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Syntheses and Biological Activities of 3-[4-(Alkoxycarbonyl)phenyl]sydnones and their Derivatives

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Four new 3-[4-(alkoxycarbonyl)phenyl]sydnones have been synthesised. The hydrazide **4** is condensed with various aromatic aldehydes to obtain the corresponding Schiff bases. Antimicrobial activities of the sydnones and some Schiff bases are reported. Mass spectral fragmentation of 3[4-(ethoxycarbonyl)phenyl]sydnone is discussed.

Synthese und biologische Aktivität von 3-(p-Alkoxycarbonylphenyl)-sydnonen und ihren Derivaten

Vier neue 3-(p-Alkoxycarbonylphenyl)-sydnone wurden hergestellt. Das Hydrazid **4** wurde mit verschiedenen aromatischen Aldehyden kondensiert, um die entsprechenden Schiffschen Basen zu erhalten. Über die antimikrobielle Aktivität aller Sydnone und einiger Schiffscher Basen wird berichtet. Die ms Fragmentierung von 3-(p-Ethoxycarbonylphenyl)-sydnon wird diskutiert.

Among the various mesoionic systems, sydnones are known to exhibit a wide range of biological properties[1,2]. Many sydnone derivatives synthesised from this laboratory have shown antibacterial[3], antiinflammatory[4] and CNS depression[5] properties. The pharmacological utility of hydrazones in tuberculosis[6,7] prompted us to investigate sydnones possessing these groups.

Because of the difficulty in converting the carboxyl group into an ester due to the susceptibility of the sydnone ring to acid and heat, the 3-(p-alkoxycarbonylphenyl)-sydnones were synthesised starting with alkyl p-aminobenzoates. The alkyl p-aminobenzoates obtained by following the standard procedure[8] were condensed with sodium chloroacetate to yield the respective glycines. These glycines were then converted[9] into the sydnones **3a–3d**.

The hydrazide of 3-(p-ethoxycarbonylphenyl)-sydnone **4** was prepared by reacting the above sydnone with hydrazine hydrate in ethanol. **4** was condensed with aromatic aldehydes to yield the Schiff bases **5a–5l** (Scheme 1).

The infrared spectra (nujol) of **3a–3d** showed bands at 1750–1770 cm^{-1} (sydnone C=O), 1700–1725 cm^{-1} (C=O of COOR) and 3160–3200 cm^{-1} (sydnone C–H). The IR spectrum of **4** showed strong absorption bands at 1750 and 1630 cm^{-1} due to sydnone C=O and hydrazone C=O, resp. Bands at 3330 and 3280 cm^{-1} are due to the N–H group of hydrazide. The IR spectra of **5a–5l** showed bands at 1770–1785 (sydnone C=O), 1735–1745 (C=O of hydrazone), 1640–1650 (C=N), 3120–3140 (sydnone C–H) and 3210–3240 cm^{-1} (N–H) vibrations.

The NMR spectrum ($CDCl_3$) of **3a** displayed two singlets at $\delta = 6.7$ ppm (1H) and at $\delta = 3.9$ ppm (3H) due to sydnone-4-H and CH_3 of the ester group, resp. A multiplet centered at $\delta = 7.85$–8.35 ppm

