**9(e)-Hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (4).**—Oxazoline **20** (200 mg, 0.70 mmole), was dissolved in 100 ml of 10% aq HCl. The mixture was heated at reflux with stirring for 3 hr. The aq solution was allowed to cool and was then extracted with $Et_2O$ to remove $PhCO_2H$. The aq layer was neutralized with aq 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($Na_2SO_4$) and evapd *in vacuo* to give 68 mg of an oil. The oil was dissolved in $CHCl_3$-$Et_2O$-hexane and placed in a refrigerator overnight. Yellow square-like crystals of **4** were collected: mp 144°; ir (KBr) 3.22 (broad-OH, N-H stretching), 3.45 and 3.52 (aliphatic C-H stretching), 6.33, 6.80, 6.95, 7.50, 9.70, 11.00, 13.35 μ. A diacetyl derivative **4A** was prepared which had identical melting point and spectral data, as previously prepared by LAH reduction and acetylation of 9(e)-acetoxy-10(a)-azido-1,2,3,4,4a,9,10,10a-*trans*-4a,10a)-octahydrophenanthrene (18).

**Pharmacological Testing.**—Experiments were performed on isolated rat vas deferens[21] *in vitro* at 37°. The cumulative dose response curves of (−)-norepinephrine were obtained before and after experimental agents. The tissue incubation time of the experimental compounds was 5 min and the dose response curve of (−)-norepinephrine was obtained in the presence of the drug. Experiments were repeated a minimum of 3 times.

**Acknowledgments.** We wish to thank Dr. P. N. Patil and Dr. O. M. Sethi, Division of Pharmacology, and Dr. J. B. LaPidus, Division of Medicinal Chemistry, The Ohio State University, for performing the vas deferens assays and to express our appreciation to Mr. Quentin E. Gilman, Raymond S. Wilson, and Paul B. Kuehn for their assistance in the laboratory. The financial support by a U. S. Public Health Service Fellowship and the State of Washington Initiative 171 Funds for Research in Biology and Medicine is gratefully acknowledged.

# Synthesis and Hypotensive Activity of N-Substituted 1-Trimethoxybenzyl-3-butenylamines and Related Compounds

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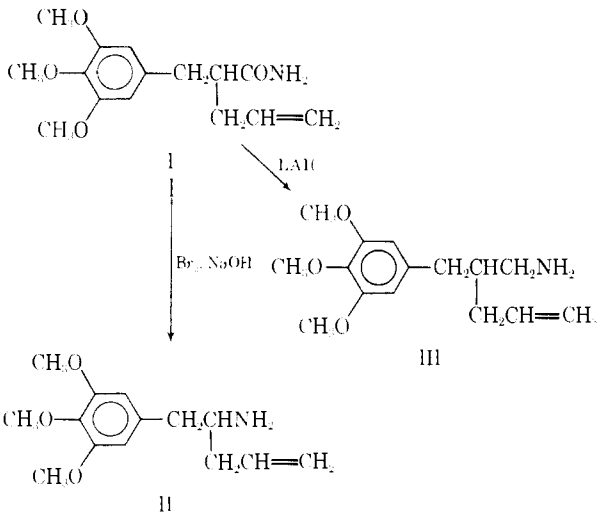
A series of N-substituted 1-trimethoxybenzyl-3-butenylamines was prepared and evaluated for hypotensive, analgetic, and antiinflammatory activity. *N*-Methyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamine·HCl (**2**) was selected for further pharmacological and clinical investigation as a hypotensive agent. Certain of the *N*-acyl-1-trimethoxybenzyl-3-butenylamines were cyclized by the Bischler-Napieralski reaction to form 3-allyl-1-substituted-6,7,8-trimethoxy-3,4-dihydroisoquinolines.

Previous[1,2] reports from these laboratories disclosed that certain compounds of the 1-aralkyl-3-butenylamine series possess hypotensive activity. The most interesting compound of this series was 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (II), which, like reserpine, possesses mild hypotensive activity. The close structural relationship of this amine to the centrally acting compound, mescaline, suggested to us that a central component might be involved in the mechanism of the hypotensive action of II. Since we considered a central mechanism to be a desirable mode of action for a hypotensive agent, we were prompted to prepare a series of analogs of II. In the present investigation we have modified structure II, principally, by substitution on N, in an attempt to obtain a more effective, orally active agent.

**Chemistry.**—1-(3,4,5-Trimethoxybenzyl)-3-butenylamine (II) (**1**, Table I) was prepared as previously described[1] (Scheme I) by a Hofmann rearrangement of 2-(3,4,5-trimethoxybenzyl)-4-pentenamide (I). Substitution of the primary N of II to prepare compounds of Table I was carried out by conventional reactions with the appropriate acyl chloride, anhydride, sulfonyl chloride, alkyl chloride, cyanate, or thioisocyanate. Certain of the amides resulting from the use of acyl chlorides were subsequently reduced with LAH to form the amine. LAH reduction of the amide I produced 2-(3,4,5-trimethoxybenzyl)-4-pentenylamine (III).[1] Three *N*-acyl derivatives of III were prepared (Table II).

