Synthesis and Antiarrhythmic Activity of α, α -Bis[(dialkylamino)alkyl]phenylacetamides

Peter K. Yonan,* Robert L. Novotney, Chi Min Woo, Kathleen A. Prodan, and Fred M. Hershenson*

G. D. Searle & Co., Research and Development Division, Chicago, Illinois 60680. Received April 30, 1980

The synthesis and biological evaluation of a series of α, α -bis[(dialkylamino)alkyl]phenylacetamides, 2, are presented. These compounds are structurally related to the antiarrhythmic agent disopyramide (1) and in many cases were found to possess greater antiarrhythmic activity in coronary ligated dogs. Within this series of compounds, a separation of the antiarrhythmic properties from the unwanted cardiac depressant side effects observed with the parent compound, 7, was also often attained. A discussion of the structure-activity relationships within this series is presented; this work has culminated in the identification of compound 35 (disobutamide) as a candidate for clinical evaluation as an antiarrhythmic agent in man.

4-(Dialkylamino)-2-phenyl-2-(2-pyridyl)butyramides have been found to possess potent antiarrhythmic activity with disopyramide phosphate (1) (Norpace) finding clinical



utility in the treatment of ventricular dysrhythmias in man.¹ Structural modifications of 1 involving replacement of the carboxamide portion of this molecule with other functional groups have been reported.^{2,3} The study presented here describes the synthesis and biological evaluation of a series of bis[(dialkylamino)alkyl]phenyl-acetamides, 2, where the α -pyridyl moiety in 1 has been replaced by a second (dialkylamino)alkyl chain.

Chemistry. The preparation of the target compounds, 2, was accomplished following literature precedent.⁴⁻⁷ As indicated in Scheme I, phenylacetonitrile or a substituted phenylacetonitrile was alkylated with (diisopropylamino)ethyl chloride. The base employed in this reaction was generally sodamide. However, a two-phase mixture of 50% sodium hydroxide solution and methylene chloride with benzyltriethylammonium chloride as the phasetransfer catalyst was also used in a few cases. Compounds 3 were isolated in 50 to 80% yields. These monoalkylated products possessed a characteristic ¹H NMR signal for the methine proton: when $R_1 = H$ or *p*-F, δ_{CH} was observed at 4.00 to 4.50 as a broad triplet; when $R_1 = o$ -Cl, δ_{CH} was present at 4.50 to 4.55 as a quartet. The methylene protons in the starting phenylacetonitriles appeared as singlets at δ 3.60 to 3.80.

Conversion of 3 into 4 was achieved by a second alkylation reaction using sodamide and a (dialkylamino)ethyl or (dialkylamino)propyl chloride. While most of these alkyl halides were commercially available, a few of the (dialkylamino)ethyl chlorides were synthesized in the usual manner by reacting a secondary amine with ethylene oxide and then converting the resultant amino alcohol into the

- (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) R. E. Stenseth and F. F. Blicke, J. Org. Chem., 34, 3007 (1969).
- (5) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, J. Med. Chem., 8, 594 (1965).
- (6) M. Borovicka and M. Protiva, Chem. Listy, 51, 2118 (1957).
- (7) F. F. Blicke and E.-P. Tsao, J. Am. Chem. Soc., 75, 4334 (1953).



Table I. α -[(Dialkylamino)ethyl]phenylacetonitriles

	R ₁	сл У-сн-с	сн ₂ сн ₂ м[сн(сн ₃) ₂] ₂	
no.	\mathbf{R}_{1}	R_2	bp, °C (mmHg)	yield,ª %
3a	Н	Н	120-125 (0.3)	67
3b	2-Cl	Н	135 - 140 (0.5)	67
3c	2-F	н	118-122 (0.3)	77
3d	$4 - C(CH_3)_3$	н	130-132 (0.1)	57
3e	2-Br	Н	145 (0.3)	51
3f	4-F	Н	125-130 (0.5)	71
3g	$2-CH_3$	н	125-130 (0.2)	57
3h	2-Cl	6-Cl	160-163 (0.5)	74
3i	$4-CH(CH_{3})_{2}$	Н	125-128 (0.3)	35 ^b

 a Compounds were prepared by alkylation of the parent phenylacetonitrile using NaNH₂ unless otherwise indicated. b Prepared by alkylation using phase-transfer procedure.

aminoalkyl chloride with thionyl chloride. Although the initial alkylation was carried out at 80 ± 5 °C, this second alkylation required slightly higher reaction temperatures (refluxing toluene). In cases where the two side chains in 4 were the same [(diisopropylamino)ethyl], the above two steps could be carried out in one operation by adding 2 equiv of sodamide to a mixture of 1 equiv of the phenyl-acetonitrile and 1 equiv of (diisopropylamino)ethyl chloride at 80 °C. The reaction mixture was then heated to reflux and a 2nd equiv of the chloride was added.

Finally, hydration of the nitrile in 4 was carried out by one of three methods: (A) 90% H_2SO_4 , (B) KOH in ethanol, or (C) H_2SO_4 , CH_3CO_2H , H_2O (2:2:1). For compounds where R_1 and/or R_2 = H or halogen, method A was used. Where electron-donating groups, such as alkyl or

R. C. Heel, R. N. Brogden, T. M. Speicht, and G. S. Avery, Drugs, 15, 331 (1978).

Table II.	α, α -Bis[Dialkylamino)alkyl]r	oheny	lacetonitril	e
-----------	------------------------	--------------	----------	-------	--------------	---



