boxyl group of I, thus making possible the approach and subsequent hydrophobic bonding of the steroid-like ring structure of neighboring molecules. This can continue until pentomers become the dominant species, after which increasing salt gives rise to secondary micelles. These are formed, as suggested by Small (1), by dehydration of the weaker nonionic groups and resultant hydrogen bond formation between primary micelles, analogous to a salting-out effect.

On a molar basis, the free energy of dimerization of I was calculated from the salt-free system. At the highest concentration studied, 74 m*M*, the molecular weight was 850. Thus, from both the expression for the *z*-average molecular weight (Eq. 1):

$$M_z = \frac{\sum_i m_i M_i^3}{\sum_i m_i M_i^2} = \frac{m_1 M_1^3 + m_2 M_2^3}{m_1 M_1^2 + m_2 M_2^2} \qquad \text{(Eq. 1)}$$

and the relationship between monomer and dimer concentrations (Eq. 2):

$$m_1 = m_{0_1} - 2m_2 \qquad \text{(Eq. 2)}$$

the concentration of monomer and dimer could be obtained, assuming ideal solution properties and the absence of larger aggregates. The equilibrium dimer concentration (m_2) was found to be 15 m*M*, and the monomer concentration (m_1) at equilibrium was 44 m*M*. The symbol used for initial monomer concentration was m_{0_1}. Then the equilibrium constant for the reaction:

$$2 \text{ fusidate} \rightleftharpoons \text{fusidate}_2$$

Scheme I

was given by:

$$K = \frac{[\text{fusidate}_2]}{[\text{fusidate}]^2} = 7.75 \qquad \text{(Eq. 3)}$$

and:

$$\Delta G^\circ_{298} = -RT \ln K = -1200 \text{ cal/mole} \qquad \text{(Eq. 4)}$$

On the other hand, with sodium chloride added to give a salt to I ratio of 0.5, dimerization was facilitated. A molecular weight of 900 was reached at a I concentration of only 18 m*M*, and repetition of the thermodynamic calculation for dimerization led to a value of 56 for *K* and of −2400 cal/mole for ΔG°_{298}. In this second computation, it was assumed, as shown by Carey and Small (3), that salt was not specifically or firmly bound to the dimer but acted only as a supporting electrolyte, that is, to mask charge at the anionic head of I. This value of ΔG°_{298} is in agreement with values calculated for dimerization of sodium lauryl sulfate (10) and in fair agreement with the −3400 cal/mole calculated for I from CMC data (3) at pH 10 in carbonate buffer, although in the latter work I dimers were not specified exclusively in the composition of the micelle. Work is continuing to interpret the multiple equilibria involved as the salt to I ratio leads to the formation of larger aggregates in solution.

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Synthesis of Potential Adrenergic Blocking Agents: 2-Substituted Aminomethylnaphtho(2,3-*b*)-1,4-dioxans

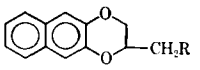
KISHOR B. PAREKH, WILLIAM H. SHELVER ˣ, AI-YU SHEN TSAI, and RICHARD REOPELLE

Abstract □ Eleven 2-substituted aminomethylnaphtho(2,3-*b*)-1,4-dioxans were synthesized. The nucleophilic displacement of 2-tosyloxymethylnaphtho(2,3-*b*)-1,4-dioxan by appropriate amines was carried out using dimethyl sulfoxide as the solvent. Preliminary pharmacological evaluation revealed a potentiation of norepinephrine at low doses and a noncompetitive antagonism at high doses in the rat vas deferens and a dose-related hypotensive action of short duration in the anesthetized rat.

Keyphrases □ Aminomethylnaphtho(2,3-*b*)-1,4-dioxans, 2-substituted—synthesized and screened as potential adrenergic blocking agents □ Dioxans—synthesis and screening of 2-substituted aminomethylnaphtho(2,3-*b*)-1,4-dioxans as potential adrenergic blocking agents □ Adrenergic blocking agents, potential—synthesis and screening of 2-substituted aminomethylnaphtho(2,3-*b*)-1,4-dioxans

Bovet and Simon (1) were the first investigators to demonstrate that 2-substituted aminomethyl-1,4-benzodioxans (I) possessed the ability to block certain actions of epinephrine. Piperoxan blocked norepinephrine by means of competitive antagonism in a study utilizing the rat vas deferens (2). The effects of

