and the reaction mixture was decomposed with wet THF. The solution was filtered and the solvents were removed.

α-(2-Piperidyl)-1-naphthalenemethanols. PtO_2 (200 mg) was added to α-(2-pyridyl)-1-naphthalenemethanol (2 g) dissolved in THF–AcOH (50:50). The mixture was hydrogenated at room temperature and 45 lbs of H_2 pressure for 2.5 hr. The catalyst was removed, and the solvents were evaporated. The product was crystallized as the acetate.

4-(4-Chlorophenyl)-5,7-dichloro-1-methylnaphthalene (26). 5,7-Dichloro-3-methyl-1-indanone[11] (13 g) was added to a Grignard reagent prepared from 4-bromochlorobenzene (16 g) and Mg (2 g). The reaction mixture on usual work-up gave 15 g of material, which was mixed with P_2O_5 (3 g) and distilled [ca. 160–180° (0.1 mm)]. The distillate was dissolved in Et_2O and dried (Na_2SO_4), and Et_2O was removed. The residue was distilled at 170–175° (0.11 mm). The distillate (14 g) was a mixture of **22** and **23** (NMR). This mixture dissolved in cold (0°) CH_2Cl_2 (60 ml) was added to a solution of K (2.8 g) in *tert*-BuOH (30 ml). The reaction mixture was stirred overnight at room temperature, and the solvents were removed. The residue was dissolved in petroleum ether (bp 30–60), washed with H_2O, and dried. Petroleum ether was removed, and the residue was distilled [174–176° (0.15–0.20 mm)], yielding 12 g of a mixture of **24** and **25** (NMR). This mixture was refluxed with HCOOH (97%, 200 ml) for 1 week and cooled. A gummy solid was separated and washed with water and $NaHCO_3$ solution, yielding 4 g of product, **26**. The procedure is based on Bavin's work.[16]

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Structure–Activity Relationships of Antiarrhythmic 6-Substituted Decahydroisoquinolines

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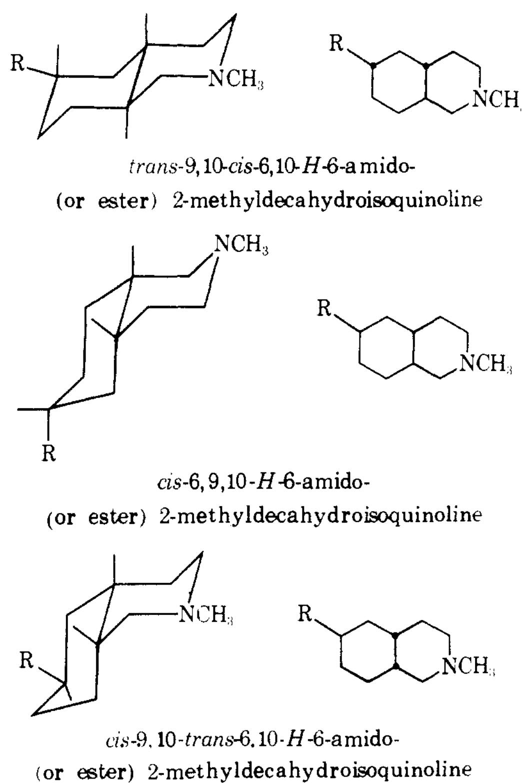
A series of diastereoisomeric 6-benzoyloxy- and 6-benzamido-2-methyldecahydroisoquinolines has been prepared and screened for antiarrhythmic effectiveness. In a continuation of our interest in identifying significant physicochemical properties of antiarrhythmic decahydroisoquinolines, octanol–water partition coefficients and pK_a values have been determined for each member of the series. In general, antiarrhythmic activities superior to that of quinidine were observed. From a general structure–activity viewpoint, substitutions possessing greater lipophilicities produced compounds with superior antiarrhythmic properties. However, there appears to be optimal lipophilic character beyond which increased lipophilicity results in a decrease in antiarrhythmic potency. No discernible correlations with pK_a values were evident. As noted in our earlier studies the esters were more potent and more lipophilic than the corresponding amides. No obvious correlations with stereochemistry were found; however, in three pairs of diastereoisomers, the more lipophilic cis compounds were found to be the superior isomers. A surprisingly high potency was noted with a tetrahydroisoquinoline benzamide—a finding unexpected from our earlier work. The 3,4-dichlorobenzamido grouping appeared to be the substituting moiety for optimal antiarrhythmic effectiveness.

