Compounds Affecting the Central Nervous System. IV. Substituted 2-Benzyl-3-dialkylaminoalkylindenes and Related Compounds

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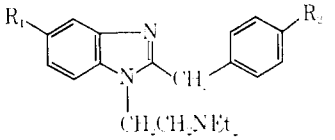
A series of substituted 2-benzyl-3-dialkylaminoalkylindenes was prepared by reaction of substituted 2-benzylindenyl anions with dialkylaminoalkyl chlorides, and a number of synthetic routes to the intermediate 2-benzylindenes were explored. Many of the compounds had activity in tests for analgesia in mice and were also found to be active in some tests for CNS depression. A number also possessed antihistaminic properties. Some related indane derivatives were also synthesized and tested. Dehydration of 1-benzyl-1-indanol yielded 1-benzalindane in addition to the expected 3-benzylindene.

Benzimidazole derivatives of structure I have been reported to be highly potent analgesics.[1] They are effective in man, but, since they produce respiratory depression and have a high addiction potential, they do not offer a therapeutic advantage over morphine as an analgesic.[2] In considering structure–activity relationships in this series of compounds and the possibility of enhancing the separation between analgesic activity and undesirable morphine-like effects, we investigated the replacement of the benzimidazole nucleus by the isosterically related indene nucleus. The use of indene simplifies the structure by removing the basic properties of the benzimidazole nucleus while retaining the steric relationship between the benzyl group and the tertiary amino function. This steric relationship is of interest because Dreiding wire models of these compounds indicate that the phenyl and amino groups can readily assume a relative spatial distribution similar to that found in the pethidine molecule.

This paper is concerned with the synthesis and biological properties of a series of 2-benzyl-3-dialkylaminoalkylindenes (IX) and some related compounds.



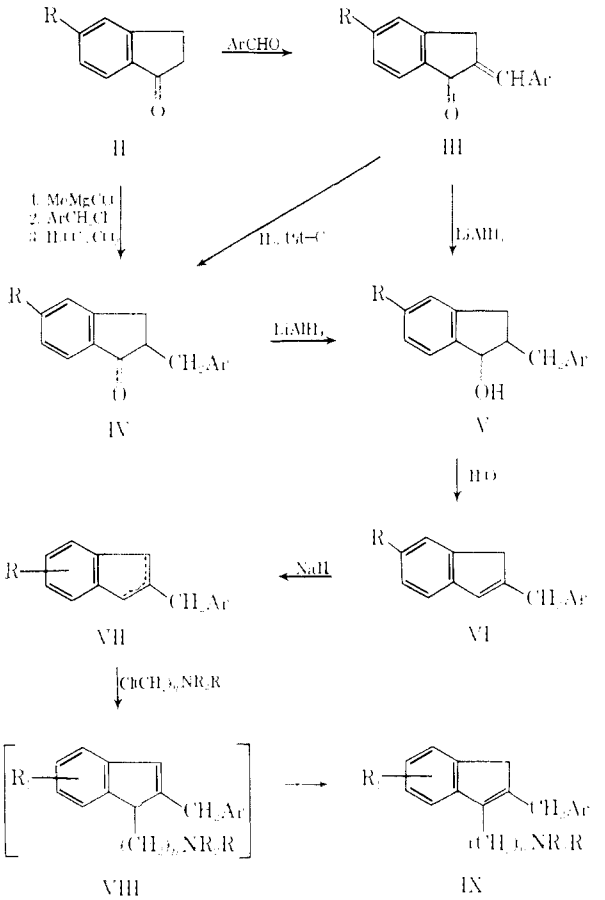
I

The 2-benzyl-3-dialkylaminoalkylindenes of Table I were synthesized from the appropriate indene (VI) and a dialkylaminoalkyl chloride *via* an indene anion (VII) which was generated by the action of NaH on the indene in boiling toluene.[3] Although the initial product of this reaction would be a 1-dialkylaminoalkylindene of structure VIII, it seems likely that this undergoes rearrangement in the presence of base to the corresponding 3 isomer (IX). Related base-catalyzed isomerization of 1,2-dialkylindenes to the corresponding 2,3 isomers had recently been described.[4]

The position of the double bond was verified for compound IX (R_1 = H; R_2 = R_3 = CH_3; n = 2; Ar = C_6H_5) from the nmr spectrum. The structural assignment follows from the integration of the signals from the methylene C-1 protons (τ 6.81) and benzylic protons (τ 6.21), which were in the ratio 1:1 (two protons each), and the nonappearance of a signal from a vinylic proton (compare 2-benzylindene where the vinylic proton produces a multiplet centered at τ 3.59). That this isomer would be the main product to be isolated from the reaction mixture was demonstrated by its recovery after being converted into the anion (by NaH in toluene) and subsequently quenched with water.

A number of synthetic routes to the 2-benzylindenes (VI) were explored, since, at the start of this work, these compounds had not been reported. 2-Benzylindene (VI, R = H; Ar = C_6H_5) was prepared from 2-benzyl-1-indanone (IV, R = H; Ar = C_6H_5) *via* reduction to the indanol (V, R = H; Ar = C_6H_5) and subsequent dehydration (Scheme I).[5] 2-Benzyl-1-

SCHEME I



(1) A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Experientia*, **13**, 400 (1957); F. Gross and H. Turrian, *ibid.*, 401 (1957).

(2) A. H. Beckett and A. F. Casy, *Progr. Med. Chem.*, **2**, 43 (1962).

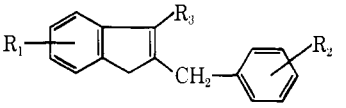
(3) *Cf.* O. Eisleb, *Ber.*, **74B**, 1433 (1941).

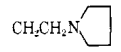
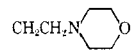
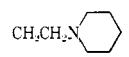
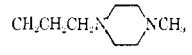
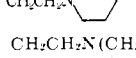
(4) F. Ménat and G. Bergson, *Arkiv Kemi*, **25**, 109 (1965).

(5) A similar synthesis using other reagents has since been described by N. Campbell, P. S. Davison, and H. G. Heller, *J. Chem. Soc.*, 993 (1963).

