Compounds Affecting the Central Nervous System. V. Substituted 3-Dialkylaminoalkylindenes

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A series of 2-aryl-3-dialkylaminoalkylindenes was prepared by reaction of 2-arylindenyl anions with dialkylaminoalkyl chlorides. Alkylation of 2-phenylindene with 2-dimethylaminoethyl chloride also yielded 1,3-bis(2-dimethylaminoethyl)-2-phenylindene. Some related substituted indenes were also synthesized. Most of the compounds had activity in tests for CNS depression.

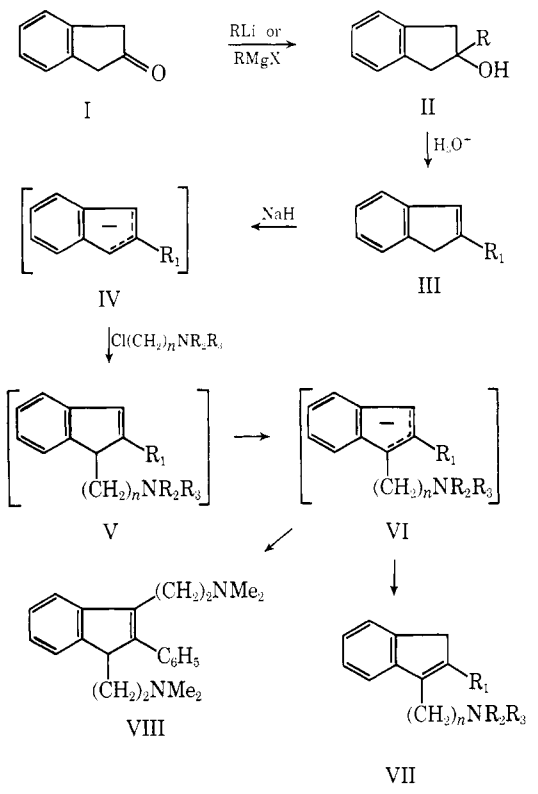
In a previous paper we reported that a series of 2-benzyl-3-dialkylaminoalkylindenes prepared as potential analgetics was also active in certain tests for CNS depression.[2] We now describe a study of related indene derivatives in which the 2-benzyl substituent is replaced by other groups. Among the compounds investigated, those comprising a series of 2-arylindenes were significantly more potent than the benzyl derivatives as CNS depressants.

The variously substituted indenylalkylamines (Table I) were prepared by the method previously described, from the appropriate indene anion (IV) and a dialkylaminoalkyl chloride[2] (Scheme I). Since this procedure may have involved rearrangement of the initially formed 1-dialkylaminoalkylindene (V) to the corresponding 3 isomer (VII),[2] the position of the double bond was verified for VII ($R_1 = C_6H_5$; $R_2 = R_3 = CH_3$; $n = 2$), as being representative of the series, from the nmr spectrum. The structural assignment followed from the integrated signals of the methylene C-1 protons (τ 6.34) and aromatic protons which were in the ratio 2:9 (the alternative 1-indene structure V should have given a ratio 1:10) and was in agreement with that reported more recently by Dykstra, *et al.*[3,4] The absence of a vinylic C-3 indenyl proton signal was not a satisfactory criterion for structural assignment in this example since the C-3 proton signal from 2-phenylindene (III, R_1 = Ph) was shifted downfield into the aromatic proton region.

It is possible that the isomerization of the initial product V to the 3 isomer VII occurs *via* the anion VI; formation of the latter under the conditions of the reaction is evident from the production of bisalkylated products. By conducting the alkylation of 2-phenylindene with 2-dimethylaminoethyl chloride on a sufficiently large scale we were able to isolate the bisamine VIII [as the dihydrochloride salt (**14**, Table III)]. The structure of VIII was determined from the nmr spectrum which showed a signal (centered at τ 5.77) from the indenyl C-1 proton and the absence of a vinylic C-3 proton signal (integration of the aromatic proton signal agreed for nine protons), thus distinguishing it from the alternative 1,1-bis(2-dimethylaminoethyl)-2-phenylindene structure.

