Synthesis of 7a-Substituted Benzoylaminoalkyl-hexahydro-1*H*-pyrrolizines and Evaluation of Their Antiarrhythmic Activity

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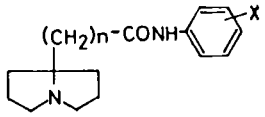
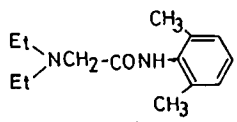
Abstract □ Several 7a-substituted benzoylaminoalkyl-hexahydro-1*H*-pyrrolizines were synthesized by acylations of 7a-aminoalkyl-hexahydro-1*H*-pyrrolizines. All compounds synthesized were evaluated for their antiarrhythmic activities using the chloroform–mouse method, and some of them were found to have significant antiarrhythmic activities, comparable to that of procainamide.

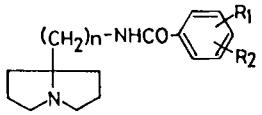
The basic amine functionality of "amide-type" antiarrhythmic agents, such as lidocaine (2), is known to have remarkable influence on the direction of their pharmacological properties (i.e., increase of the lipophilicity enhances the antiarrhythmic activity and higher pK_a value improves the therapeutic index[1]). Recently, we have reported the synthesis and desirable pharmacological activities of structural analogues of lidocaine, compounds represented by the general structure shown for compound 1.[2] They are characterized by the introduction of a hexahydro-1*H*-pyrrolizine (so-called pyrrolizidine) nucleus as the basic amine moiety. Having extended our studies, we synthesized hexahydro-1*H*-pyrrolizine derivatives 3 and 4, which are the simple reversals of the amide group in 1 and can be considered as congeners of procainamide (5). We also evaluated the antiarrhythmic activities of these analogues using the chloroform–mouse method.



1 n=1 or 2

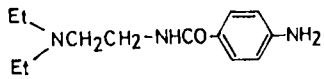


2 lidocaine



3 n=1

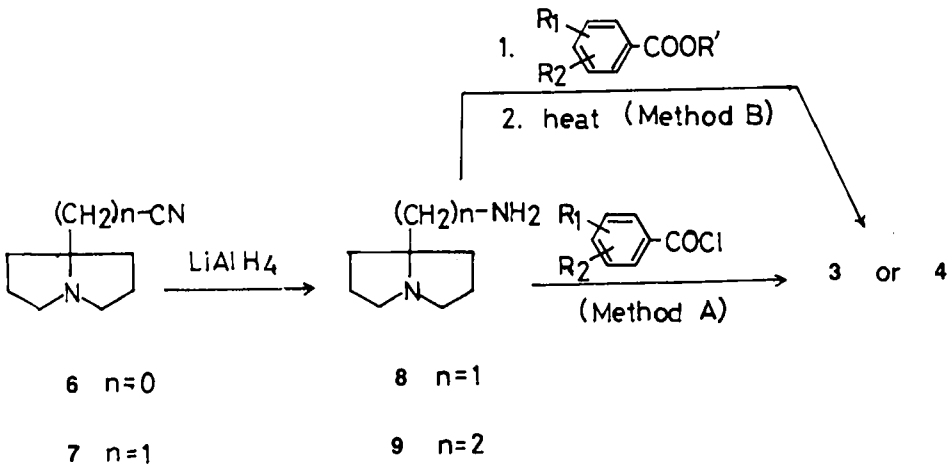
4 n=2



5 procainamide

Results

Chemistry—The target compounds (3 and 4) were synthesized by the routes shown in Scheme I. The key compounds in the preparation of the desired compounds are 7a-aminoalkyl-hexahydro-1*H*-pyrrolizines (8 and 9), which are easily obtained in good yields by the reduction of the corresponding nitriles (6 and 7) with lithium aluminum hydride (LAH). The



Scheme I

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methods for the preparation of the diamines (8 and 9) have already been reported.[3,4] The benzoylation of these amines (8 and 9) with various substituted benzoyl halides (method A) is a conventional procedure to obtain the target compounds (3 and 4). As a simple alternative procedure, the following could be employed with equal readiness. Thus, when a mixture of a methyl or ethyl ester of substituted benzoic acid and an equivalent molar amount of 7a-aminomethyl- or 7a-aminoethyl-hexahydro-1*H*-pyrrolizine (8 or 9) was fused at 100–200 °C, target compounds were also obtained in good yields (method B).

