$$\bar{f}_k = (a\alpha^2 + b\alpha + c) + (2\alpha a + b)\sum_{i=1}^{N} n_{ki}\pi_{xi} + (2\alpha a + b)\sum_{j=1}^{M} m_{kj}\pi_{yj} + a(\sum_{i=1}^{N} n_{ki}\pi_{xi})^2 + a(\sum_{j=1}^{M} m_{kj}\pi_{yj})^2 + 2a\sum_{i=1}^{N}\sum_{j=1}^{M} n_{ki}m_{kj}\pi_{xi}\pi_{yj} \quad (6)$$

consistent as can be seen by setting $a = 0$ in eq 6.

Franke[9] has also considered the case in which, although the parabolic relation (3) does hold, the data actually used all lie on one wing of the parabola, which can then be approximated by a straight line. In this case the Free–Wilson method (eq 4) and the Hansch method (eq 3) are again consistent.

However, eq 5 is only one possible assumption connecting the variables of the two methods. It might be instead that π_k^2 can be partitioned as in eq 5 to give

$$\pi_k^2 = \alpha + \sum_{i=1}^{N} n_{ki}\pi_{xi} + \sum_{j=1}^{M} m_{kj}\pi_{yj} \quad (7)$$

or perhaps the combination $(a\pi_k^2 + b\pi_k + c)$ can be partitioned.

$$(a\pi_k^2 + b\pi_k + c) = \alpha + \sum_{i=1}^{N} n_{ki}\pi_{xi} + \sum_{j=1}^{M} m_{kj}\pi_{yj} \quad (8)$$

With the assumption of eq 8, the Free–Wilson method (eq 4) and the Hansch method (eq 3) are consistent but not with the assumptions of eq 7 or 5, except in the special cases mentioned above.

Without knowledge of the relation between the variables in the Hansch and Free–Wilson treatments, and this lack of knowledge would seem to be the usual case, no statement can be made about the consistency of the two. In particular, the fact that a Hansch equation with a quadratic term gives a good prediction of biological activity does not in itself imply that the Free–Wilson equation will not also give equally good predictions in the same case.

(9) R. Franke and R. Kühne, *Eur. J. Med. Chem.*, 13, 399 (1978).

Synthesis and Evaluation of the Male Antifertility Properties of a Series of N-Unsubstituted Sulfamates

Allen F. Hirsch,* Charles Kasulanis, Larry Kraft, Robert A. Mallory, Gregory Powell, and Benny Wong

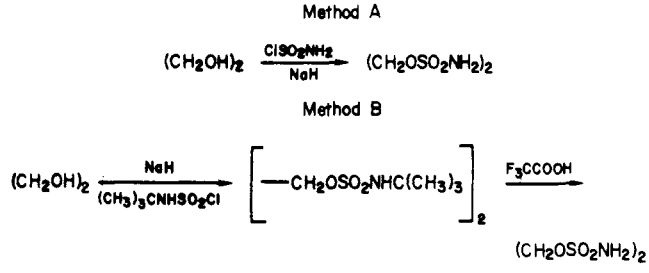
Divisions of Chemical Research and Pharmacology, Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869.
Received October 27, 1980

A series of six aliphatic and one carbocyclic N-unsubstituted sulfamates have been synthesized and evaluated as potential male antifertility agents. Three of the aliphatic sulfamates, 1,2-ethanediyl sulfamate (1), 1,3-propanediyl sulfamate (2), and 1,4-butanediyl sulfamate (3), when administered orally to male rats caused a decrease in the number of pregnant females and/or implantation coupled with increased embryonic and fetal resorption. The compounds were prepared by treating the appropriate glycol salt with sulfamoyl chloride or by the cleavage of a *tert*-butylsulfamate with trifluoroacetic acid.