The uv spectra of these compounds also merit comment. Whereas the 2-arylindenes showed the long-wavelength band at 300–330 mμ with four vibrational maxima characteristic of the *trans*-stilbene chromophore

Scheme I



("A" band[6]), the corresponding absorption of the substituted products VII showed a hypsochromic shift of *ca.* 20 mμ and a loss of vibrational fine structure. This was consistent with the expected loss in planarity of the chromophore, resulting from steric interaction between the 3-alkyl substituent and the *o*-H atoms of the aryl group, and paralleled the effects observed following α-methyl substitution in *trans*-stilbene and 2-phenylindene.[7]

The intermediate indenes (III, Table II) were prepared by established procedures, *via* dehydration of the appropriate 1- or 2-indanols. The former were obtained by hydride reduction of the requisite 1-indanones (IX

(1) To whom inquiries should be addressed.

(2) Part IV: C. R. Ganellin, J. M. Loynes, H. F. Ridley, and R. G. W. Spickett, *J. Med. Chem.*, **10**, 826 (1967).

(3) S. J. Dykstra, J. M. Berdahl, K. N. Campbell, C. M. Combs, and D. G. Lankin, *ibid.*, **10**, 418 (1967).

(4) Dykstra, *et al.*,[3] also comment on the structure described in Belgian Patent 621,933 (1963); their comments probably derive from the nomenclature used in this specification which, although being defined, does not accord to current *Chemical Abstracts* practice. The specification does, however, depict the structural formula as that of VII (R_1 = aryl). A general discussion of the alkylation of indenyl anions has been published elsewhere.[5]

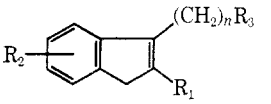
(5) C. R. Ganellin, *Advan. Drug Res.*, **4**, 163 (1967).

(6) R. N. Beale and E. M. F. Roe, *J. Chem. Soc.*, 2755 (1953).

(7) H. Christol, C. Martin, and M. Mousseron, *Bull. Soc. Chim. France*, 1969 (1960).

TABLE I

SUBSTITUTED 3-DIALKYLAMINOALKYLINDENES

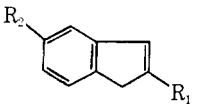


No.	R_1	R_2	n	R_3	Cryst[a] solvent	Mp, °C	Formula[b]
1	C_6H_5	H	2	$N(CH_3)_2$	A	212–216	$C_{19}H_{21}N \cdot HCl$
2	C_6H_5	H	3	$N(CH_3)_2$	B	213–214	$C_{20}H_{23}N \cdot HCl$
3	C_6H_5	H	2	$N(CH_2)_5$	A	215–217	$C_{22}H_{25}N \cdot HCl$
4	$2\text{-}CH_3C_6H_4$	H	2	$N(CH_3)_2$	C	253–255	$C_{20}H_{23}N \cdot HCl$
5	$4\text{-}CH_3C_6H_4$	H	2	$N(CH_3)_2$	D	253–256	$C_{20}H_{23}N \cdot HCl$
6	$4\text{-}FC_6H_4$	H	2	$N(CH_3)_2$	C	235–239	$C_{19}H_{20}FN \cdot HCl$
7	$4\text{-}ClC_6H_4$	H	2	$N(CH_3)_2$	E	258–260	$C_{19}H_{20}ClN \cdot HCl$
8	$4\text{-}ClC_6H_4$	Cl[c]	2	$N(CH_3)_2$	F	276–278	$C_{19}H_{19}Cl_2N \cdot HCl$
9	$4\text{-}CF_3C_6H_4$	H	2	$N(CH_3)_2$	A	264–265	$C_{20}H_{20}F_3N \cdot HCl$
10	$CH_2CH_2C_6H_5$	H	2	$N(CH_3)_2$	A	193–195	$C_{21}H_{25}N \cdot HCl$
11	$C{\equiv}CC_6H_5$	H	2	$N(CH_3)_2$	B	217–218	$C_{21}H_{21}N \cdot HCl$
12	CH_3	H	2	$N(CH_3)_2$	G	220–222	$C_{14}H_{19}N \cdot HCl$
13	H	H	2	$N(C_2H_5)_2$	H	154–156[d]	$C_{15}H_{21}N \cdot HCl$