In a continuation of the established interest of our laboratories[1] in the significance of stereochemical factors in the mechanism of action of antiarrhythmic decahydroisoquinolines, an investigation of the effects of various substitutions at the 6 position of diastereoisomeric 2-methyldecahydroisoquinolines is reported. In an earlier publication[1b] we noted the similarity of the substituted decahydroisoquinolines investigated in our laboratories to the D and E rings of reserpine, which may be considered to be a 5,6,7-trisubstituted *cis*-decahydroisoquinoline.

[†] The work reported constitutes a segment of the dissertation submitted by R.R.T. to the University of Tennessee Center for the Health Sciences in partial fulfillment of the Doctor of Philosophy degree requirements in medicinal chemistry.

The synthesis of both 6-hydroxy- and 6-amino-2-methyldecahydroisoquinolines was desired. In spite of the previous reports of the synthesis of the 6-hydroxy compounds,[2] a more suitable method for the production of both desired compounds appeared to be via the previously unreported 6-amino-2-methyldecahydroisoquinolines (I), which on deamination with nitrous acid would stereospecifically yield the 6-hydroxy compounds, thereby limiting the separation of diastereoisomers to a single step. An efficient synthetic route for the preparation of the difficult to obtain 6-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline was devised; subsequent catalytic hydrogenation of the compound yielded the desired 6-amino-2-methyldecahydroisoquinolines.[3] The mixture of diastereoisomers of I was separated by fractional crystallization of the acetamides and their stereochemistry determined.[3] Assignment of stereochemistry was in part obtained from the deamination of the amines to the alcohols which, as noted above, conveniently yielded the desired 6-hydroxy-2-methyldecahydroisoquinolines.[3] Thus derivatization of the diastereoisomeric amines and alcohols gave series of amides and esters for antiarrhythmic screening and for comparison with our previous studies toward our goal of in-depth structure–activity studies of antiarrhythmic decahydroisoquinolines. The stereochemistry of the amides and esters prepared thus corresponded with their precursor amines and alcohols and possessed the following structures: *cis*-6,9,10-*H*-6-amido (or ester); *trans*-9,10-*cis*-6,10-*H*-6-amido- (or ester) 2-methyldecahydroisoquinoline; and *cis*-9,10-*trans*-6,10-*H*-6-amido-2-methyldecahydroisoquinoline (only small amounts of this isomer were produced) as shown in Chart I.

Chart I. Stereochemistry of Substituted Decahydroisoquinolines



trans-9,10-*cis*-6,10-*H*-6-amido- (or ester) 2-methyldecahydroisoquinoline

cis-6,9,10-*H*-6-amido- (or ester) 2-methyldecahydroisoquinoline

cis-9,10-*trans*-6,10-*H*-6-amido- (or ester) 2-methyldecahydroisoquinoline

R = substituted benzamido or benzoyloxy grouping

The method of preparation of the amides utilized the classical acylation of the amine with the appropriate acid chloride while the esters were prepared from the alcohols using the general procedure outlined by Staab[4] as modified in our earlier work.[1e] In an attempt to further our concept of the molecular requirements for good antiarrhythmic potency in the decahydroisoquinolines under study, we have been identifying some significant physicochemical properties.[1c,5] In the present study pK_a values and octanol–water partition coefficients are reported.

