recrystallized (*i*-PrOH) to give the desired compound. The free base was liberated and converted to its hydrochloride salt, mp 218–220° dec.

N-[β-Hydroxy-β-(3,4,5-trimethoxyphenyl)ethyl]morpholine Hydrochloride (47).—To a solution of 5.64 g (0.015 mole) of **46** in 120 ml of dry *i*-PrOH, 45 ml of molar Al(*i*-PrO)$_3$ solution in *i*-PrOH was added. The reaction mixture was refluxed for 3 hr and the distillate was tested for the presence of acetone (2,4-dinitrophenylhydrazone test). Reflux was continued (7 hr) till the acetone test became negative. The solvent was removed under diminished pressure (100 mm), and the reaction mixture was basified with 40% aqueous NaOH and extracted with Et_2O. The combined extracts were dried (Na_2SO_4) and added to 15 ml of *i*-Pr-HCl (22%). The resulting white solid on crystallization (EtOH) gave the product.

N¹-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-N⁴-(*p*-fluorophenyl)piperazine Hydrochloride (31).—To a solution of 3.25 g (0.015 mole) of N-(*p*-fluorophenyl)piperazine hydrochloride in 60 ml of EtOH, 2.2 ml (~0.022 mole) of aqueous CH_2O (37–41%) and 3.78 g (0.018 mole) of 3,4,5-trimethoxyacetophenone were added and the mixture was refluxed for 7 hr. Additional aqueous CH_2O (2.2 ml) was added and reflux continued for 7 hr. The reaction mixture was concentrated to one-fourth of its volume and allowed to cool overnight, when a white shiny crystalline compound separated out. This was filtered, dried, and recrystallized. The hydrochloride was converted quantitatively to the free base which was recrystallized from EtOH. The maleate salt of this base was prepared by the addition of its solution in EtOH to the calculated amount of maleic acid in EtOH followed by dilution with Et_2O.

The rest of the ketonic Mannich bases (1, A = $COCH_2CH_2$) were prepared by following this method.

β,β-Bis[N⁴-(*m*-fluorophenyl)-N¹-piperazinyl]-3,4,5-trimethoxypropiophenone.—To a solution of 3.25 (0.015 mole) of 1-(*m*-fluorophenyl)piperazine hydrochloride in 70 ml of EtOH, 2.2 ml (~0.022 mole) of aqueous CH_2O and 3.47 g (0.0165 mole) of 3,4,5-trimethoxyacetophenone were added and the mixture was refluxed for 7 hr. Additional aqueous CH_2O (2.2 ml) was added and reflux continued for additional 7 hr. The reaction mixture was concentrated to one-fourth of its volume and left overnight. The resulting solid was filtered and recrystallized (EtOH); mp 190–192° dec. *Anal.* ($C_{33}H_{40}F_2N_4O_4 \cdot 2HCl$) C, H, N.

N¹-(β-Benzoylethyl)-N⁴-(*o*-methoxyphenyl)piperazine Hydrochloride (54).—To a solution of 1.92 g (0.01 mole) of N-(*o*-methoxyphenyl)piperazine in 30 ml of EtOH were added 2 g (0.02 mole) of Et_3N and a solution of 2.13 g (0.01 mole) of β-bromopropiophenone in 15 ml of EtOH. The reaction mixture was refluxed for 9 hr and then concentrated. To the ice-cooled residue 15 ml of H_2O and 5 ml of 40% aqueous NaOH were added. It was then extracted with Et_2O, and the extracts were dried (Na_2SO_4) and concentrated. The residual oil, after warming under vacuum for some time and then cooling, did not solidify. It was taken up into Me_2CO and was added to 7 ml of *i*-Pr-HCl (22%). The resulting white solid was filtered and recrystallized twice.

