observed for gnawing movement for 1 min. Absence of the typical gnawing movement during at least one of the three observation periods was regarded as a positive effect.[13] The ED_{50} in this test is defined as the dose which suppresses the gnawing movement in 50% of the rats. Furthermore, the ability of **5k** to enhance the action of apomorphine hydrochloride was examined. Rats were injected iv with 0.05 mg/kg of apomorphine hydrochloride, a dose too small to induce gnawing by itself, 1 h after a sc injection of **5k** and observed for the incidence of gnawing for 20 min.

Effect on Methamphetamine-Induced Hyperactivity in Mice. The suppression of methamphetamine-induced hyperactivity was examined according to the modified method of Ueki et al.[14] At 100 min after oral administration of test compounds, five groups of three mice were injected with methamphetamine (5 mg/kg, ip), and 10 min thereafter the locomotor activity was measured with a photocell activity counter for 20 min. The ED_{50} in this test is the dose which reduces the average counts of the treated mice to half the count of control animals.

Effect on Active Avoidance in Mice. Effect of test compounds on one-way active avoidance in mice was examined using a box with two compartments, darkened and lighted, as described previously.[15] Mice were previously trained to avoid electroshocks from the floor by moving from the darkened compartment to the lighted one in response to a warning stimulus. This test was carried out using for each group 10 mice which could avoid the shock at a rate more than 80% in 20 trials. The results are expressed as the ED_{50} values, defined as the dose that causes a 50% inhibition in the rate of the avoidance response.

Effect on Self-stimulation in Rats. Effect of test compounds on intracranial self-stimulation behavior was studied in rats with chronic electrodes implanted in the lateral posterior hypothalamus.[16] The rats which showed a constant lever-pressing response of 50–100/min were selected for the test. Groups of eight rats were used. In the test, self-stimulation rates were counted for 10 min before and 1, 2, 4, 6, 8, and 24 h after po or ip administration of test compounds. The ED_{50} in this test is the dose which causes 50% or more inhibition of the rate of the self-stimulation in 50% of the rats.

Acknowledgment. We thank Dr. M. Shimizu, the director of these laboratories, and Dr. H. Nishimura for their encouragement and Dr. S. Minami for his helpful advice throughout the course of this work. Thanks are also due to Dr. T. Karasawa for the pharmacological tests and the members of Analytical Center of these laboratories for the elemental analyses and spectral measurements.

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Glycerides as Prodrugs. 1. Synthesis and Antiinflammatory Activity of 1,3-Bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides (Aspirin Triglycerides)[1]

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A series of 1,3-bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides (aspirin triglycerides) having aspirin at the 2 position of glycerol and fatty acids at the 1 and 3 positions was prepared. The compounds were administered orally and tested for efficacy in the rat paw edema test, and the stomachs were examined for the presence of lesions. The results showed that the members of this series in which the fatty acids are of intermediate chain length (C_4–C_{12}) do not cause gastric lesions and have essentially all the systemic activity associated with aspirin.

Despite the enormous amount of work that has been done on development of antiinflammatory drugs, the classical remedy aspirin remains the drug of first choice in the treatment of arthritis. Although traditional and familiar, aspirin is not an innocuous substance. It causes a variety of side effects which limit its usefulness, often obliging the patient to switch to other medications which frequently have a similar profile of side effects. The primary unwanted effect is direct gastric irritation, due to contact of solid aspirin (or of concentrated solutions of aspirin) with the gastric mucosa. It has been reported recently[3] that aspirin in antiarthritic doses causes endoscopically observable gastric erosion in 39% of the patients tested over a 4-week period. Many attempts have been made to develop aspirin derivatives and formulations which will yield adequate blood levels after oral administration without causing gastric irritation. We wish to report on a novel approach to this problem, in which

