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Registry No. Analogue I, 67230-67-5; analogue II, 84174-12-9; AMD, 50-76-0; 7-NH_2-AMD, 7240-37-1.

Synthesis and Antiarrhythmic Activity of New [(Dialkylamino)alkyl]pyridylacetamides

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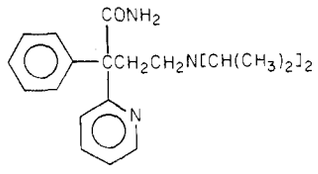
The synthesis of new [(dialkylamino)alkyl]pyridylacetamides is reported. These compounds displayed a potent antiarrhythmic activity, as demonstrated on a model of myocardial infarction in the conscious dog. Structure–activity relationships are discussed within a series of 22 homologues, comparing relative antiarrhythmic properties and cardiac side effects. One of these compounds, **15**, has been selected as a candidate for clinical evaluation in man.

Among derivatives of 2-(2-pyridyl)butyramides, 4-(dialkylamino)-2-phenyl-2-(2-pyridyl)butyramides have been found to possess antiarrhythmic activity. The leading compound in this class, disopyramide (DP, **1**), is active in



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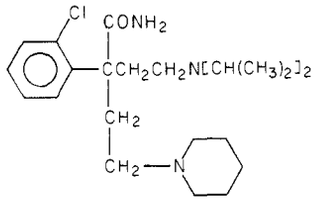

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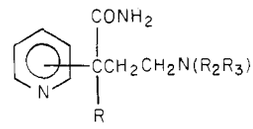
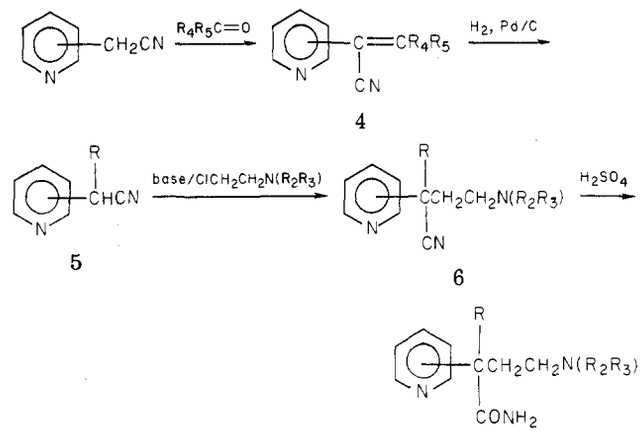


3

the treatment of ventricular dysrhythmias in man.[1] DP gave rise to further developments that led to compounds with activity modulated through variation of amide[2,3] or amine radical.[4] More recently, replacement of one aromatic group in DP by a second (dialkylamino)alkyl group led to active compounds. The most interesting derivative in this later series seems to be 2-(2-chlorophenyl)-2-[2-(diisopropylamino)ethyl]-4-(1-piperidinyl)butanamide (disobutamide, **2**).[5]

With respect to the effect of the phenyl group on the activity of these compounds, it appeared to us that it would be interesting to evaluate the influence of this radical on the antidysrhythmic activity in terms of steric hindrance and/or lipophilicity. This hypothesis led us to study the synthesis and biological properties of a series of 2-alkyl-4-(dialkylamino)-2-pyridylbutyramides, **3**, where the α-phenyl moiety in **1** has been replaced by an alkyl chain.[6]

Scheme I



Chemistry. The preparation of the target compounds was accomplished as follows (Scheme I). The different pyridylacetonitriles were condensed with a ketone or an aldehyde in benzene with piperidine/acetic acid as a catalyst[7] (Table I). When R_4 and R_5 are two different alkyl groups, **4d**, a mixture of the two isomers *E* and *Z* was obtained. Hydrogenation of the double bond with Pd/C in ethanol furnished compounds **5** in near quantitative yields. Compounds **5a** (α-cyclohexyl-2-pyridylacetonitrile) and **5b** [3-phenyl-2-(2-pyridyl)propionitrile] were prepared directly from 2-pyridylacetonitrile by alkylation with bromocyclohexane and benzyl chloride, respectively.[8] Conversion of **5** into **6** was achieved by alkylation with a (dialkylamino)ethyl or (dialkylamino)propyl chloride and sodamide in toluene at reflux temperature or sodium hydride in dimethylformamide at room temperature. Compounds **6** were used without further purification in the last

