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REVIEW ARTICLE

Arrhythmias and Antiarrhythmic Drugs: Mechanism of Action and Structure–Activity Relationships II ▲

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Keyphrases □ Antiarrhythmic drugs—classifications, mechanism of action, structure–activity relationships, review □ Structure–activity relationships—antiarrhythmic drugs, review □ Arrhythmias—related to changes in normal transmembrane action potential and electrophysiological parameters, antiarrhythmic drugs, review

CONTENTS

CLASSIFICATIONS OF ANTIARRHYTHMIC DRUGS

Several attempts have been made to classify antiarrhythmic drugs according to their electrophysiological properties. Again, disagreement arises due to the complications mentioned earlier and due to the lack of agreement over which drug-induced changes in the transmembrane action potential are most responsible for the therapeutic action in humans. The measure of success of any classification depends upon its relevance to, and usefulness in, the clinical situation.

As discussed previously, Szekeres and Papp (15) divided antiarrhythmic drugs into two broad classes: (*a*) nonspecific, for the quinidine-like membrane-stabilizing drugs, and (*b*) specific, for the β-adrenergic blocking drugs.

Vaughan Williams (13, 163, 164) proposed four classes of drugs (Table VI). Class I includes the membrane-stabilizing drugs which interfere with sodium-ion influx during rapid depolarization, resulting in a decrease in the rate of rise (dv/dt) of phase 0.

Class II antiarrhythmic drugs include bretylium, propranolol, and other antisympathetic drugs in which little if any of their action is quinidine-like at therapeutic concentrations. This class includes drugs that are β-adrenergic blocking agents or that elicit their antisympathetic action by blocking the release of the sympathetic transmitters, epinephrine and norepinephrine. The blocking of sympathetic activity by these drugs is said to reduce the probability of arrhythmias, regardless of the nature of the precipitating factor (23).

Although Vaughan Williams classified bretylium as a Class II drug, eliciting its primary effect by β-adrenergic receptor blockade, Namm *et al.* (159) reported that bretylium exhibited Class I effects on rat atrium and ventricle muscle at concentrations previously thought to effect β-blockade only. The decrease in the rate of rise of phase 0 and the lengthening of the effective refractory period were essentially equal in normal and immunosympathectomized rats, indicating direct membrane depressant action rather than indirect effects from bretylium interacting with sympathetic neurons. *In vivo* and *in vitro*

▲ *Editor's note:* Part I of this article appeared in the April 1976 issue of the *Journal of Pharmaceutical Sciences*.

Table VI—Vaughan Williams' Classification of Antiarrhythmic Drugs

Class I	Class II	Class III	Class IV
Quinidine	Propranolol	Amiodarone	Verapamil
Procaine	Pronethalol	Oxyfedrine	XIX[b]
Procainamide	Bretylium	(Sotalol)[a]	
Lidocaine	Guanethidine	XX[a]	
Phenytoin	Alprenolol		
Disopyramide	Oxprenolol		
Ajmaline	Practolol		
Mexiletine	Sotalol		
(Propranolol)[c]	XX[d]		
(Alprenolol)[c]			
(Oxprenolol)[c]			

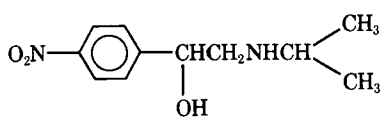
[a] These drugs have strong Class II action but also possess acute Class III action. [b] D-600. [c] These β-blocking agents possess Class I action only at high doses. [d] INPEA.

exposure of the myocardium to ^{14}C-bretylium showed that the drug was highly concentrated in the ventricle, and efflux studies indicated that the binding was tight, although slowly reversible. The subcellular distribution of the labeled drug bound to the ventricle suggested a binding to plasma membranes. The investigators concluded that their results indicate that underlying the antiarrhythmic action of bretylium is its accumulation in cardiac muscle cells and its direct effect on the electrophysiological properties of the membrane independent of any β-adrenergic receptor blockage.

The third class of antiarrhythmic drugs are those that affect the repolarization phase of the transmembrane action potential in contrast to the Class I drugs that affect the depolarization. Inhibition of repolarization causes an increase in the duration of the action potential. This has been found to occur in hypothyroid patients; in hyperthyroid patients, the action potential duration is decreased, which can result in atrial fibrillation.

After prolonged treatment (1–6 weeks) with amiodarone (157) or oxyfedrine (165, 166), a significant prolongation of repolarization and, hence, an increase in the absolute refractory period were observed and the effect did not appear to be linked with antithyroid action. The β-blocking agents, sotalol and *N*-isopropyl-1-(*p*-nitrophenyl)ethanolamine (XX) exhibit this action in addition to their Class II properties without the necessity of prolonged administration (167, 168).

Verapamil and its methoxy-substituted analog, XIX, belong to an apparent fourth class of antiarrhythmic agents. They are reported to have no significant effect on the rate of rise of phase 0, no β-blocking properties, and no effect on the repolarization phase except some shortening at 50% repolarization (28). Verapamil also is reported to be negatively inotropic (reduces the force of contraction). These effects are consistent with Vaughan Williams' postulate that verapamil probably elicits its antiarrhythmic activity by antagonizing the slow inward calcium-ion current associated with the slow response (13, 164). The slow response recently has been implicated in the genesis of arrhythmias arising in diseased tissue in which the fast response has been lost due to diminished resting potential (see earlier discussion of slow response).



XX

Table VII—Hoffman's Classification of Antiarrhythmic Drugs

Group 1	Group 2	Group 3
Quinidine	Lidocaine	Bretylium
Procainamide	Phenytoin	
Propranolol		
Antazoline		
Ajmaline		
Disopyramide		

To summarize, the fundamental electrophysiological properties upon which Vaughan Williams' classification is based are: Class I, interference with fast sodium-ion influx of phase 0; Class II, antisympathetic action; Class III, prolongation of repolarization resulting in increased duration and refractory period; and Class IV, depression of the slow calcium-ion influx associated with the slow response. Vaughan Williams emphasized that a drug may elicit more than one class of action, but the class in which he placed them appears to describe their primary beneficial action (13).

A different classification was proposed by Hoffman and coworkers (17, 137, 170) which divides antiarrhythmic drugs into three groups (Table VII). The basis of Group 1 drug action is quinidine-like in that automaticity, membrane responsiveness, and dv/dt are decreased and conduction is slowed. Group 2 drugs also decrease automaticity but are claimed to increase membrane responsiveness, dv/dt, and conduction; lidocaine and phenytoin are included in this group. The actions of these drugs are in dispute because one group of investigators claimed that they are depressant and do not improve membrane responsiveness at normal potassium-ion levels (23, 148, 151, 162). Others maintain that phenytoin and possibly lidocaine do improve membrane responsiveness and conduction at lower drug concentrations, which more closely correspond to therapeutic blood levels in humans (144, 160, 161).

A third group is proposed for bretylium because it appears to act by a different mechanism of action than the first two groups. No attempt is made in this classification to distinguish between the indirect cardiac effects of β-adrenergic blockade and the direct effects of membrane-stabilizing drugs.

To recapitulate, Hoffman's classification divides antiarrhythmic drugs into: Group 1, those that express their beneficial action by depressing membrane responsiveness and conduction; Group 2, those whose beneficial action arises from increased membrane responsiveness and improved conduction; and Group 3, those whose mechanism of action appears to be different than the first two.

Cranefield (80) proposed that arrhythmias arise almost exclusively from slow response activity in a dis-

crete and localized focus of partially depressed fibers. Based upon this concept, he tentatively divided antiarrhythmic drugs into three classes: Class 1, those that affect the fast inward sodium-ion current (membrane stabilizers); Class 2, those that affect the slow inward calcium-ion current (verapamil and XIX); and Class 3, those that affect the transitional fibers. Cranefield's classification is similar in some ways to Vaughan Williams' in that Class 1 and Class 2 of the former correspond to Class I and Class IV of the latter, respectively. Apparently, further experimentation is necessary before any specific examples can be included in Class 3.

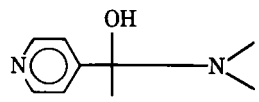
Sasyniuk and Ogilvie (144) stated recently that there is insufficient information on which to base a meaningful classification of antiarrhythmic drugs. However, they then observed that there appears to be two common actions for quinidine, procainamide, propranolol, lidocaine, and phenytoin. The first is that all five drugs are effective in suppressing automaticity in Purkinje fibers. The second is the ability to produce uniformity of the action potential duration and refractory period throughout the ventricular conducting system.