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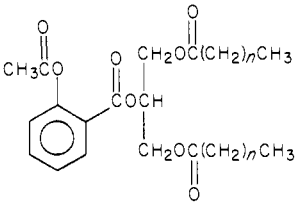
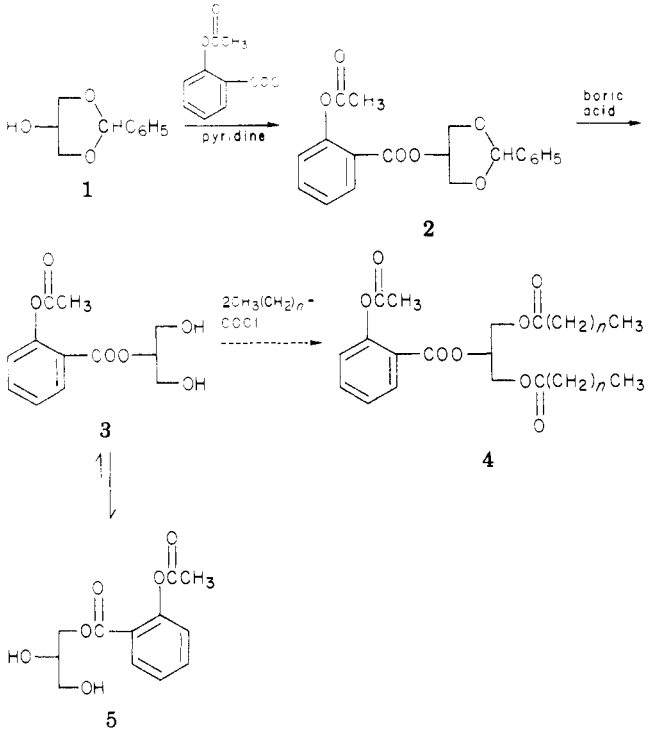
Table I. 1,3-Bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides



no.	n	M_r	aspirin, %	yield, %	physical form	formula	anal.	MS (M^+)
4a	0	338.32	53	63	mobile liq	$C_{16}H_{18}O_8$	C, H	338
4b	2	394.42	46	47	liq	$C_{20}H_{26}O_8$	C, H, O	394
4c	6	506.64	35	71	liq	$C_{28}H_{42}O_8$	C, H, O	506
4d	8	562.74	32	63[a]	visc liq	$C_{32}H_{50}O_8$	C, H, O	562
4e	10	618.85	29	61	semisolid	$C_{36}H_{58}O_8$	C, H	618
4f	14	731.08	24	82	mp 43-44 °C[b,c]	$C_{44}H_{74}O_8$	C, H, O	730

[a] A modified procedure produced a 99% yield (see Experimental Section). [b] Recrystallized from petroleum ether (bp 30-60 °C). [c] Following the completion of this work, a description of this compound was given by J. D. Billimoria and R. Kumar.[7]

Scheme I



Scheme II

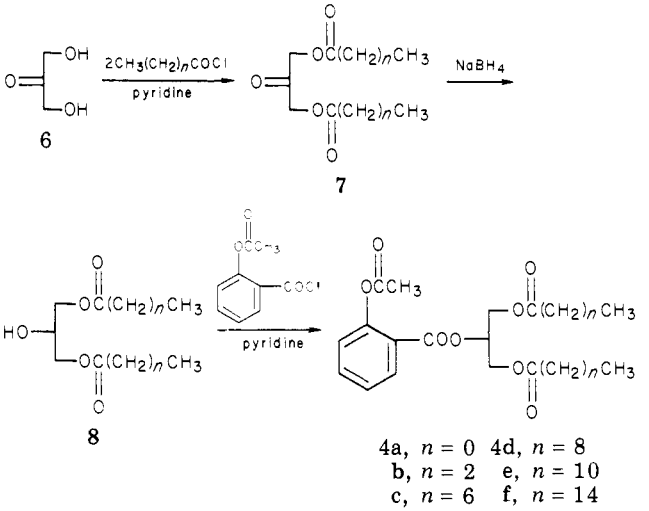


Table II. Antiedema Efficacy and Gastric Ulceration Caused by 1,3-Bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides Relative to Plain Aspirin

no.	dosage, μmol/kg	act. as % of aspirin[a]	ratio of lesion incidence[b]
4a	444	48-64	1:6
4b	444	92	0
4c	394	60	
4d	444	80-100	0
4e	323	44	
4f	273	12	
aspirin	444		6:6