				· · · · ·			
					X	ield, ^b	
no.	\mathbf{R}_{1}	\mathbf{R}_{2}	n	Α	method ^a	%	bp, °C (mmHg)
4a	Н	H	2	$N[CH(CH_3),],$	Α	70	160-165 (0.3)
4b	$4-CH_3$	н	2	NICH(CH,),],	Α	71	160-163 (0.3)
4c	4-OCH,	н	2	NICH(CH ₃),],	Α	53	150-160 (0.3)
4d	4-Cl	н	2	$N[CH(CH_{3}),],$	Α	69	170-175 (0.3)
4e	4-F	н	2	NICHICH, J. I.	В	62	158-162 (0.3)
4f	$4 \cdot C(CH_{3})_{3}$	н	2	NICH(CH.),].	В	58	150-155 (0.1)
4g	3-F	н	2	NCH(CH ₃),	Α	30	160-163 (0.2)
4h	3-CF,	н	2	NICH(CH,),],	Α	70	155-160 (0.3)
4 i	3-Cl	н	2	$N[CH(CH_3)_2]_2$	A	33	165 -1 75 (0.1)
4 j	2-F	н	2	$N[CH(CH_3)_2]_2$	В	80	148-152 (0.1)
4k	2-Br	н	2	$N[CH(CH_3)_2]_2$	В	63	185 (0.2)
41	2-CH,	н	2	$N[CH(CH_3)_2]_2$	В	55	175-185 (0.3)
4m	2-Cl	4-Cl	2	$N[CH(CH_3)_2]_2$	Α	57	175-185 (0.1)
4n	2-Cl	6-Cl	2	$N[CH(CH_3)_2]_2$	В	57	180-185 (0.3)
4 0	3-Cl	4-Cl	2	$N[CH(CH_3)_2]_2$	Α	55	170-180 (0.2)
4p	н	н	2	$N(CH_2CH_3)_2$	В	71	147-150 (0.2)
4 q	н	н	2	$N(CH_3)$ -c-C ₆ H ₁₀	В	68	185-190 (0.5)
4r	н	н	2	1-pyrrolidino	В	61	150-155 (0.2)
4 s	н	н	2	1-piperidino	В	72	165-170 (0.5)
4 t	н	н	2	1-homopiperidino	В	69	160-165 (0.1)
4u	2-Cl	н	2	1-piperidino	В	72	180-185 (0.2)
4v	2-F	н	2	1-piperidino	В	84	168-172 (0.3)
4w	$4 \cdot CH(CH_3)_2$	н	2	1-piperidino	В	54	138-143 (0.1)
4x	4-C(CH ₃) ₃	н	2	1-piperidino	В	41	152 (0.1)
4y	4-C(CH ₃) ₃	н	2	$N(CH_3)_2$	В	47	155-170 (0.2)
4z	2-Cl	н	2	$N(CH_3)_2$	В	60	160-165 (0.2)
4aa	2-F	н	2	1-pyrrolidino	В	62	155-160 (0.1)
4bb	2-F	н	2	1-homopiperidino	В	51	170-175 (0.3)
4cc	2-F	н	2	$N(CH_3)$ -c-C ₆ H ₁₀	В	70	185-190 (0.3)
4dd	2-F	н	2	1-(2-methylpiperidino)	В	44	170-175 (0.5)
4ee	2-F	н	2	1-(2,6-dimethylpiperidino)	В	55	170-175 (0.3)
4ff	H_	н	3	$N(CH_3)_2$	В	61	145-150 (0.5)
4gg	2-F	н	3	$N(CH_3)_2$	в	44	145-150 (0.5)
4hh	2-F	Н	3	1-piperidino	в	57	190 (1.0)
4ii	2-Cl	Н	3	1-piperidino	В	64	178-182 (0.3)

^a A = compound prepared from the starting phenylacetonitrile in a single operation without isolating the intermediate monoalkylated product. B = compound prepared from the corresponding monoalkylated nitrile 3. ^b When method A was used, the yield listed is the overall yield from the phenylacetonitrile; when method B was used, the yield listed is from the corresponding monoalkylated nitrile 3.

alkoxyl, were present on the phenyl ring of 4, either method B or C was used. Use of 90% H_2SO_4 in these cases resulted in the formation of ring-sulfonated products, along with the desired compounds 2. Tables I to III summarize the physical characteristics of compounds 3, 4, and 2, respectively.

In one instance, we prepared a phenylacetamide derivative where only one side chain contained a basic nitrogen atom. Compound 34 was synthesized as indicated in Scheme II. Starting with 3b, alkylation was carried out using KH as the base and the allylic bromide $5.^{8}$ Compound 6 was isolated as an oil in 75% yield. Catalytic hydrogenation of the olefin in 6 was followed by acid hydrolysis (method A) and furnished 34 in a 52% yield.

Biology. All of the target compounds (2) were evaluated in conscious dogs that had been subjected to a two-stage ligation of the anterior descending coronary artery.⁹ On the first postoperative day, these dogs exhibited arrhythmias analogous to those observed in man following acute myocardial infarction. The compounds were administered intravenously using one of two dosage regimens, depending Scheme II



upon the activity and safety of the particular compound in question. These regimens consisted of injections of either 1 or 5 mg/kg, with the total dose not exceeding 6 or 20 mg/kg, respectively. The time interval between injections was 5 min for the 1 mg/kg dose and 15 min for the 5 mg/kg dose.

Normally, compounds are rated active if the ectopic ventricular rate is reduced by $\geq 25\%$ for a minimum du-

⁽⁸⁾ M. Ohki, K. Mori, M. Matsui, and A. Sakimae, Agr. Biol. Chem., 36, 979 (1972).

⁽⁹⁾ A. S. Harris, A. Estandia, T. R. Ford, Jr., and R. F. Tillotson, Circulation, 4, 522 (1951).