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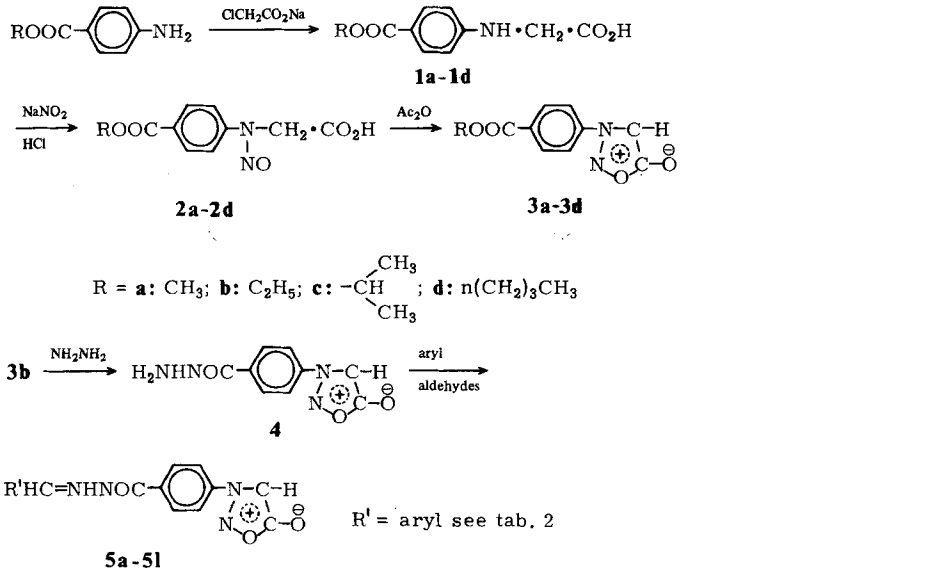
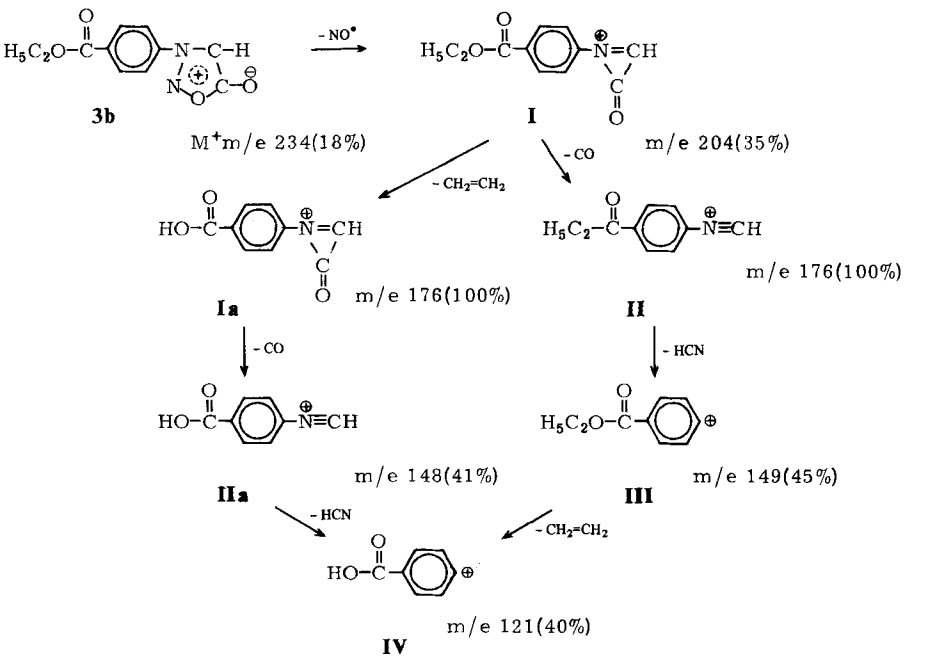
Scheme 1



Scheme 2



is due to the phenyl protons. The NMR spectrum of **3b** exhibited a one proton singlet at $\delta = 6.3$ ppm due to sydnone-4-H. The three proton triplet at $\delta = 0.7$–1.0 ppm and the two proton quartet at $\delta = 3.8$–4.1 ppm are due to CH_3 and CH_2 of the ester group, resp. The four proton multiplet at $\delta = 7.45$–7.9 ppm is assigned to phenyl protons.

The mass spectrum (Scheme 2) of **3b** exhibited the molecular ion peak $M^{+\cdot}$ at m/e 234 (18 %) and base peak **II** at m/e 176 (100 %) corresponding to the loss of nitric oxide radical and carbon monoxide which is in agreement with the established fragmentation of the sydnone ring[10]. The ion **III** obtained by the expulsion of a hydrogen cyanide molecule, further eliminates an ethylene molecule[11] to end up in an abundant ion **IV** at m/e 121 (40 %). This ion follows the well known breaking pattern for benzoic acid[12]. It is equally probable that the even electron ion **I** can eliminate a neutral fragment of ethylene to give the base peak **Ia** at m/e 176 (100 %). This ion **Ia** can further eliminate a molecule of carbon monoxide to give ion **IIa** which ends up in ion **IV** by the expulsion of a hydrogen cyanide molecule.

Screening results

The antibacterial activity of the compounds **3a–3d**, **5a–5c**, **5e** and **5l** was determined against S. aureus, E. coli. S. typhi and P. pyocyanous according to the method of *Varma* and *Nobles*[13].

For the four sydnones **3a–3d** tested no activity was observed against Gram-positive S. aureus but they inhibited partially or completely the growth of the three Gram-negative organisms. A slight increase in activity with lengthening of the alkyl side chain was observed. Schiff bases **5a–5c**, **5e** and **5l** showed higher activity against S. typhi and E. coli than the references (sulfanilamide and phenol). The presence of a chloro atom in the aldehyde part enhances the activity. No activity was observed against S. aureus and P. pyocyanous.

The compounds were tested against two fungal cultures C. albicans and A. niger. The four sydnones **3a–3d** showed better antifungal activity against C. albicans. Of the five Schiff bases, no compound showed complete inhibition of either of the fungi. Substitution in the phenyl ring of the hydrazone did not enhance the antifungal activity.

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Experimental Part

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

1) The *p-alkoxycarbonylphenylglycines* **1a–1d**, N-nitroso-p-alkoxycarbonylphenylglycines **2a–2d**, and p-(alkoxycarbonylphenyl)-sydnones **3a–3d** were prepared according to earlier methods[9] (Tab. 1).

