pressure. The solid residue was recrystallized from 1100 mL of ethanol after treatment with activated charcoal. The precipitate formed was collected by filtration, washed twice with ethanol, air-dried, and gave 342.9 g of pale yellow solid. The combined filtrate and washings above were reduced to about one-half volume, cooled to 4 °C, filtered, washed with cold ethanol, air-dried, and gave an additional 71.9 g of pale yellow solid. The combined filtrate and washings of the above solid was combined with an equal volume of diethyl ether and cooled to 4 °C. The solid formed was filtered, washed with 100 mL of 1:1 ethanol/ether, air-dried, and gave 84.7 g of a tan solid. The combined weight of 4-(3-bromopropyl)pyridine hydrobromide was 499.5 g (82.4%). To the 499.5 g of the preceding product in 500 mL of benzene was added a solution of 8.0 g of sodium hydroxide in 200 mL of cold water at 10–15 °C with stirring. The two-layered liquid was poured into a separatory funnel and an additional 50 mL of 10 N sodium hydroxide was added with thorough mixing. The aqueous layer (pH 13.0–13.5) was separated from the benzene layer and extracted with 200 mL of benzene. The benzene extracts were combined and dried over anhydrous potassium carbonate and anhydrous magnesium sulfate. The benzene solution was cooled to 5 °C and a total of 226 g of dimethylamine gas was added over a 2.5-h period with stirring. Stirring was continued while the solution was allowed to cool to room temperature overnight. A 300-mL portion of 10 N sodium hydroxide was added to the cooled reaction mixture with stirring, the layers separated and the aqueous layer was extracted with two 250-mL portions of benzene. The combined benzene extract was washed with three 100-mL portions of cold water and dried over anhydrous potassium carbonate and anhydrous magnesium sulfate. The aqueous layer was saturated with potassium carbonate, resulting in separation of an organic top layer which was insoluble in benzene. The organic layer was extracted twice with 250 mL of benzene as was the saturated aqueous layer. The combination of benzene extracts was dried over anhydrous potassium carbonate and anhydrous magnesium sulfate, stripped of solvent by water-pump evacuation, and gave 283.2 g of residual oil, which was distilled through a 15 × 2 cm Podbielniak Helipak filled column at a bath temperature ranging from 150 to 180 °C and controlled pressure of 9.0 to 10.0 mm. The 243.1-g (83%) fraction collected at a distillation temperature of 112–114 °C was 4-[3-(dimethylamino)propyl]pyridine.

A 16.4-g (0.10 mol) portion of the above product was dissolved in 100 mL of 1:1 ethyl alcohol/water and 34.2 mL of 5.85 N hydrogen chloride in isopropyl alcohol and reduced with 1 g of platinum oxide over 40 psi of hydrogen. The reduction mixture was filtered through diatomaceous earth, and the filter cake was washed with 50% aqueous ethanol. The combined filtrate and washings was stripped of solvent by water-pump evacuation. The residue was dried in vacuo over phosphorus pentoxide at 110 °C and gave 4-[3-(dimethylamino)propyl]piperidine dihydrochloride as an off-white solid, mp 233–239 °C (dec).

A mixture of 7.75 g (0.0195 mol) of *N*-[2,3-bis(4-methyl-1-piperazinyl)-6-quinoxalinyl]formimidic acid ethyl ester and 8.5 g (0.050 mol) of the preceding product (free base) above was heated at reflux in an oil bath at about 140 °C for 2.5 h. The condenser was removed and the distillate was allowed to boil off. The reaction mixture was slurried with 150 mL of boiling hexane, cooled at -10 °C, and filtered. The pasty material collected was dissolved in 90 mL of hot acetonitrile. This solution was treated with activated charcoal and filtered. The filtrate was cooled at -10 °C, and the yellow solid formed was collected by filtration, dried in vacuo at 78 °C over phosphorus pentoxide, and gave 3.9 g (38.5%) of 6-[[[4-[3-(dimethylamino)propyl]piperidino]-methylene]amino]-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (**11**), mp 135–139 °C.