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					R R R (CH1) CH1) CH1)	сн, м[сн(сн,),], А						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	_	${f R}_2$	u	A	yiel method ^a %	d, mp, °C	recrystn solvent ^b	anal.	MED, mg/kg	ARc	TR^{c}	ADI¢
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	5	N[CH(CH, J,]	A I	01-103	A I	C, H, N	5.5	6.5 2	3.4	1.31
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	~ ~	NCH(CH ₃), J	81 F	97-100	х <	C, H, N	2.0	5.0 1.0	1.9	60 F
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	3	5	N C	NCH(CH(CH ₃) ₂] ₂	31 0	7 120-124	۲	נ אים גי	4.0 2 0	0.0 6 6	0.1 0 3	0.86
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		- 2	4 C		4 4) C		0.0	0.0 V	19.0	1 10
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2	4 5	4 C			157_150			0 C		0.4	1.10
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1 3/3		4 C			118-190	יכ	z z H D C	0 C	9 9 9	C.∓ 7 6	0.66
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			10			131-139	50	N N N N N N))) 7	1 01 1 01	1 33
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	1 C		A A	102-105	0 C	C H N CI	1 2	6 9 9	6.7	1 42
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Ħ	20	NICH (CH.), I	A 70	157-158	0 C		5.6	5.5	- 10	1.57
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	ء د	NICH(CH)	A 83	121-123	•	C H N N	0.0	6.1	15.0	1.52
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$: 1	10		A F	165-166	10	C H N B	- 1 - 2	6.1	0.8	2.16
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	10			1 145-147			15	99	6.0	2.57
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	-	10-V	10			160-161	nc	C H N C		7.6	4.0	2.14
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		504	10		A A	168-170) F.	D N H C	2.7	6.9	4.6	1 20
$ \begin{array}{cccccc} H & & & & & & & & & & & & & & & & & & $			1 C		76 V	105-108	i ⊲			2 C	4.6	0.63
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		4-F	1 C		A. 40	120-121	1 ت	D H N H	4.5	7.7	4.7	0.69
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		ц	1 C		08 V	75-78			19.0	9.6	2 L /	0.40
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		= =	1 C	NICH CH	₩	90-01	4	N H C	7.5	4.6	5.5	0.94
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		= =	4 C	NICH J-6-C H	v v v	10-00		C H N	2.6	7.1	4 1	136
H 2 1-piperidino A 55 50-82 A C,H,N 5.5 6.1 82 6.4 83 6.7 4.6 1.38 6.7 4.6 1.33 6.7 4.6 1.33		H	1 C	1 -nurralidina		79-80	•	N N N	15.0	100	×3.3	0.13
H 2 1			1 C	1-pyrotiumo	u v	80-89	4	чи П С	2 L 2 L	2.1	0.0 0	0.45
H 2 4-monopoperation A 70 131-132 E C, H, N 500 <td></td> <td></td> <td>4 C</td> <td>1-homoninoridino</td> <td>5°°</td> <td>58-60</td> <td></td> <td></td> <td>0.0 0</td> <td>1.0 9</td> <td>4.0 X</td> <td>94.0</td>			4 C	1-homoninoridino	5°°	58-60			0.0 0	1.0 9	4.0 X	94.0
H 2 $$ To propried A 70 131-132 E C, H, N 10.0 2.7 >5.0 10.0 H 2 $$ A 70 131-132 E C, H, N 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 2.7 >5.0 10.0 10.0 2.7 >5.0 10.0 10.0 2.7 >5.0 10.0 10.0 2.7 >5.0 10.0 10.0 2.7 >5.0 10.0 10.0 2.7 2.0 10.0 10.0 2.7 10.0 10.0 2.6 1.46 1.38 1.76 10.0 10.0 2.7 10.0 10.0 2.7 10.0 10.0 2.6 10.0 10.0 10.0 2.6 10.0 10.0 10.0 10.0 10.0 10.0 10.0 10.0 10		4 2	N C	I-flottiopipertanto 4-morpholino	A 20	87_89	ם מ		0.0	0.0 9	7.6	00.0
H 2 $\frown O$ 131-132 E C, H, N 10.0 2.7 >5.0 H 2 $\frown O$ 3 B C, H, N 10.0 2.7 >5.0 H 2 $\frown O$ 3 B C, H, N 3.5 6.7 4.6 1.38 H 2 $\frown O$ 83-85 E C, H, N 3.5 6.7 4.6 1.38 H 2 $\frown O$ 83-85 E C, H, N 3.5 6.7 4.6 1.38 H 2 $\frown O$ 83-85 B C, H, N 2.5 7.0 12.5 0.96 H 2 $1-piperidino A 5.2 125-129 B C, H, N 2.5 7.0 12.5 0.96 H 2 1-piperidino A 8.8 114-115 F C, H, N 1.33 0.70 H 2 1-piperidino A 8.2 107-103 C C, H, N 1.6 1.30 1.46 1.30 1.47 1.30 1.47 1.30$		ч	1		io F	co_10 (2	o, 11, 11	0.0	0.0	2	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Н	2		A 7() 131-132	ы	С, Н, N	10.0	2.7	>5.0	
H 2 $(H_{3})^{1}$ H 2 $(H_{3})^{1}$ A 61 78-82 D C, H, N 2.5 7.0 12.5 0.96 H 2 1-piperidino A 52 125-129 B C, H, N, Cl 3.5 d 6.1 3.07 H 2 1-piperidino A 74 130-131 E C, H, N, Cl 3.3 8.4 8.8 1.76 H 2 1-piperidino A 82 107-108 C C, H, N Cl 3.3 8.4 8.8 1.76 H 2 1-piperidino A 86 91-93 A C, H, N Cl 2.3 4.4 3.0 0.70 H 2 1-piperidino A 66 91-93 A C, H, N Cl 2.3 4.4 3.0 0.70 H 2 1-piperidino A 52 125-127 G C, H, N Cl 3.5 6.6 1.0 0.51 H 2 1-piperidino C 2.5 $(C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 2.3 + 4.4 - 3.0 - 0.70 + 1.2 - 1-piperidino C 2.5 (C, H, N, Cl 3.5 + 6.6 - 1.0 - 0.51 + 1.3 + $		Н	5		A 70) 83-85	Э	C, H, N	3.5	6.7	4.6	1.38
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Н	2		A 61	18-82	D	С, Н, N	2.5	7.0	12.5	0.96
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		н	6	evelohexvl	A 55	1 25-1 29	B	C. H. N. CI	3.5	q	6.1	3.07
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	101	1-niperidino	A 74	130-131	E	C, H, N, CI	3.3	8.4	8.8	1.76
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Η	10	1-piperidino	A 82	107-108	C	C, H, N	1.8	6.0	18.0	1.47
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		H	י גי	1-piperidino	A 30	5 114-115	ч	C, H, N	1.5	7.2	13.0	1.20
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		H	2	1-piperidino	A 6(91-93	Α	C, H, N, CI	2.3	4.4	3.0	0.70
CH ₃), H 2 1-piperidino C 25 e A C, H, N 3.0 6.2 2.0 0.75 H, J, H 2 1-piperidino C 28 134-135 C C, H, N 2.5 7.8 2.9 0.82 0.82 0.62 0.75 0.62 0.75 0.62 0.75 0.65 0.65 0.65 0.65 0.65 0.65 0.65 0.6		Н	2	1-piperidino	A 55	2 125-127	IJ	C, H, N, CI	3.5	6.6	1.0	0.51
[H ₁), H 2 1-piperidino C 28 134-135 C C, H, N 2.5 7.8 2.9 0.82	CH	a), H	5	1-piperidino	C 23	9	A	C, H, N	3.0	6.2	2.0	0.75
	(H ₃)	H	73	1-piperidino	C C	3 134-135	U.	C, H, N	2.5	7.8	2.9	0.82

