Synthesis and Antiarrhythmic Activity of 2-Dialkylaminoalkyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine Derivatives

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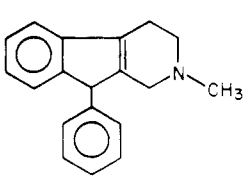
Some dihydro- and hexahydro-2-dialkylaminoalkyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridines were prepared and found to possess significant antiarrhythmic activity. Hydrogenation of the dihydro compounds **4** produced the *all-cis*-hexahydro isomers **5** which were consistently active in three assays against induced ventricular arrhythmias. On the other hand, the H_9,H_{9a}-trans isomers, which were obtained by basic equilibration of the cis isomers, were less effective.

The indenopyridine ring system was first reported to have antihistaminic properties in 1948.[1] Subsequently, phenindamine (Thephorin, **1**) has been marketed as an



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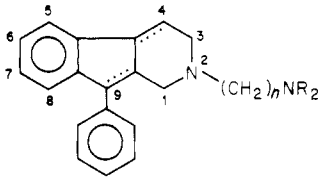

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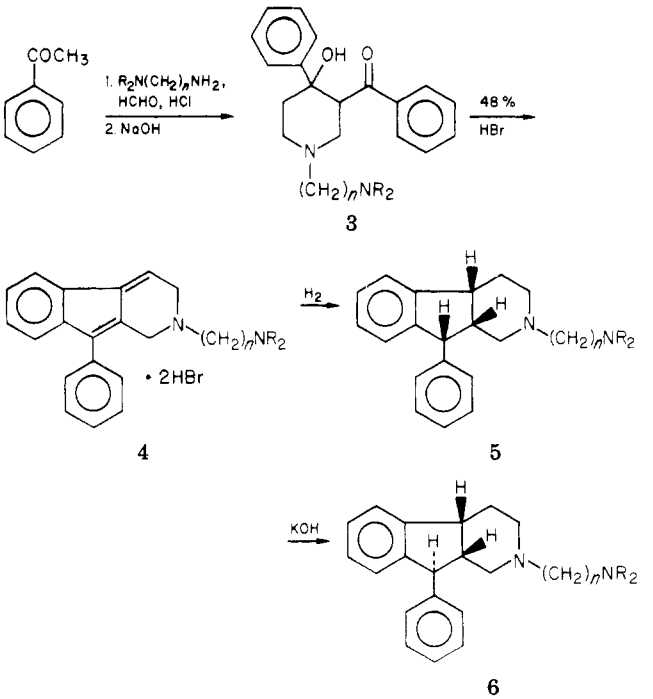
antihistaminic, anticholinergic agent.[2] Others[3] have shown that slight modifications in the N substituent and in the degree of unsaturation of the ring system can lead to antidepressant compounds with properties similar to demethylimipramine. We have prepared compounds such as **2** possessing a dialkylaminoalkyl substituent on the nitrogen and found them to be antiarrhythmic in isolated rabbit heart preparations and in dogs.

Chemistry. A sequence similar to that reported by Plati and Wenner[4] for the preparation of phenindamine (**1**) was used to prepare the cyclized products for which $n = 3$ (see Scheme I). The Mannich reaction of acetophenone, formaldehyde, a dialkylaminopropylamine, and hydrogen chloride was effected in ethanol. It proceeded to give the expected diadduct which cyclized on treatment with base to give the benzoylpiperidinol **3**. Cyclodehydration of **3** with 48% hydrobromic acid at reflux produced the tricyclic diene **4** which was unstable as the free amine and, therefore, was always maintained as the dihydrobromide.