(1) R. C. Heel, R. N. Brogden, T. M. Speicht, and G. S. Avery, *Drugs*, **15**, 331 (1978).
(2) G. W. Adelstein, *J. Med. Chem.*, **16**, 309 (1973).
(3) C. H. Yen, H. S. Lowrie, and R. R. Dean, *J. Med. Chem.*, **17**, 1131 (1974).
(4) J. W. Cusic and P. K. Yonan, U.S. Patent 3 318 869.
(5) P. K. Yonan, R. L. Novotney, C. M. Woo, K. A. Prodan, and F. M. Hershenson, *J. Med. Chem.*, **23**, 1102 (1980).
(6) H. Demarne, C. Bernhart, and J. Lansen, French Patent 025370.
(7) C. D. Gutsche and H. W. Voges, *J. Org. Chem.*, **32**, 2685 (1967).
(8) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952).
(9) Y. W. Chien, H. J. Lambert, and T. Klin, *J. Pharm. Sci.*, **64**, 961 (1975).

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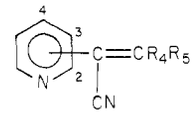
Table I. Alkylidenepyridylacetonitriles

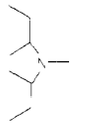
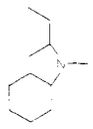
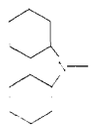


no.	R_4	R_5	position on Pyr ring	reaction time, h	bp, °C (mmHg)	yield, %
4c	CH_3	CH_3	2	135	102 (0.1)	89
4d	CH_3	C_2H_5	2	80	118 (3)	70
4e	H	CH_3	2	0.75	*a*	60
4f	C_2H_5	C_2H_5	2	168	119 (2)	51
4g	H	$(CH_3)_2CH$	2	3	103-104 (1.5)	97
4h	H	C_2H_5	2	3	80-83 (0.6)	66
4i	H	C_6H_{11}	2	3	120-122 (0.4)	84
4j	H	$CH_3(CH_2)_3$	2	3	108 (1.2)	97
4k	H	$(CH_3)_2CHCH_2$	2	1	90 (0.3)	85
4l	H	$(CH_3)_3C$	2	84	84 (0.5)	85
4m	H	$(CH_3)_2CH$	3	168	80-85 (0.5)	58
4n	H	$(CH_3)_2CH$	4	4	84 (0.2)	98

[a] Isolated by chromatography (SiO_2, pentane–ethyl acetate, 9:1).

Table II. (2-Hydroxyethyl)dialkylamines and (2-Chloroethyl)dialkylamines

$R_2R_3NCH_2CH_2X$

	X = OH		X = Cl	
R_2R_3N-	bp, °C (mmHg)	yield, %	bp, °C (mmHg)	yield, %
	115-120 (12)	66	96 (12)	50
	108-110 (15)	77	100-102 (15)	90
	130 (15)	76	122-125 (15)	88
	109-112 (0.3)	69	102-106 (0.2)	86

step. While most of the alkyl halides were commercially available, a few of the (dialkylamino)ethyl chlorides were synthesized by reaction of a secondary amine with ethylene oxide under pressure and treatment of the resulting amino alcohol with thionyl chloride (Table II). Finally, hydrolysis of the nitrile was accomplished by heating in concentrated sulfuric acid at 100 °C, leading to compound **3** (Table III).

Results and Discussion

The discovery of an antiarrhythmic activity for compound **9** lends support to our hypothesis that one aromatic group in disopyramide could participate in the antidysrhythmic activity through its lipophilic and/or steric properties. A goal of these investigations then was the synthesis of analogues with comparable or improved antiarrhythmic activity but with minimized effects on conductive tissue. Structure–activity relationships within this series of compounds can be established through modulation of four parameters: (1) influence of the alkyl chain R, (2) effect of the amine group, (3) incidence of aminoalkyl chain lengthening, and (4) position of the quaternary carbon atom relative to the nitrogen atom in the pyridine nucleus.