TABLE I

SUBSTITUTED 2-BENZYL-3-DIALKYLAMINOALKYLINDENES

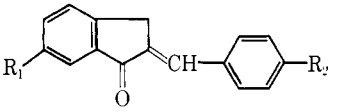


No.	R_1	R_2	R_3	Crystn[a] solvent	Mp, °C	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
1	H	H	$CH_2CH_2N(CH_3)_2$	A	214–216	$C_{20}H_{23}N \cdot HCl$	76.5	7.71	4.46	11.3	76.7	7.72	4.50	11.3
2	H	H	$CH_2CH_2N(C_2H_5)_2$	B	154–155	$C_{22}H_{27}N \cdot HCl$	77.3	8.25	4.09	10.4	77.6	8.21	4.20	10.5
3	H	H		A	232–235	$C_{22}H_{25}N \cdot HCl$	77.7	7.71	4.12	10.4	77.4	7.50	4.10	10.4
4	H	H		C	244–246	$C_{22}H_{25}NO \cdot HCl$	74.2	7.36	3.94	10.0	73.9	7.34	4.22	9.9
5	H	H		C	250–253	$C_{23}H_{27}N \cdot HCl$	78.0	7.98	3.96	10.0	77.6	8.07	4.13	10.1
6	H	H	$CH(CH_3)CHN(CH_3)_2$	A	172–174[b] 196–198[b]	$C_{21}H_{25}N \cdot HCl$	76.9	7.99	4.27	10.8	76.6 76.6	7.98 7.93	4.18 4.09	10.8 10.6
7	H	H	$CH_2CH_2CH_2N(CH_3)_2$	B	161–162.5	$C_{21}H_{25}N \cdot HCl$	76.9	7.99	4.27	10.8	76.5	7.94	4.23	10.9
8	H	H	$CH_2CH(CH_3)CH_2N(CH_3)_2$	C	190–191	$C_{22}H_{27}N \cdot C_2H_2O_4$	72.9	7.39	3.54		73.1	7.45	3.38	
9	H	H		D	220–220.5	$C_{24}H_{30}N_2 \cdot 2C_2H_2O_4$	63.9	6.51	5.32		64.1	6.47	5.31	
10	OCH_3[c]	H	$CH_2CH_2N(C_2H_5)_2$	E	161–165	$C_{23}H_{29}NO \cdot C_2H_2O_4$	70.6	7.34	3.29		70.4	7.34	3.41	
11	Cl[c]	H	$CH_2CH_2N(C_2H_5)_2$	F	198–199	$C_{22}H_{26}ClN \cdot C_2H_2O_4$	66.9	6.56	3.26	8.3	66.8	6.73	3.22	8.2
12	H	4-OC_2H_5	$CH_2CH_2N(C_2H_5)_2$	G	178–179.5	$C_{24}H_{31}NO \cdot HCl$	74.7	8.36	3.63	9.2	74.8	8.53	3.55	9.3
13	H	4-CF_3	$CH_2CH_2N(C_2H_5)_2$	B	154–157	$C_{28}H_{26}F_3N \cdot C_2H_2O_4$	64.8	6.09	3.02		64.9	6.11	3.06	
14	H	4-Cl	$CH_2CH_2N(CH_3)_2$	H	210–212	$C_{20}H_{22}ClN \cdot HCl$	69.0	6.65	4.02	20.4	68.7	6.45	4.33	20.5
15	H	4-$N(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	E	168–171	$C_{24}H_{32}N_2 \cdot C_2H_2O_4$	71.2	7.82	6.39		71.0	7.96	6.36	
16	H	4-F	$CH_2CH_2N(CH_3)_2$	B	180–183	$C_{20}H_{22}FN \cdot HCl$	72.4	6.99	4.22	10.7	72.1	6.77	4.49	10.6
17	H	4-F		A	243–245	$C_{23}H_{26}FN \cdot HCl$	74.3	7.32	3.77	9.5	74.6	7.09	3.89	9.4
18	H	4-CH_3	$CH_2CH_2N(CH_3)_2$	B	197–199	$C_{21}H_{25}N \cdot HCl$	76.9	7.99	4.27	10.8	76.5	8.00	4.33	10.7
19	H	2-CH_3	$CH_2CH_2N(CH_3)_2$	A	226–228	$C_{21}H_{25}N \cdot HCl$	76.9	7.99	4.27	10.8	77.1	8.16	4.33	10.8
20	H	4-OCH_3	$CH_2CH_2N(CH_3)_2$	J	168–171	$C_{21}H_{25}NO \cdot HCl$	73.3	7.62	4.07	10.3	73.1	7.79	4.10	10.5

[a] A, *i*-PrOH; B, *i*-PrOH–petroleum ether (bp 60–80°); C, EtOH; D, EtOH–H_2O; E, MeCOEt; F, MeOH; G, EtOH–MeCOEt; H, H_2O; J, EtOH–benzene–petroleum ether. [b] Two isomers were isolated. [c] This substituent can be at position 5 or 6; solubility probably determines which tautomer crystallizes from solution.

TABLE II

SUBSTITUTED 2-BENZAL-1-INDANONES



R_1	R_2	Crystn solvent	Mp, °C	Formula	Calcd, % C	H	Found, % C	H
OCH_3	H	EtOH	132–134	$C_{17}H_{14}O_2$	81.6	5.64	81.4	5.63
Cl	H	Benzene–EtOH	158–159	$C_{16}H_{11}ClO$	75.5	4.35	75.3	4.38
H	OC_2H_5	EtOH	123–124.5	$C_{18}H_{16}O_2$	81.8	6.10	81.8	6.20
H	CF_3	AcOEt	181–183	$C_{17}H_{11}F_3O$	70.8	3.85	70.8	3.77

indanone was obtained by cyclization of dibenzylacetyl chloride[6] or by reduction[7,8] of 2-benzal-1-indanone (III, R = H; Ar = C_6H_5). 2-Benzal-1-indanone could also be reduced directly to the indanol, either by $LiAlH_4$ which afforded a 90% yield or, in low yield, by catalytic (Pd–C) hydrogenation.

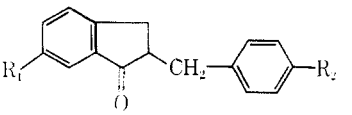
The latter route offers the possibility of a general synthesis, since 2-benzalindanones, substituted in either of the aromatic nuclei, can be readily prepared by base-catalyzed condensation between a substituted 1-indanone and a benzaldehyde.[9,10] The reduction of the substituted 2-benzal-1-indanones (Table II) was effected, however, in two stages, since the poor solubility of these compounds in ether rendered direct reduction by $LiAlH_4$ inconvenient. Partial catalytic hydrogenation gave the 2-benzyl-1-indanones (Table III) and hydride reduction of these afforded the 2-benzyl-1-indanols (Table IV) which, upon dehydration, yielded the 2-benzylindenes of Table V.

Hydride reduction of ketones may lead to isomeric products according to whether the reaction is under steric-approach (kinetic) control or product-development (thermodynamic) control.[11] Steric-approach control in the reduction of 2-benzyl-1-indanone would lead to *cis*-2-benzyl-1-indanol. In practice, hydride reduction afforded a mixture of the *cis* and *trans* isomers. The latter tended to predominate and could be isolated by crystallization. The structural assignment to *cis*- and *trans*-2-benzyl-1-indanol (V, R = H; Ar = C_6H_5) was verified in the following way. The reductive Grignard procedure of Noller and Hilmer[12] afforded

(6) H. Leuchs, J. Wutke, and E. Gieseler, *Ber.*, **46**, 2200 (1913).
(7) N. H. Cromwell and R. P. Ayer, *J. Am. Chem. Soc.*, **82**, 133 (1960).
(8) W. H. Mills and A. T. Akers, *J. Chem. Soc.*, **127**, 2475 (1925).
(9) Ng. Ph. Buu-Hoï and Ng. D. Xuong, *ibid.*, 2225 (1952).
(10) P. Pfeiffer and E. Milz, *Ber.*, **71B**, 272 (1938).
(11) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).
(12) C. R. Noller and F. B. Hilmer, *J. Am. Chem. Soc.*, **54**, 2503 (1932).

TABLE III

SUBSTITUTED 2-BENZYL-1-INDANONES

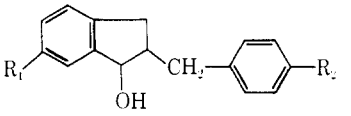


R_1	R_2	Cryst solvent	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
OCH_3	H	EtOH	59–63	$C_{17}H_{16}O_2$	80.9	6.39	80.9	6.35
Cl	H	MeOH	45–46	$C_{16}H_{13}ClO$	74.9	5.10	75.2	5.28
H	OC_2H_5	EtOH	58–59.5	$C_{18}H_{18}O_2$	81.2	6.81	80.9	6.87
H	CF_3	EtOH-H_2O	58.5–59.5	$C_{17}H_{13}F_3O$	70.3	4.51	70.3	4.79
H	Cl[a]	Benzene–petr ether	78–80.5	$C_{16}H_{13}ClO$	74.9	5.10	74.9	5.03
H	$N(CH_3)_2$[b]	EtOH	79–81.5[c]	$C_{18}H_{19}NO$	81.5	7.22	81.5	7.05

[a] Prepared from *p*-chlorobenzyl chloride and the magnesium enolate of 1-indanone-2-carboxylic acid. [b] Prepared from 2-(*p*-dimethylaminobenzal)-1-indanone, mp 163–168°, lit.[10] mp 165°. [c] G. A. Coppens, M. Coppens, D. N. Kevill, and N. H. Cromwell, *J. Org. Chem.*, **28**, 3267 (1963), report mp 79–80°.