[a] A, EtOH-Et_2O; B, EtOH; C, MeCOEt–EtOH; D, *i*-PrOH–EtOH; E, MeCOEt; F, MeOH; G, *i*-PrOH; H, *i*-PrOH–Et_2O. [b] All compounds were analyzed for C, H, Cl, N and analytical results were within ±0.4% of calculated values. [c] The position of Cl (at 5 or 6) was not determined. [d] O. Eisleb, *Ber.*, **74B**, 1433 (1941), reports mp 156–159°. Analysis for Cl only.

TABLE II

2-SUBSTITUTED INDENES

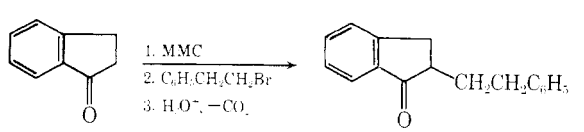


R_1	R_2	Cryst solvent	Mp, °C	Formula[a]
C_6H_5	H	C_6H_6–EtOH	167–168[b]	$C_{15}H_{12}$
C_6H_5[c]	Cl	MeOH–EtOH	160–163	$C_{15}H_{11}Cl$
$2\text{-}CH_3C_6H_4$	H	MeOH	187–188	$C_{16}H_{14}$
$4\text{-}CH_3C_6H_4$	H	Me_2CO–EtOH	188–189[e]	$C_{16}H_{14}$
$4\text{-}FC_6H_4$	H	MeOH	166–167	$C_{15}H_{11}F$
$4\text{-}ClC_6H_4$	H	MeOH	177–178	$C_{15}H_{11}Cl$
$4\text{-}ClC_6H_4$	Cl	EtOH	143–145	$C_{15}H_{10}Cl_2$
$4\text{-}CF_3C_6H_4$	H	Me_2CO–MeOH	189–190	$C_{16}H_{11}F_3$
$CH_2CH_2C_6H_5$	H	EtOH	71–73	$C_{17}H_{16}$
$C{\equiv}CC_6H_5$	H	MeOH	100–101[d]	$C_{17}H_{12}$
CH_3	H	Oil[e]		$C_{10}H_{10}$

[a] All compounds were analyzed for C, H and analytical results were within ±0.4% of calculated values. [b] Lit.[17] mp 167°. [c] Lit.[17] mp 184°. [d] Lit.[18] mp 99–100°. [e] Bp 204–206° (748 mm), $n^{20}D$ 1.5627; T. L. Yarboro, C. Karr, and P. A. Estep, *J. Chem. Eng. Data*, **6**, 421 (1961), report bp 204° (742 mm), $n^{20}D$ 1.5645.

and XII). The 2-indanols (II) were synthesized from 2-indanone (I) and the corresponding Grignard or Li reagent (Scheme I).

2-Phenethyl-1-indanone (IX), previously prepared by a multistage synthesis,[8] was advantageously synthesized *via* alkylation of the Mg enolate of 1-indanone-2-carboxylic acid with 2-bromoethylbenzene (*cf.* ref 2).

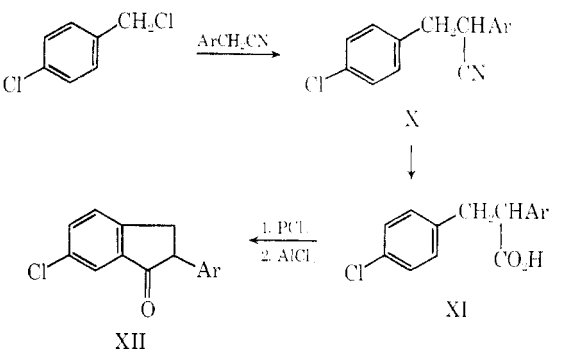


IX

The 6-chloro-1-indanones (XII) were prepared by the route outlined in Scheme II. Alkylation of benzyl (or *p*-chlorobenzyl) cyanide by *p*-chlorobenzyl chloride furnished the diarylpropionitrile (X) together with some bisalkylated material from which it was separated by crystallization. Hydrolysis of the nitrile to give the

(8) H. Rupe and G. Wolfsleben, *Ann.*, **395**, 111 (1913).