Table III. α, α -Bis[(dialkylamino)alkyl]phenylacetamides

Por C =	Cono Fi Di	NU N Lo	1		ç		f			•		00 11 200	•
0.40 0.50	3.3 6.6	2.2 4.1	13.5 6.6									udine pyramide	quin disol
0.30	4.0	6.3	7.0	C, H, N	Υ	84-85	60	A		က	Н	Н	57
1.55	5.0	4.6	3.5	С, Н, N	C	103-105	72	A	1-piperidino	ი	Η	2-CI	56
0.36	>6.0	4.2	7.5	C, H, N	D	01 - 69	60	A	1-piperidino	က	Н	2-F	55
0.12	>4.0	1.8	12.5	C, H, N,		. . .	54	Y	$N(CH_3)_2$		H	2-F	54
0.49		3.4	11.7	C, H, N, CI	B	139-143	81 57	4 <	1-morpholino	c1 r	HÞ	2-CI H	52 73
2.2	6.7	8.3	3.3	C, H, N	ပ	102 - 103	52	A	1-(2,6-dimethylpiperidino)	67	Η	2-F	51
0.60	3.2	4.6	7.5	C, H, N	D	90 - 91	57	A	1-(2-methylpiperidino)	7	Н	2-F	50
0.42	>4.0	6.0	6.0	C, H, N, F	A	132 - 133	30	A	1-piperidino	2	4-F	2-F	49
0.98	12.7	6.0	1.5	C, H, N	ы	114 - 115	74	A	N(CH ₃)-c-C ₆ H ₃₀	0	Н	2-F	48
0.78	7.5	6.9	3.0	C, H, N	D	108 - 109	72	A	1-homopiperidíno	2	Н	2-F	47
0.58	1.0	4.4	8.3	C, H, N	Α	99-101	70	A	1-piperidino	0	Н	4-F	46
0.59	7.3	3.6	7.5	C, H, N	ပ	104 - 105	81	A	1-pyrrolidino	01	Н	2-F	45
0.21	1.1	2.2	15.0	C, H, N	Ω	78-80	70	A	N(CH ₃),	2	Н	4-F	44
0.31	4.7	2.7	7.5	C, H, N, CI	C	111-112	65	A	N(CH ₃),	7	Н	2-CI	43

 α, α -Bis [(dialkylamino)alkyl] phenylacet.....

Journal of Medicinal Chemistry, 1980, Vol. 23, No. 10 1105

ration of 10 min in more than half of the dogs tested.¹⁰ In this study, virtually all of the compounds satisfied this criterion. In order to more critically evaluate the differences in the antiarrhythmic profiles of these analogues, considerations regarding potency and duration of action vs. cardiac depressant effects were examined.

As indicated in previous research from these laboratories,³ calculation of an "activity ratio" (AR) normalizes test to test variation and provides a single index for comparing potency. The formula for this ratio is:

AR =
$$\sum_{i=1}^{n}$$
 (red. ER × THR) $/5\sum_{i=1}^{n}$ MED

where n = number of dogs, red. ER = maximal reduction of extrasystolic rate divided by the pretreatment extrasystolic rate, THR = pretreatment total heart rate, and MED = minimum effective dose of the compound using the 5 mg/kg dosage regimen. The maximum value for an AR is 10.

In addition to this term, two new indexes are introduced here. The "activity duration index" (ADI) is represented by the following equation:

ADI = (area under curve $(cm^2)/5 cm^2$) × (ectopic rate/250)(1/effective dose)

In this equation, the area of the curve that is obtained by plotting the percent arrhythmia vs. time (minutes) is measured, normalized to activity units where 5 cm^2 is equal to a 25% reduction for 10 min, or one activity unit, corrected for the initial ectopic rate, and then divided by the dose of the compound.

For example, let us assume that a compound was rated active at 5 mg/kg. If this activity just met the minimum that is required by our definition, namely, a 25% reduction for 10 min, then the area under the curve would be 5 cm². If the initial ectopic rate was 150 beats/min, the ADI would be calculated as follows:

ADI =
$$\left(\frac{5 \text{ cm}^2}{5 \text{ cm}^2}\right) \left(\frac{150}{250}\right) \left(\frac{1}{5}\right) = 0.12$$

An ADI of 0.12 represents a compound which is minimally active against an average abnormal heart rate. It should be noted that the larger the ADI, the more active the compound.