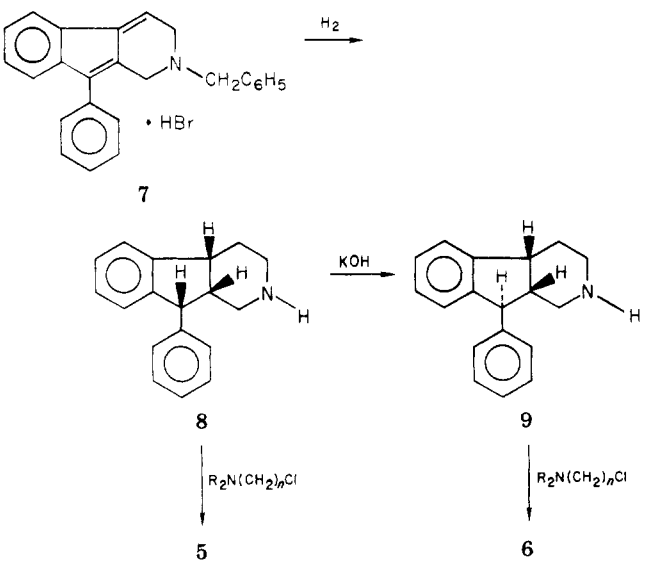
Previous reports[5,6] have established that catalytic reduction of 9-phenyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridines (such as **4**) proceeds stereospecifically to give the sterically crowded *all-cis*-2,3,4,4a,9,9a-hexahydro derivatives. When these all-cis isomers were treated with strong base, the C-9 center epimerized to give the thermodynamically more stable isomer with the C-9 and C-9a protons trans to one another. For the conversion of **4** to the *all-cis*-hexahydro isomers **5**, we used either the method of Canas-Rodriguez,[6] in which palladium was precipitated in situ, or hydrogenation over Pd black. Following treatment of **5** with KOH in refluxing 1-butanol, epimerization at C-9 occurred producing the less crowded H_9,H_{9a}-trans isomers **6**. In all cases the NMR spectra of the free amines of **5** and **6** showed a smaller coupling of the C-9 proton with the C-9a proton for the cis isomer (6 Hz) than for the trans isomer (8 Hz). This is in agreement with the values reported[3,6] for the *N*-alkyl compounds. The C-9 proton of the all-cis isomers was also found slightly farther downfield (ca. 4.47 ppm) than for the H_9,H_{9a}-trans isomer (ca. 4.35 ppm).

The sequence used in Scheme I was not effective for the preparation of the compounds where $n = 2$. In this case the benzoylpiperidines **3** could be prepared as above, but treatment of **3** with 48% hydrobromic acid resulted in decomposition and unidentified tars. Scheme II shows the

Scheme I



Scheme II



reactions that were used for the synthesis of compounds for which $n = 2$. 2-Benzyl-2,3-dihydro-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (**7**) was prepared as previously reported.[6] Hydrogenation of **7** occurred with concomitant cleavage of the benzyl group to give the *all-cis*-hexahydro compound **8**. The trans isomer **9** was obtained by equilibrating **8** with KOH in refluxing 1-butanol.