TABLE IV

SUBSTITUTED 2-BENZYL-1-INDANOLS

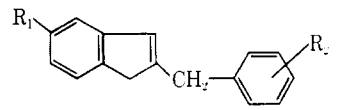


R_1	R_2	Cryst solvent	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
OCH_3	H	Benzene–petr ether	107–109.5	$C_{17}H_{18}O_2$	80.3	7.13	80.3	7.47
H	OC_2H_5	Benzene	95–96.5	$C_{18}H_{20}O_2$	80.6	7.51	80.3	7.54
H	CF_3	EtOH	137–140	$C_{17}H_{15}F_3O$	69.9	5.18	69.7	5.47
			97–100				69.7	5.28
H	Cl	EtOH	122–124	$C_{16}H_{15}ClO$	74.3	5.84	74.1	5.84
H	$N(CH_3)_2$	Benzene–petr ether	102–103.5	$C_{18}H_{21}NO$	80.9	7.92	80.5	7.87
H	OCH_3[a]	Benzene–petr ether	113–115	$C_{17}H_{18}O_2$	80.3	7.13	80.4	7.35

[a] Prepared from 2-(*p*-methoxybenzal)-1-indanone, mp 142.5–143.5°, lit.[10] mp 141°.

TABLE V

SUBSTITUTED 2-BENZYLINDENES



R_1	R_2	Cryst solvent	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
5-OCH_3[a]	H	EtOH	46–51	$C_{17}H_{16}O$	86.4	6.83	86.2	6.82
5-Cl[a]	H	MeOH	59–60	$C_{16}H_{13}Cl$	79.8	5.44	79.8	5.39
H	4-OC_2H_5	Petr ether	73.5–76	$C_{18}H_{18}O$	86.4	7.25	86.5	7.30
H	4-CF_3	*i*-PrOH	62.5–65.5	$C_{17}H_{13}F_3$	74.4	4.78	74.1	4.75
H	4-Cl	EtOH	66–68.5	$C_{16}H_{13}Cl$	79.8	5.44	80.0	5.33
H	4-$N(CH_3)_2$	EtOH	74–76	$C_{18}H_{19}N$	86.7	7.68	87.0	7.79
H	4-F	Oil	108 (0.01)	$C_{16}H_{13}F$	85.7	5.84	86.0	5.97
H	4-CH_3	Oil	130 (0.02)	$C_{17}H_{16}$	92.7	7.32	92.5	7.12
H	2-CH_3	Oil	120 (0.02)	$C_{17}H_{16}$	92.7	7.32	92.4	7.17
H	4-OCH_3	Petr ether	65–66.5	$C_{17}H_{16}O$	86.4	6.83	86.1	6.97

[a] Acid-catalyzed dehydration of 1-indanols does not usually cause prototropic isomerization of the resulting indene. There is, however, no confirmatory evidence for the position of the double bond in these compounds.

the *cis*-indanol from 2-benzyl-1-indanone and isobutylmagnesium bromide, and the *cis*-indanol was shown to be the thermodynamically less stable by its conversion into the *trans*-indanol on being heated with NaH in toluene. It was not possible to confirm the assignment from the nmr spectra, since the coupling constants of the *cis* and *trans* protons in the two isomers were similar.

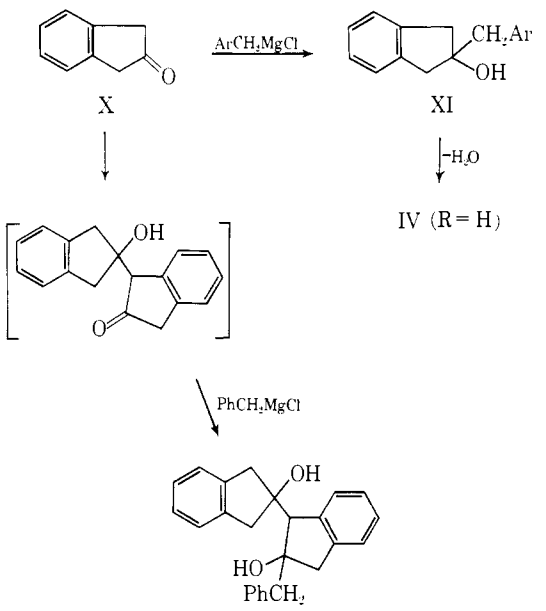
Table IV records those indanols which were isolated from the reduction-product mixtures by crystallization to constant melting point. Two isomeric indanols were isolated from the reduction of 2-(*p*-trifluoromethylbenzal)-1-indanone. Generally, in preparing the indenes, it was expedient to dehydrate the mixture of isomeric indanols.

As an alternative general route to substituted 2-benzylindanones (IV), alkylation of the magnesium enolate of 1-indanone-2-carboxylic acid (prepared *in situ* from 1-indanone (II, R = H) and magnesium methyl carbonate)[13] with a benzyl halide was investigated, since a similar reaction of α-tetralone had been reported.[13] In dimethylformamide (DMF) as solvent, *p*-chlorobenzyl chloride afforded a 60% yield of 2-(*p*-chlorobenzyl)-1-indanone after hydrolysis and decarboxylation.

(13) M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959).

In order to reduce the number of synthetic stages, some of the substituted 2-benzylindenes were prepared by dehydration of the appropriate 2-benzyl-2-indanols (XI). These were synthesized from 2-indanone (X) and the corresponding benzyl Grignard reagent (Scheme II). This route is not entirely satisfactory because of the instability of 2-indanone which readily dimerizes to 1-(2-hydroxyindan-2-yl)-2-indanone; the latter may then react with the Grignard reagent. Thus, 2-benzyl-1-(2-hydroxyindan-2-yl)-2-indanol (XII) was isolated from the reaction of X with benzylmagnesium chloride (similar observations have recently been made by Campbell and Heller[14]), and the reaction of X with *p*-methoxybenzylmagnesium chloride produced a complex mixture of products. The identity of XII was supported by its nmr spectrum.

SCHEME II



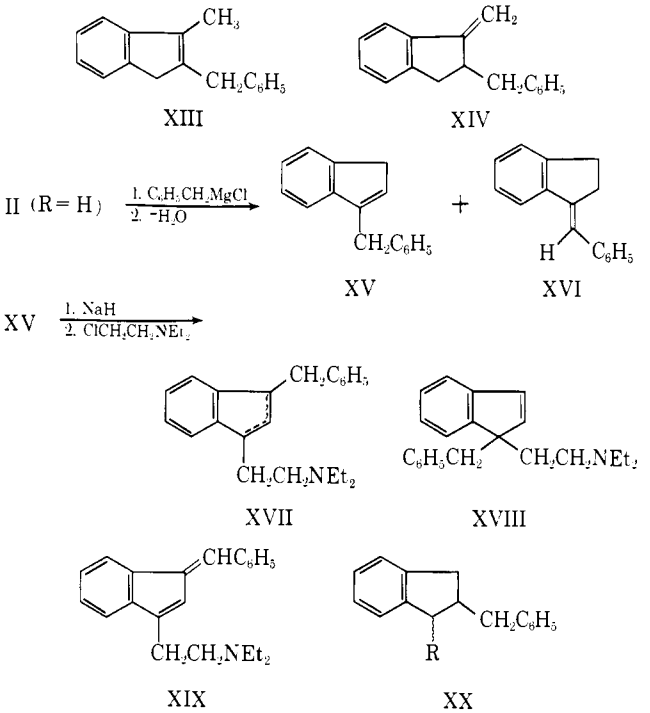
XII

2-(2-Pyridylmethyl)-2-indanol, which was synthesized from 2-pyridylmethyllithium and 2-indanone, could not be dehydrated under a variety of conditions. An isomeric 2-indanol, 1-(2-pyridylmethyl)-2-indanol, has been reported[15] to be similarly resistant to dehydration.

