bromide was obtained in 85% yield from hexyl bromide and 3·HCl (15 hr, 80°), mp 179–181°. *Anal.* ($C_{20}H_{32}BrNO_2$) C, H, N, Br.

1-Heptyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (10) Hydrobromide. This was obtained in 78% yield as described for 9 using heptyl bromide: plates, mp 147–149°, from Me_2CO. *Anal.* ($C_{21}H_{34}BrNO_2$) C, H, N, Br.

1-Allyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (11) Hydrobromide. The yield of 11·HBr (allyl bromide, 7 hr) was 74%; plates, mp 192–193° (from EtOH). *Anal.* ($C_{17}H_{24}BrNO_2$) C, H, Br, N.

1-Cyclopropylmethyl-4-*m*-hydroxyphenyl-4-(1-hydroxypropyl)piperidine (12). A mixture of 2.4 g of 4, 3.8 g of cyclopropylcarbonyl chloride, 12 ml of Et_3N, and 70 ml of CH_2Cl_2 was refluxed for 3 hr and evaporated to dryness. The residue was dissolved in C_6H_6 and H_2O. The C_6H_6 layer was washed with 10% HCl, saturated $NaHCO_3$, and H_2O, successively, dried,‡ and evaporated to give 4.2 g of the *N,O*-dicarbonyl compound: ν 1750, 1705, 1640 cm^{-1}. This was reduced with 3.6 g of $LiAlH_4$ in 100 ml of refluxing THF (24 hr) giving, after the usual work-up, 2.7 g (87%) of **12**: mp 180–182° (from EtOH); M^+ 289. *Anal.* ($C_{18}H_{27}NO_2$) C, H, N.

1-Cyclopropylmethyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (13) Hydrobromide. Ac_2O (7.5 ml), 1.5 g of 12, and 22.5 ml of DMSO were stirred at room temperature for 65 hr, treated with ice-H_2O, made alkaline with 12 *M* NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O and evaporated to give an oil which was dissolved in 10% NaOH-EtOH. This solution was refluxed for 3 hr, the EtOH was distilled, H_2O was added to the residue, and the resultant solution was washed with $CHCl_3$ and then made alkaline with 12 *M* NH_4OH. The liberated base was dissolved in $CHCl_3$ and dried.‡ Evaporation left 1.0 g of oil which contained some **12**. Column chromatography on 30 g of silica gel (9:1 AcOEt-EtOH as eluent) gave 0.93 g (52%) of 13 whose hydrobromide (from EtOH) melted at 254–255°. *Anal.* ($C_{18}H_{26}BrNO_2$) C, H, Br, N.

Oxidation of 12 by the Oppenauer method (cyclohexanone, aluminum isopropoxide) gave 30% of 13.

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Anticonvulsants. 4. Metharbital and Phenobarbital Derivatives[1]

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Several metharbital and phenobarbital derivatives were found to possess potent anticonvulsant activity and yet were either devoid of the marked hypnotic effects of the parent compounds or displayed very weak hypnotic activity. Particularly active compounds were the monomethoxymethyl derivative of phenobarbital (3), the 1-methyl-3-butoxymethyl derivative of phenobarbital (12), and the 3-methoxymethyl derivative of metharbital (10).

We reported previously[2] that 1,3-bis(alkoxymethyl) derivatives of phenobarbital possess marked anticonvulsant activity against both maximal electroshock and pentylenetetrazole induced seizures and yet are devoid of the hypnotic effects associated with the parent compound. It was reported[3,4] that the prototype of the 1,3-bis(alkoxymethyl)phenobarbital series, 1,3-bis(methoxymethyl)phenobarbital (DMMP, **16**) is converted to three major metabolites in the rat, which in order of decreasing quantities are: 1-methoxymethylphenobarbital (**3**), phenobarbital (**1**), and 1-methylphenobarbital (**15**). It was also reported[5] that in man, the major metabolites that accumulate in plasma as a result of DMMP administration in order of decreasing quantities are: phenobarbital, 1-methylphenobarbital, and 1-methoxymethylphenobarbital. In addition, smaller amounts of 1,3-dimethylphenobarbital (**7**) and 1-methyl-3-methoxymethylphenobarbital (**14**) have been identified in human plasma.