Alkyl Chain. The lengthening of the alkyl chain as in compounds **12**, **14**, and **16** provided in all cases active derivatives, but with increased intracardiac conduction times; all of them were more potent than the unsubstituted homologue **7**, which was inactive in our screening model. Branching of the alkyl chain in the α (**10**, **11**, and **13**) or β position (**15** and **19**) with regard to the quaternary carbon atom increased the antidysrhythmic activity compared to the unbranched one. The longest activity duration was observed in derivatives branched in the β position. Compound **18**, with branching at the γ position, was nearly as potent as **15**, but the incidence of the former on the intracardiac conduction was increased. The two cycloalkyl derivatives, **9** and **17**, were also active in this test but with a poorer profile (activity duration, SH, HV). In this series, increasing lipophilicity of the alkyl chain resulted in increased side effects on intracardiac conduction.

Amine Group. The variation of the amine group clearly demonstrated that only the ramified alkylamines led to active compounds (**15**, **20**, **23**, **24**, and **26**). Increasing the lipophilicity and steric hindrance of the alkyl groups resulted in an increase of toxicity; in the case of compounds **24** and **26**, the dogs died in one or two experiments. Diisopropylamine and 2,6-dimethylpiperidine remained the most suitable amine groups.

Chain Length. Examination of compounds **15** ($n = 2$) and **27** ($n = 3$), which differ only by the length of their chains, indicate that the former is more active than the latter.

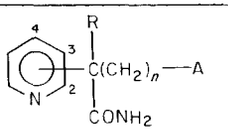
Position on the Pyridine Ring. The three isomeric positions were examined through the evaluation of compounds **15**, **28**, and **29**. The more potent compound is the one bearing the quaternary carbon atom in the α position with regard to the nitrogen atom on the pyridine ring.

This study revealed the very interesting antidysrhythmic properties of **15** (CM 7857). This compound was compared with disopyramide and quinidine (Table IV). When given orally at 50 mg/kg, CM 7857 displayed a systematic antiarrhythmic activity; it possessed a longer activity duration, as compared with the two standards. After safety evaluation studies, CM 7857 was selected for clinical evaluation.

Experimental Section

Chemistry. Melting points were taken on a Tottoli melting point apparatus (Büchi) and are uncorrected. IR and ^1H NMR