Acknowledgment. We thank L. Brancone and staff for microanalyses, W. Fulmor and staff for spectral data, Dr. P. J. Kohlbrenner and staff for large-scale preparation of intermediates, and Dr. E. J. Burden and S. Carvajal for the biological testing data.

Synthesis and Antiarrhythmic Properties of Some 5-Benzamido-2-methyl-*trans*-decahydroisoquinolines

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An efficient synthetic route to produce exclusively 5-amino-2-methyl-*trans*-decahydroisoquinoline is described. The preparation of ten 5-benzamido-2-methyl-*trans*-decahydroisoquinolines from this precursor has been accomplished, and each has been screened for both antiarrhythmic potency and toxicity. The selection of structures for synthesis was based on our previous report of the significant antiarrhythmic potency of 5-(3,4,5-trimethoxybenzamido)-2-methyl-*trans*-decahydroisoquinoline (**15**). Molecular modifications of this single structure were made in order to ascertain structure–activity relationships in this group of compounds. All the compounds synthesized showed significant antiarrhythmic potency. The lipophilicity of the benzamide moiety appears to play a significant role in developing optimal antiarrhythmic potency. Interestingly and surprisingly, the most potent compound of the present study was **15**, a compound described in our original work. Structure–activity relationships of the series are described.

In a continuing investigation of the antiarrhythmic properties of variously substituted decahydroisoquinolines, a more extensive study was conducted of some of our earlier work related to the 5-substituted decahydroisoquinoline series. The early studies indicated that the more lipophilic trans ring junctured isomers possessed the optimal antiarrhythmic potencies.[2a,b] Subsequent studies on several examples of 6-[3] and 8-substituted[4] decahydroisoquinolines yielded similar conclusions. In addition, the

(1) The work reported constituted a segment of the thesis submitted by R. J. Pennington to the University of Tennessee, Center for the Health Sciences, in partial fulfillment of the Master of Science degree requirements in medicinal chemistry.

(2) (a) I. W. Mathison, R. C. Gueldner, J. W. Lawson, S. J. Fowler, and E. R. Peters, *J. Med. Chem.*, 11, 997 (1968). (b) I. W. Mathison, P. H. Morgan, R. R. Tidwell, and C. R. Handorf, *J. Pharm. Sci.*, 61, 637 (1972).

(3) I. W. Mathison and R. R. Tidwell, *J. Med. Chem.*, 18, 1227 (1975).

(4) I. W. Mathison and P. H. Morgan, *J. Med. Chem.*, 17, 1136 (1974).

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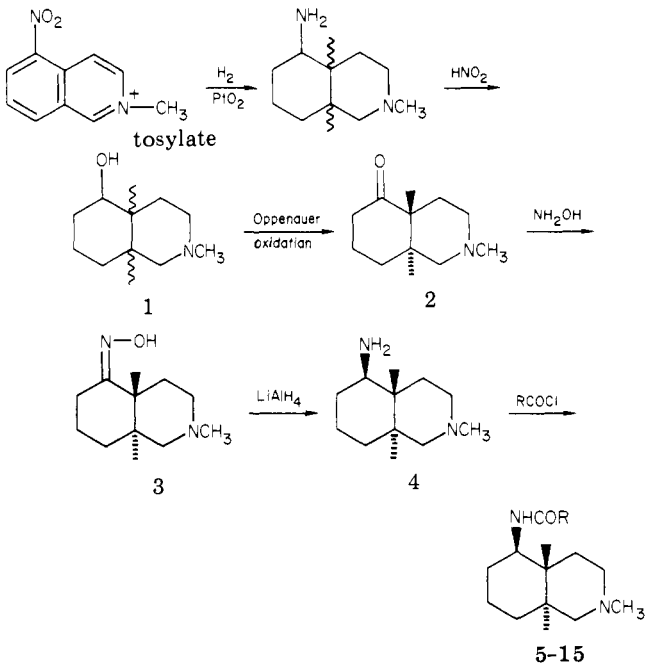
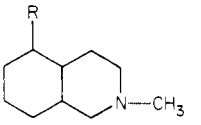
Scheme I



general observation was made that amide substitutions yielded compounds possessing higher LD_{50}/ED_{50} ratios. The optimal compounds of the 5-, 6-, and 8-substituted series were benzamide derivatives. These results prompted a more thorough investigation of the 5-substituted class of compounds to include a larger selection of *trans*-decahydroisoquinolines substituted with various benzamides.