What becomes readily apparent in reviewing these different classifications is the lack of agreement over which observed electrophysiological change caused by a drug is most basic and eventually manifests itself therapeutically. Detailed knowledge of the biofunction of the macromolecular constituents of the excitable membrane could help clarify the confusion. Such knowledge may not be achieved for many years. However, as the sophistication of the voltage clamp technique advances, one may anticipate that investigations into the effects on each different ionic channel will lead to a more basic understanding and concise classification of the actions of antiarrhythmic drugs. Also, if the time comes when the contribution of each channel to the action potential can be measured accurately and a complete kinetic model can be constructed, it may become possible to describe and quantify mathematically the changes brought about by the actions of drugs.

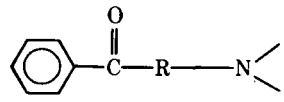
STRUCTURE–ACTIVITY RELATIONSHIPS

Nonspecific Antiarrhythmic Agents—Szekeres and Papp (15) extensively reviewed the structure–activity relationships of antiarrhythmic drugs prior to 1970 and proposed a chemical classification of these agents. Conn (171) also reviewed the structure–activity relationships of antiarrhythmic drugs, primarily restricting his discussion to quinidine and its metabolites and procainamide. These investigations indicated that most antiarrhythmic drugs possess a tertiary amine group, which appears to be essential for activity. The presence of a benzene, pyridine, quinoline, or some other form of an aromatic ring system is also important, and this moiety is usually connected to the tertiary amine *via* a hydroxy-substituted alkyl chain, ester, or amide group (XXI–XXIV).

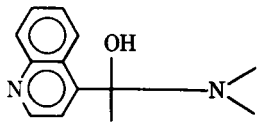
DiPalma and Lambert (172) indicated that methoxyl groups substituted on the aromatic ring portions of antiarrhythmic agents may enhance activity. For further classifications of other antiarrhythmic agents of different chemical structure, the reader is referred to Szekeres and Papp (15).



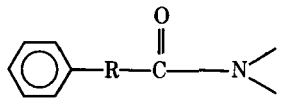
XXI



XXII: R = N or O



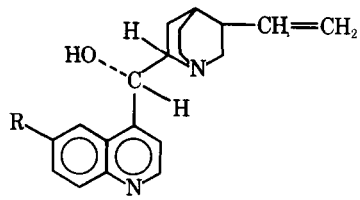
XXIII



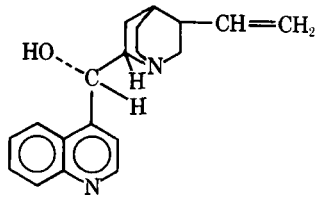
XXIV: R = N or O

The first attempt to determine the most potent compounds in a related series was by Frey in 1918 (2). He studied the antiarrhythmic potency of quinidine (I), quinine (XXV*a*), and cinchonine (XXVI); while all three possessed the ability to abolish atrial fibrillation, quinidine was the most potent. Gold *et al.* (173) compared the action of quinidine, quinine, cinchonine, and cinchonidine (XXV*b*) in slowing the rate of atrial circus movement and also found that quinidine was the most potent. Van Dongen and coworkers (174–177) reported on the action of several isomers and congeners of quinidine in increasing the myocardial resistance to arrhythmia-inducing levels of electrical shock. Some stereoselectivity was observed, but most compounds related to quinidine showed good activity.

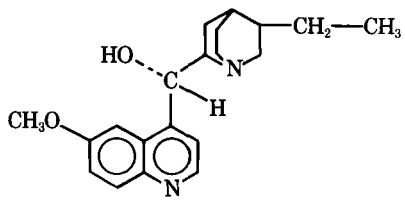
Recently, a study determined the antiarrhythmic potency and acute toxicity in mice of quinidine and a series of 10 congeners, including various isomers (178). Eight of the 10 compounds possessed significant antiarrhythmic activity, although quinidine and dihydroquinidine (XXVII) were the most potent. In



XXV*a*: R = CH_3O
XXV*b*: R = H



XXVI



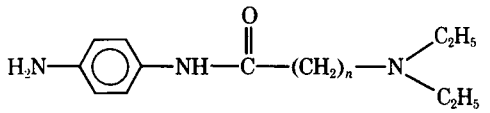
XXVII

this study, as in others (58, 179, 180), dihydroquinidine was shown to be slightly more potent than quinidine.

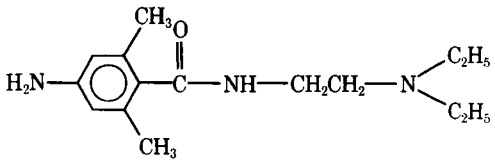
The antiarrhythmic potency was determined for a series of procainamide derivatives in which the *N*-ethyl substituents on the tertiary amine were modified or replaced (181). Replacement of both ethyl groups by related aliphatic groups (*i.e.*, isopropyl) greatly reduced activity, whereas replacement of only one ethyl group with an aromatic group greatly enhanced activity. A more recent structure–activity study on procainamide (II) involved amide reversal and *ortho*-methylation of the parent molecule (182). Results indicated that simple reversal of the amide group (XXVIII) in procainamide reduced activity about one-third whereas *ortho*-methylation (XXIX) of procainamide increased activity. The most active compounds were the *o*-methyl-substituted derivatives, in which the benzamido group of procainamide had been replaced by a benzoyl ester group (XXX).

Few structure–activity investigations that include physicochemical properties have been conducted on the nonspecific antiarrhythmic drugs, although those available have shown a correlation between physicochemical parameters (pKa and partition coefficient) and pharmacological potency. Studies on the effect of stereochemistry have been largely limited to differences in activity of diastereoisomers (*i.e.*, quinine and quinidine). However, optical isomerism (enantiomers) has been considered in the case of *d*- and *l*-propranolol and the other β-blocking agents in relation to their membrane-stabilizing properties. Activity is present in both the *d*- and *l*-forms with no significant difference in potency between the isomers (115–119).

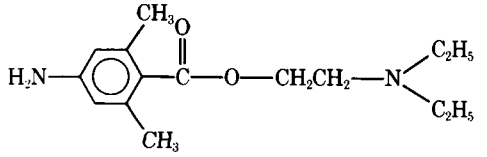
This finding seems to imply that the differences in activity observed in studies involving diastereoisomers are probably due to differences in the physical properties of the isomers and not necessarily to differences in arrangement of the atoms in space. Since it seems likely that nonspecific antiarrhythmic activity may depend largely on the physical characteristics of the molecules, studies correlating these characteristics with the differences in activity, especially in a closely related series of active compounds, should be valuable in developing superior antiarrhythmic agents.



XXVIII: $n = 1$ or 2



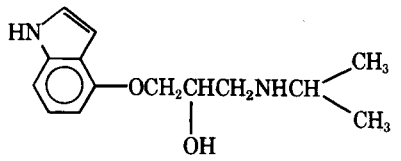
XXIX



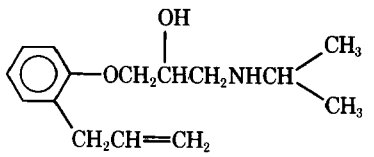
XXX

Investigations (183, 184) into the correlation between physicochemical properties and (*a*) β-blocking potency, (*b*) local anesthetic effect, and (*c*) myocardial membrane stabilization of a series of phenethanolamine and phenoxyisopropanolamine compounds led to the conclusion that there was a clear separation between β-blocking activity and the latter two actions. The physicochemical properties of these compounds were proposed to be determinants of their membrane affinity and, therefore, of their nonspecific pharmacological effects.