[a] At 444 μmol/kg; male Sprague-Dawley rats weighing 170-200 g were fasted overnight but allowed water ad libitum. Aspirin and aspirin triglycerides were suspended in 0.5% (w/v) methylcellulose plus a drop of Tween 80 and administered orally 2 h prior to the subplantar injection of 0.1 mL of a 1.5% solution of carrageenin. Paw volumes were measured prior to and 3 h after injection by immersion in a mercury-containing vessel connected to a volumetric transducer and a polygraph. [b] Gastric ulceration relative to plain aspirin. Ratio of lesion incidence refers to animals having a lesion of 1 mm in length or longer.

aspirin is administered as part of a triglyceride; this approach was based on known lipid metabolic pathways.

Chemistry. The synthesis of the desired compounds, in which the aspirin is attached to the 2 position of glycerol and fatty acids of varying chain length are at the 1 and 3 positions, was first attempted via the intermediate 2-(*O*-acetylsalicyloyl)glycerol (**3**) as outlined in Scheme I. The condensation of **1** with *O*-acetylsalicyloyl chloride gave **2**, which on hydrolysis with boric acid[4] gave **3**. This method was not satisfactory because **3**, in the same way as natural 2-monoglycerides,[5] isomerized to give a mixture in which **5** predominated. The formation of **4** from **3** was not further investigated.

An alternative synthetic route, in which 1,3-dialkanoylglycerol was obtained from dihydroxyacetone as described by Bentley and McCrae,[6] proved to be superior.

As illustrated in Scheme II, 1,3-dihydroxyacetone (**6**) is condensed with 2 mol of fatty acid chloride to give compound **7**, which on reduction with sodium borohydride yields **8**. Condensation of **8** with *O*-acetylsalicyloyl chloride gives **4**. A 53% overall yield from dihydroxyacetone was obtained for the preparation of **4d**.

All the triglycerides described in Table I were prepared by the method of Scheme II. The products were char-

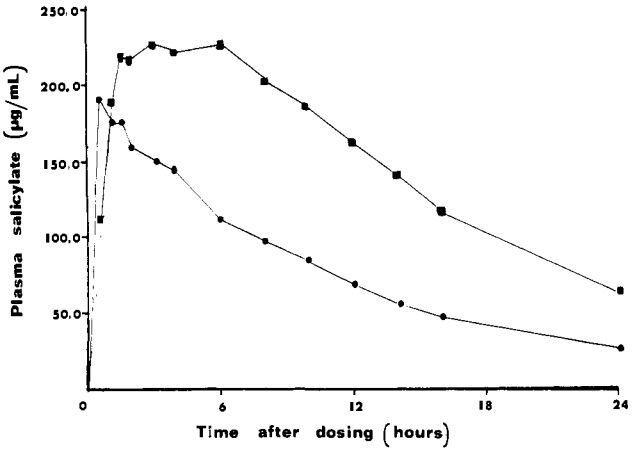


Figure 1. Rat plasma salicylate levels resulting from oral administration of emulsified **4d** (■–■, 1192 μmol/kg) and aspirin (●–●, 594 μmol/kg).

acterized by NMR, IR, MS, and elemental analysis.

Pharmacology. 1. Antiedema Efficacy and Ulcerogenicity. Compounds **4a–f** (Table I) were screened for antiinflammatory activity in the carrageenin rat paw edema assay, using a modification of the method described by Winter et al.[8] (footnote *a* in Table II), and the stomachs were examined for the presence of gastric lesions by the method of Brodie and Hansen.[9]

Potency. It can be seen from Table II that three compounds were tested at the same molar dose as the ED_{25} of aspirin (444 μmol/kg or 80 mg/kg). The ED_{25} is the dose which causes a 25% reduction in the edema. Compounds **4b** and **4d** were as potent as aspirin in inhibiting hind paw swelling induced by carrageenin. The chain length of the substituting fatty acids has a marked effect on the antiinflammatory activity. Compound **4f**, 1,3-bis(palmitoyl)-2-(*O*-acetylsalicyloyl)glyceride, (C_{16}), has only 12% of the activity of aspirin.

