entsprechenden Lösungsmittel – 1 h vor der i.p.-Gabe von 75 mg/kg Pentetrazol verabreicht. Es wurde die Anzahl der Mäuse festgestellt, bei denen innerhalb von 10 min Krämpfe auftraten.

4. Analgetische Wirkung

Jeweils 10 weibliche Mäuse bildeten eine Versuchsgruppe. Sie wurden nacheinander auf eine 56° warme Platte gesetzt und die Zeit bis zur Reaktion gemessen. Danach erfolgte Applikation der Testsubstanzen per os. Nach 30, 60, 90, 120, 180 und 240 min wurde die Reaktionszeit erneut bestimmt.

Literatur

1 95. Mitt. über Untersuchungen an Pyran-Derivaten, 94. Mitt.: F. Eiden und J. Schünemann, Arch. Pharm. (Weinheim) *316*, 201 (1983).
2 u.a. Y. Gaoni und R. Mechoulam, J. Am. Chem. Soc. *86*, 1646 (1964) und *93*, 217 (1971); T. Petrzilka, W. Haeflinger und C. Sikemeier, Helv. Chim. Act. *52*, 1102 (1909); R.K. Razdan, H.C. Dalzell und G.R. Handrick, J. Am. Chem. Soc. *96*, 5860 (1974); R. Mechoulam und Y. Shivo, Tetrahedron *19*, 2073 (1963); Z. Krejci, M. Horák und F. Santavý, Pharmazie *14*, 349 (1959); D. Shapiro, Ophthalmologia *168*, 366 (1974); B.H. Davees, S.M. Radeliffe, A. Seaton und J.D.P. Graham, Thorax *30*, 80 (1975).
3 Marijuana, Academic Press, New York 1973; R. Mechoulam, N.K. McCallum und S. Burrtem, Chem. Rev. *1976*, 75; R.A. Archer, J. Org. Chem. *42*, 2277 (1977); R.R. Razdan, B.Z. Terris und H.G. Pars, J. Med. Chem. *19*, 454 (1976); J. Melrose, Br. J. Pharmacol. *56*, 361 (1976).
4 F. Eiden und C. Gerstlauer, Arch. Pharm. (Weinheim) *314*, 995 (1981).
5 F. Eiden und C. Gerstlauer, Arch. Pharm. (Weinheim) *315*, 551 (1982).
6 W. Vogt, Phosphorus Sufur *1978*, 123.
7 P.B. Dews, Br. J. Pharmacol. *8*, 46 (1973).
8 H.B. Mann und D.R. Whitney, Ann. Math. Stat. *18*, 50 (1947). [Ph 582]

Arch. Pharm. (Weinheim) *316*, 334–339 (1983)

Synthesis and Biological Evaluation of Sydnone-4-sulfonamides

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3-Phenylsydnone-4-sulfonamides with chloro and methyl substiuents in the ortho or meta positions of the phenyl ring were prepared and evaluated for their antibacterial activity.

Synthese und biologische Prüfung von Sydnon-4-Sulfonamiden

3-Phenylsydnon-4-sulfonamide mit Chlor- und Methyl-Substituenten in ortho und meta Stellung des Phenylringes wurden hergestellt. Die Sulfonamide wurden auf ihre antimikrobielle Wirkung geprüft.

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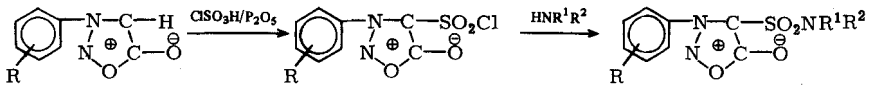
Encouraged by the previous results of the antibacterial activity of sydnone-4-sulfonamides[1], it was thought of interest to synthesize 3-phenylsydnone-4-sulfonamides with chloro and methyl substituents in the o- and m-positions of the phenyl ring.

The sulfonylchlorides were condensed with various primary, secondary and heterocyclic amines. The new compounds were subjected to antibacterial screening. Only a few showed higher activity, most of them equal activity against various bacteriae in comparison to the standard compounds.

The sydnones were prepared according to the literature methods[2]. They were converted into the sulfonamides by chlorosulfonation[3] followed by reaction with amines by the usual methods as shown in the scheme. The structures of all compounds have been confirmed by elemental analysis and spectral data (IR and NMR).



