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Original paper

Synthesis and anti-arrhythmic activity of cycloalkaneindoles

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Summary — A series of novel functionalized cycloalkaneindoles were synthesized and tested for potential anti-arrhythmic activity. Several compounds displayed moderate activity in the coronary ligated rat artery model. Carbamate **22** and the amino derivative **27** were the most potent analogs. Their anti-arrhythmic activity at a dose of 10 mg/kg, i.v., was greater than that of iprindole and ethmosin.

Résumé — **Synthèse et activité anti-arythmique de cycloalkaneindoles.** *Synthèse d'une série de nouveaux indoles substitués par des cycloalkanes et étude de leur activité anti-arythmique. Plusieurs composés ont une activité modérée vis-à-vis du modèle de la ligature de l'artère coronarienne chez le Rat. Les analogues les plus actifs sont les composés 22 et 27 et leurs effets anti-arythmiques, à une dose de 10 mg/kg, sont supérieurs à ceux de l'iprindole et de l'ethmosine.*

anti-arrhythmic agents / ethmosin / carbamates / coronary ligated rats

Introduction

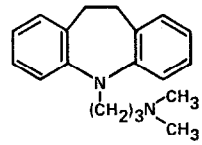
Anti-arrhythmic drugs have been classified on the basis of their mechanism of action. These categories include: Class I: 'quinidine-like' drugs, such as quinidine, lidocaine and disopyramide, act by depressing cardiac conduction; Class II: β-blockers; Class III: agents, such as amiodarone and clofilium, prolong myocardial refractoriness to premature excitation without affecting normal conduction; and Class IV: Ca^{2+}-channel blockers whose main therapeutic action is preventing vasospasm and increasing collateral coronary blood flow which result in limiting the ischemic event itself.

While several anti-arrhythmic agents are clinically used for the treatment of cardiac arrhythmias, some patients fail to respond to treatment. In recent years, synthetic efforts have been devoted to the development of more effective and safer drugs for the treatment of arrhythmias.

The direct quinine-like stabilizing effect of anti-depressants on the cardiac cell membrane [1] and the perception that they are better tolerated than most available anti-arrhythmic agents led to numerous clinical and experimental investigations into their use as anti-arrhythmic agents.

It has been reported that the tricyclic anti-depressant imipramine **1** and the phenothiazine ethmosin **2** both exhibited anti-arrhythmic efficacy in clinical trials relative to more typical Class I agents [2, 3] and the latter is being developed as an anti-arrhythmic agent.

Iprindole **3** is a typical tricyclic anti-depressant currently in clinical use [4], which possesses a more favorable cardiovascular profile than imipramine. Unlike imipramine, iprindole is not anti-cholinergic, does not inhibit norepinephrine re-uptake and has no proarrhythmic history [5].



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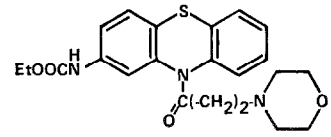

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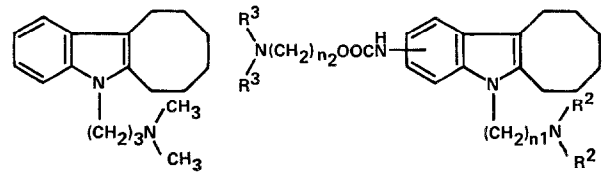
Recently, studies in our laboratories by Colatsky *et al.* [6] have shown that iprindole possesses anti-arrhythmic activity in several acute experimental models of arrhythmic activity at a higher dose than that which produces anti-depressant activity. The potential for iprindole and other classical anti-depressants to provoke severe cardiac arrhythmias [7, 8] prompted us to design molecular hybrids between the effective anti-arrhythmic agent ethmosin **2** and iprindole **3** and to examine their potential anti-arrhythmic activity.

This led to the synthesis of hybrid molecules **4** which contain, in addition to the iprindole carbon skeleton, the substituted carbamate functionality which existed in ethmosin.



