Synthesis and Pharmacology of a Series of 1-Aralkyl-3-butenylamines[1]

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A series of substituted 1-benzyl-3-butenylamines related to aletamine was prepared and evaluated biologically for analgetic, anticonvulsant, antihypertensive, and antiinflammatory activity. A related series of 2-benzyl-4-pentylamines was also prepared and evaluated.

Although various aralkylamines possess analgetic activity,[2] they have not found clinical utility in the treatment of pain mainly because of low potency and undesirable effects on the central nervous system. Previous reports[3,4] from these laboratories described the analgetic effects of 1-benzyl-3-butenylamine (aletamine) at doses below those producing overt symptomatology. In addition, this amine possesses hypotensive, antiinflammatory, anorexic, and anticonvulsant activities.[3]

With the goal of enhancing some of the properties of aletamine, a series of substituted 1-benzyl-3-butenylamines was prepared. A series of related 2-benzyl-4-pentenylamines was also prepared and investigated.

Chemistry.—The synthetic methods employed (methods A–I) are outlined by representative examples in Scheme I. Alternate methods used for the preparation of intermediate esters, acids, and amides (methods J–M) are shown in Scheme II. All of the compounds prepared by methods A–M are listed in Tables I–IX.

The ethyl α,α-disubstituted acetoacetates (I) were obtained by alkylation of ethyl sodio-α-allylacetoacetate with the appropriate benzyl chloride. The acetyl group of the disubstituted acetoacetates was readily cleaved and the esters produced (II) were converted to acids (III) by saponification. In some cases, the disubstituted acetoacetates were converted directly to the acids by refluxing with potassium hydroxide in aqueous alcohol.

The acids (III) were converted to amides (IV) by reaction of their mixed anhydrides with ammonia. Hofmann rearrangement of the amides readily produced the butenylamines (V). When the reaction was carried out in methanol, the methyl carbamates (VII) were obtained. In some cases, the corresponding butenylamine was also isolated. The methyl carbamates (VII), alternately, could be converted to the butenylamines (V) by hydrolysis.

The pentenylamines (VI) were prepared by reduction of the amides (IV) with lithium aluminum hydride.

Acyl derivatives (VIII) of the butenylamines (V) were prepared by acylation of the amine with the required acid chloride. Various other N-substituted derivatives of 1-benzyl-3-butenylamine were prepared. These are included in Table VI and described separately in the Experimental Section.

(1) Presented in part before the Division of Medicinal Chemistry at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

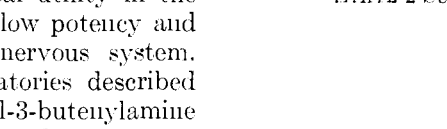
(2) E. J. Fellows and G. E. Ullyot, "Medicinal Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p 390.

(3) D. D. Micucci, U. S. Patent 3,210,424 (1965).

(4) I. Shemano, J. T. Hitchens, S. Goldstein, and J. M. Beiler, *Arch. Int. Pharmacodyn. Ther.*, in press.

Table I

Ethyl 2-Substituted 2-Allylacetoacetates



No.	Ar	Method	% yield	Bp (mm) or mp, °C	Formula[a]
1	4-F-C_6H_4	A	51	101–104 (0.2)	$C_{16}H_{19}FO_3$
2	4-*i*-PrC_6H_4	A	75	138 (0.25)	$C_{19}H_{26}O_3$
3	3-$CF_3C_6H_4$	A	70	115–120 (0.5)	$C_{17}H_{19}F_3O_3$
4	3,4-$CH_2O_2C_6H_3$	A	71	165–167 (0.4)	$C_{17}H_{20}O_5$
5	3,4,5-$(CH_3O)_3C_6H_2$	A	70	63–65	$C_{19}H_{26}O_6$
6	$C_6H_5CH{=}CH$	A	62	123 (0.05)	$C_{18}H_{22}O_3$
7	2-CH_3O-1-$C_{10}H_6$	A	25	89–90	$C_{21}H_{24}O_4$
8	2-C_4H_3S	A	49	120 (0.5)	$C_{14}H_{18}O_3S$[b]
9	2-C_5H_4N	A	89	106 (0.05)	$C_{15}H_{19}NO_3$
10	3-C_5H_4N	A	50	126–128 (0.5)	$C_{15}H_{19}NO_3$[c]
11	4-C_5H_4N	A	56	131–134 (0.4)	$C_{15}H_{19}NO_3$

[a] All analyses were for C, H or C, H, N when N was present. [b] C: calcd, 63.13; found, 63.81. [c] C: calcd, 68.94; found, 69.54.

The amides (IV) were alternately prepared as outlined in Scheme II.

The appropriate diethyl α-substituted malonate (IX) was alkylated with allyl bromide or a substituted bromopropene to form the diethyl α-allyl-α-substituted malonates (X). The malonates were hydrolyzed and decarboxylated to form the pentenoic acids (III) which were converted to the amides (IV) or esters (II) by standard methods.

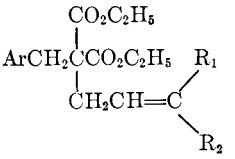
Demethylation of 1-(4-methoxybenzyl)-3-butenylamine (XI) resulted in a cycloalkylation reaction to form 2-amino-4-methyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (XII) (Scheme III).

The structure of XII was verified by the nmr spectrum which exhibited a doublet centered at 1.27 ppm, attributable to the methyl group, and signals in the aromatic region which integrated for three protons.

The attempted acid hydrolysis of ethyl 2-(4-nitrobenzyl)-4-pentenoate (XIII) resulted in lactonization to the γ-lactone (XIV)[5] (Scheme IV).

(5) Lactonization of olefinic acids and esters has been reviewed by M. F. Ansell and M. H. Palmer, *Quart. Rev.* (London), **38**, 211 (1964).

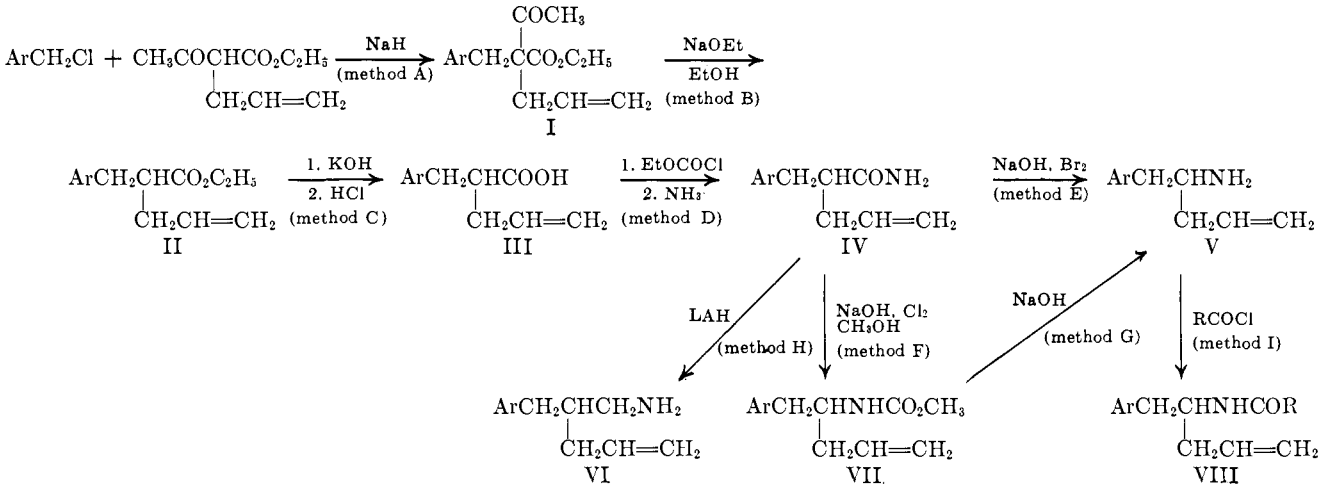
Table II: Diethyl 2-Substituted 2-Allylmalonates



