complete exchange took place after 10 hr. Heating the mixture appears to be necessary, as no significant amount of exchange was noted after standing 16 hr at 25°.

Upon treatment of the sodium salt of 4 with $SOCl_2$ in ethanol, both esterification and denitrosation took place to afford normeperidine-*d* hydrochloride (**5** · HCl). Denitrosation is due to the action of HCl generated in the reaction mixture, as cleavage also could be effected with ethanolic HCl. It was found that addition of urea greatly facilitated denitrosation by trapping NO^+ generated in this reaction.[4]

Mass spectral analysis of **5** showed it to contain 66.5% D_4, 25.3% D_3, 4.4% D_2, and 1.7% D, the balance (2.1%) being undeuterated. The pmr spectrum of **5** exhibited two doublets (J_{gem} = 14 Hz) at δ 2.35 and 2.76 which are due to the axial and equatorial protons at C-3 and C-5. This is consistent with the α positions being the sites of exchange and is in marked contrast with the pmr spectrum of the undeuterated compound **1** which exhibits an envelope absorption in the δ 2.2–3.7 region.

Radiolabeled **3** was prepared by a similar procedure using 3 *M* NaO^{3}H in ^3H_2O (250 mCi). This intermediate was not isolated but, subsequent to denitrosation-esterification, was converted by the Leuckart reaction to [^3H]-meperidine.

The ^3H_2O was recovered from the reaction mixture and possessed sufficient activity to warrant its use in another isotopic exchange reaction.

In summary, the results of this study indicate that the labeling procedure is useful for localizing isotopic hydrogen α to an amine function. The specificity of the reaction and the nonlability of isotopic hydrogen in the α position of amines offers a distinct advantage over random labeling procedures. The facility and inexpensiveness of the method make it possible to prepare labeled amines which are otherwise obtainable only by more laborious procedures.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by M-H.W Laboratories, Garden City, Mich. Glc analysis was carried out on a Varian 2100 instrument equipped with a flame ionization detector and a 0.25 × 72 in. glass column packed with 3% OV-17 on Chromosorb W (80–100 mesh) using N_2 carrier gas. Nmr spectra were obtained in $CDCl_3$ or D_2O with a Varian A-60D spectrometer using TMS or DDS as internal standards. Mass spectra were obtained on a Hitachi RMU 6 spectrometer.

N-Nitrosonormeperidine (2). A stirred solution of 1 · HCl (5.0 g, 0.0186 mol) in pH 4, acetate buffer (10 *M*, 200 ml) was maintained at 95° and treated dropwise over a 3-hr period with $NaNO_2$ (25 g) in water (50 ml). After the reaction mixture was cooled, it was extracted with $CHCl_3$ and washed successively with solutions of saturated NaCl and Na_2CO_3 (10%), and the $CHCl_3$ extract was dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded 4.8 g (98%) of 2: mp 38–40°; ir (neat) 1725 (C=O), 1425 (N=O), 980 cm^{-1} (NN). *Anal.* ($C_{14}H_{18}N_2O_3$) C, H, N.

N-Nitrosonormeperidinic Acid (3). Intermediate 2 (4.8 g, 0.0182 mol) was dissolved in an ethanolic solution of 0.6 *N* KOH (200 ml) and the mixture refluxed for 2.5 hr. The solvent was removed *in vacuo* and the solid was dissolved in H_2O. Acidification (10% HCl) afforded a precipitate which was collected by filtration, washed (H_2O), and twice crystallized (EtOH) to yield 3.4 g (80%) of 3: mp 185–186°; ir (KBr) 3200–2500 (H-bonded OH), 1725 (acid C=O), 1425 (N=O), and 985 cm^{-1} (NN). *Anal.* ($C_{12}H_{14}N_2O_3$) C, H, N.

