fraction eluted was concentrated to a colorless oil, **45** (730 mg, 90%). *Anal.* ($C_{15}H_{20}O_4$) C, H. The second fraction eluted was concentrated to give 813 mg (75%) of **43.**

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Substituted Tetrahydrofurfurylamines as Potential Antidepressants

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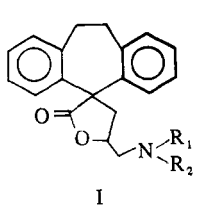
A series of substituted tetrahydrofurfurylamines was prepared from the corresponding γ,δ-unsaturated alcohols by sequential bromocyclization and substitution of the tetrahydrofurfuryl bromides with methyl- or dimethylamines. Some of these compounds were found to possess potent antidepressant activity in animals.

The high antidepressant activity observed in the compounds of general formula I[1] led us to investigate synthetic approaches to and pharmacological properties of compounds of general formula II. Both I and II, when R_2 and R_3 are aryl substiuents, are structurally related to the potent antidepressant amitriptyline III.



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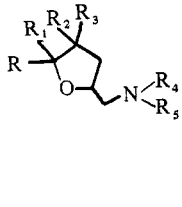

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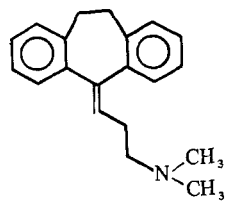


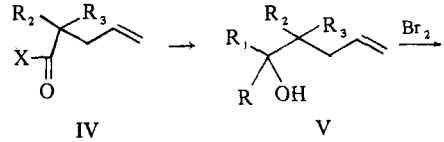
III

A simple general synthesis of substituted tetrahydrofurfuryl bromides from corresponding 1-en-4-ols by electrophilic addition of bromine with neighboring-group participation and, thus, an easy access to tetrahydrofurfurylamines enabled us to prepare and study the pharmacological properties of several compounds of type II.

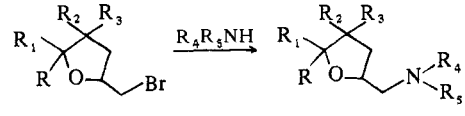
Chemistry. A series of substituted tetrahydrofurfurylamines was prepared by the following synthetic route.

Compounds IV were prepared by allylation of the corresponding esters or ketones. The reduction of IV with $NaBH_4$ or $LiAlH_4$ afforded V. (Compounds of general structure V are listed in Table III.)

Alternatively, compounds V were prepared by the reaction of CH_3Li with IV or by Grignard reaction of benzophenone with 3-buten-1-ylmagnesium bromide. Compounds V were



IV V



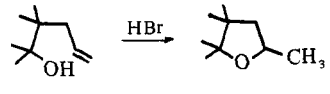
VI II

X = OCH_3, OEt, or R

converted to tetrahydrofurfuryl bromides VI by bromination.

The synthesis of heterocyclic compounds by electrophilic addition on the double bond with neighboring-group participation is well known.[2] However, there has not been wider application of bromocyclization of γ,δ-unsaturated alcohols which in our hands appears to be general and a useful synthetic tool.†

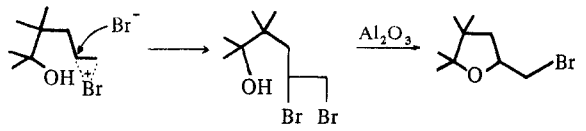
We carried out bromocyclizations in organic solvents (CCl_4, CH_2Cl_2) with 1 equiv of pyridine to neutralize the released HBr and thus prevent parallel acid-catalyzed formation of methyltetrahydrofurans. This side reaction was observed in the course of bromocyclization of alcohol **33** in the absence