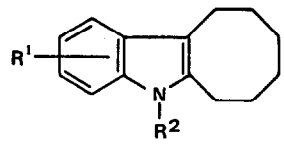
3 **4**

Chemistry

Literature procedures were adopted for the preparation of various nitrocyclooct[*b*]indoles **5**—**8**. Scheme 1 illustrates general synthetic pathways for the preparation of cyclooctindole carbamates **17**—**25**. The reaction of **5**—**8** with dialkylaminoalkyl halide afforded the corresponding nitro-*N*-alkylated derivatives **9**—**13**. Reduction of **9**—**13** in absolute ethanol in the presence of Pd/C catalyst gave the corresponding amino derivatives **14**—**16**. Acylation of **14**—**16** with ethyl chloroformate in acetonitrile in the presence of triethylamine afforded carbamates **17**—**21** in reasonable yields. The reaction of the amino compounds with trichloromethylchloroformate[l] (TCF) in methylene chloride in the presence of triethylamine afforded the isocyanate intermediates which were subsequently trapped *in situ via* their reaction with the appropriately substituted dialkylaminoethanol to afford target compounds **22**—**25** in 35—51% yields (Table I).

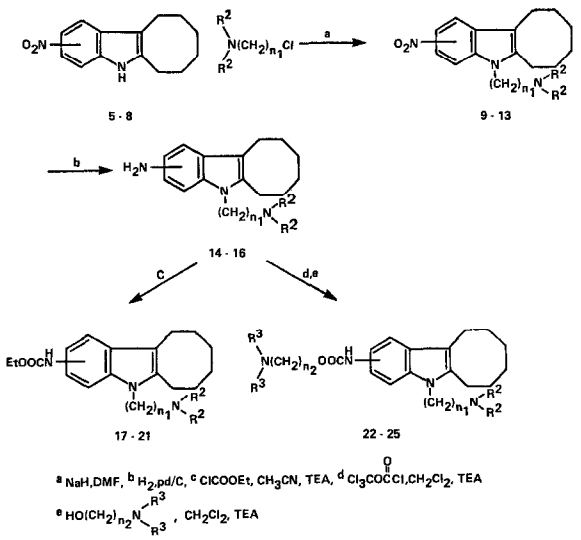
Scheme 2 describes a synthetic route for the preparation

Table I. Substituted cyclooctindoles.

