3-(Aminoalkyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones as Potential Anticholinergic Bronchodilators

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A series of 3-(aminoalkyl)benzopyrano[3,4-c]pyridin-5-ones was prepared and tested as potential orally active anticholinergic bronchodilators. Inhibition of methacholine-induced collapse in guinea pigs and inhibition of pilocarpine-induced bronchoconstriction in dogs served as in vivo models. Simultaneous measurement of salivary inhibition in the dog model allowed determination of a pulmonary selectivity ratio. The benzopyrano[3,4-c]pyridin-5-one parent ring system was prepared by Pechman condensation of phenols with a piperidine β-keto ester. Alkylation with aminoalkyl halides, or with 1-chloro-2-propanone followed by reductive amination, yielded the 3-substituted target compounds. Bronchodilator potency was related to the extent of steric crowding surrounding the side-chain terminal amine function. Addition of a methyl substituent on the carbon α to the terminal amine often increased potency or pulmonary selectivity. After secondary pharmacological evaluation, compound **7a**, designated CI-923, was selected for clinical trial as a bronchodilator.

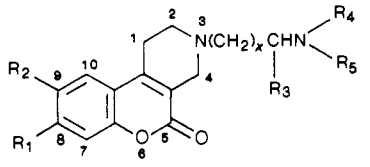
Current drugs widely used for the treatment of asthma and allergic diseases include cromolyn sodium, theophylline, β-adrenergic stimulants, and corticosteroids. All possess specific deficiencies, such as side effects or limited efficacy.

Since cholinergic mechanisms are an important factor in producing air flow obstruction, anticholinergic agents represent a possible complementary addition to the above regimens.[1] Atropine and other related natural product anticholinergics have a long history in the treatment of asthma.[2] However, the classical anticholinergic side effects (dry mouth, skin flushing, tachycardia, blurred vision, and gastrointestinal disturbances) associated with atropine led to its demise as an antiasthmatic drug, especially since the discovery of newer α- and β-adrenergic agents.

Interest in the use of anticholinergic agents has recently been revitalized with the development of newer drugs.[3] Ipratroprium bromide,[4] an inhalation agent with low systemic absorption (and thereby limited side effects), has recently received marketing approval in the United States as an anticholinergic bronchodilator. The use of anticholinergic agents in combination with β-adrenergic stimulants or theophylline is also of current interest.[5,6]

A key element in the successful development of a drug of this type is selectivity, that is, the ability to produce bronchodilation at doses that produce minimal antisecretory, CNS, and cardiovascular side effects when compared to atropine.

As part of a previous program,[7] a series of 3-substituted benzopyrano[3,4-c]pyridin-5-ones **1** were prepared and tested for their ability to protect guinea pigs from collapse induced by histamine challenge. Several compounds (**4a**, **4b**, Table I) were found to provide protection against challenge by methacholine chloride (a cholinergic spasmogen) as well as histamine. Compounds **4a** and **4b**



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served as the starting point for the further development of series **1** as potential orally active, selective, anticholinergic bronchodilators. The synthesis and biological activity of these compounds form the basis for the present paper.

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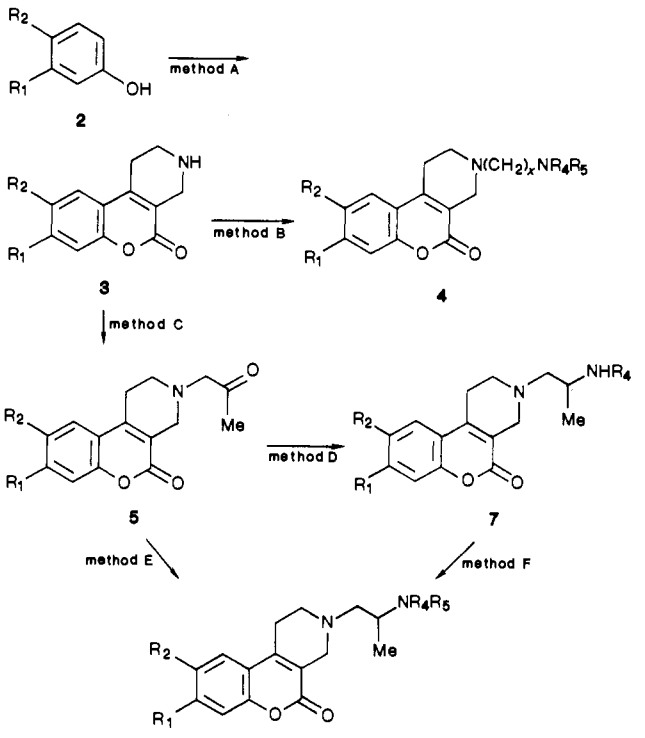
Scheme I[a]



[a]Reagents: (method A) methyl 4-oxo-3-piperidinecarboxylate hydrochloride/H_2SO_4; (method B) $Cl(CH_2)_xNR_4R_5/Et_3N$; (method C) 1-chloro-2-propanone/K_2CO_3; (method D) R_4NH_2/catalytic H_2; (method E) R_4R_5NH/catalytic H_2; (method F) $R_5CO_2H/NaBH_4$.

