Sulfonamides of Hydroxylamine Derivatives[1a]

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We report the synthesis of N-alkoxy-O-arylsulfonylacylimines (I, $ArSO_3(R)C{=}NOR$) (Table I) the isomeric N-acyl-N-arylsulfonyl-O-alkylhydroxylamines (II, $RCON(OR)SO_2Ar$), and arylsulfonyl-O-alkylhydroxylamines (III, $ArSO_2NHOR'$) (Table II) as potential bacteriostatic agents.

Several representatives of I and III showed no significant antibacterial or antifungal activity.[2]

Experimental Section

Melting points are corrected. Microanalyses were performed by Drs. Weiler and Strauss (Oxford, England) and Dr. A. Bernhardt (Mühlheim, Germany). The infrared spectra were determined with a Perkin-Elmer 137, and the nmr spectra with a Varian A-60 spectrometer. Where analyses are indicated only by the symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

Benzyl *p*-Toluenesulfonylbenzimino Ether. Method I.—When 5.0 g of 23% NaH (in mineral oil) was added to 11.35 g (0.050 mole) of N-benzoyl-O-benzylhydroxylamine[3] in 100 ml of dry C_6H_6, H_2 was evolved and a white precipitate formed. *p*-Toluenesulfonyl chloride (9.52 g, 0.050 mole) in 50 ml of C_6H_6 was added, and the mixture was refluxed for 3 days. Water was added and the benzene solution was separated and concentrated, and the residue was chromatographed on alumina. The mineral oil was eluted with petroleum ether (bp 60–90°) and 14.01 g (73%) of product was eluted with benzene, mp 95–96° after recrystallization from C_6H_6; ir (Nujol), C=N, 1580, SO_2, 1365 and a doublet at 1170–1180 cm^{-1}; nmr ($CDCl_2$), singlets at τ 8.1 (3 H), 4.92 and 4.86 (2 H), multiplet at τ 2.6 (14 H). The ratio of the two peaks τ 4.92 and 4.86 was 0.7:1.0 and was due to *syn* and *anti* structures I.[4] In CF_3CO_2H, singlet 3 H at τ 8.1, singlet 2 H at τ 5.2, multiplet 14 H τ 2.5. *Anal.* ($C_{21}H_{19}NO_4S$) C, H, N, S.

Benzyl Benzenesulfonylbenzimino Ether. Method II.—A mixture of 4.54 g (0.02 mole) of N-benzo-O-benzylhydroxylamine, 3.76 g (0.0212 mole) of $C_6H_5SO_2Cl$, and 20 ml of 20% NaOH was shaken until the odor of benzenesulfonyl chloride had disappeared. The mixture was extracted (Et_2O), and the ether was dried and distilled. The residue (1.2 g) was recrystallized from petroleum ether to give 0.90 g (12%) of product: mp 72.2–73.2°; ir (Nujol), SO_2 at 1380 and 1180, C–O at 1310, and C–O–C at 1255 cm^{-1}. *Anal.* ($C_{20}H_{17}NO_4S$) C, H, N, S.

N-Acetyl-O-propylhydroxylamine with *p*-Acetylaminobenzenesulfonyl Chloride in Pyridine. Method III.—Following the method of Robin and Winnek,[5] 5.85 g (0.050 mole) of N-acetyl-O-propylhydroxylamine[4] and 23 g (0.10 mole) of *p*-acetylaminobenzenesulfonyl chloride were dissolved in 100 ml of dry pyridine. The mixture was warmed on a steam bath overnight. When the pyridine was removed under reduced pressure, a solid formed. Part of the solid dissolved (H_2O) and the remainder was recrystallized (AcOH, EtOH), yield 6.0 g (28%), mp 126–126°. *Anal.* ($C_{13}H_{18}N_2O_5S$) C, H, N, S. The ir spectrum was as expected for I.

TABLE I
COMPOUNDS I

R	R'	Ar	Method of prepn	% yield	Mp, °C	Formula
C_6H_5	C_3H_5	*p*-$CH_3C_6H_4$	I	54	95–96	$C_{17}H_{17}NSO_4$
p-$CH_3C_6H_4$	C_3H_7	*p*-$CH_3C_6H_4$	II	35	98.5–99.5	$C_{18}H_{21}NO_4S$
p-$CH_3C_6H_4$	$C_6H_5CH_2$	*p*-$CH_3C_6H_4$	II	8	109.5–110.5	$C_{22}H_{21}NO_4S$
p-$CH_3C_6H_4$	$CH{\equiv}CCH_2$	*p*-$CH_3C_6H_4$	II	9	95.5–96.5	$C_{18}H_{17}NO_4S$
p-$CH_3OC_6H_4$	$C_6H_5CH_2$	C_6H_5	II	11	103.5–104	$C_{21}H_{19}NO_5S$

TABLE II
COMPOUNDS III

R'	Ar	Method of prepn[a]	% yield	Mp, °C	Formula
C_3H_5	*p*-$CH_3C_6H_4$	I[b]	26	92–93	$C_{10}H_{13}NSO_3$
C_3H_7	*p*-$CH_3CONHC_6H_4$	I[c]	24	139–140	$C_{11}H_{16}N_2O_4S$
$C_6H_5CH_2$	*p*-$CH_3C_6H_4$	II[d]	81	94–95	$C_{14}H_{15}NO_3S$

[a] Isolation by acidification and extraction (Et_2O). [b] Starting material, N-aceto-O-allylhydroxylamine; the N-acetyl group was lost. [c] N-Propano-O-propylhydroxylamine was the starting material. [d] Benzyloxyamine was the starting compound; purified by M. W. Mosher.

N-Benzoyl-N-*p*-toluenesulfonyl-O-benzylhydroxylamine.—A mixture of 2.77 g (0.01 mole) of N-*p*-toluenesulfonyl-O-benzylhydroxylamine in 20 ml of anhydrous pyridine and 1.40 g (0.01 mole) of C_6H_5COCl was stirred for 6 hr. A precipitate was obtained on addition of water and 3.3 g (86%) of product, mp 112–113°, was obtained (from EtOH). *Anal.* ($C_{21}H_{19}NO_4S$) C, H, N, S. Ir (Nujol) was expected for II, C=O at 1650 cm^{-1}.

(1) (a) We are indebted to the National Science Foundation for Grant NSF G 13289 and to the National Institutes of Health for Grant E-4173 in support of this work. A portion of the results was presented at the Northwest Regional Meeting of the American Chemical Society, Spokane, Wash., June 1964. (b) Taken in part from the Ph.D. thesis of B. N. Misra, Feb 1967, the M.S. thesis of W. D. Bills, June 1960, and the M.S. thesis of J. R. Throckmorton, June 1960.

(2) We thank Dr. R. E. Kent of the Chas. Pfizer Co. for the tests on I and Dr. Glen R. Gale of the Medical College of South Carolina for the tests on III.

(3) J. H. Cooley, W. D. Bills, and J. R. Throckmorton, *J. Org. Chem.*, **25**, 1734 (1960).

(4) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 2326, 2327 (1963).

(5) R. O. Robin, Jr., and P. S. Winnek, *ibid.*, **62**, 1909 (1940).

N⁴-Substituted N¹-Toluenesulfonylpiperazines

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In our continuing search for potential hypoglycemic agents, we have altered a series of sulfonylureas by replacing the toluenesulfonamido moiety by a toluenesulfonylpiperazino moiety. We wish to report the synthesis of some new 1-(*p*-toluenesulfonyl)-4-carbamoylpiperazines and 1-(*p*-toluenesulfonyl)-4-thiocarbamoylpiperazines. The compounds showed no hypoglycemic, hypotensive, or anticonvulsant activity.

Experimental Section[1]

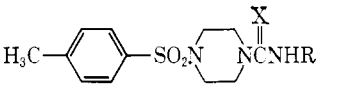
1-(*p*-Toluenesulfonyl)-4-*n*-butylcarbamoylpiperazine.—To a solution of 4.0 g (0.016 mole) of 1-(*p*-toluenesulfonyl)piperazine[2] in 25 ml of acetonitrile was added 2.6 g (0.25 mole) of *n*-butyl isocyanate all at once. The reaction was exothermic and, on stirring vigorously, 6.4 g of the product crystallized out. It was filtered and washed with cold acetonitrile. Recrystallization from acetonitrile yielded 3.8 g. The other compounds listed in Table I were prepared similarly.

(1) Melting points were taken on a Fisher-Johns block and are corrected. Analyses are by Midwest Microlab, Inc., Indianapolis, Ind.

(2) T. S. Moore, M. Boyle, and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).

TABLE I

N⁴-SUBSTITUTED N¹-TOLUENESULFONYLPIPERAZINES



No.	R	X	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	n-C_3H_7	O	181–183	90	$C_{15}H_{23}N_3O_3S$	55.38	7.07	12.92	55.62	7.32	12.71
2	n-C_4H_9	O	135–136	68	$C_{16}H_{25}N_3O_3S$	56.61	7.42	12.37	56.48	7.46	12.19
3	n-C_4H_9	S	140–142	67	$C_{16}H_{25}N_3O_2S$	54.05	7.03	11.82	54.08	7.25	11.86
4	$CH_2CH{=}CH_2$	O	191–194	77	$C_{15}H_{21}N_3O_3S$	55.70	6.54	12.99	55.92	6.81	13.00
5	$CH_2CH{=}CH_2$	S	133–135	60	$C_{15}H_{21}N_3O_2S_2$	53.09	6.19	12.39	53.14	6.17	12.28
6		O	206–207	68	$C_{18}H_{27}N_3O_3S$	59.17	7.39	11.50	58.93	7.59	11.62
7		S	200–201	80	$C_{18}H_{27}N_3O_2S_2$	56.65	7.13	11.01	56.93	7.08	11.18
8	C_6H_5	O	230–232	91	$C_{18}H_{21}N_3O_3S$	60.18	5.89	11.69	60.25	5.97	11.83
9	C_6H_5	S	183–187	87	$C_{18}H_{21}N_3O_2S_2$	57.60	5.51	11.20	57.62	5.60	10.98
10	ClC_6H_4	O	196–198	84	$C_{18}H_{20}ClN_3O_3S$	54.89	5.08	10.67	55.15	5.26	10.91
11	o-$EtOC_6H_4$	O	125–126	95	$C_{20}H_{25}N_3O_4S$	59.55	6.20	10.42	59.78	6.28	10.45
12		O	227–229	81	$C_{18}H_{20}N_4O_5S$	53.45	4.98	13.92	53.45	5.17	14.11
13[a]		O	212–214	81	$C_{18}H_{22}N_4O_3S$	57.73	5.92	14.96	57.57	6.02	14.78
14		O	248–250	72	$C_{22}H_{23}N_3O_3S$	64.54	5.62	10.24	64.72	5.82	10.28

[a] Recrystallized from ethanol.

Book Reviews

Biosynthesis of Antibiotics. Volume I. Edited by J. F. SNELL. Academic Press Inc., New York, N. Y. 1966. x + 234 pp. 16 × 23.5 cm. $10.00.

In recent years, studies on the biosynthesis of naturally occurring substances have commanded ever-increasing attention among scientists. Nowhere is this more true than in the field of antibiotics, not only because of the large structural variations these substances exhibit but also because it appeared quite possible that tailor-made antibiotics might be prepared biosynthetically, as was the case with the penicillins.

This book, edited by J. F. Snell, consists of a series of six chapters, with each except the first dealing with the biosynthesis of a major group of antibiotics. The first chapter, written by D. Perlman, presents a discussion of the preparation of radioactive antibiotics using microbial biosynthetic methods and covers this technique reasonably thoroughly. For example, some of the areas discussed involve the types and methods of addition of radioactive precursors, the recovery of labeled products, the determination of purity, and the stabilities of labeled compounds. The latter part of the chapter covers a sampling of the major groups of antibiotics which have been prepared in labeled form by microbial syntheses.

The five remaining chapters take the form of reviews and cover the biosynthesis of the following antibiotic types: the penicillins and cephalosporins by Arnold L. Demain, the tetracyclines by Roy H. Turley and J. F. Snell, streptomycin by Joseph Mendicino and J. M. Pickens, the polyacetylenes in fungi by J. D. Bu'Lock, and the macrolide antibiotics by John W. Corcoran and Malcolm Chick. The chapters differ in their completeness, but in general they cover their respective areas reasonably well.

In all of the chapters, the discussions are well referenced and each is preceded by a comprehensive table of contents which enables the reader to locate items of specific interest with ease. It is stated on the jacket that this book will appeal to industrial and experimental microbiologists, biologists, biochemists, medicinal and organic chemists, and botanists engaged in research in mycology, and it may well, for such diverse topics as fermentation methods, precursor feeding experiments, therapeutic uses of specific antibiotics, degradation sequences used to determine the positions of labeled atoms, the use of mutant strains, cell-free systems, etc., are freely discussed in many cases. Since it is written on a basic level, the book should appeal in particular to the uninitiated reader who desires more familiarization with the field. This work is entitled Volume I, and although no mention is made of future volumes, presumably there is more to come.

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A Textbook of Pharmaceutical Analysis. By KENNETH A. CONNORS. John Wiley and Sons, Inc., New York, N. Y. 1967. xvii + 614 pp. 15.5 × 23.5 cm. $12.50.

The author has presented a modern textbook of pharmaceutical analysis, which will find utility both at the student and practicing analyst levels. The approach used is one of emphasizing principles and pitfalls, although procedures and details are amply presented. Traditionalists may be surprised to find U.S.P. and N.F. assays, quoted verbatim, missing from the text since, as the author puts it, "This is not a catalog of assay methods for specific drugs, nor...a commentary on the official volumes."

Dr. Connors has organized the book in five parts: Fundamental Titrimetric Analysis, Physical Methods, Separation Techniques, Elemental Analysis, and Functional Group Analysis. This method of presentation imparts a certain degree of order as opposed to one based on classes of drugs. In keeping with a modern text, the preponderance of organic analysis in pharmaceuticals is suitably reflected. In the same vein, chapters on