Table III. 2-Alkyl-2-[(dialkylamino)alkyl]-2-pyridylacetamides



no.	R	n	A	position on ring	yield, %	mp, °C	recrystn solvent[b]	formula[c]	antiarrhythmic potential in conscious dogs: no. of expts	antiarrhythmic potential in conscious dogs: no. of positive expts	antiarrhythmic potential in conscious dogs: act. duraction, min	intracardiac conduction (His bundle electrogram) in anesthetized dogs, effects in % of variation/control: SH	intracardiac conduction (His bundle electrogram) in anesthetized dogs, effects in % of variation/control: HV
7	H	2	$N[CH(CH_3)_2]_2$	2	22	96–97[d]	A	$C_{15}H_{25}N_3O$	2	0	inactive	0	0
8	$C_6H_5CH_2$	2	$N[CH(CH_3)_2]_2$	2	31	95–96	B	$C_{22}H_{31}N_3O$	1	0	inactive	+50 to +85	+35 to +80
9	C_6H_{11}	2	$N[CH(CH_3)_2]_2$	2	51	104–105	C	$C_{21}H_{35}N_3O$	3	3	210 to 270	+30 to +55	+40
10	$(CH_3)_2CH$	2	$N[CH(CH_3)_2]_2$	2	55	85–86	C	$C_{18}H_{31}N_3O$	3	2	80 to 360	+10	0
11	$C_2H_5(CH_3)CH$	2	$N[CH(CH_3)_2]_2$	2	28	90–91	C	$C_{19}H_{33}N_3O$	2	1	240	0	+30
12	C_2H_5	2	$N[CH(CH_3)_2]_2$	2	44	93–94	C	$C_{17}H_{29}N_3O$	3	2	155 to 300	+20	0
13	$(C_2H_5)_2CH$	2	$N[CH(CH_3)_2]_2$	2	34	62–63	D	$C_{20}H_{35}N_3O$[e]	3	3	27 to 280[f]	+20 to +70	+20 to +33
14	$CH_3CH_2CH_2$	2	$N[CH(CH_3)_2]_2$	2	22	87–88	C	$C_{18}H_{31}N_3O$	1	1	35	+15	0
15	$(CH_3)_2CHCH_2$	2	$N[CH(CH_3)_2]_2$	2	54	108–109	C	$C_{19}H_{33}N_3O$	5	5	120 to 380	+15 to +35	+20 to +30
16	$CH_3(CH_2)_3CH_2$	2	$N[CH(CH_3)_2]_2$	2	22	90–91	C	$C_{20}H_{35}N_3O$	2	1	180	+70 to +120	+100 to +210
17	$C_6H_{11}CH_2$	2	$N[CH(CH_3)_2]_2$	2	38	117	C	$C_{22}H_{37}N_3O$	3	3	45 to 360	+40 to +100	+45 to +100
18	$(CH_3)_2CHCH_2CH_2$	2	$N[CH(CH_3)_2]_2$	2	42	108–109	C	$C_{20}H_{35}N_3O$	2	2	190 to 270	+10 to +50	+25 to +50
19	$(CH_3)_3CCH_2$	2	$N[CH(CH_3)_2]_2$	2	58	103–104	C	$C_{20}H_{35}N_3O$	4	3	165 to 405	+25 to +30	0 to +30
20	$(CH_3)_2CHCH_2$	2	1-(2,6-dimethylpiperidino)	2	23	119–120	C	$C_{20}H_{33}N_3O$[g]	3	2	260 to 270	+15 to +20	+25 to +30
21	$(CH_3)_2CHCH_2$	2	$N(C_2H_5)_2$	2	43	78–79	E	$C_{17}H_{29}N_3O$	1	0	inactive	+15	0
22	$(CH_3)_2CHCH_2$	2	1-morpholino	2	31	89–90	C	$C_{17}H_{27}N_3O_2$	1	0	inactive	0 to +10	0
23	$(CH_3)_2CHCH_2$	2	*N*-cyclohexyl-*N*-isopropylamino	2	50	106–107	C	$C_{22}H_{37}N_3O$	2	1	300	+40 to +85	+50
24	$(CH_3)_2CHCH_2$	2	di-*sec*-butylamino	2	58	92–93	C	$C_{21}H_{37}N_3O$	2	1	90 then death	+85 to +100	+60 to +135
25	$(CH_3)_2CHCH_2$	2	$N(CH_2CH_2CH_3)_2$	2	50	74–77	C	$C_{19}H_{33}N_3O$	2	0	inactive	+20	0
26	$(CH_3)_2CHCH_2$	2	dicyclohexylamino	2	28	139–140	C	$C_{25}H_{40}N_3O$	2	2	60 then death	+45	+75
27	$(CH_3)_2CHCH_2$	3	$N[CH(CH_3)_2]_2$	2	74	54–56	F	$C_{20}H_{35}N_3O$	2	1	30	+15	0
28	$(CH_3)_2CHCH_2$	2	$N[CH(CH_3)_2]_2$	3	54	110–111	C	$C_{19}H_{33}N_3O$	1	1	45	+20	+25
29	$(CH_3)_2CHCH_2$	2	$N[CH(CH_3)_2]_2$	4	16	127–128	C	$C_{19}H_{33}N_3O$	2	2	85 to 240	+110	+45

[a] Overall yield from compound 5. [b] A = isopropyl alcohol; B = cyclohexane; C = diisopropyl ether; D = ethyl alcohol/water; E = hexane; F = pentane. [c] All of the compounds in this table gave satisfactory analysis for C, H, and N (±0.4%) unless otherwise noted. [d] Reported in ref 9. [e] C: calcd, 72.03; found, 71.55. [f] Death of one dog. [g] C: calcd, 72.46; found, 71.77.

Table IV. Activities of CM 7857, Disopyramide, and Quinidine in Conscious Dog

compound[a]	no. of expts.	no. of positive results	act. duration, min
CM 7857	5	5	120 to 380
disopyramide	3	3	30 to 60
quinidine	4	2	50 to 60

[a] All compounds were administrated at 50 mg/kg per os.

spectra were obtained with Perkin-Elmer 397 and R 12 B spectrometers, respectively. Spectra are consistent with the structures reported. Analytical results (C, H, and N) were within 0.4% of the theoretical values.