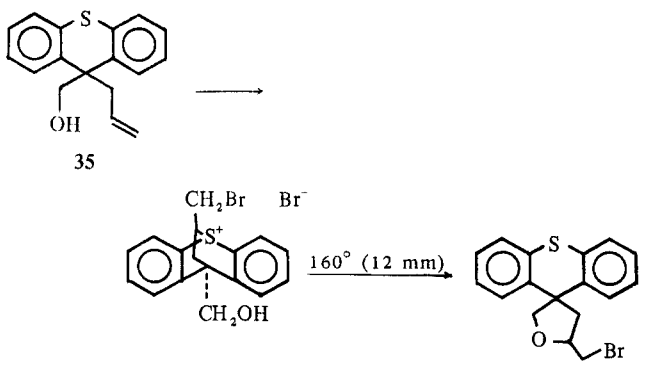
†This facile reaction was first described by Rengevich, *et al.*[3] Additional examples of bromocyclization have been reported by Levisalles and Rudler,[4] Tanaka, *et al.*,[5] and Demole and Enggist.[6]

of pyridine. A similar side reaction was observed by Klinotova and Vystrcil.[7]

The major side reaction appeared to be formation of dibromides, particularly when the substitution pattern of 1-penten-4-ols V was vicinal, rather than geminal. This was overcome by slow migration of the reaction mixture through an alumina column which effectively converted dibromides to the tetrahydrofurfuryl bromides.



A somewhat unexpected result was obtained from bromination of 9-allyl-9-hydroxymethylthioxanthene where participation of sulfur rather than oxygen occurred.



Conversion of the sulfonium salt **37** to the corresponding tetrahydrofurfuryl bromide **38** was accomplished by heating to 160° (12 mm). (Compounds of general formula VI are listed in Table IV.) Finally, reaction of bromo compounds VI with methyl- or dimethylamine afforded the amino compounds II. Compounds of general formula II are listed in Table I.

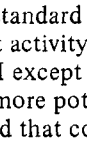
Biological Data. All of the compounds in Table I were tested for general CNS activity in the mouse according to the protocols described by Bergman and Goldschmidt.[8] In view of the fact that compound **11** exhibited good activity in the reserpine ptosis test, it became of interest to compare it with a standard reference agent, desmethylimipramine (DMI), in some additional antidepressant tests, such as prevention of tetrabenazine depression in the rat and prevention of oxotremorine in the mouse.

Results

Comparative data on compound **11** and DMI are summarized in Table II. The findings presented indicate that compound **11** was active in standard laboratory tests designed to detect the antidepressant activity. Potencywise, compound **11** was rather similar to DMI except in the oxotremorine test where DMI was considerably more potent than compound **11**. In addition, it has been found that compound **11** potentiated norepinephrine responses on the blood pressure and the nictitating membrane. In contrast to the potentiation of norepinephrine, compound **11** antagonized tyramine responses in the same tests. A similar activity pattern was observed with DMI in regard to its interaction with norepinephrine and tyramine. In general, it can be concluded that compound **11** and DMI showed a very similar activity profile in the test designed to detect antidepressant activity.

