(12) J. C. Powers, R. Seidner, and T. G. Parson, *Tetrahedron Lett.*, 1713 (1965).
(13) N. Löfgren, ref 5, p 25.
(14) U. H. Lindberg, B. Nylén, and B. Åkerman, *Acta. Pharm. Suec.*, **5**, 429 (1968).
(15) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 1786 (1950).
(16) W. S. Fones, *J. Org. Chem.*, 14, 1099 (1949); C. S. Marvel and W. W. Moyer, Jr., *ibid.*, **22**, 1065 (1957).
(17) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, **160**, 22 (1968).
(18) A. S. Harris, *Circulation*, 1, 1318 (1950).
(19) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 1897 (1971).
(20) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).
(21) (a) B. D. Clark and J. R. Cummings, *Ann. N.Y. Acad. Sci.*, **64**, 543 (1965); (b) E. R. Smith, B. R. Duce, and R. N. Boyes, *Am. Heart J.*, **83**, 365 (1972).
(22) A. Berlin-Wahlén, J. C. Barkus, J. B. Keenaghan, M. Lebeaux, and P. Tenthorey, *Acta Pharm. Suec.*, **14**, 417 (1977).

New Antiarrhythmic Agents. 3. Primary β-Amino Anilides

Paul A. Tenthorey,* Robert L. DiRubio, Hal S. Feldman, Bertil H. Takman,

Astra Research Laboratories, Framingham, Massachusetts 01701

Eugene W. Byrnes,

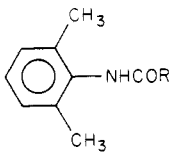
Assumption College, Worcester, Massachusetts 01609

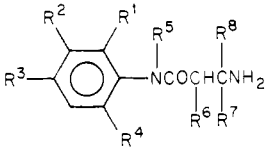
and Paul D. McMaster

College of the Holy Cross, Worcester, Massachusetts 01610. *Received April 18, 1979*

The synthesis and pharmacologic evaluation of primary β-amino anilides, as well as comparisons with tocainide, lidocaine, and its β homologue, are described. Substituted anilines were acylated with 3-bromoacyl chlorides and converted to the title compounds by direct amination or via 3-phthalimido anilides and subsequent hydrazinolysis. Alternatively, anilines were acylated with substituted acryloyl chlorides and the amines prepared by addition of ammonia to the double bond. The target compounds were evaluated for their ability to protect against chloroform-induced fibrillation in mice. All were found to have some antifibrillatory activity; several were more potent than tocainide, a compound in clinical trials as an oral antiarrhythmic drug. Four compounds were tested for their effects against ventricular arrhythmias in dogs with myocardial infarction. 3-Amino-2′,6′-butyroxylidide (**38**) was found to be more potent and less CNS toxic than tocainide.

In a previous article[1] we have described biological and chemical procedures to obtain an antiarrhythmic drug pharmacologically similar to lidocaine (**1**), with pharma-



