# Synthesis, Stereochemistry, and Antiarrhythmic Activity of Some 8-Substituted Decahydroisoquinolines

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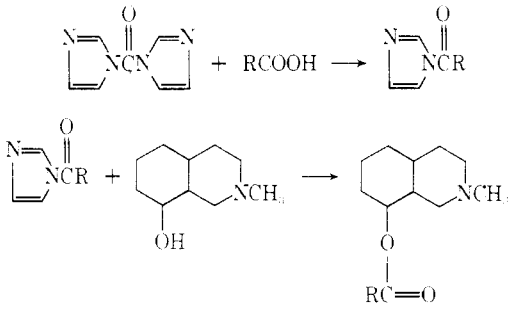
The diastereoisomeric series of 8-substituted 2-methyldecahydroisoquinolines has been synthesized and evaluated as antiarrhythmic agents. Substituted benzoyloxy and benzamido derivatives were found to yield compounds with therapeutic indices considerably higher than that of quinidine. Optimal values were obtained with compounds possessing lipophilic substitutions, most notably the 3,4-dichlorobenzamido grouping. The previous observation of some correlation of trans ring junction stereochemistry with optimal potency was further substantiated by examples in this study. The compounds prepared were much less toxic than quinidine. A tetrahydroisoquinoline benzamide derivative was equivalent to quinidine but much less effective as an antiarrhythmic than its decahydro analogs—a finding compatible with earlier studies. Support is provided for the Topliss concept for maximizing activity within a series of compounds where the aromatic moiety is a necessary grouping.

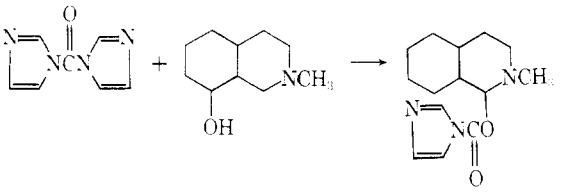
As part of a continuing study of the influence of stereochemistry on the antiarrhythmic potency of variously substituted decahydroisoquinolines,[1] a series of 8-substituted 2-methyldecahydroisoquinolines has been synthesized and evaluated for antiarrhythmic activity according to methods outlined by Lawson.[1b,2] The determination of the stereochemistry of the diastereoisomers produced during the reaction sequence has been previously reported.[3] Two types of derivatives have been synthesized, esters and amides, and, in most cases, derivatives of pairs of diastereoisomers were prepared to enable us to further substantiate the previous indications of stereoselectivity in antiarrhythmic action.[1b] The rationale for the choice of acyl substitutions was made in accordance with our limited earlier findings that aromatic lipid favoring groupings tended to provide agents of superior activity. Accordingly, a range of substitutions varying from benzoyl to various methoxybenzoyl to chlorobenzoyl moieties was used.

The synthesis[3] of 8-amino-2-methyldecahydroisoquinoline was achieved by way of a bromination and nitration of isoquinoline to give 5-bromo-8-nitroisoquinoline. Catalytic hydrogenation of the quaternary salt of the 5-bromo-8-nitro compound over platinum oxide in a buffered solvent system yielded the desired amine. The diastereoisomers produced were separated by the fractional recrystallization of the corresponding acetamide derivatives. Assignment of the stereochemistry was accomplished by a combination of spectral and chemical manipulations including the deamination with nitrous acid of the amines, obtained by hydrolysis of the purified acetamides, to hydroxyl analogs.[3] This procedure conveniently yielded a starting material for the preparation of diastereoisomeric ester derivatives. As a result of this study, the stereochemistry of the two isomers isolated in major amounts was shown to be *cis*-8,9,10*H*-8-amino- (or hydroxy-) 2-methyldecahydroisoquinoline (*i.e.*, a cis ring junction isomer with the substituent in the axial position) and *trans*-8,9,10*H*-8-amino- (or hydroxy-) 2-methyldecahydroisoquinoline (*i.e.*, a trans ring junction, equatorially substituted isomer). Thus, the stereochemistry of the derivatives synthesized and evaluated for antiarrhythmic potency corresponds with these assignments. The acylation procedures for the preparation of the derivatives involved the classic treatment with the appropriate acyl chloride or, in the case of the esters, the *N,N*-carbonyldiimidazole procedure of Staab,[4] outlined in Scheme I. While in the reported procedure, the alcohol, esterifying acid, and *N,N*-carbonyldiimidazole were mixed at one time, we found that such an approach in fact yields a carbamate derivative and that the alcohol is in fact quite reactive toward the imidazole (see Scheme II).