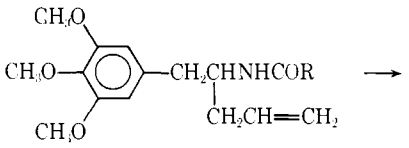
Scheme I



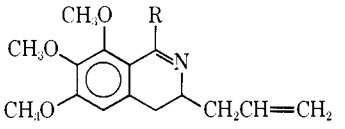

Certain of the *N*-acyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamines were refluxed with $POCl_3$ in PhMe resulting in Bischler-Napieralski cyclodehydration and

(1) F. J. McCarty, P. D. Rosenstock, J. P. Paolini, D. D. Micucci, L. Ashton, W. W. Bennetts, and F. P. Palopoli, *J. Med. Chem.*, **11**, 534 (1968).
(2) F. P. Palopoli, D. D. Micucci, and P. D. Rosenstock, U. S. Patent 3,440,274 (1969).

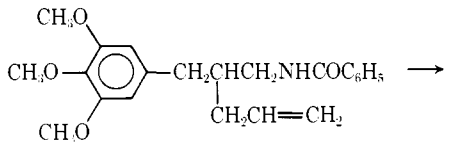
formation of 3-allyl-1-substituted-6,7,8-trimethoxy-3,4-dihydroisoquinolines IV–VIII (**42–46**, Table III).



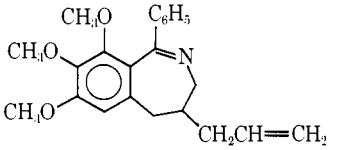
IV, R = $CH_3$
V, R = $C_6H_5$
VI, R = $C_6H_5CH_2CH_2$
VII, R = $C_6H_5CH{=}CH$
VIII, R =



*N*-Benzoyl-2-(3,4,5-trimethoxybenzyl)-4-pentenylamine (IX) (**40**, Table II) was cyclized similarly to form 1-phenyl-4-allyl-7,8,9-trimethoxy-4,5-dihydro-3*H*,-2-benzazepine (X).



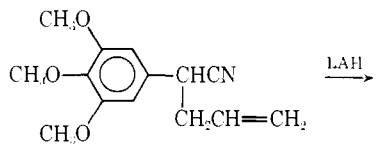
IX



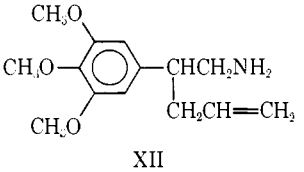
X

Catalytic hydrogenation of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (II) resulted in the formation of 1-(3,4,5-trimethoxybenzyl) butylamine.[3]

The synthesis of the isomeric 2-(3,4,5-trimethoxyphenyl)-4-pentenylamine (XII) by LAH reduction of the nitrile XI furnished a liquid for which good elemental analysis could not be obtained. A maleate salt of XII was prepared and an *N*-carbethoxy derivative was readily obtained.



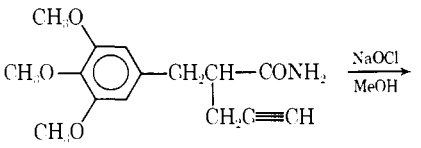
XI



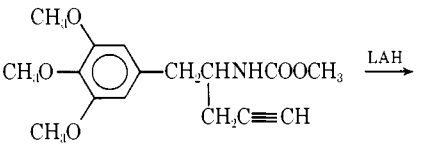
XII

The preparation of 2-(3,4,5-trimethoxybenzyl)-4-pentynamide (XIII) was carried out by a sequence of reactions similar to that employed for the corresponding pentenamide (I).[1] Thus ethyl sodio-2-propargylacetoacetate was alkylated with 3,4,5-trimethoxybenzyl-chloride, and subsequent cleavage of the acetyl group resulted in the isolation of ethyl 2-(3,4,5-trimethoxybenzyl)-4-pentynoate. This ester was then saponified and the acid produced was converted into XIII *via* reaction with ethyl chlorocarbonate, followed by $NH_3$.

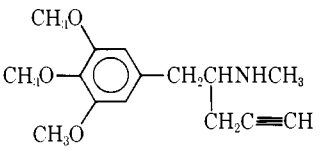
When attempts were made to convert XIII into 1-(3,4,5-trimethoxybenzyl)-3-butynylamine by the Hofmann rearrangement using $Br_2$ and NaOH, a pure product could not be isolated. However, when the



XIII



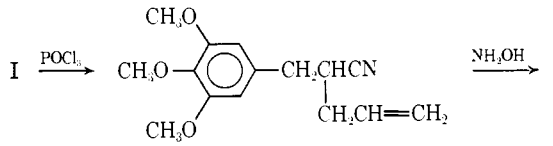
XIV



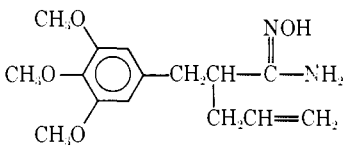
XV

Hofmann reaction was carried out in MeOH using NaOCl, the carbamate XIV was obtained. LAH reduction yielded *N*-methyl-1-(3,4,5-trimethoxybenzyl)-3-butynylamine (XV).

The amide I was readily converted into the nitrile XVI and reaction of XVI with hydroxylamine produced the amidooxime XVII.



XVI



XVII

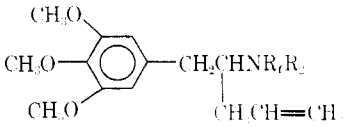
**Pharmacology.**—Compounds were screened for oral hypotensive activity in conscious, renal hypertensive rats. Male Wistar rats were made hypertensive by a modified Grollman technique.[4] Animals with a systolic pressure greater than 150 mm were considered hypertensive. Systolic blood pressure was measured indirectly by means of a Decker tail plethysmograph system. Active compounds were those producing a mean fall in systolic pressure of 20 mm or more. Compounds were administered by gastric gavage at their minimal symptomatic dose or a maximal dose of 250 mg/kg.

