

excluded, with an excess of the respective pyridine component. The precipitate which formed when the mixture cooled was quickly sucked off and dried under vacuum (≤ 1 mmHg) at 60 °C. After several hours of drying, recrystallization from a small volume of ethanol yielded a colorless hygroscopic product. The reaction of **1** (Table I) with NaI in absolute ethanol yielded compound **1a**.

General Procedure for the Preparation of the N-(β -Acetoxyethyl)pyridinium Salts 4–6. **1a**, **2**, or **3** (0.1 mol) was dissolved or suspended in acetonitrile. Acetyl chloride (0.15 mol), also dissolved in a small amount of acetonitrile, was dropped into this mixture, which was being refluxed. This mixture was stirred, and all moisture was excluded. After a maximum of 4 h of heating, the solvent and the excess of acetyl chloride were evaporated under reduced pressure. The residue was solid or oleaginous. It was ground with dry ether or acetone. After washing, it was crystallized from ethanol, 2-propanol, or acetone, if necessary, with the addition of ethyl ester.

Pharmacology. Longitudinal muscle strips of the guinea pig ileum were isolated according to Paton and Rang.²⁴ They were derived from animals of 350–600 g and suspended in an organ bath at 37 °C, containing 10 mL of Tyrode's solution of the following composition (mM): NaCl, 137; KCl, 3.7; CaCl₂, 1.8; MgCl₂, 1.05; NaH₂PO₄, 0.2; NaHCO₃, 11.9; glucose, 5.5; hexamethonium chloride, 0.01. The bath was gassed with 5% CO₂ in O₂, the pH was 7.4 \pm 0.5. Isotonic contractions were recorded on a kymograph with a magnification of 1:8. The load of the lever was 150 mg.

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Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. 6. Syntheses of 3-(Sulfamoylmethyl)-1,2-benzisoxazole Derivatives and Their Anticonvulsant Activities

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Several 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives were synthesized from 3-(bromomethyl)-1,2-benzisoxazole by the reaction with sodium bisulfite followed by chlorination and amination. Some of them displayed marked anticonvulsant activity in mice. The introduction of a halogen atom to the 5 position of the benzisoxazole ring caused increased activity and neurotoxicity; the substitution of a sulfamoyl group caused decreased activity. The activity of monoalkylated compounds might be the result of biotransformation. Among these compounds, 3-(sulfamoylmethyl)-1,2-benzisoxazole (**1a**) was thought to be the most promising as an anticonvulsant from the ratio of NTD₅₀ and ED₅₀.

During the course of routine testing, it was noted that 3-(sulfamoylmethyl)-1,2-benzisoxazole¹ (**1a**, Scheme I) exerted a potent anticonvulsant effect as measured by protection against maximal electroshock (MES) seizure.

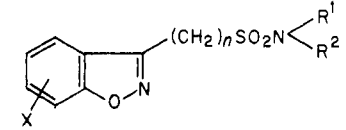
The present paper deals with the syntheses of several 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives and the results of their biological evaluation.

It is well known that some arylsulfonamides show anticonvulsant activity which is supposed to be due to the inhibition of carbonic anhydrase. However, **1a** showed

only a weak effect on carbonic anhydrase in vitro.² Therefore, derivatives of **1a** might be of interest as novel anticonvulsants.

Chemistry. In the early work,¹ **1a** was prepared by the chlorosulfonation and the successive amination of 1,2-benzisoxazol-3-acetic acid (**11**). In these reactions, 5-sulfamoyl-3-(sulfamoylmethyl)-1,2-benzisoxazole was also obtained as a side product, and the yield of **1a** was very poor (7%). Therefore, another method was chosen to prepare derivatives of **1a**.