Scheme I



Scheme II



The resulting moisture-sensitive carbamate was fully characterized by ir, nmr, and elemental analytical data. Preparation of the azolide of the esterifying carboxylic acid followed by treatment with the decahydroisoquinolinol yielded the desired esters. Some of the amides were prepared using this general procedure substituting 8-amino-2-methyldecahydroisoquinoline for the alcohol in the above scheme.

**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[5] method and the $LD_{50}$ 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.[2] 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,

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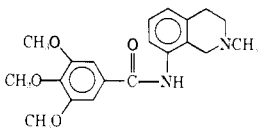
Table I. Physical Data of 8-Substituted Decahydroisoquinolines

| 8-Substituent | Isomer | Compd no. | Synthesis | Recrystn solvent | Mp, °C | % yield | Formula | Analyses |
|---|---|---|---|---|---|---|---|---|
| 2-$OCH_3C_6H_4CONH$- | Cis | 1 | a | Ethanol–water | 114–116 | 14 | $C_{18}H_{26}N_2O_2$ | C, H, N |
| | | | b | Ether–pet. ether | | 62 | | |
| | Trans | 2 | a | Ethanol–water | 123–124 | 21 | $C_{18}H_{26}N_2O_2$ | C, H, N |
| 4-$OCH_3C_6H_4CONH$- | Cis | 3 | a | Acetonitrile | 203–205 | 51 | $C_{18}H_{26}N_2O_2$ | C, H, N |
| | Trans | 4 | a | Acetonitrile | 239–241 | 75 | $C_{18}H_{26}N_2O_2$ | C, H, N |
| 3,4-$(OCH_3)_2C_6H_3CONH$- | Cis | 5 | a | Acetonitrile | 202–203 | 70 | $C_{19}H_{28}N_2O_3$ | C, H, N |
| | Trans | 6 | a | Acetonitrile | 217–219 | 61 | $C_{19}H_{28}N_2O_3$ | C, H, N |
| 3,4,5-$(OCH_3)_3C_6H_2CONH$- | Cis | 7 | a | Acetonitrile or ethyl acetate | 191.5–193 | 70 | $C_{20}H_{30}N_2O_4$ | C, H, N |
| | Trans | 8 | a | Acetonitrile | 205–207 | 74 | $C_{20}H_{30}N_2O_4$ | C. H. N |
|  | | 9 | a | Ethanol–water | 177–178 | 70 | $C_{20}H_{24}N_2O_4$ | C, H. N |
| $C_6H_5CONH$- | Cis | 10 | a | Ethyl acetate | 188–190 | 18 | $C_{17}H_{24}N_2O$ | C, H, N |
| | | | b | | | 80 | | |
| | Trans | 11 | a | Acetonitrile | 198–200 | 38 | $C_{17}H_{24}N_2O$ | C, H, N |
| 4-$ClC_6H_4CONH$- | Cis | 12 | a | Acetonitrile | 191–193 | 46 | $C_{17}H_{23}N_2OCl$ | C, H, N, Cl |
| | Trans | 13 | a | Acetonitrile | 219–221 | 65 | $C_{17}H_{23}N_2OCl$ | C, H, N. Cl |
| 3.4-$Cl_2C_6H_3CONH$- | Cis | 14 | a | Acetonitrile | 161–163 | 62 | $C_{17}H_{22}N_2OCl_2$ | C, H, N, Cl |
| | Trans | 15 | a | Acetonitrile | 209–210.5 | 52 | $C_{17}H_{22}N_2OCl_2$ | C. H. N. Cl |
| $C_6H_5SO_2NH$- | Cis | 16 | a | Acetonitrile– | 144–146 | 10 | $C_{16}H_{24}N_2SO_2$ | C. H. N, S |
| | | | b | ethyl acetate | | 0 | | |
| | Trans | 17 | a | Ethyl acetate | 204–206 | 38 | $C_{16}H_{24}N_2SO_2$ | C, H, N, S |
| $C_6H_5COO$–, HCl salt | Cis | 18 | b | Acetonitrile | 255–258 | 84 | $C_{17}H_{24}NO_2Cl$ | C, H, N. Cl |
| 4-$ClC_6H_4COO$–, HCl salt | Cis | 19 | b | Acetonitrile– ethyl acetate | 248–250 | 38 | $C_{17}H_{23}NO_2Cl_2$ | C, H, N, Cl |
| | Trans | 20 | b | Ethyl acetate | 183–185 | 22 | $C_{17}H_{23}NO_2Cl_2$ | C, H, N, Cl |
| 3,4,5-$(OCH_3)_3C_6H_2COO$–, HCl salt | Cis | 21 | b | Acetonitrile– ethyl acetate | 231–233 | 86 | $C_{20}H_{30}NO_5Cl$ | C, H, N, Cl |
| | Trans | 22 | b | Acetone | 188–190 | 17 | $C_{20}H_{30}NO_5Cl$ | C, H, N, Cl |

