Articles

l-1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine: A Potent and Selective Agonist at α_1-Adrenoceptors

Robert M. DeMarinis* and J. Paul Hieble

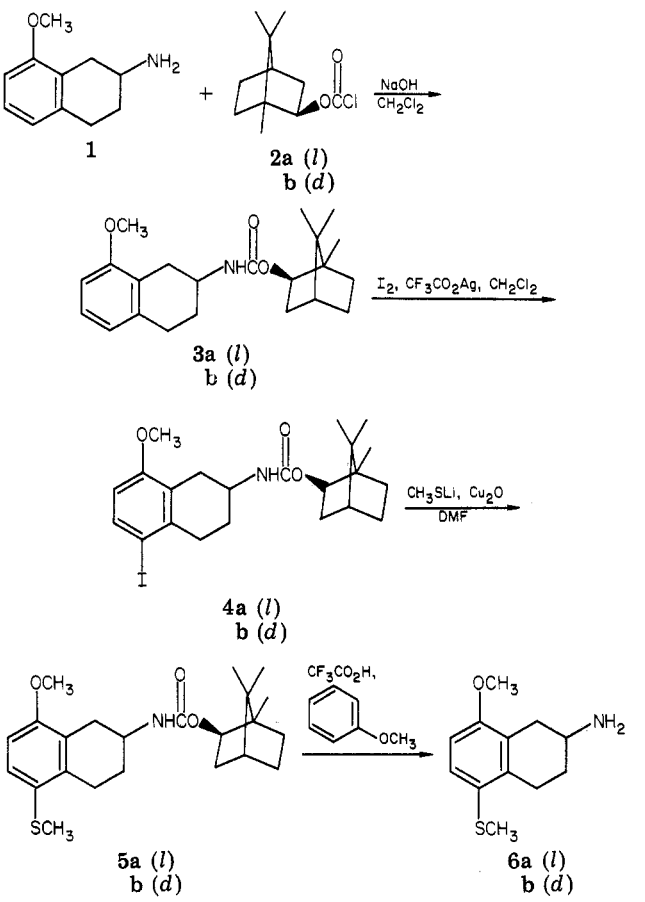
Departments of Medicinal Chemistry and Pharmacology, Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received December 23, 1982*

1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine (SK&F-89748) has been resolved into *d* and *l* enantiomers and characterized pharmacologically. The more active isomer is the *l*, which has the *S* configuration as established by single-crystal X-ray diffraction studies. This compound is a potent and selective α_1-agonist with an EC_{50} in the isolated perfused rabbit ear artery of 9 ± 2 nM. In several preparations, it has shown an α_1/α_2 selectivity ratio of over 100 and will be a useful tool for characterizing receptor subtypes.

In the last several years, the presence of at least two distinct subclasses of α-adrenoceptors has been demonstrated unequivocally.[1-3] Significant differences have been observed in drug selectivity and drug function at α-adrenoceptors located on the presynaptic terminals of the postganglionic sympathetic neurons and the postsynaptic α-receptors of effector organs.[4,5] Traditionally, a functional basis for differentiation of α-receptor subtypes has been adopted that is independent of anatomical location and based solely upon relative affinities for a series of agonists and antagonists.[5,6,7] Historically, the postsynaptic receptor that mediates vasoconstriction in vascular smooth muscle was thought to be composed entirely of receptors of the α_1 subclassfication. They could be stimulated by nonselective agonists, such as the endogenous ligand norepinephrine, or by α_1-adrenoceptor selective agents, such as phenylphrine, methoxamine, or cirazoline.[8-11]

A growing body of compelling evidence now supports the existence of a heterogeneous class of postsynaptic α-receptors in vascular smooth muscle. In addition to the classical postsynaptic α_1-adrenoceptor, it is now believed that there are also present postsynaptic α_2-receptors which have pharmacological characteristics similiar to those of the presynaptic α_2-receptors located on the terminals of postganglionic sympathetic neurons.[12-17] In the vasculature, both postsynaptic α_1- and α_2-receptors mediate vasoconstriction upon activation. In order to characterize further receptor subpopulations and to identify unambiguously the physiological responses that they mediate in various tissues, it is essential to have potent and selective agonists and antagonists of these receptor subtypes. This paper describes the resolution and pharmacological

Scheme I



(1) K. Starke and T. Endo, *Gen. Pharmacol.*, **7**, 307 (1976).
(2) K. Starke, T. Endo, and H. D. Taube, *Naunyn*-Schmiedeberg's, *Arch. Pharmacol.*, **291**, 55 (1975).
(3) S. Z. Langer, *Br. J. Pharmacol.*, **60**, 481 (1975).
(4) C. Melchiorre, *Farmaco, Ed. Sci.*, **35**, 535 (1981).
(5) S. Berthelsen and W. A. Pettinger, *Life Sci.*, **21**, 595 (1977).
(6) J. E. S. Wikberg, *Acta. Physiol. Scand.*, **103**, 225 (1978).
(7) K. Starke and S. Z. Langer, "Presynaptic Receptors", S. Z. Langer, K. Starke, and M. L. Dubocovich, Eds., Pergamon Press, Oxford, 1979.
(8) F. Lefèvre, H. Deportere, and I. Cavero, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **35**, 444, (1976).
(9) F. Lefèvre, S. Fènard, and I. Cavero, *Eur. J. Pharmacol.*, **43**, 85 (1977).
(10) R. R. Ruffolo and J. E. Waddell, *J. Pharm. Exp. Ther.*, **222**, 29 (1982).
(11) J. C. A. van Meel, A. de Jonge, P. B. M. W. M. Timmermans, and P. A. van Zwieten, *J. Pharm. Exp. Ther.*, **219**, 760 (1981).
(12) P. B. M. W. M. Timmermans, H. Y. Kwa, and P. A. van Zwieten, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **310**, 189 (1979).
(13) J. R. Docherty and J. C. McGrath, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **312**, 107 (1980).
(14) P. B. M. W. M. Timmermans and P. A. van Zwieten, *Eur. J. Pharmacol.*, **63**, 199 (1980).
(15) G. M. Drew and S. B. Whiting, *Br. J. Pharmacol.*, **67**, 207 (1979).
(16) P. B. M. W. M. Timmermans and P. A. van Zwieten, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **313**, 17 (1980).
(17) W. Kobinger and L. Pichler, *Eur. J. Pharmacol.*, **65**, 393 (1980).

0022-2623/83/1826-1215$01.50/0

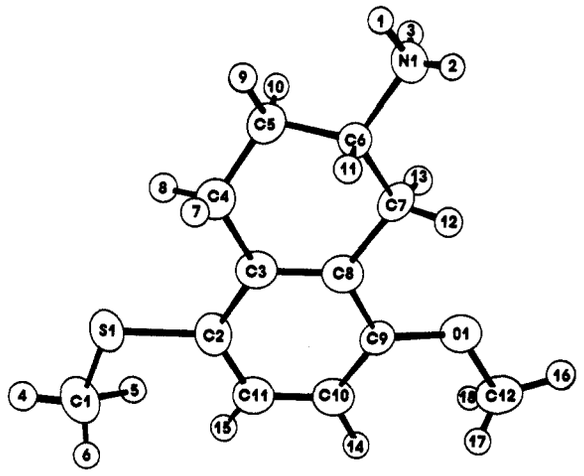


Figure 1. Single-crystal X-ray structure of **6a**.

characterization of *l*-1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine (SK&F *l*-89748), which is a highly potent and selective α_1-adrenoceptor agonist.[18]

Chemistry. The synthetic sequence used to prepare both enantiomers of **6** is shown in Scheme I. This scheme was devised such that optically active **3** could be used as an intermediate for future synthesis of optically active congeners.[19] The isobornyl carbamate was chosen as a protecting and resolving group, since it could readily be removed under SN_1 conditions at the completion of the synthesis, whereas normal amides in this series were very resistant to hydrolysis. 8-Methoxy-2-aminotetralin[20] was treated with *l*-isobornyl chloroformate[21] prepared from readily available *d*-camphor. The resulting carbamate was resolved by repeated crystallization (5 times) from absolute ethanol to give **3a** as white, shiny plates. Capillary GC indicated complete resolution of diastereoisomers. Treatment of **3a** with a stoichiometric amount of iodine in the presence of silver trifluoromethyl acetate gave **4a** as white crystals from MeOH. Displacement of iodide by $LiSCH_3$ in the presence of Cu_2O gave **5a** as white crystals. The protecting group was removed with cold TFA in the presence of anisole to give the free amine, which was purified as the hydrochloride salt by crystallization from MeOH. Single-crystal X-ray diffraction studies showed this to have the *S* configuration (Figure 1).

The *d* enantiomer was obtained by a similar method. Since we could not purify the other diastereoisomer of **3b** by crystallization, the protecting group was removed with TFA and replaced with its optical antipode (*d*-isobornyl chloroformate). Application of the same series of reactions gave **6b**, identical in all respects except for a change of sign in the rotation.

Biology. The α_1-adrenergic potency of the isomers of **6**, as well as the endogenous transmitter L-norepinephrine, in the isolated rabbit ear artery segment are shown in Figure 2.[22] In this system, the *l* isomer, **6a**, has an EC_{50} of 9 nM, while the *d* isomer, **6b**, has an EC_{50} of 60 nM.

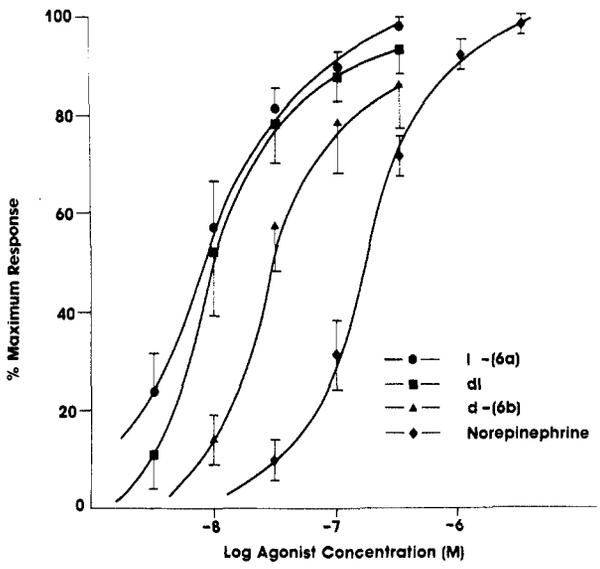


Figure 2. Concentration–effect curves for norepinephrine and the isomers of **6** acting on the α-adrenoceptor of the rabbit ear artery segment. Each point represents the mean of at least five experiments. All experiments were carried out in the presence of cocaine (3 μM).[29]

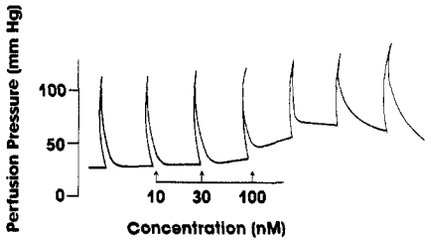


Figure 3. Effect of increasing concentrations of **6a** on the constrictor response of the isolated perfused rabbit ear artery to field stimulation of the adrenergic nerve terminals. Artery stimulated with a 500-ms train of pulses (80 V) at 10 Hz at 4-min intervals, in the presence of cocaine (3 μM).[29]

Thus, **6a** is almost 20-fold more active than norepinephrine, while it is 80-fold more active than the standard α_1-agonist methoxamine.[18] The constrictor response to **6** is competitively blocked by phentolamine with a dissociation constant in the range 5–20 nM, which has been reported for phentolamine as an α-blocker.[23,24] The postjunctional α_1-receptors in the rabbit ear artery appear to be essentially all of the α_1-subtype, since prazosin is able to produce ptoent blockade of the constrictor response to exogeneously administered L-norepinephrine (K_B = 2.7 nM), while yohimibine is very weak at blocking this response (K_B = 4000 nM).[25] In this tissue, compound **6** appears to be a full agonist, which produces 100% of the maximum response elicited by the endogenous ligand norepinephrine.

While **6** is significantly more potent than other α_1-agonists, it must have selectivity vis-ã-vis other receptor subtypes, particularly α_2-receptors, in order to be of use as a tool in the classification of receptor subtypes. Previous studies have shown that norepinephrine is equipotent on both α_1- and α_2-receptors, while other agents, such as methoxamine and phenylephrine, are much more selective for the α_1-receptor than the α_2-receptor and have been used

(18) For a preliminary report of the synthesis and in vitro characterization of a series of 2-aminotetralins including SK&F 89748, see R. M. DeMarinis, D. H. Shah, R. F. Hall, J. P. Hieble, and R. G. Pendleton, *J. Med. Chem.*, **25**, 136 (1982).
(19) The preparation of tritium-labeled **6a** will be reported at a later date.
(20) D. E. Ames, D. Evans, T. F. Grey, P. J. Islip, and K. E. Richards, *J. Chem. Soc.*, 2636 (1965).
(21) M. Fujino, S. Shinagawa, O. Nishimura, and T. Fukuda, *Chem. Pharm. Bull.*, **20**, 5, 1017 (1972).
(22) Quantitative in vitro determination of α_1-adrenergic potency was carried out by the method described in ref 18.
(23) R. R. Ruffolo and P. N. Patil, *Blood Vessels*, **16**, 135 (1979).
(24) J. C. Besse and R. F. Furchgott, *J. Pharmacol. Exp. Ther.*, **197**, 66 (1980).
(25) J. P. Hieble and D. F. Woodward, *Pharmacologist*, **24**, 234 (1982).

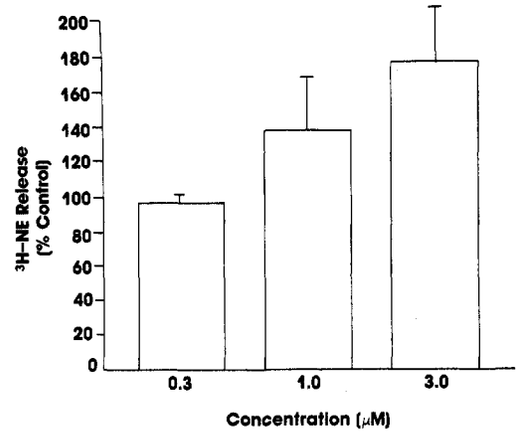


Figure 4. Effect of **6a** on tritiated norepinephrine release from the perfused rabbit ear artery. Each bar represents the mean of four experiments plus or minus SEM.

as tools to classify receptors.[5] Figure 3 illustrates the effects of **6a** on the contractile response produced by electrical stimulation of the isolated perfused rabbit ear artery. Under conditions of electrical stimulation, adrenergic nerves are activated, causing the release of norepinephrine, which produces the contractile response. Activation of presynaptic α_2-adrenoceptors on noradrenergic nerve terminals initiates a negative feedback loop, which inhibits the further release of norepinephrine evoked by electrical stimulation. This results in an inhibition of neurotransmission, which is manifested by a decrease in the constrictor response to nerve stimulation. As the data in Figure 3 indicate, there is no appreciable dimunition of neurotransmission produced by **6a** at concentrations over 100 times that required for α_1-adrenoceptor-mediated vasoconstriction (Figure 2).

The effect of **6a** on [^{3}H]norepinephrine release was determined in the rabbit ear artery as a quantitative index of of α_2-agonist acitvity. Concentrations up to 3 μM were shown to have no inhibitory effect on release (Figure 4). Therefore, the selectivity ratio of **6a** for α_1-adrenoceptors vis-à-vis α_2-adrenoceptors is at least 300, making it both more potent and more selective than phenylephrine or methoxamine,[5] the standard agonists for α_1-adrenoceptor characterization. The small dose-related increases in [^{3}H]norepinephrine release seen in this preparation may be due to some α_2-blocking activity of **6a**. However, the concentration at which this is seen (3 μM) is 300 times the EC_{50} for this agent as an α_1-agonist and further supports its selectivity. Such an agent should be a useful tool for further elucidation of the the physiological role of receptor subtypes.[26]

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover Uni-melt apparatus and are uncorrected. Elemental analyses and optical rotations were performed by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by symbols of elements, results were within 0.4% of calculated values. The X-ray structure determination was performed by Molecular Structure Corp., College Station, TX. Capillary GC determination of diastereoisomers was done on a Shimadzu capillary GC with a 30 M × 0.25 mm DB.1, fused silica column at 275 °C. NMR spectra were recorded with a Varian 90 MHz EM390 spectrometer or a Bruker 360 MHz instrument with Me_4Si as an internal standard. Satisfactory IR, NMR, and mass spectral data were obtained for all new compounds.