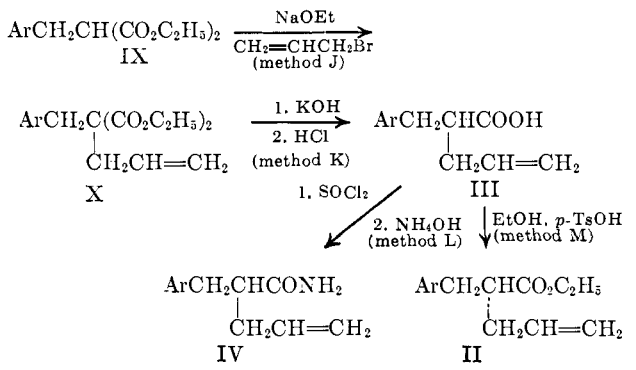
No.	Ar	R_1	R_2	Method	% yield	Bp (mm), °C	Formula[a]
12	C_6H_5	H	CH_3	J	86	135 (0.25)	$C_{18}H_{24}O_4$
13	C_6H_5	CH_3	CH_3	J	94	122 (0.05)	$C_{19}H_{26}O_4$
14	C_6H_5	H	$CH{=}CHCH_3$	J	66	146–148 (0.15)	$C_{20}H_{26}O_4$
15	C_6H_{11}	H	H	J	55	116 (0.3)	$C_{17}H_{28}O_4$
16	1-$C_{10}H_7$	H	H	J	87	160 (0.45)	$C_{21}H_{24}O_4$
17	1-$C_{10}H_7$	H	C_6H_5	J	89	222–224 (0.05)	$C_{27}H_{28}O_4$
18	$C_6H_5(CH_2)_2$	H	H	J	91	142 (0.2)	$C_{19}H_{26}O_4$
19	$C_6H_5CH{=}CH$	H	C_6H_5	J	24	198 (0.5)	$C_{25}H_{28}O_4$[b]

[a] All analyses were for C, H. [b] C: calcd, 76.50; found, 75.99.

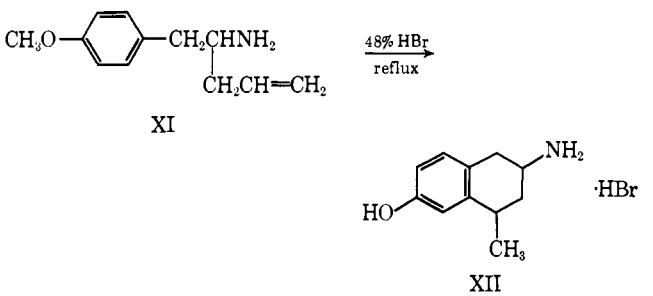
Scheme I



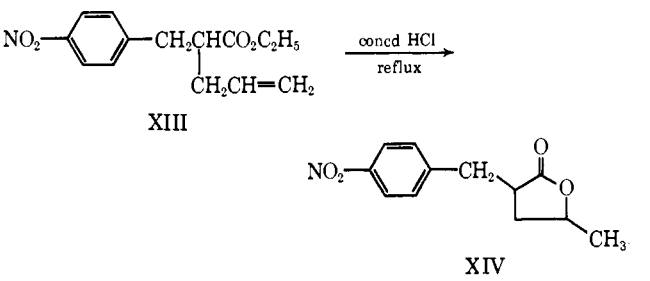
Scheme II



Scheme III



Scheme IV



Compound XIV was assigned the γ-lactone structure rather than the isomeric δ-lactone structure on the basis of the nmr spectrum which showed a doublet centered at 1.47 ppm, from the methyl group of XIV.

2-Benzyl-4-pentenamide (XV) was readily converted to 2-benzyl-4-pentenonitrile (XVI). The nitrile was converted to the amidine (XVII) and to the amidoxime (XVIII) by conventional procedures (Scheme V).

Scheme V

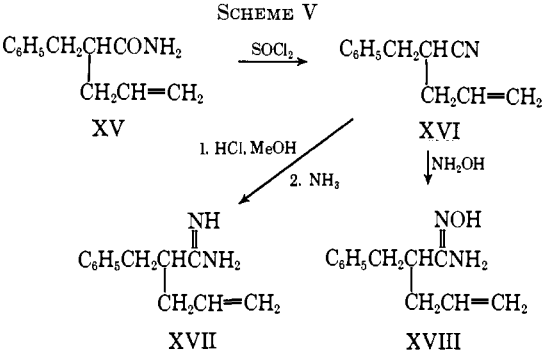


Table III

Ethyl 2-Substituted 4-Pentenoates

$ArCH_2CHCO_2C_2H_5$

$CH_2CH{=}C(R_1)(R_2)$

No.	Ar	R_1	R_2	Method	% yield	Bp (mm), °C	Formula[a]
20	4-$ClH_3C_6H_4$	H	H	B	57	95 (3.0)	$C_{15}H_{20}O_2$
21	4-*i*-PrC_6H_4	H	H	M	73	93 (0.05)	$C_{17}H_{24}O_2$
22	4-FC_6H_4	H	H	B	84	71–72 (0.12)	$C_{14}H_{17}FO_2$
23	4-$NO_2C_6H_4$	H	H	B	44	147 (0.4)	$C_{14}H_{17}NO_4$
24	3-$CF_3C_6H_4$	H	H	B	94	85 (0.25)	$C_{15}H_{17}F_3O_2$
25	3,4-$CH_2O_2C_6H_3$	H	H	B	74	124 (0.2)	$C_{15}H_{18}O_4$
26	1-$C_{10}H_7$	H	H	B	78	145 (3.0)	$C_{18}H_{20}O_2$
27	1-$C_{10}H_7$	H	C_6H_5	M	84	205–207 (0.1)	$C_{24}H_{24}O_2$
28	C_6H_5	CH_3	CH_3	M	93	95 (0.05)	$C_{16}H_{22}O_2$[b]
29	$C_6H_5CH_2CH_2$	H	H	B	85	110 (0.2)	$C_{16}H_{20}O_2$
30	$C_6H_5CH{=}CH$	H	C_6H_5	M	81	184–186 (0.05)	$C_{22}H_{24}O_2$
31	2-C_4H_3S	H	H	B	83	92 (15.0)	$C_{12}H_{16}O_2S$
32	2-C_5H_4N	H	H	B	87	82 (0.1)	$C_{13}H_{17}NO_2$
33	4-C_5H_4N	H	H	B	64	118 (0.5)	$C_{13}H_{17}NO_2$

[a] All analyses were for C, H or C, H, N when N was present. [b] C: calcd, 78.01; found, 77.54.