Experimental Section

A. Pharmacological Evaluation. The compounds shown in Table I were evaluated for acute toxicity (24 hr) in female Swiss–Webster albino mice weighing 15–25 g. Each compound was administered intraperitoneally to groups of at least five mice per group at three doses, logarithmically differing in concentration by 0.1 intervals or less. The dose–response data were evaluated by the Litchfield–Wilcoxon[6] method and the ED_{50} values together with the 95% confidence limits are shown in Table II. The values are reported in units of micromoles per kilogram to allow comparisons which take into account differences in molecular weight. The method utilized for determination of antiarrhythmic potency was that described by Lawson.[7] This screening test involves the prevention of a chloroform-induced ventricular fibrillation in mice pretreated with active agents. The mice were of the same strain, sex, and weight noted above for the toxicity determinations and the compounds were again introduced by the intraperitoneal route. Groups of at least five mice were used at three dose levels and the data obtained treated in a similar manner to the toxicity data in order to obtain ED_{50} values with the corresponding 95% confidence limits. The values are shown in Table II and are again reported in micromoles per kilogram. In both tests, compounds were solubilized in dilute hydrochloric acid. At regular intervals groups of control mice were pretreated with the vehicle and subjected to the test; in all cases ventricular fibrillation was observed. Quinidine was used as a standard for antiarrhythmic activity.

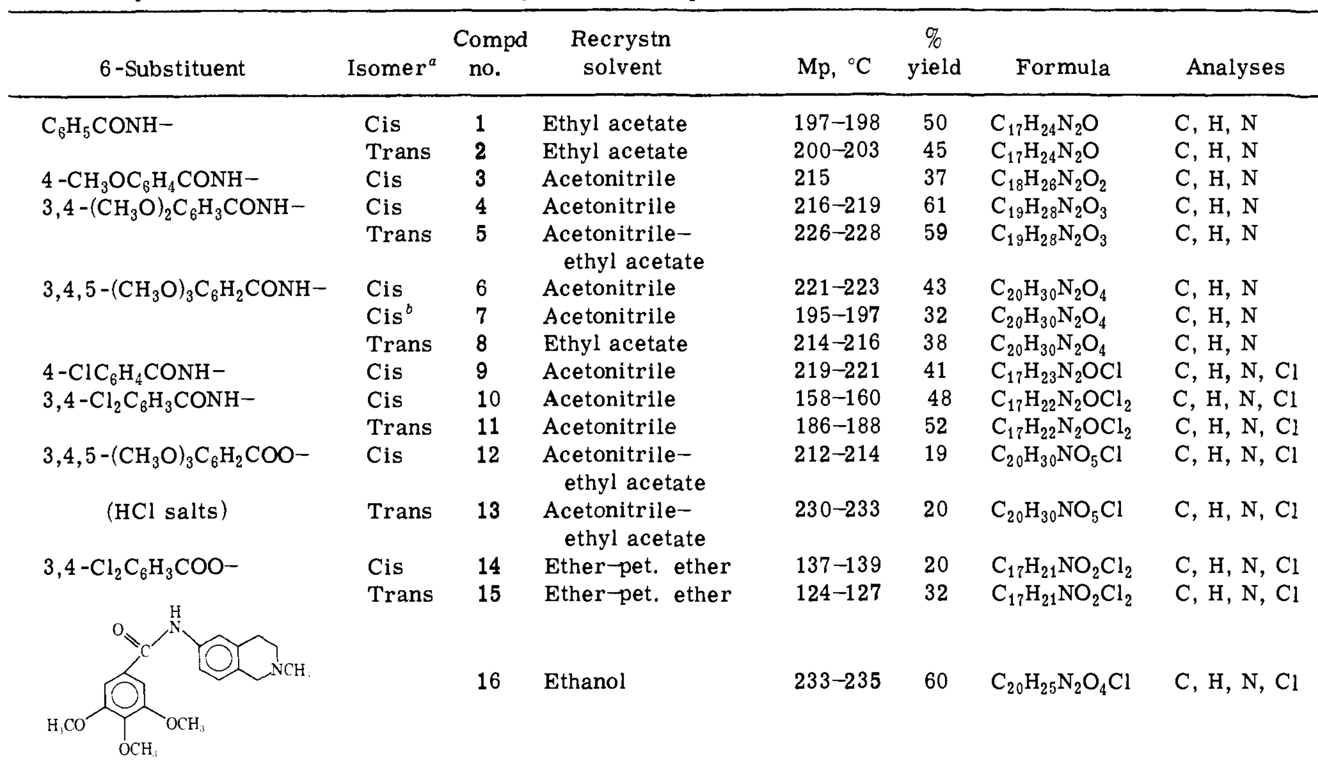
B. Chemistry. All melting points were determined using a Swissco melting point apparatus and are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. Where analyses are indicated values within ±0.4% of the theoretical values were considered acceptable. Infrared (ir) spectra were recorded on a Beckman Model IR-33 grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined on a Hitachi Perkin-Elmer Model R-24 spectrometer and deuterium exchanges were routinely performed on all compounds possessing labile hydrogens.