(26) Detailed pharamcological characterization of **6a** will be reported elsewhere.

Table I. Molecular Formulas and Optical Rotations

no.	formula	anal.	$[\alpha]^{20}_D$, deg (*c* 1, MeOH)
3a	$C_{22}H_{31}NO_3$	C, H, N	−100.8
3b	$C_{22}H_{31}NO_3$	C, H, N	+95.3
4a	$C_{22}H_{30}INO_3$	C, H, N	−64.4
4b	$C_{22}H_{30}INO_3$	C, H, N	+60.0
5a	$C_{23}H_{23}NO_3S$	C, H, N	−80.4
5b	$C_{23}H_{23}NO_3S$	H, N; C[a]	+80.7
6a	$C_{12}H_{17}NOS \cdot HCl \cdot 0.25H_2O$	C, H, N	−72.6
6b	$C_{12}H_{17}NOS \cdot HCl$	C, H, N	+74.7

[a] Theory, 68.44; found, 67.72. Exact *m/e*: theory, 403.218; found, 403.217.

***l*-Isobornyl (1,2,3,4-Tetrahydro-8-methoxy-2-naphthalenyl)carbamate (3a).** A suspension of 34.2 g (0.16 mol) of *dl*-1,2,3,4-tetrahydro-8-methoxy-2-naphthalenamine hydrochloride[20] in 400 mL of CH_2Cl_2 was cooled in an ice bath and treated with 400 mL of 10% NaOH. This was stirred rapidly while 34.5 g (0.16 mol) of *l*-isobornyl chloroformate[21] in 200 mL of CH_2Cl_2 was added over 30 min. After the addition was complete, the reaction was stirred in the cold for 30 min and then at room temperature for 1 h. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to 55 g (96%) of slightly off-white crystals, mp 105–125 °C. Five recrystallizations to constant melting point from absolute EtOH gave 10.7 g (39%) of **3a** as white shiny plates: mp 165–166 °C; $[\alpha]^{20}_D$ −95.3° (*c* 1, MeOH).

***l*-Isobornyl (1,2,3,4-Tetrahydro-8-methoxy-5-iodo-2-naphthalenyl)carbamate (4a).** Into 250 mL of CH_2Cl_2 was dissolved 7.15 g (20 mmol) of **3a**, and 8.80 g (40 mmol) of silver trifluoroacetate[27] was suspended in it. To this was added dropwise a solution of 5.54 g (22 mmol) of I_2 in 200 mL of CH_2Cl_2. It was decolorized immediately, and a yellow-green precipitate appeared. The mixture was filtered through Celite, and the filtrate was washed with 5% Na_2CO_3 and water. The organic layer was dried ($MgSO_4$) and filtered again through Celite, and the filtrate was evaporated to a colorless gum. This was dissolved in 20 mL of MeOH and cooled in the freezer. Crystallization was induced by scratching, and the resulting crystals were collected by filtration and dried to give 7.95 g (83%) of white crystals (**4a**): mp 141–142.5 °C; $[\alpha]^{20}_D$ −64.4° (*c* 1, MeOH).

Compound **4b** was prepared from compound **3b** by an analogous procedure: $[\alpha]^{20}_D$ +60.0° (*c* 1, MeOH).

***l*-Isobornyl [1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenyl]carbamate (5a).** A mixture of 6.01 g (12.5 mmol) of **4a**, 150 mL of CH_3SLi, and 2.58 g (18 mmol) of red Cu_2O in DMF[28] was heated at 60 °C for 4.5 h. It was poured into a mixture of 300 mL of H_2O and 300 mL of $CHCl_3$. The resulting emulsion was filtered through Celite. The filtrate was diluted with 200 mL of H_2O and extracted with three 200-mL portions of $CHCl_3$. The combined organic extracts were washed (2 × 200 mL of H_2O) dried, and evaporated to give 4.9 g (98%) of colorless oil, which smelled strongly of thiol. This was chromotographed on 75 g of SiO_2, eluting with hexane and then hexane-ether (1:1) to give with the latter solvent (3.8 g, 76%) of clear viscous oil, which crystallized (**5a**): mp 108–110 °C; $[\alpha]^{20}_D$ −80.4° (*c* 1, MeOH).

Compound **5b** was prepared from compound **4b** by an analogous procedure: $[\alpha]^{20}_D$ +80.7° (*c* 1, MeOH).