An efficient synthesis for 5-amino-2-methyl-*trans*-decahydroisoquinoline, or a compound which could be readily converted to this amine, was needed. Previous approaches to obtaining the pure diastereoisomers of the several decahydroisoquinolines involved time-consuming fractional recrystallization procedures.[5,6] Since the production of only a *trans*-decahydroisoquinoline was sought, utilization was made of the equilibration of 2-methyldecahydroisoquinolin-5-one to its more stable trans ring junction isomer. A diastereoisomeric mixture of 5-amino-2-methyldecahydroisoquinolines was obtained from the platinum oxide catalyzed hydrogenation of 5-nitroisoquinoline as previously reported.[7] Deamination of this amine mixture with nitrous acid according to previously reported procedures[5-7] yielded the corresponding hydroxy compounds in good yield. Oppenauer oxidation[5] of the resulting isomeric mixture of hydroxy compounds provided pure 2-methyl-*trans*-decahydroisoquinolin-5-one (**2**). Preparation of the oxime (**3**) from this ketone, followed by $LiAlH_4$ reduction, produced the desired trans ring junction isomer of 5-amino-2-methyldecahydroisoquinoline (**4**) in good yield without the tedium of isomeric separation procedures. Confirmation of the complete stereochemistry of **4** (including the expected $LiAlH_4$ reduction of the oxime to an equatorial positioned NH_2 grouping) was obtained by conversion of **4** to its 3,4,5-trimethoxybenzamide (**15**). The product **15** was identical (mp, mmp, spectral data) with that of the known compound.[2a] The amine **4** was converted to the appropriate benzamide by standard methodology. The synthesis is outlined in Scheme I. Target compounds were selected utilizing the principle of the operational scheme for analogue synthesis of Topliss,[8] in which optimization of the pharmacological activity of a lead compound is achieved by alteration of the substituents on the aromatic moiety. A total of ten 5-benzamido-2-methyl-*trans*-decahydroisoquinolines were prepared.

Table I. Physical Data of 5-Benzamido-2-methyl-*trans*-decahydroisoquinolines



R	no.	recrystn solvent	yield, %	mp, °C
$-NHCOC_6H_5$	5	EtOAc	80	203-204
$-NHCOC_6H_4$-4-Cl	6	EtOAc	61	225-226
$-NHCOC_6H_3$-2,4-Cl_2	7	EtOAc	81	200-212
$-NHCOC_6H_3$-3,4-Cl_2	8	EtOAc	54	204-205
$-NHCOC_6H_4$-4-CF_3	9	EtOAc	77	217-218
$-NHCOC_6H_4$-4-NO_2	10	EtOAc	74	238
$-NHCOC_6H_4$-4-OCH_3	11	EtOAc	73	208-209
$-NHCOC_6H_4$-4-CH_3	12	EtOAc	73	218-220
$-NHCOC_6H_4$-3-Cl	13	EtOAc	89	206-207
$-NHCOC_6H_4$-4-F	14	EtOAc	63	207-209
$-NHCOC_6H_2$-3,4,5-$(OCH_3)_3$[a]	15			

[a] Prepared previously; see ref 2a.