The synthesis of some related benzylindenes was also investigated. 2-Benzyl-3-methylindene (XIII), required for the synthesis of 2-benzyl-1-(2-dimethylaminoethyl)-3-methylindene, was prepared from 2-benzyl-1-indanone and methylmagnesium iodide. Although previously reported[16] as an oil, a solid was obtained. Since there was the possibility that the intermediate 1-methyl-1-indanol could undergo exocyclic dehydration to produce 1-methylene-2-benzylindane (XIV), the structure was established from the nmr spectrum. It contained signals from two benzylic (τ 6.22), two methylenic (doublet centered at τ 6.82), and three methyl protons (triplet of triplets centered at τ 7.87) and showed no evidence of a signal from a vinylic proton, thus confirming structure XIII. Alkylation of the anion derived from 2-benzyl-3-methylindene resulted, however, in the formation of a mixture of amines which could not be resolved.

3-Benzylindene (XV), required for the synthesis of 1-benzyl-3-(2-diethylaminoethyl)indene, was prepared by dehydration of the crude carbinol resulting from the Grignard reaction between 1-indanone and benzylmagnesium chloride. This procedure, which has been reported[17] to give 1-benzalindane as an oil, produced a mixture from which both 3-benzylindene and 1-benzalindane (XVI) were isolated as solids. The identity of 1-benzalindane was confirmed by independent synthesis (32% yield) from 1-indanone and benzaltriphenylphosphorane using the conditions described[18] by Wittig for the preparation of *trans*-stilbene. A similar synthesis under different reaction conditions has since been reported to give a 9% yield of 1-benzalindane.[19] A *trans* configuration for the 1-benzalindane was established by the ultraviolet absorption spectrum which showed the long-wavelength band at 280–330 mμ with vibrational peaks characteristic of the *trans*-stilbene chromophore ("A" band[20]). The isolation of both 3-benzylindene and 1-benzalindane from the Grignard route further illustrates the difficulty in predicting whether tertiary 1-indanols yield *exo* or *endo* double bond containing products on dehydration.[21]

Reaction between 1-chloro-2-diethylaminoethane and the anion derived from 3-benzylindene occurred readily, but only a small quantity of pure product could be isolated. Its structure (XVII) follows from the nmr spectrum which contains a signal integrating for only one vinylic proton (doublet centered at τ 3.57), thus distinguishing it from the alternative 1-benzyl-1-(2-diethylaminoethyl)indene structure (XVIII). The



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methylenic proton signals were too complex to permit positional assignment of the double bond.

1-Benzal-3-(2-diethylaminoethyl)indene (XIX) was prepared from the base-catalyzed condensation of benzaldehyde with 3-(2-diethylaminoethyl)indene. A number of indane derivatives were also synthesized. 1-(2-Dimethylaminoethyl)-2-benzylindane (XX, R = $CH_2CH_2N(CH_3)_2$) was prepared by catalytic hydrogenation of the corresponding indene. Several 1-dialkylaminoalkoxy-2-benzylindanes [XX, R = $O(CH_2)_n$-NR_1R_2] were obtained by the reaction of an appropriate dialkylaminoalkyl chloride with the sodium salt of 2-benzyl-1-indanol.

Biological Activity.—The results obtained from the biological investigation are recorded in Table VI. The methods used to assess the compounds are referred to in the footnotes to the table.

A number of the compounds were found to have potencies comparable to those of codeine and pethidine in the tests for analgesia in mice. They were active orally and appeared to be nonmorphine-like.

Further investigations of the compounds indicated, however, that they possessed other depressant effects on the central nervous system. The majority of the compounds which were active in the tests for analgesia were also effective in preventing maximal electroshock seizures or in inhibiting electrically induced fighting episodes in mice at doses which were in the same range as the analgesic ED_{50}'s. Few of the compounds, however, were found to be effective in both of these procedures. Compound **18**, which was active in the analgesic tests but inactive in the other two test procedures, was also found to act as a depressant. Thus, it suppressed the toxic effect of amphetamine in aggregated mice[22] and blocked a conditioned avoidance response in rats.[23]

3-Benzyl-2-dialkylaminoalkylindenes, which are isomeric with the compounds discussed above, have been reported to be potent antihistaminics.[24] The compounds of Table VI were examined for antihistaminic activity (isolated guinea pig ileum); compounds **3**, **5**, **16**, and **17** were found to have potencies comparable with diphenylpyraline.

Table VI

Biological Activity[a]

	LD_{50}[b]		Analgesic activity				Electro-shock[e]	Mouse cage[f]
			Hot plate[c]		Tail clip[d]			
No.	*po*	*sc*	*po*	*sc*	*po*	*sc*	*sc*	*po*
1	+	++	±	+	±	+	–	+
2	+	+	±	+	–	+	±	+
3	+	+	+	+	+	+	±	+
4	±	±		–			±	–
5	+	++		±				±
6[g]	+	+	±	+	+	+	–	±
6[h]			–	+	+	+	±	–
7	±	+	±	+		+	+	–
8	+			±			+	±
9	±	±	±	±	±	+	+	
10	+	+		+		+	±	–
11				–		–	±	–
12	+	+	±	±	±	±	±	–
13	±	±		–		–	+	
14				–		+	–	+
15				–		–	+	–
16	+	+	+	+	+	+	–	+
17	+	±	+	–	+	–	+	+
18			+	+	+	+	–	–
19	+	±		±		±	–	±
20[i]								
21	+	+		±		±	±	±
22	+	+	±	+	+	+		–
23				+			+	
24	+	+	–	+	–	+	–	–
25	±	+	–	+	–	±	+	–
26	+	+		–			+	–
27	+	+	+				+	+

[a] Activity at higher doses than the range quoted under footnotes *e–f* is represented by ±; the absence of observable effects at doses of 30% LD_{50} value is denoted by –. [b] Seven day toxicity in mice; the results are presented as ++ = LD_{50} <200 mg/kg, + = LD_{50} 200–500 mg/kg, ± = LD_{50} > 500 mg/kg. [c] Analgesic activity in mice (hot plate method) [N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952)]: + = ED_{50} (*po*) 70–110 mg/kg (comparable ED_{50} for codeine = 100 mg/kg), ED_{50} (sc) 15–60 mg/kg (comparable ED_{50} for pethidine = 20 mg/kg). [d] Analgesic activity in mice (tail clip method) [C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954)]: + = ED_{50} (*po*) 40–100 mg/kg (comparable ED_{50} for codeine = 60 mg/kg), ED_{50} (sc) 10–70 mg/kg (comparable ED_{50} for codeine = 25 mg/kg). [e] Prevention of maximal electroshock induced seizures in mice [E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952)]: + = ED_{50} (*po*) 30–100 mg/kg (comparable ED_{50} for diphenylhydantoin = 5 mg/kg). [f] Prevention of electrically induced fighting episodes in mice [R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *ibid.*, **125**, 28 (1959)]: + = ED_{50} (*po*) 40–80 mg/kg (comparable ED_{50} for meprobamate = 70 mg/kg). [g] Isomer having mp 172–174°. [h] Isomer having mp 196–198°. [i] Insufficient material for testing owing to difficulties encountered in the purification of this compound.