Pyridylacetonitriles. The three pyridylacetonitriles used in this study were prepared from the corresponding (hydroxymethyl)pyridines by literature methods: 2-pyridylacetonitrile,[10] bp 84–85 °C (1.5 mmHg) [lit. bp 79–81 °C (0.4 mmHg)]; 3-pyridylacetonitrile,[11] bp 70 °C (0.1 mmHg) [lit. bp 91 °C (2 mmHg)]; 4-pyridylacetonitrile,[12] bp 80 °C (0.2 mmHg) [lit. bp 92 °C (0.5 mmHg)].

(Dialkylamino)alkyl Chlorides. Those (dialkylamino)alkyl chlorides, which were not available commercially, were prepared by the following method: a solution of 16.3 g (0.37 mol) of ethylene oxyde in 50 mL of methanol was mixed at room temperature with a solution of 0.34 mol of amine dissolved in 100 mL of methanol. The mixture was then put into a pressure bottle and heated at 40 °C for 65 h. After the methanol was removed, the residue was distilled under reduced pressure to yield pure (dialkylamino)-ethanol (Table II). This resulting (dialkylamino)ethanol was then treated with thionyl chloride in the usual manner[13] to yield the corresponding (dialkylamino)alkyl chloride (Table II).

Cyclohexyl-2-pyridylacetonitrile (5a). To a suspension of 4.4 g of sodamide in 15 mL of dry benzene was added 11.8 g (0.1 mol) of 2-pyridylacetonitrile dissolved in 10 mL of benzene. The mixture was refluxed for 3 h, the heating was stopped, and 16.3 g (0.1 mol) of bromocyclohexane in 15 mL of benzene was added dropwise. After heating for an additional 8 h, the mixture was cooled and the excess sodamide was hydrolyzed with water. The organic layer was then removed and dried over Na_2SO_4, and the solvent was distilled in vacuo. The residual oil was distilled to give 9.9 g (49.5%) of **5a**, bp 123–128 °C (0.7 mmHg).

3-Phenyl-2-(2-pyridyl)propionitrile (5b). This compound was prepared following the preceding method. The crude product obtained after solvent removal was chromatographed on SiO_2, eluting with hexane–ethyl acetate (9:1): yield 52%.

Alkylidenepyridylacetonitriles (4). General Method. 4-Methyl-2-(2-pyridyl)-2-pentenenitrile (4a). In a flask fitted with a water separator were placed 7 g (0.059 mol) of 2-pyridylacetonitrile, 12.82 g (0.178 mol) of isobutyraldehyde, 0.9 mL of acetic acid, 0.18 mL of piperidine, and 250 mL of benzene. The mixture was stirred and refluxed for 3 h. After the mixture was cooled to room temperature, the organic layer was washed with water and dried over Na_2SO_4, and the solvent was removed in vacuo. The residual oil was distilled under reduced pressure to yield **4g** (9.9 g, 97%), bp 103–104 °C (1.5 mmHg).

Alkylpyridylacetonitrile (5). General Method. 4-Methyl-2-(2-pyridyl)pentanenitrile (5g). Compound **4g** (9 g, 0.052 mol) was dissolved in 100 mL of ethanol and hydrogenated over 3.8 g of 5% Pd/C at room temperature and normal pressure. After absorption of the theoretical amount of hydrogen, the palladium was filtered off, and the solvent was removed in vacuo to yield pure **5g** (9 g, 99%).

Alkyl[(dialkylamino)alkyl]pyridylacetonitrile and Alkyl[(dialkylamino)alkyl]pyridylacetamides. General Methods. 2-[2-(Diisopropylamino)ethyl]-4-methyl-2-(2-pyridyl)pentanenitrile (6g). In a 500-mL flask were placed 9 g (0.052 mol) of compound **5g**, 9.32 g (0.057 mol) of 2-(diisopropylamino)ethyl chloride, 2.22 g (0.057 mol) of powdered sodamide, and 150 mL of dry toluene. The mixture was refluxed for 2 h. After the mixture was cooled to room temperature, the organic layer was washed with water and dried over Na_2SO_4. The crude product obtained after solvent evaporation was used directly for the next step.