The structures of the target compounds (3 and 4) were easily confirmed by spectroscopic and elemental analyses. All of these compounds showed a characteristic absorption band for an amide group at 1620–1670 cm^{-1} in IR spectra, and the benzoyl groups introduced with the above procedures could be easily confirmed by ^1H NMR spectra (see Table I).

Pharmacological Evaluation—Antiarrhythmic effect (ED_{50}), acute toxicity (LD_{50}; both determined in mice), and the LD_{50}:ED_{50} ratio are summarized in Table II. The data are expressed on a molar basis. Procainamide (5) was adopted as a standard. The pharmacological data assembled in Table II unanimously show that the target compounds synthesized possess significant antiarrhythmic activities, comparable to that of procainamide, which ranged over about one order of magnitude.

Although it is not easy to draw a significant structure–activity relationship, the activity seems to depend on a substituent on the aromatic ring and the methylene length included in a functionality on the 7a-carbon [C(7a)]. Thus, the substitution of benzoylaminomethyl groups in the C(7a) position generally enhances the antiarrhythmic activity to a higher level than that exhibited by the compounds in which benzoylaminoethyl groups were introduced. For instance, **3a**, **3c**, and **3d** showed higher activities than those of the corresponding benzoyl aminoethyl series (**4a**, **4b**, and **4d**, respectively). In this series, antiarrhythmic activity using the chloroform–mouse method was maximized in **3e** (ED_{50} = 50 mg/kg). Since in the reversed-amide series, represented by the structure of **1**, we had observed the fact that the introduction of two ortho methyl substituents on the aromatic ring[2,5] yielded **10** (SUN-1165), which possesses a high antiarrhyth-

Table I—7a-Substituted Benzoylaminoalkyl-hexahydro-1*H*-pyrrolizines

Compound	n	R_1	R_2	Yield, %	mp, °C[a]	IR, cm^{-1} (C = O)[b]	^1H NMR, δ ppm[c]
3a	1	H	H	81	137.5–139	1645	[d]
3b	1	4-NH_2	H	53	201–204.5	1628	[d]
3c	1	4-OCH_3	H	81	148.5–150	1620	3.85 (s, 3, $-OCH_3$)[d]
3d	1	4-NO_2	H	38	246–247	1658	[d]
3e	1	4-NHCOOEt	H	49	197–199	1739 1640	1.26 (t, 3, J = 7 Hz, $-CH_3$), 4.18 (q, 2, J = 7 Hz, $-CH_2-$)[d]
3f	1	2-OEt	H	75	128–130.5	1630	1.53 (t, 3, J = 7 Hz, $-CH_3$), 4.18 (q, 2, J = 7 Hz, $-OCH_2-$)[d]
3g	1	4-OEt	H	83	137–139	1665	1.41 (t, 3, J = 7 Hz, CH_3), 4.04 (q, 2, J = 7 Hz, $-OCH_2-$)[d]
3h	1	3-$N(CH_3)_2$	H	56	142–145.5	1670	2.96 (s, 6, $-N(CH_3)_2$)[d]
3i	1	4-$N(CH_3)_2$	H	43	179–182	1660	3.16 (s, 6, $-N(CH_3)_2$)[d]
4a	2	H	H	70	[e]	1640	[d]
4b	2	4-OCH_3	H	49	155–157	1643	3.8 (s, 3, $-OCH_3$)[d]
4c	2	3-NO_2	H	83	182–184	1655	[d]
4d	2	4-NO_2	H	63	231–234	1655	[d]
11	1	2-CH_3	6-CH_3	77	220–222	1650	2.31 (s, 6, two $-CH_3$)[d]

[a] As monohydrochloride except for **3h** and **3i** (dihydrochloride), and **3b** (free base). [b] Measured as KBr tablet except for **3b**, **3c**, and **3d** (nujol), and **3f** ($CHCl_3$). [c] Measured as free bases in $CDCl_3$, except for **3b** ($CDCl_3$ + CD_3COCD_3), using TMS as an internal standard. [d] Aromatic protons were observed at δ 6.6–8.3 ppm; other aliphatic protons assignable to the hexahydro-1*H*-pyrrolizine ring and alkyl chains on C(7a) were observed at δ 1.2–4.0 ppm, and NH protons disappeared by treatment with D_2O. [e] The product was hygroscopic.