Table II. Antiarrhythmic Potencies and Toxicities of 5-Benzamido-2-methyl-*trans*-decahydroisoquinolines

compd	LD_{50},[a] μmol/kg	ED_{50},[a] μmol/kg	LD_{50}/ED_{50}
quinidine	524 (469-586)	122 (97-152)	4.30
5	866 (804-892)	101 (88-116)	8.58
6	929 (867-994)	49 (26-93)	19.0
7	624 (601-648)	88 (53-147)	7.10
8	630 (618-642)	32 (14-73)	19.55
9	661 (623-702)	48 (29-81)	13.64
10	1103 (1043-1166)	95 (57-157)	11.67
11	1141 (1108-1174)	109 (69-174)	10.45
12	803 (772-834)	110 (65-185)	7.30
13	613 (574-665)	73 (38-143)	8.36
14	992 (885-1109)	110 (63-194)	9.0
15	610 (574-646)	25 (16-41)	24.02

[a] Figures in parentheses are 95% confidence limits.

Results and Discussion

The pharmacological data assembled in Table II clearly show that the compounds synthesized possess significant antiarrhythmic potencies. Since the data are expressed on a molar basis, structure–activity trends may be readily observed. These relationships will be considered under four groupings.

(1) Compounds 5–8 and 13. It was anticipated from our studies on the 6- and 8-substituted decahydroisoquinolines that addition of the lipophilic chlorine atoms to the aromatic ring of the benzamide moiety would result in increased potency and toxicity.[3,4] The 4-chloro (**6**) and

(5) I. W. Mathison and P. H. Morgan, *J. Org. Chem.*, **39**, 3210 (1974).
(6) I. W. Mathison and R. R. Tidwell, *J. Chem. Soc., Perkin Trans. 1*, 757 (1976).
(7) I. W. Mathison and R. C. Gueldner, *J. Org. Chem.*, **33**, 2510 (1968).
(8) J. B. Topliss, *J. Med. Chem.*, **15**, 1006 (1972).

the 3,4-dichloro (8) compounds of the current series clearly confirmed our expectations in regard to antiarrhythmic potency. The 2,4-dichloro compound (7) and the 3-chloro analogue (13), however, were found to be essentially equipotent with the unsubstituted parent compound 5; a somewhat interesting observation since both 7 and 13 are positional isomers of 8 and 6, respectively. With the exception of compound 6, the chlorobenzamides were more toxic than the unsubstituted 5, a finding in agreement with our studies on other benzamidodecahydroisoquinolines. The 4-chlorobenzamide (6) was essentially equitoxic to 5. The LD_{50}/ED_{50} ratios of the chlorinated compounds as a group were of a very much higher magnitude than that of quinidine and the unsubstituted benzamide 5. While 6 and 8 demonstrated some of the highest ratios reported in this paper, the 95% confidence limits of the individual values should be noted. Limited quantities of the test compound prevented additional animals from being added to tighten the confidence limits.

(2) Compounds 5, 11, 12, and 15. This group includes the methoxy- and methylbenzamides. The most notable compound in this group was the 3,4,5-trimethoxybenzamide (15), which was the most potent compound of the entire series. Interestingly, its toxicity approximated that of the more lipophilic compounds of group 1, a finding which was not anticipated from our earlier studies.[3,4] The antiarrhythmic potency of the 4-methoxy derivative 11 and the methyl analogue 12 did not differ from the parent molecule 5. However, the toxicity of 11 was markedly less than 12, which did not differ from 5. The high potency of 15 enabled it to exhibit the largest LD_{50}/ED_{50} ratio of the series, an approximately sixfold increase over that for quinidine.

(3) Compounds 5 vs. 9 and 6 vs. 9 vs. 12. The compounds in this group represent isosteric replacements within the benzamide moiety, 4-CH_3 (12) vs. 4-CF_3 (9) vs. 4-Cl (6) and 4-H (5) vs. 4-F (14). No differences in potency or toxicity were apparent between isosteres 5 and 14. However, in the 6, 9, 12 grouping, the least lipophilic isostere, 12 (4-CH_3), possessed the lowest antiarrhythmic potency. The CF_3 analogue (9) was the most toxic of this isosteric trio.