2-[2-(Diisopropylamino)ethyl]-4-methyl-2-(2-pyridyl)-pentanamide (15). The crude compound **6g** was dissolved in 100 mL of concentrated sulfuric acid (*d* 1.83) and heated at 120 °C for 1 h. The cooled reaction mixture was then poured onto 600 g of crushed ice and made alkaline with NaOH solution (cooling). The resultant alkaline mixture was extracted with chloroform, and the organic layers were dried over Na_2SO_4. The oil obtained after solvent evaporation was chromatographed on Al_2O_3 (70–230 mesh, Merck) eluting with ethyl acetate–pentane (9:1). The solid obtained was recrystallized from diisopropyl ether, yielding white crystals (8.91 g, 54% from **5g**), mp 108–109 °C. Anal. ($C_{19}H_{33}N_3O$) C, H, N.

2-[2-(Diisopropylamino)ethyl]-4-methyl-2-(3-pyridyl)-pentanenitrile (6m). In a two-necked flask fitted with an addition funnel and a nitrogen bubbler were placed 2.6 g (0.052 mol) of NaH (55–60% dispersion in oil) and 20 mL of dry dimethylformamide (DMF). The mixture was stirred and 9.12 g (0.052 mol) of 4-methyl-2-(3-pyridyl)pentanenitrile (**5m**) dissolved in 50 mL of DMF was added dropwise. The mixture was stirred for an additional hour at room temperature. Then, 9.42 g (0.057 mol) of 2-(diisopropylamino)ethyl chloride dissolved in 20 mL of DMF was added dropwise and stirring continued for an additional hour. The DMF was removed in vacuo, and the residue was taken up in ether. The organic layer was washed with water and dried over Na_2SO_4, and the solvent was distilled in vacuo. The residual oil was used directly for the next step.

2-[2-(Diisopropylamino)ethyl]-4-methyl-2-(3-pyridyl)-pentanamide (28). Crude product **6m** was hydrolyzed in concentrated sulfuric acid as described above for **6g**. The crude oil obtained after solvent evaporation was chromatographed on Al_2O_3 (ethyl acetate–pentane, 6:4), and the solid obtained was recrystallized from diisopropyl ether to give white crystals (9.05 g, 54% from **5m**), mp 110–111 °C. Anal. ($C_{19}H_{33}N_3O$) C, H, N.

Biology. The pharmacological profiles of these compounds are assessed both in terms of antiarrhythmic properties and in terms of electrophysiological tolerancy. Antiarrhythmic activity was measured on an experimental model of arrhythmia in the dog.[14] This model is based upon (1) progressive development of coronary thrombosis following the introduction of a metallic coil and (2) occurrence of an aortic myocardial infarction and its associated dysrrhythmia.

The ECG disturbances were monitored by telemetry in the conscious animal. With mongrel dogs of either sex, weighing a minimum of 12 kg, a small metallic coil was wedged distally either in the interventricular coronary artery or in the circumflex coronary artery by catheterization under X-ray control. While the animal recovered from anesthesia, a thrombosis developed progressively. The ECG was monitored by telemetry during the following 24 h. All changes of the cardiac rhythm and/or of the QRS morphology were analyzed on a specially built electronic device. Usually, rhythm disturbances progressed in a typical sequence: from 4 to 6 h, progressive ectopic activity; from 6 to 36 h, ventricular tachycardia (VT) or runs of VT. Animals received the drug (50 mg/kg per os) during the acute phase (16–36 h). The results were considered positive when the drug suppressed ≥60% ventricular arrhythmias or induced sinus rhythm. The duration of this effect was measured. All tested compounds were administered per os at 50 mg/kg to mongrel dogs that had been subjected to myocardial infarction. The drugs were given as solutions dissolved in distilled water or acacia gum. No dog was used if the ECG revealed more than 50% beats of sinus origin.

The His bundle electrogram[15] was recorded via a left catheterization in mongrel dogs anesthetized with sodium pentobarbital

(10) K. Winterfeld and K. Flick, *Arch. Pharm. (Weinheim, Ger.)*, **26**, 448 (1956).
(11) H. S. Mosher and J. E. Tessieri, *J. Am. Chem. Soc.*, **73**, 4925 (1951).
(12) B. E. Betts and W. Davey, *J. Chem. Soc.*, 3333 (1961).
(13) B. Tchoubar, *Bull. Soc. Chim. Fr.*, 14, 792 (1947).
(14) B. Dupuis, P. Gautier, G. Richer, and M. Serre, *Br. J. Pharmacol.*, **58**, 409 (1976).
(15) S. H. Lau, G. A. Bobb, and A. N. Damato, *Circulation*, 42, 375 (1970).