Chemicals that interfere with the postmeiotic transformation of spermatozoa in either the testis or epididymis can cause the production of morphologically intact but sterile spermatozoa, a state designated as "functional sterility". These spermatozoa are either unable to penetrate and fertilize an ovum or render the embryo or fetus unable to sustain development. Trimethyl phosphate,[1] various esters of methanesulfonic acid,[2] and 3-chloropropane-1,2-diol[3] are examples of a few classes of compounds which have been shown to produce "functional sterility" in animal models. The latter compound has shown the most promise, since its antifertility action involves only spermatozoa in the epididymis and causes them to be unable to penetrate or fertilize an ovum, thus eliminating the possibility of a mutagenic effect.

This paper describes the synthesis and evaluation of a series of six aliphatic and one carbocyclic N-unsubstituted sulfamates as potential male antifertility agents, hopefully acting by causing "functional sterility". The sulfamate group was chosen because of its chemical similarity to the methanesulfonic acid esters and its occurrence in the antibiotic nucleocidin.[4]

Scheme I



Of the sulfamates reported in this paper, compounds 1–3 (Table I) exhibited "functional sterility", with the most potency exhibited by compounds 1 and 3. The compounds appear to act by altering the normal function of spermatids

(1) H. Jackson and A. R. Jones, *Nature (London)*, 220, 591 (1968).
(2) H. Jackson, "Antifertility Compounds in the Male and Female", Charles C. Thomas, Springfield, IL, 1966; H. Jackson and A. R. Jones, *Biochem. Soc. Trans.*, 1, 523 (1973).
(3) J. A. Coppola, *Life Sci.*, 8, 43 (1969); R. J. Ericson and V. F. Baker, *J. Reprod. Fertil*, 21, 267 (1970).
(4) I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Am. Chem. Soc.*, 93, 4323 (1971).

0022-2623/81/1824-0901$01.25/0

Table I. Male Antifertility Activity of N-Unsubstituted Sulfamates

no.	structure	method	yield, %	mp, °C	recrystn solvent	formula[a]	dose, mmol/kg	no. of males[b] cohabited	no. of males[b] mated	no. of males[b] fertile[d]	no. of implants/pregnancy[c]	% resorbing implants[c]
1	$(CH_2OSO_2NH_2)_2$	A, B	58, 43	98.5–101	EtOAc	$C_2H_8N_2O_6S_2$	0.18	10	9	8	10.8 ± 1.4	40.0 ± 9.8
							0.36	8	7	1	9.8 ± 1.6	98.2 ± 1.9
							0.68	5	5	0		
2	$CH_2(CH_2OSO_2NH_2)_2$	A	24	85–87.5	EtOAc	$C_3H_{10}N_2O_6S_2$	0.43	5	5	4	9.3 ± 1.6	73.6 ± 2.8
							0.64	5	5	3	6.7 ± 1.8	94.4 ± 5.6
3	$(CH_2)_2(CH_2OSO_2NH_2)_2$	A	47	126–129	EtOH	$C_4H_{12}N_2O_6S_2$	0.04	5	5	5	10.2 ± 1.8	56.0 ± 14.3
							0.40	5	5	0		
4	$(CH_2)_8(CH_2OSO_2NH_2)_2$	A	36	102–105	EtOAc	$C_{10}H_{24}N_2O_6S_2$	0.30	5	5	4	12.5 ± 0.7	17.3 ± 6.4
5		A	8	167–169	*e*	$C_6H_{14}N_2O_6S_2$	0.36	5	5	5	14.0 ± 0.9	4.4 ± 1.9
6	$(Pr)(NH_2SO_2OCH_2)_2(Me)C$	A	28	92–94	EtOAc/*n*-Hx[h]/CH_2Cl_2	$C_7H_{18}N_2O_6S_2$	0.34	4	4	4	15.5 ± 0.9	12.5 ± 4.4
7	$(CH_3CHOSO_2NH_2)_2$	A	21	115–117	EtOAc/*n*-Hx[f,h]	$C_4H_{12}N_2O_6S_2$	0.40	4	3	3	15.0 ± 1.1	0.0
8	$(CH_2OSO_2CH_3)_2$[g]						0.05	7	7	6	9.9 ± 1.7	35.2 ± 12.3
							0.07	5	4	3	12.3 ± 1.8	30.3 ± 9.5
							0.09	5	4	0		