Ulcerogenicity. Three of the compounds were tested for their tendency to cause gastric lesions in rats at the molar dosage (444 μmol/kg) at which aspirin caused lesions in six out of six rats. No visible gastric ulceration was produced by the compounds except for 1,3-bis(acetyl)-2-(*O*-acetylsalicyloyl)glyceride (**4a**) which showed some ulcerogenic activity (Table II).

1,3-Bis(decanoyl)-2-(*O*-acetylsalicyloyl)glyceride (**4d**) was selected for determination of salicylate blood levels and antipyretic activity in rats.

2-Salicylate Blood Level Determination.[10] The plasma salicylate levels following the oral administration of aspirin and of an emulsion of **4d** were compared in rats. As shown in Figure 1, the peak salicylate level produced by **4d** occurs later and is maintained longer than aspirin. With aspirin, plasma salicylate reaches the highest level (mean 196 μg/mL) after 15 min and then gradually declines to a mean value of 24 μg/mL by 24 h. At twice the molar dose of aspirin, the **4d** emulsion reaches peak salicylate (mean 219 μg/mL) 1–1.5 h after dosing, maintains this level through 6 h, and then gradually declines to 61 μg/mL by 24 h.

Comparing the mean areas under the curves after aspirin and **4d** emulsion dosing it is shown that essentially 100% of the available salicylate in **4d** is absorbed. When **4d** unemulsified (suspended in methylcellulose and a drop of Tween 80) was used, the bioavailability was 75% that of aspirin.

3-Antipyretic Studies. The antipyretic activities[11] of unemulsified **4d** (at 1068 μmol/kg) and aspirin (at 444 μmol/kg) were determined in rats (Figures 2 and 3).

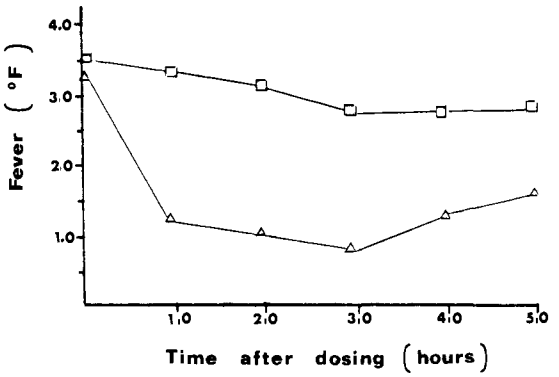


Figure 2. Effects of aspirin (Δ–Δ, 444 μmol/kg) on yeast-induced fever in rats: (□–□) vehicle control.

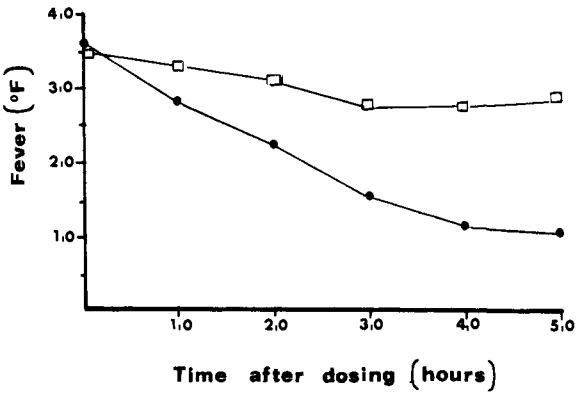


Figure 3. The effects of **4d** (●–●, 1068 μmol/kg) on yeast-induced fever in rats: (□–□) vehicle control.

Compound **4d** had a delayed onset of activity relative to aspirin, but at the dosage used the effect was prolonged. This antipyretic time profile of **4d** resembles the profile of plasma salicylate following oral administration of **4d** (Figure 1).

Discussion

It is seen from the antiedema and antipyretic activities that the members of the series in which the fatty acids are of intermediate chain length (C_4–C_{12}) have essentially all of the systemic activity associated with the aspirin incorporated into the molecule. The quantitative absorption of the active component in the case of emulsified didecanoyl derivative was shown by salicylate blood level determination in rats.

The extremely low degree of gastric ulceration caused by the active aspirin triglycerides suggested that little or no aspirin or salicylate is liberated in the stomach. The glyceride passes through the stomach without hydrolysis. Liberation of the free aspirin must occur subsequently, either in the intestine or following absorption in the plasma. It seems justified to conclude that the partially unnatural triglycerides of this series are metabolized in the gastrointestinal tract in a similar way as natural medium-chain triglycerides. Following completion of this work, Billimoria and Kumar[7] reported that they had reached similar conclusions.