Table IV

2-Substituted 4-Pentenoic Acids

$ArCH_2CHCOOH$

$CH_2CH{=}C(R_1)(R_2)$

No.	Ar	R_1	R_2	Method	% yield	Bp (mm) or mp, °C	RS[a]	Formula[b]
34	4-$ClH_3C_6H_4$	H	H	C	72	138 (3.0)		$C_{13}H_{16}O_2$
35	4-*i*-PrC_6H_4	H	H	C	96	133 (0.1)		$C_{15}H_{20}O_2$
36	4-FC_6H_4	H	H	C	92	113–117 (0.1)		$C_{12}H_{13}FO_2$
37	3-$CF_3C_6H_4$	H	H	C	93	65–66	A	$C_{13}H_{13}F_3O_2$
38	2-ClC_6H_4	H	H	C	79	132–133 (0.2)		$C_{12}H_{13}ClO_2$
39	2-$CH_3OC_6H_4$	H	H	C	95	55–56	B	$C_{13}H_{16}O_3$
40	3,4-$(CH_3O)_2C_6H_3$	H	H	C	81	67–69	A	$C_{14}H_{18}O_4$
41	2,6-$(CH_3O)_2C_6H_3$	H	H	C	81	92–94	B	$C_{14}H_{18}O_4$
42	3,4,5-$(CH_3)_3C_6H_2$	H	H	C	89	87–89	B	$C_{15}H_{20}O_5$
43	3,4-$CH_2O_2C_6H_3$	H	H	C	77	70–71	C	$C_{13}H_{14}O_4$
44	1-$C_{10}H_7$	H	H	C	92	70–72	C	$C_{16}H_{16}O_2$
45	2-CH_3O-1-$C_{10}H_6$	H	H	C	75	89–90	B	$C_{17}H_{18}O_3$
46	$C_6H_5CH_2CH_2$	H	H	K	79	137 (0.15)		$C_{14}H_{18}O_2$
47	$C_6H_5CH{=}CH$	H	H	C	69	142–144 (0.01)		$C_{14}H_{16}O_2$[c]
48	C_6H_5	H	CH_3	K	92	128 (0.25)		$C_{13}H_{16}O_2$
49	C_6H_5	CH_3	CH_3	K	74	98–99 (0.1)		$C_{14}H_{18}O_2$
50	C_6H_5	H	C_6H_5	K	58	82–83	C	$C_{18}H_{18}O_2$
51	C_6H_5	H	$CH{=}CHCH_3$	K	63	143 (0.05)		$C_{15}H_{18}O_2$
52	$C_6H_5CH{=}CH$	H	C_6H_5	K	44	88–90	D	$C_{20}H_{20}O_2$
53	1-$C_{10}H_7$	H	C_6H_5	K	71	139–140	D	$C_{22}H_{20}O_2$
54	C_6H_{11}	H	H	K	93	122 (0.5)		$C_{12}H_{20}O_2$
55	2-C_4H_3S	H	H	C	91	130 (0.6)		$C_{10}H_{12}O_2S$[d]
56	3-C_5H_4N	H	H	C	85	168 (0.35)		$C_{11}H_{13}NO_2$
57	4-C_5H_4N	H	H	C	92	112–114	C	$C_{11}H_{13}NO_2$

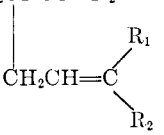
[a] Recrystallization solvent: A, C_6H_{14}; B, C_6H_6–petroleum ether (30–60°); C, Et_2O–C_6H_{14}; D, C_6H_6–C_6H_{14}. [b] All analyses were for C, H or C, H, N when N was present. [c] C: calcd, 77.75; found, 77.28. [d] C: calcd, 61.19; found, 61.68.

Biological Evaluation.—Compounds of the butenylamine and pentenylamine series were screened for their analgetic, anticonvulsant, antihypertensive, and antiinflammatory activities. A summary of the compounds which were active in the preliminary screening tests is shown in Table X.

Compounds **81** and **86** were active in both the analgetic and anticonvulsant tests. Compound **81** (aletamine) also demonstrated weak antiinflammatory and antihypertensive activity but did not meet the activity criteria established for the screening tests.

In general, no significant increase in pharmacological activity was observed for any of the butenylamine or pentenylamine analogs of aletamine; hence, no systematic structure–activity correlations could be derived.

TABLE V
2-SUBSTITUTED 4-PENTENAMIDES



No.	Ar	R_1	R_2	Method	% yield	Mp, °C	RS[b]	Formula[c]
58	C_6H_5	H	H	*a*		72–74		$C_{12}H_{15}NO$
59	4-$CH_3C_6H_4$	H	H	D	73	94–95	A	$C_{13}H_{17}NO$
60	4-*i*-PrC_6H_4	H	H	D	74	54	B	$C_{15}H_{21}NO$
61	4-FC_6H_4	H	H	L	78		C	$C_{12}H_{14}FNO$
62	3-$CF_3C_6H_4$	H	H	D	92	53–55	B	$C_{13}H_{14}F_3NO$
63	2-ClC_6H_4	H	H	L	68	104–106	D	$C_{12}H_{14}ClNO$
64	3,4-$(CH_3O)_2C_6H_3$	H	H	D	80	99–100	E	$C_{14}H_{19}NO_3$
65	3,4,5-$(CH_3O)_3C_6H_2$	H	H	D	75	113–115	F	$C_{15}H_{21}NO_4$
66	3,4-$CH_2O_2C_6H_3$	H	H	L	87	92–93	G	$C_{13}H_{15}NO_3$
67	1-$C_{10}H_7$	H	H	L	97	149–150	H	$C_{16}H_{17}NO$
68	2-CH_3O-1-$C_{10}H_6$	H	H	D	78	135–136	F	$C_{17}H_{19}NO_2$[d]
69	$C_6H_5CH_2CH_2$	H	H	D	86	81–83	B	$C_{14}H_{19}NO$
70	$C_6H_5CH{=}CH$	H	H	D	97	80–81	B	$C_{14}H_{17}NO$
71	C_6H_5	H	CH_3	D	91	95–96	G	$C_{13}H_{17}NO$
72	C_6H_5	CH_3	CH_3	D	96	71–73	G	$C_{14}H_{19}NO$
73	C_6H_5	H	C_6H_5	D	94	117–118	I	$C_{18}H_{19}NO$
74	C_6H_5	H	$CH{=}CHCH_3$	D	60	120–123	A	$C_{15}H_{19}NO$
75	1-$C_{10}H_7$	H	C_6H_5	D	90	176–177	I	$C_{22}H_{21}NO$
76	C_6H_{11}	H	H	L	94	92–94	G	$C_{12}H_{21}NO$
77	2-C_4H_3S	H	H	D	82	89–91	A	$C_{10}H_{13}NOS$
78	3-C_5H_4N	H	H	D	56	103–105	D	$C_{11}H_{14}N_2O$
79	4-C_5H_4N	H	H	D	69	153–154	J	$C_{11}H_{14}N_2O \cdot HCl$

[a] Previously reported: D. D. Micucci, S. Avakian, E. Dietrich, J. M. Beiler, and G. J. Martin, *Exp. Med. Surg.*, 11, 185 (1953). [b] Recrystallization solvent: A, Et_2O; B, C_6H_{14}; C, C_6H_{12}; D, C_6H_6–C_6H_{14}; E, EtOH–Et_2O; F, C_6H_6–petroleum ether (30–60°); G, Et_2O–C_6H_{14}; H, EtOH; I, C_6H_6; J, EtOAc. [c] All analyses were for C, H, N. [d] C: calcd, 75.81; found, 76.48.

Experimental Section

Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. The nmr spectra were run on a Varian A-60 nmr spectrometer using TMS as the internal standard. The ir spectra were obtained with a Perkin-Elmer Model 21 double-beam ir spectrophotometer. 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.

Biological Methods.—All compounds were administered by gavage either as a tragacanth suspension or in aqueous solution. The volume administered was 0.1 ml/10 g of body weight. The screening doses were selected from a preliminary mouse dose-range study and consisted of either the minimal symptomatic dose or a maximal dose of 250 mg/kg *po*.

Analgetic Test.—The phenylquinone writhing test of Hendershot and Forsaith[6] was used. Compounds protecting five or more of ten mice tested from the writhing syndrome were considered active.

Anticonvulsant Test.—The maximal electroshock seizure test of Swinyard, *et al.*,[7] was used. Active compounds were those which protected five or more of ten mice tested from the tonic hind leg extensor component of the seizure pattern.

Antihypertensive Test.—Blood pressure was determined indirectly by a caudal plethysmograph system in rats rendered hypertensive by a modified Grollman[8] technique. Three rats were tested per compound and active compounds were those producing a mean fall in blood pressure of 20% or more.