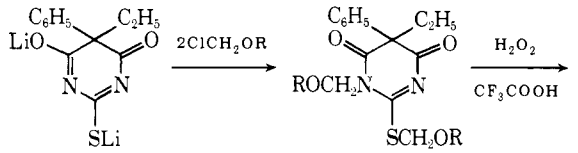
As a result of these discoveries we became interested in finding out whether the 1-alkyl, 1-alkoxymethyl, 1,3-dialkyl, and 1-alkyl-3-alkoxymethyl derivatives of 5,5-diethylbarbituric acid and 5-ethyl-5-phenylbarbituric acid would display anticonvulsant properties.

Chemistry. The synthesis of 1-benzyl-5-ethyl-5-phenylbarbituric acid (**2**) was accomplished from 5-ethyl-5-phenylbarbituric acid (**1**) with benzyl chloride in the presence of sodium hydroxide by a reported procedure.[6] As expected, this procedure yielded a mixture of unsubstituted, monosubstituted, and disubstituted benzyl derivatives of 5-ethyl-5-phenylbarbituric acid, as observed by tlc. Separation of the predominant product, 1-benzyl-5-ethyl-5-phenylbarbituric acid, from the mixture was achieved by column chromatography and crystallization.

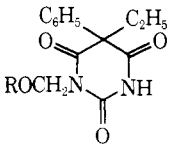
The synthesis of 1-alkoxymethyl derivatives of 5-ethyl-5-phenylbarbituric acid, **3** and **4**, was accomplished by an unequivocal method.[7] The dilithium salt of thiophenobar-

bital was converted into *N,S*-bis(alkoxymethyl)thiophenobarbital (**5** or **6**) by *in situ* treatment of the dilithium salt with 2 mol of chloromethyl alkyl ether. The *N,S*-bis(alkoxymethyl)thiophenobarbitals were converted to *N*-alkoxymethylphenobarbital derivatives by oxidation with peroxytrifluoroacetic acid (Scheme I).

Scheme I



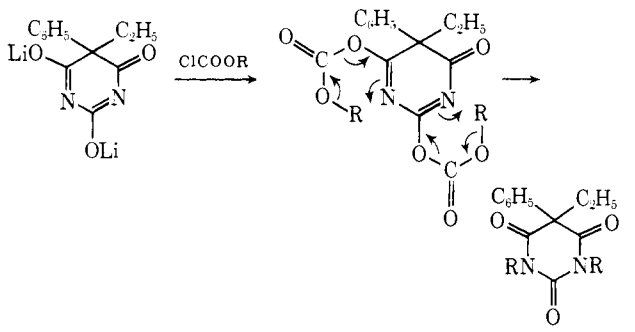
5, R = CH_3
6, R = C_4H_9



3, R = CH_3
4, R = C_4H_9

The synthesis of the 1,3-dialkyl derivatives of 5-ethyl-5-phenylbarbituric acid (**7–9**) was achieved by alkylation[8] with chloroformic esters (Scheme II).

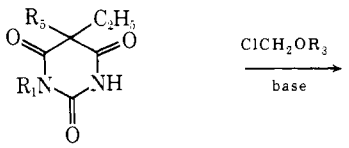
Scheme II



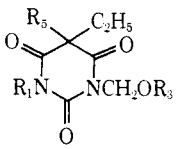
7, R = CH_3
8, R = C_2H_5
9, R = $C_6H_5CH_2$

Mixed alkylalkoxymethyl derivatives were prepared by alkylation of the 1-alkyl derivatives of barbituric acids with chloromethyl alkyl ethers in the presence of base. The respective derivatives of metharbital, **10** and **11**, and phenobarbital, **12–14**, were synthesized by this method (Scheme III).