The second term that will be introduced here is concerned with the possible cardiac depressant properties of the compound and is referred to as the "therapeutic ratio" (TR). The formula for this ratio is

$$TR = \frac{\text{dose to reduce the blood pressure by 50\%}}{MED}$$

The blood pressure determination was performed on normal, anesthetized dogs where the compound was administered by infusion until a 50% reduction of the blood pressure was achieved or until a maximum of 50 mg/kg of the compound had been given, whichever came first. In the latter case, the value for the TR is indicated by a > designation.

Since several compounds described in this study do not possess vasodilating properties,¹¹ the reduction in blood

⁽¹⁰⁾ The probabilities of a false positive can be demonstrated to be <10% at the 0.05 level of significance and appears likely to be substantially less than this figure, based on the observation of no false positives among 30 placebo-treated animals.

Table IV.Antiarrhythmic Activities afterOral Administration

compd	dose, mg/kg	onset of action, min	duration, min	max reduc- tion of ectopic beats, %	AR
7	25	200	200	89	6.5
10	25	30	>330	100	5.5
11	25	88	147	92	5.6
17	25	9 0	200	87	5.7
24	25	131	200	100	6.9
26	15	300	30	69	
28	25	169	>300	97	6.9
30	25	285	52	84	6.1
33	25		inact	ive	
34	25		letha	1	
35	25	80	>360	100	6.6
35	15	85	210	90	
35	12	135	75	49	
36	25	45	300	100	5.9
36	12	90	90	67	
48	25	203	150	67	4.7
quinidine	25	110	110	57	4.3
disopyramide	25	172	120	79	4.8
disopyramide	15		inact	ive	

pressure is considered a reflection of the depression of cardiac function.

Table III contains a tabulation of these biological results. Compounds of interest were then further evaluated by oral administration in conscious, ligated dogs. The biological data from this route of administration are presented in Table IV.

Results and Discussion

After discovering the antiarrhythmic activity of 7, a goal of this investigation was to identify analogues with comparable or improved antiarrhythmic activity (AR) but with diminished cardiac depressant properties, as indicated by their increased TR values. Furthermore, it was desirable for these compounds to possess a reasonable duration of action, as measured by their ADI values.

The structure-activity relationships within this series of compounds (2) may be examined most conveniently by dividing the molecule into three regions: (1) effects of phenyl substituents, R_1 and R_2 ; (2) variation of the chain length, n; and (3) the nature of the amine substituent on the side chain.

Phenyl Substitution. A comparison of the compounds possessing either an electron-donating or electron-withdrawing substituent at the meta or para positions of the phenyl ring with the unsubstituted compound 7 fail to provide any trends in the variation of the biological parameters, AR, TR, or ADI. When $R_1 = p$ -F, as in 11, the TR improves as compared to the related compounds 9 and 10; however, the isomeric *m*-fluoro analogue, 13, displays a TR value below that found in the parent compound, 7. Substitution at the ortho position, however, does furnish compounds (16-19) with reasonable potency, duration of action, and, in the case of 17 ($R_1 = o$ -F), reduced cardiac depressant effects. Likewise, when the second aminecontaining side chain was a piperidinoethyl group, a comparison of 28 ($R_1 = H$) with 35 ($R_1 = o$ -Cl) demonstrates that the presence of an ortho chlorine substituent improves the biological profile. Finally, examination of the three isomeric monochloro analogues, 35, 38, and 39, clearly show the o-chloro compound (35) to be the most potent, longest acting, and least cardiac depressant.

Comparison of the dichloro analogues, 20-22, indicate that the order of potency and duration of action here is 2,4-dichloro > 2,6-dichloro > 3,4-dichloro. While the ARs of the 2,4-dichloro and 2,4-difluoro compounds, 20 and 23, respectively, are similar, the dichloro compound is much longer acting.

Chain Length. Side by side examination of pairs of compounds with identical R_1 and R_2 groups and amine moieties (A in Table III) indicate that when n = 3 the compound always had a poorer profile (AR, TR, ADI) than the corresponding analogue where n = 2. For example, while 24 was weakly active (AR = 2.6), 53 was inactive (MED >20 mg/kg). In a similar manner, 36 was found to be better than 55, 35 better than 56, and 33 better than 57.

Amine Group. With acyclic amines, it appears that a diisopropylamino group confers greater potency and duration of action to the molecule than a diethylamino group, which in turn is better than a dimethylamino group; i.e., 7 > 25 > 24 (AR, ADI). While the trend in the TR values appears to be in the reverse order, this difference may be due to the diminished potencies of 24 and 25 as compared to compound 7. On the other hand, the diisopropylamino and piperidino compounds, 7 and 28, respectively, have comparable antiarrhythmic activities (ARs), but based on their TR values, compound 28 seems to have less cardiac depressant properties. Likewise, while 16 has a TR of 3.5, 35 has a TR of 8.8 and is slightly more active based on their respective AR values.

Examination of the cyclic amines used in this study reveal the following: compounds possessing six- or seven-membered-ring amines were comparable and better than the corresponding five-membered-ring amino analogue; i.e., 28 and 29 vs. 27, and 36 and 47 vs. 45. Ortho substitution on the piperidine ring also seems to have some variable effects on activity; while the 2,6-dimethylpiperidino compound, 51, is more active than 36, the 2methylpiperidino derivative, 50, is less active. Finally, although 35 is more active than its morpholino counterpart, 52, compounds 28 and 30 are similar in their antiarrhythmic profiles.

We wondered whether the antiarrhythmic effects of these phenylacetamide derivatives actually required the presence of two basic centers in the molecule; hence, we prepared the cyclohexylethyl derivative, 34. This compound did possess antiarrhythmic activity, although 34 was lethal at 5 mg/kg, and at lower doses where its antiarrhythmic effects were observed it was also found to cause emesis. The closely related amino analogue, 35, did not produce emesis at any dose where its antiarrhythmic activity was observed. Thus, it appears that, while two basic groups are not absolutely required for antiarrhythmic activity, the presence of a second amine moiety abolishes the emetic side effect found with compound 34.

