Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.42; H, 6.54; N, 9.50.

5-(2-Dimethylaminopropionyl)-3-phenylisoxazole (XIVc, Y = Y⁵) was obtained as unstable crystals in 23.3% yield in a similar manner as above. It was reduced with $NaBH_4$ without purification.

3-(2-Piperidinopropionyl)-5-phenylisoxazole (XIVa, Y = Y³). A mixture of X (Y = Y³) (3.75 g), piperidine hydrochloride (2.43 g), paraformaldehyde (0.90 g), concentrated HCl (0.05 ml), and dioxane (6 ml) was heated to reflux. After 1 hr, paraformaldehyde (0.45 g) was added and refluxing was continued for 2 hr. The reaction mixture was treated in a similar manner to yield colorless crystals (3.60 g). Recrystallization from petroleum ether (bp 60–70°) gave colorless plates, mp 94–96°.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.65; H, 7.18; N, 9.95.

3-(2-Morpholinopropionyl)-5-phenylisoxazole (XIVb, Y = Y³).—A mixture of X (Y = Y³) (3.75 g), morpholine hydrochloride (2.47 g), paraformaldehyde (0.90 g), concentrated HCl (0.1 ml), and EtOH (3 ml) was treated as the above. The resulting product consisted of colorless plates (3.22 g), mp 112–113°, when crystallized from benzene–petroleum ether (bp 60–70°).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.20; H, 6.43; N, 9.59.

Reduction of the Amino Ketones XII and XIV with $NaBH_4$ (Table I, Method B).—The amino ketone (0.5 mole) was treated with $NaBH_4$ (0.14 mole) in MeOH (1 l.) at 60° for 30 min. After cooling, the resulting solution was acidified with AcOH and evaporated *in vacuo*. After addition of 20% aqueous NaOH, the mixture was extracted with benzene and the extract was washed with water, dried over anhydrous K_2CO_3, and evaporated. The residue was dissolved in hot 1% aqueous HCl and the solution was treated with Norit and then made alkaline with 20% aqueous NaOH to give the corresponding 3-phenyl-5- or 5-phenyl-3-(α-hydroxy-ω-aminoalkyl)isoxazole (XIII or XV). The bases were converted to their hydrochlorides by the ordinary procedure.

Hydrochloride of 5-(1-Hydroxy-2-piperidinoethyl)-3-phenylisoxazole (XIIIa, Y = Y³).—A mixture of XI (Y = Y³) (2.0 g) and piperidine (1.6 g) in ether (100 ml) was treated as for XIIb (Y = Y⁵). The resulting hydrochloride of XIIa (Y = Y³) (2.42 g) was added to a solution of $NaBH_4$ (0.5 g) and MeONa (0.5 g) in EtOH (80 ml) with stirring. The mixture, stirred at 50° for 1.5 hr, was cooled in an ice bath, acidified with 10% aqueous HCl, and evaporated *in vacuo*. The residue, after addition of 10% aqueous NaOH, was extracted with $CHCl_3$ and the extract was washed with water, and dried (K_2CO_3). Evaporation of the solvent left colorless crystals which gave its hydrochloride by the ordinary procedure.

Acknowledgment.—The authors thank Professor Emeritus E. Ochiai of Tokyo University and Dr. K. Takeda, Director of this Laboratory, for continued encouragement. They are indebted to members of the Analytical Section of this Laboratory for elemental analyses.

Phenylindenes and Phenylindans with Antireserpine Activity[1]

STANLEY J. DYKSTRA, JAMES M. BERDAHL, KENNETH N. CAMPBELL, CHARLES M. COMBS, AND DONALD G. LANKIN

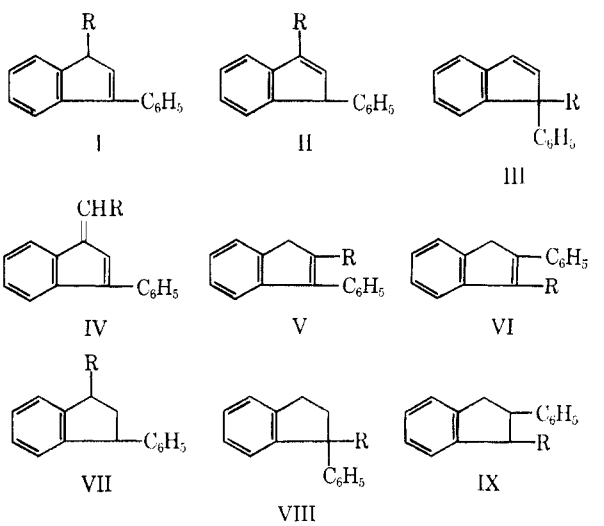
Mead Johnson Research Center, Mead Johnson and Company, Evansville, Indiana 47721

Received November 18, 1966

A series of aminoalkylphenylindenes and indans has been synthesized and pharmacologically evaluated. The majority of the phenylindene derivatives was prepared by the alkylation of phenylindene with aminoalkyl halides. A mixture of isomers is obtained when 3-phenylindene is alkylated by this procedure and the isomers of this mixture have been characterized. The final assignment of structure was based on nmr studies and these are reported in detail. An unequivocal synthesis of one isomer type, 1-aminoalkyl-1-phenylindene, is described. The indan derivatives were prepared by hydrogenation of the corresponding indenes. The indene derivatives, particularly 1-(2-dimethylaminoethyl)-1-phenylindene (**2**), were found to have potent activity in the prevention of reserpine-induced ptosis in mice, a test which has been used as a criterion for antidepressant activity. In addition, several of the indene and indan derivatives have exhibited significant antispasmodic and antiserotonin activity.

Aminoalkyl derivatives of diphenylmethane and its tricyclic analogs such as the phenothiazines have received considerable attention as useful pharmacological agents.[2a] The 1- and 3-phenylindene ring systems as well as the indan analogs also incorporate the diphenylmethane moiety. A series of aminoalkyl derivatives of phenylindene and phenylindan I–IX (R = aminoalkyl) was prepared and tested for a wide variety of activities associated with the diphenylmethane derivatives. Although compounds having the general formulas VI and IX are not diphenylmethane derivatives, we have included them for comparison purposes.

During the course of this investigation, the interesting pharmacological properties of the dibenzocycloheptenes were reported.[2b,c] Examination of molecular models



indicates that the two benzene rings in the phenylindenes and phenylindans can be spacially oriented in much the same manner as in the dibenzocycloheptenes

(1) (a) Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, Abstract, p 17N; (b) K. N. Campbell, U. S. Patent 2,884,456 (1959); K. N. Campbell, D. E. Rivard, and R. F. Feldkamp, U. S. Patent 2,992,231 (1961).

(2) (a) "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers Inc., New York, N. Y., 1960; (b) J. H. Biel, Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, pp 114–139; (c) M. Gordon, P. N. Craig, and C. L. Zirkle, *ibid.*, p 140.

and phenothiazines. We consider derivatives of the phenylindenes and phenylindans to have structural features in common with both the substituted diphenylmethanes *per se* and the derivatives of the rigid condensed tricyclic ring systems.

Our interest first focused on the aminoalkylphenylindenes I, II, and III which were prepared by the alkylation of 3-phenylindene with dialkylaminoalkyl halides in the presence of base. When sodium amide was used as the base, the products of this reaction consisted of a mixture of the three monoalkylated derivatives I, II, and III, as well as considerable quantities of two bisalkylated phenylindenes.[3]

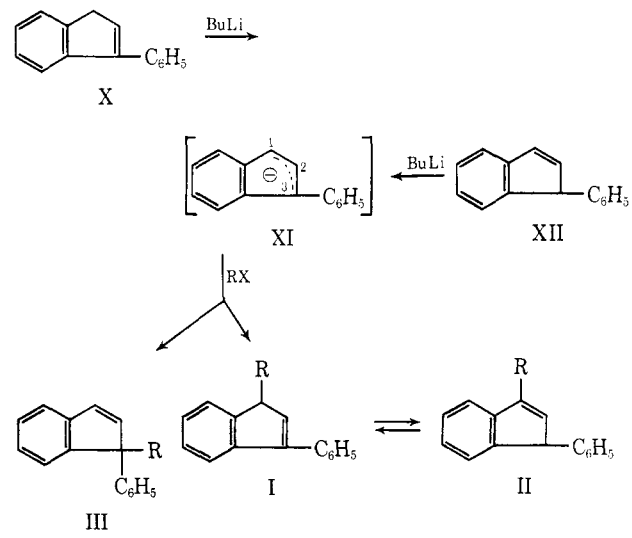
Because of the difficulty encountered in separating the components of the mixture and the concomitant low yields, the procedure was modified to eliminate the bisalkylated phenylindenes. These modifications consisted of substituting butyllithium for sodium amide and also employing the inverse addition of the phenylindenyllithium to the dialkylaminoalkyl halide. The indene derivatives are listed in Table I. The composition of the mixtures listed in the table was determined by nmr studies.