General Methods. a. 6-Amido-2-methyldecahydroisoquinolines. To a stirred solution of 6-amino-2-methyldecahydroisoquinoline (0.01 mol) prepared according to our reported procedure[3] and triethylamine (0.03 mol) in dry benzene was added the appropriate acid chloride (0.011 mol) dissolved in dry benzene. The resulting mixture was refluxed for 24 hr, after which the benzene was removed by rotary evaporation. The residue was taken up in chloroform and washed three times with 10% Na_2CO_3 solution and once with water. The chloroform solution was then dried over $MgSO_4$ and the solvent evaporated yielding a solid residue which was recrystallized from the solvents indicated in Table I.

b. 6-Benzoyloxy-2-methyldecahydroisoquinolines. *N,N*-Carbonyldiimidazole (0.0064 mol) dissolved in dry tetrahydrofuran (20 ml) was added through an addition funnel to a dry benzene solution (30 ml) of the acylating acid (0.0066 mol). The resulting mixture was gently heated and stirred until evolution of CO_2 ceased, indicating the complete formation of the azolide. To this solution was then added 6-hydroxy-2-methyldecahydroisoquinoline[3] (0.006 mol) dissolved in dry benzene (15 ml) and the resulting mixture refluxed for 12 hr. The solvents were then removed by rotary evaporation and the residue was dissolved in chloroform. This chloroform solution was washed with water to remove unreacted starting material and then dried over $MgSO_4$. The dried solution was reduced to dryness and, in the case of an oily residue (compounds 12 and 13), the hydrochloride salt prepared in the usual manner; the solid residues were recrystallized from the solvent indicated in Table I.

Determination of the Partition Coefficients. 1-Octanol was purified by washing with successive equal volumes of 0.1 *N* sulfuric acid solution, 0.1 *N* sodium hydroxide solution, and distilled water. After the washings the octanol was distilled and the fraction distilling at 194–196° collected. The distilled 1-octanol was shaken and allowed to equilibrate with a phosphate buffer of pH 7. The