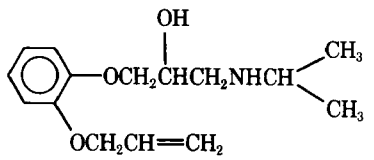
This proposal was further substantiated by quantitative correlations between surface activity, hydrophobicity (measured as octanol–water partition coefficient), local anesthesia, and changes in myocardial conduction velocity for β-adrenergic receptor blocking agents including VI, XX, pindolol (XXXI), alprenolol (XXXII), oxprenolol (XXXIII), practolol (XXXIV), sotalol (XXXV), 1-(3′-methylphenoxy)-2-hydroxy-3-isopropylaminopropane[14] (XXXVI), and 3-*tert*-butylamino-1-(6′-chloro-3′-methylphen-



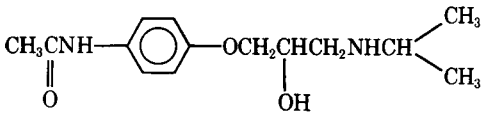
XXXI



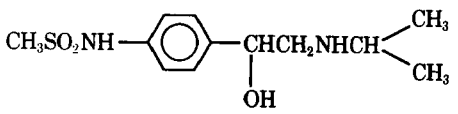
XXXII



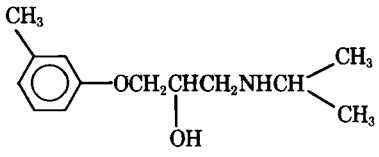
XXXIII



XXXIV

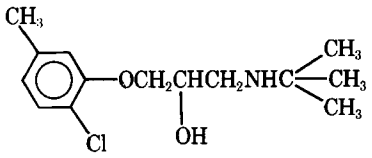


XXXV

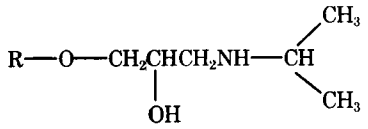


XXXVI

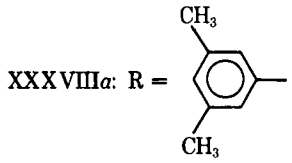
[14] Kö 592.

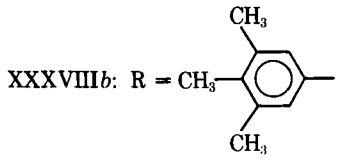


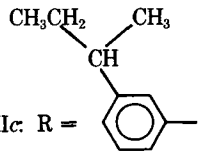
XXXVII

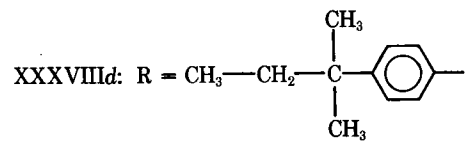


XXXVIII







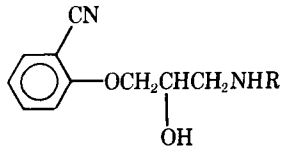


oxy)-2-propanol[15] (XXXVII) (185). A decrease in myocardial conduction velocity was considered a measure of membrane stabilization due to Class I action on cardiac fibers.

A close correlation was observed between the slowing of conduction, local anesthesia, the lowering of surface tension, and the partition coefficient, whether determined directly or calculated by the Hansch method (186, 187). Several conclusions were drawn as to the effect of various molecular modifications, all of which bear out that the nonspecific actions of the compounds studied increased in potency as the lipid solubility increased. This simple correlation allows the nonspecific actions of the series to be predicted with reasonable accuracy.

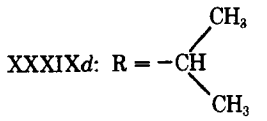
Two series of β-adrenergic receptor blocking drugs were subjected to a similar treatment in an effort to determine the effect of varying the degree of alkyl substitution on the phenyl ring in one series (XXXVI and XXXVIII*a–d*) and the effect of varying the size of alkyl substituents on the amino group in the other series (XXXIX*a–f*) (188). The difference in the degree of hydrophobicity ranged more than three orders of magnitude and was solely dependent on the sum of the hydrophobic contributions of the alkyl substituents. The degree of slowing of myocardial conduction was again used as a measure of the non-

[15] KL 255.

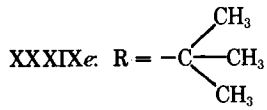


XXXIX

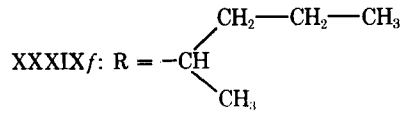
XXXIX*a*: R = −H
XXXIX*b*: R = −CH_3
XXXIX*c*: R = −CH_2−CH_3



XXXIX*d*: R = −CH(CH$_3$)$_2$



XXXIX*e*: R = −C(CH$_3$)$_3$

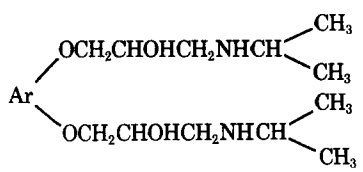


XXXIX*f*: R = −CH(CH$_2$CH$_3$)CH$_3$

specific action of the compounds, and their influence on the maximum rate of rise of intraventricular pressure (an index of the inotropic state of heart muscle) in anesthetized cats after β-blockade was measured *in vivo*. Both of these tests were purported by the authors to represent a measure of nonspecific cardiodepression.

The physicochemical and pharmacological data from both series of compounds were subjected to the Hansch analysis. This treatment revealed parabolic correlation equations between hydrophobicity and both pharmacological tests by plotting the log of the reciprocal IC_{50} or ED_{50} values *versus* log *P* (for interpretation of the parabolic case, see Ref. 189). The authors concluded that nonspecific cardiodepressant effects of β-blocking drugs can be predicted for given pharmacological systems by determination or calculation of the hydrophobicity of the drug molecules, irrespective of the site of the hydrophobic substituents.

A series of 11 bis(2-hydroxy-3-isopropylaminopropyl) ethers of dihydroxyarenes was synthesized, in which the points of substitution and the aromatic groups were varied (XL) (190). The compounds were evaluated for β-adrenergic receptor blocking action, local anesthesia, and myocardial depression in isolated guinea pig atrial muscle. The partition coefficients (octanol–pH 7.4 buffer) and dissociation constants were determined. Comparison of the β-blocking, local anesthetic, and antiarrhythmic (cardiodepressant) activities using multiple regression analysis indicated a good correlation between the latter two and insignificant correlation between β-blocking and the two nonspecific effects.



XL

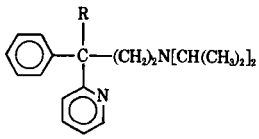


Table VIII—Data for Observed and Calculated Antiarrhythmic Potency[a]

Compound	R	π	IR, cm^{-1}, $\nu_{C=O}$	ln AP[b]		
				Obs.	Calc.[c]	Calc.[d]
1	—$CONCH_3N(CH_3)_2$	0.30	1640	2.254	2.276	2.276
2	—$CONHC_2H_5$	0.21	1656	1.891	1.936	1.965
3	—$CONHNHCH_3$	—0.35	1645	1.711	1.601	1.649
4	—$CO_2C_2H_5$	1.11	1733	1.677	1.518	1.603
5	—$CONHNHCOCH_3$	—0.57	1624	1.715	1.738	1.769
6	—$COCH_3$	0.75	1712	1.403	1.527	1.604
7	—$NHCOCH_3$	0.05	1679	1.313	1.419	1.492
8	—$CONHN{=}C(CH_3)_2$	0.21	1680	1.374	1.549	1.613
9[e]	—$CONH_2(H_3PO_4)$	0.00	1682	2.195		1.405
10	—$CONHNH_2$	—0.73	1622	1.407	1.624	1.663
11	—$CONHN(CH_3)_2$ (oxalate CH_3OH)	—0.59	1656	1.514	1.204	1.284
12	—CO_2CH_3	0.61[f]	1735	0.910	1.028	1.148
13	—$CONHC_6H_5$ ($H_2SO_4 \cdot 0.5H_2O$)	1.65	1683	2.935	2.818	2.795
14	—$CONHCH_3$	—0.31[g]	1661	1.404	1.379	1.449
15	—$CONHCH_2OH$	—0.82	1657	1.085	0.977	1.073

[a] Adapted, with permission, from T. K. Lin, Y. W. Chien, R. R. Dean, J. E. Dutt, H. W. Sause, C. H. Yon, and P. K. Yonan, *J. Med. Chem.*, **17**, 751(1974) (American Chemical Society, Washington, D.C.). [b] AP = 5 × MW × AR/1000, where MW is the molecular weight and AR is the activity ratio (described in Ref. 195). [c] The values were computed from an equation excluding disopyramide. [d] Including disopyramide. [e] Norpace. [f] This value was estimated by subtracting 0.5 from Compound 4. [g] This value was estimated by subtracting 0.5 from Compound 2.