Normeperidine-*d* (5). A 0.5-ml glass reaction vessel containing 0.25 ml of 6 *M* NaOD (prepared from 230 mg of Na_2O and 0.5 ml of D_2O) and 75 mg (0.32 mmol) of 3 was shaken over a steam bath for 9 hr. The contents of the vessel were frozen and lypholyzed (0.5 mm). Dry EtOH (3 ml) was added and $SOCl_2$ (0.7 ml) was dropped into the mixture which was cooled (ice bath) and continuously agitated. Urea (190 mg, 3.2 mmol) was then added and the reaction mixture was refluxed for 3 hr. The mixture then was diluted with H_2O (10 ml) and the EtOH was partially removed *in vacuo*. The residual acidic solution was extracted (Et_2O), made basic (10% Na_2CO_3), and partitioned into $CHCl_3$. The combined $CHCl_3$ extracts were washed with saturated NaCl and dried ($MgSO_4$), and the solvent was removed and replaced with Et_2O. Addition of ethereal HCl afforded normeperidine-*d* HCl (50 mg, 60%), mp 129–131°, which was recrystallized (EtOH–Et_2O) and dried *in vacuo*. Tlc comparisons with authentic material corresponded [mass spectrum *m/e* (M^+, rel intensity) 233 (3.3), 234 (2.6), 235 (9.9), 236 (35.0), 237 (100) (nondeuterated material *m/e* (M^+, rel intensity) 232 (10), 233 (100), 234 (10))] with mol % deuterium incorporation: 2.2, nondeuterated; 1.7, monodeuterated; 6.6, dideuterated; 23.2, trideuterated; 66.3, tetradeuterated. Nmr ($CDCl_3$): δ 1.18 (t, 3, CH_3), 2.35 and 2.76 (d, J = 14 Hz, ~3.5, CH_2CD_2), 4.15 (q, 2, OCH_2).

[^3H]-Meperidine Hydrochloride. Intermediate 3 (75 mg, 0.32 mmol) was mixed with 0.25 g of ^3H_2O (250 mCi) and 50 mg of NaOMe in a 0.5-ml glass vessel which then was sealed and heated in a steam bath for 10 hr. The reaction mixture was frozen and the ^3H_2O was removed *in vacuo* (0.5 mm) and collected in a Dry Ice trap. The residue was diluted with unlabeled 3 (225 mg), treated successively with $SOCl_2$ (1 ml), anhydrous EtOH (3 ml), and urea (190 mg), and then refluxed (1 hr). The reaction mixture was then treated with 37% CH_2O (2.5 ml) and 88% HCOOH (0.9 ml) and heated on a steam bath for 4 hr. The solvent was removed *in vacuo* and the residue dissolved in H_2O and extracted with Et_2O. The aqueous layer was basified (10% Na_2CO_3) and extracted (Et_2O). The Et_2O extract was washed with saturated NaCl, decolorized, and dried ($MgSO_4$). The ethereal solution was made acidic with ethanolic HCl and the precipitate crystallized three times (EtOH–Et_2O) to give 103 mg (30%) of [^3H]-meperidine HCl: mp 183–184°; specific activity 0.54 mCi/mmol. Chemical and isotopic purity were confirmed by ir and tlc radioassay.

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Anticancer Compounds. Further Analogs of 1-(4-Dimethylaminobenzylidene)indene†,‡

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Several years ago 1-(4-dimethylaminobenzylidene)indene (**1**) was prepared as an analog of 4-(4-dimethylaminostyryl)-quinoline[1] (**2**). Tests by Haddow, Everett, and Mitchley against the subcutaneous Walker 256 tumor by the single dose method showed that **1** was as effective as **2** in this test and that **1** was far less toxic than **2**, so that the therapeutic ratio was much more favorable. Further tests in other laboratories showed that **1** was very effective also against the established intramuscular Walker 256 tumor and against Lymphoma 8[2,§] but not against Leukemia 1210. We have reported syntheses and test results on a number of variations

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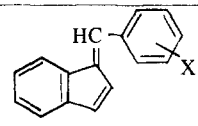
‡Part of this material was presented at the Southeastern Regional Meeting of the American Chemical Society in Richmond, Va., Nov 6, 1969, and part at the meeting in Nashville, Tenn., Nov 5, 1971.

§R. M. Folk, private communication, Battelle Memorial Institute.