2) *Hydrazide of 3-(p-ethoxycarbonylphenyl)-sydnone* **(4)**

A mixture of 2.34 g (10 mmol) sydnone in 50 ml of ethanol and 0.5 ml (10 mmol) 100 % hydrazine hydrate was refluxed on a water bath for 4 h. The solvent was evaporated and the residue crystallised from methanol-dioxan (1:1). Yield 1.9 g (90 %). m.p. 225–226 °C, $C_9H_8N_4O_3$. Calcd. C 49.1 H 3.64 N 25.5 Found: C 49.6 H 3.96 N 25.3.

Tab. 1: *Compounds* **1–3**

No.	Yield %	m.p. °C	Formula*	Analysis Calcd. N	Found N
1a	52	173–175	$C_{10}H_{11}NO_4$	6.7	6.8
1b	55	157–158	$C_{11}H_{13}NO_4$	6.3	6.2
1c	45	150–151	$C_{12}H_{15}NO_4$	5.9	5.8
1d	38	179–180	$C_{13}H_{17}NO_4$	5.6	5.5
2a	85	167–168	$C_{10}H_{10}N_2O_5$	11.8	11.6
2b	88	157–158	$C_{11}H_{12}N_2O_5$	11.1	11.3
2c	69	96–97	$C_{12}H_{14}N_2O_5$	10.5	10.5
2d	75	79–80	$C_{13}H_{16}N_2O_5$	10.0	9.9
3a	86	188–189	$C_{10}H_8N_2O_4$	12.7	12.4
3b	82	148–149	$C_{11}H_{10}N_2O_4$	12.0	12.0
3c	79	169–170	$C_{12}H_{12}N_2O_4$	11.3	11.1
3d	72	84–85	$C_{13}H_{14}N_2O_4$	10.7	11.0

* All compounds gave satisfactory analyses for C and H.

3) *Schiff bases* **5a–5l**

To an ethanolic suspension of 0.44 g (2 mmol) of **4** 0.3 ml (3 mmol) benzaldehyde was added and refluxed on a water bath for 2 h. The solvent was then evaporated and the residue crystallised from methanol. Other hydrazones are similarly prepared and listed in Tab. 2.

Tab. 2: *Compounds* **5**

5	R	Yield %	m.p. °C	Formula*	Analysis Calcd. N	Found N
a	C_6H_5	78	244–245[a]	$C_{16}H_{12}N_4O_3$	18.2	18.1
b	p-ClC_6H_4	82	247–248[b]	$C_{16}H_{11}N_4O_3Cl$	16.4	16.6
c	p-$NO_2C_6H_4$	89	279–280[c]	$C_{16}H_{11}N_5O_5$	19.8	19.5
d	p-$CH_3C_6H_4$	67	237–238[b]	$C_{17}H_{14}N_4O_3$	17.4	17.4
e	p-OHC_6H_4	90	300–301[a]	$C_{16}H_{12}N_4O_4$	17.3	17.1
f	p-$CO_2HC_6H_4$	56	232–233[a]	$C_{17}H_{12}N_4O_5$	15.9	15.9
g	o-OHC_6H_4	72	270–271[a]	$C_{16}H_{12}N_4O_4$	17.3	16.9
h	2-OH-5-Br-C_6H_3	75	258–259[b]	$C_{16}H_{11}N_4O_4Br$	13.9	13.7
i	2-OH-5-NO_2-C_6H_3	70	285–286[c]	$C_{16}H_{11}N_5O_6$	19.0	18.8
j	2,4(OCH_3)$_2C_6H_3$	65	203–204[b]	$C_{18}H_{16}N_4O_5$	15.2	15.2
k	6-CH_3-2-pyridyl	52	262–263[b]	$C_{16}H_{13}N_5O_3$	21.7	22.0
l	2-furyl	85	233–234[a]	$C_{14}H_{10}N_4O_4$	18.8	18.8

a = methanol; b = methanol-dioxan; c = methanol-acetic acid

* All the compounds gave satisfactory C and H analyses.

Pharmacology

For antimicrobial studies the concentration used was 2000 µg/ml, and 0.1 ml of the test solution was employed. All compounds were dissolved in purified DMF. The bacterial and fungal growth inhibitions were measured by the paper disc method or the turbidity method at 660 nm using a spectronic-20 spectrophotometer, resp. 5 % salicylic acid was employed as standard for the latter.

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Ether Derivatives of 3-Amino-1,2-propanediols, IV[2)]

Syntheses and Pharmacological Investigations of 1-Cycloalkoxy-3-amino-2-propanols and 1-Cycloalkoxy-3-guanidino-2-propanols

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By reaction of the 1-cycloalkoxy-2,3-epoxypropanes **1a–d** with 25 % ammonia the 1-cycloalkoxy-3-amino-2-propanols **2a–d** and the *N,N*-bis(3-cycloalkoxy-2-hydroxypropyl)amines **3a–d** were synthesized.

By condensation of **2a–d** with 2-methyl-2-thiopseudourea sulfate the guanidine derivatives **4a–c** were obtained. All compounds were investigated for β-blocking, antiarrhythmic, hypotensive and local anesthetic activities.

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