Table I. Physical Data of 6-Substituted 2-Methyldecahydroisoquinolines



6-Substituent	Isomer[a]	Compd no.	Recrystn solvent	Mp, °C	% yield	Formula	Analyses
C_6H_5CONH-	Cis	1	Ethyl acetate	197–198	50	$C_{17}H_{24}N_2O$	C, H, N
	Trans	2	Ethyl acetate	200–203	45	$C_{17}H_{24}N_2O$	C, H, N
$4-CH_3OC_6H_4CONH-$	Cis	3	Acetonitrile	215	37	$C_{18}H_{26}N_2O_2$	C, H, N
$3,4-(CH_3O)_2C_6H_3CONH-$	Cis	4	Acetonitrile	216–219	61	$C_{19}H_{28}N_2O_3$	C, H, N
	Trans	5	Acetonitrile–ethyl acetate	226–228	59	$C_{19}H_{28}N_2O_3$	C, H, N
$3,4,5-(CH_3O)_3C_6H_2CONH-$	Cis	6	Acetonitrile	221–223	43	$C_{20}H_{30}N_2O_4$	C, H, N
	Cis[b]	7	Acetonitrile	195–197	32	$C_{20}H_{30}N_2O_4$	C, H, N
	Trans	8	Ethyl acetate	214–216	38	$C_{20}H_{30}N_2O_4$	C, H, N
$4-ClC_6H_4CONH-$	Cis	9	Acetonitrile	219–221	41	$C_{17}H_{23}N_2OCl$	C, H, N, Cl
$3,4-Cl_2C_6H_3CONH-$	Cis	10	Acetonitrile	158–160	48	$C_{17}H_{22}N_2OCl_2$	C, H, N, Cl
	Trans	11	Acetonitrile	186–188	52	$C_{17}H_{22}N_2OCl_2$	C, H, N, Cl
$3,4,5-(CH_3O)_3C_6H_2COO-$	Cis	12	Acetonitrile–ethyl acetate	212–214	19	$C_{20}H_{30}NO_5Cl$	C, H, N, Cl
(HCl salts)	Trans	13	Acetonitrile–ethyl acetate	230–233	20	$C_{20}H_{30}NO_5Cl$	C, H, N, Cl
$3,4-Cl_2C_6H_3COO-$	Cis	14	Ether–pet. ether	137–139	20	$C_{17}H_{21}NO_2Cl_2$	C, H, N, Cl
	Trans	15	Ether–pet. ether	124–127	32	$C_{17}H_{21}NO_2Cl_2$	C, H, N, Cl
(structure: H, N, O, C, NCH₃, H₃CO, OCH₃, OCH₃)		16	Ethanol	233–235	60	$C_{20}H_{25}N_2O_4Cl$	C, H, N, Cl

[a]See footnote *d*, Table II. [b]See footnote *e*, Table II.

buffer-saturated octanol and the octanol-saturated buffer were retained for the partitioning experiments.

The ultraviolet (uv) wavelength at which maximum absorbance occurred (λ_{max}) was determined for each compound in buffer-saturated octanol on a Perkin-Elmer Model 202 ultraviolet-visible spectrophotometer. Beer's law plots were constructed for each compound (in buffer-saturated octanol) at their λ_{max} at concentrations ranging from 10^{-4} to 10^{-5} *M* on a Gilford 240 ultraviolet–visible spectrophotometer.

A stock solution of the compound (10^{-4} *M*) was prepared by dissolution of the compound in buffer-saturated octanol. Beer's law plots were constructed from the absorbance values obtained from serial dilutions of the stock solution. Three partitionings were carried out on both 3- and 5-ml aliquots of the stock solution. This was achieved by adding the aliquots to 50-ml portions of octanol-saturated aqueous buffer in 250-ml flasks. The flasks were capped and shaken vigorously by hand for 2–3 min and then allowed to stand for a minimum of 6 hr. During standing the octanol and aqueous layers separated. The octanol (upper layer) was pipetted off and transferred to quartz uv cuvettes and the absorption at the λ_{max} was measured. The absorption values obtained for both the 3- and 5-ml aliquots were averaged independently and the concentrations determined on these average values from the Beer's law plot. Knowing the concentration in the octanol before and after partitioning, the concentration of compound partitioned into the water was calculated and the partition coefficients for the 5- and 3-ml aliquots were calculated from the expression

$$pC = \frac{\text{concn in octanol after partitioning}}{\text{concn in water after partitioning}}$$

The partition coefficients shown in Table II were obtained by calculations of the median value from the 5- and 3-ml experiments.

During the course of the partition experiments several compounds were studied to determine the optimal shaking time needed to give a reliable value for the partition coefficient. The results from these experiments indicated that hand shaking for 1 min or less was inadequate for some of the compounds (those with low or extremely high partition coefficients). However, no significant difference in p*C* was observed between shaking for 3 min by hand and shaking for 24 hr on a mechanical shaker. The concentration of the stock solution was also varied for several compounds to ensure that saturation of the water phase was not occurring.