Correlation of the physicochemical data and antiarrhythmic activity in a stepwise multiple regression analysis gave four optimal equations, two of which were parabolic. Inclusion of the log P and pKa terms provided the most relevant equation. Although the equations were unsuitable for predictive purposes, the authors claimed that they demonstrated the important role of lipophilicity since greater antiarrhythmic and local anesthetic potency resided in the compounds with higher partition coefficients.

Unfortunately, no mention was made of toxicity studies in any of these reports (185, 188, 190). However, there appears to be sufficient evidence that quantitative structure–activity relationship analyses can be of predictive value in assessing the cardiodepression of series of compounds designed to be β-adrenergic receptor blocking agents.

The only quantitative structure–activity relationship study of antiarrhythmic drugs considered to be Class I (Vaughan Williams classification) was performed on a series of disopyramide derivatives (Table VIII) (191–193) using a newly proposed quantum statistical method of analysis[16]. Briefly, the method is based on the rate and magnitude of the biological response being dependent upon two steps:

1. The drug molecule makes a Brownian-like motion from outside the cell to reach the receptor (determined by lipid solubility).

2. A binding mechanism between the receptor and drug molecule is established, which involves coupling of vibrational states between the receptor and the drug.

The probability of binding is related to the partition function of statistical mechanics associated with the quantum energy levels of the drug molecule. These quantum energy levels are observable by various spectral methods (IR and UV) and presumably describe the contribution to binding at the receptor site of involved functional groups of molecules having different electronic characteristics. The probability of eliciting a biological response is thus related to the probability of the drug being transported to the site of action (Step 1) and to the probability of the vibrational states of the receptor and active binding centers of the drug molecule being able to couple (Step 2).

This method was first used to analyze the antiarrhythmic activity of the series of disopyramide derivatives (Table VIII) synthesized previously (195). The compounds had structural modifications near the carbonyl group, which led to wide differences in the IR absorption peaks for the carbonyl group and to substantial differences in partition coefficients (octanol–pH 7.4 buffer). The antiarrhythmic potency (AP) was determined by dividing the mean maximal reduction in extrasystoles in the coronary artery-ligated dog by the mean effective dose. The equation used to evaluate the correlation between the two physical measurements and the antiarrhythmic potency was derived from the general equation:

$$\mathrm{AP} = \frac{d(\text{response})/dt}{1000C} = A p^{a1}(\text{Brownian}) \times p^{a2}(\text{binding}) \quad \text{(Eq. 1)}$$

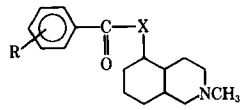
where C = molar concentration, and A = proportionality constant. The final equation is:

$$\ln \mathrm{AP} = C_1 + C_2\pi - C_3\nu_{C=O} \quad \text{(Eq. 2)}$$

where π = partition coefficient, $\nu_{C=O}$ = IR absorption in wave numbers, and C_1, C_2, and C_3 are determined by multiple regression analysis. This equation was specifically derived for correlation of the antiarrhythmic potency of the compounds in Table VIII. By using Eq. 2, the antiarrhythmic potencies were calculated for the series and correlated remarkably

[16] For a critical review of methods using quantum mechanics in assessing biological data, see Ref. 194.

Table IX—Physical and Pharmacological Data (Mice) of 5-Substituted 2-Methyldecahydroisoquinolines



R	X	Isomer[a]	Pc[b]	P.R.[c]	T.R.[d]	T.I.[e]
3,4,5-$(OCH_3)_3$	O	*cis*	0.23	1.33	2.13	2.0
3,4,5-$(OCH_3)_3$	O	*trans*	0.50	2.22	2.46	2.8
3,4,5-$(OCH_3)_3$	NH	*cis*	2.98	0.75	0.66	3.6
3,4,5-$(OCH_3)_3$	NH	*trans*	3.83	1.00	0.65	4.8
Quinidine	—	—	—	1.00	1.00	3.1

[a]These are diastereoisomers; for a full description of the stereochemistry, see Ref. 197. [b]Octanol–water partition coefficient. [c]Potency ratio compared to quinidine. [d]Toxicity ratio compared to quinidine. [e]Therapeutic index = LD_{50}/ED_{50}.

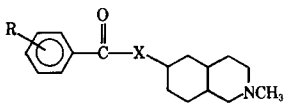
well with the experimentally determined values. The results indicated that a combination of high lipid solubility and a low wave number should give a compound of optimal potency. Again, no mention was made of the correlation, if any, of the physicochemical parameters with toxicity.

The same group of investigators also mathematically correlated the plasma protein binding capacity and lipophilicity of a series of 20 disopyramide derivatives with structural variances in the amide moiety, the phenyl ring, and the pyridyl ring (196). By using multiple regression analyses, an equation was derived to describe a linear correlation of the extent of plasma binding with the differences in lipid solubility, irrespective of the site of the structural modification. A Scatchard analysis showed that the interaction involved only a primary binding site, postulated to be the planar phenyl ring that intercalates into the plasma protein helix. Similar binding and interaction were postulated previously as the mode of action of nonspecific antiarrhythmic drugs on myocardial cell membranes (Fig. 7).

Benzoyl ester and benzamido derivatives of *cis*- and *trans*-5-, 6-, and 8-amino- and hydroxy-2-methyldecahydroisoquinolines, respectively, were synthesized (197–202). The compounds demonstrated antiarrhythmic potency in inhibition of chloroform-induced ventricular fibrillation in mice (200–202) and in prolongation of the functional refractory period of isolated guinea pig atria (200, 203). Additionally, the effects of three of the more potent 8-substituted derivatives on the transmembrane action potential of isolated canine Purkinje fibers were investigated and shown to exhibit Class I behavior (203).

Although no quantitative structure–activity analyses were performed on the series of eight 5-substituted, 23 8-substituted, and 16 6-substituted derivatives, apparent dissociation constants and measures of lipophilicity were obtained. The latter values were obtained by determination of the partition coefficient (octanol–pH 7.4 buffer) or the percentage buccal absorption. The relevant structures, lipophilicity data, potency and toxicity ratios, and LD_{50}/ED_{50} ratios from the mouse screening tests are included in Tables IX–XI. Within the entire series of compounds, the pKa values did not differ significantly and were discounted as being responsible for the differences in potencies. However, lipophilicities varied widely and were related in each series to potency and

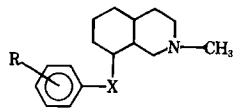
Table X—Physical and Pharmacological Data (Mice) of 6-Substituted 2-Methyldecahydroisoquinolines



R	X	Isomer	Pc[a]	P.R.[a]	T.R.[a]	T.I.[a]
Quinidine	—	—	—	1.00	1.00	3.3
H	NH	*cis*	2.96	0.43	0.39	3.6
H	NH	*trans*	2.40	0.44	0.37	4.0
4-Cl	NH	*cis*	17.1	0.53	0.59	3.0
3,4-$(Cl)_2$	NH	*cis*	50.5	1.63	0.70	7.8
3,4-$(Cl)_2$	NH	*trans*	46.2	1.10	0.63	5.8
4-OCH_3	NH	*cis*	2.75	0.48	0.34	4.7
3,4-$(OCH_3)_2$	NH	*cis*	1.98	0.63	0.35	6.0
3,4-$(OCH_3)_2$	NH	*trans*	1.87	0.56	0.36	5.1
3,4,5-$(OCH_3)_3$	NH	*cis*[b]	1.15	0.82	0.41	6.7
3,4,5-$(OCH_3)_3$	NH	*trans*	1.28	0.69	0.50	4.6
3,4,5-$(OCH_3)_3$	NH	*cis*[b]	0.97	0.64	0.39	5.5
3,4,5-$(OCH_3)_3$	O	*cis*	7.68	1.70	0.98	5.8
3,4,5-$(OCH_3)_3$	O	*trans*	6.95	1.21	1.04	3.9
3,4-$(Cl)_2$	O	*cis*	145	0.86	0.40	7.1
3,4-$(Cl)_2$	O	*trans*	127	0.60	0.47	4.3

[a]See footnotes to Table IX. [b]These are two *cis*-diastereoisomers; see Ref. 199 for a full description of stereochemistry.

