Found C	H	Analysis N
t)	p-Cl	-$N(C_2H_5)_2$	70	142–144	$C_{12}H_{14}N_3O_4SCl$	43.4 43.3	4.22 4.17	12.7 12.5
u)	p-Cl	-Morpholine	75	178–180	$C_{12}H_{12}N_3O_5SCl$	41.7 41.5	3.47 3.43	12.2 12.2
v)	p-Cl	-Piperidine	72	156–157	$C_{13}H_{14}N_3O_4SCl$	45.4 45.6	4.07 4.10	12.2 12.3

Spectral studies

The infrared spectra (KBr) of sydnone-4-sulfonyl-chlorides show a sharp peak at 1810 cm^{-1} which is a characteristic of C=O of sydnone with an electron withdrawing group at position-4[7]. Two strong absorption bands at 1385 and 1160 cm^{-1} are characteristic of the sulfonyl chloride group.
In sydnone-4-sulfonamides the sydnone C=O appears at 1760 cm^{-1}. The SO_2 of -SO_2NH_2 showed two stretching bands at 1350 and 1165 cm^{-1}. The NH_2 of -SO_2NH_2 appeard at 3360 and 3240 cm^{-1}. The stretching frequency of -NH- of -SO_2-NHR^1 was observed at 3260–3240 cm^{-1}.
In the NMR spectra of **3n** the protons of the 3-p-chlorophenyl ring appear as a singlet at δ 7.6 ppm. Two protons of -SO_2NH_2 appear at 7.5 ppm as a singlet. In the spectra of **3o**, the protons of the 3-p-chlorophenyl ring and the protons of the phenyl ring attached to sulfonamide group appeared as a multiplet in the range 7.2–7.6 ppm. The proton of -SO_2NH- appears at 9.1 ppm as a singlet.

Pharmacology

Eight compounds were selected and tested for antiinflammatory activity according to the method described by *Winter* et al[8]. Groups of six albino rats of either sex weighing about 150 g were used. Carrageenin (1 % 0.1 ml) was injected into the plantar surface of the rat's hind paw 1 h after oral administration of the test compound, as a gum acacia suspension (100 mg/kg). The edema formation was measured 3 h after injection and compared with that of carrageenin alone and with the test compound for calculation of percentage inhibition. Phenylbutazone and acetylsalicylic acid were used as standards. Results are set out in table 2.
The antibacterical activity test was carried out according to the cup-plate method, against four organisms: Staphylococcus aureus. Escherichia coli, Bacillus subtils and Proteus vulgaris. 200 µg of compound were used for the testing. Sulfanilamide and phenol were used as standards.

Table 2: *Antiinflammatory activity*

Compound	% of Inhibition	Compound	% of Inhibition
3e	38.0	3n	45.3
3g	28.0	3p	43.2
3h	20.0	3q	32.0
3i	31.0	3r	33.0

The antifungal activity test was carried out against two fungal cultures: Candida albicans and Aspergillus niger. The fungal growth inhibitory action was measured by the turbidity method using spectromic-20 spectrometer. 200 µg of compound were used for testing.

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[Ph 304]

Kurzmitteilungen

Eine Methode zur Messung der Sauerstoffdurchlässigkeit dünner Membranen[1)]

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Zum Schutz oxidationsempfindlicher Arzneistoffe werden Zubereitungen mit natürlichen, halbsynthetischen oder synthetischen makromolekularen, meist organischen Substanzen hermetisch umschlossen. Dabei kann die Schutzschicht äußerst dünn sein (z.B. bei überzogenen Tabletten) oder sie beträgt mehrere hundert bis tausend µm (z.B. bei Blisterpackungen und anderen Kunststoffbehältern). In allen Fällen muß sie dem Durchtritt atmosphärischen Sauerstoffs hinreichenden Widerstand entgegensetzen. In Unkenntnis der Sauerstoffdurchlässigkeit der zur Verfügung stehenden Materialien wird oft, um die geforderte oder erwünschte Haltbarkeit zu garantieren, kostensteigernd mehr an Qualität und Quantität aufgewendet als notwendig wäre. Daraus resultiert der Wunsch, die Sauerstoffdurchlässigkeit von Membranen messen zu können. Die Meßmethode muß

** Herrn Prof. Dr. *H. Oelschläger* zum 60. Geburtstag gewidmet.

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