The Stereochemistry of 5-Substituted Decahydroisoquinolines and Their Antiarrhythmic Activity

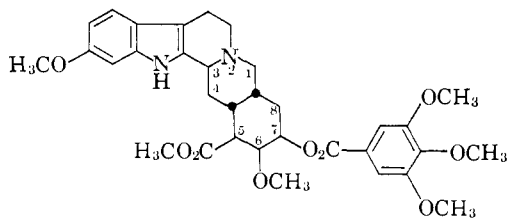
IAN W. MATHISON, RICHARD C. GUELDNER, JAMES W. LAWSON, SARA J. FOWLER, AND ELIZABETH R. PETERS

Departments of Medicinal Chemistry and Pharmaceutics, College of Pharmacy, and Department of Pharmacology, College of Basic Medical Sciences, University of Tennessee, Memphis, Tennessee 38103

Received March 28, 1968

A new class of antiarrhythmic agents is described, namely 5-(3,4,5-trimethoxybenzoyloxy)- and 5-(3,4,5-trimethoxybenzamido)-substituted decahydroisoquinolines. The antiarrhythmic potency and therapeutic index of some of the moieties reported in this paper were found to be equal to or greater than quinidine. Synthesis of the *cis*-9,10 and *trans*-9,10 isomers is reported and it has been demonstrated that the *trans*-9,10 isomers have a more favorable antiarrhythmic therapeutic index than the corresponding *cis*-9,10 isomers. The importance of the 3,4,5-trimethoxybenzoyl radical for antiarrhythmic activity is shown. An increase in the length of the alkyl side chain on the heterocyclic nitrogen causes a significant increase in both toxicity and antiarrhythmic activity (*i.e.*, CH_3 to C_2H_5).

Our interest in agents possessing cardiovascular activity led us to the synthesis of variously hydrogenated 5-substituted 2-alkylisoquinolines.[1-3] The marked antiarrhythmic activity observed with 5-(3,4,5-trimethoxybenzoyloxy)-2-ethyldecahydroisoquinoline (I) directed us to examine the stereochemistry of this molecule particularly in view of its structural resemblance to reserpine, a compound possessing antiarrhythmic properties,[4] which can be considered a 5,6,7-trisubstituted decahydroisoquinoline having a *cis* ring junction. The synthesis of I[1] by way of a platinum-



catalyzed low-pressure hydrogenation of 5-hydroxy-2-ethylisoquinolinium salt to 5-hydroxy-2-ethyldecahydroisoquinoline followed by esterification, coupled with spectral data, led us to suspect the compound as being the *cis*-9,10 isomer having the 3,4,5-trimethoxybenzoyloxy moiety in the equatorial conformation. In order to ascertain conclusively this premise, stereochemical studies were initiated on 5-substituted 2-alkyldecahydroisoquinolines. The prior report of some 5-hydroxy-2-methyldecahydroisoquinolines[5] caused us to turn our attention to the 2-methyl derivatives. A superior synthesis for 5-hydroxy-2-methyldecahydroisoquinolines was devised[3] involving a one-step platinum-catalyzed low-pressure hydrogenation of 5-nitro-2-methylisoquinolinium salt to 5-amino-2-methyldecahydroisoquinoline. Conversion of this isomeric mixture of amines to their acetamides allowed convenient separation of the *cis* and *trans* isomers. Hydrolysis of the individual acetamides yielded the pure amines which on deamination with nitrous acid produced the alcohols in pure form and good yield.[3] Esterification of the *cis*-5,9,10-H- and *trans*-9,10-t-5-H-5-hydroxy-2-methyldecahydroisoquinolines with 3,4,5-trimethoxybenzoyl chloride yielded the corresponding esters. Both these compounds were evaluated for antiarrhythmic activity by the method of Lawson[6] and the results obtained are shown in Table I.