Finally, comparing the cyclic amine (piperidine) found in 28 with the bicyclic amines present in 31-33 one finds compounds with similar AR values; 33 appears to have a higher TR value, once again indicating that a separation of antiarrhythmic activity from cardiac depressant properties has been achieved.

Additional investigations involving several of the most promising analogues are presented in Table IV. These studies were concerned with the antiarrhythmic activity observed after oral administration. Of the compounds tested by this route of administration at 25 mg/kg, 10, 24, 35, and 36 completely abolished the arrhythmia and produced a return to normal sinus rhythm. In two of the cases (10 and 35), the antiarrhythmic effect at this dose was

⁽¹¹⁾ J. Lee, Searle Laboratories, personal communication.

maintained for at least 5.5 h. When compound **35** was tested at the lower doses of 15 and 12 mg/kg, it still displayed antiarrhythmic activity; disopyramide, however, was inactive at 15 mg/kg by this route of administration. After completion of additional pharmacological¹² and safety evaluation studies, compound **35** (disobutamide) was selected for clinical evaluation.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR and ¹H NMR spectra were obtained using Beckman IR-12 and Varian A60D spectrometers, respectively. Spectra were obtained for all intermediates and final products and are consistent with the structures reported. Analytical results (listed in Table III) were within 0.4% of the theoretical values.

Phenylacetonitriles. Most of the phenylacetonitriles used in this study were commercially available, with the exception of the following compounds that were prepared using literature methods: o-bromophenylacetonitrile,¹³ bp 88–90 °C (0.2 mmHg), lit. bp 141–142 °C (12 mmHg); 2,4-difluorophenylacetonitrile,¹⁴ bp 90 °C (0.25 mmHg), lit. bp 98 °C (10 mmHg); p-tert-butylphenylacetonitrile,¹⁵ bp 98–100 °C (0.1 mmHg), lit. bp 149–152 °C (16 mmHg).

(Dialkylamino)alkyl Chlorides. The majority of the (dialkylamino)alkyl chlorides used in this study were purchased from commercial sources. Those (dialkylamino)ethyl chlorides that were unavailable commercially were prepared by the following literature methods: 1-(2-chloroethyl)-2-methylpiperidine hydrochloride,¹⁶ mp 182-185 °C; 3-(2-chloroethyl)-3-azabicyclo-[3.2.2]nonane,¹⁷ sublimation range 235-250 °C; 1-(2-chloroethyl)-2,6-dimethylpiperidine hydrochloride,¹⁸ mp 158-165 °C; N-(2-chloroethyl)-N-methylcyclohexylamine hydrochloride,¹⁹ mp 140-141 °C; 2-(2-chloroethyl)octahydropyrrolo[1,2-a]pyrazine hydrochloride,²⁰ mp 242-245 °C; 2-(2-chloroethyl)-2-azabicyclo-[2.2.2]octane hydrochloride,²¹ mp 219-221 °C.

Monoalkylated Phenylacetonitriles, 3. General Methods. α -[(Diisopropylamino)ethyl]-p-fluorophenylacetonitrile (3f). In a 2-L three-necked flask fitted with a mechanical stirrer, reflux condenser, and nitrogen inlet was placed 68 g (0.5 mol) of pfluorophenylacetonitrile and 88 g (0.53 mol) of N,N-diisopropylaminoethyl chloride in dry toluene (300 mL). The solution was heated to ca. 80 °C and then 22 g (0.56 mol) of sodamide was added portionwise over a 40-min period, keeping the temperature of the reaction mixture at 80-85 °C with cooling as necessary. Upon completion of the addition of the sodamide, the reaction mixture was kept at 80-85 °C for an additional 30 min and then cooled to room temperature. Cold water (500 mL) was added, and the organic layer was separated and extracted with dilute HCl. The HCl extract was made alkaline by the addition of dilute NaOH solution with cooling. This alkaline mixture was then extracted with Et₂O, the Et₂O extract was dried over CaSO₄, and the solvent was removed in vacuo. The residue was then distilled under high vacuum to afford 93 g (71%) of 3f as an oil, bp 125–130 °C (0.5 mmHg). Anal. (C₁₆H₂₃FN₂) C, H, N.

- (12) Recent studies of the effects of compound 35 on the heart include: M. L. Dohrmann and H. C. Strauss, Fed. Proc., Fed. Am. Soc. Exp. Biol., 39, 1001 (1980); R. E. TenEick and J. Z. Yeh, ibid., 39, 1082 (1980).
- (13) R. B. Petigara and H. L. Yale, J. Heterocycl. Chem., 11, 331 (1974).
- (14) S. Jerumanis and A. Bruylants, Bull. Soc. Chim. Belg., 69, 312 (1960).
- (15) B. VanZanten and W. Th. Nauta, Recl. Trav. Chim. Pays-Bas, 79, 1211 (1960).
- (16) W. D. Vigeluis and S. Marinis, Ger. Offen. 2246279; Chem. Abstr., 81, 63680g (1974).
- (17) Eastman Chemical Products Technical Data Report, May, 1962.
- (18) Anon., Netherlands Patent Application 6514223; Chem. Abstr., 65, 15345d (1966).
- (19) F. Reicheneder, R. Kropp, and A. Amann, Ger. Offen. 2120 208; Chem. Abstr., 78, 43497v (1973).
- (20) C. H. Lovell, U.S. Patent 3772300 (1973).
- (21) F. J. Villani and C. A. Ellis, J. Med. Chem., 9, 185 (1966).