Table I



compd	X	n	N $\begin{smallmatrix} R^1 \\ R^2 \end{smallmatrix}$	mp, °C	recrystn solvent	yield, %	formula ^a
1a	H	1	NH ₂	160-163	AcOEt	65	C ₈ H ₈ N ₂ O ₃ S
b	H	1	NHCH ₃	113-115	benzene	65	C ₉ H ₁₀ N ₂ O ₃ S
c	H	1	NHC ₂ H ₅	76-78	benzene-hexane	66	C ₁₀ H ₁₂ N ₂ O ₃ S
d	H	1	NH- <i>i</i> -C ₃ H ₇	114-117	benzene	46	C ₁₁ H ₁₄ N ₂ O ₃ S
e	H	1	N(CH ₃) ₂	105-107	MeOH	72	C ₁₀ H ₁₂ N ₂ O ₃ S
f	H	1	NH- <i>n</i> -C ₃ H ₇	86-88	MeOH	31	C ₁₁ H ₁₄ N ₂ O ₃ S
g	H	1	NHOH	140-143	ether	97	C ₈ H ₈ N ₂ O ₄ S
h	H	1	NHNH ₂	149-150 dec	AcOEt	47	C ₈ H ₈ N ₃ O ₃ S
i	H	1	NHN(CH ₃) ₂	113-114 dec	benzene	29	C ₁₀ H ₁₃ N ₃ O ₃ S
j	H	1	NHCH ₂ CH ₂ OH	138-141	AcOEt	24	C ₁₀ H ₁₃ N ₂ O ₄ S
k	H	1	NHCH ₂ C ₆ H ₅	135-137	benzene	48	C ₁₅ H ₁₄ N ₂ O ₃ S
l	H	1	NHC ₂ H ₅	139-141	benzene	46	C ₁₄ H ₁₄ N ₂ O ₃ S
m	H	1	NH-C ₆ H ₄ -2-COOCH ₃	122-123	benzene-ether	10	C ₁₆ H ₁₄ N ₂ O ₅ S
n	H	1	NH(CH ₃) ₂ N(CH ₃) ₂	113-115	benzene	22	C ₁₃ H ₁₉ N ₂ O ₃ S
o	H	1	c-NC ₅ H ₁₀	134-137	benzene	85	C ₁₃ H ₁₆ N ₂ O ₃ S
p	H	1	c-N(CH ₂ CH ₂) ₂ O	114-119	MeOH	70	C ₁₂ H ₁₄ N ₂ O ₄ S
q	H	1	c-N(CH ₂ CH ₂) ₂ N-CH ₃	119-121	benzene-hexane	27	C ₁₃ H ₁₇ N ₃ O ₃ S
r	H	1	c-N(CH ₂ CH ₂) ₂ N-C ₆ H ₅	140-142	MeOH	93	C ₁₈ H ₁₉ N ₂ O ₃ S
s	H	1	c-N(CH ₂ CH ₂) ₂ N-CH ₂ C ₆ H ₅	125-127	benzene-hexane	71	C ₁₉ H ₂₁ N ₃ O ₃ S
2a	5-F	1	NH ₂	182-185	AcOEt	71	C ₈ H ₇ FN ₂ O ₃ S
b	5-F	1	NHCH ₃	141-144	benzene	67	C ₉ H ₉ FN ₂ O ₃ S
c	5-F	1	NHC ₂ H ₅	114-117	benzene	48	C ₁₀ H ₁₁ FN ₂ O ₃ S
d	5-F	1	NH- <i>i</i> -C ₃ H ₇	127-130	benzene	42	C ₁₁ H ₁₃ FN ₂ O ₃ S
e	5-F	1	N(CH ₃) ₂	145-148	benzene	33	C ₁₀ H ₁₁ FN ₂ O ₃ S
f	5-F	1	c-N(CH ₂ CH ₂) ₂ NCH ₃	151-153	benzene	34	C ₁₃ H ₁₆ FN ₃ O ₃ S
3a	5-Cl	1	NH ₂	192-195	AcOEt	26	C ₈ H ₇ ClN ₂ O ₃ S
b	5-Cl	1	NHCH ₃	148-151	benzene	34	C ₉ H ₉ ClN ₂ O ₃ S
c	5-Cl	1	NHC ₂ H ₅	150-152	benzene	37	C ₁₀ H ₁₁ ClN ₂ O ₃ S
d	5-Cl	1	NH- <i>i</i> -C ₃ H ₇	114-116	benzene	20	C ₁₁ H ₁₃ ClN ₂ O ₃ S
e	5-Cl	1	N(CH ₃) ₂	176-179	benzene	37	C ₁₀ H ₁₁ ClN ₂ O ₃ S
4a	5-Br	1	NH ₂	221-225	AcOEt	56	C ₈ H ₇ BrN ₂ O ₃ S
b	5-Br	1	NHCH ₃	152-154	benzene	48	C ₉ H ₉ BrN ₂ O ₃ S
c	5-Br	1	NHC ₂ H ₅	144-147	benzene	73	C ₁₀ H ₁₁ BrN ₂ O ₃ S
d	5-Br	1	NH- <i>i</i> -C ₃ H ₇	95-97	benzene	52	C ₁₁ H ₁₃ BrN ₂ O ₃ S
e	5-Br	1	N(CH ₃) ₂	183-185	benzene	32	C ₁₀ H ₁₁ BrN ₂ O ₃ S
f	5-Br	1	c-N(CH ₂ CH ₂) ₂ NCH ₃	118-121	benzene-hexane	47	C ₁₃ H ₁₆ BrN ₃ O ₃ S
5	5-CH ₃	1	NH ₂	167-170	EtOH	70	C ₉ H ₁₀ N ₂ O ₃ S
6	5-NO ₂	1	NH ₂	226-229	EtOH	75	C ₈ H ₇ N ₃ O ₅ S
7	5-OCH ₃	1	NH ₂	178-181	AcOEt	25	C ₉ H ₁₀ N ₂ O ₄ S
8	6-F	1	NH ₂	187-190	AcOEt	52	C ₈ H ₇ FN ₂ O ₃ S
9	7-CH ₃	1	NH ₂	147-150	AcOEt	48	C ₉ H ₁₀ N ₂ O ₃ S
16	H	2	NH ₂	159-162	AcOEt	16	C ₉ H ₁₀ N ₂ O ₃ S
17	H	3	NH ₂	136-138	AcOEt	49	C ₁₀ H ₁₂ N ₂ O ₃ S