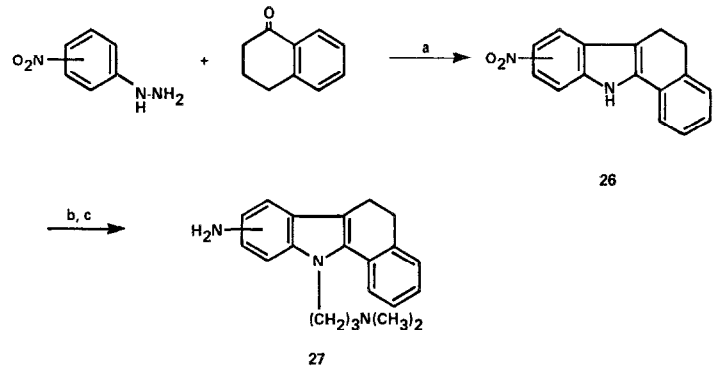


Compound	R^1	R^2	% yield	mp. °C	formula[a]	dose (mg/kg)	% VF[b]	% Dead	n[c]	Score[d]
9	1–NO_2	$-(CH_2)_3NMe_2$	90	196-199	$C_{19}H_{27}N_3O_2 \cdot HCl$	10	67	67	5	42
10	2–NO_2	$-(CH_2)_3NMe_2$	89	233-235	$C_{19}H_{27}N_3O_2 \cdot HCl$	5 10	80 40	60 0	5 5	42 22
11	3–NO_2	$-(CH_2)_3NMe_2$	79	238-239	$C_{19}H_{27}N_3O_2 \cdot HCl$[f]	10	60	40	5	32
12	4–NO_2	$-(CH_2)_3NMe_2$	91	174-176	$C_{19}H_{27}N_3O_2 \cdot HCl$	10	20	20	5	18
13	1–NO_2	$-(CH_2)_2-N\bigcirc O$	83	192-196	$C_{20}H_{27}N_3O_3$[e]$\cdot HCl$[f]	10	100	100	5	50
14	1–NH_2	$-(CH_2)_3NMe_2$	76	202-206	$C_{19}H_{29}N_3 \cdot 2HCl$[g]	10	60	60	5	33
15	2–NH_2	$-(CH_2)_3NMe_2$	80	287-289	$C_{19}H_{29}N_3 \cdot 2HCl$	10	20	20	5	
16	4–NH_2	$-(CH_2)_3NMe_2$	75	276-278	$C_{19}H_{29}N_3$[h]$\cdot 2HCl$	10	60	20	5	30
17	1–NHCOOEt	$-(CH_2)_3NMe_2$	65	119-123	$C_{22}H_{33}N_3O_2 \cdot HCl$	10	60	60	5	38
18	2–NHCOOEt	$-(CH_2)_3NMe_2$	26	234-236	$C_{22}H_{33}N_3O$[2]$\cdot HCl$	3 10	69 25	69 25	13 4	37 25
19	3–NHCOOEt	$-(CH_2)_3NMe_2$	35	119-121	$C_{22}H_{33}N_3O_2 \cdot HCl$	10	40	20	5	30
20	4–NHCOOEt	$-(CH_2)_3NMe_2$	59	192-194	$C_{22}H_{33}N_2O_2$[i]$\cdot HCl$[f]	10	60	40	5	21
21	1–NHCOOEt	$-(CH_2)_2-N\bigcirc O$	46	230-233	$C_{23}H_{33}N_3O_3 \cdot HCl$[f]	10	60	40	5	30
22	1–$NHCO_2(CH_2)_2NEt_2$	$-(CH_2)_3NMe_2$	51	220-224	$C_{26}H_{42}N_4O_2$[j]$\cdot 2HCl$[k]	10	20	0	5	12
23	2–$NHCO_2(CH_2)_2NMe_2$	$-(CH_2)_3NMe_2$	39	201-205	$C_{24}H_{38}N_4O_4 \cdot 2HCl$[k]	10 15	80 75	60 25	5 4	40 34
24	2–$NHCO_2(CH_2)_2NEt_2$	$-(CH_2)_3NMe_2$	59	188-191	$C_{26}H_{42}N_4O_2 \cdot 2HCl$[k]	10	40	20	5	26
25	1–$NHCO_2(CH_2)_2NEt_2$	$-(CH_2)_2-N\bigcirc O$	35	168-171	$C_{27}H_{42}N_4O_3 \cdot 2HCl$	10	60	40	5	34
Iprindole	H	$-(CH_2)_3NMe_2$				3 10	50 11	50 11	8 9	29 16
Ethmosin	Phenothiazine Structure					3 10	40 I	20 –	5 5	26 –

[a]All compounds had elemental analyses (C, H, N) within ±0.4% of the theoretical values.
[b]Ventricular fibrillation.
[c]Number of animals used.
[d]Weighted score reflects severity of observed arrhythmia.
[e]N: Calcd., 10.4; found, 9.99.
[f]Hemihydrate.
[g]Dihydrate.
[h]N: Calcd., 11.28; found, 11.82.
[i]C: Calcd., 63.37; found, 63.91. N: Calcd., 8.46; found, 10.47.
[j]N: Calcd., 10.50; found, 11.19.
[k]Hydrate.
[l]Toxic.



Scheme 1.



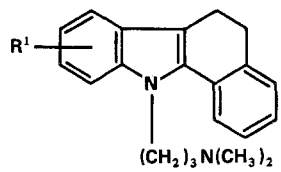
Scheme 2.

of the tetracyclic analogs in which nitrophenylhydrazine was reacted with 1-tetralone under typical Fisher's indole synthesis conditions to afford the desired nitroindole derivative **26**. The nitro compound was then reduced by catalytic hydrogenation to afford **27** as shown in Scheme 1 (Table II).

Results and Discussion

All compounds were tested for anti-arrhythmic or anti-ischemic activity in open-chest anesthetized rats subjected to sudden ligation of a major coronary artery. This procedure provokes severe ventricular arrhythmias terminating in ventricular fibrillation and death in approximately 73% of animals given vehicle only. Data were analyzed based

Table II. Substituted carbazoles.