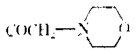
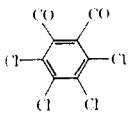
Compounds **1**, **2**, **3**, **8**, **9**, **27**, **29**, and **31** (Table I) were active in the initial screen. All other compounds in this report were inactive. Thus the only N substituents which retained the activity of **1** were Me, Et, carbo-

(3) A. T. Shulgin, *Experientia*, **19**, 127 (1963).

(4) A. Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944).

Table I



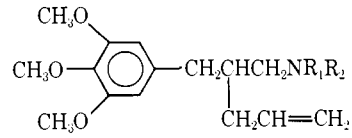
| No. | $R_1$ | $R_2$ | Method | Yield, % | Mp or bp (mm), °C | Recrystn solvent | Formula[a] |
|---|---|---|---|---|---|---|---|
| 1[b] | H | H | | | 212–213 | EtOH | $C_{14}H_{21}NO_3 \cdot HCl$ |
| 2 | H | $CH_3$ | B | 82 | 146–147 | EtCOMe | $C_{15}H_{23}NO_3 \cdot HCl$ |
| 3 | H | $C_2H_5$ | B | 44 | 144–146 | EtCOMe | $C_{16}H_{25}NO_3 \cdot HCl$ |
| 4 | H | *i*-$C_3H_7$ | B | 43 | 115–125 (0.1) | | $C_{17}H_{27}NO_3$ |
| 5 | $CH_3$ | $CH_3$ | B | 83 | 111–112 (0.05) | | $C_{16}H_{25}NO_3$ |
| 6 | $C_2H_5$ | $C_2H_5$ | B | 73 | 125–130 (0.15) | | $C_{18}H_{29}NO_3$ |
| 7 | $CH_3$ | $CH_2C{\equiv}CH$ | | 31 | 142 (0.2) | | $C_{18}H_{25}NO_3$ |
| 8 | H | $CO_2CH_3$ | A | 75 | 68–70 | Petr ether (bp 30–60°) | $C_{16}H_{23}NO_5$ |
| 9 | H | $CO_2C_2H_5$ | A | 70 | 73–74 | $C_6H_6$–petr ether (bp 30–60°) | $C_{17}H_{25}NO_5$ |
| 10 | $CH_3$ | $CO_2C_2H_5$ | A | 79 | 139–141 (0.04) | | $C_{18}H_{27}NO_5$ |
| 11 | H | $CO_2C_6H_5$ | A | 82 | 84–86 | $C_6H_6$–petr ether (bp 30–60°) | $C_{21}H_{25}NO_5$ |
| 12 | H | $COCH_3$ | A | 91 | 87–89 | $Et_2O$ | $C_{16}H_{23}NO_4$ |
| 13 | $C_2H_5$ | $COCH_3$ | A | 80 | 164–168 (0.01) | | $C_{18}H_{27}NO_4$ |
| 14 | H | $COCH_2Cl$ | A | 70 | 96–98 | EtOH–$Et_2O$ | $C_{16}H_{22}ClNO_4$ |
| 15 | H | $COCH_2C_6H_5$ | A | 57 | 122–123 | MeOH | $C_{22}H_{27}NO_4$ |
| 16 | H | $CO_2CH_2CH_2Cl$ | A | 16 | 65–68 | $Et_2O$–petr ether (bp 30–60°) | $C_{17}H_{24}ClNO_5$ |
| 17 | H | $COCH_2CH_2C_6H_5$ | A | 77 | 99–100 | $C_6H_6$ | $C_{23}H_{29}NO_4$ |
| 18 | H |  | | | 71–72 | EtOH–$Et_2O$ | $C_{20}H_{30}N_2O_5$ |
| 19 | H | $COCH_2N(CH_3)CH_2CH_2C_6H_5$ | | 48 | 230–232 (0.1) | | $C_{25}H_{34}N_2O_4$ |
| 20 | H | $COCH(OCOCH_3)C_6H_5$ | A | 76 | 115–121 | $C_6H_6$ | $C_{24}H_{29}NO_6$ |
| 21 | H | $COC_6H_5$ | A | 85 | 122–124 | EtOH | $C_{21}H_{25}NO_4$ |
| 22 | H | CO-4-$ClC_6H_4$ | A | 72 | 120–122 | *i*-PrOH | $C_{21}H_{24}ClNO_4$ |
| 23 | H | CO-2-$CO_2HC_6H_4$ | | 85 | 167–168 | MeOH | $C_{22}H_{23}NO_6$ |
| 24 | H | CO-3,4,5-$(CH_3O)_3C_6H_2$ | A | 91 | 132–133 | MeOH | $C_{24}H_{31}NO_7$ |
| 25 | H | CO-2-$C_4H_3S$ | A | 81 | 138–140 | MeOH | $C_{19}H_{23}NO_4S$ |
| 26 | H | $SO_2C_6H_5$ | A | 52 | 115–116 | EtOH | $C_{20}H_{25}NO_5S$[c] |
| 27 | H | $CH_2CH_2C_6H_5$ | B | 25 | 171–174 | EtCOMe | $C_{22}H_{29}NO_3 \cdot HCl$ |
| 28 | H | $CH_2$-4-$ClC_6H_4$ | B | 35 | 129–131 | *i*-PrOH | $C_{21}H_{26}ClNO_3 \cdot HCl$[d] |
| 29 | H | $CH_2$-3,4,5-$(CH_3O)_3C_6H_2$ | B | 18 | 141–142 | MeOH–$Et_2O$ | $C_{24}H_{33}NO_6 \cdot HCl$ |
| 30 | $CO_2C_2H_5$ | $CH_2$-3,4,5-$(CH_3O)_3C_6H_2$ | A | 42 | 220 (0.07) | | $C_{25}H_{37}NO_8$ |
| 31 | H |  | | 86 | 96–98 | $Et_2O$ | $C_{17}H_{24}N_2O_4$ |
| 32 | H | $CONH_2$ | | 69 | 124–126 | EtOH | $C_{15}H_{22}N_2O_4$ |
| 33 | H | $CONHCH_2CH_2Cl$ | | 91 | 90–92 | $C_6H_6$–petr ether (bp 30–60°) | $C_{17}H_{25}ClN_2O_4$ |
| 34 | H | $CONHC_6H_5$ | | 29 | 124–125 | MeOH | $C_{20}H_{24}N_2O_4$ |
| 35 | H | $CSNHC_6H_5$ | | 80 | 116–117 | $C_6H_6$–petr ether (bp 30–60°) | $C_{20}H_{24}N_2O_3S$ |
| 36 | |  | | 66 | 81–82 | MeOH–$H_2O$ | $C_{22}H_{23}NO_5$ |
| 37 | |  | | 81 | 167–169 | *i*-PrOH | $C_{22}H_{19}Cl_4NO_5$ |
| 38 | |  | B | 49 | 201–203 | $Me_2CO$ | $C_{22}H_{27}NO_3 \cdot HCl$ |