Having assigned the stereochemistry to the above compounds we were then able to ascribe the stereochemistry to I using the above *cis*-5,9,10-H- and *trans*-9,10-t-5-H-5-hydroxy-2-methyldecahydroisoquinolines as reference points. 5-Hydroxyisoquinoline was hydrogenated at low pressure by our previously reported procedure[1] to produce a mixture of isomers of 5-hydroxydecahydroisoquinoline (II) (*cis*-9,10:*trans*-9,10, 2:1, in keeping with our previous results using Pt as catalyst). Column chromatographic separation yielded the previously unreported pure *cis*-9,10 and *trans*-9,10 isomers of II.

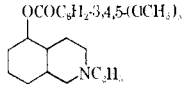
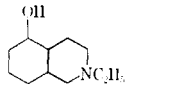
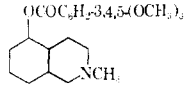
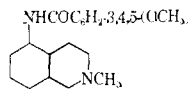
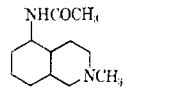
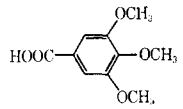
The equatorial conformation of the hydroxyl grouping in *cis*-9,10-II was shown by the methylation of the *cis*-9,10 isomer of II to the known *cis*-5,9,10-H-5-hydroxy-2-methyldecahydroisoquinoline.[3,5] The equatorial conformation of the *trans*-9,10 isomer of II was proven in a similar manner. Nmr studies verified these conformational assignments, *i.e.*, band at 3.75 ppm; half-band width with 15 cps (>CHOH). A second portion of *cis*-5,9,10-H-5-hydroxydecahydroisoquinoline was converted to its N-ethyl derivative using ethyl bromide and the resulting *cis*-5,9,10-H-5-hydroxy-2-ethyldecahydroisoquinoline was shown to be identical with the previously reported compound;[1] esterification with 3,4,5-trimethoxybenzoyl chloride yielded the corresponding ester which was also identical with I, thus confirming our suspicions of the *cis*-5,9,10-H conformation for I.

The absence of significant antiarrhythmic activity with 5-hydroxy-2-ethyldecahydroisoquinoline (III) coupled with previous reports of the importance of the 3,4,5-trimethoxybenzoyl moiety for cardiovascular activity[7] directed us to examine the effect of this grouping on the pure *cis*-5,9,10-H- and *trans*-9,10-t-5-H-5-amino-2-methyldecahydroisoquinolines produced during the course of the above study. Treatment of these amines with 3,4,5-trimethoxybenzoyl chloride yielded the appropriate amides and biological screening showed them

(1) I. W. Mathison, *J. Org. Chem.*, **30**, 3558 (1965).
(2) I. W. Mathison, *J. Med. Chem.*, **11**, 181 (1968).
(3) I. W. Mathison and R. C. Gueldner, *J. Org. Chem.*, **33**, 2510 (1968).
(4) G. G. Lu, *Fed. Proc.*, **23**, 325 (1964); B. Levitt, F. Ciofalo, and J. Roberts, *ibid.*, **25**, 382 (1966).
(5) S. Kimoto and M. Okamoto, *Yakugaku Zasshi*, **85**, 371 (1965); S. Durand-Henchoz and R. C. Moreau, *Bull. Soc. Chim. France*, 3424 (1966).
(6) J. W. Lawson, *J. Pharmacol. Exptl. Therap.*, **16**, 22 (1968).
(7) E. Schlittler, H. B. MacPhillamy, L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, J. M. Mueller, R. Schwyzer, and A. F. St. André, *Ann. N. Y. Acad. Sci.*, **59**, 1 (1954).