Compound	R^1	yield %	mp. °C	formula[a]	dose (mg/kg)	% VF[b]	% Dead	n[c]	Score[d]
26	9-NO_2	83	222-224	$C_{21}H_{23}N_3O_2 \cdot HCl$[e]	10	40	40	5	19
27	9–NH_2	90	119-121	$C_{21}H_{23}N_3O_2 \cdot 2HCl$[f]	10	20	20	5	4
Iprindole					3	50	50	8	29
					10	11	11	9	16
Ethmosin					3	40	20	5	26
					10	g	–	5	–

[a]All compounds had elemental analyses (C, H, N) within ±0.4% of the theoretical values.
[b]Ventricular fibrillation.
[c]Number of animals used.
[d]Weighted score reflects severity of observed arrythmia.
[e]Hemihydrate.
[f]Hydrate.
[g]Toxic.

on incidence and severity of the occlusion arrhythmia. Relative activity in a series of compounds was further analyzed by assigning a weighted score according to the severity of arrhythmia observed. For the purpose of these coronary ligation (CL) experiments, the percent ventricular fibrillation (VF), expressed as a percentage of the animals employed, was obtained for the purpose of comparison with the control rate (73%) in vehicle-treated animals (Tables I and II).

Among the nitrocyclooctindole compounds tested in the coronary ligated rat procedure at a dose of 10 mg/kg, i.v., compounds **11** and **12** were the most active anti-arrhythmic agents, reducing the incidence of VF from 5/7 in control rats to 3/5 and 1/5, respectively, with drug pre-treatment. Compared to the nitrocyclooctindoles, amino-cyclooctindoles **14—16** demonstrated a weak anti-arrhythmic effect. Of all carbamates tested at 10 mg/kg, i.v., the diethyl-amino carbamate derivative **22** appeared to exert the greatest anti-arrhythmic effect, reducing the incidence of VF from 5/7 in control rats to 1/5 with drug pre-treatment. Like compound **22**, the aminotetracyclic derivative **27** demonstrated good activity in the coronary ligated rat reducing the incidence of VF from 5/7 in control to 0/5 with 10 mg/kg, i.v. drug pre-treatment.

In summary, we have synthesized several tri- and tetracyclic cycloalkaneindoles that demonstrated interesting good activity in the coronary ligated rat procedure. Compounds **22** and **27** are the most potent analogs. Their anti-arrhythmic effect at a dose of 10 mg/kg, i.v., is greater than that of iprindole and ethmosin and additional preclinical pharmacological evaluation is needed to define further the spectrum and possible mechanism of anti-arrhythmic activity of these compounds compared to ethmosin.

Experimental protocols

Chemistry

Melting points were determined on a Thomas—Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on Varian XL-300 and XL-100 instruments. Mass spectra were recorded with a Kratos MS-25 instrument. IR spectra were recorded with a Perkin—Elmer 299 infrared spectrophotometer. Elemental analyses were performed with a Perkin—Elmer Model 240 elemental analyzer by the Analytical Section.

*6,7,8,9,10,11-Hexahydro-1-nitro-5*H*-cyclooct*[b]*indole and 6,7,8,9,10,11-hexahydro-3-nitro-5*H*-cyclooct*[b]*indole* **5**

3-Nitrophenylhydrazine hydrochloride (50 g, 0.26 mol) and cyclooctanone (32.2 g, 0.25 mol) were refluxed in 400 ml of glacial acetic acid for 6 h. The solution was allowed to cool and the separated solid was filtered, washed with water and recrystallized from absolute ethanol to afford 20 g (31% yield) of 6,7,8,9,10,11-hexahydro-1-nitro-5*H*-cyclooct[*b*]indole; mp: 189—191°C. Anal. $C_{14}H_{16}N_2O_2$ (C, H, N).