[a] All analyses were for C, H, N. [b] Previously reported, ref 1. [c] C: calcd, 61.36; found, 61.85. [d] C: calcd, 61.17; found, 60.67.

methoxy, carbethoxy, phenethyl, 3,4,5,trimethoxybenzyl, or oxazolinyl. In all cases, N,N-disubstituted compounds were devoid of hypotensive activity.

Intravenous injection of the active compounds also resulted in reduction of blood pressure in anesthetized, normotensive dogs. The hypotensive activity varied as to magnitude and duration of effect. For example, 1 (4 mg/kg iv) produced mean blood pressure decreases

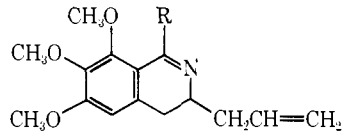
TABLE II



| No. | $R_1$ | $R_2$ | Method | Yield, % | Mp or bp (mm), °C | Recrystn solvent | Formula[a] |
|---|---|---|---|---|---|---|---|
| 39 | H | $CO_2C_2H_5$ | A | 58 | 171 (0.1) | | $C_{18}H_{27}NO_5$[b] |
| 40 | H | $COC_6H_5$ | A | 33 | 81–82 | $Et_2O$–petr ether (bp 30–60°) | $C_{22}H_{27}NO_4$ |
| 41 | H | CO-2-$CO_2HC_6H_4$ | | 40 | 117–120 | $C_6H_6$ | $C_{23}H_{27}NO_6$ |

[a] All analyses were for C, H, N. [b] C: calcd, 64.07; found, 64.50.

TABLE III



| No. | R | Method | Yield, % | Mp or bp (mm), °C | Recrystn solvent | Formula[a] |
|---|---|---|---|---|---|---|
| 42 | $CH_3$ | C | 45 | 146 | EtCOMe | $C_{16}H_{21}NO_3 \cdot HCl$ |
| 43 | $CH_2CH_2C_6H_5$ | C | 55 | 144 | $C_6H_6$ | $C_{23}H_{27}NO_3 \cdot HCl$[b] |
| 44 | $CH{=}CHC_6H_5$ | C | 10 | 91–93 | $Et_2O$ | $C_{23}H_{25}NO_3$ |
| 45 | $C_6H_5$ | C | 73 | 114–115 | Petr ether (bp 30–60°) | $C_{21}H_{23}NO_3$[c] |
| 46 | 2-$C_4H_3S$ | C | 32 | 138–140 | EtOH | $C_{19}H_{21}NO_3S$ |

[a] All analyses were for C, H, N. [b] C: calcd, 68.73; found, 69.19. [c] C: calcd, 74.75; found, 74.25.

of 44 to 80 mm, lasting up to 1 hr. Compounds **3**, **27**, and **29** at 4–8 mg/kg iv produced decreases of 20 to 40 mm which were too brief (1–3 min) in duration to be of interest.

The parent compound **1** was also studied in unanesthetized renal hypertensive dogs (Grollman technique) to compare its activity to two standards, hydralazine and reserpine. The drugs were given orally in gelatin capsules. At a dose of 25 mg/kg, 1 produced a maximum decrease in systolic pressure of 23 mm, compared with hydralazine (5 mg/kg) which produced a 65 mm decrease, and reserpine (10 mg/kg) which produced a 30 mm decrease. The maximum decrease obtained in control dogs (empty capsule) was 11 mm. Thus, **1** appeared to be less potent than hydralazine, and to possess mild hypotensive activity.