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Table I

Compd	-R[c]	Salt	n	Mp, °C	Crystn solvent	Formula	Analyses
3a	$-CH_3$		3	113.5-115.5	EtOAc-hexane	$C_{23}H_{30}N_2O_2$	C, H, N
3b	$-CH_2CH_3$		3	76-78	Et_2O	$C_{25}H_{34}N_2O_2$	C, H, N
3c	$-(CH_2)_5-$		3	121-123	$CHCl_3$-Et_2O	$C_{26}H_{34}N_2O_2$	C, H, N
3d	$-CH_3$		2	101-102	Et_2O	$C_{22}H_{28}N_2O_2$	C, H, N
4a	$-CH_3$	$2HBr\cdot 0.5H_2O$	3	[a]	HOAc	$C_{23}H_{29}Br_2N_2O_{0.5}$	C, H, N
4b	$-CH_2CH_3$	$2HBr\cdot 1.5H_2O$	3	136-138	MeOH-Et_2O	$C_{25}H_{35}Br_2N_2O_{1.5}$	C, H, N
4c	$-(CH_2)_5-$	$2HBr\cdot H_2O$	3	178-180	MeOH-Et_2O	$C_{26}H_{34}Br_2N_2O$	C, H, N
5a	$-CH_3$	$2HCl\cdot H_2O$	3	254.5-258	H_2O-acetone	$C_{23}H_{34}Cl_2N_2O$	C, H, N
5b	$-CH_2CH_3$	$2HCl\cdot 0.5H_2O$	3	220-230 dec	EtOH-Et_2O	$C_{25}H_{37}Cl_2N_2O_{0.5}$	C, H, N
5c	$-(CH_2)_5-$	$2HCl\cdot 0.5H_2O$	3	275 dec	MeOH-EtOAc	$C_{26}H_{37}Cl_2N_2O_{0.5}$	C, H, N
5e	$-CH_2CH_3$	$2HBr\cdot 1.5H_2O$	2	132-135	$CHCl_3$-Et_2O	$C_{24}H_{37}Br_2N_2O_{1.5}$	C, H, N
6a	$-CH_3$	$2HCl\cdot 0.5H_2O$	3	268.5-270	H_2O-acetone	$C_{23}H_{33}Cl_2N_2O_{0.5}$	C, H, N
6b	$-CH_2CH_3$	$2HBr\cdot H_2O$	3	117-119	MeOH-Et_2O	$C_{25}H_{38}Br_2N_2O$	C, H; N[b]
6c	$-(CH_2)_5-$	$2HCl\cdot H_2O$	3	225-235 dec	MeOH-Et_2O	$C_{26}H_{38}Cl_2N_2O$	C, H, N
6d	$-CH_3$	2HBr	2	238-240	$CHCl_3$-Et_2O	$C_{22}H_{30}Br_2N_2$	C, H, N
6e	$-CH_2CH_3$	$2HBr\cdot H_2O$	2	135-138	$CHCl_3$-Et_2O	$C_{24}H_{36}Br_2N_2O$	C, H, N

[a] Becomes a glass at 65-70 °C and darkens at $T > 120$ °C. [b] N: calcd, 5.16; found, 5.70. [c] See Scheme I for structures.

Table II. Activity against Induced Ventricular Arrhythmias[a]

Compd	Aconitine (n)[b]	Ouabain			Coronary ligation		
		MED[c]	n[b]	Duration[d]	MED[c]	n[b]	Duration[d]
Quinidine	A (2/2)	7.5 ± 2.9	4/5	>30	12.8 ± 1.7	9/11	23 ± 6
Disopyramide phosphate	A (2/3)	6.6 ± 1.7	3/4	>30	7.0 ± 0.7	22/25	23 ± 3
3a	A (2/2)	I	0/2				
3b	A (2/3)	12.5	2/3	32	7.5	2/2	16
3c	A (2/2)	10	2/2	15	I	0/2	
3d	A (2/2)	I	0/1[e]				
4a	A (2/2)	15	2/2	40	I	1/4[f]	
4b	A (2/2)	20	2/2	35	15	2/2	10
4c	A (2/2)	10	2/2	35	7.5	1/2	12
5a	A (2/2)	10	2/2	15	10	1/2[e]	17.5
5b	A (2/2)	20	2/2	15	12.5	2/2	10
5c	A (2/3)	15	2/2	15	I	0/2	
5e	A (2/2)	10	2/2	25	12.5	2/2	12.5
6a	A (2/2)	I	0/2				
6b	[g]	15	2/2	19	[g]		
6c	A (2/2)	10	2/2	30	L		
6d	A (2/2)	20	2/2	17	I	0/2	
6e	A (2/2)	I	1/2				
7	A (2/2)	15	2/3	17	I	0/2	
8	A (2/2)	17.5	2/3	15	15	1/2	12.5
9	A (2/2)	I	1/3				

[a] Ratings: active (A), inactive (I), or lethal (L) under the test conditions described in the Experimental Section. [b] n = number of tests active/number of tests. [c] Activity expressed as the average minimum effective dose (mg/kg) in the intact dog. [d] Minutes. [e] L 1/2. [f] L 1/4. [g] Not tested.