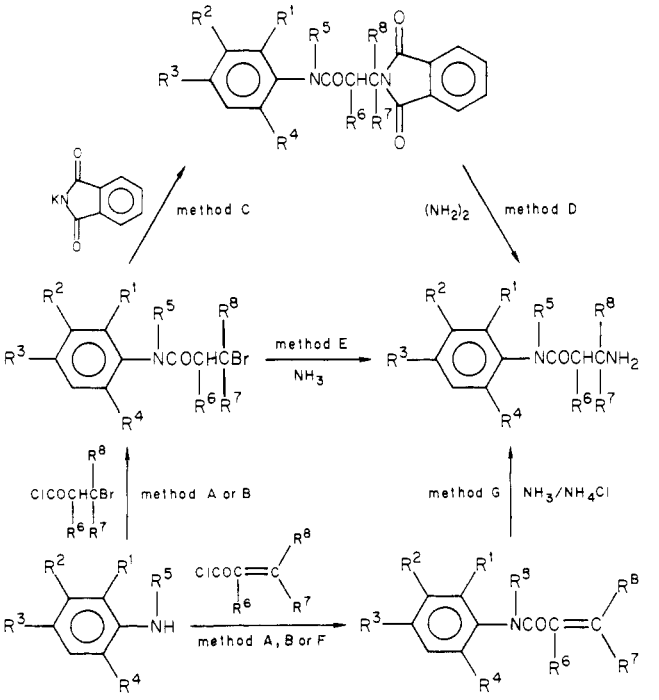


A

1, R = $-CH_2N(Et)_2$
2, R = $-CH(CH_3)NH_2$
3, R = $-CH_2CH_2N(Et)_2$

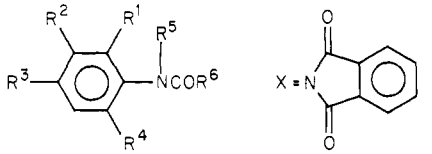
cokinetic properties allowing oral administration. Tocainide (**2**) was found to be an effective antiarrhythmic agent in animals[1-3] with suitable pharmacokinetic parameters in man[4] and is presently undergoing clinical trials.[5] Animal experiments demonstrated early that the limiting toxicity of tocainide represented effects upon the central nervous system (CNS). We therefore decided to search for a drug with improved properties, particularly lower CNS toxicity. One of the approaches utilized was an attempt to alter drug distribution in the body by increasing the basicity and, consequently, the degree of protonation at physiological pH. Primary β-amino anilides (formula A) are considerably stronger bases than the corresponding primary α-amines but remain chemically and pharmacologically closely related to this class, of which many members had shown antiarrhythmic effects.[1] A structure-modification program (formula A) encompassing variation of substitution on the aromatic ring (R^1–R^4), the amide nitrogen (R^5), and the intermediate chain (R^6–R^8) was devised according to principles previously described.[1,6] We report here the syntheses and pharmacological test results of primary β-amino anilides, as well as comparisons with tocainide (**2**), lidocaine (**1**), and its β homologue **3**.[7]

Scheme I



0022-2623/79/1822-1182$01.00/0

Table I. Structures and Physical Properties of Intermediate Anilides



no.	R^1	R^2	R^3	R^4	R^5	R^6	mp, °C	solv	yield, %	method
4	Me	H	H	Me	H	CH_2CH_2Br	133-134[a]	*b*	89	A
5	Me	H	H	Me	H	CH_2CH_2X	253-254.5[a]	*c*	85	C
6	Me	H	H	Et	H	CH_2CH_2Br	149-150	*c*	91	A
7	Me	H	H	Et	H	CH_2CH_2X	208-209.5[a]	*c*	82	C
8	Me	Me	H	Me	H	CH_2CH_2Br	125.5-126	*d*	54	A
9	Me	Me	H	Me	H	CH_2CH_2X	247.5-248[a]	*c*	89	C
10	Me	H	Me	Me	H	CH_2CH_2Br	139-141	*e*	95	A
11	Me	H	Me	Me	H	CH_2CH_2X		*c*	86	C
12	Me	H	*n*-PrO	Me	H	CH_2CH_2Br	121.5-122	*b*	93	A
13	Me	H	*n*-PrO	Me	H	CH_2CH_2X	239-240[a]	*c*	88	C
14	Me	H	*n*-BuO	Me	H	CH_2CH_2Br	101-102.5	*d*	46	A
15	Me	H	*n*-BuO	Me	H	CH_2CH_2X		*c*	~100	C
16	Me	H	H	Me	Me	$CH=CH_2$	47-50	*f*	51	B
17	H	H	H	Me	H	$C(CH_3)_2Br$	63.5-64.5[a]	*c*	88	A
18	H	H	H	Me	H	$CH(CH_3)CH_2X$	220[a]	*c*	64	C
19	Me	H	H	Me	H	$C(CH_3)=CH_2$	87-101	*g*	42	A
20	Me	H	H	Cl	H	$CH_2CH(CH_3)Br$	138-141	*h*	35	B
21	Me	H	H	Me	H	$CH=CHCH_3$	170.5-171.5	*i*	59	F
22	Me	H	H	Et	H	$CH=CHCH_3$	139-142	*i*	53	F
23	Me	H	Me	Me	H	$CH=CHCH_3$	193-195.5	*i*	70	F
24	Me	H	H	Me	Me	$CH=CHCH_3$	68-70.5	*f*	44	B
25	Me	H	H	Me	Et	$CH=CHCH_3$	oil		~100	B
26	Me	H	H	Me	H	$CH=C(CH_3)_2$		*g*	62	F
27	Me	H	H	Me	H	$CH=CHCH_2CH_3$	124-126	*i*	75	F

[a] Crude material. [b] Methanol. [c] Reaction mixture. [d] 95% ethanol. [e] Benzene/petroleum ether. [f] Hexane. [g] 95% ethanol/water. [h] Ethyl acetate. [i] Acetone.