 α -[(Diisopropylamino)ethyl]-p-isopropylphenylacetonitrile (3i). p-Isopropylphenylacetonitrile (45 g, 0.283 mol) in a 50% NaOH solution was vigorously stirred as benzyltriethylammonium chloride (0.5 g) was added. The brown mixture was stirred for 30 min and a solution of (diisopropylamino)ethyl chloride (51 g, 0.31 mol) in CH₂Cl₂ (15 mL) was added in dropwise portions. After stirring at room temperature for 24 h, water (200 mL) was added. The reaction mixture was extracted with ether, and the ether extract was washed (H₂O), dried (CaSO₄), and evaporated to dryness in vacuo. The residual oil was distilled to furnish 3i (27 g, 35%), bp 125–128 °C (0.3 mmHg). The ¹H NMR spectrum of 3i confirmed that it was the desired monoalkylated nitrile.

Dialkylated Phenylacetonitriles, 4. General Methods. Method A. α, α -Bis[(diisopropylamino)ethyl]-p-chlorophenylacetonitrile (4d). In a 500-mL three-necked flask fitted with a mechanical stirrer, thermometer, reflux condenser with a nitrogen bubbler, and an addition funnel was placed pchlorophenylacetonitrile (15.0 g, 0.1 mol), (diisopropylamino)ethyl chloride (24.5 g, 0.15 mol), and dry toluene (200 mL). The mixture was stirred and warmed to 80 °C while sodamide (9.0 g, 0.24 mol) was added in portions over a 30-min period. The reaction temperature was then raised to ca. 105 °C, and a second portion of (diisopropylamino)ethyl chloride (24.5 g, 0.15 mol) in toluene (100 mL) was added in dropwise amounts over a 20-min period. The reaction mixture was then heated to reflux (1 h), cooled to room temperature, and water (200 mL) was added. The toluene layer was separated and extracted with dilute HCl, and the aqueous acidic extract was made alkaline with dilute NaOH solution. This alkaline mixture was then extracted with Et₂O, the Et₂O extract was dried $(CaSO_4)$, and the solvent was removed in vacuo. The residual oil was distilled to yield 4d (28 g, 69%), bp 170-175 °C (0.3 mmHg). Anal. $(C_{24}H_{40}ClN_3)$ C, H, N, Cl.

Method B. α -[(Diisopropylamino)ethyl]- α -(1-piperidinoethyl)-o-chlorophenylacetonitrile (4u). Using the same reaction apparatus described in the synthesis of compound 4d, α -[(diisopropylamino)ethyl]-o-chlorophenylacetonitrile (3b) (140 g, 0.50 mol) and sodamide (22 g, 0.56 mol) were heated to 100 °C for 10 min in toluene (300 mL). The resultant dark brown mixture was then treated with a solution of 1-(β -chloroethyl)piperidine (100 g, 0.68 mol) in toluene (350 mL). This solution was added over a 30-min period, while the temperature of the reaction mixture was kept at 105–110 °C. After heating the mixture to reflux for an additional 45 min, it was cooled to room temperature and water (500 mL) was added. The organic layer was separated and dried (CaSO₄), and the solvent was removed in vacuo. Distillation of the residual oil afforded 4u (141 g, 72%), bp 180–185 °C (0.2 mmHg). Anal. (C₂₃H₃₆ClN₃) C, H, N.

 α,α -Bis[(dialkylamino)alkyl]phenylacetamides. General Methods. Method A. α,α -Bis[(diisopropylamino)ethyl]-ofluorophenylacetamide (17). Compound 4j (130 g, 0.33 mol) was added to concentrated H₂SO₄ (1235 mL) and H₂O (65 mL), and the resultant solution was heated on a steam bath for 2 h. The hot solution was poured onto ice and made alkaline with dilute NaOH solution (cooling). After extracting the alkaline mixture with Et₂O (2 × 500 mL), the combined Et₂O extract was dried (CaSO₄) and filtered, and the ether filtrate was slowly evaporated as hexane was gradually added until a slight cloudiness was observed. The solution was then cooled and provided 17 (119 g, 88%), mp 121–123 °C. Anal. (C₂₄H₄₂FN₃O) C, H, N.

Method B. α,α -Bis[(diisopropylamino)ethyl]-p-methoxyphenylacetamide (9). A solution of 4c (20 g, 0.05 mol), KOH (40 g, 0.72 mol), H₂O (4 mL), and EtOH (100 mL) was heated to reflux for 74 h. The solution was cooled and diluted with water, and the diluted solution was then extracted with Et₂O. After the Et₂O extract was dried (CaSO₄), the solvent was removed in vacuo and the residue was recrystallized from hexane to afford 9 (4.0 g, 19%), mp 123-124 °C. Anal. (C₂₅H₄₅N₃O₂) C, H, N.

Method C. α -[(Diisopropylamino)ethyl]- α -[(dimethylamino)ethyl]-*p*-tert-butylphenylacetamide (42). A solution of 4y (7.5 g, 0.020 mol) in a mixture of concentrated H₂SO₄ (25 mL), CH₃CO₂H (25 mL), and H₂O (12.5 mL) was heated on a steam bath for 24 h. The cooled solution was extracted once with ether, and the aqueous layer was made alkaline with dilute NaOH solution. The resultant alkaline mixture was extracted with Et₂O, the Et₂O extract was dried (CaSO₄), and the solvent was removed in vacuo. Recrystallization of the solid residue from hexane afforded 42 (4.0 g, 51%), mp 100–101 °C. Anal. $(C_{24}H_{43}N_3O)$ C, H, N.

 α -[(Diisopropylamino)ethyl]- α -(2-cyclohexylidenylethyl)-o-chlorophenylacetonitrile (6). A suspension of KH (0.45 g of a 26.3% dispersion in oil, 2.69 mmol) and compound 3b (0.50 g, 1.79 mmol) in toluene (10 mL) was slowly heated to 90 °C and kept at that temperature for 10 min. The orange mixture was then cooled somewhat (ca. 75 °C) and a solution of 2-cyclohexylidenylethyl bromide (5, 0.68 g, 3.6 mmol) in toluene (10 mL) was added in dropwise portions over a 30-min period. The mixture was stirred an additional 30 min at 70-75 °C, then cooled (5 °C), and water (10 mL) was slowly added. After separating the two phases, the toluene layer was washed with dilute HCl. A dark yellow layer formed between the organic and aqueous layers, and when it was separated it solidified on standing. After washing this solid several times with Et₂O, a light-yellow solid was obtained (0.57 g, 75%), mp 169-173 °C. Anal. (C₂₄H₃₅Cl-N₂·HCl·0.5H₂O) C, H, N.