The currently accepted view of gastrointestinal triglyceride metabolism and absorption is illustrated in Figure 4.[12]

On the basis of our observations on gastric irritation, salicylate blood levels, and pharmacological efficacy, it appears that replacement of a fatty acid by acetylsalicylic acid in the 2 position of triglyceride does not alter the natural pattern of the metabolism of triglycerides.

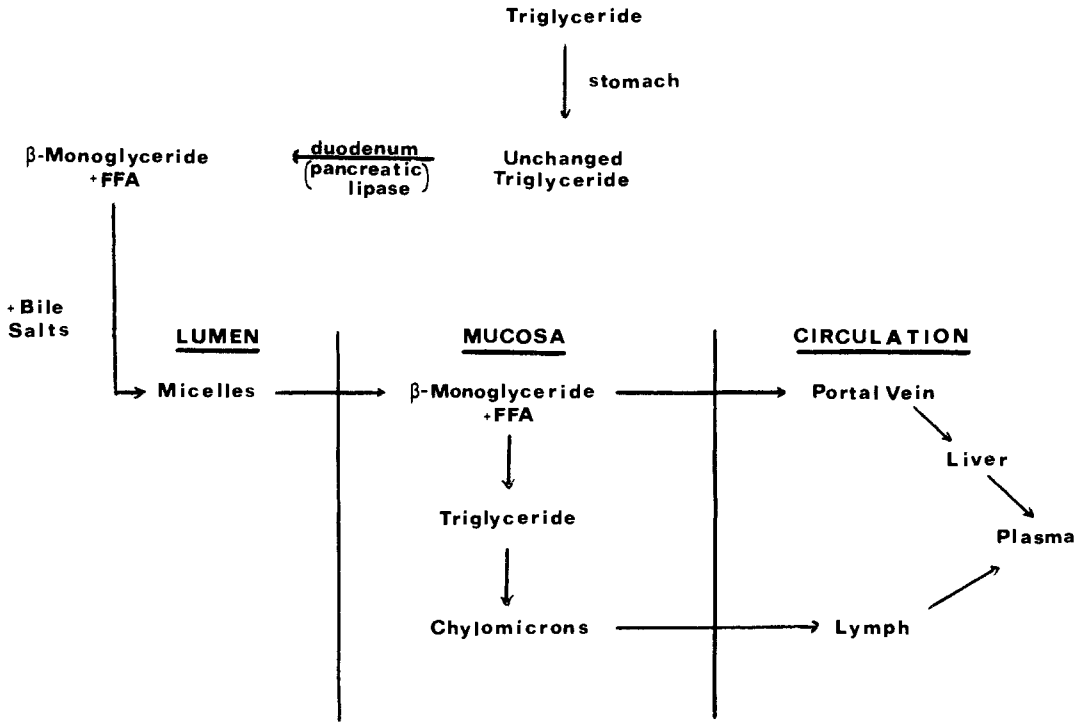


Figure 4.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Research Department, Abbott Laboratories, North Chicago, Ill. IR, UV, and NMR spectra were in agreement with the assigned structures. NMR spectra were recorded with a Varian EM-360 (Me_4Si). TLC's were performed on fluorescent silica gel GF plates; the spots were detected by UV or with $KMnO_4$ solution.

1,3-Benzylidene-2-(*O*-acetylsalicyloyl)glyceride (2). 1,3-Benzylideneglycerol (1) was prepared by the method of Hibbert and Carter[13] from glycerol, benzaldehyde, and a catalytic amount of acid. The product, 1 (9.5 g, 0.053 mol), was dissolved in 200 mL of pyridine, and *O*-acetylsalicyloyl chloride (9.9 g, 0.05 mol) was added. The reaction mixture was stirred overnight, poured into cold H_2O, and extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and evaporated: yield 12.1 g (71%); mp 126–127 °C (C_6H_6–petroleum ether). Anal. ($C_{19}H_{18}O_6$) C, H, O.