Table I—Physical Properties of the Hydrochloride Salts of 2-Substituted Aminomethylnaphtho(2,3-*b*)-1,4-dioxans



Compound	R	Melting Point	Yield, %	Analysis, % Calc.	Found
II*a*	$N(CH_3)_2$	225–227°	40	C 64.40 H 6.48 N 5.01	64.55 6.31 5.23
II*b*	$N(C_2H_5)_2$	226–227°	30	C 66.34 H 7.20 N 4.55	66.19 7.18 4.36
II*c*	$N(n\text{-}C_3H_7)_2$	198–200°	58	C 67.95 H 7.79 N 4.17	68.07 7.68 4.04
II*d*	$N(iso\text{-}C_3H_7)_2$	193–195°	22	C 67.95 H 7.79 N 4.17	67.84 7.76 4.04
II*e*	$N(n\text{-}C_4H_9)_2$	174–175°	70	C 69.31 H 8.30 N 3.85	69.48 8.42 3.68
II*f*		275–277°	60	C 67.60 H 6.93 N 4.38	67.63 7.07 4.20
II*g*		252–253°	79	C 66.77 H 6.59 N 4.58	66.96 6.71 4.45
II*h*		245–247°	70	C 63.45 H 6.26 N 4.35	63.58 6.40 4.15
II*i*		269–270°	82	C 58.32 H 6.51 N 7.54	58.34 6.60 7.41
II*j*	$HNCH_2CH(OH)C_6H_5$	244–245°	55	C 67.83 H 5.96 N 3.77	67.96 6.04 3.62
II*k*	$HNCH_2CH_2C_6H_5$	274–275°	52	C 70.88 H 6.22 N 3.94	71.00 6.34 3.77

structural variation in the dialkylaminoalkyl side chain, in the dioxan ring, and on the aromatic portion of the molecule have been reviewed (3). An extension of the aromatic area of the benzodioxan nucleus might provide an additional area for receptor binding by means of van der Waal's attraction. Additional binding would increase the potency of the compound.

Synthesis and biological evaluation of the 2-substituted aminomethylnaphtho(2,3-*b*)-1,4-dioxan (II) would indicate whether additional area on the receptor is available for this type of binding; therefore, 11 derivatives of 2-substituted aminomethylnaphtho(2,3-*b*)-1,4-dioxans were synthesized by means of the route shown in Scheme I. Previously, Augstein *et al.* (4) reported the synthesis of 2-guanidinomethylnaphtho(2,3-*b*)-1,4-dioxan.

EXPERIMENTAL[1]

2-Hydroxymethylnaphtho(2,3-*b*)-1,4-dioxan—To a stirring, refluxing mixture of 160 g (1.0 mole) of 2,3-dihydroxynaphthalene and 40 g (1.0 mole) of sodium hydroxide in 400 ml of 95% ethanol, 92 g (1.0 mole) of epichlorohydrin was added dropwise. The reaction mixture was refluxed for 4 hr and cooled. The precipitate was filtered, washed with ether and 95% ethanol, and recrystallized from benzene to yield 162 g (75%) of solid material, mp 156–157°. This compound was previously synthesized (4), but no physical or analytical data were reported.

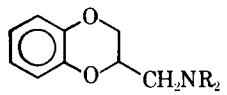
Anal.—Calc. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.34; H, 5.66.

2-Tosyloxymethylnaphtho(2,3-*b*)-1,4-dioxan—One hundred and eight grams (0.5 mole) of the above alcohol was treated with 190 g (1.0 mole) of *p*-toluenesulfonyl chloride at 0° in anhydrous pyridine for 24 hr. The reaction mixture was poured onto ice, and the solid that separated was recrystallized from acetone–water to yield 157 g (85%) of a solid material, mp 127–128.5°.

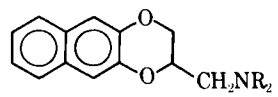
Anal.—Calc. for $C_{20}H_{18}O_5S$: C, 64.85; H, 4.89; S, 8.65. Found: C, 65.02; H, 5.01; S, 8.56.

