propyl)acridan (19 g) was dissolved in 100 ml of EtOH. After the addition of 14 g of 4-carbamoyl-4-piperidinopiperidine and 19 g of K_2CO_3, the mixture was refluxed on a steam bath for 48 hr. EtOH was removed under vacuum, the residue was dissolved in C_6H_6 and treated with EtOH–HCl. The pptd crystals were collected. Recrystallization from MeOH–H_2O yielded 16.6 g (46%) of material, mp 263–265°. *Anal.* ($C_{29}H_{34}Cl_2N_4O \cdot 0.25H_2O$) C, H, N.

5-[3-(4-Hydroxy-4-*p*-methoxyphenylpiperidino)propyl]-5*H*-dibenzo[*b*,*f*]azepine Hydrochloride (47).—A 14.5-g sample of 5-[3-(4-oxopiperidino)propyl]-5*H*-dibenzo[*b*,*f*]azepine was added to a solution of *p*-$MeOC_6H_4MgBr$ (prepared from 15.5 g of *p*-$MeOC_6H_4Br$ and 2.2 g of Mg in 100 ml of THF) at 10–20°. The mixture was stirred at room temp for 1 hr, and then refluxed for 3 hr. The resulting reaction mixture was decompd with 150 ml of satd aq NH_4Cl solution. The THF layer was sepd and concd. The residue was dissolved in 50 ml of $CHCl_3$ and shaken with 10% of aq HCl. The sepd crystals were filtered off. Recrystallization from MeOH yielded 10.9 g (53%) of yellow crystals, mp 176–177°. *Anal.* ($C_{29}H_{33}ClN_2O_2$) C, H, N.

Synthesis and Pharmacological Activity of New Basic Carbamates

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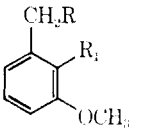
A series of bicarbamates of *N*-phenethyldiethanolamine, 2-diethylamino- and 2-piperidino-1,3-propanediol, and *N*-methyldiethanolamine, were synthesized and their nonoxalate soluble salts were evaluated in a primary mouse screen. In secondary studies, bis(*N*-butylcarbamoylethyl)-2,3-dimethoxyphenethylamine maleate (**17**) showed mild CNS depressant activity while another compound, bis-(*N*-phenylcarbamoylethyl)-2-*n*-butoxy-3-methoxyphenethylamine hydrochloride (**5**), exhibited antidepressant activity. Both decreased blood pressure.

The carbamoyl radical, which constitutes the principal characteristic of the compounds described in the present paper, is responsible for numerous pharmacological properties. Several basic carbamates[1b-3] have shown interesting pharmacodynamic activity as local anesthetics.[3] We have undertaken an exploration of the activity of the bicarbamates of some aminoalcohols, such as *N*-β-phenethyldiethanolamine, 2-diethylamino- and 2-piperidino-1,3-propanediol, and *N*-methyldiethanolamine.

Chemistry.—We have synthesized (1) bisphenylurethans of *N*-phenethyldiethanolamine (I), with or without substituents on the nucleus, and of N-substituted 2-amino-1,3-propanediol (II); (2) bisalkyl- (Et, *n*-Pr, *n*-Bu) urethans of I and of *N*-methyldiethanolamine (III); and (3) bicarbamates of I, II, and III unsubstituted on the carbamic N. The bisalkyl- and bisphenylurethans were prepared by the reaction of the amino alcohols with the corresponding alkyl[4] and phenyl isocyanate.[3] Bicarbamates unsubstituted on the carbamic N were synthesized from the amino alcohol and carbamoyl chloride.[1b,2,5] Other methods, re-