2-(*O*-Acetylsalicyloyl)glycerol (3). The benzylidene blocking group was removed from **2** (5.0 g, 0.015 mol) with boric acid (1.7 g, 0.027 mol) in triethyl borate (100 mL) following the method of Martin.[4] The crude product (3.7 g) was purified by chromatography on a column of Florisil, 100 g impregnated with boric acid (10%, w/w) and activated at 100 °C. Compound **3** was eluted from the column with $CHCl_3$–MeOH (9:1) and was found by NMR studies to isomerize readily at room temperature to give a mixture in which **5** predominated.

1,3-Bis(alkanoyl)glycerides (8). The required 1,3-bis(alkanoyl)glycerides were prepared by the general method of Bentley and McCrae[6] from the condensation of 1,3-dihydroxyacetone (**6**) with 2 mol of fatty acid chloride, followed by the reduction of the carbonyl group with sodium borohydride.

1,3-Bis(decanoyl)-2-(*O*-acetylsalicyloyl)glyceride (4d). The following experiment illustrates a general procedure used to prepare the 1,3-bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides described in Table I.

O-Acetylsalicyloyl chloride was prepared by the method of Riegel and Wittcoft[14] with slight modification. The mixture of acetylsalicylic acid and $SOCl_2$ in the presence of a catalytic amount of pyridine was refluxed for 30 min before isolation. *O*-Acetylsalicyloyl chloride (44.6 g, 0.225 mol) dissolved in 75 mL of CH_2Cl_2 was added at once to a stirred solution of 1,3-bis(decanoyl)glyceride (**8**, n = 8; 90.0 g, 0.225 mol) and dry pyridine (25 mL) in CH_2Cl_2 (400 mL). The stirring was continued for 40 h and the reaction was evaporated to dryness. The residue was triturated with 600 mL of Et_2O, and the insoluble salt was removed by filtration. The solution was washed successively with H_2O, 1% HCl, H_2O, 1% $NaHCO_3$, H_2O, and brine. The dried ($MgSO_4$) solution was evaporated, the residue was dissolved in petroleum ether, and the solution was purified by chromatography on a column of Florisil (880 g, deactivated with wet ether). Compound **4d** was eluted with petroleum ether–ether (80:20) and treated with charcoal to give a clear oil, 79.2 g (60%). The product was homogeneous by TLC (cyclohexane–EtOAc, 3:1), R_f 0.63; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H, aspirin CH_3), 4.25 (d, 4 H, 2 × OCH_2), 5.45 (m, 1 H, OCH). Anal. ($C_{32}H_{50}O_8$) C, H, O.

A quantitative yield of compound **4d** was obtained when a solution of *O*-acetylsalicyloyl chloride (3 equiv), 1,3-bis(decanoyl)glyceride (1 equiv), and pyridine (3.3 equiv) in dry CCl_4 was stirred at 25 °C for 1.5 h. The excess *O*-acetylsalicyloyl chloride was decomposed by stirring the reaction mixture in the presence of H_2O for 2 h. The product was isolated in greater than 99% purity, without chromatographic purification.

Acknowledgment. We express our thanks to G. Nettleship of Abbott Laboratories Ltd., Montreal, Ms. R. Stanaszek and Ms. S. Mueller of Abbott Laboratories, North Chicago, for ^1H NMR, ^{13}C NMR, and mass spectra, respectively, and to the staff of the Analytical Research Department of Abbott Laboratories for elemental analyses.

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β-Adrenergic Blocking Agents with Acute Antihypertensive Activity

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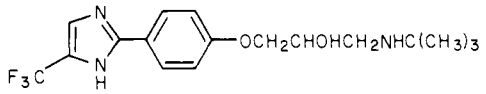
Modification of the pharmacological profile of the vasodilating/β-adrenergic blocking agent 2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-4-(trifluoromethyl)imidazole (1) has been investigated. Introduction of selected substitutents onto the imidazole ring, in place of the trifluoromethyl group, has yielded highly cardioselective β-adrenergic blocking agents such as **7**, **17**, and **18**. The placement of alkyl or chloro groups onto the aryl ring of **1**, as illustrated by **33**, has produced a class of compounds characterized as antihypertensive β-adrenergic blocking agents. In these examples, the acute antihypertensive activity does not appear to be due to either vasodilating or β_2-agonist properties.