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. Only compounds **15** and **16** were sufficiently insoluble to require suspension in 1% tragacanth. 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.

## Experimental Section

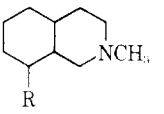
All melting points were determined using a Swissco melting point apparatus and are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. Where analyses are indicated, values within ±0.4% of the theoretical values were considered 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.

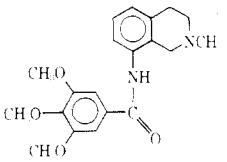
**General Methods. a. 8-Amido-2-methyldecahydroisoquinolines.** To a stirred solution of 8-amino-2-methyldecahydroisoquinoline (0.01 mol) prepared according to our reported procedure[3] and triethylamine (0.03 mol) in dry benzene was added the appropriate acid chloride (0.011 mol) dissolved in dry benzene. The resulting mixture was refluxed for 24 hr, after which time 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. 8-Amido- or 8-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 either 8-amino- or 8-hydroxy-2-methyldecahydroisoquinoline (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 **18–22**) the hydrochloride salt prepared in the usual manner; the solid residues were recrystallized from the solvent indicated in Table I.

***cis*-8,9,10*H*-2-Methyldecahydroisoquinoline-8-imidazole-*N*-carboxylate.** A mixture of *N,N*-carbonyldiimidazole (0.0118 mol), 3,4,5-trimethoxybenzoic acid (0.0118 mol), and 8-hydroxy-2-methyldecahydroisoquinoline (0.0118 mol) was dissolved in tetrahydrofuran (75 ml) and refluxed for 6 hr. The solvent was then removed by rotary evaporation and the residual oil dissolved in chloroform and washed with 10% $Na_2CO_3$ solution, followed by water. The chloroform extract was then dried over $MgSO_4$ and concentrated to yield a light tan oil (3.1 g) which solidified on standing in the refrigerator. The pure product was obtained by recrystallization from petroleum ether (bp 30–60°) or pentane to give 1.6 g of clustered needles: mp 100.5–101.5°; ir (KBr) 1745 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 8.13 (s, 1, vinyl proton), 7.45 (s, 1,