Table XI—Physical and Pharmacological Data (Mice) of 8-Substituted 2-Methyldecahydroisoquinolines



R	X	Isomer[a]	B.A.[b], %	P.R.[c]	T.R.[c]	T.I.[c]
Quinidine	—	—	—	1.00	1.00	3.3
H	CONH	*cis*	41	0.66	0.37	5.9
H	CONH	*trans*	43	0.65	0.37	5.9
2-(OCH_3)	CONH	*cis*	35	1.38	0.63	7.3
2-(OCH_3)	CONH	*trans*	41	0.91	0.70	4.3
4-(OCH_3)	CONH	*cis*	31	0.60	0.34	5.8
4-(OCH_3)	CONH	*trans*	34	0.82	0.36	7.6
3,4-$(OCH_3)_2$	CONH	*cis*	18	0.80	0.30	8.9
3,4-$(OCH_3)_2$	CONH	*trans*	27	0.98	0.33	9.8
3,4,5-$(OCH_3)_3$	CONH	*cis*	24	1.00	0.46	7.3
3,4,5-$(OCH_3)_3$	CONH	*trans*	31	1.29	0.64	6.7
4-Cl	CONH	*cis*	43	0.77	0.59	4.4
4-Cl	CONH	*trans*	54	0.80	0.56	4.8
3,4-$(Cl)_2$	CONH	*cis*	61	2.19	0.75	9.7
3,4-$(Cl)_2$	CONH	*trans*	59	1.48	0.41	12.0
H	SO_2NH	*cis*	30	0.57	0.37	5.2
H	SO_2NH	*trans*	37	0.46	0.48	3.3
H	COO	*cis*	82	0.65	0.59	3.7
4-Cl	COO	*cis*	87	0.62	0.44	4.7
4-Cl	COO	*trans*	85	1.10	0.70	5.2
3,4,5-$(OCH_3)_3$	COO	*cis*	71	0.99	1.23	2.6
3,4,5-$(OCH_3)_3$	COO	*trans*	70	2.16	1.58	4.5

[a]For a full description of the stereochemistry, see Ref. 198. [b]Percentage buccal absorption from pH 9.2 buffer. [c]See footnotes to Table IX.

toxicity, the more highly lipid-soluble compounds generally exhibiting the greater activity.

Comparison of the two *cis–trans*-diastereoisomeric pairs in the 5-substituted series revealed that the rigid, near-planar *trans*-isomers possessed higher partition coefficients and were more potent than the corresponding *cis*-isomers. A similar relationship was observed in several isomeric pairs of the 8-substituted series, which had significant differences in lipophilicity. For the isomeric pairs of near-equal lipophilicity, the *trans*-diastereomer was usually more potent. This finding prompted a proposal that the receptor area in or on the cardiac membrane possessed some degree of stereoselectivity favoring the *trans*-isomers (135). However, examination of the data in the 6-substituted series revealed that the *cis*-isomers

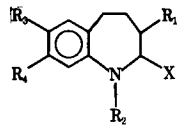
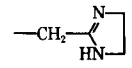
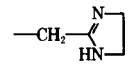
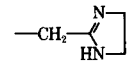


Table XII—Structures and Pharmacological Data (Mice) of 2,3,4,5-Tetrahydrobenzazepine Derivatives

R_1	R_2	R_3	R_4	X	ED_{50}[a], mg/kg	LD_{50}[a]	T.I.[b]
4-ClC_6H_5	$CH_2CH_2N[CH(CH_3)_2]_2$	H	H	=O	2.5	8	3.2
4-ClC_6H_5		H	H	=O	14.5	70	4.8
H	$CH_2CH_2N[CH(CH_3)_2]_2$	OCH_3	H	=O	46	142	3.1
H	$CH_2CH_2N[CH(CH_3)_2]_2$	H	OCH_3	=O	68	171	2.5
4-ClC_6H_5		H	H	H_2	21	71	3.4
H		H	H	H_2	Inactive	104	—

[a] Administered intraperitoneally. [b] LD_{50}/ED_{50}.

were generally more potent, toxic, and lipophilic than the corresponding *trans*-isomers.

In the 6- and 8-benzamido derivatives, potency increased stepwise with the introduction of the 4-methoxy, 3,4-dimethoxy, and 3,4,5-trimethoxy moieties into the phenyl ring, although lipophilicity did not increase accordingly. This finding supports the claim of DiPalma and Lambert (172) mentioned earlier, and it is interesting to speculate that perhaps the methoxyl groups could be affecting the IR vibrational frequency of the carbonyl group and influencing potency as proposed by Lin *et al.* (193).

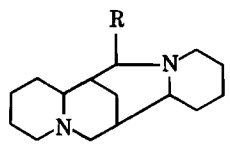
The stepwise introduction of chlorine atoms into the phenyl ring of the 6- and 8-benzamides according to the procedure reported by Topliss (204) resulted in compounds of increased lipid solubility and potency; from this scheme, the derivatives with the largest therapeutic index were obtained. There appeared to be no real advantage of one linkage between the decahydroisoquinoline ring and the aryl group over the others in the 8-substituted series, *i.e.*, ester, amide, or sulfonamide, although the esters were more lipophilic.

In assessing the importance of the point of attachment of the aryl ester or amide substituent, the 8-substituted compounds were generally more potent, with the 5- and 6-substituted compounds being nearly equipotent. The 5-substituted compounds were the most toxic, and the 6-substituted compounds were the least toxic. Again, lipophilicity appeared to be the most obvious determinant of potency.

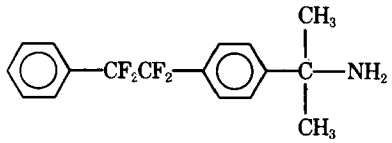
A series of 14 derivatives of 2,3,4,5-tetrahydrobenzo[*b*]-1*H*-azepine was synthesized, and their toxicity in mice and potency in protecting mice against chloroform-induced ventricular fibrillation were determined (205). No measurements of pKa or lipid solubility were reported, although some comments as to optimal structural requirements were made. Lipophilic substituents (4-chlorophenyl) appeared to improve potency and increase toxicity. The presence of the 4-chlorophenyl or a methoxy substituent seemed necessary for antiarrhythmic activity, since the compound lacking both was inactive. The structures and pharmacological data are included in Table XII. The first compound in the table exhibited remarkable potency in this test as compared to quinidine and other standard antiarrhythmic drugs (206).

A series of 17-alkyl-substituted sparteines (XLI) was investigated for effects on the functional refractory period of isolated guinea pig atria (207). The alkyl substituents ranged from methyl to hexyl, and activity was demonstrated throughout the series. The 17-butyl derivative produced the greatest prolongation of the refractory period, suggesting an optimal chain length of four carbons. The increase in potency in passing from methyl to butyl was attributed to an increasingly stronger hydrophobic interaction between the alkyl substituents and the hydrophobic side chains in the excitable membrane protein. The investigators concluded that the hydrophobic interaction is as important as the attraction of the cationic group by Coulombic forces to fixed anionic sites in the membrane.

A series of 29 2-, 3-, and 4-substituted benzylamine derivatives related to α,α-dimethyl-4-($\alpha,\alpha,\beta,\beta$-tetrafluorophenethyl)benzylamine (XLII) was synthesized to examine the structural requirements for antiarrhythmic activity. The parent compound (XLII) is a new, orally effective, and long-acting antiarrhythmic agent presently undergoing clinical trials. The derivatives were evaluated for their efficacy in

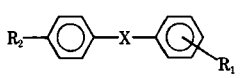


XLI



XLII

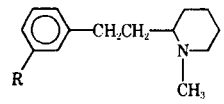
Table XIII—Structure and ED_{50} of Substituted Benzylamine Derivatives



R_1	R_2	X	Isomer	ED_{50}[a], mg/kg
Quinidine	—	—	—	7.6
p-$C(CH_3)_2NH_2$	H	CF_2CF_2	—	0.60
p-$C(CH_3)_2NH_2$	H	CH_2CH_2	—	0.32
p-$C(CH_3)_2NH_2$	H	C≡C	—	0.80
p-$C(CH_3)_2NH_2$	OCH_3	C≡C	—	Inactive
p-$C(CH_3)_2NH_2$	CH_3	C≡C	—	5.0
p-$C(CH_3)_2NH_2$	F	C≡C	—	2.9
p-$C(CH_3)_2NH_2$	*n*-Butyl	C≡C	—	1.0
o-CH_2NH_2	H	C≡C	—	2.5
o-CH_2NH_2	F	C≡C	—	5.4
o-CH_2NH_2	CH_3	C≡C	—	1.7
o-CH_2NH_2	OCH_3	C≡C	—	0.65
o-CH_2NH_2	H	C=C	*cis*	Inactive
o-CH_2NH_2	H	C=C	*trans*	1.7
o-CH_2NH_2	OCH_3	C=C	*trans*	Inactive
o-CH_2NHCH_3	H	C=C	*trans*	2.4

[a] Administered intravenously.