Chemistry

The overall synthetic sequence for the preparation of compounds of type **1** is shown in Scheme I. The parent benzopyrano[3,4-c]pyridin-5-ones **3** were prepared by a Pechman[8] condensation of methyl 4-oxo-3-piperidine-

(1) Gross, N. J.; Skorodin, M. S. *Am. Rev. Respir. Dis.* **1984**, *129*, 856.
(2) Rebuck, A. S.; Chapman, K. R.; Braude, A. C. *Chest* **1982** (Suppl.) 55S.
(3) Baigelman, W. *Chest* **1984**, *85*, 297.
(4) Pakes, G. E.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1980**, *20*, 237.
(5) Shenfield, G. M. *Drugs* **1982**, *24*, 414.
(6) Chu, S. S. *Drugs Today* **1984**, *20*, 575.
(7) Brown, R. E.; Puchalski, C.; Shavel, J. Jr. US Pat. 3,991,196, November 9, 1976.
(8) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1.

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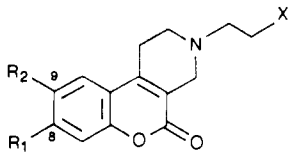
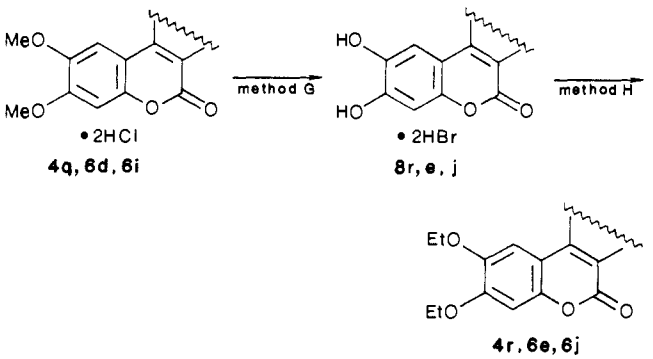
Table I. Bronchodilator Activity of 3-[2-(Alkylamino)ethyl]- and 3-[2-(Azabicyclo)ethyl]-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones



compd	R_1	R_2	X[a]	guinea pig collapse time, min[b]	cholinergic dog A: bronchospasm ID_{50}[c]	cholinergic dog B: salivation ID_{50}[d]	pulmonary selectivity (B/A)
4a	MeO	MeO	A	4.9 ± 1.2	–	–	–
4b	MeO	MeO	B	4.0 ± 1.3	–	–	–
4c[e]	MeO	MeO	A	1.6 ± 0.1	–	–	–
4d	MeO	H	A	9.5 ± 0.4	205	141	0.69
4e	MeO	H	B	8.0 ± 1.4	223	398	1.8
4f	MeO	H	C	1.9 ± 0.1	–	–	–
4g	MeO	H	D	8.0 ± 1.3	394	158	0.40
4h	MeO	H	E	7.0 ± 1.4	428	855	2.0
4i	MeO	H	F	9.1 ± 1.0	246	735	3.0
4j	MeO	H	G	6.1 ± 1.8	1141	714	0.63
4k	MeO	MeO	H	2.8 ± 0.4	–	–	–
4l	H	H	I	5.2 ± 1.6	849	68	0.08
4m	Me	H	I	5.0 ± 0.1	235	452	1.9
4n	Et	H	I	6.8 ± 1.4	74	41	0.55
4o	$(Me)_2CH$	H	I	6.2 ± 1.8	209	128	0.61
4p	MeO	H	I	6.0 ± 1.8	35	104	3.0
4q	MeO	MeO	I	5.0 ± 1.0	113	530	4.7
4r	EtO	EtO	I	6.3 ± 1.5	267	210	0.79
4s	Me	Me	I	5.1 ± 0.7	372	223	0.60
4t	MeO	H	J	7.3 ± 1.7	1026	154	0.15
4u	MeO	MeO	J	6.6 ± 1.6	119	–	–
4v	MeO	H	K	10.0 ± 0.0	63	102	1.6
4w	MeO	MeO	K	7.6 ± 1.5	137	140	1.0
atropine					7.0	3.2	0.46

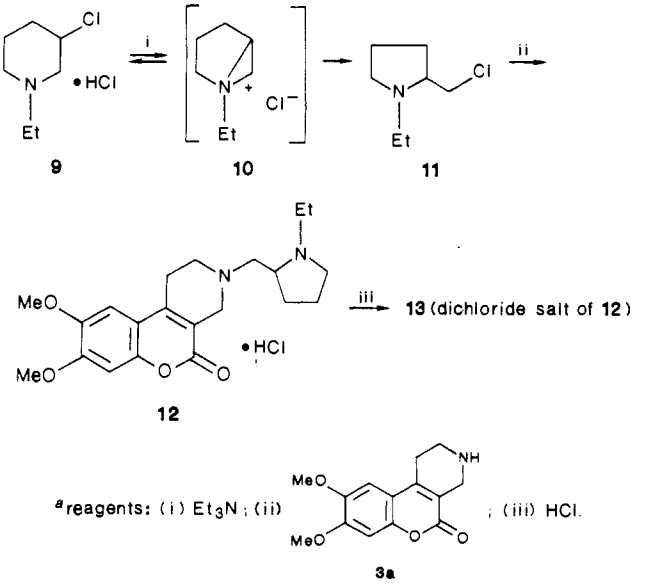
[a] For X: A = piperidino, B = hexamethyleneimino, C = dimethylamino, D = diethylamino, E = di-*n*-propylamino, F = pyrrolidino, G = morpholino, H = 2,2,6,6-tetramethylpiperidino, I = 3-azabicyclo[3.2.2]non-3-yl, *J* = 3-azabicyclo[3.3.1]non-3-yl, K = 2-azabicyclo[2.2.2]oct-2-yl. [b] Collapse time (min) observed in the guinea pig methacholine challenge test ± S.E.M. following a test drug dose of 25 mg/kg, po. [c] Dose of test compound (μg/kg) inhibiting dog cholinergic bronchoconstriction by 50% of control value. [d] Dose of test compound (μg/kg) inhibiting dog salivation by 50% of control value. [e] The side chain carbon bridge contains three methylene groups.