TABLE I

ANTIARRHYTHMIC ACTIVITY OF 5-SUBSTITUTED 2-ALKYLDECAHYDROISOQUINOLINES[a]

Compound	Isomer	No.	LD_{50}, mg/kg ip	ED_{50}, mg/kg ip	Potency[b]	T.I.[c]
Quinidine			187 (174–200)[d]	60 (53–67)	1.0	3.1
			S = 1.14[e]	S = 1.44		
	*cis*	I	63 (58–68)	21 (17–26)	2.9	3.0
			S = 1.24	S = 1.66		
	*cis*	III	~259[f]	~166[f]	...	...
	*cis*	IV	88 (85–90)	45 (35–58)	1.3	2.0
			S = 1.05	S = 1.73		
	trans	V	76 (73–79)	27 (24–29)	2.2	2.8
			S = 1.08	S = 1.18		
	*cis*	VI	285 (263–309)	80 (68–96)	0.8	3.6
			S = 1.10	S = 1.6		
	trans	VII	288 (270–307)	60 (50–72)	1	4.8
			S = 1.18	S = 1.15		
	*cis*	VIII	500–1000[f]	>1000[f]	...	...
	trans	IX	1000–2000[f]	>1000[f]	...	...
		X	>2000[f]	>1000[f]	...	...

[a] For antiarrhythmic properties of reserpine, see ref 6. [b] Potency relative to quinidine as 1. [c] Therapeutic index (LD_{50}/ED_{50}). [d] 95% confidence limits in parentheses. [e] Slope function. [f] Sufficient data were not collected to calculate either the LD_{50} or ED_{50} because screening data indicated lethal doses were required to protect a majority of the animals in the antiarrhythmic test. Values given are estimated LD_{50} or ED_{50}.

to possess significant antiarrhythmic activity (VI and VII). This prompted us to evaluate the *cis*-5,9,10-H and *trans*-9,10-t-5-H isomers of 5-acetamido-2-methyldecahydroisoquinoline for antiarrhythmic properties (VIII and IX).

Biological Activity.—Compounds listed in Table I were tested for antiarrhythmic activity in the mouse using the procedure described by Lawson.[6] Briefly, the method is based on prevention of chloroform-induced ventricular fibrillation by pretreatment of the animals with the test compound. The compounds were tested also for acute toxicity (24 hr) using separate groups of mice. In both tests, three or more groups of mice, each consisting of at least ten animals, were used to study the compounds found more active as antiarrhythmic agents. However, fewer animals were used to study the less active compounds and the largest dose administered in the antiarrhythmic test was arbitrarily established as 1000 mg/kg. All compounds were administered by the intraperitoneal route and doses are presented in terms of the free base.

LD_{50} and antiarrhythmic ED_{50} values, together with their respective 95% confidence limits and slope functions, were calculated according to the method of Litchfield and Wilcoxon.[8] Tests for parallelism of antiarrhythmic and acute toxicity dose–response curves and calculations for significance of difference in potency ratios were similarly derived. A 0.05 probability level was considered significant. Accordingly, slopes of acute toxicity and antiarrhythmic dose–response curves for the compounds reported were considered parallel to the respective slopes obtained with quinidine ($P < 0.05$).

Considerable variation in antiarrhythmic potency was found in this series of compounds (Table I). Whereas some were estimated to be equal to or more potent than quinidine (I, IV, V, and VII), others were considered either less active (III and VI) or essentially devoid of antiarrhythmic activity (VIII, IX, and X). Marked variation was also found in acute toxicity and compounds which were more potent than quinidine were also more toxic. However, two members of the series (VI, VII) were of special interest in that each possessed a therapeutic index in excess of quinidine. Compound VII was the most interesting since it was calculated to have a therapeutic index of 4.8 as compared with 3.1 for quinidine. Data presented in Table I show that, whereas this compound was estimated to be equivalent to quinidine in antiarrhythmic potency, it was considerably less toxic, accounting for the significantly increased therapeutic index.

Discussion

While a large number of chemically unrelated drugs have been reported to be useful in the treatment of arrhythmias of the heart[9–11] the outstanding compound in this area of therapeutics is quinidine. At the present time little knowledge of structure–activity relationships is available in this complex area of pharmacology. The

(8) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

(9) R. D. Tanz, *Ann. Rept. Med. Chem.*, **1**, 85 (1965).

(10) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, Macmillan and Co., New York, N. Y., 1966, pp 699–713.