Scheme III



2, R_1 = $C_6H_5CH_2$; R_5 = C_6H_5
15, R_1 = CH_3; R_5 = C_6H_5
17, R_1 = CH_3; R_5 = C_2H_5



10, R_1 = CH_3; R_3 = CH_3; R_5 = C_2H_5
11, R_1 = CH_3; R_3 = C_4H_9; R_5 = C_2H_5
12, R_1 = CH_3; R_3 = C_4H_9; R_5 = C_6H_5
13, R_1 = $C_6H_5CH_2$; R_3 = CH_3; R_5 = C_6H_5
14, R_1 = CH_3; R_3 = CH_3; R_5 = C_6H_5

Pharmacology. Various 1-alkyl and 1,3-dialkyl derivatives of barbiturates have been reported in the literature.[9] With the exception of mephobarbital and metharbital, both currently available anticonvulsant drugs, and 1,3-dimethylphenobarbital, which in animals is metabolically converted to mephobarbital,† no other alkyl derivatives of barbiturates are reported to possess considerable anticonvulsant properties. On the contrary, many alkyl derivatives of barbiturates are claimed to have convulsive properties.[9]

We found that 1,3-dimethylphenobarbital (**7**) displayed as potent anticonvulsant activities against maximal electroshock- and pentylenetetrazole-induced seizures as did mephobarbital (**15**). At the same time, the hypnotic activity and acute toxicity of **7** were also approximately the same as those of mephobarbital. On the other hand, 1,3-diethylphenobarbital (**8**) was devoid of anticonvulsant activity, while 1,3-dibenzylphenobarbital (**9**) and 1-benzylphenobarbital (**2**) displayed very weak anticonvulsant activity. Compounds **2**, **8**, and **9** had no hypnotic activity except at lethal dosage.

1-Methoxymethylphenobarbital (**3**), one of the metabolic products of 1,3-bis(methoxymethyl)phenobarbital (DMMP, **16**), possessed anticonvulsant activity against maximal electroshock seizures in the potency range of DMMP (**16**). Compound **3** had outstanding potency against pentylenetetrazole-induced seizures suggesting potential therapeutic usefulness in petit mal epilepsy. Compound **3** possessed definite, although weak hypnotic activity compared to that of phenobarbital (**1**). It is of interest that DMMP (**16**) is completely devoid of hypnotic activity. Compound **3** was less toxic than phenobarbital (**1**) with death resulting from respiratory paralysis following progressive CNS depression. 3-*n*-Butoxymethylphenobarbital (**4**) displayed moderate anticonvulsant activity against pentylenetetrazole and weak activity against maximal electroshock-induced seizures (Table I).

We reported previously[1] that 1-methyl-3-methoxymethylphenobarbital (**14**) was more effective against pentylenetetrazole than either mephobarbital or DMMP (**16**), suggesting potential therapeutic usefulness in petit mal epilepsy. Conversely, compound **14** was less active against maximal electroshock seizures than either mephobarbital or DMMP. 1-Methyl-3-butoxymethylphenobarbital (**12**) was as effective against maximal electroshock seizures as, and more effective against pentylenetetrazole-induced seizures than, compound **4**. Compound **13**, 1-benzyl-3-methoxymethylphenobarbital was more effective against maximal electroshock than compound **2** but much less effective than compound **3**. The activity of compound **13** against pentylenetetrazole was about the same as that of compound **2**. Compounds **4**, **12**, and **13** displayed no hypnotic activity except at lethal dosage.

1-Methyl-3-methoxymethyl-5,5-diethylbarbituric acid (**10**) displayed good anticonvulsant activity against both maximal electroshock- and pentylenetetrazole-induced seizures. 1-Methyl-3-butoxymethyl-5,5-diethylbarbituric acid (**11**) was much less effective against both maximal electroshock and pentylenetetrazole than compound **10**. Compounds **10** and **11** were devoid of hypnotic activity. The parent compound, metharbital (**17**), also displayed potent anticonvulsant activity against both maximal electroshock- and pentylenetetrazole-induced seizures; however, it was also hypnotic.