Table I. CCNSC Walker 256 Life-Span Test[a] Results



Compd, X =	Dose, mg/kg	Survivors[b] Day 5	Survivors[b] Day 40	T/C, %
A. Derivative of 1-(X-Benzylidene)indene				
4-Amino-[c]	400	6	1	177
4-Dimethylamino-[c]	400	6	1	202
4-Dimethylamino-, methiodide	50	6	0	
	25	6	0	116
4-Dimethylamino-, dihydro	400	6	0	114
4-Dimethylamino-, decahydro	400	1	0	
	100	4	0	182
	67	6	1	208
	44	6	0	112
4-Ethylamino-[c]	400	6	0	97
4-Diethylamino-[c]	400	6	3	333
4-Dimethylamino-3-methyl-	400	6	0	109
4-Amino-3,5-dichloro-	400	6	0	136
4-Methylamino-3-chloro-	400	2		
	200	5	1	330
	200	0	0	
	100	4	1	292
	50	6	3	451
4-Methylamino-3-bromo-	400	2	0	
	200	5	1	301
	200	2	0	
	100	6	0	121
	50	6	0	139
	25	6	0	109
4-Methylamino-3-iodo-	400	6	0	166
4-Methylamino-3,5-dichloro-	400	6	0	126
4-Methylamino-3,5-dibromo-	400	6	0	120
4-Dimethylamino-3-fluoro-[c]	400	6	1	289
4-Dimethylamino-3-bromo-	400	5	1	304
4-Methylthio-	400	6	1	229
B. Other Analogous Compounds				
1-(4-Thiomethylbenzylidene)-6-nitroindene[c]	300	6	0	175
1-(4-Thiomethylbenzylidene)-5-nitroindene[c]	400	6	0	200
	100	6	0	150
1-(4-Bis-β-chloroethylaminobenzylidene)cyclopentadiene	400	6	6	533
2-(4-Dimethylaminostyryl)quinoline[c]	400	5	0	108
	200	5	0	254
	100	6	1	218
	75	6	0	155
	50	6	1	218
	37	6	0	91
	18	6	1	185
	9	6	0	90
4-(4-Dimethylaminostyryl)quinoline	100	6	0	110
	50	6	0	145
	25	6	0	152
	12	6	0	193
4-[*p*-(Ethylnitrosoamino)styryl]quinoline	600	4	0	185
	300	5	0	98
	150	6	1	256
	75	6	1	200
	75[d]	5	0	96
	50[d]	6	0	158
	33[d]	6	0	178
	22[d]	6	0	220
	12[c]	6	0	190
	6[c]	6	0	136
	3[c]	6	0	106
	1.5[c]	6	0	129
2-(4-Aminophenyl)indole	400	6	0	104

[a] Intraperitoneal inoculation of ascitic fluid containing 10^6 Walker 256 tumor cells gives average survival time of untreated control animals of 7–8 days. Unless otherwise indicated, a single dose of compound was administered on the day following tumor implantation. Cytoxan, 2.5 mg/kg qd 1–9, is the positive control giving a *T/C* 300–525% with 50–100% 40-day survivors. [b] Six random-bred albino rats were treated. [c] Nine single daily injections. [d] See ref 3.

of the structure of **1**.[3-9] Table I lists previously unpublished results of tests against the Walker 256 ascites which reveal marked life prolongation by a number of compounds, three of which produced 50–100% 40-day survivors at the optimum test dosage. The activity of 4-(1-indanylmethyl)-*N,N*-dimethylcyclohexylamine is especially significant from the