Antiinflammatory Test.—The method used was that previously described by Goldstein and Schnall.[9] Carrageenin (2%) was injected at the base of a rat's tail and 24 hr later the abscesses were removed and weighed. Five rats were tested per compound and active compounds were those which produced a mean decrease in abscess weight, compared to controls, of 30% or greater.

General Methods for Preparation of Compounds of Tables I–IX. Method A. Ethyl 2-Substituted 2-Allylacetoacetates.—A mixture of 0.1 mole of NaH and 400 ml of C_7H_8 was stirred at 70–80° while a solution of 0.1 mole of ethyl 2-allylacetoacetate in 30 ml of C_7H_8 was added, dropwise, during a 15-min period. The reaction mixture was refluxed 1 hr and cooled to 75°, and 0.1 mole of the appropriate chloro compound dissolved in 80 ml of C_7H_8 was added during a 15-min period. The mixture was refluxed 6 hr, cooled, and filtered through Celite, and the filtrate was washed with H_2O. The C_7H_8 solution was dried (Na_2SO_4) and concentrated, and the residue was distilled.

Method B. Ethyl 2-Substituted 4-Pentenoates.—A mixture of 0.5 mole of NaOEt, 500 ml of EtOH, and 0.5 mole of the ethyl 2-substituted 2-allylacetoacetate was refluxed 6–8 hr. The EtOH was removed, 500 ml of H_2O was added, and the oily product was extracted with Et_2O. The Et_2O solution was dried (Na_2SO_4) and concentrated, and the residue was distilled.

Method C. 2-Substituted 4-Pentenoic Acids.—A mixture of 0.5 mole of the ester, 1.5 moles of KOH, 500 ml of H_2O, and 500 ml of EtOH was refluxed 4–6 hr. The reaction mixture was concentrated, and the residue was dissolved in H_2O, cooled, and acidified with HCl. The product was extracted with Et_2O or C_6H_6 and dried (Na_2SO_4), the solution was concentrated, and the residue was either distilled or crystallized.

Compounds **35** and **45** were obtained directly from the keto esters **2** and **7** in this procedure.

Method D. 2-Substituted 4-Pentenamides.—To a solution of 0.1 mole of ethyl chloroformate in 100 ml of $CHCl_3$ maintained at −30° was added a cold solution of 0.1 mole of the acid and 0.1 mole of Et_3N in 100 ml of $CHCl_3$ during a 40-min period. The reaction mixture was stirred an additional 1.5 hr at −20 to 5°, and NH_3 was bubbled through the cold mixture for 20 min. After stirring an additional 30 min at 25°, the mixture was filtered and the solid was extracted with $CHCl_3$. The $CHCl_3$ extract was combined with the filtrate and washed twice with cold 5% NaOH solution, then with H_2O. The dried solution was concentrated and the residue was recrystallized from the appropriate solvent.

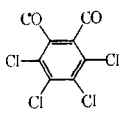
(6) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1961).
(7) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *ibid.*, **106**, 319 (1952).
(8) A. Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944).
(9) S. Goldstein and M. Schnall, *Arch. Int. Pharmacodyn. Ther.*, **144**, 269 (1963).

Table VI

1-Benzyl-3-butenylamines

$C_6H_5CH_2CHNR_1R_2$

$CH_2CH{=}CH_2$

No.	R_1	R_2	Method	% yield	Bp (mm) or mp, °C	RS[a]	Formula[b]
80	H	H	E	62	60–62 (0.3)		$C_{11}H_{15}N$
81[c]	H	H			159–161	A	$C_{11}H_{15}N\cdot HCl$
82	H	CH_3	H	70	54–57 (0.1)		$C_{12}H_{17}N$
83	H	CH_3			104–106	B	$C_{12}H_{17}N\cdot HCl$
84	H	C_2H_5	H	80	107–108	C	$C_{13}H_{19}N\cdot HCl$
85	H	n-C_3H_7	H	46	110–112	D	$C_{14}H_{21}N\cdot HCl$
86	$(CH_3)_2C{=}$			86	70 (0.2)		$C_{14}H_{19}N$
87	H	i-C_3H_7		58	110–114	E	$C_{14}H_{21}N\cdot HCl$
88	H	$HC{\equiv}CCH_2$		25	79–84 (0.1)		$C_{14}H_{17}N$
89	H	$HC{\equiv}CCH_2$			104–105		$C_{14}H_{17}N\cdot HCl$
90	H	$C_6H_5CH_2$	H	32	121–124	A	$C_{18}H_{21}N\cdot HCl$[d]
91	H	$C_6H_5CH_2CH_2$	H	26	154–157		$C_{19}H_{23}N\cdot HCl$
92	H	$HO(CH_2)_3$	H	81	150–151	G	$(C_{14}H_{21}NO_2)_2\cdot C_4H_4O_4$[e]
93	H	$CH_3O_2CCH_2CH_2$		73	123 (0.05)		$C_{15}H_{21}NO_2$
94	$CH_3O_2CCH_2CH_2$	$CH_3O_2CCH_2CH_2$		11	174 (0.03)		$C_{19}H_{27}NO_4$
95	CH_3	CH_3	H	90	69–71 (0.2)		$C_{13}H_{19}N$
96	CH_3	CH_3			123–126	B	$C_{13}H_{19}N\cdot HCl$
97	CH_3	$CO_2C_2H_5$	I	81	105 (0.1)		$C_{15}H_{21}NO_2$
98	C_2H_5	$HO(CH_2)_3$	H	79	114–115 (0.05)		$C_{16}H_{25}NO$
99	H			62	133–136		$C_{14}H_{18}N_2O$
100	CH_3			69	112–114 (0.1)		$C_{15}H_{20}N_2O$
101	H	$CO_2C_2H_5$	I	90	117–120 (0.3)		$C_{14}H_{19}NO_2$
102	H	$COCH_3$		78	60–61	E	$C_{13}H_{17}NO$
103	H	$COCH{=}CH_2$	I	68	57–62		$C_{14}H_{17}NO$
					134–137 (0.7)		
104	H	$CO(CH_2)_3CH_3$	I		138–140 (0.3)		$C_{16}H_{23}NO$
105	H	$COCH_2CH_2COOH$		83	121–123	G	$C_{15}H_{19}NO_3$[f]
106	H	$COCH_2CH(C_6H_5)_2$		86	100–102	H	$C_{26}H_{27}NO$
107	H	CO-3,4,5-$(CH_3O)_3C_6H_2$	I	62	157–168	I	$C_{21}H_{25}NO_4$
108	H	CO-3-C_5H_4N	I		74–75		$C_{17}H_{18}N_2O$
109	$CH_3O_2CCH_2CH_2$	$COCH_2N(CH_2)_5$		36	195–197 (0.05)		$C_{22}H_{32}N_2O_3$
110	H	CO-2-$CO_2CH_3C_6H_4$	I	36	108–109	H	$C_{20}H_{21}NO_3$
111	H	$CONH_2$		90	88–90	J	$C_{12}H_{16}N_2O$
112	H	$CONHC_6H_5$		86	124–127	K	$C_{18}H_{20}N_2O$
113	H	$CON(CH_3)_2$	I	91	82–84	L	$C_{14}H_{20}N_2O$
114	H	$CSNHC_6H_5$		77	86–88	K	$C_{18}H_{20}N_2S$
115	H	$C(=NH)N(CH_3)_2$		34	153–155	M	$C_{14}H_{21}N_3\cdot HCl$
116		$COCH_2CH_2CO$		77	133–135 (0.1)		$C_{15}H_{17}NO_2$
117		$CH_2CH_2CH_2CH_2$	H	58	73–74	D	$C_{15}H_{21}N\cdot C_5H_8O_7$[g]
118			75		120–121	G	$C_{19}H_{13}Cl_4NO_2$

[a] Recrystallization solvent: A, EtOH–Et_2O; B, C_6H_6–C_6H_{12}; C, EtCOMe; D, n-PrOH–Et_2O; E, Et_2O–C_6H_{14}; F, MeCN; G, i-PrOH; H, C_6H_6–C_6H_{14}; I, EtOAc; J, Et_3N; K, MeOH; L, Skellysolve B; M, MeOH–Et_2O. [b] All analyses were for C, H, N. [c] Previously reported in ref 3. [d] C: calcd, 75.11; found, 75.61. [e] Fumarate salt. [f] C: calcd, 68.97; found, 69.50. [g] Citrate salt.