We have previously reported that compounds exemplified by **1** were found to lower mean arterial blood



1

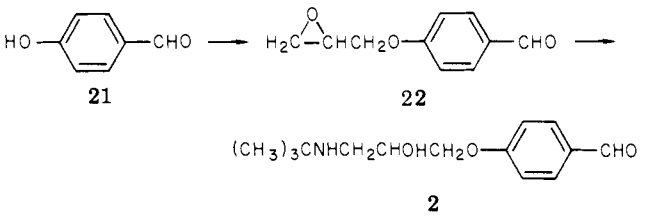
pressure in spontaneously hypertensive (SH) rats and to exhibit vasodilating and β-adrenergic blocking properties in the dog.[1] However, the reduction in peripheral vascular resistance induced by **1** was attenuated by timolol, a β-adrenoceptor antagonist. The assumption was made that the vasodilation was due, in large part, to β_2-agonist activity.

In an extention of this work, we have attempted to reduce this β-agonist component while retaining those structural features which induced the acute antihypertensive and β-adrenergic blocking effects. The approach was based on the premise that the affinity for the β-adrenergic receptor was determined by the aminohydroxypropoxy side chain, while activation of the receptor was induced by an interaction of the bound drug with an aromatic/phenolic binding site on the receptor.

The partial agonist activity of **1** was ascribed to the interaction of the acidic imidazole proton with this postulated binding site. In support of this concept, in has recently been reported that the incorporation of phenolic groups into phenoxypropanolamines was associated with the introduction of agonist properties.[2] Substitution of the imidazole ring with moieties less electronegative or more bulky than the trifluoromethyl group was therefore examined with the aim of reducing the capability of the imidazole proton to act as a phenolic equivalent. Attempts were also made to reduce this postulated interaction by substitution of the aryl ring with chloro and alkyl groups ortho to the trifluoromethylimidazolyl substituent.

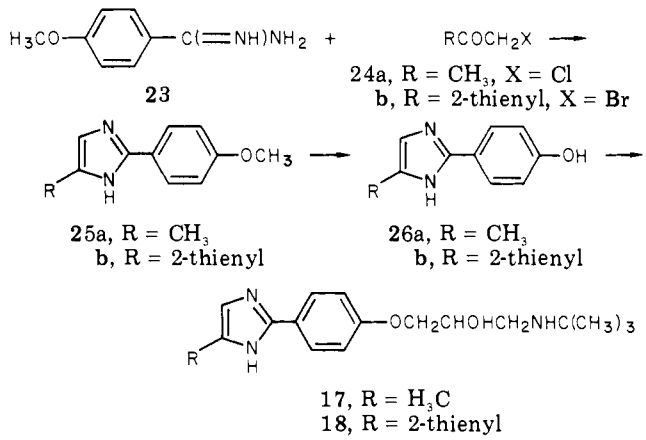
Chemistry. The various 4-substituted 2-[4-[(*tert*-butylamino)-2-hydroxypropoxy]phenyl]imidazoles prepared during this study are listed in Table I. Examples **3**–**15**

Scheme I



21 **22** **2**

Scheme II



23 **24a**, R = CH_3, X = Cl; **b**, R = 2-thienyl, X = Br

25a, R = CH_3; **b**, R = 2-thienyl **26a**, R = CH_3; **b**, R = 2-thienyl

17, R = H_3C
18, R = 2-thienyl

were synthesized via the Radziszewski reaction involving the condensation of the racemic aldehyde **2** with a substituted glyoxal in methanolic aqueous ammonia. The 4-methylimidazole derivative **16** was obtained using the Weidenhagen modification in which **2** was allowed to react with α-acetoxyacetone, aqueous ammonia, and cupric acetate.

The intermediate aldehyde **2** was prepared as outlined in Scheme I. Treatment of *p*-hydroxybenzaldehyde with epichlorohydrin in aqueous base gave **22** in 64% yield after distillation. The potential for a competing Cannizzaro reaction under these conditions did not prove to be a

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