The most extensive evaluation was done with **2**, since this compound had activity in renal hypertensive rats and anesthetized normotensive dogs which was comparable with that of **1** together with preliminary acute toxicity data in mice, rats, and dogs which suggested that it was less toxic than the parent compound.

In renal hypertensive rats a single oral dose of 125 mg/kg of **2** produced a maximal depressor response of approximately 30 mm below control levels, with a duration of 8 to 12 hr. A multiple dosing schedule of 125 mg/kg 3 times daily at 4-hr intervals, for 3 days, produced no apparent tolerance to the antihypertensive effect of the compound.

In renal hypertensive dogs the minimal effective dose of **2** was 50 mg/kg po. The onset of action was within 1 hr, a maximal decrease of 30 to 35 mm occurred at 2 hr, and the total duration was approximately 4 hr. Higher doses (100 and 200 mg/kg) exerted about the same magnitude of responses, but the duration was 6 hr or longer. However, symptoms consisting of lacrimation, vasodilation, and emesis were observed in some dogs at these higher doses.

The effects of **2** were also determined on several cardiovascular parameters in pentobarbital anesthetized, normotensive dogs. The compound was dissolved in 0.9% saline and infused into a femoral vein over a 1-min period.

TABLE IV
REPRESENTATIVE CARDIOVASCULAR EFFECTS OF **2** IN ANESTHETIZED DOGS

| Parameter | Maximum per cent change after 2[a] 1 mg/kg | 4 mg/kg | 8 mg/kg |
|---|---|---|---|
| Mean arterial blood pressure | −4 (±3) | −26 (±5) | −67 (±4) |
| Heart rate | −5 (±8) | −17 (±2) | −12 (±14) |
| Cardiac output[b] | −9 (±9) | +9 (±2) | −10 (±17) |
| Peripheral vascular resistance[c] | +8 (±11) | −7 (±5) | −60 (±10) |

[a] Mean values (± std error) of 3 or 4 dogs. [b] Dye-dilution technique. [c] Peripheral vascular resistance = mean arterial blood pressure (mm)/cardiac output (L/min).

Table IV contains a summary of the results at **1**, 4, and 8 mg/kg iv. The onset of hypotension was immediate and the maximal response was seen within 5 min. Thereupon the blood pressure gradually returned to control levels. Total duration of effect varied with the dose; higher doses produced effects lasting 1 hr or more. Heart rate was slightly to moderately reduced after doses of 4 to 8 mg/kg. Cardiac output was variably, but not markedly altered. Peripheral vascular resistance was greatly decreased after 8 mg/kg of **2**.

In order to obtain an indication of the possible mechanism of the hypotensive effect, blood pressure responses

to several types of autonomic stimuli were compared before and after iv infusion of **2**, at 4 to 8 mg/kg.

In summary, **2** failed significantly to alter responses to iv injections of epinephrine (1.5 μg/kg), acetylcholine (1.5 μg/kg), or the ganglionic stimulant 1,1-dimethyl-4-phenylpiperazinium iodide (20 μg/kg), or to electrical stimulation of the peripheral end of the severed right vagus. These results indicated that the drug probably did not lower blood pressure by either ganglionic or peripheral sympathetic blockade. Pressor responses to manual occlusion of both carotid arteries (45 sec) were reduced approximately 30% after 4 mg/kg of **2**. This was suggestive of an inhibition of central vasomotor centers, but not conclusive.

In two dogs pretreated with atropine sulfate (2 mg/kg iv), there was no diminution of the hypotensive response to **2**. Therefore, a cholinergic action did not appear to be implicated in the vasodepressor activity of the drug.

A few experiments were done in which hindlimb vascular resistance was measured in anesthetized dogs. The technique as described by Osborne, *et al.*,[5] was used. With this preparation the systemic hemodynamic actions of **2** could be dissociated from the direct action of the drug on vascular smooth muscle.

Compound **2**, injected intraarterially into the perfused hindlimb at doses of 1 and 2 mg (total dose), reduced vascular resistance as indicated by a decrease in perfusion pressure of 40–60 mm without any notable change in systemic blood pressure.

In a limited clinical study with **2**, no hypotensive effects were observed at a dose of 500 mg, 3 times daily. This is slightly below the maximally tolerated dose of the compound.

All compounds were screened for analgetic (phenylquinone writhing test)[6] and antiinflammatory activity (carrageenin abscess)[7] at either the minimal symptomatic dose or a maximal dose of 250 mg/kg po. None of the compounds possessed significant activity in these screening tests.

## Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Ir spectra were obtained with a Perkin-Elmer Model 21 double beam ir spectrophotometer for all compounds and were consistent with the structures reported.

**Preparation of Compounds of Tables I–III. Method A. *N*-Acyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamines.**—A mixture of 0.1 mole of 1-(3,4,5-trimethoxybenzyl)-3-butenyl amine (**1**, base), 0.1 mole of $Et_3N$, and 500 ml of $Et_2O$ was stirred, cooled at 5°, and treated, dropwise, with 0.1 mole of the acid chloride in 100 ml of $Et_2O$. The reaction mixture was stirred 1.5 hr at room temp and then refluxed 3–6 hr. The mixture was cooled, the residue dissolved in $CHCl_3$, and the $CHCl_3$ solution extracted, in turn, with 5% NaOH, 5% HCl, and $H_2O$. The solution was dried ($Na_2SO_4$) and concd and the residue crystd or distd.