(11) J. R. DiPalma, "Drill's Pharmacology in Medicine," 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, pp 624–635.

results outlined in Table I ascribe significant antiarrhythmic activity to 3,4,5-trimethoxybenzoyl derivatives of 5-substituted 2-alkydecahydroisoquinolines, a new class of compounds in this area of pharmacological activity. An attempt is made to define some structure–activity relationships from the results obtained.

Reserpine, a known antiarrhythmic agent,[4] has been shown to have a *cis* ring junction between rings D and E, a decahydroisoquinoline ring system. Our studies were initiated in order to evaluate the effects on cardiovascular activity produced by the various stereoisomers of decahydroisoquinolines. From Table I, it is evident that the substituted decahydroisoquinolines reported in this paper do possess significant antiarrhythmic properties and that the *trans*-9,10 conformation yields compounds possessing superior therapeutic indexes over the *cis*-9,10 analogs. It is pertinent at this point to note that the 5-substituent is in the equatorial conformation[3] in all the compounds reported in this paper. Additionally, one cannot ignore the fact that the ED_{50} values for the *trans* isomers are significantly lower than for their *cis* analogs. The implication of a steric factor in any receptor involved in antiarrhythmic activity is therefore apparently favoring the rigid *trans* conformation in contrast to the flexible *cis* conformation. We have also examined Dreiding molecular models of the above compounds and can find no differences in the interatomic distances between the 5-substituent and the heterocyclic nitrogen atom in either of the isomers. This factor does not therefore appear to be involved in the activity differences we have observed. Isosteric replacement of the oxygen of the ester function by an NH grouping provides for compounds possessing considerably diminished acute toxicity and potency, associated with enhanced therapeutic indexes (*cf.* IV with VI and V with VII). Additionally, we have demonstrated a reduction in the therapeutic index and acute toxicity as a result of the elimination of one methylene grouping on the heterocyclic nitrogen (*cf.* I and IV). The importance of the 3,4,5-trimethoxybenzoyl radical for antiarrhythmic activity in these series of compounds is well supported by our study and complements the evidence[7] for the importance of this function in the cardiovascular activity of reserpine analogs. Studies using 3,4,5-trimethoxybenzoic acid showed it to possess essentially no antiarrhythmic activity (see Table I, footnote *f*). All the compounds shown in Table I which incorporated this moiety were active, whereas the compounds which did not include this grouping were essentially devoid of antiarrhythmic properties.

Comparison of the therapeutic indexes of some of the compounds described shows that they possess values equivalent or superior to that of quinidine, the standard drug in antiarrhythmic therapy.

Experimental Section

All melting points were determined using a Swissco melting point apparatus and are corrected. Elemental analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer Model 137B Infracord spectrophotometer. Vapor phase chromatograms were recorded on a Varian Aerograph Model 700 Autoprep chromatograph using a thermal conductivity detector (He gas). Nmr spectra were recorded on a Varian A60 spectrometer in $CDCl_3$.

***cis*- and *trans*-5-Hydroxydecahydroisoquinoline (IIc and IIt).**—5-Hydroxyisoquinoline (5.0 g) was dissolved in glacial AcOH (150 ml), concentrated H_2SO_4 (1.2 ml) was added, and the solution was hydrogenated over PtO_2 (5.0 g) at 2.8 kg/cm². After 139 hr the hydrogenation was stopped and the AcOH was removed *in vacuo*. The oil obtained was made alkaline with aqueous base and the free alcohol was extracted with Et_2O. The weight of the material recovered after the removal of the Et_2O. was 45% of the calculated amount. Vapor phase chromatography (column: 10 ft, 15% SE 30 on Chromosorb W 30–60 mesh, temp 160°, flow 38 ml/min) showed this material to be a mixture of approximately 60% *cis*-9,10 (retention time 18.5 min) and 30% *trans*-9,10 isomers (retention time 20.5 min) and to also contain some impurities. Approximately 6 g of the above 5-hydroxydecahydroisoquinoline was dissolved in C_6H_6 (100 ml) and chromatographed on an alumina column (Matheson Coleman Bell, chromatographic grade alumina, 80–200 mesh; column 90 × 2 cm) (185 g). The solvents used were C_6H_6 (250 ml), Et_2O (1500 ml), and increasing strengths of MeOH (3% 2100 ml, 6% 2500 ml, 10% 1250 ml) in Et_2O, respectively. The initial fractions removed the impurities followed by the *cis*-5,9,10-H-5-hydroxydecahydroisoquinoline (IIc) (final 500 ml of Et_2O and first 100 ml of 3% MeOH–Et_2O) (0.94 g), intermediate fractions (which were rechromatographed), and finally *trans*-9,10-t-5-H-5-hydroxydecahydroisoquinoline (IIt) (final 500 ml of 10% MeOH–Et_2O). These isomeric alcohols were further purified by forming the hydrobromide salts which were recrystallized from EtOH–Et_2O.