Determination of pK_a Values. Analytically pure samples of the compounds were dissolved in distilled water, which had been boiled prior to use to ensure the absence of carbon dioxide, to make a solution of 10^{-3} *M* concentration. For all samples which proved difficult to dissolve a maximum of 7% methanol was added to promote dissolution. The titrant used in all cases was a standard 0.01 *M* solution of potassium hydrogen phthalate. The titrations were carried out using the following Radiometer equipment: pH meter (PHM28), an automatic titrator (TTT11), a titragraph recorder (SBR2c), an autoburette (ABu/c), a saturated calomel electrode (Radiometer Type K401), and a glass electrode (Radiometer Type G202c). The titrations were performed in a jacketed glass reaction vessel (Radiometer) which was maintained at 25 ± 0.2°C by a Heto (Denmark) Ultrathermostat. During the titrations the solutions were stirred with an electrical stirring motor (Radiometer) and nitrogen was bubbled slowly into the titrating media.

Previous experience in our laboratory had shown that a standard solution of 0.01 *M* potassium hydrogen phthalate was most effective as the acid in determining the pK_a values of decahydroisoquinolines. To ensure credibility of the procedure, the pK_a of morpholine was determined by this method and found to be 8.30 ± 0.05. This value compared very closely with the values reported in the literature: 8.33 at 25°C;[11] 8.36 at 25°C;[12a] and 8.39 (thermodynamic value).[12b]

The procedure used consisted of separate titrations of three 15-ml samples of approximately 10^{-3} *M* solutions of the compound with 0.01 *M* potassium hydrogen phthalate. The pK_a was calculated from the expression

$$pK_a = \text{pH at half-neutralization}$$

The neutralization point was determined from the titration curve (a plot of pH as a function of the volume of potassium hydrogen phthalate added) by drawing parallel tangents to the curve on each side of the inflection point. The midpoint of a line connecting the two points of the tangent was taken as the neutralization point. The pK_a was determined by drawing a line from the point on the curve representing the volume at half-neutralization to the pH coordinate. The point at which this line crossed the pH coordinate was taken to be the pK_a. The pK_a values determined from the three titrations for each compound were averaged and the limits determined by subtracting the average from the lowest and highest value. The values obtained are recorded in Table II.

Table II. Antiarrhythmic Potencies, Toxicities, and Physical Properties of 6-Substituted 2-Methyldecahydroisoquinolines

R	Isomer[d]	Compd no.	LD_{50}, μmol/kg ip	ED_{50}, μmol/kg ip	T.I.[a]	pK_a	Partition coeff
Quinidine			533 (513–555)[b]	160 (136–188)[b]	3.33		
C_6H_5CONH-	Cis	1	1353 (1276–1434)	375 (334–419)	3.60	9.07 ± 0.02	2.96 ± 0.11
	Trans	2	1426 (1356–1500)	360 (308–422)	3.96	8.92 ± 0.03	2.40 ± 0.13
$4\text{-}CH_3OC_6H_4CONH-$	Cis	3	1572 (1488–1660)	331 (304–360)	4.74	8.84 ± 0.06	2.75 ± 0.15
$3,4\text{-}(CH_3O)_2C_6H_3CONH-$	Cis	4	1532 (1474–1591)	255 (204–318)	6.01	8.90 ± 0.04	1.98 ± 0.03
	Trans	5	1465 (1420–1510)	285 (239–342)	5.14	9.01 ± 0.01	1.87 ± 0.01
$3,4,5\text{-}(CH_3O)_3C_6H_2CONH-$	Cis	6	1304 (1267–1353)	195 (168–227)	6.68	8.95 ± 0.02	1.15 ± 0.05
	Cis[e]	7	1371 (1305–1432)	251 (187–344)	5.46	8.92 ± 0.02	0.97 ± 0.07
	Trans	8	1063 (1025–1105)	232 (196–276)	4.58	9.02 ± 0.02	1.28 ± 0.01
$4\text{-}ClC_6H_4CONH-$	Cis	9	897 (840–958)	301 (271–333)	2.99	8.94 ± 0.06	17.05 ± 0.45
$3,4\text{-}Cl_2C_6H_3CONH-$	Cis	10	765 (706–809)	98 (85–111)	7.81	8.99 ± 0.02	50.45 ± 0.45
	Trans	11	844 (791–900)	146 (132–160)	5.78	8.85 ± 0.03	46.22 ± 0.56
$3,4,5\text{-}(CH_3O)_3C_6H_2COO-$	Cis	12	544 (501–591)	94 (85–101)	5.78	8.97 ± 0.05	7.68 ± 0.09
(HCl salts)	Trans	13	511 (481–544)	132 (118–148)	3.87	9.01 ± 0.03	6.95 ± 0.06
$3,4\text{-}Cl_2C_6H_3COO-$	Cis	14	1337 (1243–1437)	187 (168–206)	7.14	8.90 ± 0.02	145 ± 3.0
	Trans	15	1134 (1064–1207)	265 (244–288)	4.27	8.95 ± 0.07	127 ± 0.5
		16	451 (429–474)	165 (132–181)	2.71	8.30 ± 0.08	7.60 ± 0.12