Although the modified alkylation procedure eliminated the bisalkylated products, the mixtures of monoalkylated products persisted. On this basis, a study was made of the origin of the three monoalkylated derivatives.[4]

The purity of the 3-phenylindene (X) precursor was established by oxidation of 3-phenylindene with chromic acid. The only isolated acidic product, although the yield was not quantitative, was the expected 2-benzoyl-α-toluic acid.[5] The nmr spectrum of 3-phenylindene was consistent with the assigned structure and demonstrated the existence of only one component. In addition, the isomeric 1-phenylindene[6] (XII) was prepared and was shown to have physical properties and infrared and nmr spectra which were distinctly different from 3-phenylindene. The instability of 1-phenylindene was demonstrated by its rapid and irreversible conversion to 3-phenylindene in the presence of catalytic amounts of triethylamine.[7]

Since 3-phenylindene was homogeneous and was shown to be the stable isomer, we investigated the nmr spectra of the anions derived from 1-phenylindene and 3-phenylindene by treatment with butyllithium (Scheme I). These spectra were identical. The electron charge distribution for the phenylindenyl anion was estimated from the nmr spectrum using the method employed by Schaefer and Schneider.[8] The positions of the highest electron charge densities of the anion (XI) were found on the C_1 and C_3 carbon atoms, and the electron densities on these two positions were estimated to be equal. Therefore, the anion XI would be expected to be alkylated at both the C_1 and C_3 positions, in accord with the experimental results.

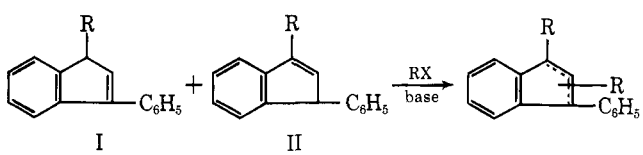
SCHEME I



Although isomer types I and III should be the only products formed by the alkylation of the phenylindenyl anion, the presence in the reaction mixture of a third isomer type (II) was demonstrated by nmr studies. Isomer type II was shown to arise from the free base of I by tautomeric equilibration. No prototropic rearrangement was observed in solutions of the hydrochloride salt of isomer type I. Apparently, the basic side chain provided the catalytic impetus for this tautomerization. A similar tautomeric equilibrium between 1-isopropyl-3-methylindene and 3-isopropyl-1-methylindene in the presence of an organic base has been reported by Weidler.[7a]

Our interest in 1-(2-dimethylaminoethyl)-1-phenylindene (IIIa) prompted us to investigate a more selective synthesis for the 1,1-disubstituted indenes. One approach employed the alkylation of the dianion of 3-phenyl-1-indanone with dimethylaminoethyl chloride. Rockett and Hauser[9] have shown that in liquid ammonia, benzyl bromide alkylates the dianion of 3-phenyl-1-indanone (XIV) at C-3. By this procedure we obtained a moderate yield of 3-(2-dimethylaminoethyl)-3-phenyl-1-indanone (XVa) when the dianion was alkylated with 2-dimethylaminoethyl chloride (Scheme II). Because the steric bulk of the two substituents on C-3 presumably prevented catalytic hydrogenation of the ketone, a lithium aluminum hydride reduction was required to prepare the amino alcohol XVIIIa. Mild acidic dehydration of the amino alcohol readily afforded 1-(2-dimethylaminoethyl)-1-phenylindene (IIIa). Although this synthesis of IIIa was unequivocal, the rather low yields in the alkylation step and the required $LiAlH_4$ reduction prompted us to

(3) These bisalkylated phenylindenes presumably arise from the alkylation of the anion derived from the monoalkylated isomers I and II. Subse-



quent to our disclosure,[1a] the isolation and characterization of these monoalkylated and bisalkylated isomers were reported by C. R. Ganellin, J. M. Loynes, and M. F. Ansell, *Chem. Ind.* (London), 1256 (1965).

(4) In contrast to this work, O. Blum-Bergmann, *Ann. Chem.*, **484**, 26 (1930); **492**, 277 (1932), reported that only one monosubstituted isomer was obtained when 3-phenylindenyllithium was carbonated with dimethyl carbonate. Methyl 3-phenylindenylcarboxylate, obtained in 54% yield, was isolated as the only product.

(5) C. F. Koelsch and R. V. White, *J. Am. Chem. Soc.*, **65**, 1639 (1943).

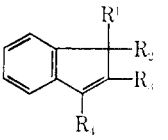
(6) K. Bott, *Tetrahedron Letters*, 4569 (1965).

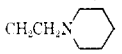
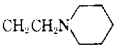
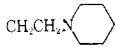
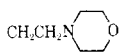
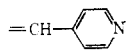
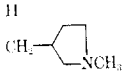
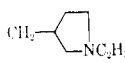
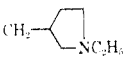
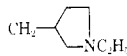
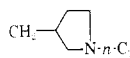
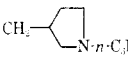
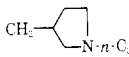
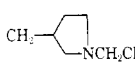
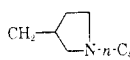
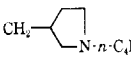
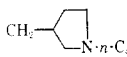
(7) (a) A. M. Weidler, *Acta Chem. Scand.*, **17**, 2724 (1963). (b) A. Bosch and R. K. Brown, *Can. J. Chem.*, **42**, 1718 (1964), reported a similar base-catalyzed complete and irreversible conversion of 1-methylindene to 3-methylindene.

(8) T. Schaefer and W. G. Schneider, *ibid.*, **41**, 966 (1963).

(9) B. W. Rockett and C. R. Hauser, *J. Org. Chem.*, **29**, 1394 (1964).

TABLE I: PHENYLINDENES



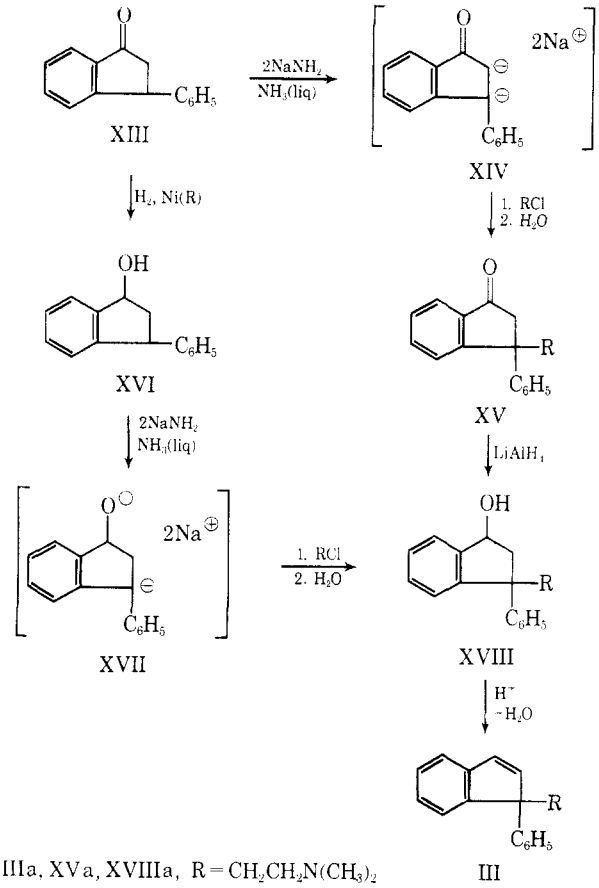
No.	R_1	R_2	R_3	R_4	Isomer, %	Method	Yield, %
1	$CH_2CH_2N(CH_3)_2$	H	H	C_6H_5	100	A, B	10, 24
2	$CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	100	A, B, C	24, 54, 94
3	$CH_2CH_2N(CH_3)_2$	4-Cl-C_6H_4	H	H	100	A	20
4	H	H	C_6H_5	$CH_2CH_2N(CH_3)_2$	100	B	30
5	$CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	100	D	71
6	$CH_2CH_2NHCH_3$	C_6H_5	H	H	100	E	60
7a	$CH_2CH_2N(C_2H_5)_2$	H	H	C_6H_5	8		
b	C_6H_5	H	H	$CH_2CH_2N(C_2H_5)_2$	11	A	30
c	$CH_2CH_2N(C_2H_5)_2$	C_6H_5	H	H	81		
8a		H	H	C_6H_5	15		
b	C_6H_5	H	H		8	A	49
c		C_6H_5	H	H	79		
9		C_6H_5	H	H	100	A	12
10	$CH_2CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	100	B	19
11a	$CH_2CH_2CH_2N(C_2H_5)_2$	H	H	C_6H_5	13		
b	C_6H_5	H	H	$CH_2CH_2CH_2N(C_2H_5)_2$	8	A	23
c	$CH_2CH_2CH_2N(C_2H_5)_2$	C_6H_5	H	H	75		
12	$=CHC(CH_3)_2CH_2N(C_2H_5)_2$		H	C_6H_5	100	G	19.5
13			H	C_6H_5	100	G	66
14	H	H		C_6H_5	100	Ref 11	17
15	H	H	$CH_2NHCH_2C_6H_5$	C_6H_5	100	F	14
16	H	H	$CH_2NHCH_2CH_2C_6H_5$	C_6H_5	100	F	22
17		C_6H_5	H	H		C	21
18a		H	H	C_6H_5	15		
b	C_6H_5	H	H		10	A	31
c		C_6H_5	H	H	75		
19a		H	H	C_6H_5	22		
b	C_6H_5	H	H		13	A	24
c		C_6H_5	H	H	65		
20		C_6H_5	H	H	100	A	13
21a		H	H	C_6H_5	23		
b	C_6H_5	H	H		13	A	16
c		C_6H_5	H	H	64		
Indene	H	H	H	H	100	*g*	
1-Phenylindene	C_6H_5	H	H	H	100	Ref 6	79
2-Phenylindene	H	H	C_6H_5	H	100		
3-Phenylindene	H	H	H	C_6H_5	100	Ref 19	