cis-5,9,10-H-5-Hydroxydecahydroisoquinoline hydrobromide, mp 208–209.5°. *Anal.* ($C_9H_{18}NOBr$) C, H, N, Br.

trans-9,10-t-5-H-5-Hydroxydecahydroisoquinoline hydrobromide, mp 258–259°. *Anal.* ($C_9H_{18}NOBr$) C, H, N, Br.

***cis*-5,9,10-H-5-Hydroxy-2-methyldecahydroisoquinoline (XIc).**—IIc·HBr (0.2 g) was mixed with 88% formic acid (0.45 g) and 37% formaldehyde (0.14 g) and refluxed over steam for 3 hr according to the method of Clarke, *et al.*[12] The solution was made alkaline with NaOH pellets and the free alcohol was extracted with Et_2O. After removal of the Et_2O, the gas chromatograph (Chromosorb W column, temp 169°) of the residual oil was identical with that of an authentic sample of XIc[3] (retention time 12.0 min). IIc under the same conditions has a retention time of 13.5 min.

***cis*-5,9,10-H-5-(3,4,5-Trimethoxybenzoyloxy)-2-ethyldecahydroisoquinoline (I).**—IIc (0.22 g) was treated with EtBr (0.16 g) in EtOH (5 ml) over a period of 6 days according to the method of Blicke and Monroe.[13] The solvent and excess reagent were evaporated to yield a viscous residual oil which was made alkaline with NaOH and extracted with Et_2O. The dried Et_2O extract was evaporated to yield a pale yellow oil which crystallized on standing (0.225 g). Vapor phase chromatographhy (Chromosorb W column, temp 165°) showed this to be a mixture of unreacted IIc (15%) (retention time 15.5 min) and *cis*-5,9,10-H-5-hydroxy-2-ethyldecahydroisoquinoline (III) (85%) (retention time 19.0 min). Column chromatography (column: 15 × 2 cm, Florisil, Fisher, 60–100 mesh, Et_2O) separated these two materials. Treatment of the separated III (0.085 g) with 3,4,5-trimethoxybenzoyl chloride (0.1 g) as outlined by Mathison[1] yielded 0.07 g of the corresponding ester. Formation of the HBr salt (mp 199–200°) and mixture melting point data showed this compound to be identical with that previously reported.[1]

***cis*-5,9,10-H-5-(3,4,5-Trimethoxybenzoyloxy)-2-methyldecahydroisoquinoline (IV).**—XIc (1.01 g) prepared by the procedure of Mathison and Gueldner,[3] was dissolved in dry pyridine (50 ml) and treated with excess 3,4,5-trimethoxybenzoyl chloride for 4 days at room temperature. The pyridine was removed *in vacuo* and the tacky residue was made alkaline with K_2CO_3 solution and extracted with Et_2O. Evaporation of the dried Et_2O extract yielded a viscous oil (1.86 g) which was recrystallized from C_6H_6–pentane to yield 0.5 g of needles, mp 91.8–93°. *Anal.* ($C_{20}H_{29}NO_5$) C, H, N.