[a] All compounds were analyzed for C, H, and N and compounds 1–5 also for S. All analyses were within ±0.4% of theoretical values. [b] 38 cohabited control males produced 12.8 ± 0.4 implants per pregnancy from 34 of 36 matings. The percentage of nonviable implants was 5.9 ± 1.4. [c] Mean plus standard error. [d] A male was considered fertile if at least one viable offspring was produced. [e] Required column chromatography on Silic AR CC-7 (20% acetone–$CHCl_3$) for purification. [f] Required column chromatography on Silic AR CC-7 (25% acetone–$CHCl_3$) for purification. [g] See ref 6 for the method of preparation. [h] *n*-Hx = *n*-hexane.

and epididymal spermatozoa, resulting in a decrease in fertilization and/or implantation along with increased embryonic and fetal resorption.

Chemistry. The sulfamates were prepared by treating a glycol with sulfamoyl chloride in the presence of sodium hydride and 1,2-dimethoxyethane (Scheme I, method A) or by the cleavage of a *tert*-butylsulfamate by trifluoroacetic acid (method B). The latter method is a modification of the cleavage of *tert*-butylsulfamides by trifluoroacetic acid forming sulfamides.[5]

Biological Activity. Females mated with males receiving high dose levels of compounds **1** and **3**, 0.68 and 0.40 mmol/kg, respectively, had no implants, thus demonstrating that the spermatozoa were either unable to fertilize the ova or the fertilized ovum could not maintain normal embryogenesis prior to implantation. Compounds **1** and **3** when administered at lower dose levels, 0.18–0.36 and 0.04 mmol/kg, respectively, and compound **2** at 0.43–0.64 mmol/kg caused a reduction in the number of normal implants and an increase in nonviable implants. The results with 1,2-ethanediyl methanesulfonate (**8**),[6] a compound known to inhibit male fertility,[2] were similar. The number of nonviable implants was increased at 0.05–0.07 mmol/kg, and no implants occurred at 0.09 mmol/kg. The known androgen-inhibiting and antispermatogenic activities of this compound were also observed as testes, ventral prostate, and seminal vesicle weights were reduced. In contrast, the testes and sex accessory organ weights from animals treated with compounds **1**–**3** were similar to the control animals. Histological preparation of the testes and epididymides after 14 days of treatment with compound **1** at 0.68 mmol/kg were normal, indicating no inhibition of spermatogenesis.

Experimental Section

General. All new compounds exhibited IR and NMR spectra consistent with the reported structures. Melting points were uncorrected. All compounds were a single spot on TLC.

Preparation of Sulfamates. Method A. To a solution of the appropriate glycol (0.05 mol) in 1,2-dimethoxyethane (100 mL) was added NaH (0.02 mol). After the mixture stirred at room temperature for 2 h, a cooled (4 °C) solution of sulfamoyl chloride (0.18 mol) in 1,2-dimethoxyethane (400 mL) was added followed by stirring at 4 °C for 24 h. The resulting precipitate was filtered, the filtrate was concentrated, and the residue was partitioned between *n*-heptane and CH_3OH. The CH_3OH solution was concentrated and the resulting residue either crystallized directly or after column chromatography.