Scheme II[a]



[a] Reagents: (method G) 48% aqueous HBr; (method H) Et_2SO_4/K_2CO_3.

Scheme III[a]



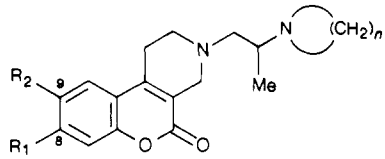
[a] reagents: (i) Et_3N; (ii) ; (iii) HCl.

carboxylate and an appropriately activated phenol **2** (method A). The Pechman reaction on phenol itself is not synthetically useful; for the preparation of **3** where R_1 = R_2 = H, an alternate procedure was employed.[9] Alkylation of **3** with aminoalkyl halides provided the 3-substituted amines **4** (method B), while alkylation with 1-chloro-2-propanone yielded intermediate methyl ketones **5** (method C). Reductive amination of **5** with primary amines produced analogues **7** containing a methyl group α to the terminal secondary amine (method D), while similar reductive amination with cyclic or other secondary amines produced the related α-methyl tertiary amines **6** (method E). N-Alkylation of **7** with a carboxylic acid and sodium borohydride[10] allowed the preparation of examples of **6** with mixed alkyl (R_4, R_5) substituents (method F).

(9) Connor, D. T.; Unangst, P. C.; Schwender, C. F.; Sorenson, R. J.; Carethers, M. E.; Puchalski, C.; Brown, R. E. *J. Heterocycl. Chem.* 1984, *21*, 1557.

(10) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* 1978, 766.

Table II. Bronchodilator Activity of 3-[2-(Alkylamino)propyl]-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-c]pyridin-5-ones. Cyclic Amines



compd	R_1	R_2	n	guinea pig collapse time, min[a]	cholinergic dog A: bronchospasm ID_{50}[b]	cholinergic dog B: salivation ID_{50}[c]	pulmonary selectivity (B/A)
6a	H	H	4	10.0 + 0.0	88	190	2.2
6b	Me	H	4	8.7 ± 1.3	100	226	2.3
6c	Me	Me	4	8.2 ± 1.3	315	699	2.2
6d	MeO	MeO	4	10.0 ± 0.0	17	23	1.4
6e	EtO	EtO	4	9.4 ± 0.6	99	163	1.6
6f	H	H	5	10.0 ± 0.0	38	219	5.8
6g	Me	H	5	9.7 ± 0.3	40	108	2.7
6h	Me	Me	5	7.7 ± 1.5	300	1158	3.9
6i	MeO	MeO	5	10.0 ± 0.0	129	168	1.3
6j	EtO	EtO	5	10.0 ± 0.0	126	194	1.5
6k	MeO	MeO	6	1.7 ± 0.1	–	–	–
6l	MeO	MeO	*d*	10.0 ± 0	–	–	–
13	MeO	MeO	*e*	2.8 ± 0.4	–	–	–

[a] Collapse time (min) observed in the guniea pig methacholine challenge test ± S.E.M. following a test drug dose of 25 mg/kg, po. [b] Dose of test compound (μg/kg) inhibiting dog cholinergic bronchoconstriction by 50% of control value. [c] Dose of test compound (μg/kg) inhibiting dog salivation by 50% of control value. [d] The side-chain terminal amine substituent is morpholino. [e] The side chain is that as shown in Scheme III.

In instances where 8,9-diethoxy substituents were desired in **1**, the corresponding 8,9-dimethoxy analogues were demethylated with HBr (method G, Scheme II), and the intermediate 8,9-dihydroxy compound **8** was alkylated with diethyl sulfate (method H).

The established[11] rearrangement of piperidine derivative **9** (Scheme III) via aziridinium ion intermediate **10** to the related pyrrolidine **11** was employed in the preparation of analogue **13**, in which the α-methyl substituent can be envisioned as being incorporated into the terminal amine substituent.

Physical data for new compounds are listed in Table IV.

Results and Discussion

Compounds were initially screened for their ability to protect guinea pigs from collapse after challenge with aerosolized methacholine chloride. This screen was employed to identify compounds with oral activity suitable for further evaluation. Secondary testing was in a pilocarpine-treated dog model, which provided quantitative data on both the bronchodilator and antisecretory properties (as measured by inhibition of salivation) of the test compound in the same animal. The ratio of ID_{50} values for inhibition of salivation compared to inhibition of bronchospasm was defined as the pulmonary selectivity of the molecule. Atropine, being a more potent inhibitor of salivation than bronchospasm in this model, has a pulmonary selectivity ratio of <1.

Analogues of **4a** and **4b** were prepared in which the aminoalkyl side chain was extended by an additional methylene group (**4c**, Table I), and the substituent pattern in the benzene ring of **1** was varied within the synthetic limitations imposed by the Pechman reaction.[8] Although most of these variations yielded compounds lacking significant activity,[12] a major exception was a series of 8-methoxy compounds (**4d–j**). In addition, several compounds (**4e**, **4h**, **4i**) were more selective for inhibition of bronchoconstriction compared to inhibition of salivation.