Method E. 1-Substituted 3-Butenylamines.—A stirred solution of 0.1 mole of NaOH in 100 ml of H_2O was cooled to −5° and Br_2 (0.04 mole) was added during a 5-min period. After the reaction mixture was stirred 30 min at 0°, the solid amide (0.02 mole) was added and stirring was continued 1.5 hr at 0–5°. The temperature was allowed to gradually increase to 25°, and stirring was continued 16 hr. The mixture was heated at 35° for 1 hr, cooled, and extracted with Et_2O. The Et_2O solution was dried (Na_2SO_4) and concentrated, and the residue was distilled or converted to the hydrochloride salt in Et_2O.

In those cases in which the amide contained one or more methoxy groups on the C_6H_6 ring, it was generally necessary to heat the mixture at 50–70° for 1 hr, after the temperature of the reaction mixture had reached 25°.

Method F. N-Carbomethoxy-1-substituted 3-Butenylamines and 1-Substituted 3-Butenylamines.—A solution of 0.1 mole of the required amide in 300 ml of MeOH was treated in a dropwise manner with a solution of NaOCl prepared from 0.37 mole of NaOH, 0.24 mole of Cl_2, and 120 ml of ice–H_2O. The mixture was refluxed 1 hr and concentrated *in vacuo* to remove MeOH. The residue was extracted with Et_2O, and the Et_2O solution was washed with dilute HCl and then with H_2O. The dried Et_2O solution was concentrated and the residue was recrystallized from the appropriate solvent.

Compounds **120**, **126**, and **142** were isolated from the HCl extract above by making it basic with Na_2CO_3 and extraction with Et_2O. The dried Et_2O extract was acidified with dry HCl to precipitate the hydrochloride salts.

Method G. 1-Substituted 3-Butenylamines.—A mixture of 0.2 mole of the carbamate and 250 ml of 40% NaOH solution was refluxed 2 hr. The reaction mixture was steam distilled and the amine was extracted from the distillate with Et_2O. The

Table VII
1-Substituted Benzyl-3-butenylamines

$$RC_6H_4CH_2CHNR_2R_3$$
$$|$$
$$CH_2CH{=}CH_2$$

No.	R_1	R_2	R_3	Method	% yield	Bp (mm) or mp, °C	RS[a]	Formula[b]
119	4-CH_3	H	H	E	26	161–163	A	$C_{12}H_{17}N\cdot HCl$
120	4-F	H	H	F	14	144–146		$C_{11}H_{14}FN\cdot HCl$
121	4-F	H	CO_2CH_3	F	41	116–119 (0.3)		$C_{13}H_{16}FNO_2$
122	3-CF_3	H	H	E	30	146–148	A	$C_{12}H_{14}F_3N\cdot HCl$
123	4-Cl	H	H	E	41	188–190	A	$C_{11}H_{14}ClN\cdot HCl$
124	4-Cl	H	CH_3	H	81	128–130	A	$C_{12}H_{16}ClN\cdot HCl$
125	4-Cl	H	CO_2CH_3	F	61	57	B	$C_{13}H_{16}ClNO_2$
126	2-Cl	H	H	F	18	129–132		$C_{11}H_{14}ClN\cdot HCl$
127	2-Cl	H	CO_2CH_3	F	42	46–50		$C_{13}H_{16}ClNO_2$
128	4-CH_3O	H	H	E	50	141–143	A	$C_{12}H_{17}NO\cdot HCl$
129	3-CH_3O	H	H	E	34	102–104		$C_{12}H_{17}NO\cdot HCl$
130	3-CH_3O	H	CH_3	H	74	108–110	C	$C_{13}H_{19}NO\cdot HCl$
131	2-CH_3O	H	H	E	46	122–123		$C_{12}H_{17}NO\cdot HCl$
132	2-CH_3O	H	CH_3	H	88	109–111	D	$C_{13}H_{19}NO\cdot HCl$
133	2-CH_3O	H	$CO_2C_2H_5$	I	76	127–130 (0.2)		$C_{15}H_{21}NO_3$
134	2-CH_3O	CH_3	$COCH_2Cl$	I	68	150–155		$C_{15}H_{20}ClNO_2$
135	3,4-$(CH_3O)_2$	H	H	E	70	165–166	E	$C_{13}H_{19}NO_2\cdot HCl$
136	2,6-$(CH_3O)_2$	H	H	E	62	219–220	F	$C_{13}H_{19}NO_2\cdot HCl$
137	2,6-$(CH_3O)_2$	H	CH_3	H	67	126–128	A	$C_{14}H_{21}NO_2\cdot HCl$
138	3,5-$(CH_3O)_2$	H	CH_3	H	74	133–134	D	$C_{14}H_{21}NO_2\cdot HCl$
139	3,5-$(CH_3O)_2$	H	CO_2CH_3	F	72	58–60	G	$C_{15}H_{21}NO_4$
140	3,4,5-$(CH_3O)_3$	H	H	E	80	212–213	E	$C_{14}H_{21}NO_3\cdot HCl$
141	3,4-(CH_2O_2)	H	H	E	35	142–143	H	$C_{12}H_{15}NO_2\cdot HCl$
142	4-CH_3O-3,5-Cl_2	H	H	F	13	196–198	F	$C_{12}H_{15}Cl_2NO\cdot HCl$[c]
143	4-CH_3O-3,5-Cl_2	H	CO_2CH_3	F	53	86–87	G	$C_{14}H_{17}Cl_2NO_3$[d]
144	3,4-$(CH_3)_2$	H	CH_3	H	32	139–141	I	$C_{14}H_{21}N\cdot HCl$
145	3,4-$(CH_3)_2$	H	CO_2CH_3	F	80	132–136		$C_{15}H_{21}NO_2$

[a] Recrystallization solvent: A, EtOH–Et_2O; B, C_6H_{14}; C, *i*-PrOH–Et_2O; D, EtCOMe; E, EtOH; F, *i*-PrOH; G, Et_2O; H, MeCN; I, Me_2CO. [b] All analyses were for C, H, N. [c] C: calcd, 48.59; found; 49.10. [d] C: calcd, 52.85; found, 53.33.