Structure-Activity Relationships. The most active com-

Table I. Tetrahydrofurfurylamines II



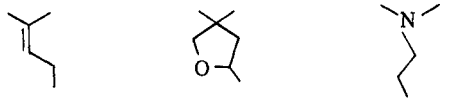
No.	R	R_1	R_2	R_3	X	Solvent	Salt	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Reserpine ptosis prevention[a]
1	C_6H_5	C_6H_5	H	H	NHMe	THF[b]	HCl	272–273	CH_3OH	71	$C_{18}H_{21}NO\cdot HCl\cdot 0.5H_2O$	*c*
2	C_6H_5	C_6H_5	H	H	NMe_2	THF[b]	HCl	230–232	CH_3OH	70	$C_{19}H_{23}NO\cdot HCl\cdot 0.5CH_3OH$	*c*
3	Me	Me	C_6H_5	C_6H_5	NHMe	THF[d]	HCl	217–219	CH_3OH-Et_2O	59	$C_{20}H_{25}NO\cdot HCl$	*c*
4	C_6H_5	H	C_6H_5	H	NHMe	DMSO	HCl	208–215	CH_3OH-Et_2O	72	$C_{18}H_{21}NO\cdot HCl$	20
5	3-C_5H_4N	H	C_6H_5	H	NHMe	DMSO	Free base	133–136 (0.05)		75	$C_{17}H_{20}N_2O$[e]	25
6	Me	H	C_6H_5	C_6H_5	NHMe	DMSO	HBr	180–182	CH_3OH-Et_2O	61	$C_{19}H_{23}NO\cdot HBr$	40
7	Me	H	C_6H_5	C_6H_5	NMe_2	DMSO	HBr	236–238	CH_3OH-Et_2O	88	$C_{20}H_{25}NO\cdot HBr$	75
8	H	2,2′-$C_6H_4CH_2C_6H_4$		H	NHMe	DMSO	$C_2H_2O_4$	166–168	CH_3OH	66	$C_{19}H_{21}NO\cdot C_2H_2O_4$	*c*
9	H	H	C_6H_5	C_6H_5	NHMe	DMSO	HCl	169–170	CH_3OH-Et_2O	62	$C_{18}H_{21}NO\cdot HCl$[f]	5
10	H	H	C_6H_5	C_6H_5	NMe_2	DMSO	HCl	160–162	CH_3OH-Et_2O	65	$C_{19}H_{23}NO\cdot HCl\cdot 0.5H_2O$	10
11	H	H	2,2′-$C_6H_4(CH_2)_2C_6H_4$		NHMe	DMSO	HCl	178–180	CH_2Cl_2-C_6H_5	65	$C_{20}H_{24}NO\cdot HCl$	2.5
12	H	H	2,2′-$C_6H_4(CH_2)_2C_6H_4$		NMe_2	DMSO	$C_2H_2O_4$	115–120	CH_3OH-Et_2O	68	$C_{21}H_{25}NO\cdot C_2H_2O_4\cdot 0.5CH_3OH$	2.5
13	H	H	2,2′-C_6H_4-O-C_6H_4		NHMe	DMSO	HCl	202–204	$EtOH$-Et_2O	50	$C_{18}H_{19}NO_2\cdot HCl$	150
14	H	H	2,2′-C_6H_4-O-C_6H_4		NMe_2	DMSO	HCl	204–206	$EtOH$-Et_2O	65	$C_{19}H_{21}NO_2\cdot HCl$	*c*
15	H	H	2,2′-C_6H_4-S-C_6H_4		NHMe	DMSO	HCl	205–207	CH_3OH-Et_2O	62	$C_{18}H_{19}NOS\cdot HCl$	*c*
16	H	H	2,2′-C_6H_4-S-C_6H_4		NMe_2	THF[g]	HCl	198–200	$EtOH$-Et_2O	76	$C_{19}H_{21}NOS\cdot HCl$	*c*
17	H	H	2,2′-C_6H_4-S(→O)-C_6H_4		NHMe	DMF	HCl	257–280	$EtOH$-Et_2O	72	$C_{18}H_{19}NO_2S\cdot HCl$	*c*
18	H	H	C_6H_5	$CH_2OC(=O)CH_3$	NMe_2	DMSO[h]	Free base	105–116 (0.02)		97	$C_{16}H_{23}NO_3$	*c*

[a] Results represent minimal effective dose (MED) in mg/kg po; DMI active at 2.5 mg. [b] 50 hr at room temperature. [c] Inactive at 300 mg/kg. [d] 60 hr. [e] *Anal.* calcd C, 70.69; found C, 75.40. [f] *Anal.* calcd C, 71.15; found C, 70.54. [g] 24 hr, 55–60°. [h] 24 hr at room temperature.

Table II. Comparative Findings with Compound 11 and DMI in Laboratory Tests

Procedure	Effective dose, mg/kg, and route 11	DMI
Acute LD_{50}, mouse	630 po	730 po
Prevention of reserpine ptosis, mouse	2.5 po	2.5 po
Prevention of tetrabenazine depression, rat	10 ip	5.0 ip
Prevention of oxotremorine hypothermia, mouse	5 ip	0.5 ip

pounds in the series, **11** and **12** (Table I), are structurally related to those of known clinically effective antidepressants such as amitriptyline and DMI. This suggests bioisostericity of the following moieties.