1 **2** **3**

Screening Results

Of all these sydnone derivatives, fifteen compounds have been screened for antibacterial activity. Only **3e** and **3o** showed activity higher than the standard compounds against E. coli. No activity was shown by any compound against S. aureus. Compounds **3f**, **3r** and **3u** have activities equal to that of the standard compounds against P. vulgaris. Compounds **3a**, **3m**, **3d'** and **3j'** were active against E. coli and **3e**, **3o**, **3v** and **3e'** against K. pneumonia. The rest of the compounds did not show appreciable inhibition against any of these organisms. Sulfanilamide and phenol were used as the standard compounds.

We thank Prof. *E. S. Jayadevappa,* Head of the Department for encouragement, and Mr. *B. M. Swamy,* Biochemistry Section for antibacterial testing. One of us *(P. P. P.)* thanks the U. G. C. for a fellowship.

Experimental Section

M. P.: Uncorr. *IR spectra:* (Nujol) Beckman spectrophotometer. *NMR spectra:* 60 MHz, varian A-60 spectrophotometer, TMS ref.

1) 3-o-Tolylsydnone-4-sulphonylchloride **(2a)**

8.8 g (5 mmol) of 3-o-Tolylsydnone was 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 of P_2O_5 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 choroform layer was decanted and the residue was rinsed with hot chloroform. The combined chloroform extract was washed with 10 % sodium hydrogencarbonate solution, followed by water and dried over anhydrous calcium chloride. Chloroform was removed under reduced pressure to leave the

residue of **2a** which was crystallised from benzene. Yield 9.8 g (70 %), m. p. 120–121°C, $C_9H_7N_2O_4SCl$. Calcd C 39.3 H 2.55 N 10.2 Found: C 39.2 H 2.45 N 10.0.

The other three sydnones were similarly chlorosulfonated.

2) 3-m-Tolylsydnone-4-sulfonylchloride **(2b)**

Yield 8 g (64 %), m. p. 123–125°C, $C_9H_7N_2O_4SCl$ Calcd. C 39.3 H 2.55 N 10.2 Found: C 39.5 H 2.48 N 9.9.

3) 3-o-Chlorophenylsydnone-4-sulfonylchloride **(2c)**

9.8 g (5 mmol) of 3-o-chlorophenylsydnone was chlorosulfonated. Yield 9.7 g (75 %), m. p. 99–100°C. $C_8H_4N_2O_4SCl_2$ Calcd. C 32.5 H 1.35 N 9.5 Found: C 32.6 H 1.28 N 9.4.

4) 3-m-Chlorophenylsydnone-4-sulfonylchloride **(2d)**

Yield: 9.6 g (74 %), m. p. 120–122°C. $C_8H_4N_2O_4SCl_2$ Calcd. C 32.5 H 1.35 N 9.5 Found: C 32.5 H 1.30 N 9.5.

5) 3-o-Tolylsydnone-4-sulfonamide **(3a)**

1.37 g (5 mmol) of 3-o-Tolylsydnone-4-sulfonylchloride was suspended in ammonia and refluxed on a water-bath till the solid dissolved. After refluxing for another 5 min, the reaction mixture was cooled and diluted with 20 ml water and neutralised with cold dil. sulfuric acid, and the solid was collected, washed with water and crystallised from ethanol.

6) 3-o-Tolylsydnone-4-(N-diethyl)sulfonamide **(3e)**

To a solution of 0.36 g (5 mmol) of diethylamine in 20 ml pyridine, 1.37 g (5 mmol) of **2a** 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 Tab. 1.

Spectral studies

The IR-spectra (nujol) of the sydnone-4-sulfonylchlorides show a sharp peak at 1810 cm^{-1} which is characteristic of C=O of sydnone with an electron with-drawing group at position-4[4]. Two strong absorption bands at 1385 and 1160 cm^{-1} are of the sulfonylchloride group. The stretching frequencies of $-NH_2$ of $-SO_2NH_2$ and -NH of $-SO_2NHR$ appear at 3360, 3240 cm^{-1} and 3260 to 3240 cm^{-1} resp. In the NMR spectra of **3f** the phenyl protons of the 3-o-tolyl ring appear as a singlet at $\delta=7.5$ ppm and of the methyl group at $\delta=2.5$ ppm. The proton of $-SO_2NH$ appears at $\delta=6.1$ ppm as a singlet.

Pharmacology

Fifteen compounds were tested for antibacterial activity by the disc method[5].