In the initial set of 8-methoxy-substituted compounds, the choice of the terminal tertiary amine function did not appear critical, as activity in the guinea pig and dog models was observed with a variety of side chains. In an effort at identifying a superior side chain, compound **4p** containing the 3-azabicyclo[3.2.2]non-3-yl terminal amine was prepared. In addition to being pulmonary selective, the potency of **4p** as a bronchodilator (ID_{50} = 35 μg/kg in the dog model) was superior to that of any of the previous compounds. Additional examples **4l–s** containing the **4p** side chain were then synthesized. Once again, the 8-methoxy (**4p**) and 8,9-dimethoxy (**4q**) analogues were among the most potent as bronchodilators, as well as having the highest pulmonary selectivity. In contrast, the unsubstituted analogue **4l** was the poorest by both criteria. Several additional azabicyclo amine side chains (**4t–w**) as well as a highly hindered monocyclic amine (**4k**) were also investigated with mixed results.

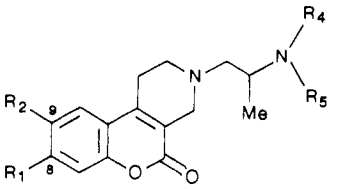
From the data of Table I, it appeared that increasing the steric crowding about the side-chain terminal nitrogen in **1** increased the anticholinergic bronchodilator activity of this chemical series. As a test of this idea, a series of analogues (Tables II and III) were prepared containing a methyl group on the carbon chain in a position α to the terminal amine.

Table II lists α-methyl-containing compounds with cyclic terminal amines, while Table III contains dialkyl terminal amines. A variety of aromatic substituents, primarily the unsubstituted, 8-methyl, 8-methoxy, and 8,9-dimethoxy, were investigated.

Inclusion of the α-methyl function produced a considerable number of active compounds, adding weight to the concept of steric crowding about the terminal amine being critical for superior bronchodilator activity. This effect can be seen by a comparison of the ID_{50} for inhibition of dog bronchospasm of **6x** vs **4g** (38 vs 394 μg/kg) and a comparison of the guinea pig collapse times of **6u** vs **4f** (10 vs 1.9 min). In addition, the α-methyl analogues with 8-methyl or no aromatic substituents (such as **6f**, **6g**, **6m**, and **6p**) had a level of potency and pulmonary selectivity not seen in the compounds in the corresponding azabicyclo series (compare **4l** and **4m**), with **6m** being the most se-

(11) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239.
(12) Unpublished results.

Table III. Bronchodilator Activity of 3-[2-(Alkylamino)propyl]-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[3,4-c]pyridin-5-ones. Noncyclic Amines



compd	R_1	R_2	R_4	R_5	guinea pig collapse time, min[a]	cholinergic dog A: bronchospasm ID_{50}[b]	cholinergic dog B: salivation ID_{50}[c]	pulmonary selectivity (B/A)
6m	H	H	Me	Me	10.0 ± 0.0	192	4147	21.6
6n	H	H	Et	Et	10.0 ± 0.0	336	2310	6.9
6o	H	H	Et	*n*-Pr	6.4 ± 1.6	1108	970	0.88
6p	Me	H	Me	Me	10.0 ± 0.0	114	421	3.7
6q	Me	H	Me	Et	8.8 ± 1.2	150	336	2.2
6r	Me	H	Me	*n*-Pr	5.4 ± 1.2	192	304	1.6
6s	Me	H	Et	Et	6.6 ± 1.7	111	510	4.6
6t	Me	H	Et	*n*-Pr	7.6 ± 1.5	116	182	1.6
6u	MeO	H	Me	Me	10.0 ± 0.0	25	27	1.1
6v	MeO	H	Me	Et	9.1 ± 0.9	15	23	1.5
6w	MeO	H	Me	*n*-Pr	10.0 ± 0.0	73	84	1.2
6x	MeO	H	Et	Et	10.0 ± 0.0	38	46	1.2
6y	MeO	H	Et	*n*-Pr	10.0 ± 0.0	58	27	0.47
6z	MeO	MeO	Me	Me	5.2 ± 1.6	98	441	4.5
6aa	MeO	MeO	Me	Et	6.0 ± 1.3	135	111	0.82
6bb	MeO	MeO	Me	*n*-Pr	2.5 ± 0.3	–	–	–
6cc	MeO	MeO	Et	Et	7.8 ± 1.4	73	257	3.5
6dd	MeO	MeO	Et	*n*-Pr	3.7 ± 1.3	–	–	–
7a	H	H	H	Et	10.0 ± 0.0	210	1232	5.9
7b	Me	H	H	Et	10.0 ± 0.0	627	225	0.36
7c	MeO	H	H	Et	7.5 ± 1.6	86	227	2.6
7d	MeO	MeO	H	Et	1.7 ± 0.2	–	–	–

[a] Collapse time (min) observed in the guinea pig methacholine challenge test ± S.E.M. following a test drug dose of 25 mg/kg, po. [b] Dose of test compound (μg/kg) inhibiting dog cholinergic bronchoconstriction by 50% of control value. [c] Dose of test compound (μg/kg) inhibiting dog salivation by 50% of control value.

lective compound prepared. In a few cases, such as the C_6-cyclic amine **6k** and incorporation of the α-methyl within the terminal amine substituents (**13**), increased steric crowding decreased bronchodilator activity.