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. Ultraviolet absorption spectra were measured on a Beckman DK2 spectrometer. Infrared spectra were recorded on a Hilger H800 or Unicam SP200 spectrometer. Nmr spectra were determined with a Varian A-60A spectrometer. NaH refers to a 53.8% dispersion of NaH in paraffin oil.

2-Benzyl-1-indanone (IV, R = H; Ar = C_6H_5). Method A. From Dibenzylacetic Acid.—Dibenzylacetic acid (83 g, 0.35 mole) was heated with $SOCl_2$ (62 g, 0.52 mole) in dry benzene (300 ml) under reflux for 3.5 hr. The mixture was then distilled to give 82 g (90%) of dibenzylacetyl chloride, bp 124° (0.3 mm). In another experiment, using only 20% excess $SOCl_2$, dibenzylacetic anhydride was also obtained; mp 75–77° (lit.[25] mp 75–76°).

Dibenzylacetyl chloride (60 g, 0.23 mole) was added dropwise to powdered anhydrous $AlCl_3$ (30 g, 0.23 mole) in CH_2Cl_2 (200 ml) at −10°. The reaction mixture was permitted to warm slowly to 20°, and, when the vigorous evolution of HCl had subsided, it was heated under reflux for 10 min. The mixture was cooled, added to cold 2 *N* HCl (125 ml), and extracted with toluene. Distillation of the toluene extracts gave 48 g (94%) of 2-benzyl-1-indanone, bp 125° (0.02 mm), $n^{20}D$ 1.6009 [lit.[7] bp 160° (1.75 mm), $n^{35}D$ 1.5954].

Method B. From 2-Benzal-1-indanone.—Hydrogenation of 2-benzal-1-indanone[26] (mp 109–112°, 12 g, 0.05 mole) at atmospheric pressure in methanol (100 ml) at 50° for 5 hr in the presence of 0.05 g of 10% Pd-C afforded a quantitative yield of 2-benzyl-1-indanone.[26] Prolonged exposure to H_2 without the addition of more catalyst did not lead to further reduction.

The compounds of Table II were synthesized in a similar manner from an 1-indanone and the appropriate aldehyde using the method of Hassner and Cromwell,[26] then hydrogenated to

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the corresponding indanones of Table III. 6-Chloro-1-indanone[27] (mp 78–80°), 6-methoxy-1-indanone[28] (mp 108–109°), and *p*-ethoxybenzaldehyde[29] (bp 74–78° (0.05 mm)) were prepared by literature procedures.

***p*-Trifluoromethylbenzaldehyde** was synthesized from *p*-trifluoromethylphenylmagnesium bromide and triethyl orthoformate. The latter (66 g, 0.45 mole) was added during 10 min to the Grignard reagent prepared[30] from *p*-bromobenzo trifluoride (82.5 g, 0.37 mole) and Mg (9.9 g, 0.41 g-atom) in ether (300 ml) at 35°. The mixture was heated under reflux for 16 hr, and the ether was distilled. Ice (150 g) then 6 *N* HCl (370 ml) were added and, after the mixture had been heated under reflux for 2 hr to hydrolyze the acetal, it was steam distilled under N_2. The distillate was extracted with ether, and the extracts were distilled under reduced pressure in a N_2 atmosphere to yield the product in 49% yield (31 g) as a colorless oil, bp 69–70° (15 mm), $n^{20}D$ 1.4630 (lit.[30] $n^{20}D$ 1.4630, 40% yield).

2-(*p*-Chlorobenzyl)-1-indanone (IV, R = H; Ar = *p*-ClC$_6$H$_4$).—A solution of magnesium methyl carbonate[31] was prepared by bubbling dry CO_2 for 2.5 hr into a suspension of freshly prepared magnesium methoxide (130 g, 1.5 moles) in dry DMF (400 ml) until the solid had dissolved. 1-Indanone (50 g, 0.38 mole) was added, and the mixture was heated at 105° for 1.5 hr. *p*-Chlorobenzyl chloride (90 g, 0.56 mole) was then added, and the mixture was stirred at 90° for 9 hr, then acidified with 10 *N* HCl (350 ml) and heated for 3.5 hr to effect decarboxylation. The mixture was cooled, and the lower aqueous layer was extracted twice with benzene. These extracts were combined with the organic layer and washed successively with water and aqueous $NaHCO_3$, dried (K_2CO_3), and concentrated. Distillation of the residue afforded the product (60 g), bp 180–190° (1 mm), which, after crystallization from benzene–petroleum ether (bp 60–80°), was obtained as colorless prisms in 52% yield (51 g), mp 78–80.5° (lit.[32] mp 76–77°) (see Table III). The structure was confirmed by reduction to 2-(*p*-chlorobenzyl)-1-indanol which, on dehydration, afforded 2-(*p*-chlorobenzyl)indene identical with that obtained by dehydration of 2-(*p*-chlorobenzyl)-2-indanol (below).

***trans*-2-Benzyl-1-indanol (V, R = H; Ar = C$_6$H$_5$). Method A. LiAlH$_4$ Reduction of 2-Benzyl-1-indanone.**—2-Benzyl-1-indanone (155 g, 0.7 mole) in 300 ml of dry ether was added slowly to $LiAlH_4$ (7.4 g, 0.2 mole) in ether (400 ml) at a rate which maintained gentle reflux. The mixture was stirred overnight, poured onto ice, and acidified with dilute H_2SO_4. The ethereal layer was dried and concentrated to give the product which, after one crystallization from petroleum ether, had mp 97–100°; yield 91 g (58%). The compounds of Table IV were synthesized in a similar manner.

Method B. NaBH$_4$ Reduction.—$NaBH_4$ (3.21 g, 0.085 mole) in 20 ml of water was added dropwise to 2-benzyl-1-indanone (61 g, 0.28 mole) in methanol (100 ml) with cooling to maintain the mixture at 20–25°. The mixture was further stirred for 1.5 hr, then diluted with water (100 ml) and extracted with ether. The ethereal extract was concentrated and the residue was crystallized from petroleum ether (bp 60–80°) to give 54.5 g (87%) of a mixture of the *cis*- and *trans*-indanols, mp 68–70°. Three further crystallizations afforded 10.1 g of the pure *trans*-isomer as silky needles: mp 103–105.5° (lit.[5] mp 104–105°); nmr ($CDCl_3$), τ 7.84 (singlet, OH), 7.70–6.75 (complex, methylenic), 5.12 (broad doublet, J = 6 cps, HCO), 2.85–2.6 (complex aromatic) in the ratio 5.85:0.94:9.

Anal. Calcd for $C_{16}H_{16}O$: C, 85.7; H, 7.19. Found: C, 85.5; H, 7.14.

Method C. Catalytic Hydrogenation.—2-Benzyl-1-indanone (2.23 g, 0.01 mole) in ethanol (50 ml) at 50° was shaken with H_2 at atmospheric pressure with 0.05 g of 10% Pd-C for 4 hr. Removal of the catalyst and concentration yielded the indanol contaminated with about 10–15% of the ketone.

Method D. LiAlH$_4$ Reduction.—2-Benzal-1-indanone (6 g, 0.027 mole) in a Soxhlet thimble was suspended in a flask containing $LiAlH_4$ (1.04 g, 0.027 mole) and ether (100 ml) under reflux, arranged so that the refluxing solvent dripped through the thimble. After all the solid had been extracted (5 hr), the mixture was poured onto ice and acidified with dilute H_2SO_4. The ethereal layer was dried and concentrated to give *trans*-2-benzyl-1-indanol (5.4 g) which, after one crystallization from petroleum ether, had mp 98–100°.

