

fraction eluted was concentrated to a colorless oil, **45** (730 mg, 90%). *Anal.* (C₁₅H₂₀O₄) 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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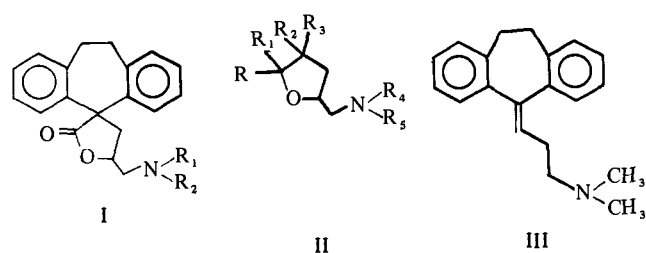
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A series of substituted tetrahydrofurfurylamines was prepared from the corresponding γ,δ -unsaturated alcohols by sequential bromocyclization and substitution of the tetrahydrofurfuryl bromides with methyl- or dimethylamines. Some of these compounds were found to possess potent antidepressant activity in animals.

The high antidepressant activity observed in the compounds of general formula I¹ led us to investigate synthetic approaches to and pharmacological properties of compounds of general formula II. Both I and II, when R₂ and R₃ are aryl substituents, are structurally related to the potent antidepressant amitriptyline III.

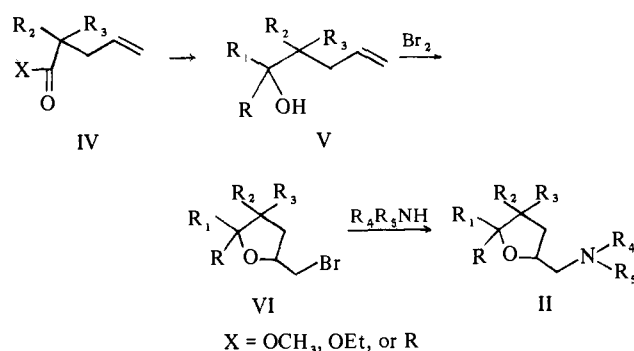


A simple general synthesis of substituted tetrahydrofurfuryl bromides from corresponding 1-en-4-ols by electrophilic addition of bromine with neighboring-group participation and, thus, an easy access to tetrahydrofurfurylamines enabled us to prepare and study the pharmacological properties of several 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 NaBH₄ or LiAlH₄ afforded V. (Compounds of general structure V are listed in Table III.)

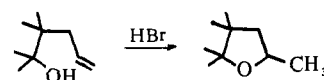
Alternatively, compounds V were prepared by the reaction of CH₃Li with IV or by Grignard reaction of benzophenone with 3-buten-1-ylmagnesium bromide. Compounds V were



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.[†]

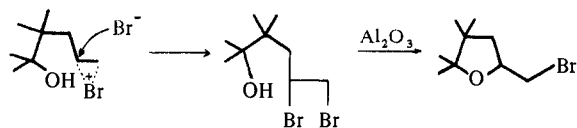
We carried out bromocyclizations in organic solvents (CCl₄, CH₂Cl₂) with 1 equiv of pyridine to neutralize the released HBr and thus prevent parallel acid-catalyzed formation of methyltetrahydrofurans. This side reaction was observed in the course of bromocyclization of alcohol **33** in the absence