The test organisms were Escherichia coli, Staphylo-coccus aureus, Klebsiella pneumonia and Proteus vulgaris. Sterile filter paper discs (10 mm diameter) saturated with test compound (200 µg/0.1 ml of DMF) was placed on the nutrient agar (1.8 % agar, 0.5 % NaCl, 0.5 % peptone, 3 % Beef extract, 0.5 % glucose, pH 6.8–7.0). The plates were incubated at 37° for 24 h and the zones of inhibition around the discs were measured.

Tab. 1: *Compounds* **3**

No. 3	R	NR^1R^2	Yield %	m.p. °C	Formula	Analysis Calcd. C Found	H	N
a	o-CH_3	$-NH_2$	75	157–158	$C_9H_9N_3O_4S$	42.3 41.9	3.53 3.41	16.5 16.2
b	o-CH_3	$-NHCH_3$	78	139–140	$C_{10}H_{11}N_3O_4S$	44.6 44.5	4.09 4.07	15.6 15.6
c	o-CH_3	$-NHC_2H_5$	65	91–92	$C_{11}H_{13}N_3O_4S$	46.6 46.6	4.59 4.58	14.8 14.7
d	o-CH_3	$-N(CH_3)_2$	62	98–100	$C_{11}H_{13}N_3O_4S$	46.6 46.5	4.59 4.55	14.8 14.6
e	o-CH_3	$-N(C_2H_5)_2$	50	135–136	$C_{13}H_{17}N_3O_4S$	50.2 50.1	5.47 5.41	13.5 13.4
f	o-CH_3	$-NH-C_4H_9$	85	98–99	$C_{13}H_{17}N_3O_4S$	50.2 50.1	5.47 5.43	13.5 13.5
g	o-CH_3	Piperidine	87	129–130	$C_{14}H_{17}N_3O_4S$	52.0 51.8	5.26 5.22	13.0 12.9
h	o-CH_3	Morpholine	78	138–140	$C_{13}H_{15}N_3O_5S$	48.0 47.6	4.62 4.60	12.9 12.8
i	o-CH_3	Pyrrolidine	67	114–115	$C_{13}H_{15}N_3O_4S$	50.5 50.4	4.85 4.81	13.6 13.5
j	m-CH_3	$-NH_2$	72	164–165	$C_9H_9N_3O_4S$	42.3 41.8	3.53 3.45	16.5 16.2
k	m-CH_3	$-NHCH_3$	70	174–175	$C_{10}H_{11}N_3O_4S$	44.6 44.5	4.09 4.02	15.6 15.5
l	m-CH_3	$-NHC_2H_5$	75	118–119	$C_{11}H_{13}N_3O_4S$	46.6 46.6	4.59 4.58	14.8 14.7
m	m-CH_3	$-N(CH_3)_2$	52	88–89	$C_{11}H_{13}N_3O_4S$	46.6 46.5	4.59 4.57	14.8 14.7
n	m-CH_3	$-N(C_2H_5)_2$	45	120–122	$C_{13}H_{17}N_3O_4S$	50.2 50.1	5.47 5.42	13.5 13.6
o	m-CH_3	$-NHC_4H_9$	78	94–95	$C_{13}H_{17}N_3O_4S$	50.2 50.1	5.47 5.44	13.5 13.6
p	m-CH_3	Piperidine	85	149–150	$C_{14}H_{17}N_3O_4S$	52.0 51.8	5.26 5.20	13.0 12.9