Treatment of **8** or **9** with a dialkylaminoethyl chloride gave compounds **5** and **6** for which $n = 2$. Details of the compounds are summarized in Table I.

Biological Results. The results from testing these compounds and two standards (disopyramide phosphate[7] and quinidine) in three assays for antiarrhythmic activity are given in Table II. In the assay against an aconitine-induced ventricular arrhythmia in the isolated rabbit heart,[8] a compound was rated active if it caused a 50% or greater reduction in the ventricular rate for drug concentrations up to 40 mg/L. Active compounds were then assayed against an ouabain-induced ventricular arrhythmia in the intact anesthetized dog.[9] A compound was rated active if there was a return to normal sinus rhythm for a period of 15 min or more in half or more of the dogs tested at a dose of 20 mg/kg or less. Finally, compounds found active in the second assay were tested against a ventricular arrhythmia induced by the Harris two-stage coronary ligation.[10] They were rated active if a 25% or greater reduction in ectopic beats was observed for at least 10 min in half or more of the dogs tested.

All compounds tested were found to be active in the assay against the aconitine-induced ventricular arrhythmia including the noncyclized compounds **3**. Of the cyclized compounds the dihydro derivatives **4** and the *all-cis*-hexahydro derivatives **5** were the most consistently active in all three assays. The H_9,H_{9a}-trans isomers **6** were not as generally active as the all-cis compounds.

The parent *all-cis*-hexahydro compound having no substituent on the nitrogen (**8**) was also active in all three assays, indicating that the basic indenopyridine ring system has significant antiarrhythmic activity. The H_9,H_{9a}-trans compound **9** was not active against the ouabain-induced ventricular arrhythmia. Substitution at the 2 position with a 2-dialkylaminoalkyl group generally produced compounds with activity greater than the parent indenopyridines (**5** vs. **8** and **4** vs. **7**). The length of the side chain did not significantly affect the activity (**5e** vs. **5b**). The results indicate that the 2-dialkylaminoalkylindenopyridines possess antiarrhythmic activity similar to but less potent than the standard drugs.

Experimental Section

NMR (Varian A-60D), IR (Beckman IR-12), and UV (Beckman DK2) spectra where applicable were consistent with all structures. Analytical results as indicated by symbols for the elements were

within 0.4% of the theoretical values. Melting points were determined in open capillary tubes in a Mel-Temp apparatus or on a Fisher-Johns hot stage and are uncorrected.

1-(3-Dimethylaminopropyl)-3-benzoyl-4-hydroxy-4-phenylpiperidine (3a). A mixture of 10.2 g (0.10 mol) of dimethylaminopropylamine, 17 mL (0.20 mol) of concentrated HCl, 24.0 g (0.20 mol) of acetophenone, and 12.0 g (0.40 mol) of paraformaldehyde in 25 mL of ethanol was stirred under reflux for 7 h and left standing at ambient temperature overnight. The solvents were removed under reduced pressure and the residue was partitioned between H_2O and ethyl acetate. The aqueous portion was made alkaline with 25 mL of 25% NaOH, stirred for several hours, and extracted with ether. The extracts were washed with H_2O and dried over anhydrous $MgSO_4$. Removal of the solvent gave 27.4 g of a crude tan solid that was recrystallized from EtOAc–hexane yielding 11.9 g (33%) of a white powder. A second recrystallization produced an analytical sample of white crystals: mp 113.5–115.5 °C; IR ν ($CHCl_3$) 1669 and 3475 cm^{-1}. Anal. C, H, N.