Within Tables II and III, the analogues without aromatic ring substitution were among those with the highest pulmonary selectivity (a reverse of that seen with the azabicyclo compounds of Table I), while the 8-methoxy and 8,9-dimethoxy compounds were again the most potent as bronchodilators. Overall, variation of the side-chain terminal amine did not seem to have as great an effect on bronchodilator activity (or selectivity) as did aromatic ring substitution or inclusion of the α-methyl substituent.

A new series of 3-substituted benzopyrano[3,4-*c*]-pyridin-5-ones has been prepared and tested in several in vivo models for utility as orally effective anticholinergic bronchodilators. A number of compounds exhibited the desired combination of bronchodilator potency and selectivity for pulmonary versus antisecretory activity. These compounds were then evaluated in several cardiovascular and CNS pharmacology models in order to further define their therapeutic potential. From those results, compound **7a**, now designated CI-923, was selected to undergo clinical trials as a bronchodilator.

Experimental Section

Melting points were determined on a Mel-Temp or Thomas-Hoover capillary apparatus and are uncorrected. The ^1H NMR spectra were determined at 90 MHz on a Varian EM-390 or at 200 MHz on a Varian XL-200 spectrometer with tetramethylsilane as an internal standard. The infrared spectra were recorded as potassium bromide disks on a Digilab FTS-14 spectrophotometer. Elemental analyses were provided by the Analytical Chemistry staff of this department. All new compounds yielded spectral data consistent with the proposed structure and microanalyses within ±0.4% of the theoretical values unless indicated otherwise.

Chemistry. General Methods A–F. Detailed procedures for these methods, as well as physical data for compounds **2–7** not described in this paper, have been previously published.[9,13]

Method G. 3-[2-(3-Azabicyclo[3.2.2]non-3-yl)ethyl]-1,2,3,4-tetrahydro-8,9-dihydroxy-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one Dihydrobromide (8r). A solution of 10.0 g (0.02 mol) of the dimethoxyamine **4q** in 100 mL of 48% aqueous HBr was stirred at reflux for 16 h. The mixture was cooled, and the precipitated HBr salt was filtered and washed with acetone to yield 10.7 g (97%) of crude product suitable for alkylation to the diethoxy analogue. A sample recrystallized from MeOH/DMF/H_2O provided analytically pure **8r**, mp 270 °C dec: IR (KBr) ν 1708, 1619, 1421, 1309, 1268 cm^{-1}; ^1H NMR (Me_2SO-d_6; run at 90 °C) δ 1.58–2.22 (m, 10 H, azabicyclo CH_2CH_2; *CH*), 3.03–3.75 (m, 12 H, #1 and #2 CH_2; NCH_2), 4.01 (s, 2 H, #4 CH_2), 6.82 (s, 1 H, Ar*H*), 7.05 (s, 1 H, Ar*H*).

Anal. ($C_{22}H_{28}N_2O_4 \cdot 2HBr \cdot 1H_2O$) C, H, N.

Method H. 3-[2-(3-Azabicyclo[3.2.2]non-3-yl)ethyl]-1,2,3,4-tetrahydro-8,9-diethoxy-5*H*-[1]benzopyrano[3,4-*c*]-pyridin-5-one (4r). A mixture of 11.5 g (0.02 mol) of the dibromide salt **8r**, 15.0 g (0.11 mol) of K_2CO_3, and 6.8 mL (8.0 g, 0.052 mol) of Et_2SO_4 in 600 mL of acetone was stirred at reflux for 20 h. The mixture was cooled, and an additional 2.0 mL (2.35 g, 0.015 mol) of Et_2SO_4 was added. Heating was continued for a total of 50 h. The mixture was cooled and filtered, and the filter cake was washed several times with fresh acetone. The combined filtrates were evaporated, and the residue was partitioned between CH_2Cl_2 (1500 mL) and H_2O (750 mL). The organic layer was separated, washed with 2.5% aqueous NaOH solution (4 × 750 mL), dried (Na_2SO_4), and evaporated. Two recrystallizations of

(13) Connor, D. T.; Unangst, P. C.; Schwender, C. F.; Sorenson, R. J.; Carethers, M. E.; Puchalski, C.; Brown, R. E. *J. Heterocycl. Chem.* **1984**, *21*, 1561.

Table IV. Physical Data for 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[3,4-c]pyridin-5-ones