TABLE I



R	R_1	Yield, %	B_p, °C (mm)	Formula	Analyses[a]
$COOCH_3$	OCH_3	32[b]	159 (10)	$C_{11}H_{14}O_4$	C, H
$COOC_2H_5$	OCH_3	65[c]	155–157 (10)	$C_{12}H_{16}O_4$	C, H
$COOCH_3$	OC_2H_5	32[b]	167 (18)	$C_{12}H_{16}O_4$	C, H
$COOC_2H_5$	OC_2H_5	50[c]	170–172 (25)	$C_{13}H_{18}O_4$	C, H
$COOCH_3$	O-*n*-C_3H_7	26	171 (16)	$C_{14}H_{18}O_4$	C, H
$COOCH_3$	O-*n*-C_4H_9	20	166 (13)	$C_{14}H_{20}O_4$	C, H
CH_2OH	OC_2H_5	74	170 (18)	*d*	
CH_2OH	O-*n*-C_3H_7	93	174–189 (13)	*e*	
CH_2OH	O-*n*-C_4H_9	54	167–169 (14)	*f*	
CH_2Cl	OC_2H_5	60	150–152 (19)	$C_{11}H_{15}ClO_2$	C, H, Cl
CH_2Cl	O-*n*-C_3H_7	78	149–152 (15)	$C_{12}H_{17}ClO_2$	C, H, Cl
CH_2Cl	O-*n*-C_4H_9	78	150 (10)	$C_{13}H_{19}ClO_2$	Cl

[a] Where analyses are indicated by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [b] Method B; yield calculated as to aldehyde. [c] Method A; yield calculated as to nitrile. [d] Phenylurethan: mp 81° (EtOH); *Anal.* ($C_{18}H_{21}NO_4$) C, H, N. [e] 3,5-Dinitrobenzoic ester: mp 105° (EtOH); *Anal.* ($C_{19}H_{20}N_2O_8$) C, H, N. [f] 3,5-Dinitrobenzoic ester: mp 93° (EtOH); *Anal.* ($C_{20}H_{22}N_2O_8$) C, H, N.

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TABLE II
$X[(CH_2)_nOCONHR]_2$