1-(3-Diethylaminopropyl)-3-benzoyl-4-hydroxy-4-phenylpiperidine (3b). Paraformaldehyde (60 g, 2 mol) and acetophenone (120 g, 1.0 mol) were added to a solution of 65 g (0.5 mol) of diethylaminopropylamine in 250 mL of approximately 4 M ethanolic HCl. The mixture was stirred under reflux for 24 h and stripped under reduced pressure, and the residue was partitioned between H_2O and ether. The aqueous solution was basified to pH 12 with 50% NaOH and stirred at ambient temperature for 2.5 h. The mixture was extracted with ethyl acetate, washed with H_2O, and dried over anhydrous $MgSO_4$. Removal of the solvent gave an oil that was dissolved in ether. On concentrating the ether solution 37.5 g (19%) of white crystals separated: mp 76–78 °C; IR ν ($CHCl_3$) 1670 and 3480 cm^{-1}. Anal. C, H, N.

1-[3-(1-Piperidinopropyl)]-3-benzoyl-4-hydroxy-4-phenylpiperidine (3c) was prepared by a method similar to **3b**, producing white crystals ($CHCl_3$–ether): mp 122–123 °C; 74% yield; IR ν ($CHCl_3$) 1670 and 3480 cm^{-1}. Anal. C, H, N.

1-(2-Dimethylaminoethyl)-3-benzoyl-4-hydroxy-4-phenylpiperidine (3d) was prepared as described for **3b**, producing white crystals which were recrystallized from ether (14%): mp 101–102 °C; IR ν ($CHCl_3$) 1670 and 3480 cm^{-1}. Anal. C, H, N.

2,3-Dihydro-2-(3-dimethylaminopropyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (4a). A mixture of 15.1 g (41.2 mmol) of **3a** in 75 mL of 48% HBr was stirred and gradually warmed to 120 °C for 3.5 h. Water was added and the solvent was evaporated under reduced pressure. Acetone was added and removed under reduced pressure, and this procedure was repeated until a filterable solid was obtained. The solid was dried, yielding 18.7 g of a yellow powder which was recrystallized from acetic acid and washed several times with ether, yielding 16.5 g (80%) of yellow crystals. An analytical sample of the dihydrobromide semihydrate was obtained by drying in vacuo at 110 °C: melting point, becomes a glass at 65–70 °C and decomposes at >120 °C; UV λ_{max}^{MeOH} 242.5 nm (ϵ 27 200), 258 (26 400), 310 (5110), and 320 (4100). Anal. C, H, N.

2,3-Dihydro-2-(3-diethylaminopropyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (4b) was prepared as described for **4a**, producing 48% of the dihydrobromide with 1.5 mol of water of hydration as yellow crystals (MeOH–ether): mp 136–138 °C; UV λ_{max}^{MeOH} 243.5 nm (ϵ 27 900), 259 (27 400), 312 (5500), and 323 (4300). Anal. C, H, N.

2,3-Dihydro-2-[3-(1-piperidinopropyl)]-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (4c) as its dihydrobromide hydrate was prepared in 21% yield following the procedure used for **4a** and yielded yellow crystals (MeOH–ether): mp 178–180 °C; UV λ_{max}^{MeOH} 243.5 nm (ϵ 27 800), 258 (26 500), 311 (5610), and 323 (4400). Anal. C, H, N.

***all-cis*-2,3,4,4a,9,9a-Hexahydro-2-(3-dimethylaminopropyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (5a).** According to the method of Canas-Rodriguez,[6] a solution of 9.0 g (18 mmol) of **4a** in 75 mL of 50% aqueous ethanol was mixed with 0.33 g of palladium(II) chloride and 0.24 g of sodium chloride in 4 mL of water. Then 0.56 g of $NaBH_4$ was added, and the mixture was hydrogenated at 60 °C and 60 psi for 8 h. The catalyst was removed by filtration and the filtrate was concentrated to a thick oil under reduced pressure. The oil was taken up in water, and the solution was made basic with potassium carbonate, extracted with ether, and dried over anhydrous $MgSO_4$. The solvent was evaporated, yielding 6.08 g of a clear oil: NMR ($CHCl_3$) H-9 at 4.48 ppm (d), $J_{9,9a}$ = 6 Hz. The oil was dissolved in 2-propanol and treated with 2-propanolic HCl, yielding a gelatinous precipitate. The solid was washed with several portions of ether, yielding 7.2 g (90%) of an off-white solid. Recrystallization from water–acetone produced white crystals of the dihydrochloride hydrate, mp 254.5–258 °C. Anal. C, H, N.