SCHEME II



acid XI, followed by ring closure, yielded the indanone XII. This was not a very satisfactory route since cyclization to the indanone was difficult in the presence of the deactivating chloro substituent. Under conditions of moderate dilution, which should have favored intramolecular acylation, 3-(*p*-chlorophenyl)-2-phenylpropionyl chloride afforded the required indanone in only 9% yield.

An alternative approach to the synthesis of 2-phenyl-3-(3-dimethylaminopropyl)indene by addition of 3-dimethylaminopropylmagnesium chloride[9] to 2-phenyl-1-indanone was unsuccessful. The failure to effect a related Grignard addition to other indanones has been reported recently.[10]

1-(2-Dimethylaminoethyl)-2-phenylindane hydrochloride (**15**, Table III) was prepared by catalytic hydrogenation of the corresponding indene.

Biological Activity.—The compounds were examined for CNS depressant activity in a variety of tests and the results are recorded in Table III. The methods used are referred to in the footnotes to the table.

The 2-aryl-3-dialkylaminoalkylindenes (**1**–**9**) were more potent CNS depressants than the corresponding 2-benzyl derivatives[2] [2-benzyl-3-(2-dimethylaminoethyl)indene hydrochloride (**16**) is included in the table for comparison], whereas compounds lacking an aryl substituent in the indene nucleus (**10**–**13**) possessed only marginal activity. Arylindenes which were not substituted in the *para* position (**1**–**4**) resembled meprobamate in their ability to protect mice against strychnine-induced convulsions.

In contrast to the recently reported discovery[3] that isomeric 1-phenyl-1-dialkylaminoalkylindenes are potent antidepressants, the active compounds described in the present study appeared to be general depressants of the CNS. Thus, **1** apparently resembled meprobamate in its anticonvulsant activity in protecting mice against the effects of pentylenetetrazole, strychnine, or electroshock and in the mouse rage test, but it also depressed the response to a heat stimulus and protected against the toxic effects of tremorine and amphetamine. A fuller discussion of the biological properties of this compound has recently been published.[5]

Experimental Section

Melting points were taken in a capillary tube on an Electrothermal apparatus comprising a gas-heated block and a thermometer calibrated for stem exposure. Microanalyses are by Mr. M. J. Graham of these laboratories and are indicated by symbols

(9) K. Miescher and A. Marxer, U. S. Patent 2,411,664 (1946).

(10) V. Paragamian and J. F. Gardocki, *J. Med. Chem.*, **11**, 1064 (1968).

Table III

Biological Activity[a]

No.	LD_{50}[b]	Analgetic[c]	Anti-pentylenetetrazole[d]	Antistrychnine[e]	Electroshock[f]	Antitremorine[g]	Mouse rage[h]
1	+	++	+	+	+	+	++
2	+	+	+	+	+	+	++
3	+	++	+	+	+	+	++
4	+	++	±	+	—	+	++
5	+	++	+	—	+	±	++
6	+	++	—	—	+	+	+
7	+	+	+	—	+	—	+
8	±	—	+	—	+	±	±
9	+	±	—	—	+	—	+
10	+	±	±	—	—	—	±
11	+	±		—	±		—
12	+	±	—	—	±		
13	±	—	—	—	±	±	±
14[i]	++	—			—		—
15[j]	+	±	—	—	+	—	+
16[k]	+	+	—	—	—	±	++

[a] Compounds were administered *per os* to mice in all tests. Activity at higher doses than the range quoted under footnotes *c–h* is represented by ±; the absence of observable effects at doses of 30% LD_{50} value is denoted by —. [b] Seven-day toxicity: ++, LD_{50} < 100 mg/kg; +, LD_{50} = 200–500 mg/kg; ±, LD_{50} > 700 mg/kg. [c] Analgetic activity (hot plate method) [N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953)]: ++, ED_{50} = 30–60 mg/kg; +, ED_{50} = 70–110 mg/kg (comparable ED_{50} for codeine = 100 mg/kg). [d] Prevention of seizures induced by pentylenetetrazol [L. S. Goodman, M. S. Grewal, W. C. Brown, and E. A. Swinyard, *ibid.*, **108**, 168 (1953)]: +, ED_{50} = 40–80 mg/kg (comparable ED_{50} for diphenylhydantoin = 5 mg/kg). [e] Prevention of strychnine-induced convulsions [F. M. Berger, *ibid.*, **112**, 413 (1954)]: +, ED_{50} = 60–110 mg/kg (comparable ED_{50} for meprobamate = 150 mg/kg). [f] Prevention of maximal electroshock induced seizures [E. A. Swinyard, W. C. Brown, and L. S. Goodman, *ibid.*, **106**, 319 (1952)]: +, ED_{50} = 15–50 mg/kg (comparable ED_{50} for diphenylhydantoin = 5 mg/kg). [g] Protection against tremorine-induced tremors [G. M. Everett, L. E. Blockus, and I. M. Shepperd, *Science*, **124**, 79 (1956)]: +, ED_{50} = 20–60 mg/kg (comparable ED_{50} for atropine = 6 mg/kg). [h] Prevention of electrically induced fighting episodes [R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **125**, 28 (1959)]: ++, ED_{50} = 10–40 mg/kg; +, ED_{50} = 60–100 mg/kg (comparable ED_{50} for meprobamate = 70 mg/kg). [i] 1,3-Bis(2-dimethylaminoethyl)-2-phenylindene dihydrochloride. [j] 1-(2-Dimethylaminoethyl)-2-phenylindane hydrochloride. [k] 2-Benzyl-3-(2-dimethylaminoethyl)indene hydrochloride.[2]

of the elements; unless otherwise stated, analytical results were within ±0.4% of the theoretical values. The uv absorption spectra were measured on a Beckmann DK2 spectrometer. Ir spectra of all compounds were recorded on a Hilger H800 or Unican SP200 spectrometer. Nmr spectra were determined with a Varian A-60A spectrometer.

2-(*p*-Chlorophenyl)-6-chloro-1-indanone (XII, Ar = *p*-ClC_6H_6).—2,3-Di(*p*-chlorophenyl)propionitrile (350 g, mp 90–92.5°, lit.[11] mp 91–92°) was hydrolyzed by being boiled with NaOH (106 g) in a mixture of diethylene glycol (700 ml) and H_2O (250 ml) for 25 hr. The cooled mixture was diluted with H_2O (3 l.), washed (PhMe), and acidified (concentrated HCl) to precipitate 2,3-di(*p*-chlorophenyl)propionic acid. The latter, after being crystallized from AcOH and washed with petroleum ether (bp 60–80°) had mp 133–135° (lit.[11] mp 163–165°), yield 306 g (81%). The melting point was unchanged after three recrystallizations. *Anal.* ($C_{15}H_{12}Cl_2O_2$) C, H, Cl, equiv wt.

2,3-Di(*p*-chlorophenyl) propionic acid (194 g) was converted into the acid chloride by being heated with PCl_5 (154 g) and removal of the resulting $POCl_3$ under reduced pressure. The residual acid chloride was cyclized by addition to $AlCl_3$ (118 g) in CH_2Cl_2 (2.2 l.) at 8°. The mixture was allowed to warm to 20° during 1.5 hr and then added slowly to 5 *N* HCl (2.5 l.) with cooling. The upper organic layer was separated, washed with 10% $NaHCO_3$ (500 ml), dried (K_2CO_3), and evaporated. The resulting oil was distilled *in vacuo* and 2-(*p*-chlorophenyl)-6-chloro-1-indanone was collected at 200–220° (0.1 mm); two crystallizations from EtOH furnished colorless needles, mp 97–100.5°, yield 46 g (22%). *Anal.* ($C_{15}H_{10}Cl_2O$) C, H, Cl.