No.	X	n	R	Salt	Mp, °C[a]	Formula	Analyses[b]	Pharmacology[c] LD50	MED50	Ratio
1	$C_6H_5CH_2CH_2N$	2	C_6H_5	HCl	177	$C_{26}H_{30}ClN_3O_4$	C, H, N, Cl	56.0	18.0	3.2
2	2,3-$(OCH_3)_2C_6H_3(CH_2)_2N$	2	C_6H_5	HCl	115	$C_{28}H_{34}ClN_3O_6$	C, H, N, Cl	56.0	5.6	10.0
3	2,3-$(OC_2H_5)(OCH_3)C_6H_3(CH_2)_2N$	2	C_6H_5	HCl	134	$C_{29}H_{36}ClN_3O_6$	C, H, N, Cl	100.0	18.0	5.6
4	2,3-$(n\text{-}OC_3H_7)(OCH_3)C_6H_3(CH_2)_2N$	2	C_6H_5	HCl	117	$C_{30}H_{38}ClN_3O_6$	C, H, N, Cl	18.0	5.6	3.2
5	2,3-$(n\text{-}OC_4H_9)(OCH_3)C_6H_3(CH_2)_2N$	2	C_6H_5	HCl	137	$C_{31}H_{40}ClN_3O_6$	C, H, N, Cl	180.0	18.0	10.0
6	$(C_2H_5)_2NCH$	1	C_6H_5	Tosylate	165	$C_{28}H_{35}N_3O_7S$	C, H, N, S	56.0	10.0	5.6
7	$C_6H_5(CH_2)_2N$	2	C_2H_5	HCl	133	$C_{18}H_{30}ClN_3O_4$	C, H, N, Cl	56.0	18.0	3.2
8				Oxalate	119	$C_{20}H_{31}N_3O_8$	C, H, N			
9	$C_6H_5(CH_2)_2N$	2	$n\text{-}C_3H_7$	HCl	134	$C_{20}H_{34}ClN_3O_4$	C, H, N, Cl	56.0	18.0	3.2
10				Oxalate	112	$C_{22}H_{45}N_3O_8$	C, H, N			
11	$C_6H_5(CH_2)_2N$	2	$n\text{-}C_4H_9$	HCl	128	$C_{22}H_{38}ClN_3O_4$	C, H, N, Cl	32.0	10.0	3.2
12				Oxalate	117	$C_{24}H_{39}N_3O_8$	C, H, N			
13	2,3-$(OCH_3)_2C_6H_3(CH_2)_2N$	2	C_2H_5	Maléate	101–102	$C_{24}H_{37}N_3O_{10}$	C, H, N	180.0	56.0	3.2
14				Oxalate	119	$C_{22}H_{35}N_3O_{10}\cdot 2H_2O$	C, H, N			
15	2,3-$(OCH_3)_2C_6H_3(CH_2)_2N$	2	$n\text{-}C_3H_7$	Maléate	106–107	$C_{26}H_{41}N_3O_{10}$	C, H, N	56.0	18.0	3.2
16				Oxalate	111	$C_{24}H_{39}N_3O_{10}\cdot 2H_2O$	C, H, N			
17	2,3-$(OCH_3)_2C_6H_3(CH_2)_2N$	2	$n\text{-}C_4H_9$	Maléate	85	$C_{28}H_{45}N_3O_{10}$	C, H, N	32.0	5.6	5.6
18				Oxalate	117	$C_{26}H_{43}N_3O_{10}\cdot 2H_2O$	C, H, N			
19	2,3-$(OC_2H_5)(OCH_3)C_6H_3(CH_2)_2N$	2	C_2H_5	Oxalate	96	$C_{23}H_{37}N_3O_{10}\cdot H_2O$	C, H, N			
20	2,3-$(OC_2H_5)(OCH_3)C_6H_3(CH_2)_2N$	2	$n\text{-}C_3H_7$	Oxalate	102	$C_{25}H_{41}N_3O_{10}$	C, H, N			
21	2,3-$(OC_2H_5)(OCH_3)C_6H_3(CH_2)_2N$	2	$n\text{-}C_4H_9$	Oxalate	93	$C_{27}H_{45}N_3O_{10}\cdot 0.5H_2O$	C, H, N			
22	2,3-$(n\text{-}OC_3H_7)(OCH_3)C_6H_3(CH_2)_2N$	2	C_2H_5	Maléate	90	$C_{26}H_{41}N_3O_{10}$	C, H, N	56.0	5.6	10.0
23				Oxalate	94	$C_{24}H_{39}N_3O_{10}\cdot H_2O$	C, H, N			
24	2,3-$(n\text{-}OC_3H_7)(OCH_3)C_6H_3(CH_2)_2N$	2	$n\text{-}C_3H_7$	Maléate	89	$C_{28}H_{45}N_3O_{10}$	C, H, N	56.0	5.6	10.0
25				Oxalate	103	$C_{26}H_{43}N_3O_{10}$	C, H, N			
26	2,3-$(n\text{-}OC_3H_7)(OCH_3)C_6H_3(CH_2)_2N$	2	$n\text{-}C_4H_9$	Maléate	91	$C_{30}H_{49}N_3O_{10}$	C, H, N	32.0	5.6	5.6
27				Oxalate	97	$C_{28}H_{47}N_3O_{10}\cdot 0.5H_2O$	C, H, N			
28	2,3-$(n\text{-}OC_4H_9)(OCH_3)C_6H_3(CH_2)_2N$	2	C_2H_5	Malonate	79–80	$C_{26}H_{43}N_3O_{10}\cdot H_2O$	C, H, N	18.0	5.6	3.2
29				Oxalate	92	$C_{25}H_{41}N_3O_{10}\cdot H_2O$	C, H, N			
30	2,3-$(n\text{-}OC_4H_9)(OCH_3)C_6H_3(CH_2)_2N$	2	$n\text{-}C_3H_7$	Malonate	84	$C_{28}H_{47}N_3O_{10}\cdot H_2O$	C, H, N	56.0	10.0	5.6
31				Oxalate	96	$C_{27}H_{45}N_3O_{10}\cdot H_2O$	C, H, N			
32	2,3-$(n\text{-}OC_4H_9)(OCH_3)C_6H_3(CH_2)_2N$	2	$n\text{-}C_4H_9$	Malonate	86–87	$C_{30}H_{51}N_3O_{10}\cdot H_2O$	C, H, N	56.0	18.0	3.2
33				Oxalate	108	$C_{29}H_{49}N_3O_{10}\cdot H_2O$	C, H, N			
34	CH_3N	2	C_2H_5	Tosylate	119–120	$C_{18}H_{31}N_3O_7S$	C, H, N, S	320.0	180.0	1.8
35				Oxalate	89	$C_{13}H_{25}N_3O_8$	C, H, N			
36	CH_3N	2	$n\text{-}C_3H_7$	HCl	128	$C_{13}H_{28}ClN_3O_4$	C, H, N, Cl	180.0	18.0	10
37				Oxalate	129–130	$C_{15}H_{29}N_3O_8$	C, H, N			
38	CH_3N	2	$n\text{-}C_4H_9$	HCl	124	$C_{15}H_{32}ClN_3O_4$	C, H, N, Cl	56.0	32.0	1.8
39				Oxalate	111	$C_{17}H_{33}N_3O_8$	C, H, N			
40	CH_3N	2	H	Base	85	$C_7H_{15}N_3O_4$	C, H, N			
41	$C_6H_5(CH_2)_2N$	2	H	Base	83	$C_{14}H_{21}N_3O_4$	C, H, N			
42	2,3-$(OC_2H_5)(OCH_3)C_6H_3(CH_2)_2N$	2	H	Base	92–93	$C_{17}H_{27}N_3O_6$	C, H, N			
43	$(C_2H_5)_2NCH$	1	H	Base	94	$C_9H_{19}N_3O_4$	C, H, N			
44	$C_5H_{10}NCH$	1	H	Base	109	$C_{10}H_{19}N_3O_4$	C, H, N			

[a] Melting points were determinated in bloc Maquenne and are corrected. [b] Where analyses are indicated by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [c] LD_{50} = lethal dose 50%; MED_{50} = minimal effective dose or smallest dose producing consistent though varied effect.

ported in the literature[1b,2,6-14] for the preparation of analogous unsubstituted bicarbamates, were not successful except in the case of *N*-methyldiethanolamine bicarbamate, which was obtained following the method of Stevens.[10] The same procedure[10] was used for the β-phenethyldiethanolamine derivatives but in this case the phenethyl group was eliminated and diethanolamine bicarbamate was formed due to the prolonged action of HCl. This fact was confirmed by the analytical data and melting point of the obtained product. The starting materials required for the preparation of aminoalcohols are summarized in Table I.

Table II summarizes the chemical and pharmacological data on the carbamates.

Experimental Section

***N*-β-Phenethyldiethanolamines (I).**—From the appropriate benzaldehydes,[15] by reduction into alcohols,[15] chlorination,[15] cyanation,[15] hydrolysis, and esterification (method A), or by treatment successively with hippuric acid, NaOH, H_2O_2[16,17] and esterification (method B) were obtained the phenylacetic esters,

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which by reduction,[18,19] chlorination,[15] and treatment with diethanolamine[20] gave the amino alcohols I.

N-Substituted 2-Amino-1,3-propanediols (II).—The bromomalonic ester was converted into N-substituted aminomalonic ester[21-24] which was reduced to the corresponding amino alcohol II.

N-Methyldiethanolamine (III) was commercially available.

Bisphenylurethans. Bisphenylurethan of N-β-Phenethyldiethanolamine.—To N-β-phenethyldiethanolamine (8 g) cooled in an ice bath, was added dropwise phenyl isocyanate (9.1 g). The mixture was allowed to recover to room temperature and then was heated on a steam bath for 2 hr (moisture avoided). After cooling, dry Et_2O and a minimum of absolute EtOH were added and the precipitate formed (diphenylurea) was filtered off. The filtrate was treated with dry HCl to give a crystalline salt (yield 77%, mp 177°).

Bisalkylurethans. Bisethylurethan of N-Methyldiethanolamine.—A solution of N-methyldiethanolamine (7 g) in 75 ml of dry C_6H_6 was treated with ethyl isocyanate (8.3 g) and the mixture was allowed to stand 4 days at room temperature. The solvent was evaporated *in vacuo* and the resulting base converted into oxalate or tosylate, melting at 89 and 120°, respectively, after recrystallization from EtOH–Et_2O. In all cases the oily bases were converted into salts without further purification.

Bicarbamates Unsubstituted on the Carbamic Nitrogen. a. N-Methyldiethanolamine Bicarbamate.—A solution of N-methyldiethanolamine (12 g) in 100 ml of $CHCl_3$ was chilled to 0°. KOCN (20 g) was added while dry HCl was bubbled through the solution with vigorous stirring, the temperature being maintained at 0–5°. At the end of 2 hr an additional 8 g of KOCN was added and dry HCl bubbled into the solution for an additional 2 hr. After standing at 0° for 30 min the $CHCl_3$ was decanted and the remaining solid treated with K_2CO_3 and a small quantity of H_2O. The mixture was extracted repeatedly with hot $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and the solvent was distilled off (the organic layer was not washed with H_2O, because of the great solubility in H_2O of the carbamate derivative). The oily residue treated with a small quantity of dry Et_2O solidified. Recrystallization from EtOH gave 5 g (25%) of bicarbamate, mp 85°.

b. N-β-Phenethyldiethanolamine Bicarbamate.—A solution of N-β-phenethyldiethanolamine (5 g) in 100 ml of $CHCl_3$ was treated with freshly prepared carbamoyl chloride (5 g) with stirring and cooling. The mixture was allowed to stand 24 hr at room temperature. H_2O was added and the undissolved solid filtered off. The filtrate was basified, the organic layer separated, and the aqueous phase was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4), the solvent was evaporated, and the oily residue was crystallized from Et_2O. Recrystallization from C_6H_6 gave 4.5 g of product (yield 64%, mp 83°).

c. N-[β-(2-n-Propoxy-3-methoxyphenyl)ethyl]-2,2′-dichlorodiethylamine·HCl.—To N-[β-(2-n-propoxy-2-methoxyphenyl)-ethyl]diethanolamine (7 g) $SOCl_2$ (4.5 ml) was added slowly, with stirring and cooling. When the addition was completed the mixture was allowed to stand for several hours at room temperature; then the excess $SOCl_2$ was removed *in vacuo*. The residue was dissolved in a small quantity of MeOH and the hydrochloride was precipitated by addition of dry Et_2O. After recrystallization from MeOH–Et_2O, 3 g (38%) of HCl salt was obtained, mp 107°. *Anal.* ($C_{16}H_{25}Cl_3NO_2$) C, H, N, Cl.

Pharmacology. 1. Primary Mouse Screen.—The iv primary mouse screen was used to characterize the gross pharmacological, toxicological, and behavioral properties of these compounds. Male albino mice of the Swiss–Webster strain (20–25 g) were used. Each animal was assessed for gross activity at 3, 15, 30, and 60 min, post injection, and thereafter at periodic intervals until the effects disappeared. The combined statistical procedure of Weil and Thompson[25] was used to calculate the minimal effective dose (MED_{50}). The ratio of the LD_{50} to the MED_{50} was determined for each compound. Preliminary pharmacologic evaluations are given in Table II for the nonoxalate soluble salts.

2. Cardiovascular Activity.—Healthy, adult cats were employed to assess the cardiovascular effects of select compounds. The animals were anesthetized surgically with sodium pentobarbital (35 mg/kg) ip. The femoral artery and vein were, respectively, cannulated for monitoring arterial blood pressure and for the administration of test materials. Both carotid arteries were isolated for bilateral carotid occlusion. The vagii were isolated and bisected for subsequent peripheral vagal stimulation. Several prototype autonomic agents were given to evaluate the effect of the test compounds on cardiovascular and autonomic response. Prior to and after the periodic administration of logarithmically spaced dose levels of the test compound, the following sequence of test procedures was performed: (a) epinephrine·HCl, iv 5 μg/kg; (b) acetylcholine·HBr, iv 5 μg/kg; (c) norepinephrine, iv 5 μg/kg; (d) bilateral carotid occlusion, 45 sec; (e) peripheral vagal stimulation, 5 V; and (f) histamine diphosphate, iv 10 μg/kg. The physiologic parameters monitored throughout the experiment were arterial blood pressure, pulse pressure, ECG, and cardiac and respiratory rates.

The cardiovascular activities of two compounds, **5** and **17**, were of interest. Both compounds produced a decrease in arterial blood pressure. Following injection of **5**, the depressor effects of acetylcholine and serotonin appeared mildly potentiated. Such actions suggest either direct vasodilation or cholinergic excitation. Compound **17** appeared to diminish peripheral autonomic responses and it enhanced the pressor effect of bilateral carotid stimulation.

3. Antidepressant Activity.—Two test procedures were employed to evaluate the antidepressant potential of test compounds.

a. Intraventricular Calcium-Induced Depression.—Male, Swiss-Webster mice (19–22 g) were administered iv 10 μg of $CaCl_2$ dissolved in 0.02 ml of saline. The technique of Adler[26] was used to assure accurate placement of the compound. Twenty minutes later, the test compound was given ip at 4 dose levels, 10 animals per dose level. General activity and appearance of the mice were used to evaluate changes in the depressant effects of $CaCl_2$.

b. Reserpine-Induced Depression.—Male, Swiss-Webster mice (20–25 g) were pretreated with reserpine 24 hr prior to the administration of the test materials. The reserpine was given ip at a dose level of 4 mg/kg. Four groups of animals, 10 mice per group, were then given 1 of 4 doses of the test compounds. The animals were observed at 3, 15, 30, and 60 min for signs of antidepressant activity. The percentage of the population exhibiting antidepressant effects was calculated to determine the ED_{50} for each compound.

Compound **3** failed to exhibit antidepressant effects in either Ca^{2+} or reserpine-induced depression. Compound **5**, however, appeared to reduce the incidence of both types of depression, having an ED_{50} of 20 mg/kg *vs.* Ca^{2+} depression and 35 mg/kg *vs.* reserpine depression. In general, peak antidepressant activity occurred 3–15 min following drug administration.

4. Analgetic and Antifighting Activity.—Analgesia was determined using the Eddy[27] hot plate procedure. A temperature-regulated hot plate was used at a constant temperature of 55°. Ten mice were used at each level. The test material was given subcutaneously at 4 dose levels. The animals were individually placed on the surface of the hot plate for a minimum of 30 sec prior to, and 15, 30, 60, and 90 min, after drug administration. The animals were immediately removed when they demonstrated pain sensation, *i.e.*, paw licking, flicking, or jumping. The time variance between the untreated and post treated exposure was used to determine the percent analgesia produced by the experimental compound(s). Antifighting activity was determined by the method of Tedeschi, *et al.*[28]

Using the Eddy hot plate technique, a 37% increase in pain threshold was observed 3 min following the sc injection of 40