Method E. Isomerization.—*cis*-2-Benzyl-1-indanol (1 g) and NaH (0.3 g) were heated together for 16 hr in 25 ml of refluxing toluene under N_2. The mixture was cooled, washed with water (10 ml), and concentrated. The oily residue was triturated with pentane (to remove the paraffin oil), then crystallized from petroleum ether to give *trans*-2-benzyl-1-indanol, mp 102.5–104°, 0.5 g. Similar treatment of *trans*-2-benzyl-1-indanol gave a 70% recovery of the *trans* isomer (after recrystallization).

***cis*-2-Benzyl-1-indanol.**—2-Benzyl-1-indanone (44.5 g, 0.2 mole) in dry ether (70 ml) was added dropwise during 30 min to isobutylmagnesium bromide [from isobutyl bromide (41.1 g, 0.3 mole) and Mg (7.30 g, 0.3 g-atom)] in 120 ml of dry ether with stirring and cooling to maintain the temperature at 0°. The addition of each drop produced a transient yellow color, but the reaction solution remained clear. The cooling bath was then removed. After 30 min, a dense white precipitate formed, and 2-methylpropane was evolved. The reaction mixture was heated under reflux for 30 min and diluted with ether to produce a fluid slurry. The white precipitate was filtered, decomposed with saturated aqueous NH_4Cl, and extracted three times with ether. Concentration of the dried, ethereal extract afforded the product which, after crystallization from the minimum of petroleum ether (bp 60–80°) and recrystallization from benzene–petroleum ether (1:3), was obtained as silky needles: mp 81–82.5°; yield 15.3 g (38%): nmr ($CDCl_3$), τ 8.25 (singlet, OH), 7.50–6.85 (complex, methylenic), 5.08 (broad doublet, J = 5 cps, HCO), 2.85–2.6 (complex, aromatic) in the ratio 0.97:4.92:0.92:9. Admixture with the *trans* isomer depressed the melting point by 10°.

Anal. Calcd for $C_{16}H_{16}O$: C, 85.7; H, 7.19. Found: C, 85.4; H, 7.06.

The identity of the product was confirmed by its dehydration in concentrated HCl–ethanol (1:6) to 2-benzylindene (melting point and infrared spectrum identical with those of material obtained from the dehydration of *trans*-2-benzyl-1-indanol).

2-Benzyl-2-indanol (XI, Ar = C$_6$H$_5$).—2-Indanone[33] (25.6 g, 0.2 mole) in dry benzene (100 ml) was added to benzylmagnesium chloride [from benzyl chloride (37.8 g, 0.3 mole) and Mg (7.1 g, 0.3 g-atom)] in 150 ml of dry ether at 0°. The mixture was refluxed for 5 hr, then poured onto saturated NH_4Cl and ice and filtered. The filtrate was extracted with ether, and the extracts were dried and concentrated to give 35.4 g of a solid which, after crystallization (charcoal) from petroleum ether (bp 60–80°), had mp 70–73°. Fractional crystallization ("triangular method") from petroleum ether (bp 40–60°) gave 28.1 g (63%) of 2-benzyl-2-indanol as colorless needles, mp 82–83.5° (lit.[14] mp 82°), and 2.4 g (6.7% yield) of **2-benzyl-1-(2-hydroxyindan-2-yl)-2-indanol (XII)** as colorless microprisms which, after crystallization from benzene–petroleum ether (bp 80–100°), had mp 159.5–161.5° (lit.[14] mp 160°).

Anal. Calcd for $C_{16}H_{16}O$ (XI): C, 85.7; H, 7.19. Found: C, 85.6; H, 6.95. Calcd for $C_{25}H_{24}O_2$ (XII): C, 84.2; H, 6.79. Found: C, 84.0; H, 6.88.

Nmr ($CDCl_3$) of 2-benzyl-2-indanol showed τ 8.19 (singlet, OH), 7.05 (quartet, J = 16 cps, indane methylenic), 7.02 (singlet, benzylic), 2.82 and 2.69 (singlets, aromatic) in the ratio 0.9:6.0:8.9.

Nmr ($CDCl_3$–D_2O) of XII showed τ 7.08 (singlet, benzylic), 7.01–6.75 (complex, methylenic), 6.63 (singlet, lone indanyl proton), 2.85–2.70 (complex, aromatic) in the ratio 1.9:5.8:1.1:13.

In an analogous manner, the following compounds were synthesized from the appropriate Grignard reagents.

2-(*p*-Chlorobenzyl)-2-indanol, mp 143.5–145° (petroleum ether).

Anal. Calcd for $C_{15}H_{13}ClO$: C, 74.3; H, 5.84. Found: C, 74.6; H, 5.83.

2-(*p*-Fluorobenzyl)-2-indanol, mp 104–106° (petroleum ether).

Anal. Calcd for $C_{15}H_{13}FO$: C, 79.3; H, 6.25. Found: C, 79.3; H, 6.18.

2-(*p*-Methyl- and 2-(*o*-methylbenzyl)-2-indanol, which were obtained as oils, were distilled and then dehydrated to the corresponding indenes without further characterization.

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(31) M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 505 (1959).

(32) D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *ibid.*, **88**, 4489 (1966).

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

2-(2-Pyridylmethyl)-2-indanol (XI, Ar = 2-C_5H_4N).—2-Indanone (33 g, 0.25 mole) in dry ether (50 ml) was added during 30 min to a stirred solution of 2-pyridylmethyllithium [prepared from phenyllithium (0.3 mole) and 2-methylpyridine (0.3 mole)] in ether (500 ml) maintained at 0°. The mixture was left for 16 hr, poured onto ice, and extracted with dilute HCl. The extracts were basified, and the oily product which separated was extracted into ether. The ethereal extract was concentrated, the residual 2-methylpyridine was removed *in vacuo*, and the product was crystallized from petroleum ether to yield 17.8 g, 32%, of colorless prismatic needles. Recrystallization gave pure material, mp 88–90°.

Anal. Calcd for $C_{15}H_{15}NO$: C, 80.0; H, 6.71; N, 6.22. Found: C, 79.9; H, 6.57; N, 6.21.

2-(2-(Pyridylmethyl)-2-indanol was not dehydrated when heated with P_2O_5, $KHSO_4$, iodine in xylene, or concentrated HCl in ethanol and was recovered. The use of Ac_2O or AcOH–HCl mixture afforded mixtures of the starting material and the corresponding acetate.

2-Benzylindene (VI, R = H; Ar = C_6H_5).—2-Benzyl-2-indanol (224 g, 1 mole) was heated with 10 *N* HCl (100 ml) in ethanol (1 l.) under reflux for 6 hr. The mixture was concentrated to half-volume, diluted with an equal volume of water, and extracted with ether. The ether extract, after being washed with 10% NaOH, was dried and concentrated. Distillation *in vacuo* of the resulting oil afforded 2-benzylindene, bp 124–130° (0.1 mm), which, after two crystallizations from ethanol, was obtained as colorless plates: mp 48–49.5° (lit.[11] mp 48°); yield 149 g (72%): λ_{max}^{EtOH} 258 mμ (log ε 4.18), shoulders at 254, 262, 269, 282, and 288 mμ; nmr ($CDCl_3$), τ 6.88 (singlet, C-1 methylenic), 6.34 (singlet, benzylic), 3.59 (multiplet, C-3 vinylic), 3.0–2.7 (complex, aromatic) in the ratio 2:2:1:9.

Anal. Calcd for $C_{16}H_{14}$: C, 93.2; H, 6.84. Found: C, 93.2; H, 6.86.

Alternatively, the benzylindanol was intimately ground with an equal weight of $KHSO_4$ and heated at 140–180° for 1 hr in a Claisen distillation flask. Water was removed by distillation at 12 mm and the product was obtained from the mixture by distillation *in vacuo*.