Chemistry. Synthetic routes to primary β-amino anilides are shown in Scheme I. Anilines were acylated with 3-bromoacyl chlorides in acetic acid with sodium acetate as base (method A[8]) or in a two-phase system consisting of toluene and an aqueous solution of sodium carbonate (method B[9]). The resulting 3-bromo anilides were treated with potassium phthalimide in dimethylformamide (method C[10]). The crude phthalimides obtained were of sufficient purity to yield the desired β-amino anilides in good yields upon hydrazinolysis in ethanol (method D[10]). Alternatively, direct amination of 3-bromo-2′-chloro-6′-methylbutyrylanilide also led to the corresponding β-amino anilide (method E). Unsaturated anilides were prepared from anilines and substituted acryloyl chlorides by refluxing in acetone with sodium bicarbonate as base (method F) or by method A or B as described above. Attempts to introduce a nitrogen function in the β position by addition to the double bond failed when ammonia in ethanol or potassium phthalimide in dimethylformamide was used; only starting materials were recovered. The use of ammonium chloride as an acid catalyst, however, led to the successful addition of ammonia (method G), yielding 3-amino anilides.

The structures and the physical properties of all compounds prepared are listed in Tables I (intermediates) and II (target compounds).

Biological Evaluation. Initial antiarrhythmic screening was performed in mice essentially according to the method described by Lawson.[11] Drugs, dissolved in 0.9% saline, were injected subcutaneously to groups of 10 mice. During a 20-min period, the mice were observed for overt signs of toxicity (ataxia, convulsion, loss of righting reflex, or death). The mice were then placed individually in an atmosphere saturated with chloroform vapor until respiration ceased. Immediately thereafter, the thorax was opened and the presence or absence of fibrillation was determined visually. If coordinated ventricular contractions were observed, the mouse was considered to be "protected" from the arrhythmogenic effects of chloroform. This procedure was used for two types of tests. In a preliminary test, each drug was administered at a dose of 100 mg/kg. For full tests, at least three doses of drug were chosen to give low, intermediate, and high degrees of protection against fibrillation. Each dose was administered subcutaneously to 10 mice. From these data, the ED_{50} and the 95% Fieller limits were calculated according to the logit chi square method of Berkson.[12]

Several of the most active compounds were also studied in dogs with myocardial infarctions produced by a two-step ligation of the left anterior descending coronary artery according to the method of Harris.[13] On the day after ligation, such dogs demonstrated a high ventricular rate with a large percentage of ectopic beats. Twenty to twenty-four hours after ligation, control data were gathered, and drug (as the hydrochloride in isotonic solution) was infused intravenously (without anesthesia or sedation) at a rate of 0.5 mg kg^{-1} min^{-1} until the arrhythmia was "cleared" and signs of toxicity were observed. Clearance was defined as a reduction in ectopic beats to ≤5% of total ventricular beats for 5 min.

Results and Discussion

Table III summarizes the antiarrhythmic and toxic effects of the target compounds **28–44** in mice. All compounds showed some antiarrhythmic effect. ED_{50} values were obtained for all but four compounds, which were either too toxic (**34**, **41**, and **42**) or too weak (**30**) to allow a determination. Except for compounds **40** and **43**, the antiarrhythmic potency of the primary β-amines was found to be lower than that of lidocaine or its β-homologue **3**. Compared to tocainide (**2**), the starting point of this investigation, most compounds were found to be more