^a All compounds were analyzed for C, H, N, S, and halogen; analytical results were within $\pm 0.4\%$ of the theoretical values.

3-(Bromomethyl)-1,2-benzisoxazole³ (12), which was prepared from 11 by bromination and successive decarboxylation, was reacted with sodium bisulfite and gave 1,2-benzisoxazole-3-methanesulfonic acid (13) (see Scheme I). The chlorination of 13 with phosphorus oxychloride afforded sulfonyl chloride 14, which was converted to several derivatives of 1a (1-9) by reactions with appropriate amines. 3-(Sulfamoyl-ethyl)- (16) and 3-(sulfamoyl-propyl)-1,2-benzisoxazole (17) (see Scheme I) were also prepared from 3-(chloroethyl)-³ and 3-(chloro-propyl)-1,2-benzisoxazole,³ respectively.

The reduction of 6 with stannous chloride gave 5-amino-3-(sulfamoylmethyl)-1,2-benzisoxazole (18), which was easily acetylated with acetic anhydride to afford the 5-(acetamino) derivative 19. The reaction of 1a with ethyl chloroformate and potassium carbonate gave *N*-(ethoxycarbonyl)-3-(sulfamoylmethyl)-1,2-benzisoxazole (20). Sulfonylurea derivative 21 was obtained from the ammonium salt of 20 by heating. The *N*-acetyl derivative of 1a (22) was obtained by the acetylation of 1a with acetyl chloride.

Biology and Discussion. Protection against MES was determined according to Swinyard,⁴ and neurotoxicity was determined by the rotarod test⁵ using mice.

Compounds 1f, h-p, r, s, 5-7, and 9 (see Table I) were ineffective at 100 mg/kg po. Median effective doses (ED₅₀) and median neurotoxic doses (NTD₅₀) were determined for the compounds which showed some activity at 100 mg/kg. ED₅₀ values and NTD₅₀ values summarized in Table II indicated marked activity against MES following administration of 1a-e, g, q, 2a-f, 3a-e, 4a-f, and 8 (see Table I).

The introduction of a halogen atom to the 5 or the 6 position of the benzisoxazole ring increased the potency. The order of increasing potency of those compounds was as follows: H < F < Cl < Br. The order of increasing neurotoxicity followed the order of increasing potency, and the increasing rate of neurotoxicity was larger than that of potency. As far as 5-halogeno derivatives were concerned, the order of increasing potency followed the order of increasing σ_m values⁶ (H, 0.00; F, 0.34; Cl, 0.37; Br, 0.39). However, the introduction of a sulfamoyl ($\sigma_m = 0.46$) or