[a] The hydrochloride salts were recrystallized from 2-propanol and the mucate salts were recrystallized from 95% ethanol. [b] Measured as 10–15% solutions in solvent mentioned. Chemical shift values in ppm with respect to internal tetramethylsilane. D_2O solutions used 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt instead of TMS. [c] Doublet, 5-cps splitting. Coupling of CH_3 with

Salt[a]	Bp (mm) or mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Nmr chemical shifts ppm[b] $R_{1,2}$ = H	R_3 = H	R_4 = H	N-CH_3	Solvent
									3.48	6.45		2.65	D_2O
HCl	170–172	$C_{19}H_{21}N \cdot HCl$	76.10	76.40	7.40	7.68	4.67	4.78	3.86	6.54		2.93[c]	CF_3COOH
									3.62	6.59		2.18	CCl_4[d]
										6.54	6.87	2.65	D_2O
HCl	202–203	$C_{19}H_{21}N \cdot HCl$	76.10	76.23	7.40	7.28	4.67	4.72		6.63	7.06	2.83[c]	CF_3COOH
										6.57	6.79	2.05	CCl_4[d]
										6.51	6.90	2.75	D_2O
HCl	198–199.5	$C_{19}H_{20}ClN \cdot HCl$	68.26	68.30	6.33	6.33	21.21[e]	21.33[e]		6.50	7.00	2.90[c]	CF_3COOH
										6.57	6.85	2.08	CCl_4[d]
	63–65	$C_{19}H_{21}N$	86.65	86.84	8.04	8.21	5.32	5.08	3.77			2.32	CCl_4
HCl	189–190	$C_{19}H_{21}NO \cdot HCl$	72.25	72.09	7.02	6.95	11.23[e]	11.19[e]		6.45	6.87	3.37	CF_3COOH
HCl	176–178	$C_{18}H_{19}N \cdot HCl$	75.64	75.87	7.04	7.14	12.41[e]	12.27[e]		6.40	6.75	2.42	$CDCl_3$
									3.58	6.66			CCl_4
	156–162 (0.3)	$C_{21}H_{25}N$					4.81	4.86	4.50	6.37			CCl_4
										6.61	6.84		CCl_4
									3.63	6.62			CCl_4
	150–154 (0.04)	$C_{22}H_{25}N$	87.14	87.24	8.24	8.25	4.62	4.90	4.52	6.31			CCl_4
										6.58	6.79		CCl_4
HCl	150–152	$C_{21}H_{23}NO \cdot HCl$					4.10	4.12		6.64	7.06		CF_3COOH
										6.51	6.78	2.55	D_2O
HCl	191.5–193	$C_{20}H_{23}N \cdot HCl$	76.53	76.54	7.71	7.81	4.46	4.27		6.70	7.06	2.40[c]	CF_3COOH
										6.59	6.86	2.05	CCl_4[d]
									3.49	6.65			CCl_4
	168–176 (0.7)	$C_{22}H_{27}N$					4.59	4.62	4.55	6.31			CCl_4
										6.60	6.83		CCl_4
HCl	179–180 dec	$C_{24}H_{20}N \cdot HCl$					3.81	3.97		6.68			CF_3COOH
HCl	272–273 dec	$C_{21}H_{18}N \cdot HCl$	79.36	79.60	5.08	4.76	4.41	4.60		6.71			CF_3COOH
HCl	234–236	$C_{21}H_{23}N \cdot HCl$							3.71				CF_3COOH
HCl	185–186	$C_{23}H_{21}N \cdot HCl$	79.64	79.92	6.10	5.98	10.22[e]	10.20[e]	3.78				CF_3COOH
HCl	191–192	$C_{24}H_{23}N \cdot HCl$	79.65	79.74	6.68	6.81	9.80[e]	9.84[e]	3.65				CF_3COOH
Mucate	159–160.5	$C_{21}H_{23}N \cdot 0.5C_6H_{10}O_8$	73.07	72.82	7.15	7.05	3.55	3.53		6.53	6.79	2.05 2.12[f]	CCl_4[d]
									3.48	6.61			CCl_4
	164 (0.15)	$C_{22}H_{23}N$					4.62	4.61	4.52	6.28			CCl_4
										6.59	6.82		CCl_4
									3.48	6.60			CCl_4
	160–163 (0.1)	$C_{23}H_{27}N$	87.02	86.86	8.57	8.34	4.41	4.84	4.51	6.28			CCl_4
										6.56	6.80		CCl_4
	158–160 (0.08)	$C_{23}H_{25}N$	87.57	87.75	7.99	7.67	4.44	4.77		6.57	6.83		CCl_4
									3.46	6.58			CCl_4
	172–178 (0.3)	$C_{24}H_{29}N$	86.96	86.92	8.82	8.39	4.23	4.59	4.48	6.26			CCl_4
										6.56	6.80		CCl_4
		C_9H_8							3.29	6.42	6.78		CCl_4
	37–38	$C_{15}H_{12}$	93.71	93.60	6.29	6.10			4.48	6.49	6.81		CCl_4
	169–171	$C_{15}H_{12}$							3.80		7.22		CCl_4
	118–125 (0.4)	$C_{16}H_{12}$							3.40	6.46			CCl_4

[a] +N–H proton. [d] Nmr observation of the free base of the salt. [e] Analysis for chloride. [f] Two 1,1-substituted isomers of this compound observed in a 1:2 ratio mixture. [g] Eastman Chemical Co.

SCHEME II



examine alternative procedures for the preparation of 1-(2-dimethylaminoethyl)-1-phenylindene.

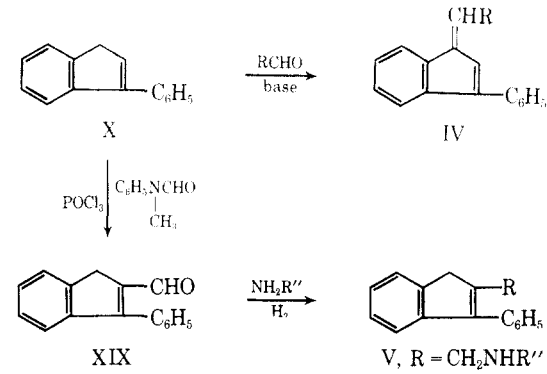
A more convenient synthesis of IIIa utilized an extension of the dianion concept. Whereas XVa could not be hydrogenated, 3-phenyl-1-indanol (XVI) was readily obtained by catalytic hydrogenation of 3-phenyl-1-indanone (XIII). The alcohol XVI should be capable of dianion formation since, like the corresponding ketone, it also possesses two potentially ionizable hydrogen atoms, the hydroxyl hydrogen and the less acidic benzhydryl hydrogen. That dianion formation did take place when XVI was treated with 2 equiv of sodium amide in liquid ammonia was demonstrated by the appearance of a dark red solution characteristic of the diphenylmethyl anion. After addition of 1 equiv of 2-dimethylaminoethyl chloride, the red color disappeared, and on hydrolysis 3-(2-dimethylaminoethyl)-3-phenyl-1-indanol (XVIIIa) was obtained in excellent yield. This was readily dehydrated to IIIa.