Table II. Structures, Physical Properties, and Yields of Target Compounds

no.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	yield, %	method	formula	mp, °C	solv	anal.
28	Me	H	H	Me	H	H	H	H	80	D	$C_{11}H_{16}N_2O\cdot HCl$	239–240	*a*	C, H, N, Cl
29	Me	H	H	Et	H	H	H	H	74	D	$C_{12}H_{18}N_2O\cdot HCl$	215.5–216	*b*	C, H, N, Cl
30	Me	Me	H	Me	H	H	H	H	36	D	$C_{12}H_{18}N_2O$	123–140	*c*	C, H, N
31	Me	H	Me	Me	H	H	H	H	49	D	$C_{12}H_{18}N_2O\cdot HCl$	272.5–273.5	*d*	C, H, N, Cl
32	Me	H	*n*-PrO	Me	H	H	H	H	53	D	$C_{14}H_{22}N_2O_2\cdot HCl$	230	*b*	C, H, N, Cl
33	Me	H	*n*-BuO	Me	H	H	H	H	27	D	$C_{15}H_{24}N_2O_2\cdot HCl$	228–229	*d*	C, H, N, Cl
34	Me	H	H	Me	Me	H	H	H	58	G	$C_{12}H_{18}N_2O\cdot HCl\cdot 0.5H_2O$	180–182	*e*	C, H, N, Cl[f]
35	H	H	H	Me	H	Me	H	H	49	D	$C_{11}H_{16}N_2O\cdot HCl\cdot 0.5H_2O$	175.5–178	*e*	C, H, N
36	Me	H	H	Me	Me	H	H	H	55	G	$C_{12}H_{18}N_2O\cdot HCl\cdot 0.75H_2O$	204–206	*b*	C, H, N
37	Me	H	H	Cl	H	H	Me	H	52	E	$C_{11}H_{16}ClN_2O\cdot HCl\cdot 0.5C_2H_6O$	210–211.5	*d*	C, H, N, Cl
38	Me	H	H	Me	H	H	Me	H	49	G	$C_{12}H_{18}N_2O\cdot HCl$	171–173	*e*	C, H, N, Cl
39	Me	H	H	Et	H	H	Me	H	41	G	$C_{13}H_{20}N_2O\cdot HCl$	173.5–175	*g*	C, H, N, Cl
40	Me	H	Me	Me	H	H	Me	H	14	G	$C_{13}H_{20}N_2O\cdot HCl$	263.5–264	*b*	C, H, N
41	Me	H	H	Me	Me	H	Me	H	54	G	$C_{13}H_{20}N_2O\cdot C_4H_6O_6\cdot 0.5H_2O$	173–174	*h*	C, H, N[f]
42	Me	H	H	Me	Et	H	Me	H	41	G	$C_{14}H_{22}N_2O\cdot C_4H_6O_6\cdot 0.5H_2O$	150–155	*d*	C, H, N[f]
43	Me	H	H	Me	H	H	Me	Me	67	G	$C_{13}H_{20}N_2O\cdot HCl$	220–222.5	*e*	C, H, N, Cl
44	Me	H	H	Me	H	H	Et	H	69	G	$C_{13}H_{20}N_2O\cdot HCl$	224.5–226	*b*	C, H, N, Cl

[a] 95% ethanol/butanone. [b] 95% ethanol/ether. [c] Ethyl acetate. [d] Absolute ethanol. [e] Absolute ethanol/ether. [f] Anal. of dried material after loss of $0.5H_2O$. [g] Acetonitrile. [h] 95% ethanol.

potent and less CNS toxic in the chloroform mouse screen. Based on the limited biological information, only tentative conclusions regarding structure–activity relationships can be drawn. While alteration of the substituents on the aromatic ring (R^2, R^3, and R^4) did not generally improve antiarrhythmic potency, it did produce the most potent compounds of the series (**40**). Alkyl substitution or the amide nitrogen (R^5) led to the most toxic compounds (**34**, **41**, and **42**). Similar to previous findings[1,6] with primary α-amino xylidides, a methyl substituent on the carbon adjacent to the amine nitrogen (R^7 = Me) improved the antiarrhythmic potency when compared to compounds with R^7 = H (**38**, **28**; **39**, **29**; **40**, **31**).