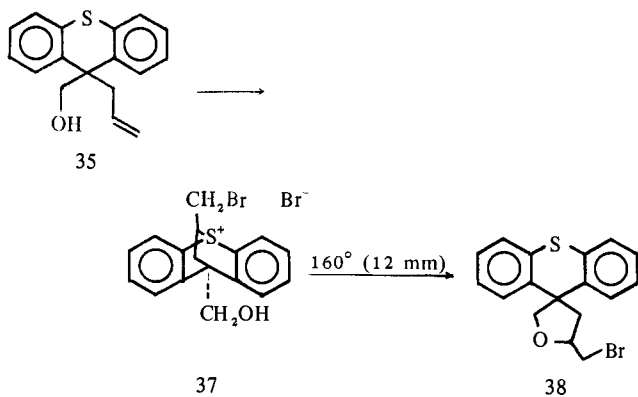
[†]This facile reaction was first described by Rengevich, *et al.*³ Additional examples of bromocyclization have been reported by Levisalles and Rudler,³ Tanaka, *et al.*,⁵ and Demole and Enggist.⁶

of pyridine. A similar side reaction was observed by Klinotova and Vystřil.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, desmethylinipramine (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

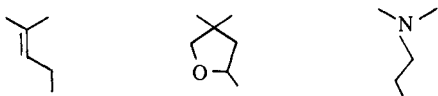
No.	R	R ₁	R ₂	R ₃	X	Solvent	Salt	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Reserpine ptosis prevention ^d
1	C ₆ H ₅	C ₆ H ₅	H	H	NHMe	THF ^b	HCl	272-273	CH ₃ OH	71	C ₁₈ H ₂₁ NO·HCl·0.5H ₂ O	c
2	C ₆ H ₅	C ₆ H ₅	H	H	NMe ₂	THF ^b	HCl	230-232	CH ₃ OH	70	C ₁₉ H ₂₃ NO·HCl·0.5CH ₃ OH	c
3	Me	Me	C ₆ H ₅	C ₆ H ₅	NHMe	THF ^d	HCl	217-219	CH ₃ OH-Et ₂ O	59	C ₂₀ H ₂₅ NO·HCl	c
4	C ₆ H ₅	H	C ₆ H ₅	H	NHMe	DMSO	HCl	208-215	CH ₃ OH-Et ₂ O	72	C ₁₈ H ₂₁ NO·HCl	20
5	3-C ₃ H ₇ N	H	C ₆ H ₅	H	NHMe	DMSO	Free base	133-136 (0.05)	CH ₃ OH-Et ₂ O	75	C ₁₇ H ₂₀ N ₂ O ^e	25
6	Me	H	C ₆ H ₅	C ₆ H ₅	NHMe	DMSO	HBr	180-182	CH ₃ OH-Et ₂ O	61	C ₁₉ H ₂₃ NO·HBr	40
7	Me	H	C ₆ H ₅	C ₆ H ₅	NMe ₂	DMSO	HBr	236-238	CH ₃ OH-Et ₂ O	88	C ₂₀ H ₂₅ NO·HBr	75
8	H	H	C ₆ H ₅	H	NHMe	DMSO	C ₂ H ₅ O ₄	166-168	CH ₃ OH	66	C ₁₉ H ₂₃ NO·C ₂ H ₅ O ₄	c
9	H	H	C ₆ H ₅	C ₆ H ₅	NHMe	DMSO	HCl	169-170	CH ₃ OH-Et ₂ O	62	C ₁₉ H ₂₃ NO·HCl	5
10	H	H	C ₆ H ₅	C ₆ H ₅	NMe ₂	DMSO	HCl	160-162	CH ₃ OH-Et ₂ O	65	C ₁₈ H ₂₁ NO·HCl·0.5H ₂ O	10
11	H	H	2,2'-C ₆ H ₄ (CH ₂) ₂ C ₆ H ₄	2,2'-C ₆ H ₄ (CH ₂) ₂ C ₆ H ₄	NHMe	DMSO	HCl	178-180	CH ₃ Cl-C ₂ H ₅	65	C ₁₉ H ₂₃ NO·HCl·0.5H ₂ O	2.5
12	H	H	2,2'-C ₆ H ₄ (CH ₂) ₂ C ₆ H ₄	2,2'-C ₆ H ₄ (CH ₂) ₂ C ₆ H ₄	NMe ₂	DMSO	HCl	115-120	CH ₃ OH-Et ₂ O	68	C ₂₁ H ₂₅ NO·C ₂ H ₅ O ₄ ·0.5CH ₃ OH	2.5
13	H	H	2,2'-C ₆ H ₄ -O-C ₆ H ₄	2,2'-C ₆ H ₄ -O-C ₆ H ₄	NHMe	DMSO	HCl	202-204	EtOH-Et ₂ O	50	C ₁₈ H ₁₉ NO ₂ ·HCl	150
14	H	H	2,2'-C ₆ H ₄ -O-C ₆ H ₄	2,2'-C ₆ H ₄ -O-C ₆ H ₄	NMe ₂	DMSO	HCl	204-206	EtOH-Et ₂ O	65	C ₁₉ H ₂₁ NO ₂ ·HCl	c
15	H	H	2,2'-C ₆ H ₄ -S-C ₆ H ₄	2,2'-C ₆ H ₄ -S-C ₆ H ₄	NHMe	DMSO	HCl	205-207	CH ₃ OH-Et ₂ O	62	C ₁₈ H ₁₉ NOS·HCl	c
16	H	H	2,2'-C ₆ H ₄ -S-C ₆ H ₄	2,2'-C ₆ H ₄ -S-C ₆ H ₄	NMe ₂	THF ^g	HCl	198-200	EtOH-Et ₂ O	76	C ₁₉ H ₂₁ NOS·HCl	c
17	H	H	2,2'-C ₆ H ₄ -S(-O)-C ₆ H ₄	2,2'-C ₆ H ₄ -S(-O)-C ₆ H ₄	NHMe	DMF	HCl	257-280	EtOH-Et ₂ O	72	C ₁₈ H ₁₉ NO ₂ ·S·HCl	c
18	H	H	C ₆ H ₅	CH ₂ OC(=O)C ₁₁	NMe ₂	DMSO ^h	Free base	105-116 (0.02)	EtOH-Et ₂ O	97	C ₁₆ H ₂₀ N ₂ O ₃	c