Method B. Preparation of 1,2-Ethanediyl Sulfamate (1). (This method was also employed in the synthesis of 1,2-ethanediyl-*1,2-*^{14}*C* sulfamate in an overall yield of 55% from ethylene-*1,2-*^{14}*C* glycol.) Ethylene glycol (0.385 mol) was added dropwise to a suspension of NaH (0.77 mol) in toluene (450 mL) at room temperature. After stirring for 15 min, the suspension was stirred for 2.5 h at 45–50 °C and then cooled to 20 °C. To the suspension was added dropwise *tert*-butylsulfamoyl chloride[7] (0.77 mol) in toluene (131 mL) while maintaining the temperature between 20 and 35 °C. The resulting suspension was stirred for 2.5 h at 20 °C, for 1.5 h at 45–50 °C, and for 16 h at room temperature, filtered, washed with toluene, and extracted twice with hot $CHCl_3$ (600 mL, 300 mL). The remaining solid was suspended in water and extracted with $CHCl_3$ until no more solid remained. The $CHCl_3$ extracts were combined and concentrated, and the resulting solid crystallized from $CHCl_3$/*n*-heptane to afford 72.26 g (56.4%) of 1,2-ethanediyl *tert*-butylsulfamate, mp 119–121 °C. This compound (0.33 mol) was added to CF_3CO_2H (330 mL) with

(5) J. D. Catt and W. L. Matier, *J. Org. Chem.*, **39**, 566 (1974).
(6) C. F. H. Allen and T. T. M. Laakso, U.S. Patent 2726162; *Chem. Abstr.*, **50**, 6986*h* (1956).
(7) W. L. Matier, W. T. Comer, and D. Deitchman, *J. Med. Chem.*, 15, 538 (1972).

stirring at 25 °C under N_2 and stirred for 20 h, and the solid was filtered, washed with $CHCl_3$ (2 × 50 mL), and dried in vacuo at 50–55 °C. The resulting solid was dissolved in acetone (185 mL) at reflux temperature, treated with charcoal (1.29 g) at reflux temperature for 5 min, filtered through Supercel, diluted with $CHCl_3$ (185 mL), cooled, and stirred at 0–5 °C for 1 h. The resulting solid was filtered and dried in vacuo to afford 54.0 g (75.5%) of 1.

Antifertility Test. The sulfamates and methanesulfonic acid ester (Table I) were evaluated in a standard short-term antifertility test involving the oral administration of the test substance in propylene glycol to male Sprague–Dawley rats for 14 consecutive days prior to mating.[8] The males were then cohabitated with proestrus females, and the latter were autopsied 14 days after mating and examined for the status of pregnancy. Positive mating was confirmed by sperm in vaginal washings. After cohabitation, all males were autopsied for examination of the testes, epididymides, and accessory sex organs. Portions of the testes and epididymides from the rats that received compound 1 at 0.68 mmol/kg were fixed in neutral formalin and subsequently embedded, sectioned, mounted, and stained with hematoxylin–eosin according to standard histological procedures.

(8) A. F. Hirsch, K. C. Kolwyck, L. A. Kraft, R. E. Homm, and D. W. Hahn, *J. Med. Chem.*, 18, 166 (1975).

Synthesis of Analogues of Acetylmethadol and Methadol as Potential Narcotic Antagonists

Danny L. Lattin,* Bill Caviness, Rick G. Hudson, David L. Greene, Pamela K. Raible, and J. Blake Richardson

College of Pharmacy, University of Arkansas Medical Sciences Campus, Little Rock, Arkansas 72205.
Received January 7, 1981

The *N*-allyl and *N*-(cyclopropylmethyl) analogues of (-)-α-acetylmethadol and (-)-α-methadol have been synthesized and evaluated for opiate agonist and opiate antagonist activity. Both acetylmethadol analogues possessed weak analgesic activity in in vivo tests for narcotic analgesia; the *N*-allyl analogue partially antagonized morphine-induced tail-flick analgesia. All four compounds possessed only opiate agonist-like activity as determined by in vitro studies measuring inhibition of [^{3}H]naloxone binding to opiate receptors.

Opiate antagonists are generally derived from opiate agonists by replacing the methyl group on the tertiary amine with an appropriate antagonist pharmacophore, e.g., allyl, dimethylallyl, cyclopropylmethyl, or cyclobutylmethyl.[1,2] All the clinically useful opiate antagonists have been obtained by structural modification of opiate analgesics that have fused ring systems, such as morphinoids, morphinans, or benzomorphans. With the exception of naloxone and naltrexone, which are "pure" narcotic antagonists derived from oxymorphone, all these agents possess both opiate agonist and opiate antagonist properties and are classified as opiate agonist–antagonists or partial agonists.