Scheme I

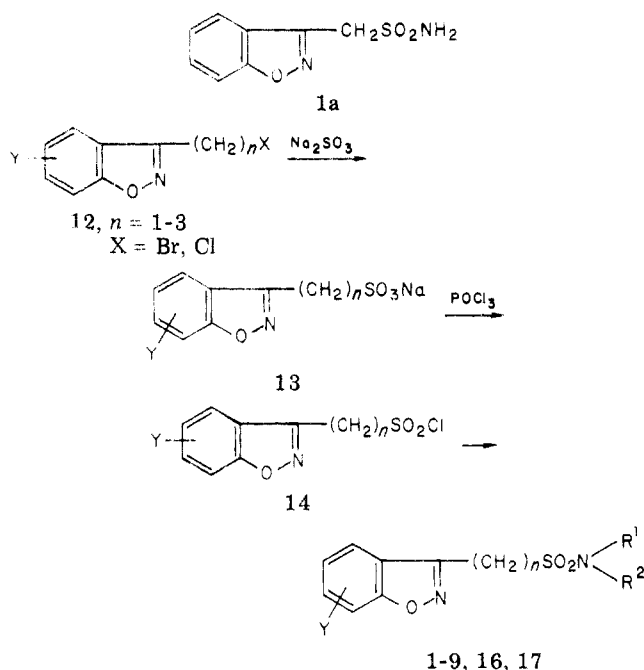


Table II. Anticonvulsant Activity and Neurotoxicity

compd	anti-MES; ED ₅₀ , mg/kg, po	neurotox; NTD ₅₀ , mg/kg, po
1a	20 (16-24) ^a	292 (252-330)
b	23 (14-37)	
c	39 (29-52)	223 (140-356)
d	56 (44-69)	340 ^b
e	37 (28-49)	
g	32 (19-54)	
q	57 (46-66)	
2a	15 (10-20)	154 (134-175)
b	35 (25-45)	168 (141-202)
c	32 (23-41)	200 ^b
d	38 (32-46)	109 (69-174)
e	32 (27-38)	350 ^b
f	100 ^b	142 (64-317)
3a	14 (10-21)	52 (38-70)
b	20 (16-25)	60 (44-83)
c	21 (17-27)	
d	100 ^b	
e	57 (41-69)	250 ^b
4a	14 (10-18)	60 (42-77)
b	15 (10-22)	
c	18 (14-23)	66 (55-79)
d	22 (16-32)	93 (59-146)
e	45 (33-58)	100-200
f	88 (72-108)	87 (60-127)
8	19 (8-46)	
16	26 (17-40)	
17	39 (23-67)	
diphenylhydantoin	10.0 (7.6-12.3)	111.0 (87.2-150)
metharbital	60.8 (79.2-97.6)	87.9 (79.2-97.6)

^a 95% confidence limits. ^b Graphically calculated.

a nitro group ($\sigma_m = 0.71$) to the 5 position contributed to the loss of potency and no acceptable QSAR analysis could be obtained among these compounds.

The study of *N*-substituted compounds revealed that the introduction of simple monoalkyl substituents did not abolish activity, but when the substituent was an amino (1h), a dimethylamino (1i), a benzyl (1k) or larger the activity was generally lost. With the exception of dimethylamino (1e, 2e, 3e, and 4e) and *N*-(methylpiperazinyl) derivatives (1q and 4f), the disubstituted compounds were inactive in the anticonvulsant test. The order of the decreasing potency for alkylated derivatives in each series of compounds 1-4 was as follows: $-\text{SO}_2\text{NH}_2 >$

$-\text{SO}_2\text{NHCH}_3 > -\text{SO}_2\text{NHEt} = -\text{SO}_2(\text{CH}_3)_2 > -\text{SO}_2\text{-i-Pr}$. This order is in general agreement with the relative extent of in vivo dealkylation of monoalkylated sulfonamide derivatives reported by Smith et al.⁷ Therefore, the potency of these compounds might be the result of biotransformation.

Smith et al.⁷ also reported that the parent sulfonamide was formed by in vivo reduction of *N*-hydroxybenzene-sulfonamide. The potency of the *N*-hydroxy derivative of 1a (1g) might be the result of in vivo reduction. Sulfamoyl ethyl derivative 16 and *N*-methyl derivative 1c exhibited approximately equivalent ED₅₀ values, and the ED₅₀ value of sulfamoylpropyl derivative 17 was comparable to those of the *N*-ethyl derivative 1c and *N*-dimethyl derivative 1e.