^aResults represent minimal effective dose (MED) in mg/kg po; DMI active at 2.5 mg. ^b50 hr at room temperature. ^cInactive at 300 mg/kg. ^d60 hr. ^eAnal. calcd C, 70.69; found C, 75.40. ^fAnal. calcd C, 71.15; found C, 70.54. ^g24 hr, 55-60°. ^h24 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 CDCl₃ 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 C₆H₆. The extract was washed with water, dried over Na₂SO₄, and concentrated *in vacuo* to yield 7.26 g (73%) of the solid product 20, mp 106–108°. *Anal.* (C₁₇H₁₄O₂S).

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 C₆H₆ 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 C₆H₆, dried, and concentrated *in vacuo* to yield 4.8 g (85%) of a solid 21, mp 164–165° (C₆H₆). *Anal.* (C₁₇H₁₄O₂S).

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.* (C₁₇H₁₆O).

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 C₁₆H₁₃NO: C, 80.99; H, 6.37; N, 5.90. Found: C, 79.89; H, 6.24; N, 5.79.

11-Allyl-5,11-dihydro-10H-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 N₂ for 3 hr. The reaction mixture was concentrated *in vacuo* and the residue treated with C₆H₆ and water. The C₆H₆ 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.* (C₁₈H₁₆O).

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-one¹² in 40 ml of anhydrous Et₂O under N₂ 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 C₆H₆-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.* (C₁₉H₁₆O). 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 Et₂O 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 Et₂O. Work-up of the mixture afforded an oil (15.3 g) which was chromatographed on an alumina column (600 g). Elution with CH₂Cl₂ afforded 3.2 g of benzophenone followed by 2.83 g (15.6%) of the product 27, bp 100–102° (0.02 mm). *Anal.* (C₁₇H₁₈O).

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 Et₂O 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 Na₂CO₃ was obtained a further 0.3 g for a combined yield of 86% of 28, mp 177–179° (C₆H₆). *Anal.* (C₁₇H₁₆O₂S).