Table XIV—Structure and Potency of Substituted 2-Phenylethyl-*N*-methylpiperidine Derivatives



R	ED_{50}[a], mg/kg	P.R.[b]
Quinidine	83	1
NH_2	Inactive	—
$NHCOCH_3$	>50	—
OCH_3	>100	—
C_6H_5CONH	7.2	12
4-ClC_6H_4CONH	>25	<3.3
4-OHC_6H_4CONH	1.7	49
4-$NH_2C_6H_4CONH$	4.0	21
4-$CH_3COOC_6H_4CONH$	2.8	29
4-$OCH_3COOC_6H_4CONH$	7.1	12
3-$OCH_3COOC_6H_4CONH$	10	8.3
3,4-$(OCH_3)_2C_6H_3CONH$	10	8.3
3,5-$(OCH_3)_2C_6H_3CONH$	>50	<1.6
3,4,5-$(OCH_3)_3C_6H_2CONH$	39	2.1

[a] Administered intraperitoneally. [b] Potency ratio compared to quinidine.

preventing or controlling ventricular fibrillation after an experimentally induced infarction in anesthetized dogs.

Although no physicochemical properties were measured, the investigators deduced some molecular modifications which gave compounds as potent as XLII. Fourteen of the most active derivatives are shown in Table XIII. Replacement of the tetrafluoroethyl bridge with an ethylene unit gave increased potency, although the oral duration was reported to be shorter. Whereas substitution on the terminal phenylethynyl group in the *para*-substituted benzylamines decreased activity, similar substitution in the corresponding *ortho*-derivatives increased activity with the exception of the fluoro group. The effect of a 4-methoxy group in the *p*-phenylethynyl- and the *o*-phenylethenylbenzylamines was to abolish antiarrhythmic activity, whereas its presence in the *o*-phenylethynylbenzylamine produced the most potent compound of that series. The fact that activity resided exclusively in the *trans* geometrical isomer of the *cis*- and *trans*-phenylethenyl (X = CH=CH) derivatives may possibly indicate receptor stereoselectivity, although the effects of the differences in physicochemical properties of the pair (not reported) may play the major role in determining the presence or absence of activity.

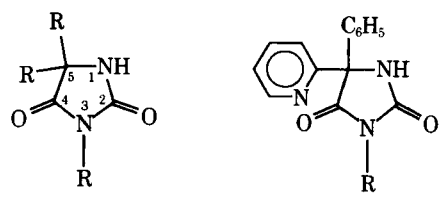
A series of 28 compounds of the structural type shown in Table XIV was synthesized, and their potency in preventing chloroform-induced ventricular fibrillation was determined in mice (209). Of the more active compounds listed, it appears that polar, hydrophilic substituents (*i.e.*, *p*-OH, *p*-NH_2, and *p*-acetoxy) in the *para*-position of the benzamide ring impart greatest potency and that the presence of the lipophilic *p*-chloro group decreases potency. Increasing degrees of methoxy substitution gave no advantage insofar as potency was concerned. No toxicity or physicochemical data were reported for the compounds, although the *p*-benzamido, *p*-hydroxy, *p*-amino, *p*-acetoxy, and *p*-methoxybenzamido derivatives were selected for further testing.

A series of 49 5,5-disubstituted 3-aminoalkylhydantoins (XLIII) was synthesized and evaluated for their activity in preventing chloroform-induced ventricular fibrillation in mice and in delaying aconitine-induced arrhythmias in guinea pig atria (210). The β-pyridyl derivatives (XLIV and XLV) appeared to be the most promising, although no toxicity or physicochemical properties were reported. Advantageous molecular modifications were discussed.

An investigation into the metabolism of lidocaine prompted the examination of the antiarrhythmic potencies of the mono- and dideethylated metabolites (211). The *N*-monoethyl derivative and the primary amine derivatives were 0.8 and 0.1 times as potent as lidocaine, respectively, probably due in part to the anticipated fall in lipophilicity.

Quaternary ammonium derivatives of various antiarrhythmic drugs have been prepared as a means to limit their actions to effects on electrophysiological properties of the heart. Although the permanent cationic head does not diminish the antiarrhythmic potency of the drug in several cases, it does eliminate the toxic manifestations on the CNS, presumably because the charged species is unable to pass through the blood–brain barrier. Generally, quaternization appears to abolish β-blocking activity and either abolish or lessen local anesthetic properties. The latter effect apparently results from the greater difficulty of the permanently charged compounds in penetrating the nerve membrane as compared to the cardiac membrane. An additional attractive feature of the quaternized drugs is the longer duration of action when compared to the parent molecules.

This approach was employed in a study in which the dimethylammonium salts of propranolol, bunolol, XX, and dichloroisoproterenol were prepared and



XLIII

XLIV: R = $CH_2CH_2N(CH_3)_2$

XLV: R = $CH_2CH(CH_3)CH_2N(CH_3)_2$

their pharmacological actions were compared with those of the parent compounds (212). In all four cases, quaternization abolished the β-blocking and local anesthetic activities and offered no protection against adrenergically induced arrhythmias, although some activity against ouabain-induced arrhythmias was observed.

Further studies on the dimethylammonium quaternary salt of propranolol[17] (XLVI) showed it to be effective against digitalis and myocardial infarction-induced arrhythmias in dogs (20). Rosen *et al.* (158) reported that XLVI demonstrated Class I behavior when applied to canine Purkinje fibers in concentrations similar to myocardial depressant concentrations of propranolol.

A series of 15 quaternary ammonium derivatives of lidocaine was synthesized, and their antiarrhythmic activity was determined (44). Although no details were included, all derivatives were reported to be effective; a consistent structure–activity relationship was observed throughout the series with regard to antiarrhythmic and other pharmacological and toxic activities. The optimal compound, XVI, recently received renewed interest and is undergoing clinical trials (22, 45–47).

The quaternary methylammonium derivative of lidocaine is as effective, or more so, than lidocaine in reversing ouabain-induced ventricular tachycardia by suppressing ectopic pacemakers, in reducing or abolishing arrhythmias resulting from experimentally produced myocardial infarction in dogs, and in raising the threshold for electrically induced fibrillation (150, 213, 214).

The activity of several antiarrhythmic compounds of widely differing molecular structures was correlated with their solubility and molecular volume (215). The physical properties of these molecules are of primary importance in determining their potency in inhibiting the automaticity of the ventricle induced by epinephrine. Therefore, the mechanism of membrane suppression by antiarrhythmic drugs may be similar to the general anesthetics (216), barbiturates (217), and local anesthetics (218), all of which appear to act in a nonspecific manner primarily resulting from their physical characteristics. This concept is consistent with the work of Frank (219), who postulated that general and local anesthetics and other drugs that depress excitable membranes by interfering with sodium influx during depolarization all act by a common mechanism which depends upon the physical properties of the molecules.

In summary, the more recent structure–activity relationship studies of nonspecific antiarrhythmic drugs offer no new information to necessitate alteration of the general structural requirements previously proposed (XXI–XXIV), with the exception that some primary and secondary amines also possess activity. The wide range of chemical structures found to possess antiarrhythmic acitivity, the dependence of potency on lipid solubility, and the lack of significant stereoselectivity at the site of action are all consistent with the proposed "physical membrane occupancy theory" of nonspecific antiarrhythmic action.

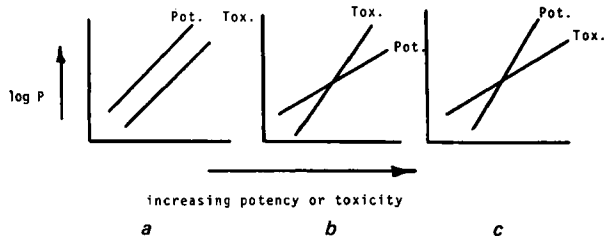


Figure 8—*Three possible ways potency (Pot.) and toxicity (Tox.) may relate to each other as lipophilicity (log P) increases.*

The most striking weakness of many studies reviewed was the lack of toxicity and physicochemical data for large series of structurally related compounds. These compounds would lend themselves readily to visual or quantitative structure–activity relationship analysis. The absence of toxicity data is surprising in view of the strong emphasis placed on early assessment of the ratio of acute toxicity to antiarrhythmic potency in a screening program (206, 220).