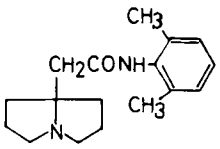
Table II—Antiarrhythmic Potencies (ED_{50}) and LD_{50} of Target Compounds

Compound	ED_{50}, mg/kg[a–c]	LD_{50}, mg/kg[c]	LD_{50}:ED_{50}[d]
3a	100 (51–196)	450	4.50
3b	>50[e]	125	—[f]
3c	70 (50–97)	298	4.26
3d	90 (61.6–131)	414	4.60
3e	50 (29.9–83.5)	120	2.40
3f	72 (18.5–281)	215	2.98
3g	77 (63.6–93.2)	212	2.75
3h	83 (53.9–128)	366	4.40
3i	140 (75.7–259)	260	1.85
4a	175 (136–226)	>500[f]	—[f]
4b	160 (121–211)	556	3.47
4c	135 (107–313)	252	1.86
4d	180 (103–313)	694	3.86
10	24 (11.5–50.2)[g]	410[g]	17.08[g]
11	92 (74–115)	469	5.09
Procainamide	190 (140–271)	660	3.47

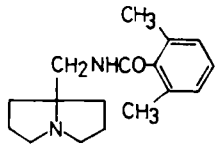
[a] Details of the screening tests are described in the experimental section. [b] Figures in parentheses are 95% confidence limits; subcutaneous administration. [c] Estimated in the mouse. [d] The data are expressed on a molar basis. [e] Not determined due to deaths at doses required for high degree of protection. [f] Not determined. [g] From ref 2.

Table III—Elemental Analysis of Target Compounds

Compound	Formula	Calculated			Found		
		C	H	N	C	H	N
3a	$C_{15}H_{21}ClN_2O$	64.16	7.54	9.98	64.18	7.60	9.82
3b	$C_{15}H_{21}N_3O$	69.46	8.16	16.21	69.53	8.23	16.16
3c	$C_{16}H_{24}ClNO_2 \cdot 1/2H_2O$	59.89	7.85	8.73	60.26	7.47	8.73
3d	$C_{15}H_{20}ClN_3O_3$	55.30	6.19	12.90	55.34	6.20	12.84
3e	$C_{18}H_{26}ClN_3O_3$	58.76	7.12	11.42	58.63	7.15	11.34
3f	$C_{17}H_{25}ClN_2O_2$	62.85	7.76	8.62	62.68	7.75	8.58
3g	$C_{17}H_{25}ClN_2O_2$	62.85	7.76	8.62	62.95	7.75	8.66
3h	$C_{17}H_{27}Cl_2N_3O$	56.66	7.55	11.66	56.24	7.61	11.43
3i	$C_{17}H_{27}Cl_2N_3O \cdot H_2O$	53.97	7.73	11.11	53.90	7.46	10.72
4a	$C_{16}H_{23}ClN_2O$	65.18	7.86	9.50	65.05	7.99	9.33
4b	$C_{17}H_{25}ClN_2O_2$	62.85	7.76	8.62	62.92	7.80	8.60
4c	$C_{16}H_{22}ClN_3O_3 \cdot 3/4H_2O$	54.39	6.49	11.89	54.25	6.67	11.88
4d	$C_{16}H_{22}ClN_3O_3 \cdot 1/3H_2O$	55.57	6.51	12.15	55.68	6.44	12.11
11	$C_{17}H_{25}ClN_2O$	66.11	8.16	9.07	66.21	8.30	8.98