***all-cis*-2,3,4,4a,9,9a-Hexahydro-2-(3-diethylaminopropyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (5b).** A mixture of 8.32 g (15.1 mmol) of **4b** and 0.8 g of palladium catalyst in 75 mL of 50% ethanol was hydrogenated at 60 psi in a Parr hydrogenator for 2 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in water, basified with K_2CO_3, and extracted with ether. The dried (anhydrous $MgSO_4$) ether solution was treated with 2-propanolic HCl. The salt was recrystallized from EtOH–ether, yielding 5.2 g (77%) of crystals as the dihydrochloride hemihydrate: mp 220–230 °C; NMR ($CDCl_3$) of the free base, H-9 at 4.47 ppm (d), $J_{9,9a}$ = 6 Hz. Anal. C, H, N.

***all-cis*-2,3,4,4a,9,9a-Hexahydro-2-[3-(1-piperidinopropyl)]-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (5c)** as the dihydrochloride hemihydrate was prepared by the procedure detailed for **5b**. Recrystallization from MeOH–ether produced white crystals (53%): mp 275 °C; NMR ($CDCl_3$) of the free base, H-9 at 4.48 ppm (d), $J_{9,9a}$ = 6 Hz. Anal. C, H, N.

***all-cis*-2,3,4,4a,9,9a-Hexahydro-2-(2-diethylaminoethyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (5e).** Diethylaminoethyl chloride (5.43 g, 40 mmol), liberated from the HCl salt in aqueous base, was added slowly to a solution of 2.0 g (8 mmol) of the free amine of **8** and 5 g of triethylamine in 75 mL of chloroform. The mixture was stirred under reflux for 6 h; then it was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was taken up in ether and treated with HBr–HOAc. The salt was recrystallized from $CHCl_3$–ether, yielding 0.9 g of the dihydrobromide (21%) with 1.5 mol of water of hydration: mp 132–135 °C; NMR ($CDCl_3$) of the free base, H-9 at 4.46 ppm (d), $J_{9,9a}$ = 6 Hz. Anal. C, H, N.

***H*$_9$,*H*$_{9a}$-*trans*-2,3,4,4a,9,9a-Hexahydro-2-(3-dimethylaminopropyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (6a).** A solution of 3.28 g (9.8 mmol) of the free amine of **5a** in 65 mL of 25% w/v potassium hydroxide in 1-butanol was stirred at reflux for 18 h. The solvent was partially removed under reduced pressure and the remaining mixture was poured into ice water. The oil that separated out was extracted into ether, washed with water, and dried over anhydrous $MgSO_4$. A TLC of the ether solution (neutral alumina, 10% MeOH–benzene) showed the product was different from **5a**. Removal of the ether gave 3.25 g of an oil that was treated in 2-propanol with 2-propanolic HCl, yielding 3.1 g (76%) of white crystals. Recrystallization from water–acetone produced the dihydrochloride hemihydrate: mp 268.5–270 °C; NMR ($CDCl_3$) of the free base, H-9 at 4.38 ppm (d), $J_{9,9a}$ = 8.5 Hz. Anal. C, H, N.

***H*$_9$,*H*$_{9a}$-*trans*-2,3,4,4a,9,9a-Hexahydro-2-(3-diethylaminopropyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (6b).** Treatment of **5b** with KOH in 1-butanol as described for **6a** produced the free base of **6b**: NMR ($CDCl_3$) H-9 at 4.34 ppm (d), $J_{9,9a}$ = 8 Hz. The amine was taken up in ether and treated with HBr–HOAc, yielding salt that was recrystallized from MeOH–ether producing the dihydrobromide hydrate (12%), mp 117–119 °C. Anal. ($C_{25}H_{38}Br_2N_2O_2$) C, H; N: calcd, 5.16; found, 5.70.