**Compounds 39 and 40.**—The amine employed was 2-(3,4,5-trimethoxybenzyl)-4-pentenylamine.

**Method B. N-Substituted 1-(3,4,5-Trimethoxybenzyl)-3-butenylamines.**—To a stirred mixture of 0.1 mole of LAH and 250 ml of THF was added, dropwise, a solution of 0.05 mole of the required amide or carbamate in THF. The reaction mixture was refluxed 5–7 hr, cooled, and, in turn, 4 ml of $H_2O$, 4 ml of 15% NaOH, 12 ml of $H_2O$, and 20 g of $Na_2SO_4$ were added. The mixture was stirred 1 hr and filtered and the filtrate concd. The residue was dried by azeotropic distillation with $C_6H_6$ and purified by distillation or converted into the hydrochloride in $Et_2O$.

Compound **4** was prepared by the use of *N*-isopropylidene-1-(3,4,5-trimethoxybenzyl)-3-butenylamine in method B. The latter compd was prepared by a condensation reaction between 1-(3,4,5-trimethoxybenzyl)-3-butenylamine and $Me_2CO$, followed by distillation of the product: bp 158–162° (1.5 mm); yield 73%.

**Method C. 3-Allyl-1-substituted-6,7,8-trimethoxy-3,4-dihydroisoquinolines.** A mixture of 0.05 mole of the required amide, 65 g of $POCl_3$, and 100 ml of PhMe was refluxed 2–4 hr. The reaction mixture was concd *in vacuo*, the residue was dissolved in 10% HCl, and the solution was extracted with $Et_2O$. The aq layer was made basic with 10% NaOH and extracted with $Et_2O$. The dried $Et_2O$ solution was concd and the residue crystd or converted into the hydrochloride.

**1-Phenyl-4-allyl-7,8,9-trimethoxy-4,5-dihydro-3*H*-2-benzazepine.**—*N*-Benzoyl-2-(3,4,5-trimethoxybenzyl)-4-pentenylamine (**40**) was employed in procedure C and the product was distd: yield 48%; bp 155° (0.07 mm); $\lambda_{max}^{Nujol}$ 6.1 (C=N), 10.8 μ (CH=CH$_2$). *Anal.* ($C_{22}H_{25}NO_3$) C, H, N.

***N*-[5-(3,4,5-Trimethoxyphenyl)-1-penten-4-yl]urea (32).** A solution of 16.5 g (0.05 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine·HCl (**1**) in 60 ml of $H_2O$ was stirred while a solution of 4 g (0.05 mole) of KOCN in 25 ml of $H_2O$ was added dropwise. The reaction mixture was stirred 1 hr, concd to 0.5 volume, cooled, and filtered. The product was recrystd from EtOH.

***N*-Phenyl-*N'*-[5-(3,4,5-trimethoxyphenyl)-1-penten-4-yl]urea (34).**—A solution of 14.7 g (0.05 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**1**, base) in 80 ml of EtOH was stirred while 6 g (0.05 mole) of phenyl isocyanate was added dropwise. After the addition, the reaction mixture was allowed to remain at room temp for 18 hr. The mixture was concd and the residue crystd from MeOH.

***N*-Phenyl-*N'*-[5-(3,4,5-trimethoxyphenyl)-1-penten-4-yl]-thiourea (35).**—A mixture of 14.7 g (0.05 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**1**, base), 6.8 g (0.05 mole) of phenylisothiocyanate, and 70 ml of EtOH was refluxed 5 hr. The reaction mixture was concd and the residue was crystd from $C_6H_6$–petroleum ether (30–60°).

***N*-2-Chloroethyl-*N'*-[5-(3,4,5-trimethoxyphenyl)-1-penten-4-yl]urea (33).**—A solution of 15 g (0.06 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**1**, base) in 250 ml of $Et_2O$ was stirred and treated dropwise with 6.9 g (0.06 mole) of 2-chloroethylisocyanate. The reaction mixture was stirred 6 hr and concd *in vacuo* and the residue was recrystd from $C_6H_6$–petroleum ether (30–60°).

***N*-(2-Oxazolinyl)-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (31).**—A mixture of 12 g (0.05 mole) of *N*-(2-chloroethyl)-*N'*-[5-(3,4,5-trimethoxyphenyl)-1-penten-4-yl]urea (**33**), 50 ml of $Me_2CO$, and 500 ml of $H_2O$ was refluxed 20 min. After cooling, the mixture was made basic with $NH_4OH$ and extracted with $Et_2O$ and the extract dried ($MgSO_4$) and concd. The residue was recrystd from $Et_2O$–petroleum ether (30–60°).

**1-(3,4,5-Trimethoxybenzyl)butylamine.**—A solution of 6.3 g (0.03 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**1**, base) in 250 ml of EtOH was acidified with HCl, mixed with 0.2 g of $PtO_2$, and shaken with $H_2$ at 3–4 atm. After the theoretical amount of $H_2$ had been absorbed, the catalyst was removed by filtration, the filtrate was concd *in vacuo* to about 0.5 vol, cooled, and filtered: yield 5.3 g (73%); mp 227–229° (lit.[8] mp 214–218°). *Anal.* ($C_{14}H_{23}NO_3$·HCl) C, H, N.