This hydrochloride salt was dissolved in water and converted to its free base in the usual manner. The free base (oil) was used in the subsequent preparation of compound 34.

 α -[(Diisopropylamino)ethyl]- α -(2-cyclohexylethyl)-ochlorophenylacetamide (34). A solution of compound 6 (18.53 g, 0.048 mol) in EtOH was hydrogenated in a 500-mL Parr shaker apparatus at room temperature and 2.0 psi pressure. Platinum oxide was the catalyst used in this reduction. After 2 h, the mixture was filtered and the filtrate evaporated to dryness in vacuo, yielding a yellow oil (17.87 g, 96%). The ¹H NMR spectrum of this oil indicated that the vinyl proton, present in 6 tt δ 5.1, was no longer present. This oil was then immediately used, without further purification, as follows: 14.77 g of this oil (0.038 mol) in concentrated H₂SO₄ (125 mL) was heated on a steam bath for 45 min. The acidic solution was then poured onto ice, basified with 10% NaOH solution, and the alkaline mixture was extracted with Et₂O. After washing the Et₂O extract with brine, it was dried (MgSO₄), and the solvent was removed in vacuo. Crystallization of the residue from ether-pentane afforded 34 as an off-white solid (8.0 g, 52%), mp 125–129 °C. Anal. ($C_{24}H_{39}ClN_2O$) C, H, N, Cl.

Biological Methods. All test compounds (2) were administered by the iv route to mixed-breed or beagle dogs that had been subjected to a two-stage ligation of the left anterior descending coronary artery.⁹ No dog was used if the ECG revealed more than 25% beats of sinus origin as determined by an upright QRS complex preceded by a P wave (i.e., a normally conducted ventricular complex). A minimum of two dogs were used with each test compound. Compounds were administered by the dosage regimens described previously, and the arrhythmia was then monitored at 2.5-min intervals.

For the determination of oral activity, the animals were prepared in a similar manner; however, after the oral dose (administered in a lactose-filled gelatin capsule), the ECG was taken at 15-min intervals for at least 6 h. A compound was rated active after oral administration if it produced a 25% reduction in the ectopic rhythm for at least 30 min.

For the determination of potential cardiovascular toxicity, normal dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). The lead II ECG was monitored for heart rate and electrocardiographic intervals. A femoral artery was catheterized for the measurement of blood pressure, and compounds were continually infused at 0.5 (mg/kg)/min until the blood pressure decreased by 50% from control levels or the cumulative dose reached 50 mg/kg.

Acknowledgment. The authors are indebted to Mrs. A. Pahn, Mrs. F. Hatley, and Mr. D. Pilipauskas. Furthermore, we thank M. Scaros, for the catalytic hydrogenation of 6; J. Damascus and his group, for spectral determinations; Ms. L. Swenton, for assistance with interpretation of spectral data; and E. Zielinski and his group, for microanalytical determinations.

Synthesis and Antibacterial Activity of New 1-Oxa-1-dethiacephalosporins

Daijiro Hagiwara, Hidekazu Takeno, Matsuhiko Aratani, Keiji Hemmi, and Masashi Hashimoto*

Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan. Received February 13, 1980

A series of 3-(deacetoxymethyl)-1-oxa-1-dethiacephalosporins (1) bearing the 7-(α -alkoxyimino)acyl side chain were synthesized and their antibacterial properties were examined in comparison with that of FK-749 (2). (Z)-2-(Eth-oxyimino)-2-(2-aminothiazol-4-yl)acetic acid was found to be a prefered side chain in the 1-oxa series, and the derivative **18b** with this side chain proved to be a potential broad-spectrum antibiotic not at all inferior to **2**.

Considerable efforts by a number of laboratories to prepare the 1-oxa isosteric analogues of the natural cephalosporin antibiotics have appeared in the past few years.¹ The significant antimicrobial activity of these 1-oxa analogues was first reported by Christensen et al.^{1b} and, subsequently, in extensive work of Nagata et al.^{1e,g} In our continuing research for unique and potent β -lactam antibiotics, we have now synthesized a series of 3-(deacetoxymethyl)-1-oxa-1-dethiacephalosporins (1).² This work



has been undertaken because of an interest in determining

 ⁽a) S. Wolfe, J.-B. Ducep, K. C. Tin, and S.-L. Lee, Can. J. Chem., 52, 3996 (1974); (b) L. D. Cama and B. G. Christensen, J. Am. Chem. Soc., 96, 7582 (1974); (c) R. A. Firestone, J. L. Fahey, N. C. Maciejewicz, C. S. Patel, and B. G. Christensen, J. Med. Chem., 20, 551 (1977); (d) E. G. Brain, C. L. Branch, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, J. C. Smale, R. Southgate, and P. Tolliday, Spec. Publ. Chem. Soc., no. 28, 204 (1977); (e) M. Narisada, H. Onoue, and W. Nagata, Heterocycles, 7, 839 (1977); (f) C. U. Kim and D. N. McGregor, Tetrahedron Lett., 409 (1978); (g) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, J. Med. Chem., 22, 757 (1979); (h) C. L. Branch and M. J. Pearson, J. Chem. Soc., Perkin Trans. 1, 2268 (1979).

⁽²⁾ Two independent syntheses of this nucleus have appeared very recently: (a) ref 1h; (b) Y. Hamashima, S. Yamamoto, T. Kubota, K. Tokura, K. Ishikura, K. Minami, F. Matsubara, M. Yamaguchi, I. Kikkawa, and W. Nagata, *Tetrahedron Lett.*, 4947 (1979).