The indenes of Table V were obtained by one of these procedures.

2-Benzyl-3-(2-dimethylaminoethyl)indene Hydrochloride (IX, R_1 = H; R_3 = R_4 = CH_3; *n* = 2; Ar = C_6H_5).—2-Benzylindene (10.3 g, 0.05 mole) and NaH (2.23 g, 0.05 mole) were heated in dry toluene (100 ml) under reflux for 6 hr under N_2. Hydrogen was evolved, and benzylindenylsodium precipitated as a viscous, brown oil which tended to adhere to the wall of the flask. 1-Chloro-2-dimethylaminoethane in toluene [obtained by neutralization of 14.4 g (0.1 mole) of the hydrochloride with 40% NaOH and extraction into toluene; the toluene extract was dried twice over KOH] was added, and the mixture was stirred under reflux for 16 hr. The reaction mixture was cooled, filtered, and extracted with dilute HCl. The acidic extract was basified, and the oil which separated was recovered with ether. Distillation *in vacuo* gave 6.1 g (44%) of oil, bp 148° (0.05 mm). This, in ether, was converted into hydrochloride (6.7 g) which, after three crystallizations from 2-propanol, furnished analytically pure product as colorless prisms: mp 214–216° (see Table I); λ_{max}^{EtOH} 259 mμ (log ε 4.14), shoulders at 256, 263, 270, 281, and 287 mμ.

A pure sample of the **amine**, which was required for nmr study and was obtained by neutralization of the hydrochloride, had $n^{24}D$ 1.5805. It solidified at 0° to −5°; nmr ($CDCl_3$), τ 7.68 [singlet, $N(CH_3)_2$], 7.65–7.0 (complex, aliphatic), 6.81 (singlet, C-1 methylenic), 6.21 (singlet, benzylic), 3.0–2.4 (complex, aromatic) in the ratio 6.2:4:2:2:9.

The amine was treated with an equimolar quantity of NaH in benzene–DMF or KOH in ethanol for 3 hr at 23°, and the mixture was worked up in the usual manner to afford the hydrochloride (85% recovery) which was identical (infrared and melting point) with that described above.

The indenes of Table I were synthesized by a similar procedure. Hydrogen oxalates were prepared if the hydrochloride was hygroscopic or not easily crystallized.

2-Benzyl-1-(2-dimethylaminoethyl)indane Hydrochloride (21).—2-Benzyl-3-(2-dimethylaminoethyl)indene hydrochloride (7.0 g, 0.02 mole) in ethanol (200 ml) at 26° was shaken with H_2 at atmospheric pressure with 50 mg of 10% Pd–C. Absorption of H_2 was initially rapid but soon slowed, and three further 50-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 (4.0 g, 57%) separated as colorless blades, and, after crystallization from ethyl methyl ketone, had mp 206–209° (mixture melting point with starting material 180–185°).

Anal. Calcd for $C_{20}H_{25}N \cdot HCl$: C, 76.0; H, 8.30; N, 4.43; Cl, 11.2. Found: C, 76.0; H, 8.29; N, 4.43; Cl, 11.3.

***trans*-1-(2-Dimethylaminoethoxy)-2-benzylindane Hydrochloride (22).**—*trans*-2-Benzyl-1-indanol (11.2 g, 0.05 mole) and NaH (3.35 g, 0.075 mole) were heated in refluxing toluene (100 ml) for 2 hr. A dry solution of 1-chloro-2-dimethylaminoethane in toluene (from 8.62 g, 0.06 mole of hydrochloride) was added, and the mixture was stirred under reflux for 4.5 hr. The reaction mixture was cooled, filtered, and extracted with dilute HCl. The acidic extract was basified, and the oil which separated was extracted into ether and converted into the hydrochloride by addition of ethereal HCl. The product which precipitated was crystallized once from ethyl methyl ketone–ether, then twice from ethyl methyl ketone, to afford colorless plates, mp 126–128°, yield 6 g (36%).

Anal. Calcd for $C_{26}H_{29}NO \cdot HCl$: C, 72.4; H, 7.90; N, 4.22; Cl, 10.7. Found: C, 72.3; H, 7.70; N, 4.30; Cl, 10.8.

The following compounds were prepared in a similar way but were isolated as hydrogen oxalates.

***trans*-1-(2-Piperidinoethoxy)-2-benzylindane hydrogen oxalate (24)** was obtained in 22% yield, mp 130–131.5° dec (ethanol).

Anal. Calcd for $C_{24}H_{29}NO \cdot C_2H_2O_4$: C, 70.6; H, 7.34; acid equiv, 213. Found: C, 70.5; H, 7.42; acid equiv, 210.

***trans*-1-[3-(4-Methylpiperazino)propoxy]-2-benzylindane dioxalate (25)** was obtained in 21% yield, mp 217–217.5° dec (ethanol).

Anal. Calcd for $C_{24}H_{32}N_2O \cdot C_4H_2O_4$: C, 61.8; H, 6.66; acid equiv, 136. Found: C, 61.8; H, 6.83; acid equiv, 133.

In an analogous manner, *cis*-2-benzyl-1-indanol yielded ***cis*-1-(2-dimethylaminoethoxy)-2-benzylindane hydrochloride (23)** as colorless plates (ethyl methyl ketone), mp 128–130°, yield 34%.

Anal. Calcd for $C_{26}H_{29}NO \cdot HCl$: C, 72.4; H, 7.90; N, 4.22; Cl, 10.7. Found: C, 72.3; H, 7.86; N, 4.13; Cl, 10.6.

The melting point of the *trans*-amine hydrochloride was not noticeably depressed by the *cis* salt. The infrared spectra of the two compounds as Nujol mulls, however, showed considerable differences in the region of 700–1400 cm^{-1}. Since *cis*-2-benzyl-1-indanol is converted into the *trans*-indanol upon heating with NaH in toluene, the possibility existed that the two hydrochlorides were the same compound and that the differences in the infrared spectra were due to the presence of two crystalline forms. This was not the case. The spectrum of a mixture, obtained by evaporating to dryness a solution containing equal amounts of the two hydrochlorides in ethyl methyl ketone, was found to be a complete combination of the spectra of the two separate products.

2-Benzyl-3-methylindene (XIII). 2-Benzyl-1-indanone (29.3 g, 0.13 mole) in dry ether (60 ml) was added dropwise during 1 hr to the Grignard reagent prepared from methyl iodide (23 g, 0.15 mole), Mg (3.36 g, 0.14 g-atom), and ether (80 ml), at 0° under N_2. The reaction mixture was stirred at 23° for 3 hr, then at 40° for 1 hr and poured onto crushed ice and dilute H_2SO_4. The oil which separated was collected by ether extraction and distilled *in vacuo* to give XIII, bp 120–121° (0.2 mm), which solidified: yield 19.2 g (67%). Crystallization from ethanol gave analytically pure material as colorless plates: mp 36–38.5° [lit.[28] bp 134–139° oil (0.02 mm)]: λ_{max}^{EtOH} 259 mμ (log ε 4.19), shoulders at 243, 248, 253.5, 264, and 269 mμ; nmr ($CDCl_3$), τ 7.87 (triplet of triplets, CH_3), 6.82 (doublet, C-1 methylenic), 6.22 (singlet, benzylic), 3.1–2.5 (complex, aromatic), in the ratio 3:2:2:9.

Anal. Calcd for $C_{17}H_{16}$: C, 92.7; H, 7.32. Found: C, 92.7; H, 7.22.