Table II. Analogs of 1-(4-Dimethylaminobenzylidene)indene

Compd no.	Mp, °C[a]	Recrystn solvent[b]	Formula[c]	Color[d]	Effect[e] Tumor wt, T/C	Effect[e] Dose, mg/kg	Lethality[e] No. killed	Lethality[e] Mg/kg
3[f]	125–126	H[g]	$C_{18}H_{15}NO_2$	OY				
4	96–97	H	$C_{18}H_{17}N$	OY	0.2	625[h]	0/3	625[h]
5	68–69	H	$C_{16}H_{11}NO_2$	Y				
6	130–132	B	$C_{16}H_{11}NO_2$	O				
7	250	B	$C_{32}H_{22}N_2O$	O	0.9	1500[i]	0/3	1500[i]
8[f]	112–113	H	$C_{18}H_{16}N_2O_2$	B	0.7	1500	0/3	1500
9	99	H, M[j]	$C_{18}H_{16}N_2$	Y				
10[f]	142–143	H	$C_{22}H_{19}N$	OY	0.6	600		
11[f]	105–106	H, E[k]	$C_{24}H_{19}N$	Y	0.4	600	0/3	1500
12					0.9	240	1/2	1500
					0.6	600		
13	214–215	O	$C_{14}H_{12}N_2$	Pi	0.7	600	0/3	600
					0.9	1500	1/3	1500
17a	177	E	$C_{18}H_{16}N_2O_2$	Pu	0.1	240	0/3	600
					0	600	3/3	1500
17b	244	E	$C_{18}H_{16}N_2O_2$	Pu	0.9	1500	0/3	1500
18	*l*		$C_{18}H_{11}NO_2$	Y	0.9	600	0/3	1500
19a	88	H	$C_{16}H_{13}N$	Y	0.7	600	0/3	600
							3/3	1500
19b	105	H	$C_{16}H_{13}N$	Y	1.2	240	2/3	600
19c	135	H	$C_{16}H_{13}N$	Y	1.0	240	3/3	600
20a	144[m]	O, M	$C_{17}H_{13}O_2NS$	Y				
20b	172[m]	O, M	$C_{17}H_{13}O_2NS$	Y				
21	154–156	H, M	$C_{20}H_{15}N_2Fe$	R				
22	151	H, M	$C_{20}H_{16}Fe$	B	0.6	250	0/3	625
					0.7	625		

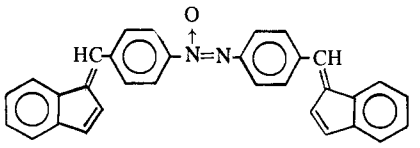
[a]Determined with a Mel-Temp melting point apparatus. [b]B, C_6H_6; E, absolute EtOH; H, commercial mixed branched hexanes (isohexane); M, MeOH; O, commercial mixed branched octanes (isooctane). [c]All new compounds were analyzed for C and H; analytical results were within ±0.4% of the theoretical values. [d]B, burgandy; O, orange; OY, orange yellow; Pi, pink; Pu, purple; R, red; Y, yellow. [e]We are grateful to Professor Sir Alexander Haddow, Professor A. B. Foster, Mr. J. E. Everett, and Mr. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was administered as a single ip injection in 10% dimethylacetamide in arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor-bearing animals were sacrificed approximately 8 days later. [f]The KOH-absolute EtOH condensation method was used. [g]Chromatographed on alumina with isohexane, eluting with C_6H_6. [h]Injection administered in 10% acetone in arachis oil. [i]Arachis oil. [j]Chromatographed on cellulose with MeOH. [k]Chromatographed on silica gel with isohexane. [l]Mixture of isomers; a small amount of one isomer, mp 144°, was isolated. *Anal.* Calcd for $C_{18}H_{11}NO_2$: C, 77.09; H, 4.45. Found: C, 76.79; H, 4.16. [m]Mr. Harold E. Kinder of the Tennessee Eastman Research Laboratories has suggested on the basis of nmr spectra that the higher melting compound is 5-nitro and the lower melting isomer is 6-nitro.

structure-activity viewpoint, since it does not contain an aromatic amine group. In order to delineate further the structural characteristics required for activity against Walker 256, we have synthesized a variety of additional compounds.

A long-asked question has been whether it is necessary to have an unsubstituted position ortho to the amino group. While we have not obtained the 3,5-dimethyl-4-dimethylamino compound, we have succeeded in preparing the 1-(4-nitro-3,5-dimethylaminobenzylidene)indene (**3**) and reducing it to 1-(4-amino-3,5-dimethylbenzylidene)indene (**4**), which was found to be active. See Table II. (Unless otherwise indicated, activity means that the compound showed activity in one or more of the Walker 256 screening tests.)