Next on the activity scale were compounds **9** and **10**. However, additional substitution on the tetrahydrofuran ring (**3**, **6**, **7**) or positional isomerism (**1**, **2**, **4**, **5**, **8**) was found to diminish or completely abolish the activity.

Heteroatom in the place of hydrogens or ethylene bridge such as in compounds **14–17** also abolishes activity. In this series only **13** showed slight activity.

Experimental Section

Melting and boiling points are uncorrected; nmr spectra were determined on a Varian A-60A instrument in $CDCl_3$ with TMS as the internal standard. Microanalyses were provided by Micro Tech Laboratories, Skokie, Ill. All compounds reported have been analyzed for C, H, and N where applicable within 0.4%, unless specified otherwise.

Pharmacology Materials and Methods. Prevention of Reserpine Ptosis in the Mouse. Male albino mice (20–25 g, Taconic Farm) in groups of three were pretreated with graded oral (po) doses of test compounds, and 3 hr later they were injected with reserpine (5 mg/kg iv). Prevention of reserpine-induced ptosis for 30 min was used as a criterion of drug action. The lowest dose inducing such an effect in 3/3 mice was defined as the minimal effective dose (MED).

Prevention of Tetrabenazine Depression in the Rat. Male albino rats (175–200 g, Carworth Farm) in groups of three were pretreated with graded doses of test compounds (ip) and 1 hr later doses with tetrabenazine methanesulfonate (35 mg/kg ip). Ptosis reversal, spontaneous locomotor activity or hyperactivity, and characteristic body posture (extended hind legs, "tip-toe" walk) were the criteria signifying antagonism of tetrabenazine action. The control rats, those receiving saline and tetrabenazine, exhibited immobility, skeletal muscle spasticity, "hunch-back" posture, and closed eyes.

Oxotremorine Hypothermia Prevention in the Mouse. Male albino mice in groups of four were pretreated with graded doses (ip) of test compounds, and 1 hr later they were dosed with oxotremorine (0.6 mg/kg ip). The rectal temperature was measured and antagonism of parasympathetic signs (diarrhea, lacrimation, and salivation) was evaluated 30 min later. A minimal difference of 2° in mean temperatures between control and treated groups was considered a significant drug effect.

Carbonyl Compounds IV. 5-Allyl-5-carbomethoxydibenzo[*a,d*][1,4]cycloheptadiene (19). This compound was prepared by alkylation of the anion of 5-carbomethoxydibenzo[*a,d*][1,4]cycloheptadiene with allyl bromide in DMF according to the procedure given in ref 1, bp 140–150° (0.01 mm).

Thioxanthene-9-carboxylic Acid Allyl Ester (20). To a suspension of 730 mg (32 mmol) of NaH in 20 ml of DMF were added with stirring and cooling (10–15°) 7.26 g (30 mmol) of thioxanthene-9-carboxylic acid (prepared according to the method given in ref 9) in 40 ml of DMF and 3.87 g (32 mmol) of allyl bromide. After standing at room temperature for 4 hr, the mixture was poured into water and extracted with C_6H_6. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to yield 7.26 g (73%) of the solid product **20**, mp 106–108°. *Anal.* ($C_{17}H_{14}O_2S$).

Thioxanthene-9-allyl-9-carboxylic Acid (21). A mixture of 0.48 g (20 mmol) of NaH, 5.64 g (20 mmol) of thioxanthene-9-carboxylic acid allyl ester, and 150 ml of anhydrous C_6H_6 was refluxed for 4 hr. The clear orange solution was extracted with water and the aqueous extract acidified with HCl. The free acid was taken up in C_6H_6, dried, and concentrated *in vacuo* to yield 4.8 g (85%) of a solid **21**, mp 164–165° (C_6H_6). *Anal.* ($C_{17}H_{14}O_2S$).