and left in spontaneous breathing. The hexapolar-electrode catheter inserted via a femoral artery into the noncoronary cusp of the aorta was connected to an Elema Mingograf 61 recorder, equipped with EMT 12 preamplifiers. With a bipolar electrode facing the sinus node area, the heart was paced at progressively increased rates. Before injection of the drug and 5 and 15 min after each dose administered intravenously, His bundle potentials were recorded at different pacing. The following intervals were measured: SH, the interval between the stimulation and the intrinsic His bundle deflection (this interval represents atrial His bundle conduction time); HV, the interval between the His bundle intrinsic deflection and the onset of ventricular activation (this interval represents conduction time in specific intraventricular tissue). For the determination of conduction times (His bundle electrogram), the dogs were anesthetized with sodium phenobarbital (30 mg/kg iv). The drugs were administered by the iv route at 5 mg/kg.

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Registry No. **4c**, 29950-40-1; (*E*)-**4d**, 29946-73-4; (*Z*)-**4d**, 29946-74-5; (*E*)-**4e**, 35365-37-8; (*Z*)-**4e**, 83918-31-4; **4f**, 29950-41-2; (*E*)-**4g**, 83917-89-9; (*Z*)-**4g**, 83918-32-5; (*E*)-**4h**, 83917-90-2; (*Z*)-**4h**, 83918-33-6; (*E*)-**4i**, 83917-91-3; (*Z*)-**4i**, 83918-34-7; (*E*)-**4j**, 83917-92-4; (*Z*)-**4j**, 83918-35-8; (*E*)-**4k**, 83917-93-5; (*Z*)-**4k**, 83918-36-9; (*E*)-**4l**, 83917-94-6; (*Z*)-**4l**, 83918-37-0; (*E*)-**4m**, 83917-95-7; (*Z*)-**4m**, 83918-38-1; (*E*)-**4n**, 83917-96-8; (*Z*)-**4n**, 83918-39-2; **5a**, 83917-97-9; **5b**, 4226-82-8; **5c**, 32081-58-6; **5d**, 83917-98-0; **5e**, 13427-10-6; **5f**, 83917-99-1; **5g**, 78833-04-2; **5h**, 83918-00-7; **5i**, 83918-01-8; **5j**, 74607-41-3; **5k**, 83918-02-9; **5l**, 83918-03-0; **5m**, 83918-04-1; **5n**, 72434-26-5; **6** [2-pyridyl; R = H; R_2, R_3 = $N[CH(CH_3)_2]_2$], 68284-77-5; **6** [2-pyridyl; R = $C_6H_5CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-05-2; **6** [2-pyridyl; R = C_6H_{11}; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-06-3; **6** [2-pyridyl; R = $(CH_3)_2CH$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-07-4; **6** [2-pyridyl; R = $C_2H_5(CH_3)CH$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-08-5; **6** [2-pyridyl; R = C_2H_5; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-09-6; **6** [2-pyridyl; R = $(C_2H_5)_2CH$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-10-9; **6** [2-pyridyl; R = $CH_3CH_2CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-11-0; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 78833-05-3; **6** [2-pyridyl; R = $CH_3(CH_2)_3$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-12-1; **6** [2-pyridyl; R = $C_6H_{11}CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-13-2; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2CH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-14-3; **6** [2-pyridyl; R = $(CH_3)_2CCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-15-4; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = 1-(2,6-dimethylpiperidino)], 83918-16-5; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N(C_2H_5)_2$], 83918-17-6; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = 1-morpholino], 83918-18-7; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = *N*-cyclohexyl-*N*-isopropylamino], 83918-19-8; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = di-*sec*-butylamino], 83918-20-1; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-21-2; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = dicyclohexylamino], 83918-22-3; **6** [2-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-24-5; **6** [4-pyridyl; R = $(CH_3)_2CHCH_2$; R_2, R_3 = $N[CH(CH_3)_2]_2$], 83918-25-6; **7**, 56265-38-4; **8**, 83918-26-7; **9**, 78833-08-6; **10**, 78833-09-7; **11**, 78833-10-0; **12**, 78833-11-1; **13**, 78833-12-2; **14**, 78833-13-3; **15**, 78833-03-1; **16**, 78833-14-4; **17**, 78833-15-5; **18**, 78833-18-8; **19**, 78833-20-2; **20**, 78833-16-6; **21**, 78833-17-7; **22**, 78833-19-9; **23**, 78833-21-3; **24**, 83918-27-8; **25**, 78833-23-5; **26**, 78833-25-7; **27**, 78833-24-6; **28**, 78833-27-9; **29**, 78833-26-8; $[C_2H_5(CH_3)CH]_2NH$, 626-23-3; $[C_2H_5(CH_3)CH]NHC_6H_{11}$, 42966-62-1; $(C_6H_{11})_2NH$, 101-83-7; $[C_2H_5(CH_3)CH]_2NCH_2CH_2OH$, 4535-71-1; $[C_2H_5(CH_3)CH]C_6H_{11}NCH_2CH_2OH$, 83918-28-9; $(C_6H_{11})_2NCH_2CH_2OH$, 4500-31-6; $[C_2H_5(CH_3)CH]_2NCH_2CH_2Cl$, 83918-29-0; $[C_2H_5(CH_3)CH]C_6H_{11}NCH_2CH_2Cl$, 83918-30-3; $(C_6H_{11})_2NCH_2CH_2Cl$, 75308-28-0; 2-(2,6-dimethylpiperidinyl)ethanol, 23502-32-1; 2-(2,6-dimethylpiperidinyl)ethyl chloride, 34846-30-5; 2-[2-(diisopropylamino)propyl]-4-methyl-2-(2-pyridyl)pentanenitrile, 83918-23-4; 2,6-dimethylpiperidine, 504-03-0; 2-pyridineacetonitrile, 2739-97-1; 3-pyridineacetonitrile, 6443-85-2; 4-pyridineacetonitrile, 13121-99-8.