Table VIII
1-Substituted 3-Butenylamines

$$ArCH_2CHNHR_1$$
$$|$$
$$CH_2CH{=}CR_2R_3$$

No.	Ar	R_1	R_2	R_3	Method	% yield	Bp (mm) or mp, °C	RS[a]	Formula[b]
146	C_6H_5	H	H	CH_3	E	26	140–142	A	$C_{12}H_{17}N\cdot HCl$
147	C_6H_5	CH_3	H	CH_3	H	58	146–147	B	$C_{13}H_{19}N\cdot HCl$
148	C_6H_5	H	H	C_6H_5	G	45	191–192	A	$C_{17}H_{19}N\cdot HCl$
149	C_6H_5	CO_2CH_3	H	C_6H_5	F	57	80–82	C	$C_{19}H_{21}NO_2$
150	C_6H_5	H	CH_3	CH_3	G	82	109–111	C	$C_{13}H_{19}N\cdot HCl$
151	C_6H_5	CO_2CH_3	H	$CH{=}CHCH_3$	F		48–54 138 (0.05)		$C_{16}H_{21}NO_2$
152	$C_6H_5CH_2$	H	H	H	G	79	141–146	B	$C_{12}H_{17}N\cdot HCl$[c]
153	$C_6H_5CH_2$	CO_2CH_3	H	H	F	65	104 (0.05)		$C_{14}H_{19}NO_2$
154	$C_6H_5CH_2CH_2$	H	H	H	G	24	117–118	B	$C_{13}H_{19}N\cdot HCl$
155	$C_6H_5CH{=}CH$	H	H	H	G	83	188–190	A	$C_{13}H_{17}N\cdot HCl$
156	$C_6H_5CH{=}CH$	CO_2CH_3	H	H	F	61	40–42		$C_{15}H_{19}NO_2$
157	1-$C_{10}H_7$	H	H	H	G	30	230–231	B	$C_{15}H_{17}N\cdot HCl$
158	1-$C_{10}H_7$	CH_3	H	H	H	34	131–133	B	$C_{16}H_{19}N\cdot HCl$
159	1-$C_{10}H_7$	CO_2CH_3	H	H	F	59	84–85	C	$C_{17}H_{19}NO_2$
160	1-$C_{10}H_7$	CO_2CH_3	H	C_6H_5	F	18	125–129	D	$C_{23}H_{23}NO_2$
161	2-CH_3O-1-$C_{10}H_6$	H	H	H	E	23	165–166	B	$C_{16}H_{19}NO\cdot C_6H_8O_7$[d]
162	C_6H_{11}	H	H	H	E	35	118–119	E	$C_{11}H_{21}N\cdot HCl$
163	2-C_4H_3S	H	H	H	E	41	121–123	B	$C_9H_{13}NS\cdot HCl$
164	3-C_5H_4N	H	H	H	G	27	178–180	A	$C_{10}H_{14}N_2\cdot 2HCl$
165	4-C_5H_4N	H	H	H	E		187–190	F	$C_{10}H_{14}N_2\cdot 2HCl$[e]

[a] Recrystallization solvent: A, MeCN; B, EtOH–Et_2O; C, C_6H_{14}; D, MeOH; E, EtOAc; F, MeOH–Me_2CO. [b] All analyses were for C, H, N. [c] C: calcd, 68.07; found, 67.55. [d] Citrate salt. [e] C: calcd, 51.07; found, 51.69.

Et_2O solution was dried over Na_2SO_4 and acidified with dry HCl to precipitate the hydrochloride salt.

Method H. 1-Substituted 3-Butenylamines and 2-Substituted 4-Pentenylamines.—To a stirred mixture of 0.2 mole of $LiAlH_4$ and 400 ml of THF was added, dropwise, a solution of 0.1 mole of the required amide or carbamate in THF. The reaction mixture was refluxed 6–8 hr and cooled, and, in turn, 10 ml of 10% NaOH solution, 10 ml of saturated Na_2SO_4 solution, and 30 g of Na_2SO_4 were added. The mixture was refluxed 30 min and filtered, the solid was washed with THF, then with Et_2O, and the filtrate

Table IX

2-Substituted 4-Pentenylamines

$$\begin{array}{l} ArCH_2CHCH_2NHR_1 \\ | \\ CH_2CH{=}CR_2R_3 \end{array}$$

No.	Ar	R_1	R_2	R_3	Method	% yield	Bp (mm) or mp, °C	RS[a]	Formula[b]
166	C_6H_5	H	H	H	H	96	128–129	A	$C_{12}H_{17}N \cdot HCl$
167	C_6H_5	$CO_2C_2H_5$	H	H	I	70	131–132 (0.2)		$C_{15}H_{21}NO_2$
168	C_6H_5	H	H	C_6H_5	H	84	80–85	B	$C_{18}H_{21}N \cdot HCl$[c]
169	4-$CH_3C_6H_4$	H	H	H	H	90	85–87 (0.3)		$C_{13}H_{19}N$[d]
170	4-$CH_3OC_6H_4$	H	H	H	H	83	86–87	A	$C_{13}H_{19}NO \cdot HCl$
171	2-$CH_3OC_6H_4$	H	H	H	H	82	90–95 (0.2)		$C_{13}H_{19}NO$
172	2-$CH_3OC_6H_4$	CH_3	H	H	H	90	105–109 (0.6)		$C_{14}H_{21}NO$
173	2-$CH_3OC_6H_4$	$CO_2C_2H_5$	H	H	I	78	133–136 (0.2)		$C_{16}H_{23}NO_3$[e]
174	3,4-$(CH_3O)_2C_6H_3$	H	H	H	H	55	107–109	A	$C_{14}H_{21}NO_2 \cdot HCl$
175	2,6-$(CH_3O)_2C_6H_3$	H	H	H	H	79	120–124 (0.3)		$C_{14}H_{21}NO_2$[f]
176	3,4,5-$(CH_3O)_3C_6H_2$	H	H	H	H	49	71–73	A	$C_{15}H_{23}NO_3 \cdot HCl$
177	3,4-$CH_2O_2C_6H_3$	H	H	H	H	90	99–102	A	$C_{13}H_{17}NO_2 \cdot HCl$
178	$C_6H_5CH_2CH_2$	H	H	H	H	92	97–98 (0.3)		$C_{14}H_{21}N$[g]
179	$C_6H_5CH_2CH_2$	$CO_2C_2H_5$	H	H	I	74	146–147 (0.05)		$C_{17}H_{25}NO_2$
180	1-$C_{10}H_7$	H	H	H	H	44	156–157	A	$C_{16}H_{19}N \cdot HCl$
181	2-CH_3O-1-$C_{10}H_6$	H	H	H	H	63	120–121	A	$C_{15}H_{21}NO \cdot C_4H_4O_4$[h]
182	C_6H_{11}	H	H	H	H	72	65 (0.2)		$C_{12}H_{23}N$

[a] Recrystallization solvent: A, EtOH–Et_2O; B, MeOH–Et_2O. [b] All analyses were for C, H, N. [c] C: calcd, 75.09; found, 74.40. H: calcd, 7.70; found, 8.28, very hygroscopic. [d] C: calcd, 82.48; found, 82.01. [e] C: calcd, 69.29; found, 69.77. [f] C: calcd, 71.46; found, 70.79. [g] C: calcd, 82.71; found, 81.98. [h] Maleate salt.

Table X

Test	Active compounds
Analgetic	81, 83, 86, 92, 96, 117, 123, 142, 147, 152, 166, 171, 175
Anticonvulsant	81, 86, 101, 156, 157
Antihypertensive	58, 67, 101, 140, 167, 175
Antiinflammatory	58, 83, 107, 108, 138, 152

was concentrated. The residue was extracted with Et_2O and the Et_2O solution was dried (Na_2SO_4). After removal of the Et_2O, the product was purified by distillation or converted to the hydrochloride in Et_2O.

Compound 84.—The amide employed was 1-benzyl-N-acetyl-3-butenylamine (**102**) and the reaction mixture was refluxed 20 hr; bp 67° (0.1 mm).

Compound 85.—The amide employed was 1-benzyl-N-acryloyl-3-butenylamine (**103**) in a 1:4 molar ratio to $LiAlH_4$; bp 70° (0.1 mm).

Compound 92.—The amide employed was 1-benzyl-N-(2-carbomethoxyethyl)-3-butenylamine (**93**) in a 1:4 molar ratio to $LiAlH_4$ and the mixture was refluxed 24 hr; bp 117° (0.025 mm). The fumarate salt was prepared by dissolving equivalent amounts of the base and fumaric acid in EtOH, followed by the addition of ether to precipitate the salt.

Compound 98.—The amide employed was 1-benzyl-N-acetyl-N-(3-acetoxypropyl)-3-butenylamine and the mixture was refluxed 18 hr.