(4) Compound 10. It was anticipated that the addition of a compound possessing a benzamide substituent with markedly different electronic characteristics than those of the other substituent groupings considered might produce interesting data. Addition of the NO_2 grouping to the benzamide moiety would be expected to impart a marginal increase in lipophilicity compared to the unsubstituted analogue 5 but would result in a compound with increased σ character relative to 5. The antiarrhythmic potency of the nitrobenzamide 10 did not differ from 5, although it was somewhat less toxic; indeed, 10 was one of the least toxic members of the entire group prepared in this study.

Conclusion

The current series was developed to expand on the preliminary observations on the 5-substituted decahydroisoquinolines, the group of compounds which provided the lead for several studies on a large range of compounds. The compounds in the current study were chosen in an attempt to determine if parameters in addition to lipophilicity are involved in the mechanism of action of these antiarrhythmic structures. The Topliss Scheme[8] would readily identify the involvement of electronic parameters. The potencies of the compounds synthesized in the present study deviate from the pattern anticipated from Topliss postulates. None of the molecular structures synthesized in the present study showed antiarrhythmic potencies superior to that of the 3,4,5-trimethoxybenzamide (15), a compound prepared in our original work.[2a]

Experimental Section

Pharmacological Evaluation. All compounds synthesized were evaluated for acute toxicity (24 h) in female, Roswell Park (ICR) white mice, weighing approximately 15–25 g. The intraperitoneal route of administration was chosen, and groups of at least ten mice were injected at a minimum of three dose levels differing logarithmically by intervals of 0.1 or less. Dose–response data were treated according to Litchfield and Wilcoxon[9] and are expressed in Table II in micromoles/kilogram, together with the associated 95% confidence limits. For the most part, if death did not occur within 5 h of injection, the animals survived. The immediate toxic symptoms were drowsiness, writhing, gasping, loss of motor control, tremors, and convulsions, which in most cases preceded death.

Antiarrhythmic potency was determined in mice of the same strain, sex, and weight as used in the toxicity testing, using a slightly modified version of the Lawson[10] chloroform-induced ventricular fibrillation assay which has been traditionally used in our work. Compounds were administered to groups of animals with an interval of 2 min between the dosing of each animal. After the compounds were administered, the animals were placed in separate glass beakers where they could be observed for toxic symptoms. Ten minutes after drug administration, a mouse was transferred to a covered 300-mL glass beaker which contained cotton saturated with approximately 20 mL of chloroform. The animal was observed closely and removed from the beaker immediately after respiratory arrest. At this time, heart rate and rhythm was monitored with an electrocardiogram employing lead 2, where pin hooks were inserted just below the right clavicle and the left lower side of the rib cage of the test mouse. Electrocardiograms were recorded on an E and M Instrument Co. Physiograph, No. 6. The test compound was considered to have given a positive response (i.e., suppression of the heart rate) if the rate and rhythm were regular and less than 200 beats per minute. Control mice were injected with 0.9% saline intermittently throughout the test procedure. The antiarrhythmic potencies of the test compounds, together with their 95% confidence limits, are included in Table II and are expressed in micromoles/kilogram.

Solubilization was achieved by dissolving the compounds in a few milliliters of 0.9% saline with the addition of a drop or two of dilute hydrochloric acid. The solution was made up to volume with 0.9% saline. The pH of the solutions prepared was found to approximate physiological pH.

Quinidine was utilized as an antiarrhythmic standard, and data collected for the standard compared favorably with the previous reports from our laboratory.[3,4]

Chemistry. All melting points were determined using a Swissco melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. Where analyses are indicated, values within ±0.4% of the theoretical values were considered acceptable. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 457 grating spectrophotometer. Vapor-phase chromatography (VPC) was carried out using a Packard Model 407 chromatograph, employing a flame-ionization detector with a 4 ft × $^1/_8$ in. 3% OV-17 on Supelcort 100/120 M column.