2-Phenyl-6-chloro-1-indanone (XII, Ar = C_6H_5).—2-Phenyl-3-(*p*-chlorophenyl)propionitrile was prepared from $PhCH_2CN$ (351 g, 3 mole) and *p*-chlorobenzyl chloride (483 g, 3 mole) in refluxing Et_2O (1.5 l.) in the presence of $NaNH_2$ (117 g, 3 mole) according to the procedure described for the preparation of 2,3-diphenylpropionitrile;[12] it was obtained in 32% yield (211 g) as colorless plates from EtOH; mp 111–114° (lit.[13] mp 113–114°). *Anal.* ($C_{15}H_{12}ClN$) C, H, Cl.

Evaporation of the EtOH crystallization liquor afforded a mixture of solids (345 g) from which **1,3-di(*p*-chlorophenyl)-2-cyano-2-phenylpropane** was isolated, after several crystallizations from EtOH, as large colorless prisms, mp 92.5–95°. *Anal.* ($C_{22}H_{17}Cl_2N$) C, H, Cl, N.

2-Phenyl-3-(*p*-chlorophenyl)propionitrile (205 g) was hydrolyzed as above to furnish 2-phenyl-3-(*p*-chlorophenyl)propionic acid in 85% yield, mp 140.5–141° (C_6H_6) (lit.[13] mp 144°). *Anal.* ($C_{15}H_{13}ClO_2$) C, H, Cl, equiv wt.

The propionic acid (30 g) was converted into the acid chloride and cyclized in the presence of $AlCl_3$, under the conditions described above, to furnish 2-phenyl-6-chloro-1-indanone which, after distillation and two crystallizations from EtOH, was obtained in 9% yield as colorless prisms, mp 90–92°. *Anal.* ($C_{15}H_{11}ClO$) C, H, Cl. Increasing the dilution of the reactants (up to tenfold) gave less satisfactory results.

2-Phenethyl-1-indanone (IX).—1-Indanone (66 g, 0.5 mole) was heated with magnesium methyl carbonate[2,14] [from 2.0 moles of $Mg(OMe)_2$] in a mixture of xylene (100 ml), DMF (400 ml), and MeOH (200 ml) under reflux for 2 hr. 2-Bromoethylbenzene (277 g, 1.5 mole) in PhMe (450 ml) was then added and the mixture was stirred under reflux for 20 hr, then acidified with 10 *N* HCl (450 ml) and heated for 2 hr to effect decarboxylation. After being cooled, the upper organic layer was separated, washed successively with H_2O and aqueous $NaHCO_3$, dried (K_2CO_3), and concentrated. Distillation of the residue afforded the product (31 g), bp 168–174° (0.2 mm), which, after two crystallizations from petroleum ether (bp 40–60°), was obtained as colorless prisms, mp 58–61° (lit.[8] mp 56–57°). *Anal.* ($C_{17}H_{16}O$) C, H.

Preparation of the Indenes of Table II. Method A. From 1-Indanols.—2-Phenethyl-1-indanone (14.3 g, 0.06 mole) in dry Et_2O (100 ml) was added to $LiAlH_4$ (0.76 g, 0.02 mole) in Et_2O (50 ml) during 15 min at a rate which maintained reflux. The mixture was heated for 3 hr, then cooled, decomposed with ice, and acidified. Concentration of the Et_2O layer afforded the crude indanol as an oil. The latter was dehydrated by being heated for 1.5 hr in boiling EtOH (35 ml) containing concentrated HCl (4 ml). 2-Phenethylindene was collected and crystallized from EtOH as colorless platelets (see Table II), yield 9.0 g (69%).

(11) P. Weiss, M. G. Cordasco, and L. Reiner, *J. Am. Chem. Soc.*, **71**, 2650 (1949).

(12) N. Campbell and E. Ciganek, *J. Chem. Soc.*, 3834 (1956).

(13) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 493 (1958).

(14) M. Stiles and H. L. Finkbeiner, *ibid.*, **81**, 505 (1959).

2-(*p*-Chlorophenyl)-6-chloro-1-indanone and 2-phenyl-6-chloro-1-indanone were similarly converted into the corresponding indenes.