Xanthene-9-allyl-9-carboxylic Acid Methyl Ester (22). This compound was prepared by alkylation of the anion of xanthene-3-carboxylic acid methyl ester with allyl bromide in DMF, mp 59.5–60.5°.‡

2-Phenyl-4-pentenophenone (23). A solution of 19.6 g (50 mmol) of desoxybenzoin and 6 g (50 mmol) of allyl bromide in 50 ml of DMF was added over 30 min to a cooled (10–15°) and stirred suspension of 1.2 g (50 mmol) of NaH in 50 ml of DMF. Stirring was continued for 45 min at room temperature. Work-up in the usual manner afforded an oil which was distilled and the fraction boiling at 82–84° (0.01 mm) was collected. There was obtained 18 g (76%) of **23**. *Anal.* ($C_{17}H_{26}O$).

2-Phenyl-1-(3-pyridyl)-4-penten-1-one (24). In a similar procedure 2-phenyl-1-(3-pyridyl)-4-penten-1-one was obtained in 95% yield by allylation of 3-pyridyl benzyl ketone,[10] bp 105–110° (0.05 mm). *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 79.89; H, 6.24; N, 5.79.

11-Allyl-5,11-dihydro-10*H*-dibenzo[*a,d*]cyclohepten-10-one (25). A mixture of 10.0 g (48 mmol) of dibenzo[*a,d*]cyclohepta[1,4]dien-10-one,[11] 5.5 g (48 mmol) of KO-*tert*-Bu, 5.9 g (48 mmol) of allyl bromide, and 50 ml *tert*-BuOH was refluxed under N_2 for 3 hr. The reaction mixture was concentrated *in vacuo* and the residue treated with C_6H_6 and water. The C_6H_6 layer was washed with water, dried, and concentrated *in vacuo*. The residue was crystallized from EtOH and there was obtained 5.5 g (45%) of white product **25**, mp 99–102°. *Anal.* ($C_{18}H_{16}O$).

Alcohols V. 3,3-Diphenyl-1-methyl-5-hexen-2-ol (26). To a solution of 10 g (40 mmol) of 3,3-diphenyl-5-hexen-2-one[12] in 40 ml of anhydrous Et_2O under N_2 was added 47 ml of 1.7 *M* MeLi in hexane and the mixture refluxed for 40 min. After cooling, the excess of MeLi was decomposed with MeOH; the mixture was washed with water, dried, and concentrated *in vacuo* to yield 11 g of an oil. This was chromatographed on an alumina column (200 g). Elution with C_6H_6–petroleum ether (bp 30–60°) afforded 5.8 g of starting material, followed by 3.8 g (35%) of the product as an oil whose ir and nmr spectra were in accord with the structure **26**. *Anal.* ($C_{19}H_{26}O$). Attempted distillation led to decomposition.

1,1-Diphenyl-4-penten-1-ol (27). 4-Buten-1-ylmagnesium bromide was prepared from 10 g (0.08 mol) of 4-bromo-1-butene in 40 ml of Et_2O and this was added with stirring and cooling during 20 min to a solution of 14.6 g (0.08 mol) of benzophenone in 30 ml of Et_2O. Work-up of the mixture afforded an oil (15.3 g) which was chromatographed on an alumina column (600 g). Elution with CH_2Cl_2 afforded 3.2 g of benzophenone followed by 2.83 g (15.6%) of the product **27**, bp 100–102° (0.02 mm). *Anal.* ($C_{17}H_{18}O$).

Thioxanthene-9-allyl-9-hydroxymethyl *S*-Oxide (28). To a cooled (0–5°) and stirred solution of 2.68 g (10 mmol) of 9-allyl-9-hydroxymethylthioxanthene (**35**) (see Table III) in 25 ml of Et_2O was added in small portions 2.19 g (10 mmol) of 78% *m*-chloroperbenzoic acid. After standing for 4 hr at room temperature, the precipitated solid was filtered off to yield 2.1 g, mp 175–177°. From the mother liquors after treatment with Na_2CO_3 was obtained a further 0.3 g for a combined yield of 86% of **28**, mp 177–179° (C_6H_6). *Anal.* ($C_{17}H_{16}O_2S$).

