TABLE III
LOCAL ANESTHETIC ACTIVITY AND DURATION OF ACTION

No.[a]	R	NR′R″	Local anesthetic act.[b] %	Local anesthetic act.[b] % equimolar conen[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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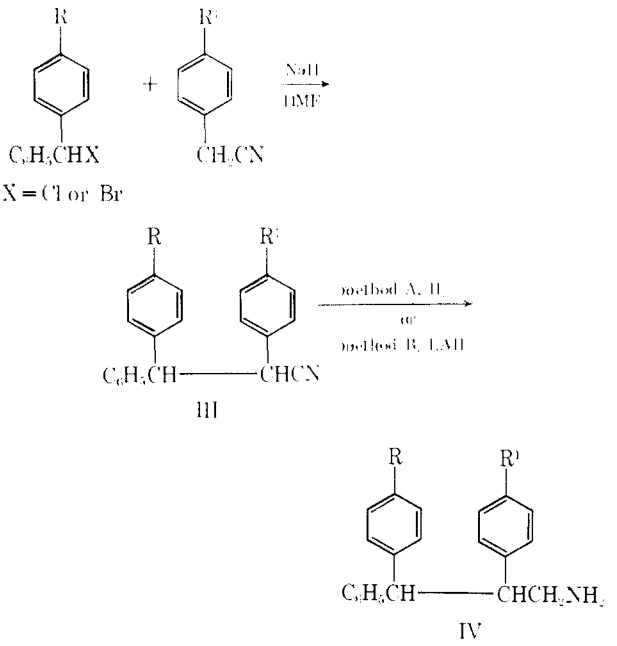
Several 2,3,3-triphenylpropylamines were prepared and studied as specific inhibitors of aldosterone biosynthesis. All the compounds caused a significant natriuresis in a rat antialdosterone assay. Two compounds (IVa and j) completely inhibited the *in vitro* biosynthesis of aldosterone without altering 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).

SCHEME I



prepared conveniently (Scheme I) by the reduction of 2,3,3-triphenylpropionitriles (III), which, in turn, were readily available from benzhydryl halides (I) and phenylacetonitriles (II). The reduction of III to IV was accomplished either catalytically in the presence of Raney Ni (method A) or with LAH (method B). 2-(*p*-Aminophenyl)-3,3-diphenylpropylamine (IVj) was obtained simply by the acid hydrolysis of the corresponding acetamido derivative IVi. Attempts to prepare the sulfone of IVf were unsuccessful. Although IIIj could be prepared readily, it did not prove useful as a precursor of the amine. Alternatively, the N-acetyl derivative of IVf was prepared and oxidized to a sulfone that melted at 162–164°. Unfortunately, neither the sulfone amide nor the amine derived from it could be purified sufficiently to obtain satisfactory analytical data.

Experimental Section[4]

Benzhydryl Halides (I).—*p*-Trifluoromethylbenzhydryl chloride[5] and *p*-methylbenzhydryl chloride[6] were prepared using reported procedures.

p-Methylthiobenzhydryl bromide was obtained by treating *p*-methylthiobenzhydrol[7] (17.5 g, 0.075 mole) in dry C_6H_6 with gaseous HBr. After 4 hr the mixture was diluted with H_2O and the layers were separated. The organic layer was washed, dried, and concentrated. The residual yellow oil crystallized, and was recrystallized from hexane to give 21.2 g (95%) of crystals, mp 48–49°. The crystals rapidly lost halogen and were used without further purification or analysis.

***p*-Acetaminophenylacetonitrile.**—For large-scale preparations, the following procedure proved useful. Commercial *p*-aminophenylacetonitrile hydrochloride (115 g, 0.68 mole) was dissolved in H_2O, and 5% Na_2CO_3 and solid Na_2CO_3 were added to pH 8. After 200 ml of THF was added to form a homogeneous solution, acetylation was accomplished with 340 ml of Ac_2O. The solution was stirred for 2 hr at 0°, and for 1 hr at room temperature. After diluting with H_2O, the THF was removed, and the resulting solid was filtered. The filtrate was extracted with $CHCl_3$ and the $CHCl_3$ extracts were concentrated to give a second crop of product. Recrystallization of the combined crops from boiling H_2O yielded 112.5 g of product, mp 85–86° after being dried in a vacuum desiccator. A sample recrystallized from C_6H_6–petroleum ether (bp 40–60°) and dried *in vacuo* at 65° melted at 95–97° (lit.[8] mp 95–97°).

***p*-Methylsulfonylphenylacetonitrile.**—To a stirred solution of 4.2 g (0.025 mole) of *p*-methylthiophenylacetonitrile[9] in 50 ml of HOAc was added dropwise 50 ml of 30% H_2O_2 in 50 ml of HOAc. After being stirred for 15 min at room temperature and for 2 hr on a steam bath, the mixture was cooled and diluted with several volumes of ice water. The resulting solid was filtered, washed, dried, and recrystallized from C_6H_6, yield 4.0 g (82%), mp 130–131°. *Anal.* ($C_9H_9NO_2S$) C, H, N, S.

2,3,3-Triphenylpropionitriles (III) (Table I).—An equivalent amount of II in a minimum volume of dry DMF was added carefully to a stirred suspension of NaH (mineral oil dispersion) in dry DMF (100 ml/mmole of II). After the slight initial exothermic reaction had subsided, an equimolar quantity of I in a small volume of dry DMF was added dropwise below 50–55°. The mixture was stirred for 15 min; an additional 10% of the original amount of I in dry DMF was added and stirring was continued for 20 min at room temperature, and for 1 hr on a steam bath. The resulting mixture was cooled, carefully diluted with several volumes of H_2O, and acidified if necessary with a small volume of HOAc. The product was isolated by filtration or by extraction into EtOAc. The EtOAc extracts were washed, dried, and concentrated. If the residue was an oil, it was distilled or triturated with an appropriate solvent. The solids produced were recrystallized.

2,3,3-Triphenylpropylamines (IV) (Table II). A.—A solution of 0.40 mole of IIIa, b, e, or i in MeOH saturated with NH_3 was hydrogenated at 80° under a pressure of 70 kg/cm² of H_2 in the presence of Ra(Ni). The catalyst was removed, and the filtrate was concentrated. The residue was recrystallized or converted to a hydrochloride with ethereal HCl.

B.—A solution of 0.031 mole of IIIc, d, f, g, or h in 50 ml of THF was added dropwise to a stirred suspension of 3.6 g (0.094 mole) of LAH in 200 ml of Et_2O. The mixture was stirred under reflux for 3 hr and cooled, and the complex was decomposed by the sequential dropwise addition of 3.6 ml of H_2O, 3.6 ml of 10% NaOH, and 10.7 ml of H_2O. The resulting mixture was stirred for 45 min, and the granular precipitate was filtered and washed well with Et_2O. The filtrate was dried (Na_2SO_4) and concentrated. The residue was redissolved in Et_2O and converted to a hydrochloride.

2-(*p*-Aminophenyl)-3,3-diphenylpropylamine Dihydrochloride Hemihydrate (IVj).—A mixture of 137 g (0.4 mole) of IVi, 210 ml of concentrated HCl, 420 ml of HOAc, and 420 ml of H_2O was stirred under reflux overnight. An additional 50 ml of HCl was added, and heating was continued for 5 hr. After being cooled and concentrated, the residue was azeotroped three times with fresh portions of dry EtOH and three times with fresh portions of C_6H_5Me. The residual brown solid was recrystallized.

N-Acetyl-2-(*p*-methylthiophenyl)-3,3-diphenylpropylamine. A mixture of 6.1 g (0.018 mole) of IVf (free base), 2.5 ml of Ac_2O, 0.5 g of NaOAc, and 5 ml of HOAc was warmed on a steam bath for 2 hr. The resulting solution was mixed with ice and extracted with EtOAc. The extracts were washed (H_2O, 5% $NaHCO_3$) and dried (Na_2SO_4), the solvent was removed, the residue was triturated with hexane–Et_2O, and the solid was recrystallized from C_6H_6–petroleum ether and then from MeOH–H_2O to give 62% of product, mp 127–129°. *Anal.* ($C_{24}H_{25}NOS$) C, H, N, S.

2,3,3-Triphenylprop-2-enylamine Hydrochloride (V).—A solution of 34.7 g (0.12 mole) of 2,3-diphenylcinnamonitrile[10] in MeOH saturated with NH_3 was hydrogenated at 60° under a pressure of 4.2 kg/cm² of H_2 in the presence of Ra(Ni). The catalyst was removed, the filtrate was concentrated, and the residue was recrystallized from MeOH. In this way 5.3 g of starting material was recovered. The methanolic filtrate was taken to dryness, and the residue was azeotroped three times with fresh portions of C_6H_6 to give 28.1 g (80%) of the desired amine. A portion was converted to the hydrochloride and recrystallized from EtOH–Et_2O, mp 214°. *Anal.* ($C_{21}H_{19}N \cdot HCl$) C, H, Cl, N.

(4) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected.

(5) S. Rossi and W. Butta, *Farmaco, Ed. Sci.*, **16**, 326 (1961).

(6) A. G. Davies, J. Kenyon, B. J. Lyons, and T. A. Rohan, *J. Chem. Soc.*, 3474 (1954).

(7) A. Mustafa, *ibid.*, 352 (1940).

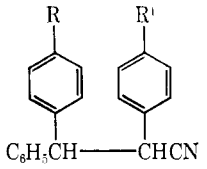
(8) S. Gabriel, *Ber.*, **15**, 834 (1882).

(9) J. M. van der Zanden, J. Nieuwenhuis, and H. J. T. Bos, *Rec. Trav. Chim.*, **76**, 669 (1957).

(10) S. Wawzonek and E. M. Smolin, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 387.

TABLE I

2,3,3-TRIPHENYLPROPIONITRILES

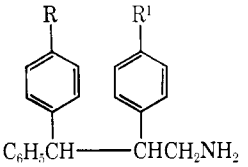


No.	R	R¹	Mp or bp (mm), °C	Recrystn solvent	% yield	Formula	Analyses
IIIa	H	H	99–100.5[a]	MeOH	72	$C_{21}H_{17}N$	
b	CH_3	H	195–197 (2)		48	$C_{22}H_{19}N$	C, H, N
c	SCH_3	H	128–130	C_6H_6–petr ether[b]	13	$C_{22}H_{19}NS$	C, H, N, S
d	CF_3	H	180–182	EtOH	30	$C_{22}H_{16}F_3N$	C, H, N
e	H	CH_3	88–89	Hexane	35	$C_{22}H_{19}N$	C, H, N
f	H	SCH_3	104–105	MeOH[b]	47	$C_{22}H_{19}NS$	C, H, N, S
g	H	OCH_3	133–134	MeOH	38	$C_{22}H_{19}NO$	C, H, N
h	H	Cl	123–125	MeOH	65	$C_{21}H_{16}ClN$	C, H, Cl, N
i	H	$NHCOCH_3$	232–234	EtOH	61	$C_{23}H_{20}N_2O$	C, H, N
j	H	SO_2CH_3	160–162	MeOH–H_2O	38	$C_{22}H_{19}NO_2S$	C, H, N, S

[a] E. P. Kohler, *Am. Chem. J.*, **35**, 386 (1950), reported mp 102°. [b] Initial purification was effected by chromatography on a silica gel column with C_6H_6–petroleum ether (bp 40–60°) (1:1 and 2:1 by volume).

TABLE II

2,3,3-TRIPHENYLPROPYLAMINES



No.	R	R¹	Mp, °C	Method	Recrystn solvent	% yield	Formula	Analyses
IVa	H	H	269–271[a]	A	EtOH–Et_2O	87	$C_{21}H_{21}N \cdot HCl$	C, H
b	CH_3	H	236–238	A	MeOH–EtOAc–petr ether	20	$C_{22}H_{23}N \cdot HCl$	C, H, Cl, N
c	SCH_3	H	227–230	B	*n*-BuOH–Et_2O	25	$C_{22}H_{23}NS \cdot HCl$[b]	C, H, Cl, N
d	CF_3	H	223–224	B	EtOAc–Et_2O	54	$C_{22}H_{20}F_3N \cdot HCl$	C, H, Cl, N
e	H	CH_3	254–257	A	EtOH–Et_2O	71	$C_{22}H_{23}N \cdot HCl$	C, H, Cl, N
f	H	SCH_3	140[c]	B	EtOH–Et_2O	4	$C_{22}H_{23}NS \cdot HCl$[d]	C, H, Cl, N
g	H	OCH_3	230–232	B	EtOH–Et_2O	70	$C_{22}H_{23}NO \cdot HCl$	C, H, Cl, N
h	H	Cl	274–276	B	*n*-BuOH–Et_2O	59	$C_{21}H_{20}ClN \cdot HCl$	C, H, Cl, N
i	H	$NHCOCH_3$	216	A	C_6H_5Me	99	$C_{23}H_{24}N_2O$	C, H, N
j	H	NH_2	300[c,e]	*f*	EtOH–Et_2O	93	$C_{21}H_{22}N \cdot 2HCl$[b]	C, H, Cl, N

[a] Lit.[3] mp 269–272°. [b] Hemihydrate. [c] With decomposition. [d] Hydrate. [e] Uncorrected. [f] Prepared by hydrolysis of IVi.

Biological Testing.—The natriuretic effects of the test compounds were determined in an antialdosterone assay.[11] Three of the most interesting compounds, IVa and j and V, were evaluated in an *in vitro* assay[1] designed to study the effect of the compounds on adrenal corticosteroid biosynthesis.

Discussion

All compounds in Table III exerted a significant ($P < 0.05$) natriuretic effect at oral doses of 40 mg/kg. The reference compounds, 2-(*p*-aminophenyl)-2-phenethylamine,[1] 2,2-bis(*p*-aminophenyl)butan-3-one (amphenone), and 3-(1,2,3,4-tetrahydro-1-oxo-2-naphthyl)pyridine (VII),[12] were inactive at oral doses of 70 mg/kg or greater. Compound VII has been reported to be an effective natriuretic agent in dogs and humans, and this activity has been related to the compound's ability to decrease aldosterone secretion.[13] Of the reference compounds tested, only VII inhibited aldosterone production in the isolated rat adrenal system at a concentration (5×10^{-4} *M*) which did not alter either corticosterone or deoxycorticosterone levels. Compounds IVa and j and V produced similar alterations in the corticosteroid pattern *in vitro*, but at a lower concentration (5×10^{-5}

TABLE III

ACTIVITY IN RAT ANTIALDOSTERONE ASSAY

No.	Activity[a]
IVa	++
b	±
c	±
d	±
e	+
f	±
g	++
h	++
j	++
V	++

[a] ±, weak activity, urinary Na^+ levels of 1–2 mg; +, moderate activity, urinary Na^+ levels of 2–4 mg; ++, potent activity, urinary Na^+ levels >4 mg.

(11) H. L. Saunders, B. Steciw, V. Kostos, and J. Tomaszewski, *Steroids*, **7**, 513 (1966).

(12) W. L. Bencze and L. I. Barsky, *J. Med. Pharm. Chem.*, **5**, 1298 (1962).

(13) T. Bledsoe, D. P. Island, A. M. Riondel, and G. W. Liddle, *J. Clin. Endocrinol. Metab.*, **24**, 740 (1964).

M). A comparable potency relationship was observed *in vivo*.

In cold-stressed rats,[11] IVa and j and V did not decrease peripheral plasma corticosterone levels at oral doses which exceeded those used to induce a natriuretic response (100 mg/kg).[14] However, in rats, V caused adrenal hypertrophy, decreased male sex accessory organ weights, and decreased the rate of gain in body weight. These effects have not been observed with IVa and j.

Earlier studies[1,2] had established that VI possessed a highly desirable spectrum of activity in natriuretic and adrenal corticosteroid inhibition assays. It caused marked natriuresis in Na^+-depleted rats (a finding consistent with, but not proof of, aldosterone inhibition) at oral doses which did not suppress peripheral plasma corticosterone levels.[1] *In vitro* findings supported the *in vivo* observations.[1,2] Among the natriuretic agents tested in our laboratories, VI had been the most potent of those which appeared to act by selectively inhibiting aldosterone biosynthesis.[14] In the present series of compounds, both IVa and j had the same desirable biological selectivity as VI but were more active. In comparative studies, it was shown that VI was about two to three times as potent as VII. In turn, IVa was about twice as potent as VI, and IVj was about twice as potent as IVa (about four times as potent as VI and about eight to twelve times as potent as VII).[14] The biological activity of IVj will be described in greater detail elsewhere.

(11) W. A. Zuccarello and G. J. Frishmuth, unpublished observations.

Psychosedative Agents. N-(4-Phenyl-1-piperazinylalkyl)-Substituted Cyclic Imides

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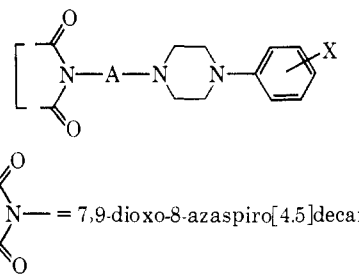
Fifty-two N-substituted cyclic imides bearing a 4-phenyl-1-piperazinylalkyl moiety were synthesized and screened as psychosedative agents. The results of two test methods, (a) antagonism of amphetamine–aggregation stress in mice and (b) suppression of the conditioned avoidance response in rats, indicate that these compounds possess in varying degrees psychotropic properties typical of major tranquilizers.

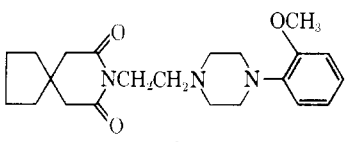
As part of an effort to develop nonphenothiazine psychosedative agents, we have prepared a series of N-(4-phenyl-1-piperazinylalkyl)-substituted cyclic imides of the following structure. The series is an extension of an earlier lead compound (**25**), which has been shown in preliminary screening to exert a selective depressant effect in mice.



N— = 7,9-dioxo-8-azaspiro[4.5]decanyl,

2,4-dioxo-3-azaspiro[5.5]undecanyl, or glutarimido radicals

A = alkylene chain
X = various substituents



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(1) To whom inquiries should be addressed.

Chemical Synthesis.—The compounds were generally synthesized either by condensing 1-(ω-aminoalkyl)-4-phenylpiperazine with the corresponding anhydride in pyridine, or by a nucleophilic substitution of an ω-chloroalkylimide with the appropriate phenylpiperazine (Scheme I). Other synthetic methods leading to special compounds are described in the Experimental Section. The physical constants of 52 N-(4-phenyl-1-piperazinylalkyl)-substituted cyclic imides are listed in Table I.

Biological Data.—The difference between "phenothiazine"-type psychosedative agents and other nonspecific sedative–hypnotic drugs on the behavior of test animals has been discussed by Domino.[2] Of special interest to us are the effects of the test compound on the conditioned avoidance response and on amphetamine toxicity. The effect of a compound on the conditioned avoidance response differentiates the compound as a tranquilizing drug from a nonspecific sedative–hypnotic drug. Its effect on amphetamine toxicity is to detect its possible value in treating stressful conditions in man. For the evaluation of the conditioned response the method generally used is that of Cook and Weidley.[3] A modified test[4] was developed in these laboratories which utilizes the environment of the test chamber itself as the conditioned stimulus. The ED_{50}'s for

(2) E. F. Domino in "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 391.
(3) L. Cook and E. Weidley, *Ann. N. Y. Acad. Sci.*, **66**, 740 (1957).
(4) J. R. Albert, *Pharmacologist*, **4**, 152 (1962).