Interestingly, Borovicka and Protiva[10] obtained only the O-alkylated product when they treated 3-phenyl-1-indanol with 2 equiv of sodium amide and 2-dimethylaminoethyl chloride in benzene. Their choice of this solvent apparently precluded the formation of the dianion. Consequently, alkylation at C-3 could not take place.

Compounds of structure type IV also appear in Table I. These aminoalkylidene-3-phenylindenes were obtained by the condensation of an aminoaldehyde with 3-phenylindene using basic conditions (Scheme III).

(10) M. Borovicka and M. Protiva, *Cesk. Farm.*, **6**, 129 (1957); *Chem. Abstr.*, **52**, 1125 (1958).

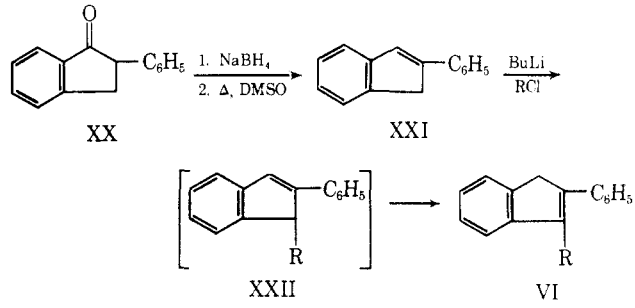
SCHEME III



Compounds having the general structure V were synthesized by two methods. The tertiary amino derivatives (V, R = $CH_2NR''_2$) were prepared according to the procedure described by Hoffmann[11] in which 1-indanone was subjected to a Mannich reaction to give 2-dialkylaminomethyl-1-indanone. Treatment of this ketone with phenylmagnesium bromide and dehydration gave the desired indenes. For the preparation of the secondary amines (V, R = CH_2NHR'), which were difficult to obtain by the Mannich reaction, we first prepared 3-phenyl-2-indenylcarboxaldehyde (XIX) by the formylation of 3-phenylindene with N-methylformanilide and phosphorus oxychloride. The carboxaldehyde was reductively aminated with the desired primary amines (Scheme III).

Compounds having the general structure VI were obtained by the alkylation of 2-phenylindene (XXI) (Scheme IV). This intermediate was prepared by

SCHEME IV



dehydration of 2-phenyl-1-indanol which in turn was obtained from 2-phenyl-1-indanone[12] (XX) by a sodium borohydride reduction. Alkylation of 2-phenylindene with 2-dimethylaminoethyl chloride gave 3-(2-dimethylaminoethyl)-2-phenylindene [VI, R = $CH_2CH_2N(CH_3)_2$]. The nmr spectrum was consistent with the assigned structure (a singlet for the two alicyclic protons at 3.77 ppm, CCl_4 solvent). Under the alkylation conditions used, the 1,2-disubstituted indene (XXII) would first be formed. However, based on our previous tautomerization studies, it was not surprising to find that this intermediate had rearranged into the more stable 2,3-disubstituted indene VI.[13]

(11) K. Hoffmann and H. Schellenberg, *Helv. Chim. Acta*, **27**, 1782 (1944).

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

(13) Our assignment of structure VI for the product of the alkylation reaction conflicts with the structure assigned in the patent literature, *e.g.*, Smith Kline and French Laboratories, Belgium Patent 621,933 (1963). In this patent, structure XXII was given for the alkylation product.

The aminoalkylphenylindans (VII–IX) listed in Table II were routinely prepared by catalytic hydrogenation of the indene derivatives. 1-(2-Dimethylaminoethyl)-1-phenylindan was also prepared by direct alkylation of 1-phenylindan.

Experimental Section

Determination of Structures by Nmr Spectroscopy.—The chemical shifts of phenylindenes and their derivatives are given in Table I. The structure proofs for monoalkylphenylindenes from their nmr spectra are unambiguous. The assignments of structure are in agreement with those published in the recent note of Ganellin, *et al.*[3] If the alkyl and phenyl groups are both located at the 1 position of the indene ring (structure III), the olefinic protons in the 2,3 positions show a typical AB pair of doublets with a coupling constant of about 5.7 cps. This value is in good agreement with the coupling constants found in indene[14] and in methylindenes.[15,16] The lines for the AB patterns are observed at ~6.5–6.7 and ~6.8–7.0 ppm, corresponding to the 2 and 3 positions, respectively. The absorption peaks for the proton in the 3 position of these compounds were neither further split nor broadened by coupling with the proton in the 7 position. The spectra of indene and methylindenes[15,16] show this proton to have a long-range coupling, $J_{3,7}$, of about 0.7 cps.

When the indene substitutions are 1-alkyl-3-phenyl (structure I), two distinct resonance signals are observed. The olefinic proton at the 2 position gives a narrow line doublet at ~6.6 ppm with a splitting of about 2 cps and the proton at the 1 position appears as a very broad multiplet at ~3.6 ppm.

When the substituents are 3-alkyl-1-phenyl (structure II), the 2 position olefinic proton absorbs at ~6.3 ppm as a poorly resolved doublet while the benzhydryl proton in the 1 position is observed as a slightly broadened band at ~4.5 ppm. The coupling between the protons in the 1,2 positions in these compounds was not resolved, apparently due to broadening by allylic couplings.[17]

Certain regularities are apparent from the spectra of the phenylindenes. Whereas alkyl substitution on the alicyclic ring of indene tends to shift the alicyclic ring proton absorptions toward higher magnetic field[17] (smaller parts per million values), phenyl substitution deshields these protons and causes a low-field shift of their resonance absorptions (giving larger parts per million values). Olefinic protons in the 2 position of phenylindenes show lines in the region 6.3–6.6 ppm; olefinic protons in the 3 position absorb in the region 6.8–7.2 ppm; and protons in the 1 position show lines in the region 3.4–3.8 ppm, unless the indene molecule has the phenyl group substituted at this position. Benzyhydryl protons of this type absorb at ~4.5 ppm. This categorized information is helpful in determining the composition of isomer mixtures and can also be used in the identification of disubstituted phenylindenes.

The chemical shifts of monoalkyl phenylindans are given in Table II. The 1-alkyl-1-phenylindans (structure VIII) are characterized by the absence of any alicyclic ring proton absorption in the region 3.5–4.5 ppm. The 1-alkyl-3-phenylindan (structure VII) spectra show a multiplet at ~4.2–4.4 ppm for the benzhydryl proton in the 3 position of the indan molecule.

The spectrum of the phenylindenyl anion in an ether–hexane solution, prepared from either 1-phenylindene or 3-phenylindene, consisted of a one-proton doublet at 6.01 ppm and a ten-proton complex multiplet from 6.6 to 8 ppm. The doublet at 6.01 ppm, assigned to the hydrogen at the C_1 position, had a splitting of 3.7 cps from coupling with the C_2 position hydrogen and also a smaller doublet splitting of 0.75 cps due to long-range coupling with the hydrogen in the 4 position. The position of the hydrogen doublet from the C_2 position (6.88 ppm) was determined by the double-resonance technique using a Varian V-6058 spin decoupler.

The electron density distribution was determined[8] from the above values to be 1.17 at the C_1 position and 1.10 at the C_2 position. From the close correspondence of these values with those found for the unsubstituted indenyl anion, 1.17 at the C_1 and C_3 position and 1.09 at the C_2 position,[8] it was estimated that the electron density at the C_3 position in the phenylindenyl anion was very nearly that found at the C_1 position.

The pmr spectra were obtained with a Varian A-60 spectrometer. Accuracies of the chemical shifts measurements are within ±0.02 ppm, with the spectrometer calibration checked according to the method of Tiers and Hotchkiss.[18]

2-Benzoyl-α-toluic Acid.—3-Phenylindene (X)[19] (20 g, 0.1 mole), was suspended in 110 ml of 65% H_2SO_4 and a solution of 30 g of CrO_3 in 64 ml of water was added over 15 min. During the addition, the mixture was kept at 30–50° by cooling. After the addition, the mixture was allowed to stand at room temperature for 2 hr, then, after dilution with 500 ml of water, it was extracted with four 100-ml portions of ether. The ethereal extracts were washed (saturated $NaHCO_3$) and after acidification of the bicarbonate layer 16.9 g (70% yield) of crude product was isolated. Recrystallization from ethyl acetate gave pure acid, mp 132–134° (lit.[5] mp 130–131°).

3-(3-Methoxyphenyl)propiophenone.—A solution of 23.8 g (0.1 mole) of 3-methoxychalcone[20] in 115 ml of ethyl acetate was reduced in the presence of 0.2 g of PtO_2. One mole equivalent of hydrogen was absorbed after 2 hr and the catalyst and solvent were removed. The solid residue was recrystallized from absolute ethanol, to give 19.2 g (80%) of pure dihydro compound, mp 67–68°.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.80; H, 6.97.