Among these compounds, 1a was thought to be the most promising compound as an anticonvulsant from the ratio of NTD₅₀ and ED₅₀. The further investigation of 1a is now in progress in our laboratories.

Experimental Section

Melting points were determined in a Yanagimoto apparatus and are uncorrected. The IR, NMR, and mass spectral data of all compounds were consistent with structure. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within $\pm 0.4\%$ of the theoretical values.

3-(Sulfamoylalkyl)-1,2-benzisoxazoles 1a, 2a, 3a, 4a, and 5-9 (Table I). General Procedure. To a solution of 12 (0.038 mol) in MeOH (130 mL) was added Na₂SO₃ (8.1 g, 0.064 mol) in H₂O (130 mL). The mixture was stirred at 50 °C for 4 h and evaporated in vacuo. To the residue was added MeOH (250 mL), and the insoluble material in MeOH was removed. The solution was concentrated, and the residue was washed with ether and dried. To the dried residue was added POCl₃ (100 mL), the mixture was refluxed for 3 h, and then the excess of POCl₃ was removed in vacuo. Thus, crude 14 was obtained. Crude 14 was dissolved in AcOEt (200 mL). Under cooling, NH₃ was saturated in the solution. The solid separated and was filtered off, and the solvent was removed. The residue was washed with AcOEt and recrystallized from the appropriate solvent.

***N*-Substituted 3-(Sulfamoylmethyl)-1,2-benzisoxazoles 1b-s, 2b-f, 3b-e, and 4b-f (Table I). General Procedure.** To the AcOEt solution of 14, above mentioned, was added the appropriate amine (0.114 mol, 3 molar equiv), and the mixture was stirred at room temperature for 30 min. The solid separated and was filtered off, and the filtrate was evaporated in vacuo. The resulting residue was recrystallized from the appropriate solvent.

5-Amino-3-(sulfamoylmethyl)-1,2-benzisoxazole (18). To the suspension of 6 (11 g) in concentrated HCl was added a solution of SnCl₂ (60 g in 60 mL of concentrated HCl), and the mixture was stirred at 25-30 °C for 3 h. The solution was made alkaline with NaHCO₃ and extracted with AcOEt. After being dried over Na₂SO₄, the solvent was removed in vacuo. The recrystallization of the residue from MeOH gave 6 g of 18 (62%), mp 224-227 °C. Anal. (C₈H₉N₃O₃S) C, H, N, S.

5-(Acetylamino)-3-(sulfamoylmethyl)-1,2-benzisoxazole (19). To the solution of 18 (2.5 g) in pyridine (20 mL) was added Ac₂O (3.4 g). After being kept overnight at room temperature, the mixture was poured into H₂O and extracted with AcOEt. The extract was washed with H₂O and evaporated. The residue was recrystallized from MeOH to give 0.7 g of 19 (24%), mp 261-266 °C. Anal. (C₁₀H₁₁N₃O₄S) C, H, N, S.

***N*-(Ethoxycarbonyl)-3-(sulfamoylmethyl)-1,2-benzisoxazole (20).** To a solution of 1a (4.0 g in 80 mL of acetone) were added ethyl chloroformate (6.1 g) and K₂CO₃ (7.8 g). The mixture was refluxed for 24 h and then filtered. The filtrate was evaporated, and the residual oil was dissolved in H₂O. The solution was acidified with HCl. The resulting precipitate was collected, washed with H₂O, and recrystallized from AcOEt to give 20 (4.0 g, 75%), mp 139-141 °C. Anal. (C₁₁H₁₂N₂O₅S) C, H, N, S.

***N*-Carbamino-3-(sulfamoylmethyl)-1,2-benzisoxazole (21).** A solution of 20 (2.0 g in 150 mL of MeOH) was saturated with

NH₃. After being kept at room temperature overnight, the solution was concentrated in vacuo to give the ammonium salt of **20** (2.0 g) which was heated on an oil bath (150–160 °C) under reduced pressure for 10 min. To the cooled residue was added AcOEt. The insoluble solid was collected and recrystallized from MeOH to give **21** (0.9 g, 53%), mp 189–194 °C. Anal. (C₉H₉N₃O₄S) C, H, N, S.