5-Hydroxy-2-methyldecahydroisoquinolines (1). An isomeric mixture of 5-amino-2-methyldecahydroisoquinoline was prepared by way of a low-pressure catalytic hydrogenation of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate over PtO_2 according to the procedure outlined by Mathison and Gueldner.[7] The crude amines (84%) were distilled under vacuum (50–60 °C at 0.2 mm) to yield an oil, which on IR and VPC examination compared favorably with material previously reported.[7] This isomeric mixture (10.0 g, 0.06 mol) was deaminated with nitrous acid according to the procedure of Mathison and Morgan[5] to give an isomeric mixture of the desired hydroxy compounds: yield

(9) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(10) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, 16, 22 (1967).

9.15 g (91%); bp 110–125 °C (0.1 mm); IR 3400 cm^{-1}.

2-Methyl-*trans*-decahydroisoquinolin-5-one Oxime (3). The diastereoisomeric mixture of alcohols 1 (20.8 g, 0.12 mol) was dissolved in 300 mL of benzene and refluxed in a flask equipped with a Dean–Stark trap for 30 min to ensure dryness. To this solution were added 34.6 g (0.31 mol) of potassium *tert*-butoxide and 112.3 g (0.62 mol) of benzophenone. The mixture was purged with dry nitrogen and refluxed for 6 h with a continuous stream of dry nitrogen slowly passing through the reaction flask. After cooling, the reaction medium was extracted with a 10% HCl solution. The acidic extract was poured over ice and then made strongly alkaline with NaOH solution. The resulting basic solution was extracted with ether. The ethereal extract was washed twice with a saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and concentrated. The crude 2-methyl-*trans*-decahydroisoquinolin-5-one (**2**), 20 g (97%), was obtained as a dark brown oil. Purification was achieved by distillation at 55–65 °C (0.1 mm) [lit.[11] 85 °C (0.3 mm)]: IR 1710 cm^{-1}; picrate (recrystallized from methanol) mp 213 °C (lit.[11] 211–213 °C. Conversion of the ketone **2** to its oxime was achieved according to the method of Fryer et al.[12] Compound **2**, 1 g (0.006 mol), and hydroxylamine hydrochloride, 1.6 g (0.023 mol), were dissolved together with 3.19 g (0.023 mol) of hydrated sodium acetate in 10 mL of H_2O and 20 mL of 95% EtOH. The mixture was heated under reflux for 30 min. The volume of the mixture was then concentrated under reduced pressure by rotary evaporation until a precipitate formed. The precipitate was collected by vacuum filtration. A further product crop was obtained by concentration of the filtrate. The combined fractions of precipitated oxime and salts were added to water, which conveniently separated the aqueous soluble salts from the H_2O-insoluble oxime. The oxime was collected by vacuum filtration and washed with H_2O, yielding 0.78 g (72%) of the desired 2-methyl-*trans*-decahydroisoquinolin-5-one oxime (**3**) as a white solid: mp 182–183 °C; IR (C=NOH) 1667 cm^{-1}. Anal. ($C_{10}H_{18}N_2O$) C, H, N.

5-Amino-2-methyl-*trans*-decahydroisoquinoline (4). 2-Methyl-*trans*-decahydroisoquinolin-5-one oxime (**3**) was reduced to the desired amine 4 according to the procedure of Burger and Bennet.[13] Compound **3**, 1 g (0.005 mol), was suspended in 65 mL of hot, dried ($LiAlH_4$) tetrahydrofuran and added dropwise to a stirring suspension of 0.67 g (0.02 mol) of $LiAlH_4$ in 50 mL of dried tetrahydrofuran. The mixture was heated to reflux and maintained for 24 h. After cooling, the reaction complex was decomposed by the careful dropwise addition of H_2O. The decomposed reaction mixture was treated with 50 mL of a 10% HCl solution and then poured into a separatory funnel. The tetrahydrofuran layer was washed three times with 10% HCl solution. The acid extracts were combined, made strongly alkaline with NaOH, and extracted with ether. The ethereal extract was dried over anhydrous Na_2SO_4 and concentrated. The crude 5-amino-2-methyl-*trans*-decahydroisoquinoline, 0.82 g (89%), was obtained as a dark yellow oil. Purification was achieved by distillation at 50–60 °C (0.1 mm): IR (NH) 3300 cm^{-1}.