Method B. From 2-Substituted 2-Indanols.—2-Indanone[15] (41 g, 0.31 mole) in dry Et_2O (100 ml) was added to the Grignard solution prepared from *p*-bromochlorobenzene (115 g, 0.6 mole), Mg (14.6 g, 0.6 g-atom), and dry Et_2O (300 ml), at 0°. The mixture was heated under reflux for 2 hr, and then cooled and decomposed with aqueous NH_4Cl. Concentration of the dried Et_2O layer and distillation of the residue *in vacuo* afforded **2-(*p*-chlorophenyl)-2-indanol**, bp 200–204° (0.2 mm), a portion of which was crystallized from MeOH to give colorless needles, mp 83–86°. *Anal.* ($C_{15}H_{13}ClO$) C, H. The remaining carbinol was dehydrated in boiling EtOH–concentrated HCl (10:1, 200 ml, 3 hr) to furnish 2-(*p*-chlorophenyl)indene in 24% yield (17.2 g) after crystallization (see Table II).

In an analogous manner, the following compounds were synthesized from the appropriate Grignard reagents and dehydrated to the corresponding indenes: **2-(*p*-trifluoromethylphenyl)-2-indanol**, mp 95–96° (petroleum ether) [*Anal.* ($C_{16}H_{13}F_3O$) C, H]; **2-methyl-2-indanol**, mp 51–53° (pentane) (lit.[16] mp 52°); **2-*p*-tolyl-2-indanol**, mp 84–85° (petroleum ether) (lit.[17] oil) [*Anal.* ($C_{16}H_{16}O$) C, H]; **2-*o*-tolyl-2-indanol** and **2-(*p*-fluorophenyl)-2-indanol** were obtained as oils and were distilled and then dehydrated without further characterization.

2-Phenylethynyl-2-indanol.—Phenylacetylene (75 g, 0.74 mole) was added during 40 min to PhLi [from PhBr (120 g, 0.77 mole) and Li (12 g, 1.73 g-atoms)] in dry Et_2O (150 ml) under N_2. The mixture was stirred for 30 min, then 2-indanone (66 g, 0.5 mole) in Et_2O (100 ml) was added during 40 min and, after 16 hr at 20°, the mixture was filtered and decomposed with ice. The Et_2O layer was separated, washed (H_2O), dried (K_2CO_3), and concentrated. The residue was distilled *in vacuo* to afford 2-phenylethynyl-2-indanol, bp 184–188° (0.002 mm), which, after crystallization from petroleum ether, was obtained as colorless prisms (36 g, 31%), mp 85–86° (lit.[18] mp 86.5–87.5°). *Anal.* ($C_{17}H_{14}O$) C, H. The indanol (33 g) was dehydrated by being heated for 8 hr in boiling MeOH (250 ml) containing concentrated HCl (10 ml) to furnish **2-phenylethynylindene**: the latter was purified chromatographically on an alumina column, by elution with petroleum ether, and then crystallized from MeOH (see Table II); yield 23.4 g (77%): λ_{max}^{EtOH} 232 mμ (log ε 3.98), 238 (3.95), 251, 302, and 308 (infl), 315 (4.55), 321 (4.42), 337 (4.35).

2-Phenyl-3-(2-dimethylaminoethyl)indene Hydrochloride (VII, R_1 = C_6H_5; R_2 = R_3 = CH_3; n = 2).—NaH (61 g of 54% dispersion in paraffin oil, 1.37 moles) was added portionwise during 45 min to a stirred suspension of 2-phenylindene (240 g, 1.25 moles) in dry DMF (1200 ml) containing Et_2O (100 ml) to prevent frothing. Formation of the soluble indenylium ion was rapid and exothermic (15° rise in temperature). After 1.5 hr, a dry solution of 1-chloro-2-dimethylaminoethane in PhMe (500 ml) [obtained by neutralization of 360 g (2.5 moles) of the hydrochloride with 40% NaOH and extraction into PhMe; the toluene extract was dried twice over KOH] was added during 5 min; the temperature of the mixture rose from 30 to 68° and was then maintained at 60–70°, initially by cooling and later by heating, for 2 hr. After a further 16 hr at 20° the mixture was diluted with 2 l. of H_2O and the lower aqueous DMF layer was separated and extracted (Et_2O). The Et_2O extract was combined with the toluene layer, washed (H_2O), filtered from unchanged 2-phenylindene which had crystallized, and acidified by the addition, with stirring, of cold 10 *N* HCl (200 ml). The product, which precipitated, was collected (the acidic filtrate being retained, see below) and washed successively with hot PhH (500 ml) and hot Me_2CO (500 ml) to afford the hydrochloride, mp 208–212°, in 46.5% yield (174 g); three crystallizations from EtOH–Et_2O raised the melting point to 212–216° and furnished analytically pure product as colorless prisms: λ_{max}^{EtOH} 227 mμ (log ε 4.43), 288 (4.28); *cf.* 2-phenylindene: λ_{max}^{EtOH} 230 mμ (log ε 4.14), 237 (4.12), 245 (3.86), 301, 307, and 314 (4.39), 328 (infl).