compd	method[a]	yield, %	mp, °C	crystn solvent	formula[b]
4b	B	28	233–234	MeOH	$C_{22}H_{30}N_2O_4 \cdot 2HCl \cdot 0.50MeOH$
4c	B	47	225–227	EtOH/H_2O	$C_{22}H_{30}N_2O_4 \cdot 2HCl \cdot 1.50H_2O$
4e	B	50	258–260	MeOH	$C_{21}H_{28}N_2O_3 \cdot 2HCl \cdot 1.0H_2O$
4f	B	63	214–216	MeOH	$C_{17}H_{22}N_2O_3 \cdot 2HCl \cdot 2.0MeOH$
4h	B	77	255–256	EtOH	$C_{21}H_{30}N_2O_3 \cdot 2HCl \cdot 0.33H_2O$
4i	B	59	237–240	MeOH	$C_{19}H_{24}N_2O_3 \cdot 2HCl \cdot 0.75H_2O$
4j	B	81	237–240	MeOH	$C_{19}H_{24}N_2O_4 \cdot 2HCl$
4k	B	50	154–156	MeOH	$C_{25}H_{36}N_2O_4$
4n	B	68	295–300	EtOH	$C_{24}H_{32}N_2O_2 \cdot 2HCl$
4o	B	22	273–275	EtOH	$C_{25}H_{34}N_2O_2 \cdot 2HCl$
4r	H	61	132–134	MeCN	$C_{26}H_{36}N_2O_4$
4t	B	48	102–103	EtOH	$C_{23}H_{30}N_2O_3$
4u	B	61	122–125	EtOH	$C_{24}H_{32}N_2O_4$
4v	B	45	112–113	–	$C_{22}H_{28}N_2O_3$
4w	B	12	133–135	EtOAc	$C_{23}H_{30}N_2O_4$
6a	E	17	248 dec	–	$C_{19}H_{24}N_2O_2 \cdot 2HCl \cdot 0.50H_2O$
6b	E	46	192–194	EtOH	$C_{20}H_{26}N_2O_2 \cdot 2HCl \cdot 0.25H_2O$
6c	E	52	146–148	MeOH	$C_{21}H_{28}N_2O_2$
6d	E	30	139–141	MeOH	$C_{21}H_{28}N_2O_4$
6e	H	64	112–115	MeOH	$C_{23}H_{32}N_2O_4$
6j	H	29	101–104	MeCN	$C_{24}H_{34}N_2O_4$
6k	E	3	172–175	MeOH	$C_{23}H_{32}N_2O_4$
6l	E	36	138–140	MeOH	$C_{21}H_{28}N_2O_5$
6o	F	44	238–dec	–	$C_{20}H_{28}N_2O_2 \cdot 2HCl \cdot 0.80H_2O$
6q	F	29	245–dec	EtOH	$C_{19}H_{26}N_2O_2 \cdot 2HCl \cdot 0.50H_2O$
6r	F	52	238–dec	EtOH	$C_{20}H_{28}N_2O_2 \cdot 2HCl \cdot 0.20H_2O$
6t	F	72	248–dec	EtOH	$C_{21}H_{30}N_2O_2 \cdot 2HCl \cdot 0.20H_2O$
6v	F	76	102–104	$(i\text{-Pr})_2O$	$C_{19}H_{26}N_2O_3$
6w	F	56	69–71	hexane	$C_{20}H_{28}N_2O_3$
6y	F	59	100–101	MeCN	$C_{21}H_{30}N_2O_3$[c]
6bb	F	9	81–85	$(i\text{-Pr})_2O$	$C_{21}H_{30}N_2O_4$
8r	G	97	270 dec	MeOH/DMF/H_2O	$C_{22}H_{28}N_2O_4 \cdot 2HBr \cdot 1H_2O$
13	*d*	62	218 dec	EtOH	$C_{21}H_{28}N_2O_4 \cdot 2HCl \cdot 0.50H_2O$

[a] Methods are as described in Schemes I and II. [b] Analyses of all compounds for (C, H, N) were within 0.4% of the theoretical values. [c] Anal. C, H, N: Calcd, 7.82; Found: 7.22. [d] See Experimental Section for specific procedure.

the residue from MeCN yielded 5.4 g (61%) of analytically pure **4r** as the free base, mp 132–134 °C: IR (KBr) ν 1710, 1617, 1514, 1430, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.60 (overlapping t, 6 H, CH_2CH_3), 1.60–2.00 (m, 10 H, azabicyclo CH_2CH_2; CH), 2.50–2.85 (m, 8 H, #1 and #2 CH_2; azabicyclo NCH_2), 2.88 (s, 4 H, NCH_2CH_2N), 3.54 (s, 2 H, #4 CH_2), 4.06–4.19 (overlapping q, 4 H, CH_2CH_3), 6.83 (s, 1 H, ArH), 6.93 (s, 1 H, ArH). Anal. ($C_{26}H_{36}N_2O_4$) C, H, N.

3-[(1-Ethyl-2-pyrrolidinyl)methyl]-1,2,3,4-tetrahydro-8,9-dimethoxy-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one Dihydrochloride (13). A mixture of 8.0 g (0.031 mol) of lactone **3a**,[9] 7.0 g (0.038 mol) of 3-chloro-1-ethylpiperidine hydrochloride (**9**),[14] and 9.5 mL (6.9 g, 0.068 mol) of Et_3N in 200 mL of EtOH was stirred at reflux for 16 h. After hot filtration, the cooled reaction mixture deposited 9.6 g of crude product characterized after recrystallization from EtOH as the monohydrochloride **12** (7.7 g; 62%). A 3.0-g (0.0073 mol) sample of **12** was dissolved in 70 mL of warm EtOH, and the solution was saturated with gaseous HCl. Cooling yielded 2.8 g (86%) of the analytically pure dihydrochloride **13**, mp 218 °C dec: IR (KBr) ν 1714, 1579, 1429, 1251, 1162 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.29 (t, 3 H, CH_2CH_3), 1.85–2.54 (m, 4 H, pyrrolidine CH_2), 2.95–3.73 (m, 11 H, CH_2; CH), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.05 (br s, 2 H, #4 CH_2), 7.15 (s, 1 H, ArH), 7.19 (s, 1 H, ArH).