***l*-1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine Hydrochloride (6a).** A solution of 3.5 g (8.75 mmol) of **4a** and 3.5 g of anisole in 25 mL of CH_2Cl_2 was cooled in an ice bath. To this was added, over 1 min, 40 mL of cold TFA. After 5 min, the ice bath was removed, and the solution was stirred at room temperature for 1 h. The solvent was evaporated under vacuum, and the residue was taken up in Et_2O and treated with excess ethereal HCl. The resulting precipitate was collected, dissolved in water, washed with Et_2O, made basic with 10% NaOH to pH 11, and extracted with CH_2Cl_2. The CH_2Cl_2 was treated with excess etherial HCl, and the solution was evaporated to give

(27) D. E. Janssen and C. V. Wilson, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 547.

(28) J. R. Berk and J. A. Yahner, *J. Org. Chem.*, **43**, 2048 (1978).

1.5 g of off-white solid. Crystallization from MeOH gave crystals of **6a**: mp 285 °C dec; yield 1.02 g (45%); $[\alpha]^{20}_D$ −72.6° (*c* 1, MeOH).

By a similiar procedure, **6b** was prepared from **5b**: $[\alpha]^{20}_D$ +74.7° (*c* 1, MeOH).

Attempts to isolate the other diastereoisomer from the mother liquor were not successful. The combined residues from the mother liquors were dissolved in 100 mL of CH_2Cl_2 and added dropwise over 15 min to an ice-cold solution of 50 mL of anisole in 200 mL of trifluoroacetic acid. After the addition was complete, the solution was stirred at room temperature for 1 h and then evaporated under vacuum to a dark brown oil. This was added dropwise to a solution of 500 mL of ether saturated with HCl. The resulting precipate was removed by filtration, stirred with 300 mL of Et_2O, collected, and sucked dry to give 26.4 g (93%) of pale tan powder. This was acylated with *d*-isobornyl chloroformate as described above and purified by crystallization to give 47% of **3b**, mp 163–166 °C.

Measurement of [^{3}H]Norepinephrine Release in the Rabbit Ear Artery. The rabbit ear artery was isolated and cannulated as described in ref 29; before mounting in the perfusion chamber, the artery was labeled by equilibration with [^{3}H]norepinephrine (150 μCi in 10 mL of Krebs solution) at 37 °C for 45 min with constant gassing with 95% O_2/5% CO_2. The artery was then mounted and allowed to slowly be perfused with Krebs solution for 7–8 h before the experiment was begun; the artery was usually stimulated periodically (5 Hz for 10 s at 12-min intervals) during this washout period.

Basal and stimulated norepinephrine release were determined in the following manner. Extraluminal and intraluminal outflow tubes were joined with a "T" connector; flow rate was adjusted to exactly 2 mL/min for the combined flow. A basal sample was collected for 2 min, directly into a glass scintillation vial (4-mL volume). The artery was then stimulated at 1.5–2 Hz for 2 min, and a second sample was collected. Collection of this sample was delayed 30 s to allow for dead space in the perfusion chamber; i.e., collection was begun 30 s after initiation of stimulation and continued for 30 s following termination of stimulation. Basal and stimulation samples were then mixed with 10 mL of scintillation fluid (Aquasol-II, New England Nuclear Corp.) for counting. This procedure was repeated at 20-min intervals.

Registry No. (±)-**1**·HCl, 86238-66-6; **2a**, 34771-95-4; **3a**, 86238-67-7; **3b**, 86287-10-7; **4a**, 86238-68-8; **4b**, 86287-11-8; **5a**, 86238-69-9; **5b**, 86287-12-9; **6a**, 86238-70-2; **6a** (free base), 86238-71-3; **6b**, 86238-73-5; **6b** (free base), 86238-72-4; (±)-**6**, 86287-13-0.

(29) J. P. Hieble, H. M. Sarau, J. J. Foley, R. M. DeMarinis, and R. G. Pendleton, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **310**, 267 (1982).