2-Substituted Aminomethylnaphtho(2,3-*b*)-1,4-dioxans (Table I)—A solution of 10 g (0.027 mole) of 2-tosyloxymethylnaphtho(2,3-*b*)-1,4-dioxan in 100 ml of dimethyl sulfoxide was treated with an excess of the appropriate amine and heated to 80° for 36 hr. Then the reaction mixture was poured into ice, and the amine was isolated and converted to the hydrochloride salt.

Blood Pressure Experiments—Male Wistar rats (300 g) were anesthetized with 35 mg/kg of secobarbital, and the arterial blood pressure was monitored at the carotid artery by means of a linear core pressure transducer and recorded using a physiograph[2]. The drugs were injected into the femoral vein which had been previously cannulated. Normal blood pressure varied between 120 and 140



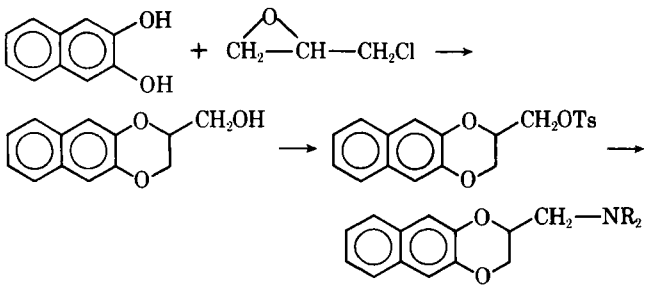
I



II

[1] The melting points of the compounds were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer model 337 IR spectrophotometer from potassium bromide pellets. NMR spectra were determined on a Varian model A-60A in $CDCl_3$ solution, using tetramethylsilane as a reference. Microanalyses were performed by Alfred Bernhardt mikroanalytische Laboratorium, West Germany.

[2] E&M electronic physiograph.



Scheme I

mm Hg. The data were plotted as the percent reduction of blood pressure *versus* dose of the drug (Fig. 1).

Vas Deferens Experiments—Male Wistar rats were killed by a blow on the head, and the vas deferens was dissected free. The vas deferens was placed in a tissue bath (23 ml) containing Tyrodes solution[3] and connected to an isotonic writing lever registering on a kymograph. The Tyrodes solution was maintained at 35° and aerated with 95% O_2–5% CO_2. The vas deferens was made to contract maximally with high doses of norepinephrine prior to beginning the cumulative response curves. Cumulative response curves were prepared by adding norepinephrine, allowing the muscle to equilibrate, adding twice the previous concentration of norepinephrine, and allowing the equilibration to occur until the muscle failed to contract further. The vas deferens was then washed with Tyrodes solution until the muscle relaxed to the original state.

Two cumulative curves of norepinephrine were obtained prior to beginning experiments on the naphthodioxans. The naphthodioxan was then added to the bath, and the response to norepinephrine was again determined. The minimal dose of naphthodioxan used was 4.4×10^{-6} mole/liter, and the maximum dose was 4.4×10^{-4} mole/liter. The percent response to the drugs was then compared to norepinephrine controls (Fig. 2).

PHARMACOLOGICAL EVALUATION

In a preliminary pharmacological study, the dimethylamino, diethylamino, dipropylamino, and the piperidino compounds were tested for their effects on blood pressure in rats. Each drug was tested on one rat in the preliminary screen. All of these compounds lowered the blood pressure of the rat, with the piperidino compound being the most active; however, the duration of the blood pressure response was extremely short.

Figure 1 shows the dose–response curve obtained with piperidinonaphthodioxan. When the piperidino compound was tested using the vas deferens preparation, the compound first potentiated

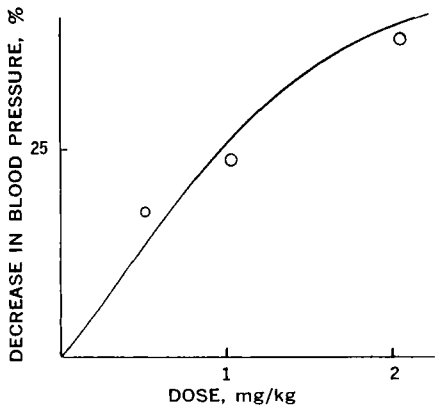


Figure 1—*Effects of 2-piperidinomethylnaphtho(2,3-b)-1,4-dioxan on the blood pressure of the rat. The points represent results on an individual rat, and the curve is arbitrarily drawn to go through the origin.*

[3] Containing (per liter) 8.0 g of NaCl, 0.1 g of KCl, 0.2 g of $CaCl_2$, 0.005 g of NaH_2PO_4, 1.0 g of $NaHCO_3$, and 1.0 g of glucose.

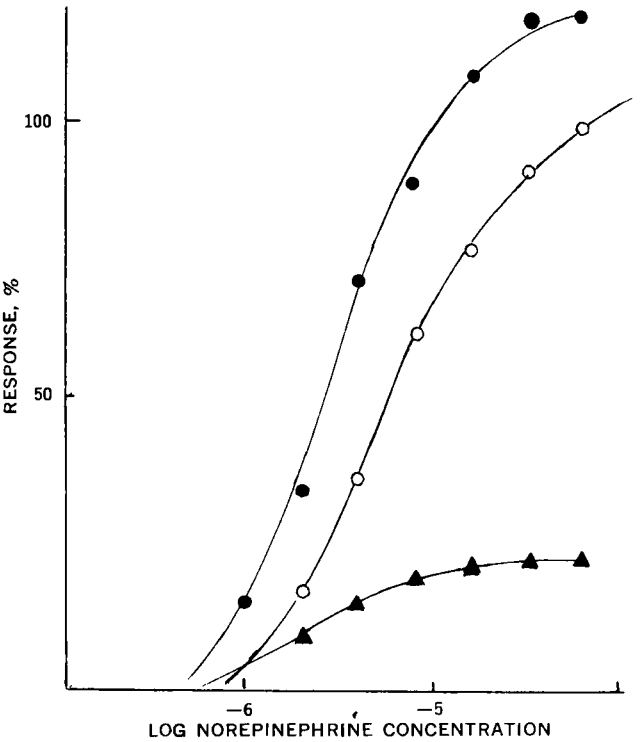


Figure 2—*Effects of 2-piperidinomethylnaphtho(2,3-b)-1,4-dioxan on the rat vas deferens. The points were obtained on an individual vas deferens. All concentrations are in moles per liter. Key:* ●, *4.4×10^{-6};* ○, *control; and* ▲, *4.4×10^{-4}.*

norepinephrine and then antagonized the effect of norepinephrine in a noncompetitive manner. The concentrations appropriate for the vas deferens experiment were found in a preliminary experiment, and a new vas deferens was utilized in the final test. Figure 2 shows the effect of piperidinonaphthodioxan relative to the response demonstrated by norepinephrine.

DISCUSSION

The synthesis of these compounds is straightforward and calls for little discussion except for the utilization of dimethyl sulfoxide as the solvent for the displacement of the tosylate with the amine. This solvent greatly improves yields and shortens reaction times in the synthesis of dialkylaminomethyl-1,4-benzodioxans.

The dose-related drop in blood pressure (Fig. 1) indicated that 2-piperidinomethylnaphtho(2,3-*b*)-1,4-dioxan was an extremely potent hypotensive agent, producing a noticeable drop of 28 mm Hg at 0.5 mg/kg. Unfortunately, the duration was extremely short, less than 30 sec, when the drug was given intravenously.

The experiments on the rat vas deferens indicate that these compounds act by a different mechanism than the model compounds, the benzodioxans (I). The benzodioxans act by competitive inhibition, shifting the norepinephrine dose–response curve to the right. The response curve of norepinephrine was shifted to the left and the maximum response was increased at low doses of piperidinomethylnaphtho(2,3-*b*)-1,4-dioxan whereas high doses depressed the maximum response. A similar type of response has been observed for protriptyline and desipramine (5). Avner and Triggle (6) observed an enhanced contraction to norepinephrine in the rat vas deferens exposed to 2-diethylamino-1,4-benzodioxans and attributed the enhancement to increased mobilization of calcium.

Two possible explanations exist for the naphthodioxans' ineffectiveness on the benzodioxan receptor. The transport of antagonists to the benzodioxan receptor may be partition coefficient dependent (Hansch-type relationship), or the naphthodioxans have a much greater lipid solubility than the corresponding benzodioxans and thus the naphthodioxans may not be transported to the receptor in an optimum fashion. An alternative and more attractive ex-

planation may be that the receptor for the benzodioxans will not accommodate the larger naphthodioxan.

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Influence of Particle Size on Rectal Absorption of Aspirin

EUGENE L. PARROTT

Abstract □ The rectal absorption of aspirin from theobroma oil suppositories was studied in seven human subjects using urinary excretion measurements. The effect of particle size on the excretion rate and cumulative amount of total salicylate excreted was demonstrated by the administration of a 600-mg dose as powdered aspirin and as aspirin disks having 0.023 as much surface as powdered aspirin. *In vitro* dissolution profiles of aspirin from the suppositories were studied. By the NF XIII Method II, the time required for 50% of the aspirin to dissolve from the suppository was 50 and 100 min for the powdered aspirin and the aspirin disks, respectively. In the bioavailability study, the diffusion equilibrium was attained at approximately 4–5 and 9–10 hr after the rectal administration of powdered aspirin and aspirin disks, respectively. No correlation was found between bioavailability and the dissolution profiles as determined by the USP XVIII dissolution method.

Keyphrases □ Aspirin—absorption from theobroma oil suppositories, effect of particle size □ Dissolution—aspirin from suppositories, effect of particle size □ Bioavailability—aspirin, effect of particle size, correlation with *in vitro* dissolution profiles □ Particle-size effect—aspirin absorption from suppositories □ Absorption, rectal—effect of particle size on aspirin absorption from suppositories

Since early studies (1, 2), numerous investigations have demonstrated the influence of particle size on bioavailability from oral dosage forms. For poorly soluble drugs, it is widely recognized that a smaller particle size (greater surface) brings about more rapid dissolution and more rapid GI absorption. If absorption is rate limited by slow dissolution so that the drug is not completely absorbed from a solid dosage form, the more rapid absorption obtained by increasing the surface may also cause an increase in the total amount of the drug absorbed from a given dose (3–6).

The purpose of this investigation was to demonstrate that the particle size of aspirin incorporated in a rectal suppository could influence absorption. As shown by plasma salicylate concentration (7) and urinary salicylate excretion (8), rectal administration of aspirin is as effective as oral administration. Wagner (9) cited certain general conclusions regarding absorption of drugs following rectal administration in humans. The emphasis in investigating suppositories has been on physical characteristics (10, 11), the influence of the base (12–14), and the *in vitro* release of the drug (15). By use of a simple aspirin and theobroma oil suppository, which melted at body temperature, the effect on absorption of approximately a 40-fold difference in surface area of the aspirin was studied.

EXPERIMENTAL

Protocol—Six healthy male and one healthy female subjects, 25–49 years of age and 60–82 kg, participated. Subjects were ambulatory and permitted to ingest food and fluids as desired. Urine samples were collected at hourly intervals after rectal insertion of the suppository. Volumes of the urine samples were measured, and aliquots were retained for analysis. Although the pH of each sample was measured, no attempt was made to control the pH. The formulations were coded, and a crossover technique was used with an interval of 1 week between bioavailability studies.

Preparation of Suppositories—When using mineral oil in the pycnometer, the density of powdered aspirin[1] was 1.40 g/cm^3. An 80–100-mesh fraction of the powdered aspirin was separated by a sieve shaker[2]. The average size of the fraction was assumed to be 163 μm. Aspirin powder of 163-μm size was quantitatively mixed with theobroma oil[3], placed in a suppository machine[4], and pressed into a suppository containing 600 mg of aspirin and 475 mg of theobroma oil.

Disks of aspirin were made by compressing the powdered aspirin with a 0.3175-cm (0.125-in.) flat-faced punch and die set. The length and diameter of each disk were measured using an optical micrometer[5]. Disks were selected so that 13 disks weighed 600 mg.

Suppositories containing the disks were prepared by the fusion method. The cavity of the mold was approximately one-third filled with melted theobroma oil, several disks were added, and the mass was allowed to congeal. This procedure was repeated until all disks had been added and the cavity was filled. The mold was immediately placed in a refrigerator so that the disks were not in contact

[1] USP, fine crystal, J. T. Baker Chemical Co.
[2] Allen-Bradley sonic sifter.
[3] Cocoa butter.
[4] Armstrong suppository machine No. 3.
[5] Gaertner Scientific Corp.