N¹-[γ-(3,4,5-Trimethoxybenzoyl)propyl]-N⁴-(α,α,α-trifluoro-*m*-tolyl)piperazine Hydrochloride (36).—A mixture of 2.73 g (0.01 mole) of γ-chloro-3,4,5-trimethoxybutyrophenone and 4.6 g (0.02 mole) of N-(α,α,α-trifluoro-*m*-tolyl)piperazine was warmed and kept for 6 hr at room temperature and then heated at 100° for 4 hr. After cooling, H_2O was added and the reaction mixture was extracted twice with 40 ml of $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was recrystallized from hexane to give the free base of **36**. The base was converted to the desired monohydrochloride salt by the usual procedure.

Other members of this series (1, A = $COCH_2CH_2CH_3$) were prepared following the above method. The resulting products were either crystallized, when solid, from the appropriate solvents, or converted, when oily, to the HCl salts.

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Synthesis and Pharmacological Activity of Alkylaminoalkyl Esters and Amides of 2-Hydroxy- (or Alkoxy-) 3-methoxybenzoic Acid

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A series of alkylaminoalkyl esters and amides of 2-hydroxy- (or alkoxy-) 3-methoxybenzoic acid were synthesized and their hydrochloride, methiodide, or oxalate salts were tested for local anesthetic activity. Only the diethylamino and *n*-butylamino ethyl esters of 2-butoxy-3-methoxybenzoic acid and morpholinoethyl 2-ethoxy-3-methoxybenzoate exhibited greater local anesthetic activity than lidocaine. However, these compounds were highly irritating and generally more toxic.

As a continuation of our investigation on local anesthetics,[2–5] studies of the well-known local anesthetic activity of alkylaminoalkyl esters and amides of substituted benzoic acids and the reported physiological activity of the ester, amides, and alkoxy derivatives of vanillic acid[6–9] suggested that an exploration of the activity of alkylaminoalkyl esters and amides of 2-hydroxy- (or alkoxy-) 3-methoxybenzoic acid might result in the discovery of potentially useful local anesthetic agents.

Chemistry.—The ester derivatives synthesized were the dimethylamino-, diethylamino-, piperidino-, and morpholinoethyl esters of 2-hydroxy-3-methoxybenzoic acid, 2,3-dimethoxybenzoic acid, 2-ethoxy-3-methoxybenzoic acid, 2-propoxy-3-methoxybenzoic acid,

(1) Part of this work was supported by the University of Athens and was carried out with the technical assistance of Miss Carmen Nieto, Miss M. Catradi, and Mr. S. Chiotellis.

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(3) G. Tsatsas and N. Vassiliadore, *ibid.*, 734 (1962).

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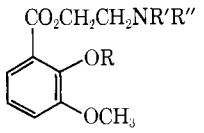
TABLE I