Four primary β-amino anilides (**28**, **38**, **40**, and **43**) were subjected to additional testing in the coronary artery ligated dog (Table IV). Although all four compounds reduced the percentage of ectopic beats, only **38** consistently abolished the severe ventricular arrhythmias observed in these dogs. CNS toxicity (head tremors, tonic convulsions) or cardiovascular toxicity (prolongation of PR interval, AV dissociation) was observed in the majority of experiments. In the case of **38**, cardiovascular toxicity developed at doses and plasma levels substantially greater than those required to clear the arrhythmia. The oral bioavailability in dogs[14] was found to be higher than 90%, and the half-life was very similar to that of tocainide.

Compound **38**, the β homologue of tocainide, emerges as the most interesting drug from this investigation. It has a markedly higher antiarrhythmic potency and a lower acute CNS toxicity than tocainide, thus fulfilling the criteria stated in the introduction. The results of subsequent investigations of **38** will be published elsewhere.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The microanalyses were performed by Alfred Bernhardt Microanalytical Laboratory, Elbach über Engelskirchen, West Germany, or Chemalytics, Inc., Tempe, Ariz. Where analyses are indicated by symbols of elements, the analytical results are within ±0.4% of the theoretical values. All new compounds were characterized by IR spectra (Perkin-Elmer 257 spectrophotometer). Target compounds were additionally characterized by elemental analyses, NMR spectra (JEOL C 60 H or Hitachi Perkin-Elmer R-20 with Me_4Si as internal standard), and in many cases by mass spectra (Finnigan 10 15 D quadrupole GC–MS). All spectra were in accord with the assigned structures. Progress of reactions and purity of products were determined on gas chromatographs (Varian 1200, OV 101 1.5%; Varian 200, OV 17 3% or JXR 3%).

Bromo Anilides. Method A. Substituted aniline (0.1 mol) was mixed with 85 mL of glacial acetic acid and cooled to 13 °C. A solution of 0.25 mol of sodium acetate trihydrate in 135 mL of water was cooled to 3 °C. Haloacyl halide, 0.11 mol, was added rapidly to the amine solution, and immediately afterwards the sodium acetate solution was added. The mixture was shaken for 45 min, and the precipitate was filtered off, washed with water until the filtrate was neutral, and dried. Recrystallization yielded anilides of adequate purity (for melting points, solvents, and yields, see Table I).

Method B follows the same procedure as described under "Acryloyl anilides" but utilizing haloacyl halide.

Acryloyl Anilides. Method B. A two-phase system containing 0.2 mol of substituted aniline, 150 mL of toluene, 0.43 mol of potassium carbonate, and 300 mL of water was cooled to 10 °C. With cooling and stirring, 0.35 mol of substituted acryloyl chloride was added dropwise within 20 min. The mixture was stirred at room temperature for 30 min, 200 mL of petroleum ether was added, and the crystals were filtered off and washed with water and petroleum ether. The crystalline material was dissolved in ethyl acetate, the solution was dried, and the solvent was evaporated. If the crude anilides did not crystallize in the reaction mixture, ethyl acetate was added, the phases were separated, the organic layer was washed with 0.1 M sodium hydroxide and dried,

Table III. Antiarrhythmic and Toxic Effects in Mice[11]

no.	dose,[a] mg/kg	protection[b]	toxicity at[c]	toxicity c[d]	toxicity lrr[e]	toxicity d[f]	ED_{50} for protection, mmol/kg (95% Fieller Limits)	potency[g]
28	100	1	0	0	0	0	0.56 (0.40-0.90)	0.5
29	100	3	0	0	0	0	1.99 (0.83-7.36)	0.1
30	100	2	0	0	0	0	*h*	
31	100	3	0	0	0	0	0.76 (0.28-1.17)	0.3
32	100	0	0	0	0	0	1.42 (0.88-2.69)	0.2
33	100	1	0	0	0	0	0.82 (0.48-1.33)	0.3
34	100	0	0	0	0	0	*i*	
	200	1	10	2	0	2		
35	100	1	0	0	0	0	1.49 (1.11-2.57)	0.2
36	100	1	0	0	0	0	0.44 (0.28-0.82)	0.6
37	100	0	0	0	0	0	0.46 (0.33-0.80)	0.6
38	100	9	0	0	0	0	0.46 ± 0.16[k]	0.6
39	100	8	0	0	0	0	0.54 (0.39-0.86)	0.5
40	100	9	0	0	0	0	0.18 (0.07-0.30)	1.4
41	100	2	10	4	0	0	*i*	
42	100	5	10	10	1	3	*i*	
43	100	3	0	0	0	0	0.25 (0.11-0.45)	1.0
44	100	5	0	0	0	0	0.38 (0.19-1.16)	0.7
1	100	10	10	10	10	0	0.26 ± 0.09[l]	1.0
2	100	2	1	0	0	0	1.30 ± 0.60[m]	0.2
3	100	7	10	4	0	0	0.28 (0.21-0.38)	0.9