10 SUN-1165



11

mic activity with improved LD_{50}:ED_{50}, we carried out such a transformation for the purpose of comparison. The result was that **11** slightly reduces activity (ED_{50} = 92 mg/kg) compared with the monosubstituted derivatives (such as **3c–h**), and improves the LD_{50}:ED_{50} value (2.40 → 5.09; see Table II). Such indistinct effects of the substituents on an aromatic ring seem to be related to the difference of the mode of action between the lidocaine and procainamide series. Thus, it is well known that these antiarrhythmic drugs (Class 1) are further classified into different subdivisions.[6]

In summary, a number of the compounds in the present study were found to possess higher antiarrhythmic activity compared with that of procainamide (**5**). However, with regard to ED_{50} and LD_{50}:ED_{50} values, none of the compounds was found to be superior to **10** (SUN-1165), as reported in our previous paper.[2]

Experimental Section

Melting points were determined on a Yanako melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Hitachi MH-100 or R-24B spectrometer, using tetramethylsilane as an internal standard, and IR spectra were obtained with either a Hitachi 260–10 or a Hitachi EPI-G-3 instrument. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. High-resolution mass spectra were obtained with a JEOL JMS-ISG instrument with a direct inlet system.

7a-Aminoalkyl-hexahydro-1*H*-pyrrolizines (8 and 9)—According to the procedure reported recently,[3] 7a-aminomethyl-hexahydro-1*H*-pyrrolizine (**8**) was obtained in 76% yield from the reduction of 7a-cyano-hexahydro-1*H*-pyrrolizine with lithium aluminum hydride (LAH), and 7a-aminoethyl-hexahydro-1*H*-pyrrolizine (**9**) was obtained in 84% yield from the reduction of 7a-cyanomethyl-hexahydro-1*H*-pyrrolizine (**7**) with LAH. Characterizations of these compounds have been mentioned in the previous paper.[4]

Preparation of 7a-(Substituted Benzoylaminomethyl)-hexahydro-1*H*-pyrrolizines—*Method A*—To a solution of substituted benzoyl chloride (0.01 mol) in benzene (50 mL), a solution of 7a-aminoalkyl-hexahydro-1*H*-pyrrolizine (0.01 mol) in benzene (50 mL) was added in a dropwise manner while the solution was stirred and kept cool in an ice bath. The resulting mixture was stirred at room temperature for 3 h. After evaporation of the solvent, the oily residue was recrystallized from ethanol–ether to give a product; **3e**, **3f**, **3g**, **4a–d**, and **11** were obtained by this procedure and the results are summarized in Table I.

Method B—A mixture of the methyl or ethyl ester of substituted benzoic acid and an equivalent molar amount of 7a-aminomethyl-hexahydro-1*H*-pyrrolizine was fused at 100–200 °C for 2–14 h. The desired product, as a free base, was purified by column chromatography on alumina and then transformed to the corresponding hydrochloride by the usual manner. The results are shown in Table I. Satisfactory analytical data (0.42% for C, H, and N) were obtained for all new compounds listed in Table I (see Table III).

Antiarrhythmic Activity—The target compounds shown in Table I were evaluated for antiarrhythmic activity essentially according to the method described by Lawson.[7] Groups of 10 male mice (DDY strain), weighing 18–22 g, were used and all compounds were injected subcutaneously. Thirty minutes after drug administration, the mice were exposed to chloroform vapor in a glass beaker until respiratory arrest occurred. A lead II electrocardiogram was used to observe whether ventricular fibrillation took place or not, and then the heart was exposed for visual inspection of ventricular rhythm. According to the method of Litchfield and Wilkoxon,[8] the antiarrhythmic ED_{50} value (50% of animals were protected from ventricular fibrillation induced by chloroform) was calculated. The acute LD_{50} value (24 h) was calculated by the up-and-down method described by Brownlee[9] in order to assess the therapeutic index (LD_{50}:ED_{50}). The results are summarized in Table II.

References and Notes

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Acknowledgments

This publication is Part 11 in a series on the study of pyrrolizidines and related compounds. See Miyano et al. (ref 4) for Part 10.