N-Acetyl-3-(sulfamoylmethyl)-1,2-benzisoxazole (22). To 50 mL of AcCl was added **1a** (2.3 g). The mixture was refluxed for 48 h and then evaporated. The residue was washed with benzene, dried, and recrystallized from acetone to give **22** (2.5 g, 91%), mp 183–185 °C. Anal. (C₁₀H₁₀N₂O₄S) C, H, N, S.

Biological Methods. All experiments were carried out in male mice of STD-dd strain weighing 20–22 g. Diet and water were given ad libitum to animals until the time of experiment. All compounds were administered by gavage as a suspension of 5% tragacanth solution. In preliminary screenings, all compounds were tested for anticonvulsant activity at 100 mg/kg. For the determination of ED₅₀ and NTD₅₀, groups of ten mice were used per dosage level, using at least four dosage levels.

Anticonvulsant Activity. Drugs were evaluated for their ability to prevent the hind-limb extensor component of maximal electroshock seizure induced using a 60-Hz, 25-mA current for 0.2 s, delivered through corneal electrodes 2 h after dosing. ED₅₀ values were calculated by the method of Litchfield and Wilcoxon.⁸

Neurotoxicity. NTD₅₀ was determined employing the rotarod. The end point for minimal neurotoxicity was muscle incoordination and was based upon the inability of the mouse to retain

on a horizontal rod (2.5-cm in diameter) rotating at 11 rpm 2 h after dosing. NTD₅₀ values were calculated by the method of Litchfield and Wilcoxon.⁸

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Azetidine Derivatives of Tricyclic Antidepressant Agents

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Tricyclic derivatives of azetidine were synthesized and screened for their potential antidepressant activity. The active series had the tricyclic rings attached to position 1 and a basic group in position 3 of the azetidine. The most interesting compounds were comparable to the reference standards for reserpine antagonism in mice, the most active being the dextrorotatory methylamino derivative **84**.¹ The pharmacological profile classifies it as a CNS stimulant devoid of peripheral anticholinergic activity.

One of the best represented classes in the field of psychoactive drugs with antidepressant effects is without doubt that of the tricyclic antidepressant agents. There has been a great deal of research on these structures in attempts to separate the documented therapeutic activity from the side effects, which are for the most part associated with their anticholinergic and cardiotoxic activities.^{1–5} The novelty of the products synthesized is based on the association of the azetidine ring with the tricyclic structure. Some derivatives of this series were found in pharmacological screening to have potential antidepressant activity, the most encouraging results coming from products with two aliphatic amine groups, which is uncommon in the field of drugs with antidepressant activity.

Chemistry. The *tert*-butyl derivatives in Table I were obtained by alkylation of suitable substrates with 3-chloro-1-*tert*-butylazetidine, prepared by the method of Gaertner.⁶ The other compounds were prepared according to Scheme I.

The alkylation was found to be difficult for *n* = 1 and A = –CH₂CH₂–. Compound **11** was so obtained by reductive dealkylation of the corresponding unsaturated derivative (A = –CH=CH–), which alkylates more easily. The yields of alkylation were 40–60%. Reductive dealkylation was, as expected, difficult for A = S, so that only the *tert*-butyl derivatives **2–4** and the unsubstituted azetidine **1** were prepared. To carry out the reductive

Scheme I^a

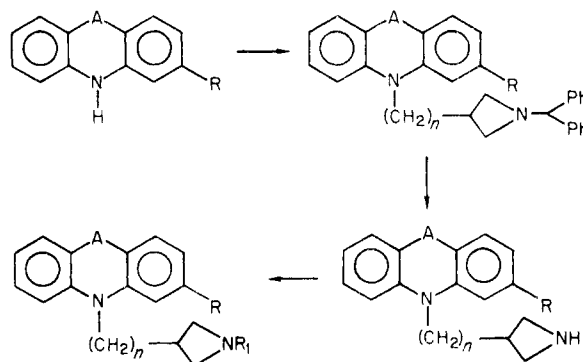


Table I

^a For *n* = 0, the alkylating halide was a bromide; for *n* = 1, a chloride.

amination,⁸ it was necessary to carefully control times and temperatures for the compounds with A = –CH₂O–, in order to avoid cleavage of the benzyl ether.

The azetidines of Table V were synthesized from the corresponding mesylates prepared by the method of Anderson.⁷ Tables II–IV list the intermediates, with their physical properties and yields. The general scheme (Scheme II) of synthesis is shown below. The methods