[a]Therapeutic Index (LD_{50}/ED_{50}). [b]95% confidence limits. [c]This tetrahydroisoquinoline derivative[9] was included for comparison with the fully reduced compounds 6–8. [d]Cis and trans refer to the stereochemistry at the C(9)–C(10) junction, i.e., cis-6,9,10-*H* or trans-9,10-cis-6,10-*H*. [e]The stereochemistry of this cis diastereoisomer is cis-9,10-trans-6,10-*H*.

Results and Discussion

The data obtained from both the biological and physicochemical studies are shown in Table II. Consideration of the results will be made following the general structural types of compounds prepared.

In general the compounds exhibited effects of both a toxic and therapeutic nature similar to those identified in our earlier studies.[1b,e] All compounds exhibited antiarrhythmic effectiveness, in general more effective than quinidine and the 5-position isomers but less than the corresponding 8-substituted analogs. in agreement with our earlier findings[1b,e] the ester series was found to be more potent and more toxic than their corresponding amides (e.g., compounds **12** and **13** vs. **6** and **8**), a factor compatible with the differences in lipophilicity—the esters being significantly more lipophilic than the amides. Of surprising interest in relation to our earlier data was the antiarrhythmic potency of compound **16** (a tetrahydroisoquinoline derivative). While this compound was certainly not one of the most potent in the series it possessed significantly greater potency than the other tetrahydro compounds prepared to date[1b,e] and but for its toxicity (a factor noted with both the 5- and 8-position analogs) would have yielded a compound with a significantly high T.I. value. A considerable range of lipophilicities was noted in the series; in general the greater lipophilicities were associated with compounds possessing higher potency values (e.g., compounds **10–14**, **16**) although there were notable exceptions (e.g., **6** and **15**). The pK_a values did not differ significantly within the series (with the exception of the tetrahydroisoquinoline derivative **16**); thus differences in the degree of ionization of the compounds at physiological pH would be small and would not be expected to account for the potency differences observed between the members of the series. As an example of the degree of ionization, compound **1** would be 98% ionized and **3** would be 96.6% ionized at pH 7.4. This physicochemical parameter was therefore not considered further as a factor influencing antiarrhythmic potency differences.

A. Compounds 1–8. In a continuation of our studies designed to ascertain the importance of methoxyl groupings on the aromatic substituting moiety, the cited compounds were prepared. As in our previous studies the 3,4,5-trimethoxybenzamides (**6–8**) were found to be the most potent and toxic of the substitutions studied and it was noted that an increase in the number of methoxyl groupings was accompanied by increases in both potency and toxicity, e.g., for the cis isomers **3** < **4** < **6** in both toxicity and potency. As expected an increase in the number of methoxyl groupings was accompanied by a decrease in lipophilic character, e.g., for the cis isomers **3** > **4** > **6**. While the statistics in regard to antiarrhythmic activity do not permit a clear correlation between increased potency and decreased lipophilicity there is certainly a trend in this direction. No correlations between stereochemistry and antiarrhythmic potency were observed. In comparing the unsubstituted compounds (**1** and **2**) with the methoxyl-substituted analogs (**3–8**) it is apparent that the addition of methoxyl groupings results in increased potency (not toxicity, however), in accordance with our earlier findings.