The condensation of nitrobenzaldehyde with indene has been recognized as difficult. We obtained a very small yield of 1-(2-nitrobenzylidene)indene (**5**) by condensation of 2-nitrobenzaldehyde with indene in boiling alcohol with KOH catalyst. Later we succeeded in finding conditions for obtaining a satisfactory yield of 1-(4-nitrobenzylidene)indene (**6**). Attempts to reduce **6** to the *N*-hydroxylamine were unsuccessful but did lead to other new compounds. Hydrogenation over Pd apparently formed a dihydro derivative of **6**, while Zn dust and NH_4Cl produced an azoxy compound **7** which was not active.

An amino group adjacent to the dimethylamino group was obtained by reduction of 1-(3-nitro-4-*N*,*N*-dimethylaminobenzylidene)indene (**8**) to produce 1-(3-amino-4-*N*,*N*-dimethylaminobenzylidene)indene (**9**) which was inactive. 1-(4-*N*,*N*-Dimethylamino-1-napthylmethylene)indene (**10**) was prepared and found to be active in spite of the extra



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aromatic ring but less potent than **1**. *N*-Ethyl-3-(inden-1-ylidenemethyl)carbazole (**11**) was prepared because Gutman[10] had suggested that a second phenyl group attached to the nitrogen in aromatic amines reduces or destroys the carcinogenic effect of these compounds. This compound did exhibit some activity. It has not been tested for carcinogenic effects.

The known compound, 1-dimethylaminoethyleneindene[11] (**12**), was prepared to test the effect of omitting the benzene ring between the amino group and olefinic carbon to carbon double bond of **1**. It was inactive. 2-(4-Aminophenyl)-indole (**13**) was prepared as a remote analog of **1** and was not active.

1-(4-Aminobenzylidene)indene and **1** seem to be much more effective against Walker 256 tumors than 4-dimethylaminostilbene (**14**) to which they are closely related in structure.

The 5 position of the indene in **1** corresponds to the 4′ position in **14**. Haddow, *et al.*,[12] found that compounds containing a substituent at the 4′ position in **14** were inactive, but the activity of 1-(4-dimethylaminobenzylidene)-5- and -6-methoxyindenes suggested that the corresponding 5- and 6-nitro compounds, 1-(4-dimethylaminobenzylidene)-5-

and -6-nitroindene, should be tested. Attempts to condense 5-nitroindene[13] (**15**) with 4-dimethylaminobenzaldehyde (**16**) by use of alcoholic KOH produced black polymeric material instead of the desired product, but piperidine acetate catalysis produced good yields of the desired condensation product **17**, one of which was active. (Although **15** was used as starting material, a shift of the double bonds in the cyclopentene ring could lead to a 6-nitro product.)

The question arises whether the activity would be increased if the amino group were at the indene end of the system of conjugated bonds instead of at the phenyl end. By reduction of 1-benzylidene-5- (and/or 6-) nitroindene (**18**), three isomers (**19**) were obtained. None of the three compounds were active, so it is inferred that an amino group at the 5 or 6 position on benzylideneindene does not have the same antitumor effect as does an amino group at the opposite end of the molecule. The position of the amino group is critical for activity.

Although 1-(4-thiomethylbenzylidene)indene was not found active in the standard Walker test, a later report revealed that it produced life extension in the Walker survival test. (See Table I.) Two isomers (**20**) have been prepared by condensation of 5-nitroindene with *p*-thiomethylbenzaldehyde.

Both 5-nitroindene and indene were condensed with ferrocenecarboxaldehyde to give **21** and **22**, respectively.

Experimental Section

1-(4-Amino-3,5-dimethylbenzylidene)indene (4). To 0.01 mol of 1-(3,5-dimethyl-4-nitrobenzylidene)indene in 600 ml of boiling MeOH was added 1.6 ml of concentrated HCl and 2.1 g of Fe over a 40-min period. After refluxing 5.5 hr 1.0 g of Fe and 0.5 ml of HCl were added, and refluxing was continued for 15.5 hr. The MeOH was evaporated under reduced pressure at 38° and the residue dissolved in isohexane and chromatographed on an alumina column, yield 40%. *Anal.* ($C_{18}H_{17}N$) C, H.

1-(2-Nitrobenzylidene)indene (5). To 0.101 mol of indene and 0.02 mol of KOH in 75 ml of EtOH was added dropwise with stirring 0.066 mol of 2-nitrobenzaldehyde in 250 ml of EtOH. After standing 3 days the EtOH was removed under vacuum, and the residue was chromatographed on alumina in benzene. Yellow crystals recrystallized from isohexane: mp 68–69°; yield 0.06%. *Anal.* ($C_{16}H_{11}NO_2$) C, H. A red crystalline by-product, recrystallized from EtOAc, mp 225°, was also obtained.

1-(4-Nitrobenzylidene)indene (6). Kresze, *et al.*,[14] obtained 6 in 6% yield from indene and *p*-nitrobenzaldehyde (23). After testing numerous variations of conditions, we were able to obtain a much more satisfactory yield. In a typical run 3.0 g (0.053 mol) of KOH in 150 ml of boiling EtOH was added quickly to 30.8 g of redistilled indene in 1 l. of EtOH. Then 20.0 g of 23 in 2 l. of EtOH was added dropwise during 3 hr, while the temperature was kept at about 38°. (Higher or lower temperatures reduced yields.) Stirring was continued 8–10 hr and the solution was allowed to stand 4–6 days at room temperature. The EtOH was removed under vacuum at 38° and the unreacted indene was removed at 0.2 mm. The product was dissolved in C_6H_6 and chromatographed on alumina: crude product, mp 105–119°; yield, 57%; after recrystallization from C_6H_6, mp 130–132°. The piperidine acetate method was not satisfactory for this compound.

7. After mixing 1.0 g (0.004 mol) of 1-(4-nitrobenzylidene)-indene with 0.25 g of NH_4Cl in 150 ml of THF, enough water was added to dissolve the NH_4Cl. Zn dust (0.6 g, 0.008 mol) was added over a period of 45 min. The mixture was heated to 60° with stirring for 2 hr and was immediately filtered. The filtrate was flash evaporated and the residue recrystallized from C_6H_6: orange crystals; mp 250° dec. *Anal.* ($C_{32}H_{22}N_2O$) C, H, N.

1-(3-Amino-4-dimethylaminobenzylidene)indene (9). To 0.0205 mol of 8 dissolved in 700 ml of MeOH at reflux was added with stirring 1.8 ml of HCl and 7.0 g of Fe over a 20-min period. After refluxing for 10 hr the mixture was made basic with 1 *N* KOH and filtered. The yellow precipitate was recrystallized from MeOH and isohexane and chromatographed on a cellulose column in MeOH, yield 33%. *Anal.* ($C_{18}H_{18}N_2$) C, H.

2-(4-Aminophenyl)indole (13). The phenylhydrazone of 4-nitroacetophenone was cyclized with PPA to form 2-(4-nitrophenyl)-indole, 5 g of which was added to a mixture of 100 ml of HCl and 50 g of $SnCl_2 \cdot H_2O$ which was stirred for 0.5 hr and then refluxed 0.5 hr. After neutralization the solid 13 was extracted with C_6H_6 and recrystallized from isooctane. *Anal.* ($C_{14}H_{12}N_2$) C, H. 13 was prepared more conveniently by hydrogenation of 5.0 g (0.02 mol) of 2-(4-nitrophenyl)indole in 150 ml of EtOAc over 0.5 g of 5% Pd on C. The reaction stopped when 3 mol of H_2/mol of 2-(4-nitrophenyl)-indole had been absorbed. After removal of the catalyst and solvent, the residue was recrystallized from isooctane, yield 77%.

1-Benzylidene-5- (and/or 6-) nitroindene (18). A mixture of 0.03 mol of piperidine, 0.03 mol of AcOH, 0.03 mol of benzaldehyde (freshly purified), and 0.03 mol of 15 in 175 ml of dry toluene was refluxed 45 min (optimum) under a Dean-Stark trap. By first cooling the reaction mixture to −15°, filtering, and recrystallizing from EtOAc and isohexane, a white by-product was obtained, mp 106–108°. The desired product was obtained by chromatographing the reaction mixture on Alcoa F-20 alumina. (Later experience indicated that Florisil had less tendency than alumina to cause formation of dark by-products.) The column was eluted with benzene, and the first fractions were recrystallized from C_6H_6, using Soxhlet extraction: yellow crystals; mp 122–125°; yield 85%. This material, which was probably a mixture of isomers, was used for reduction to amino compounds.

1-Benzylidene-5- (and/or 6-) aminoindene (19).[15] To 4.69 g of 18 dissolved in 800 ml of boiling MeOH was added 2.5 ml of HCl with stirring. After the mixture was refluxed 10 min 3.45 g of Fe was added in 20 min. Refluxing was continued 22 hr and 3.45 g of Fe was added. The mixture was refluxed 28 hr, heating ceased, and stirring continued 1 hr to cool. After filtering, the solution was partially evaporated at reduced pressure, and the remaining solution was neutralized with 8 *N* NaOH and allowed to air dry. Recrystallization from isohexane yielded 21% red crystals, mp 84–85°. A lesser yield of 15% was obtained using 100 ml of THF and 200 ml of MeOH and refluxing 21 hr.

19 was also prepared as follows. 18 (5.47 g, 0.02 mol) in 500 ml of acetic acid was added dropwise to $SnCl_2 \cdot H_2O$ (17.8 g, 0.08 mol) dissolved in 18 ml of HCl over a 2.5-hr period. The mixture was refluxed 1.25 hr, cooled, and filtered, and the residue was dissolved in MeOH and neutralized. The solvent was removed under vacuum and recrystallization of the solid from isohexane gave a yellow solid, mp 105°. The filtrate from the reaction mixture was neutralized and extracted with C_6H_6. After removal under vacuum of the C_6H_6, the residue was recrystallized from isohexane: yellow solid; mp 135°. A red-brown by-product was obtained, mp 295°. *Anal.* C, 83.25; H, 5.44.

1-(4-Thiomethylbenzylidene)-5- (and/or 6-) nitroindene (20). The piperidine acetate method was used,[16,17] refluxing for 4.5 hr and producing a crude yield of 47%. The isomers were separated by crystallization from isooctane and MeOH and chromatographing on on Florisil. *Anal.* ($C_{17}H_{13}O_2NS$) C, H.

21. To a mixture of 1.6 g (0.01 mol) of 5-nitroindene, 2.1 g (0.01 mol) of ferrocenecarboxaldehyde (24), and 175 ml of dry toluene refluxing under a Dean-Stark trap was added 0.015 mol of piperidine and 0.015 mol of AcOH. Additional refluxing 10 min gave a dark purple product which was purified by placing on an alumina column and eluting with C_6H_6. The material recovered from the C_6H_6fractions was recrystallized from MeOH and isohexane: red plates; mp 154–156°. *Anal.* ($C_{20}H_{15}N_2Fe$) C, H.

22. Indene and 24 were condensed similarly and recrystallized from MeOH and isohexane: red-purple plates; mp 151–152°. *Anal.* ($C_{29}H_{16}Fe$) C, H.

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N-Alkylaminocarbazoles as Potential Anticonvulsant and Diuretic Agents†

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Carbazoles, in view of incorporating an indole nucleus in their structure and their close structural resemblance to phenothiazine, have been attracting increasing attention as pharmacodynamic agents.[1-5]

The present communication describes the synthesis and biological evaluation of *N*-alkylaminocarbazoles, tetrahydrocarbazoles, and those in which one of the phenyl rings has been enlarged to a seven-membered ring system.

Chemistry. The desired intermediate biphenyls were readily obtained by condensing the appropriate 2-bromonitrobenzene with the corresponding iodobenzene under Ullmann's conditions[6] and the products were purified by silica gel column chromatography.

The biphenyls were cyclized by refluxing with triethyl phosphite[7] to give the desired carbazoles. In cases where more than one product was expected, column chromatography in conjunction with tlc and nmr techniques was employed for isolation and characterization of the different isomers.

The synthesis of halogen-substituted tetrahydrocarbazoles and 6,7,8,9-10*H*-cyclohept[*b*]indoles was carried out by a Japp-Klingemann reaction on hydroxymethylcyclohexanone or -heptanone with aryldiazonium chloride followed by cyclization and Huang-Minlon reduction. The tetrahydrocarbazoles in turn were aromatized to carbazoles with chloranil. The corresponding N-alkylated compounds were obtained by reaction with the appropriate *tert*-aminoalkyl halides in the presence of NaH.

Biological Activity. CNS Activity. Acute toxicity, gross observational effects, and ability of the compounds to modify electroshock (SMES, 48 mA × 0.2 sec), pentylenetetrazole (80 mg/kg sc), and strychnine (1.5 mg/kg ip) induced seizures[8] were studied in male mice at the 0.2 ALD_{50} dose level. The end point employed in the SMES test was the abolition specifically of the hind limb tonic-extensor component of maximal seizure, while for the pentylene-

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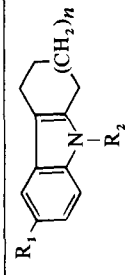
Table I



Compd no.	n	R_1	R_2	Mp, °C	Formula[a]	ALD_{50},[f] mg/kg ip	Gross effects at 0.2 ALD_{50}	SMES test, % protection at 0.2 ALD_{50}, mg/kg ip	SMES test, % protection at 0.1 ALD_{50}, mg/kg ip	Diuretic activity,[b] % urinary output at 0.25 ALD_{50}	Remarks
1	1	F	$(CH_2)_2N(CH_3)_2$	205	$C_{16}H_{21}FN_2 \cdot C_2H_2O_4$	100	↓[c]	0[e]		86	Depressant, diuretic
2	1	F	$(CH_2)_2N(C_2H_5)_2$	154–155	$C_{18}H_{25}FN_2 \cdot C_2H_2O_4$	300	0	0		81	Diuretic
3	1	F	$(CH_2)_2NC_4H_8$	192	$C_{18}H_{23}FN_2 \cdot C_2H_2O_4$	100	0	0		54	Diuretic
4	1	F	$(CH_2)_3N(CH_3)_2$	141–142	$C_{17}H_{23}FN_2 \cdot C_2H_2O_4$	150	0	0		87	Diuretic
5	1	Cl	$(CH_2)_2N(C_2H_5)_2$	140–141	$C_{18}H_{25}ClN_2 \cdot C_2H_2O_4$	100	0	0		52	Diuretic
6	1	Cl	$(CH_2)_2NC_4H_8$	170–171	$C_{18}H_{23}ClN_2 \cdot C_2H_2O_4$	100	0	0		16	
7	1	Cl	$(CH_2)_3N(CH_3)_2$	191–192	$C_{17}H_{23}ClN_2 \cdot C_2H_2O_4$	300	0	100	20	66	Anticonvulsant, diuretic
8	2	Cl	$(CH_2)_2N(CH_3)_2$	136	$C_{17}H_{25}ClN_2 \cdot C_2H_2O_4$	150	↓	0		–[d]	Depressant
9	2	Cl	$(CH_2)_2NC_4H_8$	220	$C_{19}H_{25}ClN_2 \cdot C_2H_2O_4$	100	↓	0		–	Depressant
10	2	CH_3O	$(CH_2)_2N(C_2H_5)_2$	126	$C_{20}H_{30}N_2O \cdot C_2H_2O_4$	200	0	0		–	
11	2	CH_3O	$(CH_2)_2NC_4H_8$	205	$C_{20}H_{28}N_2O \cdot C_2H_2O_4$	300	↓	0		–	Depressant

[a] All compounds were analyzed for C, H, and N except compounds **1**–**4** which were analyzed for N only. [b] Urinary output of chlorothiazide treated rats taken as 100. [c] ↓, CNS depressant. [d] –, not tested. [e] 0, no effect. [f] ALD_{50} = approximate LD_{50}.