Experimental Section

Pharmacology. All compounds were administered orally in 10% aqueous acacia suspension. Adult male albino mice (18–30 g,

† M. T. Bush, personal communication.

Table I. Pharmacological Activity of Metharbital and Phenobarbital Derivatives

Compd no.	MES ED_{50}, mg/kg	Met ED_{50}, mg/kg	HD_{50}, mg/kg	LD_{50}, mg/kg
1 (phenobarbital)	20.0 (13.8–29.0)	9.8 (6.7–14.2)	100 (72.5–138.0)	270 (216–337.5)
2	~340	~120	>800	>800
3	22.5	3.9 (2.7–5.6)	>100 <250	>250 <500
4	~125	~62.5	~750	~750
7	~21	~15	~190	>250 <500
8	None	None	None	>1000
9	>100 <500	~500	>500	>500
10	>50 <100	~25	>500	>500
11	~125	>100 <250	>1000	>1000
12	~125	32 (22.9–44.8)	>1000	>1000
13	~100	<100 <250	>500	>500
14	~50	16	>500 <1000	>500 <1000
15 (mephobarbital)	16 (11.4–22.4)	24 (16.9–34.1)	180 (148.7–217.8)	~300
16 (DMMP)	13.5 (8–22.7)	47.0 (29.4–75.2)	None	470 (376–588)
17 (metharbital)	30 (18.8–48.0)	18.0 (11.8–27.4)	>200 <400	~820

Charles River) were used throughout this study. Protection against maximal electroshock (MES) and pentylenetetrazole (Met) and toxicity (LD_{50}) were determined according to Swinyard, *et al.*[10]

Peak Time. Time of peak anticonvulsant activity (maximal electroshock seizures) was determined according to Swinyard, *et al.*,[10] except that different groups of five mice were tested at the approximate ED_{50} at intervals of 0.5, 1, 2, and 3 hr (or longer) following drug administration. In our experience different groups were necessary since repeated shocking of animals leads to false positive results. The peak time was taken to be the time at which maximum protection occurred.

HD_{50}. Compounds were administered to groups of ten animals generally at five dosage levels. Hypnotic activity (sleep) was determined by loss of righting reflex without regard to the duration of effect, *i.e.*, the interval between loss and return of the righting reflex. The number of mice sleeping was recorded for each dose, and the dose required to induce sleep in 50% of the animals (HD_{50} with 95% fiducial limits) was determined graphically according to Litchfield and Wilcoxon.[11] LD_{50}'s were also determined graphically, death being the end point. In this study a compound was considered to have hypnotic activity only if the LD_{50} and HD_{50} values differed significantly.

Analyses. Microanalyses were within ±0.3% of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were obtained on a Fisher-Johns hot stage and are corrected. Ir spectra were recorded on a Perkin-Elmer 337 grating ir spectrophotometer. Nmr spectra were run on a Varian A-60A spectrometer in $(CD_3)_2SO$ with Me_4Si as internal reference. Mass spectra were determined on a Hitachi RMU-6D double-focusing spectrometer at 70 eV. Merck HF-254 and 366 silica gel, according to Stahl, was used for tlc development with PhH-EtOAc mixtures. Ir, nmr, uv, mass spectra, and tlc were all appropriate.