***H*$_9$,*H*$_{9a}$-*trans*-2,3,4,4a,9,9a-Hexahydro-2-[3-(1-piperidinopropyl)]-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (6*c*). 5c** (4.0 g, 8 mmol) was treated with refluxing KOH in 1-butanol as described for **6a**. The salt obtained on treatment with HCl was recrystallized from methanol–ether, producing 3.6 g (97%) of the dihydrochloride hydrate: mp 225–235 °C dec; NMR ($CDCl_3$) of the free base, H-9 at 4.34 ppm (d), $J_{9,9a}$ = 8 Hz. Anal. C, H, N.

***H*$_9$,*H*$_{9a}$-*trans*-2,3,4,4a,9,9a-Hexahydro-2-(2-dimethylaminoethyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (6d).** Dimethylaminoethyl chloride (10 g, 92 mmol), liberated from the hydrochloride, was added dropwise to a solution of 3.0 g (12 mmol) of **9** and 5 mL of triethylamine in 50 mL of chloroform. The

mixture was stirred under reflux for 6 h, washed with water, and dried over anhydrous $MgSO_4$. Removal of the solvent gave an oil that was taken up in ether and treated with HBr–HOAc. The salt was recrystallized from chloroform–ether, yielding 1.8 g (31%) of the dihydrobromide: mp 238–240 °C; NMR (Me_2SO-d_6) of the free base, H-9 at 4.35 ppm (d), $J_{9,9a}$ = 8 Hz. Anal. C, H, N.

***H*$_9$,*H*$_{9a}$-*trans*-2,3,4,4a,9,9a-Hexahydro-2-(2-diethylaminoethyl)-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (6e).** Reaction of **9** with diethylaminoethyl chloride as described for the preparation of **6d** produced the dihydrobromide hydrate (13%): mp 135–138 °C; NMR ($CDCl_3$) of the free base, H-9 at 4.38 ppm (d) $J_{9,9a}$ = 8 Hz. Anal. C, H, N.

2-Benzyl-2,3-dihydro-9-phenyl-1*H*-indeno[2,1-*c*]pyridine Hydrobromide (7). This compound was prepared as described for the preparation of **4a**. Recrystallization from methanol–ether produced yellow crystals (91%): mp 189–192 °C (lit.[6] mp 188–190 °C); UV λ_{max}^{MeOH} 243 nm (ε 29 600), 254 (28 100), 310 (5620), 322 (4160). Anal. ($C_{25}H_{22}BrN$) C, H, N.

***all-cis*-2,3,4,4a,9,9a-Hexahydro-9-phenyl-1*H*-indeno-[2,1-*c*]pyridine Hydrobromide (8).** A mixture of 15.4 g (37 mmol) of **7** (·HBr) and 1.5 g of palladium black was hydrogenated at 60 °C and 51 psi in a Parr hydrogenator for 11 h. The catalyst was filtered off and the filtrate was concentrated to give an oil that crystallized as the hemihydrate from chloroform–ether (42%): melting point, softens at 145 °C and melts at 192–195 °C; NMR ($CDCl_3$) H-9 at 4.56 ppm (d), $J_{9,9a}$ = 6 Hz. Anal. ($C_{18}H_{21}BrNO_{0.5}$) C, H, N.

***H*$_9$,*H*$_{9a}$-*trans*-2,3,4,4a,9,9a-Hexahydro-9-phenyl-1*H*-indeno[2,1-*c*]pyridine Hydrochloride (9).** A mixture of 4.0 g (12 mmol) of **8** in 100 mL of 25% (w/v) KOH in 1-butanol was stirred at reflux for 24 h. The solvent was removed under reduced pressure, and the residue was mixed with ice water, extracted with ether, washed with water, and dried over anhydrous $MgSO_4$. The solution was treated with 2-propanolic HCl and the salt was recrystallized from chloroform–ether to yield 0.8 g of **9** (23%): mp 258–260 °C (lit.[3] mp 265–267 °C); NMR (Me_2SO-d_6) H-9 at 4.74 ppm (d), $J_{9,9a}$ = 8 Hz. Anal. ($C_{18}H_{20}NCl$) H, N; C: calcd, 75.64; found, 75.17.