Of surprise was the fact that the tetrahydroisoquinoline derivative **16** was more potent and considerably more toxic than its decahydro analogs **6–8**. It should also be noted that **16** was considerably more lipophilic than the fully reduced compounds. This is the first example we have observed of

the superiority of the partially reduced isoquinoline over the completely saturated system. This observation may be a reflection of the differences in pK_a value between **16** and the only comparable example studied, 5-(3,4,5-trimethoxybenzamido)-2-methyl-1,2,3,4-tetrahydroisoquinoline,[9] which has been found[10] to possess a pK_a of 7.85, significantly lower than **16** (pK_a = 8.30). Thus at physiological pH a significantly greater percentage of the un-ionized 5-position analog would be present than un-ionized **16**. We are currently investigating the physical parameters of the tetrahydroisoquinolines, synthesized earlier,[9] in greater detail.

B. Compounds 9–11. The considerably potency noted in the 8-substituted decahydroisoquinolines with the chlorobenzamide derivatives[1e] prompted us to synthesize similar analogs for the 6-substituted decahydroisoquinolines. In concurrence with our previous studies a 3,4-dichlorobenzamide (**10**) yielded the most efficacious member of the series; however, the superior compound in the current studies was a cis rather than the trans isomer noted earlier.[1e] Increases in lipophilicity were clearly correlated with increased potency in this series, i.e., **10** > **11** > **9**, the dichlorobenzamides as expected being considerably more lipophilic than any of the benzamides prepared. Comparing the unsubstituted compounds **1** and **2** with **9–11** provides further evidence for correlations between potency and lipophilicity, the more lipophilic chlorobenzamides (**9–11**) being significantly more potent. In spite of the lipophilicity differences in the members of this series, differences in toxicity were not apparent although the group as a whole was considerably more toxic than the unsubstituted less lipophilic benzamides **1** and **2**. Some evidence of stereoselectivity was noted by **10** over **11** although caution should be exercised in view of the increased lipophilicity of **10** with respect to **11**.

C. Compounds 12–15. As noted earlier, the synthesis of esters of a reserpine-like structure was one of the initial goals of our study. Due to the lack of material the synthesis of only two pairs of diastereoisomeric esters was possible, the 3,4,5-trimethoxybenzoyloxy and the 3,4-dichlorobenzoyloxy derivatives. As anticipated the lipid solubility of these compounds was greater than the corresponding amides (cf. compounds **14** and **15** vs. **10** and **11**). The dichloro esters **14** and **15** were found to be more lipophilic, less potent, and less toxic than the trimethoxy esters **12** and **13**. The implication of stereoselectivity is noted in these compounds in that the cis isomers **12** and **14** were significantly more potent than the trans analogs **13** and **15**. However, it should be pointed out that this may be a reflection of the higher lipophilicities of the cis isomers over their trans counterparts.

Conclusion

A series of substituted aromatic derivatives of diastereoisomeric 6-hydroxy- and 6-amino-2-methyldecahydroisoquinoline has been prepared and shown to exhibit antiarrhythmic activity, in general, superior to that of quinidine. Studies of the lipophilic character of the various derivatives indicate that compounds possessing greater lipophilicities generally exhibited increased potency. Of six pairs of diastereoisomers prepared, no differences in antiarrhythmic potency were noted in three; however, in the three in which differences were noted the more lipophilic cis isomers were the more potent compounds. In the series of benzamides, increased lipophilicity resulted in increased antiarrhythmic potency. In the ester series the reverse appeared to be true since the highly lipid-soluble dichlorobenzoyl esters were less potent than the moderately lipid-soluble trimethoxybenzoyl esters. For these series it appears therefore that an increase in lipid solubility leads to increased potency up to a point beyond which increased lipophilicity is detrimental to antiarrhythmic activity. This is not an unrecognized phenomenon of medicinal agents.[8]

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