1-Benzyl-5-ethyl-5-phenylbarbituric Acid (2). To a solution of sodium 5-ethyl-5-phenylbarbiturate (50.8 g, 0.2 mol) in H_2O (200 ml) was added benzyl chloride (25.2 g, 0.2 mol) and the mixture was stirred 3 hr at reflux and then 16 hr at 25°. The oily product was separated and chromatographed over silica gel. Elution with C_6H_6–hexane gave **2**. Crystallization from EtOH afforded pure **2** (18.7 g, 29%), mp 113°.[6]

***N,S*-Bis(methoxymethyl)-5-ethyl-5-phenyl-2-thiobarbituric Acid (5).** To a solution of 5-ethyl-5-phenyl-2-thiobarbituric acid (24.8 g, 0.1 mol) in DMF (100 ml) was added lithium hydride (2.0 g, 0.25 mol). To the resulting suspension $ClCH_2OCH_3$ (20.8 g, 0.26 mol) was added over a period of 30 min. The temperature of the mixture was kept below 50° at all times. After 90 min the mixture was poured into ice-H_2O (500 g). The product was extracted into EtOAc and the solvent evaporated to provide **5** (32.6 g, 97%). An analytical sample of **5** was obtained by chromatography over silica gel. Elution with C_6H_6–EtOAc (95:5) gave pure **5**, an oil. *Anal.* ($C_{16}H_{20}N_2O_4S$) C, H, N, S.

1-Methoxymethyl-5-ethyl-5-phenylbarbituric Acid (3). To a cooled solution of **5** (3.36 g, 0.01 mol) in trifluoroacetic acid (50 ml) was added 37% aqueous H_2O_2 (15 ml) dropwise with caution. The solution was kept at 45–50° for 20 hr and then poured into ice-H_2O (200 g). The product was extracted into EtOAc and the solvent evaporated to provide crude **3** (2.68 g, 97%). Chromatography over silica gel was used for purification. First, elution with C_6H_6–EtOAc (999:1) yielded 1,3-bis(methoxymethyl)-5-ethyl-5-phenylbarbituric acid (**16**, 0.14 g, 4.3%). Elution with C_6H_6–EtOAc (9:1) gave pure **3** (2.5 g, 90%). *Anal.* ($C_{14}H_{16}N_2O_4$) C, H, N.

***N,S*-Bis(*n*-butoxymethyl)-5-ethyl-5-phenyl-2-thiobarbituric Acid (6).** Compound **6** was prepared from 5-ethyl-5-phenyl-2-thiobarbituric acid (24.8 g, 0.1 mol) and $ClCH_2OC_4H_9$ (32 g, 0.26 mol) in the same way as described for the preparation of compound **5**. Obtained was compound **6** (40.3 g, 96%), an oil. *Anal.* ($C_{22}H_{32}N_2O_4S$) C, H, N, S.

1-*n*-Butoxymethyl-5-ethyl-5-phenylbarbituric Acid (4). Compound **4** was prepared from **6** (4.2 g, 0.01 mol) in the same way as described for the preparation of compound **3**. Obtained was compound **4** (2.86 g, 90%). *Anal.* ($C_{17}H_{22}N_2O_4$) C, H, N.

1,3-Dimethyl-5-ethyl-5-phenylbarbituric Acid (7). To a solution of 5-ethyl-5-phenylbarbituric acid (23.2 g, 0.1 mol) in DMF (100 ml) was added LiH (1.75 g, 0.22 mol). The mixture was heated to 65° and $ClCOOCH_3$ (20 g, 0.21 mol) was added over a period of 30 min. Vigorous CO_2 evolution was observed. After 90 min the mixture was poured into ice-H_2O; the product was filtered and crystallized from aqueous EtOH (100 ml, 66%) to give **7** (22 g, 85%), mp 88–89°. *Anal.* ($C_{14}H_{16}N_2O_3$) C, H, N.

1,3-Diethyl-5-ethyl-5-phenylbarbituric Acid (8). Compound **8** was prepared from 5-ethyl-5-phenylbarbituric acid (23.2 g, 0.1 mol) and $ClCOOC_2H_5$ (22 g, 0.2 mol) in the same way as described for the preparation of compound **7**. Obtained was **8** (23 g, 80.0%), mp 128°. *Anal.* ($C_{16}H_{20}N_2O_3$) C, H, N.