General Methods. A. Reduction of Ketones IV with $NaBH_4$. To a solution of 50 mmol of ketone in 100 ml of EtOH (99%) was added 1 g of $NaBH_4$ and the mixture refluxed for 1 hr. It was then treated with water and with diluted HCl and the product extracted with Et_2O. Drying and concentration afforded the product V (Table III).

B. Reductions of Ketones, Acids, and Esters IV with $LiAlH_4$. To a stirred suspension of 2.3 g of $LiAlH_4$ in 150 ml of anhydrous Et_2O was added dropwise a solution of 0.1 mol of ester, 0.075 mol of acid, 0.05 mol of diester, or 0.1 mol of ketone, respectively, in 50 ml of Et_2O. The mixture was refluxed for 2 hr and after cooling excess $LiAlH_4$ decomposed with 10 ml of 1 *N* NaOH. Filtration and concentration of filtrate afforded V (Table III).

Brominations. Bromination of 9-Allyl-9-hydroxythioxanthene (Sulfonium Salt 37). To a stirred solution of 2.68 g (10 mmol) of 9-allyl-9-hydroxymethylthioxanthene in 80 ml of $CHCl_3$ was added 10 ml of 1 *M* bromine solution in CCl_4 during 10 min. On cooling, the product separated as colorless water-soluble crystals; there was obtained 3.4 g, mp 138–140°. From the mother liquor there was ob-

‡D. E. Horning and J. M. Muchowski, unpublished work from these laboratories.

Table III. γ,δ-Unsaturated Alcohols V

No.	R	R_1	R_2	R_3	Method	Yield, %	Mp, °C (solvent)	Bp (mm), °C	Formula
29	C_6H_5	H	C_6H_5	H	A	94	61–64 (petroleum ether)		$C_{17}H_{18}O$
30	3-C_5H_4N	H	C_6H_5	H	A	79	92–94 (petroleum ether)		$C_{16}H_{15}NO$[a]
31	Me	H	C_6H_5	C_6H_5	A	98		130–135 (0.03)	$C_{18}H_{20}O$
32	H	2,2′-C_6H_4-$CH_2C_6H_4$		H	B	95		140–145 (0.03)	$C_{12}H_{16}O_2$
33	H	H	2,2′-$C_6H_4(CH_2)_2C_6H_4$		B	98		130–138 (0.03)	$C_{19}H_{20}O$[b]
34	H	H	2,2′-C_6H_4-O-C_6H_4		B	92		100–103 (0.05)	$C_{17}H_{16}O_2$
35	H	H	2,2′-C_6H_4-S-C_6H_4		B	76	110–112 (benzene)		$C_{17}H_{16}OS$
36	H	H	C_6H_5	CH_2OH	B	72	52–53 (Et_2O–petroleum ether)		$C_{12}H_{16}O_2$[c]

[a] *Anal.* calcd C, 80.30; found C, 79.87. [b] *Anal.* calcd C, 86.32; found C, 85.76. [c] The starting material, diethyl(phenylallyl) malonate was prepared according to the procedure given by A. C. Cope, L. Field, D. W. H. MacDowel, and M. E. Wright, *J. Amer. Chem. Soc.*, 78, 2745 (1956).