6-Methoxy-3-phenylindene.—Using the same procedure as reported for 5,6-dimethoxy-3-phenylindene,[21] 72 g (0.3 mole) of 3-(3-methoxyphenyl)propiophenone was cyclized in 550 g of polyphosphoric acid at 90° for 0.5 hr. After decomposition of the polyphosphoric acid with ice, the precipitate was removed by filtration and recrystallized from 700 ml of methanol. A first crop of 51 g (76.5%), mp 64–65°, was analytically pure.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.22; H, 6.46.

2-Phenylindene (XXI).—To a solution of 2-phenylindanone (XX)[12] (30 g, 0.14 mole) in 300 ml of 2-propanol was added in small portions 5.3 g (0.14 mole) of $NaBH_4$, followed by cautious addition of 150 ml of anhydrous methanol. After stirring 2.5 hr at room temperature, the mixture was concentrated to 150 ml and then brought to pH 3 with dilute HCl. Water was added and the mixture was extracted with three 100-ml portions of ether. After drying, the combined ether extracts were evaporated and the residue was distilled yielding 25.5 g (83%) of 2-phenyl-1-indanol, bp 120–130° (0.1 mm). The indanol was dehydrated using a procedure described by Traynellis, *et al.*,[22] to give after crystallization from methanol 17.5 g (75%) of pure XXI, mp 167–168° (lit.[23] mp 167.5°).

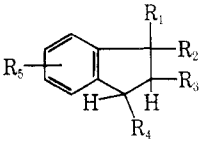
3-(2-Dimethylaminoethyl)-3-phenyl-1-indanone Hydrochloride (XVa).—To a stirred suspension of $NaNH_2$ [from 4.6 g (0.2 g-atom) of Na in 500 ml of liquid NH_3] was added dropwise a solution of 20.8 g (0.1 mole) of 3-phenyl-1-indanone (XIII).[24] The liquid NH_3 was replaced with 200 ml of benzene and a catalytic amount of KI. To the stirred suspension was added a solution of 10.8 g (0.1 mole) of 2-dimethylaminoethyl chloride in a mixture of xylene (25 ml) and benzene (75 ml). The mixture was heated at 55–60° for 1 hr and stirred at room temperature overnight. It was washed with water, then extracted with 4.5 *N* HCl (100 ml). The acidic extract was made basic and the precipitated oil was extracted with ether. After drying the ethereal solution, 6 *N* 2-propanolic HCl was added. The precipitated hydrochloride salt was recrystallized from ethanol to give 14.6 g (46%) of the product, mp 242–244° dec. An analytically pure sample was prepared by recrystallization from acetone–ethanol, mp 245.5–246.5°. The nmr and infrared spectra were consistent with the assigned structure.

Anal. Calcd for $C_{19}H_{23}NO \cdot HCl$: C, 71.79; H, 7.69; Cl, 11.16. Found: C, 71.51; H, 7.60; Cl, 11.14.

3-(2-Dimethylaminoethyl)-3-phenylindan-1-ol Hydrochloride (XVIIIa). A. From 3-(2-Dimethylaminoethyl)-3-phenylindan-

(14) D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 2346 (1962).
(15) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 590 (1963).
(16) A. R. Hawdon and I. J. Lawrenson, *Chem. Ind.* (London), 1690 (1963).
(17) H. Dressler and R. J. Kurland, *J. Org. Chem.*, **29**, 175 (1964).
(18) G. V. D. Tiers and D. R. Hotchkiss, *J. Phys. Chem.*, **66**, 560 (1962).
(19) J. V. Braun, *Ber.*, **50**, 1659 (1917).
(20) P. Pfeiffer, *Ann. Chem.*, **412**, 309 (1917).
(21) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).
(22) V. J. Traynellis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).
(23) F. Mayer, A. Sieglitz, and W. Ludwig, *Ber.*, **54**, 1397 (1921).
(24) P. Pfeiffer and H. deWaal, *Ann. Chem.*, **520**, 185 (1935).

TABLE II
PHENYLINDANS



No.	R_1	R_2	R_3	R_4	R_5	Isomer, %	Method	Yield, %	Bp (mm) or mp,[a] °C	Formula
22	$CH_2CH_2N(CH_3)_2$	H	H	C_6H_5	H	100	H	27	207–208.5	$C_{19}H_{23}N \cdot HCl$
23	$CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	H	100	H, I	85, 95	226–227	$C_{19}H_{23}N \cdot HCl$
24	$CH_2CH_2N(CH_3)_2$	H	C_6H_5	H	H	100	H	51	235–236	$C_{19}H_{23}N \cdot HCl$
25	$CH_2CH_2N(CH_3)_2$	H	H	C_6H_5	5-CH_3O	100	H	53	245–246.5	$C_{20}H_{25}NO \cdot HCl$
26	$CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	5-CH_3O	100	H	20	236.5–238	$C_{20}H_{25}NO \cdot HCl$
27	$CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	5,6(CH_3O)$_2$	100	H	66	235–237	$C_{21}H_{27}NO_2 \cdot HCl$
28	$CH_2CH_2N(CH_3)_2$	H	H	C_6H_5	5-OH	100	*f*	28	226–227	$C_{19}H_{23}NO \cdot HCl$
29a	$CH_2CH_2N(C_2H_5)_2$	H	H	C_6H_5	H	25	H	50	142–143 (0.65)	$C_{21}H_{27}N$
b	$CH_2CH_2N(C_2H_5)_2$	C_6H_5	H	H	H	75				
30a	CH_2CH_2N⟨pyrrolidine⟩	H	H	C_6H_5	H	10	H	63	172–180 (0.1)	$C_{21}H_{25}N$
b	CH_2CH_2N⟨pyrrolidine⟩	C_6H_5	H	H	H	90				
31a	CH_2CH_2N⟨piperidine⟩	H	H	C_6H_5	H	40	H	88	173–174 (0.1)	$C_{22}H_{27}N$
b	CH_2CH_2N⟨piperidine⟩	C_6H_5	H	H	H	60				
32	$CH_2CH_2CH_2N(CH_3)_2$	C_6H_5	H	H	H	100	H	44	127–130	$C_{20}H_{25}N \cdot HCl$
33	$CH_2CH_2CH_2N(C_2H_5)_2$	C_6H_5	H	H	H	100	H	21	115–117	$C_{22}H_{29}N \cdot HCl$
34	$CH_2C(CH_3)_2CH_2NHCH_3$	H	H	C_6H_5	H	100	H	29	207–208	$C_{21}H_{27}N \cdot HCl$
35	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	H	H	C_6H_5	H	100	H	68	194–195	$C_{22}H_{29}N \cdot HCl$
36	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	H	H	C_6H_5	H	100	H	19	190–191	$C_{24}H_{33}N \cdot HCl$
37	$CH_2C(CH_3)_2CH_2N$⟨piperidine⟩	H	H	C_6H_5	H	100	H	62	198–199	$C_{25}H_{33}N \cdot HCl$
38	CH_2⟨pyrrolidine⟩-NCH_3	H	H	C_6H_5	H	100	H	66	197–198	$C_{21}H_{25}N \cdot HCl$
39	CH_2⟨pyrrolidine⟩-NCH_3	C_6H_5	H	H	H	100	H	32	134–136	$C_{21}H_{25}N \cdot HCl$
40a	CH_2⟨pyrrolidine⟩-NC_2H_5	H	H	C_6H_5	H	60	H	70	160–165 (0.13)	$C_{22}H_{27}N$
b	CH_2⟨pyrrolidine⟩-NC_2H_5	C_6H_5	H	H	H	40				
41	CH_2⟨pyrrolidine⟩-N-*n*-C_3H_7	H	H	C_6H_5	H	100	H	35	156–158 (0.05)	$C_{23}H_{29}N$
42	CH_2⟨pyrrolidine⟩-N-*i*-C_3H_7	H	H	C_6H_5	H	100	H	75	158–162 (0.05)	$C_{23}H_{29}N$
43a	CH_2⟨pyrrolidine⟩-N-*n*-C_4H_9	H	H	C_6H_5	H	70	H	71	162–164 (0.05)	$C_{24}H_{31}N$
b	CH_2⟨pyrrolidine⟩-N-*n*-C_4H_9	C_6H_5	H	H	H	30				
44	CH_2⟨pyrrolidine⟩-$^+N(CH_3)_2$	H	H	C_6H_5	H	100	*j*	30	200–204[k]	$C_{22}H_{28}IN$

[a] Melting points are of the hydrochloride salts. [b] Measured as 10–15% solutions in solvents noted. Chemical shift values in ppm with respect to internal Me_4Si. [c] Obscured by broad aliphatic proton absorption band. [d] Doublet, 5 cps splitting. Coupling of CH_3 with ^+NH proton. [e] R_3 = H in this compound. [f] Prepared by HBr demethylation of **25**. [g] Pair of doublets, splitting of 7–8,

1-one (XVa).—To a stirred suspension of $LiAlH_4$ (9.5 g, 0.25 mole) in tetrahydrofuran (THF) (100 ml) was added a solution of 6.8 g (0.025 mole) of XVa in THF (100 ml.) The mixture was stirred at reflux for 2 hr, then allowed to stand at room temperature overnight. After decomposition of the excess $LiAlH_4$ with aqueous THF, the mixture was heated at 55–60° for 1 hr and filtered. The solvent was distilled from the filtrate and the residue was dissolved in anhydrous ethanol and acidified with 6 *N* HCl in 2-propanol. Isopropyl ether was added to cloudiness and the product was allowed to crystallize to give 6.2 g (78%) of the indanol, mp 193–194° dec. The nmr spectrum was consistent with the assigned structure as an 80:20 mixture of the two possible stereoisomers.

Anal. Calcd for $C_{19}H_{23}NO \cdot HCl$: C, 71.79; H, 7.61; Cl, 11.16. Found: C, 71.51; H, 7.60; Cl, 11.14.

B. From 3-Phenylindan-1-ol (XVI).—To a stirred suspension of $NaNH_2$ [from 4.6 g (0.2 g-atom) of Na in 1 l. of NH_3] was added dropwise a solution of 21 g (0.1 mole) of 3-phenyl-1-

C, %		H, %		N, %		Cl, %		Nmr chemical shifts, ppm[b]			
Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	R_2 = H	R_4 = H	N–CH_3	Solvent
75.60	75.75	8.01	8.16	4.64	4.51			*c*	4.38	3.06[d]	CF_3COOH
75.60	75.31	8.01	8.03			11.75	11.61	*c*	*c*	2.96[d]	CF_3COOH
75.60	75.80	8.01	8.19	4.64	4.58	11.75	11.86	3.85[e]	*c*	2.66[d]	CF_3COCH
72.38	72.15	7.90	7.99	4.22	3.94	10.68	10.96	*c*	4.37	3.09[d]	CF_3COOH
72.38	72.08	7.90	7.97	4.22	4.06	10.68	10.65	*c*	*c*	3.00[d]	CF_3COOH
69.69	69.52	7.79	7.83	3.87	3.92			*c*	*c*	3.08[d]	CF_3COOH
71.79	71.71	7.61	7.61	4.41	4.32	11.16	11.16	*c*	4.22[g]	3.02[d]	CF_3COOH
85.95	85.51	9.28	8.84					3.30	4.20[g]		CCl_4
								c	*c*		CCl_4
86.55	86.21	8.65	7.95	4.81	4.89			*c*	4.16		CCl_4
								c	*c*		CCl_4
86.50	86.73	8.91	8.58	4.59	4.98			3.28	4.23[g]		CCl_4
								c	*c*		CCl_4
				4.44	4.64	11.23	11.23	*c*	*c*	2.88[d]	CF_3COOH
				4.07	4.00			*c*	*c*		$CHCl_3$
76.45	76.06	8.85	8.92	4.25	4.33			*c*	4.17[g]	2.68[h]	$CHCl_3$
				4.07	4.15	10.31	10.38	*c*	4.22[g]	2.92[d]	$CHCl_3$
				3.77	3.88	9.53	9.23	*c*	4.30[g]		CF_3COOH
78.19	77.87	8.92	9.13			9.23	8.95	*c*	4.16[g]		$CHCl_3$
76.92	76.88	7.99	7.96			10.81	10.99	*c*	4.22[g]	2.86	$CHCl_3$
								3.10	4.16[g]	2.24	CCl_4[i]
76.92	76.90	7.99	8.28	4.27	4.29			*c*	*c*	2.12	CCl_4[i]
86.50	86.20	8.91	8.89	4.59	4.74			*c*	4.20[g]		CCl_4
								c	*c*		CCl_4
86.47	86.82	9.15	9.05					*c*	4.17[g]		CCl_4
86.47	86.67	9.15	9.04					*c*	4.08[g]		CCl_4
86.43	86.58	9.37	8.99	4.20	3.98			*c*	4.21[g]		CCl_4
								c	*c*		CCl_4
60.97	61.04	6.51	6.72	3.23	3.11			*c*	4.37[g]	3.25 3.35	CF_3COOH

10–11 cps. [h] Triplet, 8-cps splitting. Coupling of CH_3 with $^+NH_2$ protons. Nmr observations of the free base of the hydrochloride salt. [i] Prepared by quaternization of **38**. [k] Methiodide salt.

indanol (XVI)[25] in ether (200 ml). To the resulting red suspension was added a solution of 10.7 g (0.1 mole) of 2-dimethylaminoethyl chloride in a mixture of xylene (11 ml) and ether (100 ml). Stirring was continued until the liquid ammonia had evaporated. The residual ethereal solution was washed with water and the basic fraction was extracted with 4.5 *N* HCl. The acidic extract was made basic and the precipitated oil was extracted with ether. After drying, the ethereal solution was concentrated to an oil which was dissolved in ethanol, acidified with 6 *N* HCl in 2-propanol, and allowed to crystallize. A white crystalline solid was obtained; yield 20.0 g (71%), mp 204–205° dec. The nmr spectrum was consistent with the assigned structure as an 85:15 mixture of the two stereoisomers.

Anal. Calcd for $C_{19}H_{23}NO \cdot HCl$: C, 71.79; H, 7.61; Cl, 11.16. Found: C, 71.86; H, 7.81; Cl, 11.00.

(25) H. Richter and H. Jansen, German Patent 912,093 (1958); *Chem. Abstr.*, **52**, P11943*a* (1958).

A mixture melting point of 197–199° dec was obtained when a sample was combined with material from method A.

3-Phenylindene-2-carboxaldehyde (XIX).—A mixture of $POCl_3$ (18.2 ml, 0.2 mole) and N-methylformanilide (27.2 g, 0.2 mole) was allowed to stand for 0.5 hr. Keeping the temperature at <30° with an ice bath, 38.4 g (0.2 mole) of 3-phenylindene was added dropwise. After stirring for an additional 2 hr, the mixture was allowed to stand overnight. The resulting tar was decomposed with ice and the organic fraction was extracted with an ether–benzene mixture. After washing with dilute HCl and water, the solution was dried ($MgSO_4$) and filtered and the solvent was removed. The residual yellow solid was recrystallized from Skelly B; yield 27 g (64%), mp 97–98°.

Anal. Calcd for $C_{10}H_{12}O$: C, 87.24; H, 5.49. Found: C, 87.18; H, 5.63.

The infrared spectrum was consistent for an α,β-unsaturated carbonyl and the nmr spectrum showed the presence of the two uncoupled methylene protons.

(2-Dimethylaminoethyl)phenylindenes from Alkylation of 3-Phenylindene. Method A.—A suspension of 19.5 g (0.5 mole) of $NaNH_2$ and 96 g (0.5 mole) of 3-phenylindene in dry benzene was refluxed for 1 hr. To this mixture was added over 1 hr at reflux a solution of dimethylaminoethyl chloride [from 71.5 g (0.5 mole) of dimethylaminoethyl chloride hydrochloride] in dry benzene (100 ml). Heating was continued for an additional 2 hr. After cooling, the reaction mixture was poured into an excess of dilute HCl and the layers were separated. The acid layer was made basic and the resulting oil which separated was extracted with ether. Concentration of the ethereal extract and fractionation of the residue gave three principal fractions. Fraction 1, bp 150–157° (0.3 mm), $n^{20}D$ 1.5865 (21.8 g), contained primarily 1-(2-dimethylaminoethyl)-1-phenylindene (IIIa) which was isolated and characterized as its hydrochloride salt (mp 202–203°). Fraction 2, bp 166–168° (0.3 mm), $n^{20}D$ 1.6905 (12.7 g), was characterized by its nmr spectrum as a 3:1 mixture of 1-(2-dimethylaminoethyl)-3-phenylindene (Ia) and 3-(2-dimethylaminoethyl)-1-phenylindene (IIa). Ia was isolated from this fraction as the hydrochloride (mp 170–172°). Fraction 3, bp 168–174° (0.2 mm), $n^{20}D$ 1.7535 (26.3 g), contained a mixture of bisalkylated products.