**Table II.** Antiarrhythmic Potencies and Toxicities of 8-Substituted Decahydroisoquinolines



| Structure, R = | Isomer | Compd no. | $LD_{50}$, μmol/kg ip | $ED_{50}$, μmol/kg ip | Therapeutic Index[a] |
|---|---|---|---|---|---|
| Quinidine | | | 533 (513–555)[b] | 160 (136–188)[b] | 3.3 |
| 2-$OCH_3C_6H_4CNH$– (O) | Cis | 1 | 847 (790–906) | 116 (890–149) | 7.3 |
| | Trans | 2 | 761 (714–810) | 175 (149–208) | 4.3 |
| 4-$OCH_3C_6H_4CNH$– (O) | Cis | 3 | 1560 (1430–1700) | 268 (251–284) | 5.8 |
| | Trans | 4 | 1490 (1360–1620) | 195 (163–233) | 7.6 |
| 3,4-$(OCH_3)_2C_6H_3CNH$– (O) | Cis | 5 | 1770 (1740–1810) | 199 (183–213) | 8.9 |
| | Trans | 6 | 1600 (1440–1780) | 164 (141–190) | 9.8 |
| 3,4,5-$(OCH_3)_3C_6H_2CNH$– (O) | Cis | 7 | 1170 (1130–1210) | 160 (135–188) | 7.3 |
| | Trans | 8 | 835 (786–883) | 124 (113–138) | 6.7 |
|  | | 9 | 701–1400[c] | 314 (236–421) | ~3.3 |
| $C_6H_5CNH$– (O) | Cis | 10 | 1430 (1210–1690) | 242 (217–268) | 5.9 |
| | Trans | 11 | 1450 (1360–1550) | 246 (224–272) | 5.9 |
| 4-$ClC_6H_4CNH$– (O) | Cis | 12 | 909 (873–948) | 209 (189–231) | 4.4 |
| | Trans | 13 | 952 (912–991) | 200 (160–247) | 4.8 |
| 3,4-$Cl_2C_6H_3CNH$– (O) | Cis | 14 | 712 (697–727) | 73 (53–97) | 9.7 |
| | Trans | 15 | 1304 (1204–1409) | 104 (90–124) | 12.7 |
| $C_6H_5SO_2NH$– | Cis | 16 | 1460 (1370–1560) | 282 (269–298) | 5.2 |
| | Trans | 17 | 1113 (1050–1230) | 347 (340–353) | 3.3 |
| $C_6H_5CO$– (O) | Cis | 18 | 900 (871–929) | 245 (223–271) | 3.7 |
| 4-$ClC_6H_4CO$– (O) | Cis | 19 | 1200 (1150–1250) | 257 (231–286) | 4.7 |
| | Trans | 20 | 757 (728–789) | 146 (127–175) | 5.2 |
| 3,4,5-$(OCH_3)_3C_6H_2CO$– (O) | Cis | 21 | 421 (402–440) | 162 (146–182) | 2.6 |
| | Trans | 22 | 338 (316–360) | 74 (61–94) | 4.5 |

[a] Therapeutic index ($LD_{50}/ED_{50}$). [b] 95% confidence limits. [c] Obtained from data in ref 6. [d] This tetrahydroisoquinoline derivative was included at this point for comparison with the decahydroisoquinoline analogs.

vinyl proton), 7.10 (s, 1, vinyl proton), 5.14 (b, 1, CHOC=O), and 2.24 ppm (s, 3, $NCH_3$). *Anal.* ($C_{14}H_{21}N_3O_2$) C, H, N.

The hydrolysis of this compound was followed by the disappearance of the band at 227 mμ in the ultraviolet and indicated its half-life to be approximately 30–45 min.

## Results and Discussion

In order to develop structure-activity relationships within this group of compounds, consideration will be given to both toxicity and antiarrhythmic potency; however, their combined effects are reflected in the therapeutic index values shown in Table II.

In general, compounds were synthesized with distinct decreases in toxicity when compared to quinidine. It was noted that lethality was a result of respiratory depression. Animals that survived for the first 4 hr following injection of the test compounds (except **12–15**) survived for the next 5–7 days. With compounds 12–15, animals that survived the 24-hr period continued to die up to 7 days following injection of the compounds and demonstrated toxic effects throughout the period following injection. It should be noted that for comparable compounds the 8-substituted derivatives (*e.g.*, **7**, **8**, **21**, and **22**) were generally less toxic than the 5-substituted analogs.[1b] The tetrahydroisoquinoline derivative **9** did not appear to be more toxic than its fully reduced analogs **7** and **8**. In general, the ester derivatives were more toxic than the amides, a finding consistent with our earlier studies on the 5-substituted derivatives.[1b] Of overall significance was the fact that antiarrhythmic potency was evident throughout the whole series of compounds. In order to detect structure-activity relationships, the data will be discussed under four headings following the general structural types synthesized.