Pharmacology. (a) Assay against Aconitine-Induced Ventricular Arrhythmia. The procedure was essentially that described by Lucchesi[8] but modified in certain particulars. Hearts were obtained from adult albino rabbits of either sex and perfused in apparatus modeled after that devised by Anderson and Craver.[11] The composition of the perfusion solution was the same as Lucchesi's, but the volume was increased to 200 mL and the temperature lowered to 28 °C. Aconitine (ordinarily as the nitrate) was administered as soon as the heart beat was regular and the EKG pattern normal, the dose being so selected as to at least double the rate. Typically, 0.05 mL of 0.1% aconitine nitrate in physiological saline was injected. EKG's were recorded at 5-min intervals after onset of ventricular tachycardia until two successive readings showed stabilization of the rate. Perfusate collected during this time was discarded and replaced with a fresh solution, q.s., 200 mL. Promptly following stabilization, 2 mg of compound dissolved or suspended in 1 mL of physiological saline was mixed with the perfusion solution. Ten minutes later a like amount was introduced, followed after a further 10 min by double the first amount. The final concentration of compound in the perfusion solution was thus 40 mg/L. Recording of EKG's was continued at 5-min intervals throughout this time and for 10 min thereafter. A compound was considered antiarrhythmic if, at any time during the 30 min immediately following initial administration in at least half of a minimum of two tests, a reduction by 50% or more of the rate recorded 10 min after onset of tachycardia was observed.

(b) Assay against Ouabain-Induced Ventricular Arrhythmia.[9] Male mongrel dogs were connected to a physiograph to follow heart and blood action. At the onset of the testing, an initial dose of 40 μg/kg of ouabain was administered intravenously in a saline solution. This was followed 30 min later by a dose of 20 μg/kg of ouabain and, at 15-min intervals, by a dose of 10 μg/kg of ouabain until ventricular arrhythmia occurred and persisted for 20 min. A saline solution of the test compound was then administered intravenously at a dose of 5 mg/kg. If the heart action did not become normal, additional test compound was administered at a dose of 5 mg/kg at 15-min intervals until heart action became normal or until the total dose of test compound administered was 20 mg/kg. A compound was considered antiarrhythmic if it caused a return to normal heart action for a period of 15 min or more in half or more of the dogs tested at a dose of 20 mg/kg or less.

(c) Assay against Ventricular Arrhythmia Induced by Harris Two-Stage Coronary Ligation.[10] The ligation technique involved anesthetizing the animal with 32.5 mg/kg of sodium pentobarbital, administered intravenously, and maintaining respiration mechanically via tracheal intubation while the chest cavity was opened on the left side at the fourth interspace and (1) the artery was tied against a 20-guage hypodermic needle at a point approximately 1 cm from the atrial tip, (2) the needle was removed, (3) 30 min later the artery was completely occluded by ligation, and (4) the opening was closed. On the first postoperative day, if an EKG reveals at least 75% ectopic beats, 5 mg/kg of compound dissolved or suspended at a concentration of 1% in aqueous 0.9% sodium chloride or other physiologically inert vehicle was administered during 5 min via a scalp-vein needle placed in the cephalic vein. EKG's were recorded at 2.5-min intervals, and the drug dose was repeated at 15-min intervals until there was either a reduction in ectopic beats amounting to at least 25% and lasting for a minimum of 10 min or a total drug dose of 20 mg/kg had been administered. A compound was considered antiarrhythmic in this test if the aforesaid reduction was induced in more than half of at least two dogs.

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