***N*-Methyl-*N*-propargyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (7).**—A mixture of 6.7 g (0.025 mole) of *N*-methyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**2**, base), 4 g (0.04 mole) of $Et_3N$, and 75 ml of EtOH was stirred and cooled with ice while a solution of 3.0 g (0.025 mole) of propargyl bromide in 25 ml of EtOH was added, dropwise, during 15 min. The reaction mixture was stirred at 25° for 30 min, then refluxed 16 hr. After the addition of 45 ml of $H_2O$, the mixture was concd *in vacuo* and the residual aq mixture was extracted with $Et_2O$. The $Et_2O$ solution was dried ($Na_2SO_4$), concd, and the residue distd, $n^{25}D$ 1.5321.

***N*-(*N'*-Methyl-*N'*-phenethylaminoacetyl)-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (19).**—A mixture of 9.7 g (0.03 mole) of *N*-chloroacetyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**14**), 8.1 g (0.06 mole) of *N*-methyl-2-phenethylamine, and 500 ml of

(5) M. W. Osborne and M. M. Winbury, *J. Pharmacol. Exp. Ther.*, **147**, 212 (1965).

(6) L. C. Hendershot and J. Forsaith, *ibid.*, **125**, 237 (1961).

(7) S. Goldstein and M. Schnall, *Arch. Int. Pharmacodyn. Ther.*, **144**, 269 (1963).

$C_6H_6$ was refluxed 6 hr, cooled, and filtered. The filtrate was concd *in vacuo* and the residue was distilled.

***N*-Morpholinoacetyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (18).**—The reaction was carried out as in the preceding example using morpholine in place of *N*-methylphenethylamine.

**2-(3,4,5-Trimethoxyphenyl)-4-pentenonitrile.**—A solution of 10.4 g (0.05 mole) of 3,4,5-trimethoxyphenylacetonitrile in 100 ml of PhMe was added dropwise, to a stirred, cooled mixture of 2.0 g (0.05 mole) of $NaNH_2$ and 100 ml of PhMe under $N_2$. The mixture was stirred at room temp for 1.5 hr. After the dropwise addition of allyl bromide (7.3 g, 0.06 mole) the reaction mixture was refluxed 3 hr, cooled, and treated, dropwise, with 200 ml of $H_2O$. The PhMe was dried ($Na_2SO_4$) and concd *in vacuo* and the residue distd: yield 11.7 g (95%); bp 137–141° (0.1 mm); $n^{21}D$ 1.5315. *Anal.* ($C_{14}H_{17}NO_3$) H, N; C: calcd, 68.00; found, 67.26.

**2-(3,4,5-Trimethoxyphenyl)-4-pentenylamine.**—The amine was prepared by LAH reduction of 2-(3,4,5-trimethoxyphenyl)-4-pentenonitrile (0.033 mole), using the procedure of method B: yield 18.2 g (73%); bp 127–130° (0.1 mm). *Anal.* ($C_{14}H_{21}NO_3$) H; C: calcd, 66.91; found, 66.30.

The maleate salt was prepared in IPA–$Et_2O$, mp 124–126° dec. *Anal.* ($C_{14}H_{25}NO_7$) H; C: calcd, 58.85; found, 58.19.

***N*-Carbethoxy-2-(3,4,5-trimethoxyphenyl)-4-pentenylamine.**—A mixture of 8 g (0.03 mole) of 2-(3,4,5-trimethoxyphenyl)-4-pentenylamine, 4 g (0.04 mole) of $Et_3N$, and 250 ml of $Et_2O$ was stirred, cooled, and treated, dropwise, with 4 g (0.04 mole) of ethyl chlorocarbonate. The reaction mixture was stirred 1 hr at room temp and filtered and the filtrate was concd. The residue was distd: yield 8 g (77%); bp 165–173° (0.1 mm); $n^{25}D$ 1.5265. *Anal.* ($C_{17}H_{25}NO_5$) C, H, N.

**Ethyl 2-(3,4,5-Trimethoxybenzyl)-4-pentynoate.**—A mixture of 6.9 g (0.3 g-atom) of Na and 300 ml of EtOH was stirred at 0° until all Na had reacted. Ethyl 2-propargylacetoacetate, 55 g (0.32 mole), dissolved in 100 ml of EtOH was added dropwise to the reaction mixture and stirring at 0° was continued for 1 hr. A solution of 64.8 g (0.33 mole) of 3,4,5-trimethoxybenzyl chloride in 300 ml of EtOH was added, dropwise, and after stirring for 1.5 hr, the mixture was refluxed 2 hr and filtered and the filtrate was concd *in vacuo*. The residue was extracted with $Et_2O$, the $Et_2O$ solution was washed with $H_2O$, dried, concd, and the residue was distd; yield 20 g (20%); bp 175° (0.2 mm). *Anal.* ($C_{17}H_{22}O_5$) H; C: Calcd, 66.63; found, 65.76.

**2-(3,4,5-Trimethoxybenzyl)-4-pentynoic Acid.**—A mixture of 230 g (0.75 mole) of ethyl 2-(3,4,5-trimethoxybenzyl)-4-pentynoate, 470 g (0.75 mole) of KOH, 1.8 l. of $H_2O$, and 2 l. of EtOH was refluxed 16 hr. The mixture was concd to remove the EtOH and the aq solution was cooled and acidified with concd HCl. After extraction with $Et_2O$, the extract was dried ($MgSO_4$), concd to a volume of 200 ml, cooled, and filtered: yield 133 g (64%); mp 113–114°. *Anal.* ($C_{15}H_{18}O_5$) C, H.