Anal. ($C_{21}H_{28}N_2O_4 \cdot 0.5H_2O$) C, H, N.

Biological Methods. Guinea Pigs Methacholine Challenge. Hartley guinea pigs are exposed to 0.1% methacholine chloride for 10 min by means of two de Vilbiss #40 nebulizers positioned at the back of a closed, six unit plexiglass chamber (19 × 12.5 × 9 in). Air flow is adjusted to give a pressure of 10 lb/in.^{2} The time from onset of the aerosol challenge to collapse for each animal is recorded; six animals per treatment are averaged. Control animals in this test collapse in 1.8 to 2.1 min. Guinea pigs that do not collapse are removed from the chamber after 10 min and the maximum score of 10 is recorded. The test compounds (25 mg/kg, po) are given 15 min before exposure to spasmogen. Compounds that provide 5 min or more protection from collapse are arbitrarily considered active.

Dog Cholinergic Bronchoconstriction Inhibition. Mongrel dogs of either sex, 10.6 to 15.3 kg, are anesthetized with sodium pentobarbital (30 mg/kg, iv) and then surgically prepared for the monitoring of pulmonary mechanics. A Buxco pulmonary mechanics computer is used to calculate pulmonary resistance, dynamic compliance, and tidal volume from transpulmonary pressure and flow data. Respiratory rate, heart rate, and mean arterial blood pressure are also monitored. The femoral vein is cannulated for the delivery of drugs.

Pilocarpine nitrate (0.2 mg/kg/h) is then infused to induce a bronchospasm and salivary flow. Bunolol (0.5 mg/kg, iv) is given 30 min prior to the pilocarpine to reduce the protein content, and, hence, the viscosity, of the saliva. Salivary output is collected from a catheterized Wharton's duct at 5-min intervals. After salivation has stabilized, three control collections are taken at 5-min intervals followed by a series of cumulative iv doses of test compound (1, 3, 30, 100, 300, 1000, 3000, and 10,000 μg/kg) that are injected every 5 min for 45 min.

The percent inhibition of pulmonary resistance and salivation are then calculated by using the formula

$$\frac{\text{post pilocarpine value} - \text{post drug value}}{\text{post pilocarpine value} - \text{pre pilocarpine value}} \times 100 = \% \text{ inhibition}$$

The ID_{50} values for both the resistance and the antisalivation response to drug are calculated by linear regression analysis (log cumulative dose vs response) of the data. The selectivity ratio is then calculated by using the formula

$$\frac{ID_{50} \text{ for inhibition of salivation (B)}}{ID_{50} \text{ for inhibition of bronchospasm (A)}} = \text{selectivity}$$

Due to the surgical complexity of this test system, most compounds were initially evaluated in only one dog. In instances where a compound was tested in multiple dogs, the ID_{50} values for

(14) Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1948**, *70*, 2760.

bronchospasm and salivation generally varied within a range of 10–20%.

Registry No. **3** (R_1 = MeO; R_2 = H), 54504-36-8; **3** (R_1 = Et; R_2 = H), 86371-00-8; **3** (R_1 = $(Me)_2CH$; R_2 = H), 118514-03-7; **3a**, 59456-03-0; **4a**, 41806-52-4; **4b**, 118513-80-7; **4b**·2HCl, 61709-32-8; **4c**, 118513-81-8; **4c**·2HCl, 118514-08-2; **4d**, 118513-82-9; **4e**, 118513-83-0; **4e**·2HCl, 118514-09-3; **4f**, 118513-84-1; **4f**·2HCl, 118514-10-6; **4g**, 118513-85-2; **4h**, 118513-86-3; **4h**·2HCl, 118514-11-7; **4i**, 118513-87-4; **4i**·2HCl, 118514-12-8; **4j**, 59456-04-1; **4j**·2HCl, 54504-40-4; **4k**, 62124-26-9; **4l**, 118537-26-1; **4m**, 87942-30-1; **4n**, 118513-88-5; **4n**·2HCl, 87942-25-4; **4o**, 87942-54-9; **4o**·2HCl, 87942-31-2; **4p**, 118513-89-6; **4q**, 87942-53-8; **4r**, 87942-43-6; **4s**, 87942-35-6; **4t**, 87942-45-8; **4u**, 87942-46-9; **4v**, 87942-50-5; **4w**, 87942-51-6; **5** (R_1 = R_2 = H), 86371-21-3; **5** (R_1 = Me; R_2 = H), 86371-16-6; **5** (R_1 = R_2 = Me), 86371-12-2; **5** (R_1 = R_2 = MeO), 60629-83-6; **6a**, 118513-90-9; **6a**·2HCl, 118514-13-9; **6aa**, 118514-01-5; **6b**, 118575-11-4; **6b**·2HCl, 118514-14-0; **6bb**, 86371-52-0; **6c**, 118513-91-0; **6cc**, 86371-77-9; **6d**, 60629-85-8; **6dd**, 86371-64-4; **6e**, 118513-92-1; **6f**, 118513-93-2; **6g**, 118513-94-3; **6h**, 95571-28-1; **6i**, 60629-86-9; **6j**, 118513-95-4; **6k**, 118513-96-5; **6l**, 60629-84-7; **6m**, 86371-74-6; **6n**, 86371-76-8; **6o**, 118513-97-6; **6o**·2HCl, 86371-61-1; **6p**, 86371-73-5; **6q**, 86503-95-9; **6q**·2HCl, 86371-48-4; **6r**, 118513-98-7; **6r**·2HCl, 86371-54-2; **6s**, 86371-75-7; **6t**, 118513-99-8; **6t**·2HCl, 86371-59-7; **6u**, 118514-00-4; **6v**, 86371-51-9; **6w**, 86371-53-1; **6x**, 86371-49-5; **6y**, 86371-50-8; **6z**, 86371-71-3; **7** (R_1 = R_2 = H; R_4 = Et), 86371-40-6; **7** (R_1 = R = Me; R_2 = H), 86371-44-0; **7** (R_1 = Me; R_2 = H; R_4 = Et), 86371-43-9; **7** (R_1 = MeO; R_2 = H; R_4 = Me), 86371-46-2; **7** (R_1 = MeO; R_2 = H; R_4 = Et), 86371-45-1; **7** (R_1 = R_2 = MeO; R_4 = Me), 86371-47-3; **7a**, 86371-40-6; **7b**, 86371-43-9; **7c**, 86371-45-1; **7d**, 118514-02-6; **8e**, 118514-04-8; **8j**, 118514-05-9; **8r**, 87942-41-4; **9**, 50461-27-3; **12**·HCl, 118514-06-0; **12**·2HCl, 118514-07-1; $(CH_2)_8NH$, 111-49-9; butanoic acid, 107-92-6; propionic acid, 79-09-4; 1-(2-chloroethyl)piperidine, 1932-03-2; *N*-(2-chloroethyl)-hexamethylimine, 2205-31-4; 2-chloro-*N*,*N*-dimethylethanamine, 107-99-3; 2-chloro-*N*,*N*-diethylethanamine, 100-35-6; 2-chloro-*N*,*N*-dipropylethanamine, 36716-60-6; 1-(2-chloroethyl)pyrrolidine, 5050-41-9; *N*-(2-chloroethyl)morpholine, 3240-94-6; 1-(2-chloroethyl)-2,2,6,6-tetramethylpiperidine, 773-50-2; 3-(2-chloroethyl)-3-azabicyclo[3.2.2]nonane, 54777-55-8; 3-(2-chloroethyl)-3-azabicyclo[3.3.1]nonane, 87942-52-7; 2-(2-chloroethyl)-2-azabicyclo[2.2.2]octane, 59882-35-8; 1-(3-chloropropyl)piperidine, 1458-63-5; pyrrolidine, 123-75-1; piperidine, 110-89-4; morpholine, 110-91-8.

