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

P. M. G. BAVIN, C. R. GANELLIN,[1] J. M. LOYNES, AND R. G. W. SPICKETT

Smith Kline and French Laboratories Ltd., Welwyn Garden City, Hertfordshire, England

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
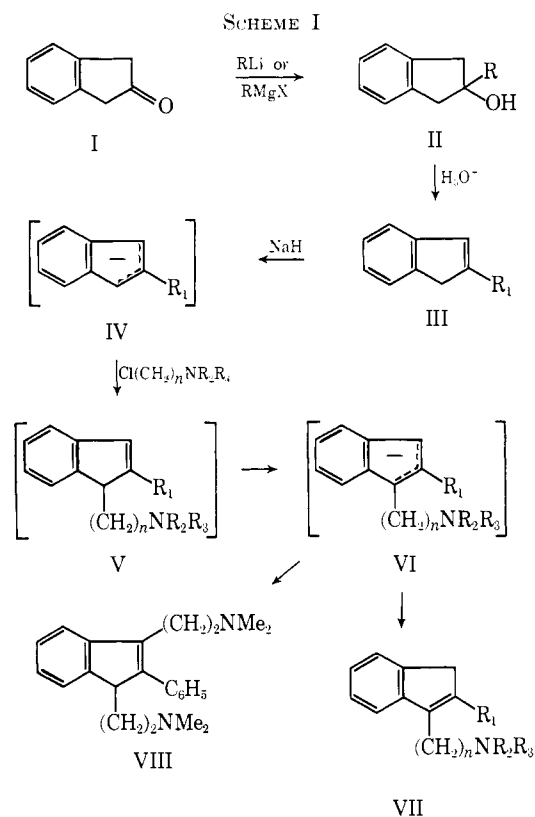
("A" band[6]), the corresponding absorption of the substituted products VII showed a hypsochromic shift of *ca.* 20 mμ and a loss of vibrational fine structure. This was consistent with the expected loss in planarity of the chromophore, resulting from steric interaction between the 3-alkyl substituent 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).
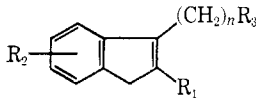
(4) Dykstra, *et al.*,[3] also comment on the structure described in Belgian Patent 621,933 (1963); their comments probably derive from the nomenclature used in this specification which, although being defined, does not accord to current *Chemical Abstracts* practice. The specification does, however, 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).

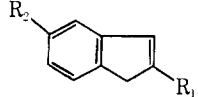(7) H. Christol, C. Martin, and M. Mousseron, *Bull. Soc. Chim. France*, 1969 (1960).

TABLE I

SUBSTITUTED 3-DIALKYLAMINOALKYLINDENES

No.	R₁	R₂	n	R₃	Cryst[a] solvent	Mp, °C	Formula[b]
1	C₆H₅	H	2	N(CH₃)₂	A	212–216	C₁₉H₂₁N·HCl
2	C₆H₅	H	3	N(CH₃)₂	B	213–214	C₂₀H₂₃N·HCl
3	C₆H₅	H	2	N(CH₂)₄	A	215–217	C₂₂H₂₅N·HCl
4	2-CH₃C₆H₄	H	2	N(CH₃)₂	C	253–255	C₂₀H₂₃N·HCl
5	4-CH₃C₆H₄	H	2	N(CH₃)₂	D	253–256	C₁₀H₂₃N·HCl
6	4-FC₆H₄	H	2	N(CH₃)₂	C	235–239	C₁₉H₂₀FN·HCl
7	4-ClC₆H₄	H	2	N(CH₃)₂	E	258–260	C₁₉H₂₀ClN·HCl
8	4-ClC₆H₄	Cl[c]	2	N(CH₃)₂	F	276–278	C₁₉H₁₉Cl₂N·HCl
9	4-CF₃C₆H₄	H	2	N(CH₃)₂	A	264–265	C₂₀H₂₀F₃N·HCl
10	CH₂CH₂C₆H₅	H	2	N(CH₃)₂	A	193–195	C₂₀H₂₃N·HCl
11	C≡CC₆H₅	H	2	N(CH₃)₂	B	217–218	C₂₀H₂₁N·HCl
12	CH₃	H	2	N(CH₃)₂	G	220–222	C₁₄H₁₉N·HCl
13	H	H	2	N(C₂H₅)₂	H	154–156[d]	C₁₅H₂₁N·HCl

[a] A, EtOH–Et₂O; B, EtOH; C, MeCOEt–EtOH; D, i-PrOH–EtOH; E, MeCOEt; F, MeOH; G, i-PrOH; H, i-PrOH–Et₂O. [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

R₁	R₂	Cryst solvent	Mp, °C	Formula[a]
C₆H₅	H	C₆H₆–EtOH	167–168[b]	C₁₅H₁₂
C₆H₅	Cl	MeOH–EtOH	160–163	C₁₅H₁₁Cl
2-CH₃C₆H₄	H	MeOH	187–188	C₁₆H₁₄
4-CH₃C₆H₄	H	Me₂CO–EtOH	188–189[c]	C₁₆H₁₄
4-FC₆H₄	H	MeOH	166–167	C₁₅H₁₁F
4-ClC₆H₄	H	MeOH	177–178	C₁₅H₁₁Cl
4-ClC₆H₄	Cl	EtOH	143–145	C₁₅H₁₀Cl₂
4-CF₃C₆H₄	H	Me₂CO–MeOH	189–190	C₁₆H₁₁F₃
CH₂CH₂C₆H₅	H	EtOH	71–73	C₁₇H₁₆
C≡CC₆H₅	H	MeOH	100–101[d]	C₁₇H₁₂
CH₃	H	Oil[e]		C₁₀H₁₀