Conversion of this amine to its 3,4,5-trimethoxybenzamide according to the procedure described by Mathison[2a] yielded a solid, mp 217–219 °C. Mixture melting point with an authentic sample[2a] of 5-(3,4,5-trimethoxybenzamido)-2-methyl-*trans*-decahydroisoquinoline produced no depression of the melting point.

General Preparation of 5-Benzamido-2-methyl-*trans*-decahydroisoquinolines 5–15. The appropriate acid chloride (0.0065 mol) was dissolved in dried benzene and added to a stirring solution of 5-amino-2-methyl-*trans*-decahydroisoquinoline (**4**; 0.0057 mol) and triethylamine (0.015 mol) dissolved in dry benzene. The mixture was allowed to reflux with stirring for 48 h. Removal of the benzene under reduced pressure by rotary evaporation yielded a solid residue, which was dissolved in chloroform and washed three times with a 10% Na_2CO_3 solution followed by H_2O. The chloroform extract was dried over anhydrous Na_2SO_4 and concentrated to yield the crude product. The structures of the compounds, recrystallization solvents, melting points, and percentage yields are listed in Table I.

Acknowledgment. The authors acknowledge the valuable assistance and interest of Drs. Robert L. Stanley and Ben R. Durian, Ferris State College, School of Pharmacy, at several stages of this investigation.

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(12) R. I. Fryer, J. V. Earley, E. Evans, J. Schneider, and L. H. Sternbach, *J. Org. Chem.*, **35**, 2455 (1970).
(13) A Burger and W. Bennett, *J. Am. Chem. Soc.*, **72**, 5414 (1950).

Synthesis and Biological Activity of Flavipucine Analogues

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A series of analogues of flavipucine was prepared possessing side chain as well as nuclear variants. The analogue with an octyl side chain (**5d**) was found to exhibit enhanced activity against several bacteria and fungi as compared with the natural product itself. The separation and characterization of the individual diastereoisomeric pairs both spectroscopically and with respect to chromatographic mobility have been effected.

In 1968 Casinovi et al.[1] reported the moderate activity of flavipucine (isolated from *Aspergillus flavipes*) against certain Gram-positive and Gram-negative organisms. The total synthesis of flavipucine in 1976[2] made possible the selective synthesis of nuclear as well as side-chain variants of this antibiotic. In the process of preparing these analogues, the original synthesis has been materially improved, especially in the epoxidation sequence, thereby permitting yields in several instances in excess of 70% to be realized. The mechanism of this reaction, as well as other chemistry related to the flavipucine structure, has already been published elsewhere.[3,4]

The single most remarkable aspect regarding the biological activity of flavipucine is the finding that both synthetic (±)-flavipucine and its (±) diastereoisomer exhibit activity against a variety of organisms equal to that of natural (−)-flavipucine itself.[5] A degree of differenti-

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(2) N. N. Girotra, Z. S. Zelawski, and N. L. Wendler, *J. Chem. Soc., Chem. Commun.*, 566 (1976). See also J. A. Findlay, J. W. H. Tam, and J. Krepinsky, *Synth. Commun.*, 149 (1977).
(3) (a) N. N. Girotra, A. A. Patchett, and N. L. Wendler, *Heterocycles*, **6**, 1299 (1977); (b) J. A. Findlay, J. Krepinsky, A. Shum, C. G. Casinovi, and L. Radics, *Can. J. Chem.*, **55**, 600 (1977).
(4) N. N. Girotra and N. L. Wendler, *Heterocycles*, **9**, 417 (1978); J. A. Findlay, *ibid.*, **12**, 389 (1979).
(5) Similar observations were made with racemic natural and unnatural dihydroquinine with respect to activity and toxicity in mice infected with *Plasmodium berghei*. Cf. A. Brossi, *Heterocycles*, **5**, 631 (1976), and references therein.

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