Heterocyclic Analogues of Benzamide Antiarrhythmic Agents[1]

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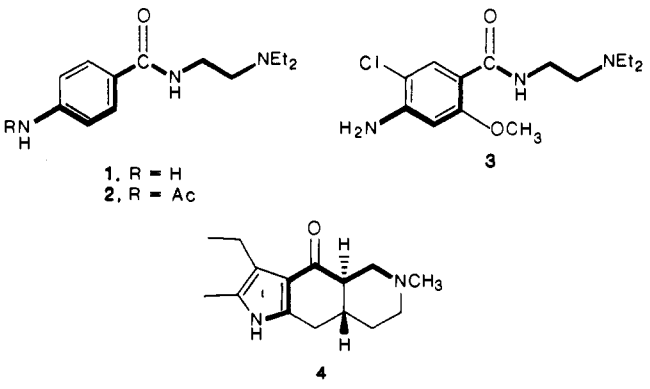
A series of heterocyclic *N*-[(diethylamino)alkyl]arenamides related to acecainide was prepared and examined for antiarrhythmic activity. The compounds were synthesized from the corresponding known heterocyclic carboxylic acids or esters by using standard amide formation methods. The effects of the compounds on the electrophysiological properties of canine Purkinje fibers and ventricular muscle strips were determined. Most of the compounds showed effects consistent with weak class I activity. Two compounds, *N*-[2-(diethylamino)ethyl]-3,4,5-trimethyl-1*H*-pyrrole-2-carboxamide and *N*-[2-(diethylamino)ethyl]-1*H*-indole-2-carboxamide, displayed prolongation of the action potential duration and functional refractory period indicative of modest class III electrophysiological activity. Representative compounds were examined by using molecular modeling techniques. Compounds of differing activity classes displayed qualitatively different electrostatic potential maps.

In the course of our studies aimed at the preparation of novel antiarrhythmic agents,[2] we noted structural similarities (highlighted below) between the known antiarrhythmic compounds procainamide, **1**, and acecainide, **2**, and the dopamine antagonists metoclopramide, **3**, and piquindone, **4**.[3] We noted that for the dopamine antagonists, certain heterocycles such as the pyrrole subunit found in **4** can substitute for the aniline seen in compounds such as **3**. In both **3** and **4** a hydrogen-bearing nitrogen is positioned so as to be in conjugation with a carbonyl group. Given the structural similarities between antiarrhythmic compounds such as **1** and **2** and the dopamine antagonist **3**, we reasoned that substitution of certain heterocycles for aniline might also be applicable to the preparation of analogues of benzamide antiarrhythmic agents.

There is some suggestion in the literature that this substitution might yield antiarrhythmic activity. In a study of the antiarrhythmic activity of a series of (dialkylamino)ethylamides, Giannini and co-workers[4] prepared compound **5**; they reported however that it displayed



less than half the activity of quinidine against aconitine-induced arrhythmias in the isolated guinea pig heart. To

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