The mother liquor was concentrated and diluted with 200 ml of cold water. The separated solid was filtered, dried and recrystallized from ether to afford 7 g (11.5% yield) of 6,7,8,9,10,11-hexahydro-3-nitro-5*H*-cyclooct[*b*]indole **6**; mp: 119—120°C. Anal. $C_{14}H_{16}N_2O_2$ (C, H, N).

Compounds **7** and **8** were prepared following the procedures described above for the preparation of compounds **5** and **6** *via* the reaction of cyclooctanone and the appropriately substituted nitrophenylhydrazine (Table I).

*6,7,8,9,10,11-Hexahydro-*N,N*-dimethyl-1-nitro-5*H*-cyclooct*[b]*indole-5-propanamine, hydrochloride* **9**

To a stirred mixture of sodium hydride (4.6 g, 0.19 ml) in 60 ml of dry dimethylformamide (DMF) was added 6,7,8,9,10,11-hexahydro-1-nitro-5*H*-cyclooct[*b*]indole (24.4 g, 0.1 mol) over a period of 30 min. To this solution was added, while stirring, a solution of *N,N*-dimethyl-aminopropyl chloride hydrochloride (15.8 g, 0.1 mol) in 60 ml of DMF. The reaction mixture was stirred overnight at 80°C. DMF was removed under reduced pressure and the residue was extracted with 3 × 500 ml of methylene chloride. The methylene chloride extracts were combined, washed with water and dried. Evaporation of the methylene chloride afforded 30 g (90% yield) of the title compound as a red oil. The oil was converted into the hydrochloride salt using ether saturated with HCl and was recrystallized from ethanol, mp: 196—199°C (EtOH). Anal. $C_{19}H_{27}N_3O_2HCl$ (C, H, N). Compounds **10—12** were prepared following the above procedure for the preparation of **9** using the appropriately substituted nitrocyclooct[*b*]indole.

*6,7,8,9,10,11-Hexahydro-5-[2-(4-morpholinyl)ethyl]-1-nitro-5*H*-cyclooct-*[b]*indole-5-propanamine, hydrochloride* **13**

To a stirred mixture of sodium hydride (4.6 g, 0.19 mol) in 60 ml of dry DMF was added 6,7,8,9,10,11-hexahydro-1-nitro-5*H*-cyclooct-[*b*]indole (24.4 g, 0.1 mol) over a period of 30 min. To this solution was added, while stirring, a solution of morpholinoethylchloride hydrochloride (18.5 g, 0.1 mol) in 60 ml of DMF. The reaction mixture was stirred overnight at 80°C. DMF was removed under reduced pressure and the residue was extracted with 3 × 500 ml of methylene chloride. The methylene chloride extracts were combined, washed with water and dried. Evaporation of the methylene chloride afforded 30 g (90% yield) of the title compound as a red oil. The oil was converted into the hydrochloride salt using ether saturated with HCl and was recrystallized from ethanol, mp: 192—196°C. Anal. $C_{20}H_2N_{37}O_3HCl$ (C, H, N).

*1-Amino-6,7,8,9,10,11-hexahydro-*N,N*-dimethyl-5*H*-cyclooc*[b]*indole-5-propanamine dihydrochloride* **14**

6,7,8,9,10,11-Hexahydro-*N,N*-dimethyl-1-nitro-5H-cyclooct[*b*]indole-5-propanamine (6 g, 0.01 mol) was dissolved in 50 ml of absolute ethanol. To this solution was added 1 g of 10% Pd/C and the reaction mixture was hydrogenated for 60 min (no further hydrogen uptake was observed). The catalyst was filtered and the ethanolic solution was evaporated under reduced pressure.

The dark residue was converted into the dihydrochloride salt; mp: 202—206°C (EtOH). Anal. $C_{19}H_{29}N_3 \cdot 2\,HCl \cdot 2\,H_2O$ (C, H, N). Similarly, compounds **15** and **16** were prepared *via* reduction of the appropriately substituted nitrocyclo[*b*]indoles.