General Methods. A. Reduction of Ketones IV with NaBH₄. To a solution of 50 mmol of ketone in 100 ml of EtOH (99%) was added 1 g of NaBH₄ and the mixture refluxed for 1 hr. It was then treated with water and with diluted HCl and the product extracted with Et₂O. Drying and concentration afforded the product V (Table III).

B. Reductions of Ketones, Acids, and Esters IV with LiAlH₄. To a stirred suspension of 2.3 g of LiAlH₄ in 150 ml of anhydrous Et₂O 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 Et₂O. The mixture was refluxed for 2 hr and after cooling excess LiAlH₄ 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 CHCl₃ was added 10 ml of 1 M bromine solution in CCl₄ 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 ₆ H ₅	H	C ₆ H ₅	H	A	94	61–64 (petroleum ether)		C ₁₇ H ₁₈ O
30	3-C ₂ H ₄ N	H	C ₆ H ₅	H	A	79	92–94 (petroleum ether)		C ₁₆ H ₁₅ NO ^a
31	Me	H	C ₆ H ₅	C ₆ H ₅	A	98		130–135 (0.03)	C ₁₈ H ₂₀ O
32	H		2,2'-C ₆ H ₄ -CH ₂ C ₆ H ₄	H	B	95		140–145 (0.03)	C ₁₂ H ₁₆ O ₂
33	H	H		2,2'-C ₆ H ₄ (CH ₂) ₂ C ₆ H ₄	B	98		130–138 (0.03)	C ₁₉ H ₂₀ O ^b
34	H	H		2,2'-C ₆ H ₄ -O-C ₆ H ₄	B	92		100–103 (0.05)	C ₁₇ H ₁₆ O ₂
35	H	H		2,2'-C ₆ H ₄ -S-C ₆ H ₄	B	76	110–112 (benzene)		C ₁₇ H ₁₆ OS
36	H	H	C ₆ H ₅	CH ₂ OH	B	72	52–53 (Et ₂ O-petroleum ether)		C ₁₂ H ₁₆ O ₂ ^c

^aAnal. calcd C, 80.30; found C, 79.87. ^bAnal. calcd C, 86.32; found C, 85.76. ^cThe 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 ₆ H ₅	C ₆ H ₅	H	H	A	CCl ₄	36		122–124 (0.02)	C ₁₇ H ₁₇ BrO
40	Me	Me	C ₆ H ₅	C ₆ H ₅	A	CCl ₄	100	105–107 (petroleum ether)		C ₁₉ H ₂₁ BrO ^b
41	C ₆ H ₅	H	C ₆ H ₅	H	B	CCl ₄	67	53–64	124–126 (0.03)	C ₁₇ H ₁₇ BrO ^{c,f}
42	3-C ₂ H ₄ N	H	C ₆ H ₅	H	B	CH ₂ Cl ₂	77		^a	C ₁₆ H ₁₆ BrNO ^{d,f}
43	Me	H	C ₆ H ₅	C ₆ H ₅	A	CCl ₄	98		115–120 (0.02)	C ₁₈ H ₁₉ BrO
44	H		2,2'-C ₆ H ₄ CH ₂ C ₆ H ₄	H	B	CCl ₄	62		^a	C ₁₈ H ₁₇ BrO ^f
45	H	H	C ₆ H ₅	C ₆ H ₅	A	CCl ₄	97		125–130 (0.03)	C ₁₇ H ₁₇ BrO ^e
46	H	H		2,2'-C ₆ H ₄ (CH ₂) ₂ C ₆ H ₄	A	CCl ₄	85	103–104 (benzene-petroleum ether)		C ₁₉ H ₁₉ BrO
47	H	H		2,2'-C ₆ H ₄ -O-C ₆ H ₄	B	CCl ₄	68		^a	C ₁₇ H ₁₅ BrO ₂
48	H	H		$\begin{array}{c} \text{O} \\ \\ 2,2'-\text{C}_6\text{H}_4-\text{S}-\text{C}_6\text{H}_4 \end{array}$	A	CH ₂ Cl ₂	95	86–88 (Et ₂ O)		C ₁₇ H ₁₅ BrO ₂ S
49	H	H	C ₆ H ₅	CH ₂ OH	A	CH ₂ Cl ₂	95		125–130 (0.02)	C ₁₂ H ₁₅ BrO ₂ ^f