**A. Compounds 1–9.** This series of compounds was designed to ascertain the influence of methoxyl groupings on the benzamide moiety. While our earlier studies had implicated the importance of these substitutions, a thorough

study was not conducted. Inspection of the data in Table II shows that an increase in potency occurs as the number of methoxyl groupings is increased and that this trend occurs in both cis and trans isomers; *i.e.*, **7** > **5** > **3** and **8** > **6** > **4**. Compounds **1** and **2**, the 2-methoxybenzamides, however, did not follow the pattern set by the former compounds in that the cis isomer **1** was more potent that its trans diastereoisomer **2**. With regard to toxicity all the trans compounds in the group possessed greater toxicities than the corresponding cis isomers. The 2-methoxybenzamides **1** and **2** were both more toxic and more potent than the isomeric 4-methoxybenzamides **3** and **4**. The tetrahydro derivative[6] **9**, although of equal toxicity to the fully reduced analogs **7** and **8**, was significantly less potent, confirming our previous findings of the importance of the decahydroisoquinoline ring system for optimal antiarrhythmic effectiveness. The therapeutic indices of the compounds in this group were 1.3 to 3.0 times greater than that of quinidine.

**B. Compounds 10–15.** This series of modifications was designed as a tool for the detection of the effects on antiarrhythmic potency of increased lipophilicity by the stepwise transformation from the unsubstituted to the monochloro to the dichlorobenzamide derivatives according to proposals outlined by Topliss.[7] This scheme theoretically should lead to the synthesis of the most effective derivative if indeed the physicochemical properties produced during the modification of the substitutions in the aromatic portion of the drug molecule are important in elicitation of the biological response. Examination of the data for compounds **10–15** clearly shows that the increased lipophilicity in the transition in the cis isomers **10** → **12** → **14** and the trans isomers **11** → **13** → **15** resulted in the production of more effective antiarrhythmic agents. It was of interest to note that the toxicities did not follow the therapeutic trends in that the trans compound **15** was of intermediate toxicity between trans compounds **11** and **13**; in the cis series an increase in toxicity was noted with the increased lipophilic nature of the benzamide substituent. No significant differences in potency were noted between the pairs of diastereoisomers **10** and **11**, **12** and **13**. However, in the 3,4-dichlorobenzamides the cis isomer **14** appeared to be the more potent isomer. It is of note that compounds **14** and **15** possessed therapeutic indices three to four times that of quinidine and yielded the optimal compounds of the entire series. The findings of this series provide support for Topliss' concept.[7]

**C. Compounds 10, 11, and 16–18.** An attempt was made to ascertain the importance of the nature of the linkage between the decahydroisoquinoline and the aromatic substituent. Benzamides **10** and **11**, benzenesulfonamides **16** and **17**, and benzoyloxy **18** derivatives were thus prepared and evaluated. The nature of the linkage appears to have little effect on antiarrhythmic potency. However, the toxicity of the ester derivative **18** was significantly greater than the remaining compounds in this series. Insufficient material prevented the synthesis of the trans isomer of **18**. The therapeutic indices of this group of compounds were equal to, or slightly in excess of, that of quinidine.

**D. Compounds 18–22.** This limited series of ester derivatives demonstrated the superiority of the trans isomers over their cis counterparts in both antiarrhythmic potency and toxicity (*i.e.*, **20** > **19** > **22** > **21**). As a group these compounds exhibited the greatest toxicities encountered in the entire series, which was reflected in the therapeutic index values of a magnitude similar to that of quinidine.

## Conclusion

A series of 8-substituted diastereoisomeric 2-methyldecahydroisoquinolines has been synthesized and shown to possess significant antiarrhythmic properties of a magnitude far superior to that of quinidine. The data indicate that lipophilic aromatic substitutions of the trans ring junction isomer provide agents with outstanding activities. The implications noted in our previous studies of some stereoselectivity in antiarrhythmic activity have been supplemented by some examples in the present study.

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## References

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