Compound 117.—The amide was N-(5-benzyl-1-buten-4-yl)-succinimide (**116**) in a 1:5 molar ratio to $LiAlH_4$. The mixture was refluxed 16 hr; bp 80–86° (0.1 mm). The citrate salt was prepared in *i*-PrOH–Et_2O from equimolar amounts of the base and citric acid.

Method I. N-Acyl-1-substituted 3-Butenylamines.—A mixture of 0.03 mole of the appropriate amine, 0.03 mole of Et_3N, and 200 ml of Et_2O or C_6H_6 was cooled and stirred while the acid chloride (0.03 mole) was added dropwise. The reaction mixture was then stirred at 25° for 5 hr and filtered, and the filtrate was washed with 10% HCl, 10% KOH solution, and then with H_2O. The filtrate was dried ($MgSO_4$) and concentrated and the residue either was distilled or recrystallized.

Method J. Diethyl 2-Substituted 2-Allylmalonates.—A solution of NaOEt, prepared from 2 g-atoms of Na and 1 l. of EtOH, was treated with 2.0 moles of the 2-substituted diethyl malonate during a 2-hr period. The reaction mixture was refluxed 2 hr and cooled and the required bromo- or chloropropene was added during a 2-hr period. After refluxing 6–8 hr, the mixture was concentrated and the residue was mixed with 800 ml of H_2O and 800 ml of Et_2O. The Et_2O layer was separated, dried over $MgSO_4$, and concentrated, and the residue was distilled.

Compound **19** was prepared from diethyl malonate and 3-chloro-1-phenylpropene using this procedure.

Method K. 2-Substituted 4-Pentenoic Acids.—The procedure was similar to method C except 3.5 moles of KOH was used and the mixture was refluxed 24 hr. The residue obtained was heated at 160–180° for 2–3 hr. The product was purified by distillation or crystallization.

Method L. 2-Substituted 4-Pentenamides.—A mixture of 0.05 mole of the acid and 20 ml of $SOCl_2$ was refluxed 2 hr. $SOCl_2$ was removed and the acid chloride was distilled. NH_3 was bubbled through benzene at 5–15° while the acid chloride in C_6H_6 solution was added dropwise. The reaction mixture was stirred 1 hr at 25°, and the product was filtered and washed with H_2O.

In one instance (**64**), the acid chloride was poured into cold NH_4OH solution with stirring and the product was filtered.

Method M. Ethyl 2-Substituted 4-Pentenoates.—A mixture of 0.1 mole of the acid, 40 ml of EtOH, 200 ml of $CHCl_3$, and 0.5 g of *p*-TsOH was refluxed 16 hr in a flask fitted with a Hercules trap. After the theoretical amount of H_2O had been collected, the mixture was concentrated. The residual oil was dissolved in Et_2O and washed with 10% NaOH solution and then with H_2O. The Et_2O solution was dried (K_2CO_3) and concentrated and the ester was purified by distillation.

1-Benzyl-N-acetyl-3-butenylamine (102).—1-Benzyl-3-butenylamine (**80**) (10 g, 0.06 mole) was added dropwise to 20 ml of Ac_2O with stirring. After the addition was complete, stirring was continued for 15 min, and the mixture was poured into ice. The C_6H_6 extract was dried (Na_2SO_4) and concentrated and the residue was crystallized from Et_2O–C_7H_{16} solution.

1-Benzyl-N-(2-propynyl)-3-butenylamine Hydrochloride (89).—A mixture of 40.3 g (0.25 mole) of 1-benzyl-3-butenylamine (**80**), 40.5 g (0.40 mole) of Et_3N, and 100 ml of DMSO was stirred during a 75-min period while 35.7 g (0.3 mole) of propargyl bromide was added. After the addition was complete, the mixture was stirred 30 min at room temperature and 30 min at 95° and mixed with ice and the mixture was extracted with Et_2O. The Et_2O solution was extracted with 10% HCl, the extract was made basic with 50% NaOH solution, and the basic solution was extracted with Et_2O. After drying ($MgSO_4$), the Et_2O was removed and the residue (**88**) distilled; $n^{21}D$ 1.5277.

The hydrochloride was prepared in *i*-PrOH–Et_2O.

1-Benzyl-N-isopropylidene-3-butenylamine (86).—A mixture of 24 g (0.15 mole) of 1-benzyl-3-butenylamine (**80**), 50 ml of Me_2CO,

and 250 ml of $CHCl_3$ was refluxed 18 hr during which time H_2O was removed from the reaction mixture by the use of an attached Hercules trap. After concentration, the residual oil was distilled.

1-Benzyl-N-isopropyl-3-butenylamine Hydrochloride (87).—To a stirred mixture of 7 g (0.16 mole) of $LiAlH_4$ and 300 ml of Et_2O, maintained at 5–10°, was added a solution of 26 g (0.13 mole) of 1-benzyl-N-isopropylidene-3-butenylamine (**86**) in 120 ml of Et_2O during a 2-hr period. The reaction mixture was stirred 48 hr at room temperature, ice–H_2O and 10% NaOH solution in turn were added, the mixture was filtered, and the filtrate was dried with Na_2SO_4. After removal of the Et_2O, the residual oil was distilled, yield 15.3 g (58%), bp 65–80° (0.2 mm). The product was dissolved in Et_2O and acidified with dry HCl and the precipitated salt was filtered.

1-Benzyl-N-(β-phenethyl)-3-butenylamine Hydrochloride (91).—The procedure was identical with the preceding experiment. In this instance the amide was crude 1-benzyl-N-phenacyl-3-butenylamine, prepared by method I.

1-Benzyl-N-(2-carbomethoxyethyl)-3-butenylamine (93) and 1-Benzyl-N,N-bis(2-carbomethoxyethyl)-3-butenylamine (94).—A solution of 433 g (3.0 mole) of 1-benzyl-3-butenylamine (**80**) in 600 ml of MeOH was maintained at 0–5° while 750 g (8.7 moles) of methyl acrylate was added during a 1-hr period. The reaction mixture was allowed to remain at room temperature for 1 week and concentrated and the residue was distilled, yield 540 g (73%), bp 140–146° (0.15 mm). The bis addition product (**94**) was obtained as a higher boiling fraction.

1-Benzyl-N-(2-carbomethoxyethyl)-N-piperidinoacetyl-3-butenylamine (109).—A mixture of 75 g (0.3 mole) of 1-benzyl-N-(2-carbomethoxyethyl)-3-butenylamine (**93**), 30 g (0.3 mole) of Et_3N, and 400 ml of C_6H_6 was maintained at 5° during a 1-hr period while a solution of 35 g (0.3 mole) of chloroacetyl chloride in 100 ml of C_6H_6 was added. The mixture was stirred 1 hr at room temperature and filtered. The C_6H_6 solution was added dropwise during a 2-hr period to a solution of 51 g (0.6 mole) of piperidine in 200 ml of Me_2CO and the reaction mixture was refluxed 24 hr. After concentration, the residue was mixed with 1 l. of C_6H_6 and extracted with four 500-ml portions of H_2O. The C_6H_6 solution was dried (Na_2SO_4) and concentrated and the residue distilled.

1-Benzyl-N-acetyl-N-(3-acetoxypropyl)-3-butenylamine.—A mixture of 21.9 g (0.1 mole) of 1-benzyl-N-(3-hydroxypropyl)-3-butenylamine (**92** base), 25 g (0.25 mole) of Et_3N, and 400 ml of $CHCl_3$ was stirred, maintained at 0°, and treated with a solution of 40 g (0.51 mole) of AcCl in 50 ml of $CHCl_3$ during a 1-hr period. The reaction mixture was refluxed 1 hr, cooled, and extracted in turn with 100 ml of H_2O, 100 ml of 10% HCl, 100 ml of 10% NaOH, and 100 ml of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated, and the oil distilled; yield 28 g (92%), bp 170° (0.05 mm). *Anal.* Calcd for $C_{18}H_{25}NO_3$: N, 4.62. Found: N, 5.21.

