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1-Substituted Vinyl-1-phthalanpropylamines as Potential Antidepressant Agents

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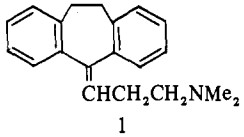
The preparation of a series of 1-substituted vinyl-1-phthalanpropylamines (**5**) and their ability to antagonize the effects of tetrabenazine in mice are described. The subject compounds were obtained from diethyl phthalate in three stages. Reaction of this ester with excess methylmagnesium bromide gave 1,3,3-trimethyl-1-phthalanol (**7**) which on treatment with perchloric acid afforded 1,1,3-trimethyl-1*H*-isobenzofurylium perchlorate (**8**) in 60% overall yield. The last substance condensed with a variety of arylaldehydes to give a series of 3-substituted vinyl-1,1-dimethyl-1*H*-isobenzofurylium perchlorates (**9**), which reacted with certain substituted aminopropylmagnesium halides to give the title compounds.

The clinical utility of amitriptyline (**1**), imipramine (**2**), and structurally similar substances has prompted the preparation of a variety of related compounds for testing as potential antidepressants.† The 11-substituted-5,10-epoxy-5*H*-dibenzo[*a,d*]cycloheptene-5-propylamines (**3**)[2] are particularly interesting, for they represent a departure from the tricyclic system characteristic of many of the analogs of amitriptyline, and one clinical report indicates that daily doses of 8–24 mg of *trans*-11-hydroxy-**3** (R = α-OH) stimulate depressed patients.[3] Phthalan (**4**),[4] which can be viewed as an analog of **3** arising from cleavage of the 11–11a bond, also possesses thymoleptic properties.[5] The activity of **4** in reversing tetrabenazine-induced depression in mice (Table I) prompted us to search for a more interesting congener, and in the present paper we describe the synthesis and certain biological properties of a series of related 1-substituted vinyl-1-phthalanpropylamines (**5**) and a congener in which the phthalan system is completely reduced, *e.g.*, **6**.



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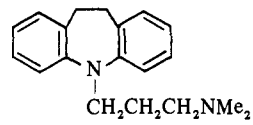

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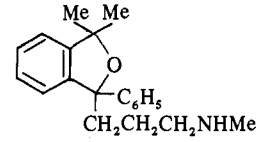

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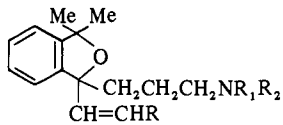

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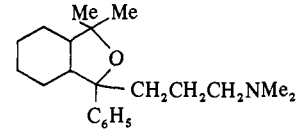

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†For a recent comprehensive review see ref 1.

Table I. Activity of Phthalans in Reversing Tetrabenazine Effects in Mice[a]

Compound	Lowest effective dose, mg/kg, ip
Amitriptyline (1)	3
Imipramine (2)	1.3
N,3,3-Trimethyl-1-phenyl-1-phthalanpropylamine (4) hydrochloride	0.8
N,N,3,3-Tetramethyl-1-styryl-1-phthalanpropylamine (14b) oxalate	0.8
N,N,3,3-Tetramethyl-1-styryl-1-phthalanpropylamine (14b) fumarate	1.6
N,3,3-Trimethyl-1-styryl-1-phthalanpropylamine (16) fumarate	1.6
N,N,3,3-Tetramethyl-1-(*p*-methoxystyryl)-1-phthalanpropylamine (**5j**) hydrochloride	0.8
N,N,3,3-Tetramethyl-1-(*p*-methylstyryl)-1-phthalanpropylamine (**5h**) oxalate	3
N,N,3,3-Tetramethyl-1-(*o*-methylstyryl)-1-phthalanpropylamine (**5j**) oxalate	6
N,N,3,3-Tetramethyl-1-(*p*-isopropylstyryl)-1-phthalanpropylamine (5m)	3
N,N,3,3-Tetramethyl-1-(3,4-dimethoxystyryl)-1-phthalanpropylamine (**5k**)	12.5

[a]See Greenblatt and Osterberg[9] for details of this assay.

The former compounds were prepared in three stages from diethyl phthalate (see Scheme I). Reaction of this ester with methylmagnesium bromide gives the phthalanol

Scheme I

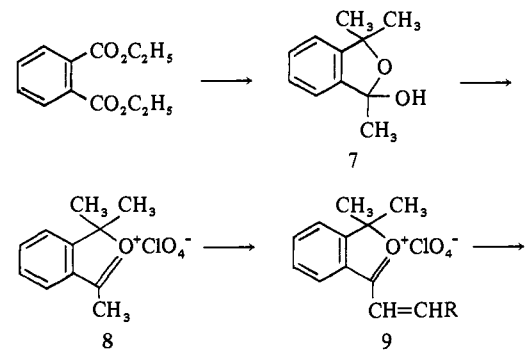
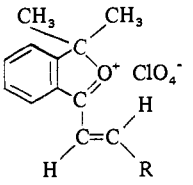


Table II. 3-Substituted Vinyl-1,1-dimethyl-1*H*-isobenzofurylium Perchlorates (9)