Method B.—To 3-phenylindene (X, 76.8 g, 0.4 mole) in anhydrous ether (150 ml) under N_2 was added 0.4 mole of butyllithium in hexane. A temperature of 20–30° was maintained by external cooling during the addition. After refluxing for 0.5 hr the solution was diluted with ether (200 ml) and added to an ethereal solution (100 ml) of 2-dimethylaminoethyl chloride [from 71.5 g (0.5 mole) of the hydrochloride]. The mixture was refluxed for 2 hr, then cooled and extracted with 6 *N* HCl (200 ml). The acid extract was made basic and the precipitated oil was isolated as in the preceding experiment. Two main fractions were obtained corresponding to fractions 1 and 2 of method A (fraction 1, 56.7 g, and fraction 2, 25.6 g).

1-(2-Dimethylaminoethyl)-1-phenylindene Hydrochloride (IIIa). Method C.—Sodium amide was prepared from 86.4 g (3.75 g-atoms) of Na with liquid NH_3 (13 l.). To the stirred suspension was added 315 g (1.5 moles) of 3-phenyl-1-indanol (XVI) in anhydrous ether (3 l.). To the resulting red suspension was added a solution of 241 g (2.25 moles) of 2-dimethylaminoethyl chloride in a mixture of xylene (250 ml) and ether (1.5 l.). The brown suspension was stirred until the ammonia had evaporated. The ethereal suspension was washed with 1 l. of water and then extracted with 4.5 *N* HCl (1 l.). The acid extract was heated at 90° for 2.5 hr and made basic and the oil which separated was extracted with ether. After drying and concentrating the ethereal solution, the oil was dissolved in 2-propanol and acidified with 2-propanolic HCl. The precipitate (410 g, 91%), mp 200–202°, was recrystallized from 2-propanol to give analytically pure IIIa·HCl, mp 202–203°. A mixture melting point determination with the hydrochloride from fraction 1 of method A gave no depression.

1-(2-Dimethylaminoethyl)-1-phenylindene N-Oxide Hydrochloride. Method D.—A mixture of 9.8 g (0.037 mole) of IIIa and 12 ml of 30% H_2O_2 in 40 ml of methanol was allowed to stand 1 week at room temperature. After dilution with 100 ml of water and concentrating *in vacuo* to near dryness, the residue was extracted with 50 ml of ether to remove any starting free base, and the ether-insoluble material was dissolved in acetone. After the addition of dry HCl, ether was added to the cloud point. The precipitated crystals were filtered to give 8.4 g (71%) of the hydrochloride salt, mp 180–181°. Recrystallization from 2-propanol gave pure material, mp 189–190°. The infrared and nmr spectra were consistent with the assigned structure.

TABLE III
PREVENTION OF RESERPINE-INDUCED PTOSIS

Compd	ED_{50}, mg/kg
1	17.4 ± 5.0
2	1.0 ± 0.2
3	9.7 ± 2.4
4	Inactive
5	3.8 ± 1.3
6	1.2 ± 0.3
7a–c	25
8a–c	Inactive
9	Inactive
10	17.1 ± 4.3
12	Inactive
14	6.9 ± 2.1
15	Inactive
16	Inactive
17[a]	10.4 ± 4.3
20	10.2 ± 2.6
22	25.0 ± 7.0
23	10.4 ± 4.3
24	>25
26	>25
27	>25
33	>25
38[b]	24.9 ± 7.2
39[b]	11.2 ± 2.7

[a] As a 1:2 mixture of two racemates. [b] As the mucate salt.

1-(2-Methylaminoethyl)-1-phenylindene Hydrochloride. Method E.—To a stirred solution of 16 g (0.15 mole) of ethyl chloroformate at 40° in dry benzene (15 ml) was added as rapidly as possible (to promote a rapid elimination of CH_3Cl) 13.2 g (0.05 mole) of 1-(2-dimethylaminoethyl)-1-phenylindene (IIIa). After the initial reaction, the mixture was allowed to reflux for 2 hr, cooled, and washed with water (25 ml) and dilute HCl (25 ml). The neutral benzene solution was concentrated and the residue of N-carbethoxy-1-(2-methylaminoethyl)-1-phenylindene (11.5 g) was hydrolyzed by heating at reflux for 6 hr in a solution of 95% ethanol (100 ml) and KOH (45 g). The ethanolic solution was diluted with water (100 ml) and the ethanol was partially removed under vacuum. The residue was extracted with ether and dried ($MgSO_4$). After removal of the drying agent, dry HCl was added. The precipitated hydrochloride salt was recrystallized from acetone. The yield of analytically pure material was 6.1 g (60%), mp 176–178°.

Reductive Amination of 3-Phenylindene-2-carboxaldehyde (XIX). Method F.—In 200 ml of 95% ethanol, 11 g (0.05 mole) of 3-phenylindene-2-carboxaldehyde and 0.5 mole of primary amine were mixed and hydrogenated on a Parr hydrogenator in the presence of Raney Ni catalyst. After the theoretical uptake of hydrogen (0.05 mole), the reduction was stopped, the catalyst was removed, and the solvent was evaporated. The residue was dissolved in ether and gaseous HCl was added. The oil which precipitated was crystallized from 1-propanol several times until analytically pure hydrochlorides of 2-alkylaminomethyl-3-phenylindenes were obtained.

1-(3-Diethylamino-2,2-dimethylpropylidene)-3-phenylindene Hydrochloride [IV (12)]. Method G.—A solution of 15.7 g (0.1 mole) of 3-(diethylamino)-2,2-dimethylpropionaldehyde, 19.2 g (0.1 mole) of 3-phenylindene, and 0.1 g of Na in 100 ml of absolute ethanol was heated at reflux for 3 hr. On cooling, the solution was poured into water and the oils were extracted with ether. After drying the ether extract ($MgSO_4$) and filtering, anhydrous HCl was added. The hydrochloride salt which precipitated was recrystallized from ethyl acetate; yield 5.5 g (15%), mp 179–180° dec.

Dialkylaminoalkyl Phenylindans (VII–IX). By Hydrogenation of the Corresponding Indenes. Method H.—In a Parr hydrogenator 4.0 g of 10% Pd–C in 30 ml of 95% ethanol was subjected to a hydrogen atmosphere for several minutes. A solution of 0.35 mole of the dialkylaminoalkylphenylindene in 160 ml of 95% ethanol was added and the mixture was subjected to hydrogen at 4.2 kg/cm² until the theoretical amount of H_2

TABLE IV
SUMMARY OF BIOLOGICAL DATA

	Compd 2	Imipramine	Amitriptyline
Reserpine-induced ptosis			
Prevention, mg/kg oral	1.03	5.00	5.50
Reversal	Inactive	Inactive	Inactive
Antisinistro torsion	Inactive	Inactive	Weakly active
Antiparkinson activity			
ED_{50}, mg/kg oral	Inactive	104	29.5
Antispasmodic activity *vs.*			
acetylcholine as % atropine	0.1	0.32	0.22
ALD_{50}, mg/kg (mouse)	41	107	80
Inhib of kynuramine			
oxidation *in vitro* AIC_{50}, *M*	6.2×10^{-5}	...	None at 5×10^{-5}
Tryptamine potentiation *in vivo*	None at 25 mg/kg ip	16% at 100 mg/kg *po*	None at 100 mg/kg *po*
5-Hydroxytryptophan	None at 10 mg/kg	None at 10 mg/kg	...
potentiation	6 doses on 3 days	6 doses on 3 days	

TABLE V
ANTISPASMODIC ACTIVITY

	Isolated rabbit ileum		
Compd	Neurotropic action antagonism of acetylcholine EC_{75}, μg/ml	Musculotropic action antagonism of $BaCl_2$ EC_{75}, μg/ml	Isolated rat uterus antagonism of serotonin IC_{50}, μg/ml
1·HCl	...	...	0.067
2·HCl	>10	>10	0.21
4	10	4.0	...
5	...	...	0.00002
6	...	...	1.00
7a-c	4.5	>10	...
8a-c	1.0	3.9	...
9·HCl	>10	>10	...
10·HCl	1.6	1.0	...
11a-c	1.0	1.5	...
12·HCl	...	>10	5.0
14·HCl	4.5	>10	...
16·HCl	>10	>10	1.8
18a-c	1.0	1.0	0.58
19a-c	0.7	2.2	0.18
20	5.1	2.0	0.12
21a-c	2.8	>10	0.28
23·HCl	4.5	4.0	0.36
24·HCl	4.0	...	1.4
25·HCl	>10	1.7	1.2
26·HCl	>10	1.5	...
27·HCl	>10	7.0	0.95
28·HCl	9.6	2.5	0.38
29a-c	1.0	2.0	...
30a, b	1.8	2.0	...
31	1.0	2.0	...
32	0.4	2.8	0.18
33	1.7	1.3	0.21
34	6.8	>10	...
35	>8	3.3	...
36	6.8	>10	...
37	>10	>10	...
38 free base	0.7	2.5	...
·HCl	0.34	1.6	...
mucate	6.0	5.0	...
39 free base	0.1	3.0	...
·HCl	0.2	4.0	...
mucate	0.3	5.8	...
40a, b	0.5	8.5	...
41	3.1	2.8	0.16
42	1.0	8.0	0.14
43a, b	0.26	4.0	0.26
44	5	8	...
Papaverine	2.9	5.6	0.0016
Methyl-sergide	...	...	0.0025

was taken up (2–4 hr). After removal of the catalyst and solvent, the resulting indan was purified either by distillation or by isolation of the appropriate salts. Yields of 20–95% were obtained.