Derivatives of β-Adrenergic Antagonists. *N*-Nitrosopropranolol and *N*-Hydroxypropranolol and Its Aldonitrone

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Potential precursors to chemically reactive species derived from the β-adrenergic antagonist propranolol were synthesized and tested for mutagenicity in the Ames *Salmonella* assay. *N*-Hydroxypropranolol (1), the corresponding aldonitrone, 3-(1-naphthoxy)-2-hydroxypropionaldehyde *N*-isopropylnitrone (2), and *N*-nitrosopropranolol (3) were prepared and tested. *N*-Hydroxypropranolol (1) was obtained by direct alkylation of 3-(1-naphthoxy)-1-bromo-2-propanol with *N*-isopropylhydroxylamine and isolated as its neutral oxalate or HBr salt. The aldonitrone (2) was obtained by mercuric oxide oxidation of the hydroxylamine. *N*-Nitrosopropranolol (3) was prepared by treating propranolol with nitrous acid. None of the compounds was mutagenic in the Ames assay with *Salmonella typhimurium* TA-98 and TA-100 strains, either in the absence or in the presence of the S-9 liver fraction from Arochlor 1254 treated rats. None of the compounds was significantly toxic to the bacteria, except for slight toxicity of the oxalate salt of 1.

Propranolol is a β-adrenergic antagonist widely used in the treatment of a variety of cardiovascular disorders. It is extensively metabolized in man and other species via several pathways, including oxidative N-dealkylation, aromatic hydroxylation, and glucuronidation.[1-7] Radiolabel from [^{3}H]propranolol has been shown to be covalently bound to the rat liver microsomal fraction when propranolol is administered systemically, suggesting the formation of a chemically reactive metabolite(s).[8,9] A marked inhibition of propranolol metabolism occurred when rats

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(1) Hayes, A.; Cooper, R. G. *J. Pharmacol. Exp. Ther.* **1971**, *176*, 302.
(2) Walle, T.; Conradi, E. C.; Walle, U. K.; Fagan, T. C.; Gaffney, T. E. *Clin. Pharmacol. Ther.* **1978**, *24*, 668.
(3) Bond, P. A. *Nature (London)* **1967**, *213*, 721.
(4) Walle, T.; Gaffney, T. E. *J. Pharmacol. Exp. Ther.* **1972**, *182*, 83.
(5) Tindell, G. L., Walle, T.; Gaffney, T. E. *Life Sci., Part 2* **1972**, *11*, 1029.

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