3-Benzylindene (XV).—1-Indanone (66.1 g, 0.5 mole) in 120 ml of dry ether was added during 30 min to the Grignard reagent prepared from benzyl chloride (69.5 g, 0.55 mole), Mg (12.75 g, 0.525 g-atom), and 100 ml of ether at 0° under N_2. The mixture was stirred for a further 30 min at 0°, for 1 hr at 23°, and finally for 30 min under reflux. The pale cream precipitate was filtered, washed with ether, decomposed with saturated NH_4Cl, and extracted with ether. Evaporation of the ether extract afforded the indanol (69 g). The latter was heated for 1 hr in ethanol (250 ml) containing 10 ml of 10 *N* HCl to effect dehydration. The mixture was concentrated to 100 ml, diluted with water (150 ml), and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract afforded a viscous oil (59 g) which, on distillation *in vacuo*,

yielded three fractions of bp (0.3 mm) 79–91, 134–142, and 145–158°. The second fraction was redistilled [bp 132–136° (0.3 mm), 31 g] and then crystallized from pentane at −40° to afford pure 3-benzylindene as colorless prisms, mp 31.5–33° (lit.[34] mp 33–34°), yield 27.1 g (27%).

The last fraction solidified in the condenser and was recrystallized from petroleum ether to yield 15.2 g (15%) of colorless, prismatic needles, mp 75–77°, identified as *trans*-**1-benzalindane**.

trans-**1-Benzalindane (XVI).**—Benzyltriphenylphosphonium chloride (45 g, 0.11 mole) was added to sodium ethoxide (from 2.3 g, 0.1 g-atom of Na) in 250 ml of dry ethanol under N_2. 1-Indanone (13.2 g, 0.1 mole) was then added to the yellow solution. The reaction mixture was stirred at 20° in the dark under N_2 for 60 hr, poured into 250 ml of 10% aqueous HBr, and filtered. The buff-colored residue was washed with 1:1 ethanol–water and crystallized (after being treated with active charcoal) first from ethanol, then from petroleum ether (bp 60–80°) to afford XVI, mp 75–76.5° (lit.[19] mp 73–74.5°), yield 6.6 g (32%).

Anal. Calcd for $C_{16}H_{14}$: C, 93.2; H, 6.84. Found: C, 93.4; H, 7.02.

The ultraviolet spectrum (typical *trans*-stilbene absorptions) had λ_{max}^{EtOH} 229 mμ (log ε 4.12), 236 (4.06), 244 (3.79), 275 (infl), 284.5 (4.31), 296 (4.34), 306 (infl), 317 (4.46), and 331 (4.29).

2-(Indan-1′-ylidene)-1-indanone (0.2 g) crystallized from the ethanolic mother liquor, and, after recrystallization from petroleum ether, had mp 142–144° (lit.[35] mp 142°).

1(3)-Benzyl-3(1)-(2-diethylaminoethyl)indene Hydrogen Oxalate (26).—3-Benzylindene (20.6 g, 0.1 mole), NaH (4.45 g, 0.1 mole), and dry toluene (200 ml) were heated under reflux for 6 hr under N_2. Then, 1-chloro-2-diethylaminoethane (from 0.14 mole of hydrochloride) in 50 ml of dry toluene was added to the resulting suspension of buff solid sodium derivative. Reaction was rapid and exothermic, and a white precipitate formed. After being stirred under gentle reflux for 12 hr, the mixture was extracted with dilute HCl, and the amine was isolated in the usual manner. Distillation *in vacuo* yielded 19 g of pale yellow oil, bp 158–178° (0.4 mm), which, with oxalic acid in ethanol, afforded 6.1 g (15%) of the hydrogen oxalate after dilution with ether. Three crystallizations from water furnished the product, mp 139–145°.

Anal. Calcd for $C_{22}H_{27}N \cdot C_2H_2O_4$: C, 72.9; H, 7.39; N, 3.54; acid equiv, 198. Found: C, 72.8; H, 7.45; N, 3.80; acid equiv, 196.

The ultraviolet absorption spectrum showed several low-intensity maxima at 292–330 mμ which suggest the presence of 1% of an impurity containing a 1-benzalindane chromophore: λ_{max}^{EtOH} 257 mμ (log ε 3.95), 282 (2.47), 292 (2.46), 303 (2.44), 315 (2.42), shoulders at 296 and 330; nmr (D_2O at 75°), τ 8.55 (triplet, CH_3), 8.0–6.0 (complex, aliphatic), 3.57 (doublet, vinylic), 3.1–2.2 (complex, aromatic) in the ratio 5.9:11.4:1.1:9.

1-Benzal-3-(2-diethylaminoethyl)indene Hydrochloride (27).—Indene (87 g, 0.75 mole) was treated with NaH (33.6 g, 0.75 mole) in dry DMF (650 ml) at 20° under N_2. After 2.5 hr, 1-chloro-2-diethylaminoethane (from 344 g, 2 mole of hydrochloride) in 250 ml of dry toluene was added. After being stirred at 40–50° for 15 hr, the mixture was diluted with water (750 ml), and the toluene layer was separated, washed with water, and extracted with 5 *N* HCl. **3-(2-Diethylaminoethyl)indene**, which was isolated by basification of the acidic extract, was distilled twice *in vacuo* and obtained as a colorless mobile oil (62 g, 39%), bp 148–150° (0.2 mm), $n^{21}D$ 1.5356 [lit.[3] bp 140° (0.4 mm)].

Anal. Calcd for $C_{15}H_{21}N$: C, 83.7; H, 9.83; N, 6.51. Found: C, 83.6; H, 9.97; N, 6.48.

To 3-(2-diethylaminoethyl)indene (10 g, 0.046 mole) and benzaldehyde (5.35 g, 0.05 mole) in 100 ml of ethanol was added ethanolic KOH (85 ml containing 3.85 g, 0.068 mole). The mixture was stirred at 21° for 4 hr, then concentrated to 50 ml, diluted with water (100 ml), and extracted with ether. The ether solution was extracted with 5 *N* HCl, and the acid extract was basified to liberate the oily amine (13.4 g) which was converted to the hydrochloride. After recrystallization from 2-propanol–ether, it was obtained as bright yellow needles: mp 189–191°; yield 11.8 g (76%); λ_{max}^{EtOH} 240–242 mμ (log ε 3.96), 283–284 (4.12), and 341 (4.17).

Anal. Calcd for $C_{22}H_{25}N \cdot HCl$: C, 77.7; H, 7.71; N, 4.12; Cl, 10.4. Found: C, 77.9; H, 7.87; N, 3.93; Cl, 10.4.

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Sympathetic Nervous System Blocking Agents. III. Derivatives of Benzylguanidine[1-3]

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A series of 25 derivatives of benzylguanidine and related compounds was synthesized and investigated for sympathetic nervous system blocking activity by their effect on the nictitating membrane of the unanesthetized cat. Selected members were also screened for hypotensive activity in the anesthetized cat by the intravenous route. The most active compounds, *p*-trifluoromethylbenzylguanidine sulfate (Table I, **14**) and α-methyl-*p*-trifluoromethylbenzylguanidine sulfate (**23**), were subjected to extensive pharmacological evaluation. Both effectively lower the blood pressure in both renal and neurogenic hypertensive dogs. Compound **23** is notable for its lack of side effects.

The first two drugs found capable of blocking the sympathetic nervous system without concomitantly blocking the parasympathetic system, thus making them superior to the ganglionic blocking agents for the treatment of hypertension, were guanethidine[4] (I) and bretylium tosylate[5] (II).

Inevitably the attractive possibility of combining the *o*-bromobenzyl portion of bretylium with the guanidine moiety of guanethidine was undertaken by medicinal chemists. Boura, *et al.*,[6] was the first to report compounds of this sort. The most active mem-

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