From Alkylation of 1-Phenylindan. Method I.—To $NaNH_2$ freshly prepared from 4.6 g (0.2 g-atom) of Na in 500 ml of liquid NH_3 was added with stirring a solution of 19.4 g (0.1 mole) of 1-phenylindan in ether (200 ml). To the resulting red suspension was added a solution of 0.2 mole of the appropriate dialkylaminoalkyl halide in 20 ml of xylene and 60 ml of ether. Stirring was continued until the liquid ammonia had evaporated. Work-up of the reaction in the usual manner gave the 1-dialkylaminoalkyl-1-phenylindan (VIII) in quantitative yield.

Pharmacology

The ability of a drug to prevent but not to reverse the ptosis induced by reserpine was used as an indication of antidepressant activity. In this assay the test compound is administered orally 1 hr before the administration of reserpine (2.0 mg/kg iv). One hour following the reserpine administration the mice are placed on a platform away from light and the extent of closure of the palpebral fissure is estimated. Ptosis is only significant if the opening is less than 50% of normal. Compounds found to possess a high degree of activity in the prevention of reserpine-induced ptosis were further tested to determine their ability to reverse the effects of reserpine. In this part of the test reserpine (2.0 mg/kg iv) is administered first and 1 hr later the test compound is given orally. The amount of ptosis is determined as previously described. The use of this test serves to distinguish imipramine-type antidepressants and MAO inhibitors from adrenergic α-receptor stimulants which both prevent and reverse reserpine-induced ptosis. The differentiation between the imipramine-type compound and MAO inhibitors was determined by *in vitro* and *in vivo* enzyme inhibition studies.

The antispasmodic effects were determined using standard *in vitro* procedures. The musculotropic activity was indicated by the ability of a drug to inhibit $BaCl_2$-induced spasms on rabbit ileum. The neurotropic activity was measured by the ability of a drug to inhibit acetylcholine-induced spasms on rabbit ileum. Antiserotonin activity was determined using the rat uterus procedure of Gaddum, *et al.*[26]

Listed in Table III are the results from the reserpine ptosis tests. A number of the indenes were active in

(26) J. H. Gaddum, K. A. Hameed, D. E. Hathway, and F. F. Stephens, *Quart. J. Exptl. Physiol.*, **40**, 49 (1955).

this test; 1-[2-(dimethylamino)ethyl]-1-phenylindene hydrochloride (**2**) was the most active.[27] Relatively minor structural changes reduced the activity markedly. The corresponding indan (**23**) was only one-tenth as active as **2**. Moreover, 1-[2-(dimethylamino)-ethyl]-3-phenylindene (**1**) was even less active and 3-[2-(dimethylamino)ethyl]-2-phenylindene (**4**) was inactive. Extension of the side chain by one CH_2 (**10**) also lowered the activity considerably, a surprising result since the dimethylaminopropyl group is the side chain of both imipramine and amitriptyline. Changes in the amine portion of the molecule revealed an inverse relationship between the bulk of the amine group and the activity of the compounds. The demethyl derivative (**6**) and the N-oxide (**5**) both had activities on the same order as **2**, while the diethylaminoethyl derivative (**7**) was only weakly active and the morpholinoethyl analog (**9**) was inactive.

A comparison of some of the pharmacological activities of **2** and the clinically active compounds, imipramine and amitriptyline, is summarized in Table IV. 1-(2-Dimethylaminoethyl)-1-phenylindene hydrochloride (**2**) has a greater milligram potency in the reserpine test. Of special interest is the lack of central anticholinergic effects of **2** as shown in the antisinistro torsion[28] and antiparkinsonism[29] tests. Compound **2** does show considerable MAO inhibition *in vitro*, using as the criteria the change of the rate of kynuramine oxidation in liver homogenates, in the presence of the test compound. By the more indicative *in vivo* tests, using both tryptamine and 5-hydroxytryptophan potentiation as a measure of MAOI activity, **2** did not behave as an MAO inhibitor. Thus, the *in vitro* MAOI activity appears to be an artifact due to liver cell disruption, although some MAO inhibition *in vivo* is not completely ruled out. This combination of greater milligram potency and lack of anticholinergic effects of **2** may result in significant reduction of the undesirable atropine-like side effects encountered clinically with the standard agents.

Table V summarizes the results obtained in the antispasmodic and antiserotonin tests. The indans were the most potent compounds in this area. 3-(1-Methyl-3-pyrrolidinylmethyl)-1-phenylindan hydrochloride (**38**) was the most active of this series, having approximately twice the potency of the reference agent papaverine as a musculotropic agent with only 0.3–1.0% of the neurotropic effects of atropine sulfate. Its isomer, 1-(1-methyl-3-pyrrolidenylmethyl)-1-phenylindan hydrochloride (**39**), was equally active as a musculotropic agent; however, **39** had neurotropic effects which were ten times greater than its isomer (**38**).

Acknowledgments.—We wish to thank Drs. J. W. Kissel and A. Kandel and Mr. K. W. Dungan for the pharmacological evaluations. The assistance of Drs. D. E. Rivard and R. F. Majewski and Messrs. R. D. Dennis, J. P. Elkins, R. R. Covington, J. C. Simms, and L. Jones at various times during the course of this investigation is gratefully acknowledged. We also wish to thank Dr. A. A. Larsen for his many helpful suggestions.

(27) A. Kandel and P. M. Lish, Mead Johnson and Co., British Patent 1,041,989 (1966).

(28) M. C. DeJonge & A. B. H. Funcke, *Arch. Intern. Pharmacodyn.*, **137**, 375 (1962).

(29) G. M. Everett, L. E. Blockus, and I. M. Shepperd, *Science*, **124**, 79 (1956).

Substituted Anilinopyridine Carboxylic Acids with Antiinflammatory Activity

D. EVANS, K. S. HALLWOOD,

Chemistry Department, Lilly Research Laboratories Ltd., New Ferry, Wirral, Cheshire, England

C. H. CASHIN, AND H. JACKSON

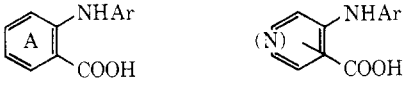
Pharmacology Department, Lilly Research Laboratories Ltd., Speke, Liverpool 24, Lancashire, England

Received November 18, 1966

The synthesis of eleven substituted anilinopyridinecarboxylic acids, of which seven were novel, is described and their antiinflammatory activity is compared with that of mefenamic acid and flufenamic acid. Comparable activity was found with 2-(2,3-dimethylanilino)-, 2-(*m*-trifluoromethylanilino)-, and 4-(*m*-trifluoromethylanilino)-nicotinic acid. The novel 8,9-dimethylpyrido[2,3-*b*]quinol-5-one was also synthesized and found to be inactive.

The recent publication of a patent[1] claiming derivatives of 2-anilinonicotinic acid as analgesic–antiinflammatory agents prompts us to report our experience with these and related anilinopyridinecarboxylic acids in which the substituted anilino and carboxyl groups are in different positions around the heterocyclic nucleus.

This study was initiated to determine if the antiinflammatory activity of mefenamic acid[2a] (**1a**) and flufenamic acid[2b] (**1b**) was affected appreciably when the phenyl ring A in these compounds was replaced by a pyridine nucleus as in **2**. For this reason the compounds which have been synthesized have been mostly confined to the 2,3-dimethylanilino and *m*-trifluoromethylanilino derivatives.



1 **2**

a, Ar = 2,3-$(CH_3)_2C_6H_3$
b, Ar = 3-$F_3CC_6H_4$

(1) Société Anonyme Laboratoires U.P.S.A., Belgian Patent 657,266 (April 16, 1965).

(2) (a) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol.*, **138**, 405 (1962); (b) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963).