[a] Subcutaneous administration. [b] Number of animals protected against fibrillation induced by chloroform; 10 animals tested, except when deaths occurred prior to exposure to chloroform, as with 34 and 42. [c-f] Number of animals with ataxia, convulsions, loss of righting reflex, and death of 10 tested. [g] Potency: $P = ED_{50}$ (mmol/kg) of lidocaine/ED_{50} (mmol/kg) of investigated compound. [h] ED_{50} not determined due to weak activity. [i] ED_{50} not obtainable due to deaths at doses required for high degree of protection. [k] Mean and standard deviation of 11 determinations. [l] Mean and standard deviation of 72 determinations. [m] Mean and standard deviation of 14 determinations.

Table IV. Antiarrhythmic and Toxic Effects in Dogs[13]

no.	control values[a] % vent. ect	control values vent. rate	control values MABP	clearing values % vent. ect	clearing values vent. rate	clearing values MABP	dose, mmol/kg, to cause clearing	dose, mmol/kg, to cause toxicity
28	98	216	85	18[b]	129[b]	85[b]	1.04[b]	
	95	210	75	50[b]	135[b]	85[b]	1.56[b]	
	100	192	105	5	120	115	0.23	*c*
38	93 ± 6[d]	200 ± 21[d]	99 ± 14[d]	0 ± 1[d]	148 ± 8[d]	97 ± 16[d]	0.10 ± 0.04[d]	0.33 ± 0.08[e]
40	100	210	70	69[f]	174[f]	75[f]	0.08[f]	0.08[g]
	99	207	80	0	138	105	0.16	0.38[g]
	95	174	85	13	141	115	0.29	0.33[g]
43	99	222	90	65[b]	138[b]	95[b]	0.07[b]	0.33[h]
	89	198	90	39[b]	165[b]	95[b]	0.04[b]	0.17[h]
1	96 ± 5[i]	174 ± 34[i]	81 ± 11[i]	4 ± 3[i]	133 ± 16[i]	101 ± 21[i]	0.21 ± 0.19[i]	0.27 ± 0.15[g,j]
2	94 ± 5[k]	207 ± 25[k]	91 ± 19[k]	2 ± 2[k]	148 ± 16[k]	108 ± 21[h]	0.32 ± 0.11[k]	0.30 ± 0.06[g,l]
3	91	198	85	15[b]	138[b]	115[b]	0.06[b]	0.06[g,m,n]
	99	153	115	18[b]	132[b]	125	0.01[b]	0.04[g,o]

[a] Values of percent ventricular ectopic beats, ventricular rate (beats/min), and mean arterial blood pressure (mmHg) before start of drug infusion. [b] Values and dose at the time of the lowest incidence of ectopic beats. [c] No toxicity until end of infusion (1.40 mmol/kg). [d] Means and standard deviations of nine experiments. [e] Mean and standard deviation of four experiments. [f] Infusion stopped at toxic level. [g] Convulsions. [h] Death. [i] Means and standard deviations of five experiments. [j] Means and standard deviations of three experiments. [k] Means and standard deviations of 14 experiments. [l] Means and standard deviations of eight experiments. [m] Cardiovascular toxicity. [n] Death at 0.20 mmol/kg. [o] Death at 0.25 mmol/kg.

and the solvent was evaporated. Recrystallization yielded substituted acryloyl anilides of adequate purity (for melting points, solvents, and yields, see Table I).

Method F. A solution of 0.23 mol of substituted acryloyl chloride in 90 mL of dry acetone was added dropwise to a mixture of 0.2 mol of substituted aniline, 225 mL of acetone, and 0.27 mol of sodium bicarbonate. After 1 h of refluxing, the mixture was filtered hot. The desired substituted acryloyl anilides crystallized from the filtrate.