Fortsetzung Tab. 1

No.	R	NR^1R^2	Yield %	m.p. °C	Formula	Analysis Calcd. C	H	N
3						Found		
q	m-CH_3	Morpholine	75	167–168	$C_{13}H_{15}N_3O_5S$	48.0	4.62	12.9
						47.6	4.58	12.8
r	m-CH_3	Pyrrolidine	65	135–136	$C_{13}H_{15}N_3O_4S$	50.5	4.85	13.6
						50.4	4.83	13.5
s	o-Cl	$-NH_2$	78	173–174	$C_8H_6N_3O_4SCl$	34.9	2.18	15.3
						34.7	2.15	15.2
t	0-Cl	$-NHCH_3$	75	138–139	$C_9H_8N_3O_4SCl$	37.3	2.76	14.5
						37.4	2.72	14.5
u	o-Cl	$-NHC_2H_5$	68	171–172	$C_{10}H_{10}N_3O_4SCl$	39.5	3.29	13.8
						39.6	3.28	13.9
v	o-Cl	$-N(CH_3)_2$	69	122–123	$C_{10}H_{10}N_3O_4SCl$	39.5	3.29	13.8
						39.6	3.28	14.0
w	o-Cl	$-N(C_2H_5)_2$	52	100–101	$C_{12}H_{14}N_3O_4SCl$	43.4	4.22	12.7
						43.5	4.19	12.6
x	o-Cl	$-NHC_4H_9$	88	106–107	$C_{12}H_{14}N_3O_4SCl$	43.4	4.22	12.7
						43.4	4.20	12.6
y	o-Cl	Piperidine	81	140–141	$C_{13}H_{14}N_3O_4SCl$	45.4	4.08	12.2
						45.5	4.07	12.3
z	o-Cl	Morpholine	63	146–147	$C_{12}H_{12}N_3O_5SCl$	41.7	3.47	12.2
						41.5	3.45	12.1
a′	o-Cl	Pyrrolidine	58	126–127	$C_{12}H_{12}N_3O_4SCl$	43.7	3.64	12.8
						43.8	3.62	12.7
b′	m-Cl	$-NH_2$	75	171–172	$C_8H_6N_3O_4SCl$	34.9	2.18	15.3
						34.8	2.15	15.2
c′	m-Cl	$-NHCH_3$	82	173–174	$C_9H_8N_3O_4SCl$	37.3	2.76	14.5
						37.4	2.74	14.5
d′	m-Cl	$-NHC_2H_5$	60	152–153	$C_{10}H_{10}N_3O_4SCl$	39.5	3.29	13.8
						39.6	3.28	13.9
e′	m-Cl	$-N(CH_3)_2$	68	87–89	$C_{10}H_{10}N_3O_4SCl$	39.5	3.29	13.8
						39.5	3.27	13.9
f′	m-Cl	$-N(C_2H_5)_2$	57	101–102	$C_{12}H_{14}N_3O_4SCl$	43.4	4.22	12.7
						43.5	4.20	12.5

Fortsetzung Tab. 1

No. 3	R	NR^1R^2	Yield %	m.p. °C	Formula	Analysis Calcd. C	H	N
						Found		
g'	m-Cl	$-NHC_4H_9$	85	110–112	$C_{12}H_{14}N_3O_4SCl$	43.4	4.22	12.7
						43.5	4.19	12.6
h'	m-Cl	Piperidine	72	107–108	$C_{13}H_{14}N_3O_4SCl$	45.5	4.08	12.2
						45.4	4.06	12.2
i'	m-Cl	Morpholine	73	132–133	$C_{12}H_{12}N_3O_5SCl$	41.7	3.47	12.2
						41.6	3.46	12.1
j'	m-Cl	Pyrrolidine	63	145–146	$C_{12}H_{12}N_3O_4SCl$	43.7	3.64	12.8
						43.7	3.62	12.7

References

1 K. G. Upadhya, B. V. Badami and G. S. Puranik, Arch. Pharm. (Weinheim) *314,* 470 (1981).
2 W. Baker, W. D. Ollis and V. D. Poole, J. Chem. Soc. *1949,* 307.
3 B. G. Ugarkar, B. V. Badami and G. S. Puranik, Arch. Pharm. (Weinheim) *312,* 977 (1979).
4 C. V. Greco, J. Tobias and C. Kier, J. Heterocycl. Chem. *4,* 160 (1967).
5 R. S. Varma and W. L. Nobles, J. Pharm. Sci. *57,* 1801 (1968). [Ph 583]

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Lactone, 2. Mitt.[1)]

Synthese dihydroxylierter Diphenylalkylamine über Azalactone

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Durch Umsetzung von Aminosäuren wie Sarcosin, Prolin und N-Methylanthranilsäure mit verschiedenen Oxiranen erhält man Azalactone, die mit Phenyllithium in neuartige dihydroxylierte Diphenylalkylamine überführt werden können. **11** zeigt hohe histaminolytische Aktivität.

Lactones, II: Synthesis of Dihydroxylated Diphenylalkanamines via Azalactones

Treatment of amino acids like sarcosine, proline and *N*-methylanthranilic acid with various oxiranes yields azalactones, which can be transformed to dihydroxylated diphenylalkanamines. Compound **11** shows high histaminolytic activity.

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