Opiate antagonists have also been derived from opiate agonists not possessing fused rings. Although no narcotic antagonist activity was reported for analogues of meperidine,[3-6] Oh-ishi and May[7] found that the *N*-hexyl and *N*-heptyl derivatives of norketobemidone were partial agonists with antagonist activity on the order of that of pentazocine. More recently, Zimmerman et al.[8] reported a series of 3,4-dimethyl-4-phenylpiperidines that are pure narcotic antagonists. The most potent pure antagonist in the series is the (+)-*N*-(2-propiophenone) derivative which has activity equal to that of naloxone. Iorio and Casy[9,10] observed that the *N*-allyl and *N*-(cyclopropylmethyl) derivatives of 2,3-dimethyl-3-(3-hydroxyphenyl)piperidine were pure narcotic antagonists with antagonist activity similar to that of nalorphine.

Jacoby and colleagues[11] found no narcotic antagonist activity in a series of N-substituted 3-phenylpyrrolidines. However, Bowman et al.[12] reported mixed agonist–antagonist activity for *N*-alkyl derivatives of 3-(3-hydroxyphenyl)pyrrolidines. In compounds derived from bicyclic systems, Ong and co-workers[13] observed opiate agonist–antagonist activity in *N*-alkyl-5-aryl-2-azabicyclo[3.2.1]-octanes. Clarke et al.[14] synthesized pure narcotic antagonists utilizing 2-phenyl- and 2-(3-hydroxyphenyl)tropanes.

The apparent requirement of a phenolic hydroxyl group for opiate antagonist activity must not be overlooked. With few exceptions, all the compounds noted above that exhibit either partial agonist or pure antagonist activity also possess a phenolic hydroxyl group. The exceptions involve some of the tropane derivatives having opiate antagonist activity synthesized by Clarke and co-workers;[14]

(1) H. W. Kosterlitz, H. O. J. Collier, and J. E. Villareal, Eds., "Agonist and Antagonist Actions of Narcotic Analgesic Drugs", University Park Press, Baltimore, MD, 1973.
(2) L. S. Harris, *Adv. Biochem. Psychopharmacol.*, 8, 13 (1973).
(3) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, 7, 123 (1964).
(4) P. J. Costa and D. D. Bonnycastle, *J. Pharmacol. Exp. Ther.*, 113, 310 (1955).
(5) A. F. Casy, A. B. Simmonds, and D. Staniforth, *J. Pharm. Pharmacol.*, 20, 768 (1968).
(6) L. S. Harris, in ref 2, p 17.
(7) T. Oh-ishi and E. L. May, *J. Med. Chem.*, 16, 1376 (1973).
(8) D. M. Zimmerman, R. Nickander, J. S. Horng, and D. T. Wong, *Nature (London)*, 275, 332 (1978).
(9) M. A. Iorio and A. F. Casy, *J. Pharm. Pharmacol.*, 27, 140 (1975).
(10) M. A. Iorio and A. F. Casy, *J. Med. Chem.*, 21, 812 (1978).
(11) R. L. Jacoby, K. A. Nieforth, and R. E. Willette, *J. Med. Chem.*, 17, 453 (1974).
(12) R. E. Bowman, H. O. J. Collier, P. J. Hattersley, I. M. Lockhart, D. J. Peters, C. Schneider, N. E. Webb, and M. Wright, *J. Med. Chem.*, 16, 1177 (1973).
(13) H. H. Ong, V. B. Anderson, and J. C. Wilker, *J. Med. Chem.*, 21, 758 (1978).
(14) R. L. Clarke, A. J. Gambino, A. K. Pierson, and S. J. Daum, *J. Med. Chem.*, 21, 1235 (1978).

0022-2623/81/1824-0903$01.25/0