Table IV. Tetrahydrofurfuryl Bromides VI

No.	R	R_1	R_2	R_3	Method	Solvent	Yield, %	Mp, °C (solvent)	Bp (mm), °C	Formula
39	C_6H_5	C_6H_5	H	H	A	CCl_4	36		122–124 (0.02)	$C_{17}H_{17}BrO$
40	Me	Me	C_6H_5	C_6H_5	A	CCl_4	100	105–107 (petroleum ether)		$C_{19}H_{21}BrO$[b]
41	C_6H_5	H	C_6H_5	H	B	CCl_4	67	53–64	124–126 (0.03)	$C_{17}H_{17}BrO$[c,f]
42	3-C_5H_4N	H	C_6H_5	H	B	CH_2Cl_2	77		*a*	$C_{16}H_{16}BrNO$[d,f]
43	Me	H	C_6H_5	C_6H_5	A	CCl_4	98		115–120 (0.02)	$C_{18}H_{19}BrO$
44	H	2,2′-$C_6H_4CH_2C_6H_4$		H	B	CCl_4	62		*a*	$C_{18}H_{17}BrO$[f]
45	H	H	C_6H_5	C_6H_5	A	CCl_4	97		125–130 (0.03)	$C_{17}H_{17}BrO$[e]
46	H	H	2,2′-$C_6H_4(CH_2)_2C_6H_4$		A	CCl_4	85	103–104 (benzene–petroleum ether)		$C_{19}H_{19}BrO$
47	H	H	2,2′-C_6H_4-O-C_6H_4		B	CCl_4	68		*a*	$C_{17}H_{15}BrO_2$
48	H	H	2,2′-C_6H_4-S-C_6H_4		A	CH_2Cl_2	95	86–88 (Et_2O)		$C_{17}H_{15}BrO_2S$
49	H	H	C_6H_5	CH_2OH	A	CH_2Cl_2	95		125–130 (0.02)	$C_{12}H_{15}BrO_2$[f]

[a] Thermally unstable oil. [b] *Anal.* calcd C, 66.99; found C, 66.49. [c] *Anal.* calcd C, 64.36; found C, 63.84. [d] *Anal.* calcd C, 60.39; found C, 58.31. [e] *Anal.* calcd C, 64.36; found C, 65.06. [f] Examination of nmr spectra [**41**, d 5.26 (J = 6.0 Hz), d 5.18 (J = 9.0 Hz); **42**, d 5.28 (J = 5.5 Hz), d 5.39 (J = 4.5 Hz); **44**, d 5.27 (J = 9.0 Hz), d 5.28 (J = 7.5 Hz)] revealed that **41**, **42**, and **44** were mixtures of two isomers (two sets of doublets for 5-CH). Tlc analysis confirmed the above observation and revealed that the same applies for **49**. No attempt was made to separate these isomers so that the corresponding tetrahydrofurfurylamines II (**5**, **6**, **8** and **18**) were also mixtures.

tained a further 0.5 g for a total yield of 91% of **37**. A sample recrystallized from MeOH-Et_2O melted at 139–140°. *Anal.* ($C_{17}H_{16}Br_2OS$).

Conversion of Sulfonium Salt 37 to the Corresponding Tetrahydrofurfuryl Bromide (38). The sulfonium salt **37**, 6.6 g (15 mmol), was heated at 160° (12 mm) for 30 min and then distilled at 158–162° (0.02 mm) to yield 4.35 g (81%) of the solid product **38**, mp 68–71°. *Anal.* ($C_{17}H_{15}BrOS$).

General Procedures for the Preparation of VI. Procedure A. To a stirred and cooled (0–5°) solution of 0.1 mol of γ,δ-unsaturated alcohol and 0.1 mol of pyridine in 100 ml of CCl_4 (or CH_2Cl_2) was added dropwise a solution of 0.1 mol of bromine in 100 ml of CCl_4 during 15 min. The mixture was then washed with water and dilute HCl, dried over Na_2SO_4, and concentrated *in vacuo* to yield VI (Table IV).

Procedure B. When procedure A failed to give tetrahydrofurfuryl bromide VI, which was easily detected by ir spectra and tlc, cyclization was accomplished by chromatography on alumina (activity 2–3 on the Brockman scale)[13] and slow elution with C_6H_6.

4-Acetoxymethyl-4-phenyltetrahydrofurfuryl Bromide (50). 4-Hydroxymethyl-4-phenyltetrahydrofurfuryl bromide **(49)**, 4.34 g (16 mmol), was treated with 2.02 g (20 mmol) of Ac_2O and 1.6 g (20 mmol) of pyridine in 20 ml of C_6H_6. After standing at room temperature for 16 hr the mixture was treated with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield 4.94 g (98%) of **50**. The product distills at 125–130° (0.02 mm). *Anal.* ($C_{14}H_{17}BrO_3$).