1,3-Dibenzyl-5-ethyl-5-phenylbarbituric Acid (9). Compound **9** was prepared from 5-ethyl-5-phenylbarbituric acid (23.2 g, 0.1 mol) and $ClCOOCH_2C_6H_5$ (38 g, 2.2 mol) in the same way as described for the preparation of **7**. Obtained was **9** (39 g, 94%), mp 86–87°. *Anal.* ($C_{26}H_{24}N_2O_3$) C, H, N.

1-Methyl-3-methoxymethyl-5,5-diethylbarbituric Acid (10). To a solution of 5,5-diethylbarbituric acid (19.8 g, 0.1 mol) in DMF (250 ml) was added LiH (0.8 g, 0.1 mol). Then $ClCH_2OCH_3$ (8.9 g, 0.11 mol) was added at 25° over a period of 30 min. After 90 min the mixture was poured into ice-H_2O (750 g). The product was extracted into EtOAc; the solvent was evaporated to provide an oily product, which was chromatographed over silica gel. Elution with C_6H_6 gave **10** (12.1 g, 50%), mp 28–29°. *Anal.* ($C_{11}H_{18}N_2O_4$) C, H, N.

1-Methyl-3-*n*-butoxymethyl-5,5-diethylbarbituric Acid (11). Compound **11** was obtained from 5,5-diethylbarbituric acid (19.8 g, 0.1 mol) and $ClCH_2OC_4H_9$ (12.3 g, 0.1 mol) in the same way as

described for the preparation of **10**. Obtained was **11** (16.8 g, 60%), bp 130° (1 mm). *Anal.* $C_{14}H_{24}N_2O_4$) C, H, N.

1-**Methyl-3-*n*-butoxymethyl-5-ethyl-5-phenylbarbituric Acid** (**12**). LiH (0.8 g, 0.1 mol) was added to an ice-cold, stirred solution of 1-methyl-5-ethyl-5-phenylbarbituric acid (24.2 g, 0.1 mol) in DMF (250 ml). After 90 min $ClCH_2OC_4H_9$ (12.3 g, 0.1 mol) was added dropwise over a period of 30 min. The solution was stirred for 2 hr and then poured into ice-H_2O (600 g). The solid precipitate was filtered, washed with H_2O, and crystallized from aqueous EtOH to give **12** (27.3 g, 82%), mp 55.5-56.5°. *Anal.* ($C_{18}H_{24}N_2O_4$) C, H, N.

1-**Benzyl-3-methoxymethyl-5-ethyl-5-phenylbarbituric Acid** (**13**). LiH (0.176 g, 0.022 mol) was added to a solution of **2** (6.44 g, 0.02 mol) in DMF (25 ml). After 30 min $ClCH_2OCH_3$ (1.77 g, 0.022 mol) was added dropwise. The solution was stirred for 2 hr and then poured into ice-H_2O (100 g). The solid precipitate was filtered, washed with H_2O, and crystallized from Et_2O to provide **13** (4.9 g, 67%), mp 78-79°. *Anal.* ($C_{21}H_{22}N_2O_4$) C, H, N.

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Platelet Aggregation Inhibitors. 6.[1] 2-Thioadenosine Derivatives