Attempts to correlate physicochemical properties with toxicity are also conspicuously absent in the quantitative structure–activity relationship investigations on antiarrhythmic drugs and other classes of drugs as well. Correlations predicting maximal potency alone are of limited use to the medicinal chemist in choosing the most promising compound for development unless information on toxicity trends is also available. If feasible, studies that detect correlations between physicochemical properties and the LD_{50}/ED_{50} ratio could be of great practical value.

More likely would be the determination of separate correlations of potency and toxicity with physicochemical properties. If, for example, both were linearly related to lipophilicity, the slopes of the plots of potency or toxicity *versus* the partition data in its appropriate form (Fig. 8) may relate to each other in one of three possible ways: (*a*) rates of increase in potency and toxicity parallel each other (Fig. 8*a*), (*b*) toxicity increases at a faster rate than potency (Fig. 8*b*), or (*c*) potency increases at a faster rate than toxicity (Fig. 8*c*). Obviously, knowledge of these relationships would prove useful in designing a drug with an optimum toxicity–potency ratio.

Of course, if no correlation between physicochemical properties and toxicity is observed, the toxicity of a whole range of active compounds would need to be determined to enable one to choose the optimal compound for development.

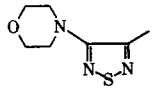
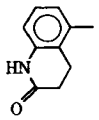
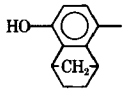
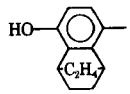
An irritating feature of many structure–activity relationship studies is the presentation of ED_{50} and LD_{50} data in milligrams per kilogram. It is totally invalid to relate potencies expressed in that way when the compounds of a series differ significantly in molecular weight. The data could be acceptably presented as millimoles per kilogram or micromoles per kilogram.

Cardioselective β-Adrenergic Antagonists—Structure–activity relationship studies on the β-blocking agents possessing antiarrhythmic activity

[17] UM-272.

Table XV—Structural Formulas of Some Myocardial Selective (+) and Nonselective (−) β-Adrenergic Receptor Antagonists

Ar—O—$CH_2CHOHCH_2NHR$

Compound	Ar	R	β_1 Selective	Reference
Propanolol	1-Naphthyl	$CH(CH_3)_2$	—	244
XLIX[a]	8-Thiochromanyl	$CH(CH_3)_2$	—	246
Pindolol	4-Indolyl	$CH(CH_3)_2$	—	244
Bifuralol	2-(7-Ethylfuranyl)	$C(CH_3)_3$	—	247
Bufetalol	2-Furfuryl	$C(CH_3)_3$	—	248
Timolol		$C(CH_3)_3$	—	249
L[b]		$C(CH_3)_3$	—	250, 251
LI		$C(CH_3)_3$	+	235
LII		$C(CH_3)_3$	+	235
LIII	1-Naphthyl	3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	+	236
LIV	p-$CH_3CONHC_6H_4$	3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	++	236
LV	p-$C_6H_5CH_2CONHC_6H_4$	3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	++	236
LVI	o-CH_2=$CHCH_2C_6H_4$	3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	+	236
LVII	m-$CH_3C_6H_4$	3,4-$(OCH_3)_2C_6H_3CH_2CH_2$	+	236

[a] S-2395. [b] OPC-1085.

have been quite successful. The correlations seen between structure, physicochemical properties, and activity are highly indicative of a very stereoselective, defined receptor site. Structure–activity relationship investigations of β-blocking agents in general were discussed in several recent publications (17, 19–21, 115, 116, 118, 221–228).

Much recent attention has been directed to delineating structural requirements that impart cardioselectivity to β-adrenergic receptor antagonists. This work was given impetus in 1967 by the proposal that two types of β-adrenergic receptors existed (229). Lands *et al.* (229) found significant differences between the quantitative structure–activity correlation of β-adrenergic stimulants that mediate cardiac stimulation, lipolysis, and inhibition of small intestine motility and that of β-adrenergic stimulants responsible for bronchodilatation and vasodilation. The former were termed β_1- and the latter β_2-adrenergic effects. Although this classification remains a subject of controversy (21, 230, 231), it has become fairly well accepted.

Several successful attempts to synthesize β-receptor blocking agents eliciting β_1 actions (*e.g.*, block sympathetic drive of heart) to a much greater degree than β_2 actions (*e.g.*, block sympathetic-mediated bronchodilatation and vasodilation) have been reported. These findings prompted Levy and Wilkenfield (232) to categorize β-blocking drugs into three groups: (*a*) those that selectively block vascular and bronchial β-receptors, *e.g.*, butoxamine; (*b*) those that selectively block cardiac receptors, *e.g.*, practolol; and (*c*) those that block β-receptors in all tissues and are nonselective, *e.g.*, propranolol. The advantage of cardioselective β-blockade is that β_2-blockade in patients prone to bronchospasm could conceivably bring on breathing difficulty.

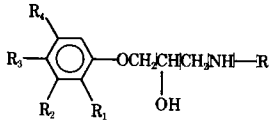
Some β-blocking agents investigated with respect to β_1/β_2 selectivity are listed in Tables XV and XVI. There is growing evidence from several structure–activity relationship studies that the presence of a *para*-substituent in the phenyl ring imparts greater β_1 activity while reducing overall β-blocking potency (233). Of course, the nature of the *para*-substituent is also important in determining the differential affinity of β-blockers. For example, sotalol, XX, 1-isopropylamino-3-(4-tolyloxy)-2-propanol[18] (XLVII), and 1-isopropylamino-3-(4-isopropylphenoxy)-2-propanol[19] (XLVIII) are *para*-substituted but exhibit no cardioselectivity. Also, some non-*para*-substituted β-blockers do possess cardioselectivity, *e.g.*, tolamolol, in which the *o*-methyl derivative is β_1 selective whereas the *p*-methyl derivative is not.

The effects on cardioselectivity of varying the size of the *N*-substituent in *o*-cyanophenoxypropanolamines were investigated (234). The affinity for the β_2-receptor was much more sensitive to this structural change than for the β_1-receptor. Whereas increasing the size of the *N*-substituent from hydrogen to *tert*-butyl increased β_1 affinity, it increased β_2 affinity at a much faster rate, resulting in the *N-tert*-butyl derivative (bunitrolol, Table XVI) being four times more potent on the β_2- than on the β_1-receptor. In contrast, the primary amine derivative (XXXVIII*a*), although less potent, had a sixfold greater affinity for the β_1-receptor.

A series of 34 derivatives of 3-amino-2-hydroxy-

[18] Kö 612.
[19] L 8429.

Table XVI—Structural Formulas of Some Myocardial Selective (+) and Nonselective (−) β-Adrenergic Receptor[a] Antagonists