Further work of the mother liquors yielded additional amounts of this ester.

***trans*-9,10-t-5-H-5-(3,4,5-Trimethoxybenzoyloxy)-2-methyldecahydroisoquinoline (V).**—*trans*-9,10-t-5-H-5-Hydroxy-2-methyldecahydroisoquinoline (XIt) (2 g) prepared by the method of Mathison and Geuldner[3] was dissolved in dry pyridine (50 ml) and treated with 3,4,5-trimethoxybenzoyl chloride (3 g) and allowed to stand at room temperature for 4 days. Work-up of

(12) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4576 (1933).

(13) F. F. Blicke and E. Monroe, *ibid.*, **61**, 91 (1939).

the product, as described for IV, yielded 2 g of viscous oil. Column chromatography of this oil (column: 20 × 2 cm, Florisil, Fisher, 60–100 mesh, Et_2O 2000 ml) yielded 1.4 g of a waxy solid, mp 103–104° (fractions 300–1500 ml). *Anal.* ($C_{26}H_{29}NO_3$) C, H, N.

***cis*-5,9,10-H-5-(3,4,5-Trimethoxybenzamido)-2-methyldecahydroisoquinoline (VI).**—A solution of *cis*-5,9,10-H-5-acetamido-2-methyldecahydroisoquinoline (VIII) (8.0 g) and concentrated H_2SO_4 (8.0 ml) in H_2O (100.0 ml) was refluxed 24 hr. The solution was concentrated, made basic with NaOH, and extracted with Et_2O. The Et_2O solution was dried (Na_2SO_4) and concentrated to yield 6.16 g of *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline. A solution of this amine (3.0 g) in anhydrous C_6H_6 and 3,4,5-trimethoxybenzoyl chloride (5.0 g) in anhydrous C_6H_6 was refluxed 24 hr with the addition of anhydrous $KHCO_3$ (1.0 g). The crystalline product was collected by filtration and then recrystallized from EtOH to yield 5.90 g, mp 218.0–218.5°. Examination of the ir spectra of this amide showed it to be consistent with the proposed structure. An analytical sample melted at 218.0–218.5°. *Anal.* ($C_{20}H_{30}N_2O_4$) C, H, N.

***trans*-9,10-t-5-H-5-(3,4,5-Trimethoxybenzamido)-2-methyldecahydroisoquinoline (VII).**—A solution of *trans*-9,10-t-5-H-5-acetamido-2-methyldecahydroisoquinoline (IX) (3.0 g) and concentrated H_2SO_4 (7.6 ml) in H_2O (70.0 ml) was refluxed 144 hr. The solution was concentrated, made basic with NaOH, and extracted with Et_2O. The Et_2O solution was dried over Na_2SO_4 and concentrated to yield 2.0 g of *trans*-9,10-t-5-H-5-amino-2-methyldecahydroisoquinoline. A solution of this amine (2.0 g) in anhydrous C_6H_6 was treated with 3,4,5-trimethoxybenzoyl chloride (3.5 g) in a manner like that described above for the preparation of VI. The precipitated amide was isolated similarly and recrystallized from EtOH–Et_2O to yield 2.5 g of VII, mp 217.0–219.0°. The ir spectra of this amide was consistent with the proposed structure. An analytical sample melted at 217.0–219.0°, mmp 194–204° (VII and VI). *Anal.* ($C_{20}H_{30}N_2O_4$) C, H, N.

Acknowledgment.—The authors are indebted to Marion Laboratories Inc., Kansas City, Mo., for their continued generous financial support of this research work. Thanks are also due Dr. Norbert Wojciechowski for useful discussions during the course of this work and to Miss Mailand Stevens and Mrs. Amy Klyman for screening the compounds.