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2-Thioadenosine (VI) was prepared in an overall yield of 7.6% from guanosine *via* 2′,3′,5′-tri-*O*-acetyl-6-chloroguanosine (I), 2,6-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (II), and 2-chloroadenosine (III). Oxidations of VI with iodine and hydrogen peroxide gave disulfide VII and sulfonate VIII, respectively. VI was readily oxidized to disulfide VII or unidentified substance(s) in alkali media without special oxidants. Various S-substituted 2-thioadenosines (X, 1-20) were prepared in 20-80% yields by reaction of VI with the requisite halide in the presence of alkali. Whereas VI, VII, and IX were inactive as inhibitors of platelet aggregation, most of the compounds X were strong inhibitors of platelet aggregation. Thus, 2-ethyl- (**2**), 2-*n*-amyl- (**3**), 2-isoamyl- (**4**), 2-*n*-hexyl- (**5**), 2-*n*-heptyl- (**6**), 2-*n*-octyl- (**7**), 2-*n*-nonyl- (**8**), 2-*n*-decyl- (**9**), 2-(2-ethyl-*n*-hexyl)- (**10**), 2-cyclopentyl- (**11**), 2-cyclohexyl- (**12**), 2-cyclohexylmethyl- (**13**), 2-benzyl- (**14**), 2-(*p*-chlorobenzyl)- (**15**), 2-(*p*-nitrobenzyl)- (**16**), 2-allyl- (**17**), 2-(*trans*-crotyl)- (**18**), and 2-(β-methallyl)thioadenosine (**19**) inhibited 50–100% of ADP- and collagen-induced rabbit platelet aggregation at 10^{-4} *M*. The inhibitory activity of 11 and 12 was the most powerful showing 50-90% inhibition at 10^{-5} *M* and comparable to that of III. Some of the compounds (**14** and **17**) were also active when tested against ADP-induced human platelet aggregation. These active compounds were characterized by long-lasting activity as they were not degraded by adenosine deaminase bound to platelets with incubation at 37° for 120 min.

Predominance of platelets in the white clot of blood in arteries has attracted attention of their primary importance in arterial occlusion or thrombosis.[2] Standard anticoagulant therapy is of little effect against arterial thrombosis and it is suggested that the inhibitors of platelet aggregation might be useful agents that prevent arterial thrombosis.[3] Several compounds that inhibit adenosine 5′-diphosphate (ADP)- and/or collagen-induced platelet aggregation have been investigated,[4,5] but few of them have been evaluated as antithrombotic agents because of their undesirable side effects or toxicity.

Adenosine, a structural analog of ADP, is a powerful inhibitor of platelet aggregation,[6] but it has intense effects on the cardiovascular system and is readily inactivated by contact with erythrocytes[7] or platelets.[8,9] Among the derivatives of adenosine, 2-chloroadenosine[10] has more potent and long-lasting inhibitory action, but with rather serious undesirable side effects.[11] Our previous studies have shown that certain N^6-substituted adenosines are also active inhibitors with long-lasting activity.[12-14] 2-Methylthioadenosine[15] and its 5′-monophosphate ester[16] are known as less active inhibitors; nevertheless, the ester has been recently evaluated by Michael, *et al.*,[16] to be an antithrombotic agent owing to its nontoxicity. This time, in order to obtain further information on the structure–activity relationships in the series of 2-methylthioadenosine derivatives, some additional 2-thioadenosine derivatives were prepared and examined for the inhibitory effect of platelet aggregation. This study revealed that activity is distributed broadly throughout the series.

Synthesis. 2-Alkylthioadenosines and their derivatives have been synthesized by (1) condensation of 2-alkylthioadenines with appropriate ribose derivatives,[17-20] (2) amination of the condensation products of 2-alkylthio-6-chloropurines[19] or 2,6-dimethylthiopurine[21] with ribose derivatives, or (3) reaction of alkylmercaptans with 2-chloroadenosine.[19,22] Several 2-alkylthioadenosines such as 2-methyl-,[17-19,22] 2-ethyl-,[19] 2-*n*- (and -iso-) propyl-,[19] and 2-*n*- (and -iso-) butylthioadenosines[19] have so far been synthesized according to either of the above procedures. However, the procedures are not readily accessible routes for the synthesis of a variety of 2-thioadenosine derivatives. In procedures 1 and 2, a purine having a given thio substituent at the 2 position has to be prepared in every case prior to condensation, and in procedure 3 the synthesis is restricted by availability of the required mercaptan. This time attempts were made to prepare a variety of S-substituted 2-thioadenosines X by reaction of 2-thioadenosine (VI) obtained from 2-chloroadenosine (III) with readily available halides (Scheme I).