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mg/kg of **17**. However, further investigation using the Hardy, *et al.*,[29] procedure to detect analgesia in squirrel monkeys failed to yield any significant analgetic activity. Because a degree of docility was observed in squirrel monkeys following administration of **17**, this compound was examined for potential tranquilizing activity. The antifighting procedure of Tedeschi, *et al.*, indicated a 55% decreae in the incidence of fighting following the administration of 120 mg/kg, sc, of the test compound. A statistical ED_{50} of 135 mg/kg was calculated by the Litchfield and Wilcoxon technique.[30]

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Acetylene Compounds of Potential Pharmacological Value. XIV. *N*-(*t*-Aminoalkynyl)-Substituted Succinimides and Maleimides. A Class of Central Anticholinergic Agents[1]

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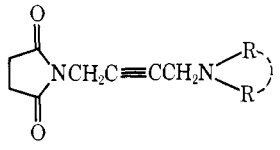
A series of 34 *N*-(*t*-aminoalkynyl)-substituted succinimides and maleimides has been prepared through the Mannich reaction from an *N*-alkynylimide, formaldehyde, and a secondary amine or by ring closure of an *N*-(*t*-aminoalkynyl)-substituted succinamic acid. These compounds have been investigated for antagonistic activity toward acetylcholine on isolated guinea pig ileal preparations and for mydriatic activity and blockade of oxotremorine in intact mice. Some of the compounds exceed atropine in tremorolytic activity, and are relatively selective in their central anticholinergic effects. The latter property tends to be associated with compounds which show evidence of partial agonism *in vitro*.

In two recent publications[2,3] we reported on the synthesis and pharmacological properties of a series of *N*-(4-*t*-amino-2-butynyl)-substituted succinimides.



Some compounds of this class were found to be quite potent in blocking the motor effects of oxotremorine, 1-(2-oxopyrrolidino)-4-pyrrolidino-2-butyne, while the effect on peripheral cholinergic symptoms, such as acetylcholine-induced spasms of guinea pig ileal strips, is of lower magnitude. Consequently, these compounds can be regarded as specific central anticholinergic agents. This discovery has led to the synthesis of a number of analogs with the aim of defining the limits of activity in the series and of enhancing the activity found in the parent compounds. In most of the compounds described in this paper, the chain connecting the imide and the amino nitrogens has been branched or lengthened, though structural modifications have been made also in the imido and amino groups. The most potent of the new compounds are about 100 times as active as the most potent compound in the parent series when tested for oxotremorine antagonistic activity.

Chemistry.—Two methods of synthesizing the *N*-(*t*-aminoalkynyl)-substituted cyclic imides listed in Tables I and II were utilized: Mannich reaction between an *N*-alkynylimide, formaldehyde, and a secondary amine in dioxane in the presence of small amounts of CuCl (method A) and ring closure of an *N*-(*t*-aminoalkynyl)-substituted succinamic acid (method B). The *N*-alkynylimides used as starting materials in method A were generally obtained by treating an alkynylamine with a succinic or maleic anhydride and subsequent ring closure of the *N*-alkynylsuccinamic or *N*-alkynylmaleamic acid formed. The *N*-(*t*-aminoalkynyl)-substituted succinamic acids used as starting materials in method B were prepared by treating succinic anhydride with a *t*-aminoalkynylamine, obtained either by aminoalkylation of an alkynylamine in the presence of $NaNH_2$ or by the reaction of the Grignard reagent of the alkynylamine with a ternary iminium salt. The reaction sequences are shown in Scheme I.

Pharmacological Results and Discussion.—Table III summarizes the pharmacological data. All but four of the compounds antagonized the tremorogenic effect of oxotremorine, and the dose required was in every case less than that which produced mydriasis, with the exception of the weakly active compound **8**. This is in marked contrast to atropine, which is less effective in blocking oxotremorine than in producing mydriasis. Nevertheless, as in previous series of compounds related to oxotremorine, there was a highly

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