[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), n²⁰D 1.5627; T. L. Yarboro, C. Karr, and P. A. Estep, J. Chem. Eng. Data, 6, 421 (1961), report bp 204° (742 mm), n²⁰D 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,[5] was advantageously synthesized via alkylation of the Mg enolate of 1-indanone-2-carboxylic acid with 2-bromoethylbenzene (cf. ref 2).
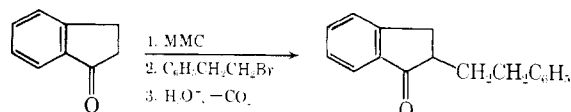
IX

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
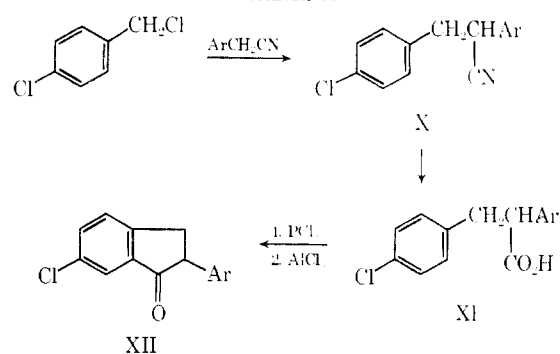
acid XI, followed by ring closure, yielded the indanone XII. This was not a very satisfactory route since cyclization to the indanone was difficult in the presence of the deactivating chloro substituent. Under conditions of moderate dilution, which should have favored intramolecular acylation, 3-(p-chlorophenyl)-2-phenyl-propionyl 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-dimethylamino-ethyl)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 Electro-thermal apparatus comprising a gas-heated block and a thermom-eter 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-Dimethyl-aminoethyl)-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-ClC₆H₆). —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 H₂O (250 ml) for 25 hr. The cooled mixture was diluted with H₂O (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.* (C₁₅H₁₂Cl₂O₂) C, H, Cl, equiv wt.

2,3-Di(p-chlorophenyl) propionic acid (194 g) was converted into the acid chloride by being heated with PCl₅ (154 g) and removal of the resulting POCl₃ under reduced pressure. The residual acid chloride was cyclized by addition to AlCl₃ (118 g) in CH₂Cl₂ (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% NaHCO₃ (500 ml), dried (K₂CO₃), 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.* (C₁₅H₁₀Cl₂O) C, H, Cl.

2-Phenyl-6-chloro-1-indanone (XII, Ar = C₆H₅).—2-Phenyl-3-(p-chlorophenyl)propionitrile was prepared from PhCH₂CN (351 g, 3 mole) and p-chlorobenzyl chloride (483 g, 3 mole) in refluxing Et₂O (1.5 l.) in the presence of NaNH₂ (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.* (C₁₅H₁₂ClN) 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.* (C₂₂H₁₇Cl₂N) 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° (C₆H₆) (lit.[13] mp 144°). *Anal.* (C₁₅H₁₃ClO₂) C, H, Cl, equiv wt.

The propionic acid (30 g) was converted into the acid chloride and cyclized in the presence of AlCl₃, 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.* (C₁₅H₁₁ClO) 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 H₂O and aqueous NaHCO₃, dried (K₂CO₃), 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.* (C₁₇H₁₆O) 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 Et₂O (100 ml) was added to LiAlH₄ (0.76 g, 0.02 mole) in Et₂O (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 Et₂O 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$_2$O (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$_2$O (300 ml), at 0°. The mixture was heated under reflux for 2 hr, and then cooled and decomposed with aqueous NH$_4$Cl. Concentration of the dried Et$_2$O 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 85–86°.   *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$_3$O) 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$_2$O (150 ml) under N$_2$. The mixture was stirred for 30 min, then 2-indanone (66 g, 0.5 mole) in Et$_2$O (100 ml) was added during 40 min and, after 16 hr at 20°, the mixture was filtered and decomposed with ice. The Et$_2$O layer was separated, washed (H$_2$O), dried (K$_2$CO$_3$), 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$_6$H$_5$: 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$_2$O (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

(15) W. Treibs and W. Schroth, *Ann.*, **639**, 204 (1961).

(16) J. v. Braun, O. Kröber, and E. Danziger, *Ber.*, **49**, 2653 (1916).

(17) J. v. Braun and G. Manz, *ibid.*, **62B**, 1059 (1929).

(18) W. Deuschel, *Helv. Chim. Acta*, **34**, 2403 (1951).

diluted with 2 l. of H$_2$O and the lower aqueous DMF layer was separated and extracted (Et$_2$O). The Et$_2$O extract was combined with the toluene layer, washed (H$_2$O), 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$_2$CO (500 ml) to afford the hydrochloride, mp 208–212°, in 46.5% yield (174 g): three crystallizations from EtOH–Et$_2$O raised the melting point to 212–216° and furnished analytically pure product as colorless prisms: λ_{max}^{EtOH} 227 mμ (log ϵ 4.15), 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.[?] 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$_2$O, colorless prisms: mp 248.5–249°; λ_{max}^{EtOH} 287 mμ (log ϵ 4.21); nmr (D$_2$O), 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$_2$·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$_2$O, 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^{25}D 1.5356; 2-methyl-3-(2-dimethylaminoethyl)indene was a colorless oil, bp 76–78° (0.2 mm), n^{25}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.[3] mp 235–236°).   *Anal.* (C$_{19}$H$_{23}$N·HCl) C, H, N, Cl.

(19) Ch. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Org. Chem.*, **15**, 918 (1950).