3-Phthalimidopropionoanilides. Method C. A solution of 0.1 mol of substituted bromo anilide and 0.1 mol of potassium phthalimide in 85 mL of dimethylformamide was refluxed for 2 h. A mixture of 30 mL of acetic acid and 75 mL of water was added to the solution, and the resulting suspension was stirred for 1 h. The precipitate was filtered off, washed with water, and dried. The resulting substituted 3-phthalimidopropionoanilides were of adequate purity as intermediates.

β-Amino Anilides. Method D. A mixture of 0.05 mol of substituted 3-phthalimidopropionoanilide and 115 mL of ethanol was heated to 75 °C. With stirring, 4.63 mL (0.082 mol) of hydrazine hydrate (85%) was added within 5 min, resulting in a thick precipitate. Ethanol (115 mL) was added and the mixture stirred at 75 °C for 1.5 h. Concentrated hydrochloric acid (9.3 mL) was added to the mixture and the mixture was stirred at 60 °C for 1 h. It was cooled in an ice–water bath, and the precipitated phthalhydrazide was filtered off and washed with ethanol. The filtrate was concentrated to 115 mL, 115 mL of ether was added, and the precipitate was filtered off. Recrystallization gave pure β-amino anilide hydrochloride.

Method E. A suspension of 0.05 mol of β-bromo anilide in 140 mL of 95% ethanol and 105 mL of 27% aqueous ammonia was cooled to 5 °C and saturated with ammonia gas. The mixture was heated in a steel autoclave to 67 °C for 45 h. The solvent was evaporated and the product was taken up in ether and extracted with 2 M hydrochloric acid. The aqueous phase was alkalinized to pH 11 and the amine extracted with ether. The hydrochloride was precipitated in ether by adding anhydrous hydrogen chloride and recrystallized from absolute ethanol/ether.

Method G. A solution of 0.05 mol of substituted acryloyl anilide and 0.8 g of ammonium chloride in 120 mL of 95% ethanol was cooled to 0 °C. The solution was saturated with ammonia gas, placed into a steel autoclave, and heated to 80 °C for 48 h. The solvent was evaporated, and the product was taken up in ether and extracted with 1 M hydrochloric acid. The aqueous phase was alkalinized to pH 11 with sodium hydroxide and the amine extracted with methylene chloride. The organic phase was dried and the solvent evaporated. Recrystallization of the base, or a salt, yielded pure β-amino anilide.

Acknowledgment. We thank L. A. Dadah, R. Heideger, M. Hogan, L. J. Kofos, and L. S. Åberg for skillful technical assistance and M. R. Blair and G. H. Kronberg for many valuable discussions. We also thank J. B. Keenaghan for the mass spectral data.