Substituted Tetrahydrofurfurylamines II. To a cooled (ice-salt) solution of 50 mmol of tetrahydrofurfuryl bromides VI in 50 ml of the solvent indicated in Table I was introduced 15–20 g of methylamine or dimethylamine, respectively, and the mixture was heated in a pressure bomb for 18 hr at 50–55° unless specified otherwise (see Table I). After cooling, it was poured into water and extracted with Et_2O. The ether extract was washed with water and extracted with 1 *N* HCl. The acidic extract was basified with NH_4OH and the free base taken up in C_6H_6. Drying and evaporation of C_6H_6 extracts afforded crude products which were purified by crystallization of suitable salts. Exceptions were compounds **5** and **18** where purification was done by distillation of free bases.

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Amidines. 4.[1] Synthesis of Tricyclic Guanidines Related to 1,2,3,5-Tetrahydroimidazo[2,1-*b*]quinazoline, a New Antihypertensive Agent

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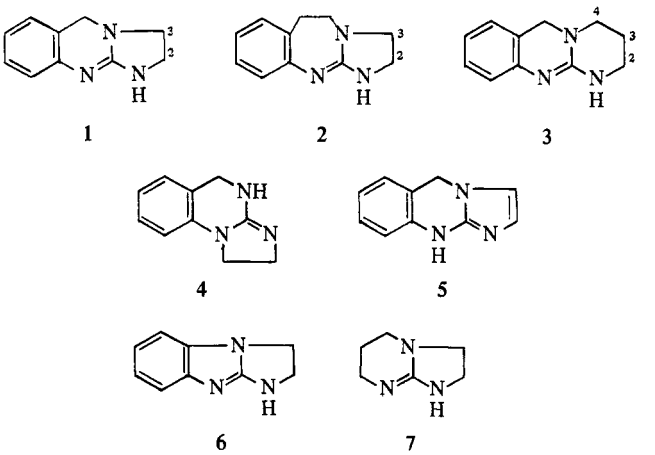
To study the influence of structural modification of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**1**) on antihypertensive activity, a series of tricyclic compounds containing a guanidine moiety was synthesized and evaluated. This series included derivatives of imidazo[2,1-*b*]benzo-1,3-diazepine (**2**), pyrimido[2,1-*b*]quinazoline (**3**), imidazo[1,2-*a*]quinazoline (**4**), imidazo[2,1-*b*]quinazoline (**5**), and imidazo[1,2-*a*]-benzimidazole (**6**). The synthetic routes to the new compounds and assignment of tautomeric structures based on nmr spectral data are discussed. Compounds **3** and **6** showed antihypertensive activity at oral doses of 2 and 10 mg/kg, respectively, in unanesthetized neurogenic hypertensive dogs.

We have recently reported a new antihypertensive agent 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**1**) and the effect of some basic structural modifications on its activity.[2,3] The present paper describes the synthesis of related heterocycles **2–7** (Chart I) containing a guanidine moiety and the influence of ring size and electron distribution on antihypertensive activity.

Chart I



1 **2** **3**

4 **5**

6 **7**

Chemistry. The first synthetic approach (Scheme I) to **2** required linking a phenethyl moiety to an imidazoline followed by cyclization to the fused diazepine. The bromide **9**[4] was prepared efficiently *via* reduction of *o*-nitrophenylacetic acid to the alcohol **8**[5] followed by treatment with HBr. The diamine **10** was obtained when **9** was heated with a large excess of ethylenediamine. Treatment of **10** with CS_2 and MeI gave **11** and **12**, respectively. Reduction of the nitro group of **12** with Zn in AcOH solution afforded **2**, presumably *via* **13**. Treatment of the diamine **10** with BrCN gave the imidazoline **14** which was reduced to **15** by catalytic hydrogenation. Attempts to convert **15** to **2** were unsuccessful.

Alternative approaches for the synthesis of **2** were also explored. One involved preparation of the benzo-1,3-diazepine system **21** (Scheme II) capable of cyclization to **2**. The diamine **18**[6] was prepared by reduction of **16** to **17** with BH_3 followed by catalytic hydrogenation. Treatment of **18**