**2-(3,4,5-Trimethoxybenzyl)-4-pentynamide.**—To a solution of 50.3 g (0.46 mole) of ethyl chloroformate in 600 ml of $CHCl_3$ maintained at −60° was added, dropwise, a mixture of 129 g (0.46 mole) of 2-(3,4,5-trimethoxybenzyl)-4-pentynoic acid, 47 g (0.46 mole) of $Et_3N$, and 900 ml of $CHCl_3$ which had previously been cooled to −20°. After the addition was complete, the reaction mixture was stirred 1 hr, satd with $NH_3$, and allowed to remain at room temp 48 hr. The mixture was filtered, the filtrate concd *in vacuo*, and the residue recrystd from $C_6H_6$: yield 92.5 g (73%); mp 130–132°. *Anal.* ($C_{15}H_{19}NO_4$) C, H, N.

***N*-Carbomethoxy-1-(3,4,5-trimethoxybenzyl)-3-butynylamine.**—To a solution of 13.9 g (0.05 mole) of 2-(3,4,5-trimethoxybenzyl)-4-pentynamide in 150 ml of MeOH was added a solution of NaOCl prepared from 0.3 mole of NaOH, 0.1 mole of $Cl_2$, and 65 ml of ice–$H_2O$. The mixture was refluxed 1 hr and concd *in vacuo* to remove MeOH and the aq layer was extracted with $Et_2O$. The $Et_2O$ extract was washed with 5% HCl, $H_2O$, dried over $MgSO_4$, concd to 0.5 volume, cooled, and filtered: yield 7.6 g (50%); mp 90–91°. *Anal.* ($C_{16}H_{21}NO_5$) C, H, N.

***N*-Methyl-1-(3,4,5-trimethoxybenzyl)-3-butynylamine Hydrochloride.**—*N*-Carbomethoxy-1-(3,4,5-trimethoxybenzyl)-3-butynylamine (10 g, 0.03 mole) was reduced by the procedure described in method B: yield 4.7 g (47%); mp 173–174°. *Anal.* ($C_{15}H_{21}NO_3 \cdot HCl$) C, H, N.

***N*-(2-Carboxybenzoyl)-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (23).**—A mixture of 25.1 g (0.1 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**1**, base), 14.8 g (0.1 mole) of phthalic anhydride, and 500 ml of dioxane was refluxed 10 min and concd *in vacuo*. The residue was recrystd from MeOH.

***N*-(2-Carboxybenzoyl)-2-(3,4,5-trimethoxybenzyl)-4-pentenylamine (41).**—The reaction was carried out as in the preceding example using 2-(3,4,5-trimethoxybenzyl)-4-pentenylamine.[1]

***N*-[5-(3,4,5-Trimethoxyphenyl)-1-penten-4-yl]phthalimide (36).**—A mixture of 26 g (0.06 mole) of *N*-(2-carboxybenzoyl)-1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**23**) and 300 ml of xylene was stirred and refluxed 4 hr. During this period, the theoretical amount of $H_2O$ collected in an attached Dean–Stark trap. The mixture was concd and the residue recrystd from MeOH–$H_2O$.

***N*-[5-(3,4,5-Trimethoxyphenyl)-1-penten-4-yl]-3,4,5,6-tetrachlorophthalimide (37).**—A mixture of 23 g (0.09 mole) of 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (**1**, base), 26.2 g (0.09 mole) of 3,4,5,6-tetrachlorophthalic anhydride, and 150 ml of xylene was stirred and refluxed in a flask fitted with a Dean–Stark trap. After a 2-hr period, the theoretical amount of $H_2O$ had been collected, the reaction mixture was concd and recrystd from *i*-PrOH.

**2-(3,4,5-Trimethoxybenzyl)-4-pentenonitrile.**—A mixture of 52 g (0.19 mole) of 2-(3,4,5-trimethoxybenzyl)-4-pentenamide and 1400 ml of PhMe was stirred while 154 g (1.0 mole) of $POCl_3$ was added during a 20-min period. The reaction mixture was refluxed 3 hr and concd *in vacuo*. The residue was mixed with ice–$H_2O$ and the product extracted ($Et_2O$). The dried ($MgSO_4$) extract was concd and the residue distd: yield 41.2 g (85%); bp 156–158° (0.3 mm). *Anal.* ($C_{15}H_{19}NO_3$) H, N; C: calcd, 68.94; found, 68.45.

**2-(3,4,5-Trimethoxybenzyl)-4-pentenamidoxime Hydrochloride.**—A mixture of 17.2 g (0.07 mole) of 2-(3,4,5-trimethoxybenzyl-4-pentenonitrile, 11.5 g (0.17 mole) of $NH_2OH \cdot HCl$, 7.0 g (0.07 mole) of $Na_2CO_3$, 75 ml of $H_2O$, and 75 ml of EtOH was heated at 70° for 24 hr. The reaction mixture was concd *in vacuo* to remove EtOH and the aq mixture was extracted with $Et_2O$. The $Et_2O$ extract was dried ($MgSO_4$) and acidified with HCl and the ppt was recrystd from EtOH–$Et_2O$: yield 7.7 g (35%); mp 170–171°. *Anal.* ($C_{15}H_{22}N_2O_4 \cdot HCl$) C, H, N.