1-Benzyl-N-(3,3-diphenylpropionyl)-3-butenylamine (106).—The mixed anhydride of 3,3-diphenylpropionic acid was prepared by method D and allowed to react with an equimolar amount of 1-benzyl-3-butenylamine (**80**). The mixture was extracted with H_2O, 10% HCl, and H_2O. The dried $CHCl_3$ solution was concentrated and the residue crystallized from Et_2O.

1-Benzyl-N-methyl-N-(2-oxazolinyl)-3-butenylamine (100).—A mixture of 15 g (0.053 mole) of 1-benzyl-N-methyl-N-(2-chloroethylcarbamoyl)-3-butenylamine, 50 ml of Me_2CO, and 500 ml of H_2O was refluxed 15 min, cooled, and made basic with 50% NaOH and the oil was extracted with Et_2O. The Et_2O solution was dried and concentrated and the residue was distilled, $n^{24}D$ 1.5379.

1-Benzyl-N-(2-oxazolinyl)-3-butenylamine (99).—1-Benzyl-N-(2-chloroethylcarbamoyl)-3-butenylamine (15 g, 0.056 mole) was employed in the preceding procedure and the product was distilled, $n^{26}D$ 1.5487.

N-(5-Phenyl-1-penten-4-yl)-3,4,5,6-tetrachlorophthalimide (118).—A mixture of 23 g (0.14 mole) of 1-benzyl-3-butenylamine (**80**), 40.9 g (0.14 mole) of 3,4,5,6-tetrachlorophthalic anhydride, and 150 ml of xylene was stirred and refluxed in a flask with a Dean–Stark trap attached. After a 4-hr period, the theoretical amount of H_2O had been collected and the reaction mixture was concentrated.

1-Benzyl-N-succinoyl-3-butenylamine (105).—A mixture of 16.6 g (0.17 mole) of succinic anhydride, 25 g (0.17 mole) of 1-benzyl-3-butenylamine (**80**), and 400 ml of xylene was employed in the preceding procedure. In this instance, H_2O did not collect in the trap.

N-(5-Phenyl-1-penten-4-yl)succinimide (116).—A mixture of 20 g (0.08 mole) of 1-benzyl-N-succinoyl-3-butenylamine (**105**) and 250 ml of Ac_2O was refluxed 3 hr. The reaction mixture was concentrated and the oily residue was distilled.

N-(5-Phenyl-1-penten-4-yl)urea (111).—A solution of 8 g (0.1 mole) of KOCN in 50 ml of H_2O was added dropwise to a stirred solution of 19 g (0.1 mole) of 1-benzyl-3-butenylamine hydrochloride (**81**) in 100 ml of H_2O. The reaction mixture was stirred for 75 min, cooled, and filtered; yield 18 g (90%), mp 76–84°. After two recrystallizations from Et_3N, there was obtained 16.5 g (81%), mp 88–90°.

N-Phenyl-N'-(5-phenyl-1-penten-4-yl)urea (112).—A solution of 16 g (0.1 mole) of 1-benzyl-3-butenylamine (**80**) in 70 ml of EtOH was stirred while 12 g (0.1 mole) of phenyl isocyanate was added, dropwise. After the addition, the reaction mixture was allowed to remain at room temperature for 16 hr. The mixture was cooled and filtered; yield 26 g, mp 109–114°. After recrystallization from MeOH there was obtained 24 g (86%), mp 124–127°.

N-Phenyl-N'-(5-phenyl-1-penten-4-yl)thiourea (114).—The reaction was carried out as in the preceding example using phenyl isothiocyanate in place of phenyl isocyanate.

N,N-Dimethyl-N'-(5-phenyl-1-penten-4-yl)guanidine Hydrochloride (115).—A mixture of 19.7 g (0.1 mole) of 1-benzyl-3-butenylamine hydrochloride (**81**), 16.1 g (0.1 mole) of 1-benzyl-3-butenylamine (**80**), 7.0 g (0.1 mole) of $(CH_3)_2NCN$, and 70 ml of *n*-BuOH was refluxed 8 hr. The reaction mixture was concentrated and the residual oil crystallized from Me_2CO–petroleum ether (30–60°).

2-Benzyl-4-pentenonitrile.—A mixture of 189 g (1.0 mole) of 2-benzyl-4-pentenamide (**58**), 500 ml of C_6H_6, and 110 ml of $SOCl_2$ was refluxed 4.5 hr. The reaction mixture was poured into ice and made basic with 50% NaOH, the C_6H_6 layer was dried and concentrated, and the residual oil was distilled; yield 136 g (80%), bp 86–88° (0.3 mm). *Anal.* ($C_{12}H_{13}N$) C, H, N.

2-Benzyl-4-pentenamidine Hydrochloride.—Cold MeOH (80 ml) was saturated with dry HCl, mixed with 15 g (0.09 mole) of 2-benzyl-4-pentenonitrile, and stored in a stoppered bottle at room temperature for 24 hr. The reaction mixture was concentrated, and the oily residue was dissolved in 80 ml of MeOH and saturated with NH_3. After remaining at room temperature for 48 hr in a pressure bottle, the mixture was heated at 55° for 7 hr and concentrated to one-half volume. The solution was diluted with Et_2O, and the precipitate was filtered and recrystallized in turn from H_2O and EtOH–Et_2O; yield 8.6 g (44%), mp 163–164°. *Anal.* ($C_{12}H_{16}N_2 \cdot HCl$) C, H, N.

2-Benzyl-4-pentenamidoxime Hydrochloride.—A mixture of 85.6 g (0.5 mole) of 2-benzyl-4-pentenonitrile, 86.9 g (1.25 moles) of $NH_2OH \cdot HCl$, 53 g (0.5 mole) of Na_2CO_3, 600 ml of EtOH, and 500 ml of H_2O was stirred and heated at 70–80° for 23 hr. The reaction mixture was concentrated and the residue was dried by azeotropic distillation with C_6H_6. The residue was converted to the hydrochloride in ether. The product was recrystallized from *i*-PrOH–Et_2O; yield 54 g (45%), mp 145–146°. *Anal.* ($C_{12}H_{16}N_2O \cdot HCl$) H, N; C: calcd, 59.87; found, 60.37.

2-Amino-4-methyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene Hydrobromide.—A mixture of 26.7 g (0.14 mole) of 1-(4-methoxybenzyl)-3-butenylamine (**128** base) and 50 ml of 48% HBr was refluxed 2 hr. The mixture was concentrated *in vacuo* and the residue was mixed with C_6H_6 three times followed by concentration *in vacuo*. The residue was dissolved in EtOH, cooled, and filtered; after recrystallization from *i*-PrOH, mp 265–267°; yield 20.4 g (56%); λ_{max}^{Nujol} 3.1 (OH), 11.6, 12.3 μ (1,2,4-substituted benzene); nmr, doublet 1.27 (3 H, CH_3) (J = 6.5 cps), multiplet 6.8 ppm (3 H, 1,2,4-substitutedben zene). *Anal.* ($C_{11}H_{15}NO \cdot HBr$) C, H, N.

β-(*p*-Nitrobenzyl)-δ-hydroxyvaleric Acid Lactone.—A mixture of 20 g (0.076 mole) of ethyl 2-(4-nitrobenzyl)-4-pentenoate (**23**) and 150 ml of concentrated HCl was refluxed 18 hr. The oil was separated, washed with H_2O, and triturated with Et_2O whereupon it solidified. After three recrystallizations from C_6H_6–C_6H_{14} the product melted at 123–125°; yield 8.5 g (47%); λ_{Max}^{KBr} 5.7 μ (γ-lactone C=O); nmr, doublet 1.47 ppm (3 H, CH_3) (J = 6.5 cps). *Anal.* ($C_{12}H_{13}NO_4$) C, H, N.

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