^aThermally unstable oil. ^bAnal. calcd C, 66.99; found C, 66.49. ^cAnal. calcd C, 64.36; found C, 63.84. ^dAnal. calcd C, 60.39; found C, 58.31. ^eAnal. calcd C, 64.36; found C, 65.06. ^fExamination 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-Et₂O melted at 139–140°. *Anal.* (C₁₇H₁₆Br₂OS).

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.* (C₁₇H₁₅BrOS).

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 CCl₄ (or CH₂Cl₂) was added dropwise a solution of 0.1 mol of bromine in 100 ml of CCl₄ during 15 min. The mixture was then washed with water and dilute HCl, dried over Na₂SO₄, 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)³ and slow elution with C₆H₆.

4-Acetoxyethyl-4-phenyltetrahydrofurfuryl Bromide (50). 4-Hydroxymethyl-4-phenyltetrahydrofurfuryl bromide (49), 4.34 g (16 mmol), was treated with 2.02 g (20 mmol) of Ac₂O and 1.6 g (20 mmol) of pyridine in 20 ml of C₆H₆. After standing at room temperature for 16 hr the mixture was treated with water, dried (Na₂SO₄), and concentrated *in vacuo* to yield 4.94 g (98%) of 50. The product distills at 125–130° (0.02 mm). *Anal.* (C₁₄H₁₇BrO₃).

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 Et₂O. The ether extract was washed with water and extracted with 1 N HCl. The acidic extract was basified with NH₄OH and the free

base taken up in C₆H₆. Drying and evaporation of C₆H₆ 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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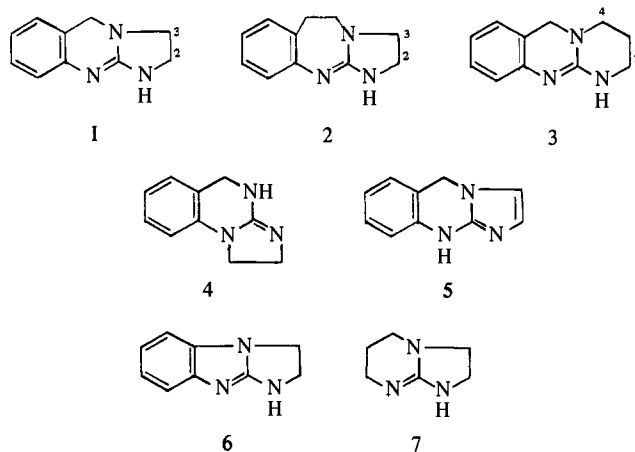
To study the influence of structural modification of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (1) on antihypertensive activity, a series of tricyclic compounds containing a guanidine moiety was synthesized and evaluated. This series included derivatives of imidazo[2,1-*b*]benzo-1,3-diazepine (2), 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.

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 9⁴ was prepared efficiently *via* reduction of *o*-nitrophenylacetic acid to the alcohol 8⁵ followed by treatment with HBr. The diamine 10 was obtained when 9 was heated with a large excess of ethylenediamine. Treatment of 10 with CS₂ 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 ex-

Chart I



plored. One involved preparation of the benzo-1,3-diazepine system 21 (Scheme II) capable of cyclization to 2. The diamine 18⁶ was prepared by reduction of 16 to 17 with BH₃ followed by catalytic hydrogenation. Treatment of 18