*[5-[3-(Dimethylamino)propyl]-6,7,8,9,10,11-hexahydro-5*H*-cyclooct*[b]*-indol-1-yl]-carbamic acid ethyl ester, hydrochloride* **17**

To a stirred solution of 1-amino-6,7,8,9,10,11-hexahydro-*N,N*-dimethyl-5*H*-cyclooct[*b*]indole-5-propanamine (5 g, 0.017 mol) in 50 ml of acetonitrile were added 5 ml of triethylamine and 5 ml of ethylchloroformate (5.6 g, 0.05 mol). The reaction mixture was stirred overnight at room temperature. The solvent was removed and the residue was chromatographed on silica gel (300 g) using 50% methanol/ethylacetate to afford 1.8 g (26% yield) of the title compound as a thick oil which was converted into the hydrochloride salt; mp: 119—123°C. Anal. $C_{22}H_{33}N_3O_2 \cdot HCl$ (C, H, N, Cl). In a similar manner, compounds **18—20** were prepared using the appropriate amino derivative as the starting material.

*6,7,8,9,10,11-Hexahydro-[5-[2-(4-morpholinyl)ethyl]-5*H*-cyclooct*[b]*indol-1-yl]-carbamic acid ethyl ester, hydrochloride* **21**

To a stirred solution of 6,7,8,9,10,11-hexahydro-1-amino-5*H*-cyclooct-[*b*]indole-5-morpholinopropane (2.2 g, 0.006 mol) in 70 ml of methylene chloride was added 1 ml of trichloromethylchloroformate. The reaction mixture was stirred for 4 h at room temperature and to this mixture were added 5 ml of absolute ethanol and 2 ml triethylamine and stirring was continued for 16 h. The methylene chloride layer was washed with water, dried and evaporated under reduced pressure. The residue was dissolved in ether and to this solution was added an ether saturated with HCl solution. The separated solid was recrystallized from ethanol—ether (1:1) to afford 1.5 g of the title compound (46% yield) as the hydrochloride salt; mp: 230—233°C (1:1, EtOH—ether). Anal. $C_{23}H_{33}N_3O_3 \cdot HCl \cdot 1/2\,H_2O$ (C, H, N, Cl).

[5-[3-(Dimethylamino)propyl]-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]-indol-1-yl]-carbamic acid 2-(diethylamino)ethyl ester, dihydrochloride **22**
Trichloromethylchloroformate (1 g, 0.005 mol) was added dropwise to a solution of 1-amino-5*H*-6,7,8,9,10,11-hexahydro-*N,N*-dimethyl-cyclooct[*b*]indole-5-propanamine (2.9 g, 0.01 mol) in 60 ml of dry dioxane. The reaction mixture was stirred at 60°C for 4 h, cooled and dioxane was evaporated under reduced pressure. The resulting residue was dissolved in 70 ml of methylene chloride and to this solution was added, while stirring, *N,N*-diethylaminoethanol (2.3 g, 0.02 mol) and the reaction was stirred overnight. The methylene chloride was washed with water, dried and evaporated. The residue was converted into the dihydrochloride salt; mp: 220—224°C (EtOH). Anal. $C_{26}H_{42}N_4O_2 \cdot 2\ HCl \cdot H_2O$ (C, H, N, Cl).

Compounds **23** and **24** were prepared following the procedure adopted for the synthesis of carbamate **22** using appropriately substituted aminocyclooct[*b*]indoles as the starting materials.

6,7,8,9,10,11-Hexahydro-[5-[2-(4-morpholinyl)ethyl]5H-cyclooct[b]indol-1-yl]-carbamic acid 2-(diethylamino)ethyl ester, dihydrochloride **25**
Trichloromethylchloroformate (1 g, 0.005 mol) was added dropwise to a solution of 1-amino-5*H*-6,7,8,9,10,11-hexahydro-cyclooct[*b*]-indole-5-morpholinoethane (2.9 g, 0.01 mol) in 60 ml of dry dioxane. The reaction mixture was stirred at 60°C for 4 h, cooled and dioxane was evaporated under reduced pressure. The resulting residue was dissolved in 70 ml of methylene chloride and to this solution was added, while stirring, *N,N*,-diethylaminoethanol (2.3 g, 0.02 mol) and the reaction was stirred overnight. The methylene chloride was washed with water, dried and evaporated. The residue was converted into the dihydrochloride salt; mp: 168—171°C (1:1, EtOH—ether). Anal. $C_{27}H_{42}N_4O_3 \cdot 2\ HCl$ (C, H, N, Cl).