Gastric Antisecretory 9*H*-Xanthen-9-amines

Paul E. Bender,* Carl D. Perchonock, William G. Groves, Robert C. Smith, Jr., Orum D. Stringer, Rayvon Sneed, Jack H. Schlosser, Linda S. Hostelley, Bruce Y-H. Hwang, Roy Z. Eby, George Konicki, Patricia G. Lavanchy, James W. Wilson III, and Bernard Loev

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101.
Received September 20, 1982

A series of 9*H*-xanthen-9-amines possessing a wide variety of nitrogen substituents at C-9 was prepared for evaluation of gastric antisecretory activity. These substituents included the acetamidine, imidate, pyrimidine, thiazoline, quinuclidine, 2-hydrazinopyridine, aminopiperidine, aminoalkylimidazole, and aminoalkylpyridine moieties. The majority of compounds in this series inhibited gastric acid secretion when tested orally in the pylorus-ligated rat. Potency was increased by intraduodenal administration and diminished by incubation with gastric juice, suggesting partial degradation of the compounds in the gastric environment. A representative example, 3-(9*H*-xanthen-9-ylamino)-1-ethylpiperidine, exhibited similar activity in dogs, although no free compound could be detected in the blood. It is therefore hypothesized that this compound is either rapidly bound to tissue and/or metabolized to an active species.

Numerous and diverse examples of N-substituted 9*H*-xanthen-9-amines have been reported in the patent literature along with descriptions of antisecretory and antiulcer activity.[1] These claims are particularly interesting in light of the reported chemical instability of these compounds, a finding that apparently discouraged several investigators[2,3] from pursuing further studies. Thus, despite earlier interest in xanthene chemistry, a more detailed description of biological activity and its relation to molecular structure has only recently appeared for a series of 9-substituted (alkylthio)-9*H*-xanthenes.[4] In our own efforts to identify a promising antisecretory agent, we investigated a series of N-substituted 9*H*-xanthen-9-amines and describe our results at this time.

Chemistry. A variety of synthetic methods was employed to prepare the compounds described in this paper (see Scheme I). The classical reaction of 9*H*-xanthen-9-ol (I) with nucleophiles (Nu-H) in mildly acidic solution was used to synthesize a number of 9*H*-xanthen-9-yl amides (**2**, **3**, **5**, and **7**), as well as the allylamine (**14**), the formic acid hydrazide (**18**), and the piperazine carbamate (**21**).[5-8] Alkylation of less reactive or less stable nucleophiles by 9-hydroxy-9*H*-xanthenyl *N*-methylcarbamate (II) was selected for the preparation of sulfonamide **1**, hydrazines **19** and **20**, and aminothiazoline **27**.[9,10] Alkaline hydrolysis

(1) (a) Bender, P. E.; Loev, B.; Perchonock, C. D. U.S. Patents 3 949 076 and 3 996 364, 1976. (b) Bender, P. E.; Loev, B. U.S. Patents 3 980 788, 1976, and 4 005 208, 1977. (c) Adams, S. S.; Armitage, B. J.; Heathcote, B. V.; Bristow, N. W. U.S. Patents 3 681 373, 1972, and 3 755 593, 1973.
(2) Mann, F. G.; Turnbull, J. H. *J. Chem. Soc.* **1951**, 757.
(3) Witiak, D. T.; Hsu, S. Y.; Ollmann, J. E.; Griffith, R. K.; Seth, S. K.; Gerald, M. C. *J. Med. Chem.* **1974**, *17*, 690.
(4) Bristol, J. A.; Gold, E. H.; Gross, I.; Lovey, R. G.; Long, J. F. *J. Med. Chem.* **1981**, *24*, 1010.
(5) Fosse, R. *C. R. Hebd. Seances Acad. Sci.* **1906**, *143*, 749; *Chem. Abstr.*, 1907, *1*, 421.
(6) Phillips, R. F.; Pitt, B. M. *J. Am. Chem. Soc.* **1943**, *65*, 1355.
(7) Sawicki, E.; Oliverio, V. T. *J. Org. Chem.* **1955**, *21*, 183.
(8) Cusic, J. W.; Yonan, P. U.S. Patents 3 157 658, 1964, and 3 290 313, 1966.
(9) Capuano, L.; Zander, R. *Chem. Ber.* **1971**, *104*, 2212.
(10) Capuano, L.; Zander, P.; Bolourtschi, A. *Chem. Ber.* **1971**, *104*, 3750.

0022-2623/83/1826-1218$01.50/0