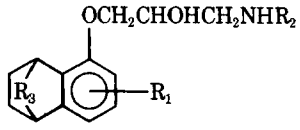


Compound	R_1	R_2	R_3	R_4	R	β_1 Selective	Reference
Practolol	H	H	$NHCOCH_3$	H	$CH(CH_3)_2$	+	120
o-Practolol	$NHCOCH_3$	H	H	H	$CH(CH_3)_2$	—	120
Alprenolol	CH_2—CH=CH_2	H	H	H	$CH(CH_3)_2$	—	237
p-Alprenolol	H	H	CH_2—CH=CH_2	H	$CH(CH_3)_2$	+	237
Oxprenolol	OCH_2—CH=CH_2	H	H	H	$CH(CH_3)_2$	—	120
p-Oxprenolol	H	H	OCH_2—CH=CH_2	H	$CH(CH_3)_2$	+	120
LVIII[b]	H	H	$OCH_2CH_2OCH_3$	H	$CH(CH_3)_2$	+	238
LIX[c]	H	H	$CH_2CH_2OCH_3$	H	$CH(CH_3)_2$	+	238
LX[d]	$COCH_3$	H	$NHCOC_3H_7$	H	$CH(CH_3)_2$	+	239
Trimepranol	CH_3	CH_3	$OCOCH_3$	CH_3	$CH(CH_3)_2$	—	240
LXI[e]	CH_3	CH_3	OH	CH_3	$CH(CH_3)_2$	—	240
LXII[f]	CH_3	CH_3	NH_2	CH_3	$CH(CH_3)_2$	—	240
LXIII[g]	CH_3	CH_3	$NHCOCH_3$	CH_3	$CH(CH_3)_2$	+	240
XLVII	H	H	CH_3	H	$CH(CH_3)_2$	—	221
LXIV	H	H	$CONH_2$	H	$CH(CH_3)_2$	—	241
LXV	H	H	H	$CONH_2$	$CH(CH_3)_2$	—	241
LXVI[h]	H	H	OCH_3	H	$C(CH_3)_3$	+	242
LXVII[i]	OCH_3	H	H	H	$C(CH_3)_3$	—	242
XLVIII	H	H	$C(CH_3)_2$	H	$CH(CH_3)_2$	—	242
Tolamolol	CH_3	H	H	H	$(CH_2)_2O$—C_6H_4—$CONH_2$	+	243
LXVIII	H	H	CH_3	H	$(CH_2)_2O$—C_6H_4—$CONH_2$	—	243
LXIX	H	H	$NHCOCH_3$	H	$(CH_2)_2OC_6H_4NHCOCH_3$	+	243
LXX	H	H	CH_2CONH_2	H	$(CH_2)_2O$—C_6H_4—$NHCOCH_3$	+	243
LXXI	H	H	$NHCOOC_2H_5$	H	$(CH_2)_2O$—C_6H_4—$NHCOCH_3$	+	243
LXXII	CH_3	H	$NHCOCH_3$	H	$(CH_2)_2O$—C_6H_4—$NHCOCH_3$	+	243
LXXIII	H	H	$NHCOC_2H_5$	H	$(CH_2)_2O$—C_6H_4—$NHCOCH_3$	+	243
LXXIV	H	H	$NHCOCH_3$	H	$(CH_2)_2O$—C_6H_4—NHCHO	+	243
Bunitrolol	CN	H	H	H	$C(CH_3)_3$	—	234
XXXVIII*a*	CN	H	H	H	H	+	234
Sotalol	H	H	$NHSO_2CH_3$	H	$CH(CH_3)_2$	—	244
Acebutolol	$COCH_3$	H	$NHCOCH_2CH_3$	H	$CH(CH_3)_2$	+	244
LXXV[j]	H	H	CH_2CONH_2	H	$CH(CH_3)_2$	+	245

[a] Adapted in part, with permission, from S. Zakhari, *Eur. J. Pharmacol.*, 29, 22(1974) (ASP Biological and Medical Press, Amsterdam, The Netherlands). [b] H 87/07. [c] H 93/26. [d] M + B 17803A. [e] VUBF 6502. [f] VUBF 8227. [g] VUBF 8101. [h] M 66368. [i] M 66527. [j] ICI 66082.

propoxy-1,2,3,4-tetrahydro-1,4-ethano- and 1,4-methanonaphthalenes (LXXVI, R_3 = CH_2 or C_2H_4) was synthesized, and the β_1- and β_2-blocking potency was determined (235). The results confirmed the importance of a *para*-substituent relative to the side chain. However, in contrast to the previous study, enhanced β_1 affinity resided in the *N-tert*-butyl (R_2) derivatives. The most cardioselective compounds possessed an 8-hydroxy group (R_1) and the *N-tert*-butyl group (LI and LII in Table XV).

The effect of varying the amino substituent on the β-blocking properties and cardioselectivity of a series of 1-amino-3-(*m*-tolyloxy)-2-propanols (LXXVII) was studied (236). The presence of an *N*-aralkyl (R) group was necessary to confer cardioselectivity, and the *N*-phenylethyl group was superior to the *N*-benzyl, *N*-phenylpropyl, or *N*-α-methylphenylethyl groups. The nature and position of substituents on the phenyl ring of the *N*-phenylethyl group had a profound effect on the degree of β_1 affinity, with the 3,4-dimethoxy (LVII in Table XV) group imparting the greatest cardioselectivity.

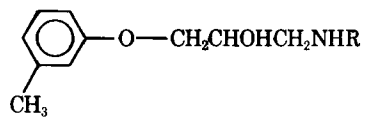


LXXVI

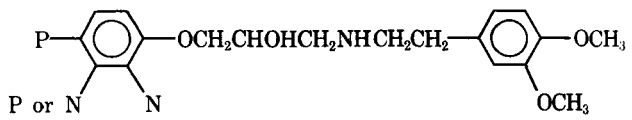
Subsequent investigation of the effects of varying the substituents on the phenoxy ring showed that the presence of more than one substituent caused a decrease in β_1 selectivity. The monosubstituents appeared to fall into two categories regarding their nature and position. For nonpolar substituents (alkyl or halogen), greater β_1 selectivity was observed when they were in the *ortho*- or *meta*-position; the presence of a polar substituent in the *meta*- or *para*-position conferred greater β_1 selectivity, the *para*-isomer generally giving the optimal β_1/β_2 ratio.

Since the 3,4-dimethoxyphenylethylamino group was shown to be unique in imparting β_1 selectivity, the effects of replacing the isopropyl moiety in propranolol, alprenolol, and practolol and its α-phenylacetanilide analog with the aforementioned group were investigated (LIII, LVI, LIV, and LV, respectively, in Table XV) (236). The β_1/β_2 ratio was improved in all four new compounds, particularly in the latter two compounds.

In assessing the importance of the reviewed investigations, there appears to be sufficient experimental evidence to justify some guidelines to chemists at-



LXXVII



LXXVIII

tempting to synthesize cardioselective β-adrenergic blocking agents. Incorporation of an *N*-(3,4-dimethoxy)phenylethyl group into the basic structure (LXXVIII) and placement of a *para* or *meta* polar substituent (P) or an *ortho* or *meta* nonpolar substituent (N) onto the phenoxy ring appears to maximize the chances of success, although there are undoubtedly exceptions.

This review covers a wide range of topics. The intentions were to present the mechanism of action and structure–activity relationship studies of antiarrhythmic drugs with sufficient background material to enable the uninitiated reader to grasp more fully the complexities involved in the diagnosis and treatment of arrhythmias with drugs and to outline the basic research leading to antiarrhythmic drugs. The extensive literature citations will enable the reader to delve into this extremely fascinating area of chemotherapy.

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RESEARCH ARTICLES

Programmed Diffusional Release Rate from Encapsulated Cosolvent System

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Abstract □ The programmed diffusional release rate of an active agent through a rate-controlling membrane from a cosolvent system is discussed. At initial conditions, the drug is present below saturation in solution in a solvent mixture, enclosed by the rate-controlling membrane; the solvent is composed of the main solvent and a cosolvent, which increases the drug solubility in the main solvent. During operation, the active agent and cosolvent diffuse from the capsule at a rate controlled by the membrane. Equations were derived describing the release rate of the active agent as a function of the permeability of the cosolvent and agent, the capsule dimensions, and the system's initial conditions. A great variety of release rate profiles can be programmed from declining to increasing delivery rate patterns as a function of time. Experimental data are presented for the drug progesterone in solution in cyclohexane with methyl, heptyl, or cetyl alcohol as the cosolvent in a polyethylene capsule. The theory qualitatively predicts the experimental results.

Keyphrases □ Diffusion—progesterone through rate-controlling membrane (polyethylene capsule), programmed release rate, cosolvent system □ Release rate, programmed—progesterone diffusion through rate-controlling membrane (polyethylene capsule) □ Drug delivery systems—progesterone diffusion through rate-controlling membrane (polyethylene capsule) □ Membranes, rate controlling—polyethylene capsule, progesterone diffusion □ Progesterone—diffusion through polyethylene capsule, programmed release rate □ Polyethylene capsule—rate-controlling membrane, progesterone diffusion, programmed release rate

During the past 5 years, considerable effort has been undertaken to achieve embodiments of a new class of dosage form, specified not by the quantity of drug but by the rate and duration of drug release (1). Both rate and duration are parameters that should be designed to be independent of the body environment in which the system is deployed.

The mechanism of diffusion provides one basis for accomplishing this objective. Such systems were discussed in detail in a recent review article (2). The release patterns are governed by Fick's law, and different time profiles are obtained, depending on the system design. Important well-known (2) release rate profiles are: