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Antiinflammatory Sydnones. 1

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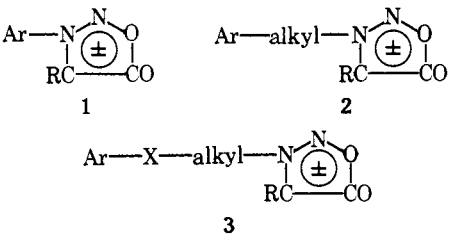
Mesoionic compounds have been studied extensively as possible medicinal agents but, while many have proved interesting, none has shown activity at levels sufficiently high to be of practical interest.[1]

In an attempt to develop a series of mesoionic compounds with consistent biological activity, the synthesis of several series of sydnones was undertaken.

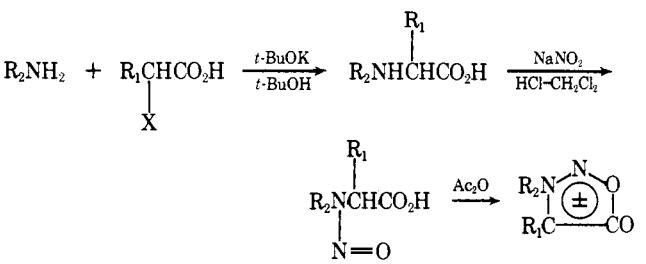


1 2

3

Encouraged by the finding that 3-(*o*-biphenyl)sydnone (1, Ar = 2-biphenylyl; R = H) possesses high antiinflammatory activity, the synthesis of other 3-aryl-4-alkyl (or 4-H) sydnones was carried out (see Scheme I). Pharmacological screening results were disappointing and attention was next focused on the synthesis of 3-aralkyl-4-H or 4-alkylsydnones (2). Again, little activity was noted, and the synthesis of a series of sydnones with a heteroatom in the 3-alkyl side chain (3) was initiated.

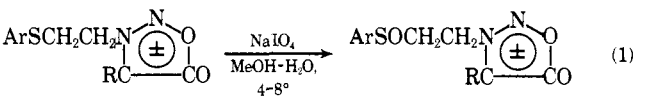
Scheme I



Standard procedures[2] were employed in the preparation of these sydnones. Alkylation of the appropriate amines with α-halo acids yielded the requisite N-substituted amino acids. When the reactions were carried out in *tert*-butyl alcohol with potassium *tert*-butoxide as base, nearly quantitative yields of substituted amino acids were obtained. The amino acids were then treated with sodium nitrite in aqueous hydrochloric acid-methylene chloride and the resulting *N*-nitrosamino acids, without purification, subjected to cyclodehydration in acetic anhydride to yield the desired sydnones.

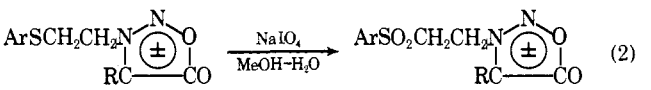
2-Phenylthioethylamine, 2-phenoxyethylamine, and *p*-chlorophenylthio-2-propylamine were prepared by treating the appropriate phenol or thiol with ethanolamine in propionic acid, followed by acidic hydrolysis.[3] Ethylenediamine was treated with tosyl chloride to give 2-aminoethyl-*p*-toluenesulfonamide, and thiophenol reacted with 3-bromopropylamine to give 3-phenylthiopropylamine.[4]

Generation of the sulfoxides 13 and 14 and sulfones 15 and 16 in the presence of the readily oxidized sydnone ring[5,6] was accomplished by treatment with sodium metaperiodate in aqueous methanol. At temperatures of 4-8° the sulfoxide is obtained in quantitative yield (eq 1). At



(1)

ambient temperatures, the sulfone is obtained in comparable yield, even in the presence of excess oxidant (eq 2).

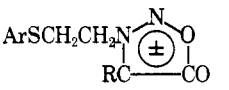


(2)

As can be seen from Table I, a series of potent antiinflammatory sydnones is obtained when the *o*-biphenyl group in 1 is replaced by 2-arylthio and 2-arylsulfoxyethyl substituents. The ED_{50} of 5 mg/kg shown by 10 is equal to hydrocortisone or phenylbutazone in this test. Comparing the sulfides 11 and 12 with the sulfoxides 13 and 14 and sulfones 15 and 16, potency is diminished as the oxidation state increases.

Activity is greatly reduced when sulfur is replaced by oxygen (17) and is eliminated entirely when it is replaced by a sulfonamide (18) or methylene (19) group. Lengthening the ethylene bridge (20) and branching† (21) also adversely affect potency.

Consideration of these results indicates that 22 constitutes a general structure type which can be expected to exhibit potent antiinflammatory activity.



22

Ar = phenyl or substituted phenyl
R = H or CH_3

Studies are in progress to define the structural requirements for activity in greater detail by examining the effects of changes in R and Ar.

Experimental Section‡

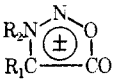
General Synthesis of Sydnones. (a) Alkylation. The appropriately substituted α-bromoacetic acid (0.1 mol), 2-arylthioethylamine (0.1 mol), and *t*-BuOK (0.1 mol) in 600 ml of *t*-BuOH were heated at reflux under nitrogen overnight. The solvent was removed under reduced pressure and the residue was taken up in 250 ml of 2% aqueous NaOH. The aqueous solution was extracted with Et_2O and acidified to pH 5 with concentrated HCl. Filtration and washing with H_2O gave the amino acid sufficiently pure for nitrosation.

(b) Nitrosation. The amino acid (0.08 mol) and $NaNO_2$ (0.09 mol) in 400 ml of 1:1 CH_2Cl_2-H_2O were stirred at 0° while 8 ml of concentrated HCl was added dropwise over a 1-hr period. Stirring

† The presence of a *p*-chloro substituent on the phenyl ring increases antiarthritic activity: H. Wagner and J. Hill, unpublished results.

‡ Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Elemental analyses, indicated by symbols of the elements, were within ±0.4% of the theoretical values. Ir, uv, and nmr spectra of all new compounds were consistent with proposed structures.

Table I



Compd	R_1	R_2	Mp, °C	Crystn solvent	Formula	Analyses	Activity[a]	ED_{50}[b]
1	H	o-PhC_6H_4-	139–139.5	MeOH–Et_2O	$C_{14}H_{10}N_2O_2$	C, H, N	1 (++)	
2	H	p-$PhOC_6H_4$-	149–150	MeOH	$C_{14}H_{10}N_2O_3$	C, H, N	25 (0)	
3	CH_3	p-$PhOC_6H_4$-	132–133	MeOH	$C_{15}H_{12}N_2O_3$	C, H, N	25 (0)	
4	H	Ph_2CH-	80–81	Et_2O	$C_{15}H_{12}N_2O_2$	C, H, N	25 (+)	
5	CH_3	Ph_2CH-	93–94	Et_2O	$C_{16}H_{14}N_2O_2$	C, H, N	25 (0)	
6	$(CH_3)_3C$-	Ph_2CH-	111–112	Et_2O–CH_2Cl_2	$C_{19}H_{20}N_2O_2$	C, H, N	25 (0)	
7	$PhCH_2$-	$PhCH_2CH_2$-	88	Et_2O	$C_{17}H_{16}N_2O_2$	C, H, N	25 (0)	
8	$(CH_3)_3C$-	p-$ClC_6H_4CH_2CH_2$-	70–70.5	Et_2O	$C_{14}H_{17}ClN_2O_2$	C, H, N, Cl	25 (0)	
9	$(CH_3)_3C$-	3,4-$(CH_3O)_2C_6H_3$-	66–67	Et_2O–CH_2Cl_2	$C_{16}H_{22}N_2O_4$	C, H, N	25 (0)	
10	CH_3	$PhSCH_2CH_2$-	69–71	Et_2O–$(CH_3)_2CO$	$C_{11}H_{12}N_2O_2S$	C, H, N, S	2.5 (++)	5
11	CH_3	p-$(CH_3)_3CC_6H_4S(CH_2)_2$-	60–61	Et_2O	$C_{15}H_{20}N_2O_2S$	C, H, N, S	2.5 (++)	1.7
12	H	$PhS(CH_2)_2$-	40–42	Et_2O	$C_{10}H_{10}N_2O_2S$	C, H, N	2.5 (++)	2
13	CH_3	p-$(CH_3)_3CC_6H_4SO(CH_2)_2$-	101–103	Et_2O	$C_{15}H_{20}N_2O_3S$	C, H, N, S	2.5 (++)	3.5
14	H	$PhSO(CH_2)_2$-	118–119	Et_2O	$C_{10}H_{10}N_2O_3S$	C, H, N, S	5 (+++)	4.3
15	CH_3	p-$(CH_3)_3CC_6H_4SO_2(CH_2)_2$-	135–137	Et_2O	$C_{15}H_{20}N_2O_4S$	C, H, N, S	32 (++)	
16	H	$PhSO_2(CH_2)_2$-	141–142	$(CH_3)_2CO$	$C_{10}H_{10}N_2O_4S$	C, H, N, S	10 (++)	
17	CH_3	$PhO(CH_2)_2$-	78–80	THF–H_2O	$C_{11}H_{12}N_2O_3$	C, H, N	15 (+)	
18	CH_3	p-$CH_3C_6H_4SO_2NH(CH_2)_2$-	158–160	$(CH_3)_2CO$	$C_{12}H_{15}N_3O_4S$	C, H, N, S	30 (0)	
19	CH_3	$Ph(CH_2)_3$-	61–65	Et_2O–$(CH_3)_2CO$	$C_{12}H_{14}N_2O_2$	C, H, N	25 (0)	
20	CH_3	$PhSO(CH_2)_3$-	127–128	Et_2O–$(CH_3)_2CO$	$C_{12}H_{14}N_2O_3S$	C, H, N, S	30 (0)	
21	CH_3	p-$ClC_6H_4SCH_2CH(CH_3)$-	84–85	Et_2O–$(CH_3)_2CO$	$C_{12}H_{13}ClN_2O_2S$	C, H, N, S	30 (0)	

[a] Lowest dosage (mg/kg) at which compound was tested in adjuvant arthritis assay and degree of activity at that dose level. Inhibition of arthritic swelling: 70–100% (+++), 40–69% (++), 25–39% (+). [b] mg/kg.

was continued for 2 hr and the CH_2Cl_2 layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residual oil was cyclized without further purification.

(c) **Cyclization.** The nitrosamino acid (0.075 mol) was dissolved in 300 ml of Ac_2O and allowed to stand at ambient temperatures under nitrogen for 4 days. The solution was poured into 600 ml of H_2O and stirred. When hydrolysis was complete, the two-phase mixture was extracted with CH_2Cl_2. The combined extracts were washed with H_2O, aqueous $NaHCO_3$, and H_2O, dried (Na_2SO_4), and evaporated to dryness. Crystallization from the appropriate solvent gave pure sydnone.

Oxidation to Sulfoxides. A solution of the sydnone (0.02 mol) in a minimum amount of MeOH was added at once to a stirred solution of 8.7 g (0.04 mol) of $NaIO_4$ in 75 ml of H_2O at 4–8° and maintained at that temperature for 16 hr. The resulting mixture was filtered and the filter cake washed with $CHCl_3$. The filtrate was extracted with $CHCl_3$ and the combined $CHCl_3$ washes and extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. Recrystallization from the appropriate solvent gave the pure sydnone.

Oxidation to Sulfones. A solution of the sydnone (0.02 mol) in a minimum amount of methanol was added at once to 15 g (0.135 mol) of $NaIO_4$ in 100 ml of H_2O and the mixture stirred at ambient temperatures for 48 hr. The mixture was diluted with 300 ml of water and extracted with $CHCl_3$. The extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. Recrystallization from the appropriate solvent gave the pure sydnone.

Pharmacological Method. A modification of the method of Pearson, *et al.*,[7] was employed to induce an arthritic syndrome in rats which resembles rheumatoid arthritis.

Intact, male Sprague-Dawley rats initially weighing approximately 170 g were divided into groups of 12 each and inoculated intradermally on the base of the tail with a suspension of 0.6 mg of dry, heat-killed *Mycobacterium butyricum* (Difco) in 0.05 ml of paraffin oil to which 2% digitonin had been added.

Test compounds were suspended in saline with 1 drop of Tween 80 added per 20 ml as a suspending agent. Daily, intragastric treatment was initiated on the day of inoculation and continued for 19 days. Inoculated control groups received the saline vehicle only (with Tween 80 added).

Twenty-four hours after the last injection, the rats were sacrificed and weighed; their hind paw volumes were measured by mercury displacement and the per cent inhibition of arthritic swelling was determined for each group. Hydrocortisone treated groups, run simultaneously, served as a standard. Treated groups were rated active if there was a significant reduction in arthritic swelling from the control group ($p \leq 0.05$, one-tailed, Wilcoxon rank sum method).

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