No.	R	NR'R"	Salt	Yield, %[a]	Mp, °C[b]	Formula	Analyses[d]	Approx LD_{50}, mg/kg iv	Local anesthetic act.[e]
1	CH_3	Me_2N	HCl	86	142–143	$C_{13}H_{20}ClNO_4$	N, Cl	102	+
			Picrate		145–146	$C_{19}H_{22}N_4O_{11}$	C, H, N		
2	CH_3	Et_2N	HCl	77	144–145	$C_{15}H_{24}ClNO_4$	N, Cl	60	−
			Picrate		113–114	$C_{21}H_{26}N_4O_{11}$	C, H, N		
3	CH_3	$C_5H_{10}N$	HCl	83	110	$C_{16}H_{24}ClNO_4$	N, Cl	67	+
			Picrate		141–142	$C_{22}H_{26}N_4O_{11}$	C, H, N		
4	CH_3	C_4H_8NO	HCl	79	158–159	$C_{15}H_{22}ClNO_5$	N, Cl	220	−
			Picrate		200–201	$C_{21}H_{24}N_4O_{12}$	C, H, N		
5	C_2H_5	Me_2N	HCl	75	84–86	$C_{14}H_{22}ClNO_4$	N, Cl	72	−
			Picrate		131–132	$C_{20}H_{24}N_4O_{11}$	C, H, N		
6	C_2H_5	Et_2N	HCl	71	89–91	$C_{16}H_{26}ClNO_4$	N, Cl	45	−
			Picrate		116–117	$C_{22}H_{28}N_4O_{11}$	C, H, N		
7	C_2H_5	$C_5H_{10}N$	HCl	69	84[c]	$C_{17}H_{26}ClNO_4$	N, Cl	55	+
			Picrate		139–140	$C_{23}H_{28}N_4O_{11}$	C, H, N		
8	C_2H_5	C_4H_8NO	HCl	78	102–103	$C_{16}H_{24}ClNO_5$	N, Cl	180	−
			Picrate		177–178	$C_{22}H_{26}N_4O_{12}$	C, H, N		
9	n-C_3H_7	Me_2N	HCl	73	96–97	$C_{15}H_{24}ClNO_4$	N, Cl	40	−
			Picrate		120–121	$C_{21}H_{26}N_4O_{11}$	C, H, N		
10	n-C_3H_7	Et_2N	HCl	69	75–76	$C_{17}H_{28}ClNO_4$	N, Cl	17	+
			Picrate		90–91	$C_{23}H_{30}N_4O_{11}$	C, H, N		
11	n-C_3H_7	$C_5H_{10}N$	HCl	81	97[c]	$C_{18}H_{28}ClNO_4$	N, Cl	*f*	*g*
			Picrate		114–115	$C_{24}H_{30}N_4O_{11}$	C, H, N		
12	n-C_3H_7	C_4H_8NO	HCl	84	108–111	$C_{17}H_{26}ClNO_5$	N, Cl	92	−
			Picrate		167–168	$C_{23}H_{28}N_4O_{12}$	C, H, N		
13	H	Me_2N	HCl	60	116	$C_{12}H_{15}ClNO_4$	N, Cl	55	−
			Picrate		183–184	$C_{18}H_{20}N_4O_{11}$	C, H, N		
14	H	Et_2N	HCl	60	109–110	$C_{13}H_{20}ClNO_4$	N, Cl	36.5	−
			Picrate		176–177	$C_{19}H_{22}N_4O_{11}$	C, H, N		
15	H	$C_5H_{10}N$	HCl	63	108–110	$C_{15}H_{22}ClNO_4$	N, Cl	*f*	*g*
			Picrate		207–209	$C_{21}H_{24}N_4O_{11}$	C, H, N		
16	H	C_4H_8NO	HCl	55	175–176	$C_{14}H_{20}ClNO_5$	N, Cl	175	−
			Picrate		195–196	$C_{20}H_{22}N_4O_{12}$	C, H, N		
17	n-C_4H_9	Me_2N	HCl	61	50[c]	$C_{16}H_{26}ClNO_4$	N, Cl	38.5	+
			Picrate		116–117	$C_{22}H_{28}N_4O_{11}$	C, H, N		
18	n-C_4H_9	Et_2N	HCl	53	92[c]	$C_{18}H_{30}ClNO_4$	N, Cl	6.7	+
			Picrate		69–70	$C_{24}H_{32}N_4O_{11}$	C, H, N		
19	n-C_4H_9	$C_5H_{10}N$	HCl	47	111[c]	$C_{19}H_{30}ClNO_4$	N, Cl	*f*	*f*
			Picrate		123–124	$C_{25}H_{32}N_4O_{11}$	C, H, N		
20	n-C_4H_9	C_4H_8NO	HCl	55	118[c]	$C_{18}H_{28}ClNO_5$	N, Cl	40	+
			Picrate		144–145	$C_{24}H_{30}N_4O_{12}$	C, H, N		
21	n-C_4H_9	Me_2N	MeI	77	86	$C_{17}H_{18}INO_4$	C, H, N, I	40	+
22	n-C_4H_9	C_4H_8NO	MeI	88	107	$C_{19}H_{30}INO_5$	C, H, N, I	15	−
23	n-C_4H_9	n-BuNH	HCl	47	128–129	$C_{18}H_{30}ClNO_4$	N, Cl	17.5	+
24	n-C_4H_9	N-i-PrNH	HCl	62	148–150	$C_{17}H_{28}ClNO_4$	N, Cl	42.5	+