References and Notes

(1) E. W. Byrnes, P. D. McMaster, E. R. Smith, M. R. Blair, R. N. Boyes, B. R. Duce, H. S. Feldman, G. H. Kronberg, B. H. Takman, and P. A. Tenthorey, *J. Med. Chem.*, **22**, first paper in a series of three in this issue.
(2) (a) B. R. Duce, E. R. Smith, R. N. Boyes, and E. W. Byrnes, *Pharmacologist*, **15**, 192 (1973); (b) E. W. Byrnes, M. R. Blair, H. S. Feldman, G. H. Kronberg, in preparation.
(3) D. J. Coltart, T. B. Berndt, R. Kernoff, and D. C. Harrison, *Am. J. Cardiol.*, **34**, 35 (1974).
(4) D. Lalka, M. B. Meyer, B. R. Duce, and A. T. Elvin, *Clin. Pharmacol. Ther.*, **19**, 757 (1976).
(5) (a) D. G. McDevitt, A. S. Nies, G. R. Wilkinson, R. F. Smith, R. L. Woosley, and J. A. Oates, *Clin. Pharmacol. Ther.*, **19**, 396 (1976); (b) R. A. Winkle, P. J. Meffin, J. W. Fitzgerald, and D. C. Harrison, *Circulation*, **54**, 884 (1976); (c) P. J. Meffin, R. A. Winkle, T. F. Blaschke, J. Fitzgerald, D. C. Harrison, S. R. Harapat, and P. A. Bell, *Clin. Pharmacol. Ther.*, **22**, 42 (1977); (d) R. L. Woosley, D. G. McDevitt, A. S. Nies, R. F. Smith, G. R. Wilkinson, and J. A. Oates, *Circulation*, **56**, 980 (1977); (e) R. A. Winkle, P. J. Meffin, and D. C. Harrison, *Circulation*, **57**, 1008 (1978).
(6) P. D. McMaster, E. W. Byrnes, H. S. Feldman, B. H. Takman, and P. A. Tenthorey, *J. Med. Chem.*, **22**, second paper in a series of three in this issue.
(7) N. Löfgren and B. Lundqvist, *Svensk. Kem. Tidskr.*, **58**, 206 (1946).
(8) N. Löfgren, "Studies on Local Anesthetics", Ivar Haeggstroms, Stockholm, 1948, p 25.
(9) U. H. Lindberg, B. Nylén, and B. Akerman, *Acta Pharm. Suec.*, **5**, 429 (1968).
(10) J. C. Sheehan and B. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).
(11) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, **160**, 22 (1968).
(12) J. Berkson, *J. Am. Stat. Assoc.*, **48**, 565 (1953).
(13) S. A. Harris, *Circulation*, 1, 1318 (1950).
(14) D. T. Korkin, Astra Research Laboratories, unpublished.

Troponoids. 3. Synthesis and Antiallergy Activity of *N*-Troponyloxamic Acid Esters

Jehan F. Bagli,* T. Bogri, B. Palameta,

Department of Chemistry

R. Martel,

Department of Pharmacology

W. Robinson,

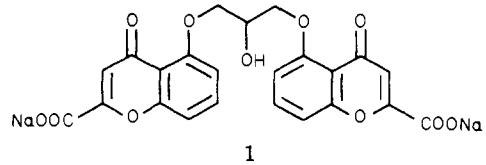
Department of Biochemistry

T. Pugsley, and W. Lippmann

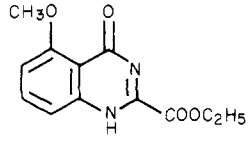
Department of Biochemical Pharmacology, Ayerst Laboratories, Montreal, Quebec, Canada. *Received February 23, 1979*

A number of oxamic acid derivatives of tropones and tropolones were synthesized and their antianaphylactic activity was determined in passive paw anaphylaxis (PPA). Several of these esters possessed oral activity. A comparison of the effect on the biological activity of the esters and the corresponding acid and its salt is reported. The experiments suggesting a relationship between the activity and the bioavailability of the ester **19** are also described. A study of the fate of ester **19** in serum on oral or intravenous administration to rats and dogs is reported. In vitro results of the effect of the compounds **19**, **45**, and **45a** on the activity of the guinea pig lung and beef heart phosphodiesterase are presented. The various factors that may contribute to the antiallergy activity of compounds of this series are discussed.

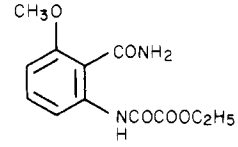
The discovery[1] of disodium cromoglycate (DSCG, **1**) has



1



2



3

opened the way to the treatment of allergic rhinitis and asthma by the prophylactic action of chemotherapeutic agents. DSCG has been shown to exert its effect by inhibiting the liberation of mediators of the immediate-type hypersensitivity reaction initiated by an antigen–antibody interaction.[2] This reaction is usually studied in the passive cutaneous anaphylaxis (PCA) assay in rats, induced by reagenic antibody.[1] Recently, a method of inducing passive anaphylaxis in the hind paw (PPA) of rats was reported from our laboratories and its utility as a screening procedure for compounds of this type was demonstrated.[3]

Various heteroaromatic structures incorporating chromones,[4] xanthones,[5] and quinazolinones[6] have been reported to possess antiallergic activity of the type exhibited by DSCG. Many of these products were found to be orally active in the PCA assay.

It was found[6] that quinazolinecarboxylic acid esters of the type **2** were contaminated with an intermediate, which was found to have structure **3**. These oxamates were found

0022-2623/79/1822-1186$01.00/0