9-Nitro-5,6-dihydro-1[H]*benzo[α]carbazole* **26**
3-Nitrophenylhydrazine hydrochloride (50 g, 0.26 mol) and 1-tetralone (48.3 g, 0.25 mol) were refluxed in 400 ml of glacial acetic acid for 6 h. The solution was allowed to cool and the separated solid was filtered, washed with water and recrystallized from absolute ethanol to afford 50 g (83% yield) of 9-nitro-5,6-dihydro-1[*H*]benzo[α]carbazole; mp: 222—224°C.

*9-Amino-5,6-dihydro-*N,N*-dimethyl-*1[H]*benzo[α]carbazole-11-propanamine* **27**
To a stirred mixture of sodium hydride (4.6 g, 0.19 mol) in 60 ml of dry DMF was added 9-nitro-5,6-dihydro-1[*H*]benzo[α]carbazole (23.2 g, 0.1 mol) over a period of 30 min. To this solution was added, while stirring, a solution of *N,N*,-dimethylaminopropyl chloride hydrochloride (15.8 g, 0.1 mol) over a period of 30 min. To this solution was added, while stirring, a solution of *N,N*-diethylaminopropyl chloride hydrochloride (15.8 g, 0.1 mol) in 60 ml of DMF. The reaction mixture was stirred overnight at 80°C. DMF was removed under reduced pressure and the residue was extracted with 3 × 500 ml of methylene chloride. The methylene chloride extracts were combined, washed with water and dried. Evaporation of the methylene chloride afforded 40 g (90% yield) of the title compound as an orange solid; mp: 119—121°C (EtOH). Anal. $C_{21}H_{23}N_3O_2$ (C, H, N).

The above nitrocarbazole (6 g, 0.01 mol) was dissolved in 50 ml of absolute ethanol. To this solution was added 1 g of 10% Pd/C and the reaction mixture was hydrogenated for 2 h (no further hydrogen uptake was observed). The catalyst was filtered and the ethanolic solution was evaporated under reduced pressure. The dark residue was converted into the dihydrochloride salt; mp: 286—288°C (EtOH). Anal. $C_{21}H_{25}N_3\ HCl \cdot H_2O$ (C, H, N).

Pharmacology

The compounds were evaluated for anti-arrhythmic or anti-ischemic activity in open-chest anesthetized rats subjected to sudden ligation of a major coronary artery [10, 11]. Rats weighing between 400—500 g were anesthetized with 35—40 mg/kg of sodium pentobarbital i.p. Rats were close-clipped on the neck and left side prior to cannulation of the jugular vein and tracheotomy. In some experiments, a catheter was introduced into the carotid artery for measurement of arterial blood pressure. Respiration was provided by a Harvard Model 681 respirator at a rate of approximately 55/min and a volume of 4 cc/cycle. The rat was then placed upon its right side and the heart was exposed by making an incision and separating the ribs. 4-0 silk on a taper RB-1 needle was passed under the left anterior descending coronary artery (LAD) at a location just under the tip of the left atrial appendage. The suture was left to be tied upon occlusion. Lead II ECG and cardiotachometer output were recorded on a Beckman R612.

The rat was allowed to stabilize for several minutes before the administration of drug *via* the cannulated jugular vein. Compounds were suspended in carbowax, with total dose volumes kept below 0.20—0.25 ml. 15 min after dosing, the LAD was occluded by tying the suture. This procedure provokes several ventricular arrhythmias, terminating in ventricular fibrillation and death in a majority of animals (73%) given vehicle only. Data were analyzed based on incidence and severity of the occlusion arrhythmia. Relative activity in a series of compounds was further analyzed by assigning a weighted score according to the severity of the arrhythmia observed.

For the purpose of these ligation (CL) experiments, the percent ventricular fibrillation, expressed as a percentage of the animals employed, was obtained for the purpose of comparison with the control rate of 73% in vehicle-treated animals.

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