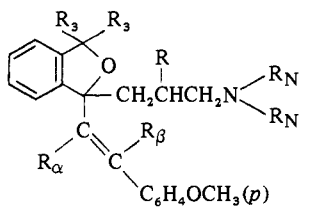
No.	R	Yield, %	Mp, °C[a]	Formula	Analyses
9a		100	196-198	$C_{16}H_{15}ClO_5S$	C, H, Cl, S
9b		87	169-170	$C_{16}H_{15}ClO_6$	C, H; Cl[b]
9c	*p*-BrC_6H_4	88	196-199	$C_{18}H_{16}BrClO_5$	C, H, Br; Cl[c]
9d	*p*-ClC_6H_4	95	195-198	$C_{18}H_{16}Cl_2O_5$	C, H, Cl
9e	*m*-ClC_6H_4	81	179-181	$C_{18}H_{16}Cl_2O_5$	C, H, Cl
9f	*o*-$CH_3C_6H_4$	93	184-185	$C_{19}H_{19}ClO_5$	C, H, Cl
9g	*m*-$CH_3C_6H_4$	87	186-187	$C_{19}H_{19}ClO_5$	C, H, Cl
9h	*p*-$CH_3C_6H_4$	98	210-212	$C_{19}H_{19}ClO_5$	C, H; Cl[d]
9i	*o*-$CH_3OC_6H_4$	96	199-200	$C_{19}H_{19}ClO_6$	C, H, Cl
9j	*p*-$CH_3OC_6H_4$	96	225-226	$C_{19}H_{19}ClO_6$	C, H, Cl
9l		98	204-205	$C_{21}H_{21}ClO_5$	C, H, Cl
9m	*p*-$(CH_3)_2CHC_6H_4$	57	180-183	$C_{21}H_{23}ClO_5$	C, H, Cl
9n	3,4,5-$(CH_3O)_3C_6H_2$	56	184-185	$C_{21}H_{23}ClO_8$	C, H, Cl
9o	2-$C_{10}H_7$	98	243	$C_{22}H_{19}ClO_5$	C, H, Cl
9p	1-$C_{10}H_7$	92	209-210	$C_{22}H_{19}ClO_5$	C, H, Cl
9q	4-CH_3O-1-$C_{10}H_6$	98	252	$C_{23}H_{21}ClO_6$	C, H, Cl
9r	*p*-$C_6H_5C_6H_4$	91	218	$C_{24}H_{21}ClO_5$	C, H, Cl

[a] All isobenzofurylium perchlorates decomposed on melting. [b] Cl: calcd, 10.47; found, 9.91. [c] Cl: calcd, 8.29; found, 9.31. [d] Cl: calcd, 9.77; found, 10.27.

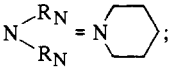
7, which is converted in 60% yield into the oxonium perchlorate **8** without isolation.[6]

A variety of aromatic aldehydes condense with the oxonium perchlorate **8** to give the 3-substituted vinyl-1,1-dimethyl-1*H*-isobenzofurylium perchlorates (**9**) of Table II. This procedure is also applicable to aromatic ketones as the preparation of 3-(*p*-methoxy-β-methylstyryl)-1,1-dimethylisobenzofurylium perchlorate from *p*-methoxyacetophenone demonstrates (see Experimental Section). The isobenzofurylium perchlorates react with dimethylaminopropylmagnesium chloride to give the analogs of *N*,3,3-trimethyl-1-phenyl-1-phthalanpropylamine (**4**) listed in Table II.

The adaptability of this three-stage sequence to the synthesis of other analogs of **4** is apparent, and it was used to vary the *gem*-dialkyl group as in **10a** and introduce methyl substituents at the α and β positions of the 1-styryl function (**10b** and **10c**, respectively) and the 2 position of the propylamine side chain (**10d**). Moreover, appropriate choice of the γ-substituted aminopropyl halide gave the nitrogen-substituted analogs **10e** and **10f**.



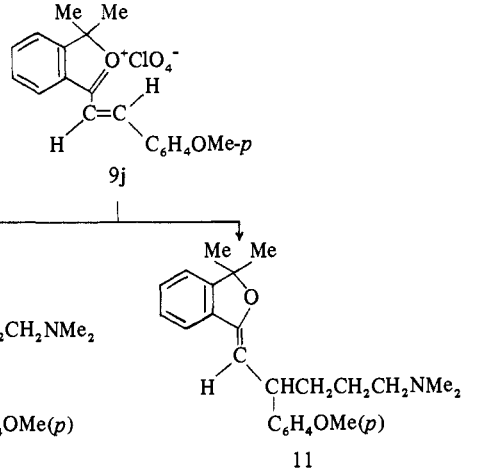
10a, R_3 = Et; R_N = Me; R = R_α = R_β = H
b, R_3 = R_N = R_α = Me; R = R_β = H
c, R_3 = R_N = R_β = Me; R = R_α = H
d, R_3 = R_N = R = Me; R_α = R_β = H
e, R_3 = Me; R_N = Et; R = R_α = R_β = H



f, R_3 = Me; R = R_α = R_β = H

In general, no effort was made to attain optimum yields for the products of Table II and those of general structure **10**. However, the reaction mixture derived from 3-(*p*-methoxystyryl)-1,1-dimethyl-1*H*-isobenzofurylium perchlorate (**9j**) and dimethylaminopropylmagnesium chloride was investigated carefully, inasmuch as we recognized the possibility of concurrent 1,2 and 1,4 additions of Grignard reagents to oxonium salts such as **9**. Indeed, these pathways are competitive, since **5j** (54%) and **11** (19%) were isolated from the cited reaction.

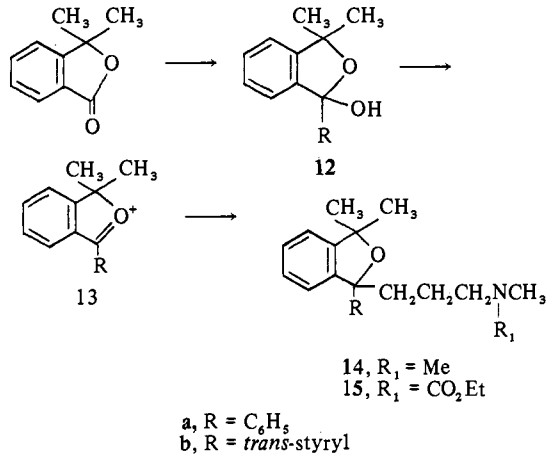
The structure of the major product, as well as certain other members of Table II, is dictated by the presence of vinyl proton resonances in their nmr spectra at δ 6.27–6.42 and 6.47–6.52 having the usual trans-olefinic coupling constants of 15.5–16.0 Hz. Other products of 1,2 addition had nmr spectra in which the vinyl protons appeared as a single resonance at δ 6.50–6.67. In contrast, the nmr spectrum of **11** exhibited a *single* olefinic proton resonance at δ 4.95 possessing the expected multiplicity.



9j

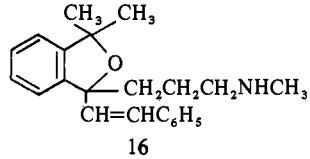
5j **11**

Scheme II



Our method for the preparation of **4** involved a modification of the above general procedure. Thus, reaction of 3,3-dimethylphthalide with phenylmagnesium bromide furnished 3,3-dimethyl-1-phenyl-1-phthalanol (**12a**) in moderate yield (see Scheme II). The absence of a carbonyl stretching frequency in the ir spectrum of the product precluded any appreciable quantity of the tautomeric ketone, and recovery of **12a** from treatment with dimethylaminopropylmagnesium chloride necessitated an alternate procedure for its conversion into **4**. Treatment of phthalanol **12a** with perchloric acid gives the oxonium perchlorate **13a**,[7] which then reacts with dimethylaminopropylmagnesium chloride to furnish **14a**. Conversion of the tertiary amine into **4** proceeded well by reaction with ethyl chlorocarbonate and saponification of the resulting **15a**. A similar sequence, in which styrylmagnesium bromide was substituted for the phenyl Grignard reagent, constituted our initial preparation of *N,N*,3,3-tetramethyl-1-styryl-1-phthalanpropylamine (**14b**) (Scheme II).

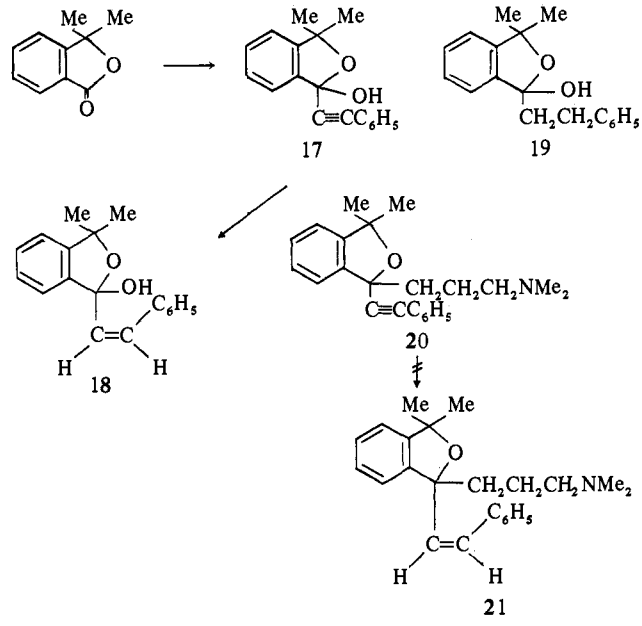
1-(*p*-Methylstyryl)-1-phthalanpropylamine (**5h**) was converted into a quaternary salt by treatment with methyl iodide, and the monomethylamino derivative **16** was prepared from **14b** by the usual procedure (see Experimental Section).



The method of preparation, as well as the nmr spectra, of the styryl derivatives **5**, **10**, and **16** requires trans disposition of the substituents about the olefinic center. The preparation of the cis isomer corresponding to **14b**, *e.g.*, **21**, was attempted by addition of phenylethynylmagnesium bromide to 3,3-dimethylphthalide, which gave the phthalanol **17** in good yield (Scheme III). Catalytic hydrogenation of **17** in pyridine using a Pd–$BaSO_4$ catalyst furnished the *cis*-styrylphthalanol **18**. If methanol was used as the solvent for the hydrogenation, 2 equiv of gas was rapidly absorbed to give the phenethylphthalanol **19**. The *cis*-styryl derivative **18** proved to be quite susceptible to isomerization. Thus, if cadmium chloride was used to remove traces of pyridine in the attempted isolation of **18**, it isomerized to the trans derivative **12b**.‡ Moreover, conversion of **18** into an oxonium salt with perchloric acid gave the trans isomer **13b**.

‡ For a discussion of metal-catalyzed cis-trans isomerizations see ref 8.

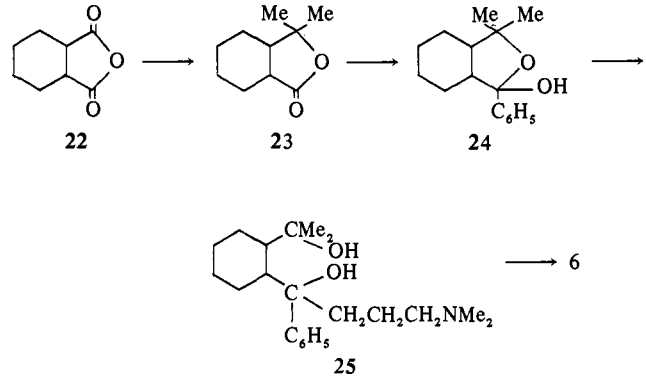
Scheme III



Since **18** could not be used to prepare the desired *cis*-styryl derivative, the acetylenic derivative **17** was converted into the phthalanpropylamine **20**. However, all attempts to hydrogenate under conditions which would maintain the desired stereochemistry failed to give reduction. Apparently the catalyst was poisoned by the amine function in **26**.

The preparation of the saturated derivative **6** was accomplished by a series of Grignard reactions using hexahydrophthalic anhydride (**22**) as the starting material (see Scheme IV). Reaction of **22** with methylmagnesium bromide and treatment of the intermediate alcohol with hydrochloric acid gave the lactone **23** in about 50% yield. Lactone **23** was converted essentially quantitatively into the octahydroisobenzofuranol **24** by treatment with phenylmagnesium bromide. Submission of **24** to the action of dimethylaminopropylmagnesium chloride afforded 34% of diol **25**, which was readily cyclized into **6** with hydrochloric acid. The facility with which the cyclization of **25** occurred suggests that the cis geometry of anhydride **22** is preserved in product **6**, but this feature was not demonstrated rigorously.

Scheme IV



Biology. Many of the phthalans have a high degree of activity in antagonizing the effects of tetrabenazine in mice, a property which indicates potential antidepressant effects. Data for the most interesting compounds and two standard drugs are given in Table I; the lowest effective dose for the remaining compounds prepared in our investigation was >25 mg/kg. Thus, the data indicate that the severe restrictions

exist on the structure of the 1-substituted vinyl-1-phthalanpropylamines for high activity in this assay. The 1-phenyl (**4**) and 1-styryl (**16**) derivatives of *N*,3,3-trimethyl-1-phthalanpropylamine are equivalent, and the latter derivative is not significantly more active than the tertiary amine **14b**. Substitution in the benzene ring of the styryl group by alkyl (methyl, isopropyl) and methoxy gives compounds with good activity. However, substitution by chlorine, bromine, and phenyl has a deleterious effect. Moreover, those compounds wherein the benzene ring is replaced by thienyl (**5a**), furyl (**5b**), indanyl (**5l**), and naphthyl (**5o–q**) nuclei are also less interesting than **16**.

Homologation of the 3,3-dimethyl grouping as in **10a** and of the dimethylamino function (**10e**) and substitution of alkyl groups on the double bond of the styryl function (**10b**, **10c**) gave compounds having less activity than **16**. The sensitivity of activity to variations in the propylamine is further illustrated by the branched analog **10d** and the piperidino derivative **10f**, which were among the less interesting analogs.

Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The petr ether used was that fraction with bp 30–60°.

1,1,3-Trimethyl-1*H*-isobenzofurylium Perchlorate (8). A. A solution of 100 g (0.45 mole) of diethyl phthalate in 400 ml of ether was added dropwise over 1 hr to 1.2 l. of mechanically stirred 1.5 *M* ethereal methylmagnesium bromide; the reaction temperature was maintained at −3 to 0° through the addition. On completion of the addition stirring was continued at 0–5° for 3 hr. The reaction was then treated *cautiously* with 250 ml of saturated NH_4Cl solution by dropwise addition. The ether solution was decanted from the inorganic residue which was treated with ether, H_2O, and 20% HCl in order to dissolve the solids. All ether solutions were combined, washed with water, dried, and evaporated to 67 g (86%) of 1,3,3-trimethyl-1-phthalanol (7). Although this crude product could be crystallized with much loss, it proved advantageous to convert the crude into the perchlorate directly.

In a typical preparation 6.0 g (35 mmoles) of the crude phthalanol was dissolved in 60 ml of HOAc and treated with 3 ml of 72% $HClO_4$. Scratching of the container walls induced crystallization. The mixture was chilled in an ice bath, and the solid was collected, washed with ether and then petr ether, and dried to give 6.08 g (69%) of white plates: mp 164–166° (lit. mp[7] 160–161°).

B. In the manner described above treatment of 2.60 g (16 mmoles) of dimethylphthalide in 30 ml of ether with 6.7 ml of a 3 *M* ethereal methylmagnesium bromide solution gave 2.44 g of a crude oil from which 0.82 g (31%) of dimethylphthalide, mp 59–61°, was recovered by crystallization from petr ether. The filtrate was evaporated and the residue was dissolved in ether. Addition of a $HClO_4$–HOAc–Et_2O (3.4:9.6:100) solution caused precipitation of 1.01 g (24%) of the perchlorate as white crystals: mp 160–161° dec.

3-Substituted Vinyl-1,1-dimethyl-1*H*-isobenzofurylium Perchlorates (9). The following preparation indicates the general procedure.[10] A warm solution of 14.0 g (0.054 mole) of 1,1,3-trimethyl-1*H*-isobenzofurylium perchlorate in 280 ml of HOAc was treated with 8.85 g (7.9 ml, 0.065 mole) of *p*-anisaldehyde. The solution was heated at reflux temperature for 30 min, cooled, and filtered. The collected solid was washed successively with HOAc, Et_2O, and petr ether to give 19.9 g (96%) of 3-(*p*-methoxystyryl)-1,1-dimethyl-1*H*-isobenzofurylium perchlorate as brilliant red crystals, mp 225–226° dec. The characterization of this substance and the other 1*H*-isobenzofurylium perchlorates is given in Table II.

N,*N*,3,3-Tetramethyl-1-substituted-vinyl-1-phthalanpropylamines (5). The following preparation of *N*,*N*,3,3-tetramethyl-1-(*p*-methoxystyryl)-1-phthalanpropylamine illustrates the general procedure.

A solution of dimethylaminopropylmagnesium chloride in 300 ml of tetrahydrofuran was prepared in the usual way from 4.6 g (0.208 g-atom) of magnesium and 25.4 g (0.208 mole) of dimethylaminopropyl chloride. This solution was heated to reflux temperature, and with stirring 19.1 g (0.052 mole) of 3-(*p*-methoxystyryl)-1,1-dimethyl-1*H*-isobenzofurylium perchlorate was added portionwise. Decolorization of the perchlorate was almost instantaneous upon addition; the solution was heated at reflux temperature for 3 hr after completion of the addition. The cooled reaction was decomposed with NH_4Cl solution, and the mixture was extracted with Et_2O. The extracts were washed with H_2O, and these washings were discarded.

The organic solution was extracted with three 150-ml portions of 20% HOAc. The acid solution was washed with Et_2O, then cooled, and rendered alkaline with NaOH. The alkaline solution was extracted with ether, and the extract was washed with H_2O, dried, and evaporated to give 16.6 g of a gum. This material was dissolved in 40 ml of EtOH, treated with a hot solution of 4.1 g of oxalic acid in 20 ml of EtOH, and cooled for 18 hr to give in several crops 8.17 g (35%) of white crystals: mp 195–199°. The characterization of this salt is given in Table III.

Evaporation of the filtrates gave a residue that was dissolved in H_2O and rendered alkaline with 10% NaOH. The liberated bases were isolated with CH_2Cl_2 in the usual manner to give 9.80 g of an amber gum. This material was subjected to partition chromatography using a heptane–methanol (1:1) system. The fraction with peak hold-back volume 2.2 (V_m/V_S = 1.74) was evaporated to give an additional 3.50 g (54% total) of *N*,*N*,3,3-tetramethyl-1-(*p*-methoxystyryl)-1-phthalanpropylamine (**5j**); the identity of this material was established by conversion of an aliquot into the oxalate salt.

The column was then washed with methanol, and the wash was evaporated to give 3.60 g (19%) of *N*,*N*,3,3-tetramethyl-δ-(*p*-methoxyphenyl)-$\Delta^{1,6}$-phthalanpentylamine (11) as an amber oil. This material was converted into an oxalate salt; this salt failed to melt definitively despite several recrystallizations from EtOH–heptane and CH_2Cl_2–petr ether: *m/e* 365 (parent ion, 25), 292 (2), 279 (5), 84 (CH_2=$CHCH$=NMe_2·$^+$, 60), 71 (CH_2=$CHNMe_2$·$^+$, 70), 58 (CH_2=NMe_2·$^+$, 100). *Anal.* ($C_{24}H_{31}NO_2 \cdot C_2H_2O_4$) C, H, N.

In addition to the products of Table III, the following substances were prepared by the general procedure.

3,3-Diethyl-1-(*p*-methoxystyryl)-*N*,*N*-dimethyl-1-phthalanpropylamine (10a). The crude product was purified by chromatography on diatomaceous silica using a heptane–methanol (1:1) system; the fraction with peak hold-back volume 1.6 (V_m/V_S = 1.67) gave 37% of amber oil, the oxalate of which was recrystallized from EtOH to give white crystals: mp 168–169°. *Anal.* ($C_{26}H_{35}NO_2 \cdot C_2H_2O_4$) C, H, N.

1-(*p*-Methoxystyryl)-*N*,*N*,β,3,3-pentamethyl-1-phthalanpropylamine (10b). The product was converted into the oxalate salt in the usual manner. Repeated crystallizations of the salt from EtOH gave 38% of white crystals: mp 187–190°. *Anal.* ($C_{25}H_{33}NO_2 \cdot C_2H_2O_4$) C, H, N.

N,*N*-Diethyl-1-(*p*-methoxystyryl)-3,3-dimethyl-1-phthalanpropylamine (10e). Distillation of the free base under reduced pressure gave 66% of amber liquid: bp 188–190° (0.15 mm). *Anal.* ($C_{26}H_{35}NO_2$) C, H, N.

1-[3-(3,3-Dimethyl-1-styryl-1-phthalanyl)propyl]piperidine (10f). This material was converted into its oxalate salt in the usual manner; several recrystallizations from EtOH gave 330 mg (8%) of white crystals: mp 145–147°. *Anal.* ($C_{26}H_{33}NO \cdot C_2H_2O_4$) C, H, N.

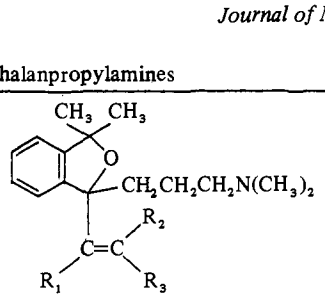
3,3-Diethyl-1-methyl-1*H*-isobenzofurylium Perchlorate. Treatment of a solution of 9.50 g (50 mmoles) of diethylphthalide[11] in 130 ml of tetrahydrofuran with 20 ml of 3 *M* ethereal methylmagnesium bromide as described above gave 9.33 g (90%) of an amber oil. A 3.0-g aliquot of this material was dissolved in 40 ml of HOAc–Et_2O (1:1) and treated with 1.3 ml of 72% $HClO_4$. Crystallization was induced in the usual manner, and the mixture was chilled in ice. The solid was collected by filtration, washed successively with ether and petr ether, and dried to give 2.15 g (49%) of crystals: mp 125–126° dec. *Anal.* ($C_{13}H_{17}ClO_5$) C, H, Cl.

3-(*p*-Methoxystyryl)-1,1-diethyl-1*H*-isobenzofurylium perchlorate was prepared in 95% yield from 1,1-diethyl-3-methyl-1*H*-isobenzofurylium perchlorate and *p*-anisaldehyde by the above procedure: mp 144–146° dec. *Anal.* ($C_{21}H_{23}ClO_6$) C, H, Cl.

3-(*p*-Methoxy-α-methylstyryl)-1,1-dimethyl-1*H*-isobenzofurylium Perchlorate. A solution of 8.10 g (50 mmoles) of dimethylphthalide in 130 ml of tetrahydrofuran was treated with 20 ml of 3 *M* ethylmagnesium bromide in Et_2O by the usual procedure. The intermediate 1-ethyl-3,3-dimethyl-1-phthalanol was isolated as a gum in 90% yield.

A solution of 4.00 g (20.8 mmoles) of the intermediate phthalanol in 40 ml of HOAc was treated with 1.8 ml of 70–72% $HClO_4$

Table III. *N,N*,3,3-Tetramethyl-1-substituted-vinyl-1-phthalanpropylamines



No.	R_1	R_2	R_3	Salt	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
5a	H	H		Oxalate	24	EtOH	181–183	$C_{21}H_{27}NOS \cdot C_2H_2O_4$	C, H, N, S
5b	H	H		Oxalate	12	EtOH–heptane	165–167	$C_{21}H_{27}NO_2 \cdot C_2H_2O_4$	C, H, N
5c	H	H	*p*-BrC_6H_4	Oxalate	35	EtOH	219–220	$C_{23}H_{28}BrNO \cdot C_2H_2O_4$	C, H, N, Br
5d	H	H	*p*-ClC_6H_4	Oxalate	29	EtOH	222–223	$C_{23}H_{28}ClNO \cdot C_2H_2O_4$	C, H, N, Cl
5e	H	H	*m*-ClC_6H_4	Oxalate	8	Acetone–hexane	192–194	$C_{23}H_{28}ClNO \cdot C_2H_2O_4$	C, H, N, Cl
14b	H	H	C_6H_5	Oxalate	27	EtOH–heptane	196–197	$C_{23}H_{29}NO \cdot C_2H_2O_4$	C, H, N
				Fumarate		EtOH	156–158	$C_{23}H_{29}NO \cdot C_4H_4O_4$	C, H, N
5f	H	H	*o*-$CH_3C_6H_4$	Oxalate	27	EtOH	184–186	$C_{24}H_{31}NO \cdot C_2H_2O_4$	C, H, N
5g	H	H	*m*-$CH_3C_6H_4$	Oxalate	22	EtOH–heptane	206–207	$C_{24}H_{31}NO \cdot C_2H_2O_4$	C, H, N
5h	H	H	*p*-$CH_3C_6H_4$	Oxalate	24	EtOH	186–188	$C_{24}H_{31}NO \cdot C_2H_2O_4$	C, H, N
5i	H	H	*o*-$CH_3OC_6H_4$	Oxalate	30	EtOH	171–172	$C_{24}H_{31}NO_2 \cdot C_2H_2O_4$	C, H, N
				Fumarate		EtOH–heptane	135–137	$C_{24}H_{31}NO_2 \cdot C_4H_4O_4$	C, H, N
5j	H	H	*p*-$CH_3OC_6H_4$	Oxalate	34	EtOH	198–200	$C_{24}H_{31}NO_2 \cdot C_2H_2O_4$	C, H, N
				HCl		CH_2Cl_2–petr ether	167–168	$C_{24}H_{31}NO_2 \cdot HCl$	H, Cl, N; C[a]
10b	CH_3	H	*p*-$CH_3OC_6H_4$		59		Oil[b]	$C_{25}H_{33}NO_2$	C, H, N
10c	H	CH_3	*p*-$CH_3OC_6H_4$		30		Oil[c]	$C_{25}H_{33}NO_2$	C, H, N
5k	H	H	3,4-$(CH_3O)_2C_6H_3$		30		Oil[d]	$C_{25}H_{33}NO_3$	C, H, N
5l	H	H		Oxalate	8	EtOH	196–198	$C_{26}H_{33}NO \cdot C_2H_2O_4$	C, H, N
5m	H	H	*p*-$(CH_3)_2CHC_6H_4$		18		Oil[e]	$C_{26}H_{35}NO$	C, H, N
5n	H	H	3,4,5-$(CH_3O)_3C_6H_2$	Oxalate	14	EtOH	132–135	$C_{26}H_{35}NO_4 \cdot C_2H_2O_4 \cdot H_2O$	C, H, N, H_2O
5o	H	H	2-$C_{10}H_7$	Oxalate	11	EtOH–heptane	155–165	$C_{27}H_{31}NO \cdot C_2H_2O_4$	C, H, N
5p	H	H	1-$C_{10}H_7$	Oxalate	20	EtOH	191–192	$C_{27}H_{31}NO \cdot C_2H_2O_4$	C, H, N
5q	H	H	4-CH_3O-1-$C_{10}H_6$	Oxalate	7	EtOH–heptane	162–167	$C_{28}H_{33}NO_2 \cdot C_2H_2O_4$	C, H, N
5r	H	H	*p*-$C_6H_5C_6H_4$	Oxalate	31	EtOH	186–187	$C_{29}H_{33}NO \cdot C_2H_2O_4$	C, H, N

[a] C: calcd, 71.71; found, 70.59. [b] Purified by partition chromatography on diatomaceous silica using heptane–MeOH (1 : 1); the product was eluted at peak hold-back volume 1.0 (V_m/V_S = 2.96). [c] Purified by partition chromatography on diatomaceous silica using heptane–Methyl Cellosolve (1 : 1); the product was eluted at peak hold-back volume 1.6 (V_m/V_S = 2.72). [d] Purified by partition chromatography on diatomaceous silica using a heptane–MeOH (1 : 1) system; the product was eluted at peak hold-back volume 2.1 (V_m/V_S = 2.5). [e] Purified by partition chromatography on diatomaceous silica using a heptane–Methyl Cellosolve (1 : 1) system; the product was eluted at peak hold-back volume 0.75 (V_m/V_S = 1.43).

and stirred at room temperature for 5 min. The solution was then treated with 3.16 g (2.82 ml, 23.2 mmoles) of *p*-methoxybenzaldehyde and heated at reflux temperature for 30 min. The cooled solution was diluted with Et_2O until crystals appeared, and the mixture was chilled in an ice bath. Filtration gave 5.02 g (61%) of purple-red crystals: mp 154–155° dec. *Anal.* ($C_{20}H_{21}ClO_6$) H, Cl; C: calcd, 61.15; found, 60.54.

3-(*p*-Methoxy-β-methylstyryl)-1,1-dimethyl-1*H*-isobenzofurylium Perchlorate. A warm solution of 2.00 g (7.65 mmoles) of 1,-1,3-trimethyl-1*H*-isobenzofurylium perchlorate in 40 ml of HOAc was treated with 2.30 g (9.2 mmoles, 2.1 ml) of *p*-methoxyacetophenone, and the solution was stirred at reflux temperature for 5 hr. The solid which separated from the cooled solution was collected by filtration and washed with HOAc, Et_2O, and petr ether to give 520 mg (17%) of rust crystals: mp 180–190° dec. *Anal.* ($C_{20}H_{21}ClO_6$) C, H, Cl.

3,3-Dimethyl-1-phenyl-1-phthalanol (12a). A solution of 9.20 g (57 mmoles) of 3,3-dimethylphthalide[11] in 75 ml of ether was added over 30 min to a stirred, refluxing solution of 23 ml of commercial 3 *M* phenylmagnesium bromide and 100 ml of ether. Heating at reflux temperature was continued for 15 min after completion of the addition. The cooled solution was poured onto cracked ice, treated with 30 ml of 20% HCl solution, and stirred until the solids dissolved. The ethereal layer was separated, washed successively with H_2O, 5% Na_2CO_3 solution, and H_2O, dried, and evaporated. The residue was triturated with petr ether to give 9.70 g (41%) of white crystals: mp 110–114°. A sample was recrystallized from Et_2O–petr ether to give crystals: mp 117–119° (lit.[11] mp 117–118°).

1,1-Dimethyl-3-phenyl-1*H*-isobenzofurylium Perchlorate (13a). A solution of 8.50 g (37 mmoles) of 3,3-dimethyl-1-phenyl-1-phthalanol (12a) in 200 ml of ether was treated with a solution of 24 ml of HOAc and 8.5 ml of 70% $HClO_4$ in 200 ml of ether. The crystals which separated on cooling and stirring were collected by filtration, washed with ether and petr ether, and dried to give 11.25 g (98%) of yellow crystals: mp 182–185° (lit.[7] mp 180°).

N,3,3-Trimethyl-1-phenyl-1-phthalanpropylamine (4) Hydrochloride. Magnesium turnings (1.86 g, 77 mg-atoms) were covered with dibutyl Carbitol (previously dried over KOH pellets for 5 days) and treated with 0.5 ml of ethyl bromide. The mixture was heated to 65° with stirring, and reaction was initiated by addition of a small quantity of freshly prepared ethylmagnesium bromide. An additional 25 ml of dibutyl Carbitol was added to the mixture, and then a solution of 9.45 g (78 mmoles) of dimethylaminopropyl chloride in 25 ml of dibutyl Carbitol was added dropwise over 90 min. The mixture was then stirred at 80° for 4 hr, at the end of which most of the magnesium had been consumed. The resulting mixture was treated with 6.20 g (19.3 mmoles) of 1,1-dimethyl-3-phenyl-1*H*-isobenzofurylium perchlorate (13a) and stirred at 75–80° for 16 hr. The cooled solution was treated with a saturated $(NH_4)_2SO_4$ solution, and the layers were separated. The organic solution was washed with water and then extracted with 20% HOAc. The combined acid extracts were rendered alkaline with NaOH pellets, and 3.00 g of crude *N,N*,3,3-tetramethyl-1-phenyl-1-phthalanpropylamine (14a) was isolated with Et_2O.

A 2.60-g aliquot of this amine in 25 ml of benzene was treated with 3.1 ml of ethyl chlorocarbonate and stirred at 40° for 2 hr. The solution was distributed between ether and 2 *N* HCl solution.

The dried organic solution gave 1.50 g of crude urethane 15a on evaporation. This material was dissolved in 10 ml of methyl Carbitol and treated with 1.4 g of KOH in 1.4 ml of H_2O. The solution was heated at reflux temperature for 20 hr, cooled, diluted with H_2O, and extracted with Et_2O. The ether solution was extracted with 20% HOAc. The organic base was liberated from the acid solution in the usual manner. The hydrochloride was prepared by treatment with ethereal HCl and crystallized to give 575 mg (10% overall) of white crystals: mp 184–186°. A sample recrystallized from EtOH–heptane had mp 186–188°. *Anal.* ($C_{20}H_{25}NO \cdot HCl$) C, H, N.

1,1-Dimethyl-3-styryl-1*H*-isobenzofurylium Perchlorate (13b). A Grignard reagent was prepared in 20 ml of tetrahydrofuran from 5.50 g (33 mmoles) of styryl bromide and 0.72 g (30 mg-atom) of magnesium. The Grignard soln was added *via* syringe over 15 min to a boiling soln of 3.20 g (20 mmoles) of 3,3-dimethylphthalide[11] in 20 ml of tetrahydrofuran. The reaction was stirred at reflux temperature for 18 hr, cooled, and treated with a saturated NH_4Cl soln. The mixture was distributed between H_2O and Et_2O, and the dried organic soln was evaporated. The residue was dissolved in 40 ml of hot petr ether and cooled to room temperature to give 2.61 g (49%) of 1-styryl-3,3-dimethyl-1-phthalanol (12b) as white crystals: mp 130–135°.

A 1.10-g aliquot of this material was dissolved in 220 ml of ether and chilled in ice; this soln was treated with 8 ml of a $HClO_4$–HOAc–Et_2O (3.4:9.6:100) soln. Filtration furnished 1.10 g (77%) of the perchlorate as yellow crystals: mp 185–188° (lit.[10] mp 180–182° dec.)

{3-[3,3-Dimethyl-1-(*p*-methylstyryl)-1-phthalanyl]propyl}trimethylammonium Iodide. A suspension of 400 mg (0.82 mmole) of *N,N*,3,3-tetramethyl-1-(*p*-methylstyryl)-1-phthalanpropylamine (5h) oxalate in 25 ml of H_2O was treated with a 10% NaOH soln. The mixture was extracted with CH_2Cl_2, and the dried extracts were evaporated to give 320 mg of oil that was dissolved in 30 ml of Et_2O and treated with a soln of 1 ml of MeI in 20 ml of Et_2O. The soln was stirred at ice-bath temperature for 1 hr and filtered to remove some solid. The filtrate was allowed to stand at room temperature for 18 hr; filtration of the resulting mixture gave 247 mg (50%) of white plates: mp 170–174°. The analytical sample was obtained as a complex with acetone, mp 179–180°, after two recrystallizations from acetone–petr ether. *Anal.* ($C_{25}H_{34}INO \cdot 0.5C_3H_6O$) C, H, N.

N,3,3-Trimethyl-1-styryl-1-phthalanpropylamine (16) Fumarate. Using the procedure described for the preparation of 4 from 14a, 3.85 g (9.0 mmoles) of *N,N*,3,3-tetramethyl-1-styryl-1-phthalanpropylamine oxalate gave 2.02 g (51%) of white crystals of 16·fumarate: mp 145–149°. The analytical specimen was obtained after two recrystallizations from EtOH–heptane: mp 153–155°. *Anal.* ($C_{22}H_{27}NO \cdot C_4H_4O_4$) C, H, N.

3,3-Dimethyl-1-phenylethynyl-1-phthalanol (17). Phenylethynylmagnesium bromide was prepared by adding 2.44 g (24 mmoles) of phenylacetylene to 8.5 ml of 3 *M* ethylmagnesium bromide in Et_2O.[12] The resulting soln was heated at reflux temperature for 3.5 hr. A soln of 3.20 g (20 mmoles) of dimethylphthalide in 25 ml of Et_2O was added over 5 min, and the resulting mixture was maintained at 50° for 1 hr. Decomposition with NH_4Cl soln and isolation of the product from the Et_2O layer were achieved in the usual manner. Crystallization of the product from acetone gave 3.92 g (78%) of white crystals: mp 179–180°. *Anal.* ($C_{18}H_{16}O_2$) C, H.

3,3-Dimethyl-1-*cis*-styryl-1-phthalanol (18). A mixture of 0.3 g of 5% Pd/$BaSO_4$ and 2.64 g (10 mmoles) of 3,3-dimethyl-1-phenylethynyl-1-phthalanol (17) in 60 ml of pyridine was shaken under hydrogen; 1 equiv of gas was absorbed in 10 min. The mixture was filtered, collecting the filtrate in 500 ml of H_2O. The aqueous soln was extracted with Et_2O, and the dried combined extracts were evaporated at less than 30°. The residue was triturated with petr ether to give solid that was recrystallized from Et_2O–petr ether to give 1.41 g (53%) of white crystals: mp 91–94°. *Anal.* ($C_{18}H_{18}O_2$) C, H.

If the reduction was conducted as above, but $CdCl_2$ was used to complex and remove the pyridine, the trans isomer, mp 135–138°, resulted.

3,3-Dimethyl-1-phenethyl-1-phthalanol (19). Hydrogenation of 2.64 g (10 mmoles) of 3,3-dimethyl-1-phenylethynyl-1-phthalanol (17) in MeOH using 5% Pd/$BaSO_4$ gave rapid (4 min) consumption of 2 equiv of hydrogen. The product crystallized from hexane to give 1.58 g (59%) of white crystals: mp 92–94°. *Anal.* ($C_{18}H_{20}O_2$) C, H.

N,N,3,3-Tetramethyl-1-phenylethynyl-1-phthalanpropylamine (20). Application of the general procedure to 1.74 g (6.6 mmoles) of 3,3-dimethyl-1-phenylethynyl-1-phthalanol (17) and 20 mmoles of dimethylaminopropylmagnesium chloride resulted in 1.49 g of crude product as an oil. A 1.05-g aliquot of this material was converted into the oxalate salt, which was recrystallized from EtOH–Et_2O to give 0.82 g (38%) of white powder: mp 153–156°. *Anal.* ($C_{23}H_{27}NO \cdot C_2H_2O_4 \cdot 0.66H_2O$) C, H, N.

2-(1-Hydroxy-1-methylethyl)cyclohexanecarboxylic Acid Lactone (23). 1,2-Cyclohexanedicarboxylic acid anhydride (22) (15.4 g, 0.1 mole) was treated with 0.2 mole of ethereal methylmagnesium bromide in the usual manner. The solid remaining after decomposition of the reaction was collected by filtration to give 20.0 g of a H_2O-insoluble, white solid. This material was suspended in 250 ml of boiling water, treated with concd HCl, cooled, and filtered to give 8.23 g (49%) of white crystals: mp 75–77°. Several crystallizations from dil acetone gave white crystals: mp 81–82°. *Anal.* ($C_{10}H_{16}O_2$) C, H.

Octahydro-*N,N*,3,3-tetramethyl-1-phenyl-1-isobenzofuranpropylamine (6). An ether solution of 1.55 g (9.25 mmoles) of 2-(1-hydroxy-1-methylethyl)cyclohexanecarboxylic acid lactone (23) was treated with 3.7 ml of 3 *M* phenylmagnesium bromide in ether by the usual procedure. The resulting octahydro-3,3-dimethyl-1-phenyl-1-isobenzofuranol (24) (2.19 g, 96%) was isolated as an unstable white solid which was used immediately.

A Grignard reagent was prepared in tetrahydrofuran from 480 mg (20 mg-atoms) of magnesium and 2.44 g (20 mmoles) of dimethylaminopropyl chloride. The reagent was treated with 1.65 g (6.7 mmoles) of octahydro-3,3-dimethyl-1-phenyl-1-isobenzofuranol (24) at reflux temperature for 18 hr, and the reaction was decomposed with NH_4Cl solution and extracted with Et_2O. The organic phase was washed with 1 *N* HCl solution, and these washes were rendered alkaline with 10% NaOH solution. Extraction with Et_2O and removal of the solvent from the dried extracts gave 1.65 g of residue. Crystallization of this material from dil acetone gave 760 mg (34%) of diol 25 as white crystals: mp 111–113°.

A solution of 250 mg (0.75 mmole) of diol 25 in 1 ml of 37% HCl was heated at reflux temperature for 15 min and then poured onto cracked ice. The solution was rendered alkaline with concd NH_4OH and extracted with Et_2O. Evaporation of solvent from the dried extracts gave 220 mg of residue. An ether solution of this material was treated with EtOH–HCl to give 170 mg (64%) of 6 hydrochloride as white crystals: mp 192–195°. Recrystallization from EtOH–heptane gave white crystals: mp 194–196°. *Anal.* ($C_{21}H_{33}NO \cdot HCl$) H, N; C: calcd, 71.66; found, 70.99.

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