[a] Yields of HCl salts. [b] Melting points were determined in capillary tubes and are uncorrected. [c] Hygroscopic compounds. [d] Where analyses are indicated by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [e] Qualitative screening for local anesthetic activity by the method of Bianchi.[15] The compounds exhibiting local anesthetic activity in this test were further quantitatively evaluated using the method of Bulbring and Wajda[16] (Table III). [f] Pharmacological evaluation was not made. [g] These compounds were too insoluble in H_2O to test by the Bianchi procedure and thus unsuitable for use as local anesthetics as per criteria for the selection of local anesthetics (L. S. Goodman and A. Gilman "The Pharmacological Basis of Therapeutics," W. B. Saunders Co., Philadelphia, Pa., 1965).

and 2-butoxy-3-methoxybenzoic acid as the hydrochloride and, in some cases, as the picrate and methiodide salts. The *n*-butylamino and isopropylamino esters of 2-butoxy-3-methoxybenzoic acid were also prepared (Table I). Preparation of the β-dialkylaminoethyl esters consisted of treating β-dialkylaminoethanol with 2-hydroxy- (or alkoxy-) 3-methoxybenzoyl chloride in Et_2O; in this case the HCl salt is obtained directly. The β-monoalkylaminoethyl esters were prepared by dissolving the β-monoalkylaminoethanol in a small volume of $CHCl_3$, saturating the solution with dry HCl, and adding 2-alkoxy-3-methoxybenzoyl chloride.[10]

The amide derivatives synthesized were the dimethylamino, piperidino-, and morpholinoethyl amides of 2-ethoxy-3-methoxybenzoic acid, 2-propoxy-3-methoxybenzoic acid, and 2-butoxy-3-methoxybenzoic acid. Diethylaminopropyl amides of these acids were also

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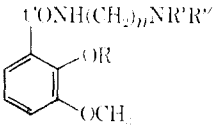
TABLE II



No.	R	n	NR'R''	Yield, %[a]	Salt	Mp, °C[b]	Formula[c]	Approx LD_{50}, mg/kg iv	Local anesthetic act.[d]
25	C_2H_5	2	Me_2N	75	HCl	96–98	$C_{14}H_{23}ClN_2O_3$	90	–
26	C_2H_5	3	Et_2N	72	Oxalate	109–110	$C_{19}H_{30}N_2O_7$	102	–
27	C_2H_5	2	$C_5H_{10}N$	74	Oxalate	168–169	$C_{19}H_{28}N_2O_7$	45	–
28	C_2H_5	2	C_4H_8NO	70	Oxalate	170–171	$C_{18}H_{26}N_2O_8$	92	–
29	n-C_3H_7	2	Me_2N	77	HCl	121–123	$C_{15}H_{25}ClN_2O_3$	70	–
30	n-C_3H_7	3	Et_2N	68	Oxalate	88–90	$C_{20}H_{32}N_2O_7$	50	–
31	n-C_3H_7	2	$C_5H_{10}N$	75	Oxalate	144–145	$C_{20}H_{30}N_2O_7$	34	–
32	n-C_3H_7	2	C_4H_8NO	69	Oxalate	133–135	$C_{19}H_{28}N_2O_8$	130	–
33	n-C_4H_9	2	Me_2N	71	Oxalate	123–125	$C_{18}H_{28}N_2O_7$	55	–
34	n-C_4H_9	3	Et_2N	69	Oxalate	114–115	$C_{21}H_{34}N_2O_7$	93	–
35	n-C_4H_9	2	$C_5H_{10}N$	78	Oxalate	131–133	$C_{21}H_{32}N_2O_7$	27	–
36	n-C_4H_9	2	C_4H_8NO	74	Oxalate	157–159	$C_{20}H_{30}N_2O_8$	78	–

[a] Yields of unpurified bases. [b] Melting points of purified salts were determined in capillary tubes and are uncorrected. [c] All compounds were analyzed for C, H, and N and analytical results obtained were within ±0.4% of the theoretical values. [d] Qualitative screening for local anesthetic activity by the method of Bianchi.[15]

prepared (Table II), by treating the acid chloride with the corresponding ω-dialkylaminoalkylamine in an alkaline (Na_2CO_3) medium.

Experimental Section

2-Hydroxy-3-methoxybenzoic acid was prepared by fusing *o*-vanillin with a mixture of NaOH and KOH or by oxidation with Ag_2O.[10] The 2-alkoxy-3-methoxybenzoic acids were obtained by alkylation of *o*-vanillin with dialkyl sulfate (methoxy or ethoxy derivatives) or with alkyl halide (propoxy or butoxy derivatives) in an alkaline medium, followed by oxidation of the aldehyde with $KMnO_4$.[12] Acid chlorides were prepared by refluxing the acid with $SOCl_2$ and distillation under reduced pressure. Boiling points of the acid chlorides prepared were 2-ethoxy, 155–157° (22 mm), 2-*n*-propoxy, 158–160° (17 mm), and 2-*n*-butoxy, 167–170° (16 mm).

β-Dialkylaminoethyl 2-Alkoxy-3-methoxybenzoates.—2-Alkoxy-3-methoxybenzoic acid (0.05 mole) was dissolved in excess $SOCl_2$ (0.2 mole) with slight heating and allowed to stand 6 hr at room temperature. The excess $SOCl_2$ was evaporated *in vacuo* with moderate heating. The residue was extracted three times with anhydrous C_6H_6, dissolved in anhydrous Et_2O, and filtered if necessary. Dialkylaminoethanol (0.05 mole), dissolved in approximately 10 ml of anhydrous Et_2O, was added dropwise to the filtrate with stirring to obtain the HCl salt. Yields, melting points, and analytical data are given in Table I. Methiodides were prepared by dissolving the HCl salt in an aqueous alkaline medium and extracting the liberated base with Et_2O. The Et_2O was evaporated, and the residue was dissolved in absolute EtOH and refluxed with excess MeI for 2 hr. The crude methiodide salt was recrystallized from absolute EtOH–anhydrous Et_2O. Yields of the purified salts, melting points, and analytical data are given in Table I.

β-Monoalkylaminoethyl 2-Alkoxy-3-methoxybenzoates.—*n*-Butylamino- or isopropylaminoethanol (0.05 mole) was dissolved in 10 ml of $CHCl_3$ in an autoclave and the solution was saturated with dry HCl while cooling. 2-Alkoxy-3-methoxybenzoyl chloride (0.05 mole) dissolved in 10 ml of $CHCl_3$ was added to the syrupy mixture and allowed to stand at 30–35° for about 60 hr. H_2O (100 ml) was added and the mixture was made alkaline with saturated Na_2CO_3. The $CHCl_3$ layer was removed and the aqueous layer was extracted twice with Et_2O. The combined $CHCl_3$ and Et_2O extracts were dried (Na_2CO_3) and filtered. The solvents were evaporated and the oily residue was converted to the HCl salts which were recrystallized from absolute EtOH–anhydrous Et_2O. Yields of purified hydrochlorides, melting points, and analytical data are shown in Table I.

β-Dialkylaminoethyl 2-hydroxy-3-methoxybenzoates were prepared as described under β-dialkylaminoethyl 2-alkoxy-3-methoxybenzoates. Low yields (30%) were encountered when the acid chloride, 2-hydroxy-3-methoxybenzoyl chloride, was prepared by refluxing *o*-vanillic acid with excess $SOCl_2$ in C_6H_6 for 2 hr.[13] When synthesized by the method previously described, and allowing the mixture to stand for 10 hr, a yield of 70% was obtained. Yields of the purified hydrochlorides, melting points, and analytical data are given in Table I.

ω-Dialkylaminoalkyl Amides of 2-Alkoxy-3-methoxybenzoic Acid.—A solution of 50 ml of 2 *M* Na_2CO_3 was added to ω-dialkylaminoalkylamine (0.05 mole) previously dissolved in 80 ml of $CHCl_3$. 2-Alkoxy-3-methoxybenzoyl chloride (0.05 mole) dissolved in 30 ml of $CHCl_3$ was added dropwise with vigorous stirring. Stirring was continued for 30 min after completion of the addition. The $CHCl_3$ layer was separated, washed (H_2O), dried (Na_2CO_3), and distilled. The oily bases were converted into either oxalate or HCl salts without further purification. Most of the salts are oxalates because the corresponding hydrochlorides were too hygroscopic to crystallize. Yields, of nonpurified bases, melting points of purified hydrochlorides or oxalates, and analytical data are given in Table II.

Pharmacology.—Initial qualitative pharmacological screening was done by intravenous injection of the test compounds in mice according to the method of Smith.[14] The method of Bianchi[15] was utilized for preliminary local anesthetic screening. Compounds which exhibited local anesthetic activity using the Bianchi method were quantitatively evaluated for local anesthetic potency in guinea pigs by the method of Bulbring and Wajda.[16] These active agents were tested at 1% concentration and relative potency was compared with 1% lidocaine on a molar basis. Those compounds which exhibited preliminary vasodilator properties were further examined by determining the action of the compounds on the blood pressure of a dog.

Toxicity in Mice.—Male CD$_1$ (Charles River) strain mice weighing between 20 and 30 g were used for acute toxicity determination. An approximate intravenous LD_{50} was determined in several groups of mice employing five mice per dose level.

Results and Discussion

In Tables I and II, 33 compounds are listed which were screened for local anesthetic activity and toxicity as described in the Experimental Section. Of the 33,

(11) I. A. Pearl, *J. Am. Chem. Soc.*, **68**, 429 (1946).
(12) G. Tsatsas, *Ann. Pharm. Franc.*, **10**, 276 (1952).
(13) *Congr. Sci. Farm. Conf. Comun., 21°, Pisa, 1961*, 472 (1962).
(14) W. G. Smith, *Progr. Med. Chem.*, **1**, 9 (1961).
(15) C. Bianchi, *Brit. J. Pharmacol.*, **11**, 104 (1956).
(16) E. Bulbring and I. Wajda, *J. Pharmacol. Exptl. Therap.*, **85**, 78 (1945).

TABLE III
LOCAL ANESTHETIC ACTIVITY AND DURATION OF ACTION

No.[a]	R	NR′R″	Local anesthetic act.[b] %	Local anesthetic act.[b] % equimolar concn[c]	Duration, %	ALD_{50}, mg/kg iv
Lidocaine			100	100	100	31.5[e]
1	CH_3	Me_2N	4	4.4	9	102.0
3	CH_3	$C_5H_{10}N$	36.2	44	42.4	67.0
7	C_2H_5	$C_5H_{10}N$	86.7	110[d]	81.8	55.0
10	n-C_3H_7	Et_2N	47.5	67.7	63.2	41.7
17	n-C_4H_9	Me_2N	26.5	31.9	42.4	38.5
18	n-C_4H_9	Et_2N	113.5	148[d]	121.2	6.7
20	n-C_4H_9	C_4H_8NO	27.2	37.6	72.7	40.0
21	n-C_4H_9	Me_2N	15.5	24.9	69.8	40.0
23	n-C_4H_9	n-BuNH	82.8	110[d]	75.6	17.5
24	n-C_4H_9	i-PrNH	64.8	83	97	42.5

[a] Hydrochlorides, except **21**, which is a methiodide. [b] Quantitative local anesthetic activity determined by method of Bulbring and Wajda.[16] Activity and duration are expressed as per cent of equal concentrations of lidocaine. [c] As per cent of lidocaine activity based on equimolar concentrations. [d] Moderate to marked erythema observed in the test wheal within 24 hr. [e] LD_{50} reported by C. D. Barnes and L. G. Eltherington, "Drug Dosage in Laboratory Animals," University of California Press, Berkeley, Calif., 1966, p 131.

ten compounds, all ester derivatives, exhibited a local anesthetic action.

Structural analysis reveals that local anesthetic potency was generally related to the length of the 2-alkoxy substituent as six of the ten active compounds contained the 2-butoxy group. Among the compounds with this butoxy grouping, potency seemed to be enhanced in those with a monoalkylamino substituent (NRR′), although the most intense local anesthetic action was found in **18** which contains a diethylamino substituent (Table III).

In some cases, local anesthetic action was observed in compounds with alkoxy groups of lower molecular weight in position 2. This activity disappears in compounds with an OH group in position 2 and when the CO–O group is replaced by the isosteric CO–NH group (Table II).

It is of interest that **21**, a quaternary methyl iodide salt, exhibited local anesthetic activity. This is in contrast to the findings of Nador, *et al.*,[17] and Löfgren and Fisher,[18] who reported a loss of activity after methyl quaternization of active compounds.

Three compounds, **7**, **18**, and **23**, displayed a local anesthetic potency greater than that of lidocaine. However, tissue necrosis, defined by moderate to marked erythema, occurred within 24 hr after administration. The erythematous area covered most of the wheal site. In general, the compounds became more toxic as local anesthetic potency increased.

Although many of the compounds exhibited vasodilator action in mice, only **5**, **6**, and **16** displayed activity at sublethal, nontoxic doses. Their effect on dog blood pressure was negligible.

(17) K. Nador, F. Herr, G. Pataky, and J. Borsy, *Nature*, **171**, 788 (1953).
(18) N. Löfgren and I. Fisher, *Svensk Kem. Tidskr.*, **58**, 219 (1946).

Synthesis and Antialdosterone Activity of Substituted 2,3,3-Triphenylpropylamines

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Several 2,3,3-triphenylpropylamines were prepared and studied as specific inhibitors of aldosterone biosynthesis. All the compounds caused a significant natriuresis in a rat antialdosterone assay. Two compounds (IVa and j) completely inhibited the *in vitro* biosynthesis of aldosterone without altering deoxycorticosterone or corticosterone levels.

Earlier studies[1,2] from our laboratories demonstrated the effects of simple structural changes on the degree and nature of adrenal corticosteroid inhibition. One compound, 2-amino-1,1-diphenylpropane (VI), emerged from these studies as a potent, specific inhibitor of aldosterone biosynthesis. Its homolog, 2-amino-1,1-diphenylbutane, was less active than the propane.[2] To further examine the effect of substituents on the alkyl side chain of diphenylpropylamines, 2,3,3-triphenylpropylamine (IVa) was prepared and evaluated in a rat antialdosterone assay. The marked natriuretic effect of IVa in this assay led us to prepare a number of similar compounds with a *para* substituent in either a 2- or 3-phenyl group.

Compound IVa has been prepared by Wawzonek and Smolin[3] by the hydrogenation of 2,3-diphenylcinnamonitrile. In our hands, the only product isolated under a variety of conditions was the corresponding unsaturated amine, 2,3,3-triphenylprop-2-enylamine (V). However, IVa and the other amines listed in Table II were

(1) W. A. Zuccarello, B. Blank, G. J. Frishmuth, S. R. Cohen, D. Scaricaciottoli, and F. F. Owings, *J. Med. Chem.*, **12**, 9 (1969).
(2) B. Blank, W. A. Zuccarello, S. R. Cohen, G. J. Frishmuth, and D. Scaricaciottoli, *ibid.*, **12**, 271 (1969).
(3) S. Wawzonek and E. M. Smolin, *J. Org. Chem.*, **16**, 746 (1951).