β-Adrenergic Blocking Agents. 1. Pronethalol and Related N-Alkyl and N-Aralkyl Derivatives of 2-Amino-1-(2-naphthyl)ethanol

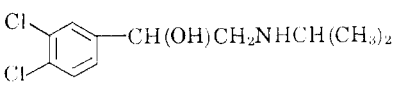
R. HOWE, A. F. CROWTHER, J. S. STEPHENSON, B. S. RAO, and L. H. SMITH

Imperial Chemical Industries Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England

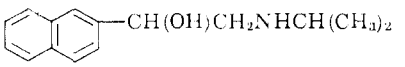
Received January 9, 1968

A series of 76 N-substituted derivatives of 2-amino-1-(2-naphthyl)ethanol (1) has been prepared by a variety of methods. One member of the series, pronethalol (**5**), was of some interest clinically as a β-adrenergic blocking agent but was found to cause thymic tumors after prolonged administration to mice. Structure-activity relationships in this series of β-adrenergic blocking agents resemble those previously reported for the isoproterenol series of β-mimetic agents.

For the past few years we have devoted considerable effort to the search for compounds possessing potent β-adrenergic blocking activity which would not also give rise to β-sympathomimetic effects. 1-(3,4-Dichlorophenyl)-2-isopropylaminoethanol (DCI)[1] (**72**) is unsatisfactory in the latter respect since for example it is capable of causing a marked increase in heart rate in the anesthetized cat.[2] At an early stage in our program 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol,[3] **5**) was synthesized[4] and found to meet to a large extent the criteria laid down at that time.[2] It proved clinically effective in the treatment of angina of



72



5

effort[5] and various types of cardiac arrhythmias,[6] and in the management of pheochromocytoma,[7] but was subsequently found to cause thymic tumors after prolonged administration to mice.[8]

We report here the synthesis of pronethalol (**5**) and a series of 75 related N-alkyl and N-aralkyl derivatives of 2-amino-1-(2-naphthyl)ethanol (**1**) (see Table I).[9] Many methods of synthesis were used for pronethalol and the more useful ones (methods A–H), given in the Experimental Section, were applied to the synthesis of analogs.

A few compounds were made by the route: $RCOCH_2Br + R^1R^2NH \rightarrow RCOCH_2NR^1R^2 \rightarrow RCH(OH)CH_2NR^1R^2$, where R = 2-naphthyl (throughout this paper), R^1 = H, alkyl, or aralkyl, and R^2 = alkyl or aralkyl.

This method has previously been used by Immediata and Day[10] for the preparation of compounds **2**, **3**, **6**, **37**, **39**, **41**, and **45**. No generally applicable conditions were found for the preparation and isolation of the intermediate amino ketones; each compound required specific conditions. Catalytic reduction of the amino ketone (method A) gave an almost quantitative yield of the corresponding amino alcohol, and reduction by $NaBH_4$ (method B) was effective and convenient. Reduction of isopropylaminomethyl 2-naphthyl ketone (**73**) with $LiAlH_4$ gave **5** but reduction with aluminum

(1) C. E. Powell and I. H. Slater, *J. Pharmacol. Exptl. Therap.*, **122**, 480 (1958).

(2) J. W. Black and J. S. Stephenson, *Lancet*, ii, 311 (1962).

(3) Alderlin®.

(4) J. S. Stephenson, British Patent 909,357 (1962).

(5) G. A. O. Alleyne, C. J. Dickinson, A. C. Hornhorst, R. M. Fulton, K. G. Green, I. D. Hill, P. Huest, D. R. Laurence, T. Pilkington, B. N. C. Prichard, B. Robinson, and M. L. Rosenheim, *Brit. Med. J.*, 1226 (1963).

(6) J. P. P. Stock and N. Dale, *ibid.*, 1230 (1963).

(7) A. C. Hornhorst and D. R. Laurence, *ibid.*, 1250 (1963).

(8) (a) S. J. Mecock and P. A. Bond, *Proc. European Soc. Drug Tox., 11th, Cambridge, England, July 1964*, 30 (1964); (b) R. Howe, *Nature*, **207**, 594 (1965).

(9) A. F. Crowther, R. Howe, and L. H. Smith, British Patent 1,105,925 (1965).

(10) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940).