A pure sample of the **amine**, obtained by neutralization of the hydrochloride, crystallized from petroleum ether as colorless cubes: mp 63–66° (lit.[5] mp 63–65°); nmr ($CDCl_3$), τ 7.72 [singlet, $N(CH_3)_2$], 7.5–6.9 (complex, aliphatic), 6.34 (multiplet, C-1 indenyl), 2.9–2.4 (complex, aromatic) in the ratio 6:4:2:9; *cf.* 2-phenylindene: nmr ($CDCl_3$), τ 6.29 (multiplet, C-1 indenyl), 2.9–2.3 (complex, aromatic and C-3 indenyl) in the ratio 2:9.8. *Anal.* ($C_{19}H_{21}N$) C, H, N.

Basification of the acidic filtrate (from above) and extraction with ether afforded a dark red viscous oil (40 g) which, on distillation *in vacuo*, gave 19.4 g of **1,3-bis(2-dimethylaminoethyl)-2-phenylindene**, bp 175–179° (0.05 mm), equiv wt 171 (calcd 167). Conversion into the **dihydrochloride (14)** furnished, after several crystallizations from EtOH–Et_2O, colorless prisms: mp 248.5–249°; λ_{max}^{EtOH} 287 mμ (log ε 4.21); nmr (D_2O), τ 8.0–6.4 (complex, aliphatic), 7.35, 7.11 [two singlets, $N(CH_3)_2$], 5.77 (multiplet, C-1 indenyl), 2.7–2.1 (complex, aromatic) in the ratio 19.6:1.2:9.0 (calcd 20:1:9). *Anal.* ($C_{23}H_{30}N_2 \cdot 2HCl$) C, H, N, Cl.

The indenes of Table I were synthesized by a similar procedure. In cases where oily hydrochloride precipitates were obtained they were induced to solidify by trituration with ether. The hydrochlorides **12** and **13**, which were soluble in H_2O, were prepared from the corresponding amines in anhydrous *i*-PrOH–HCl; the amines were isolated in the usual manner by neutralization of the acidic extracts and were distilled; 3-(2-diethylaminoethyl)indene was obtained as a colorless oil, bp 148–150° (1.5 mm) [lit.[19] bp 166° (21 mm)], $n^{24}D$ 1.5356; 2-methyl-3-(2-dimethylaminoethyl)indene was a colorless oil, bp 76–78° (0.2 mm), $n^{22}D$ 1.5429.

1-(2-Dimethylaminoethyl)-2-phenylindane Hydrochloride (15).—3-(2-Dimethylaminoethyl)-2-phenylindene hydrochloride (7.3 g) in EtOH (500 ml) at 23° was shaken with PtO_2 (60 mg) and H_2 at atmospheric pressure. Four further 60-mg portions of catalyst were added in order to complete the reduction. The reaction mixture was filtered through Hyflo, concentrated to 25 ml, and cooled. The product (6.1 g, 83%) which separated was recrystallized twice from EtOH to give analytically pure material, mp 248–251° (lit.[5] mp 235–236°). *Anal.* ($C_{19}H_{23}N \cdot HCl$) C, H, N, Cl.

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