

phase column eluted with water-MeOH, 95:5. All velocities were determined from at least four time points that were within the initial reaction rate period.

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Registry No. 1, 71609-59-1; 2, 113548-90-6; 3, 113548-91-7; 4, 113548-92-8; 5, 3871-66-7; 6, 113548-93-9; 7, 113548-94-0; 8, 113548-95-1; 9, 113548-96-2; 10, 113548-97-3; FUra, 51-21-8; uridine phosphorylase, 9030-22-2.

Synthesis and Oral Antiallergic Activity of Carboxylic Acids Derived from Imidazo[2,1-*c*][1,4]benzoxazines, Imidazo[1,2-*a*]quinolines, Imidazo[1,2-*a*]quinoxalines, Imidazo[1,2-*a*]quinoxalinones, Pyrrolo[1,2-*a*]quinoxalinones, Pyrrolo[2,3-*a*]quinoxalinones, and Imidazo[2,1-*b*]benzothiazoles

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4*H*-Imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylic acid (**3**) was found to possess potent activity in the IgE-induced rat passive cutaneous anaphylaxis model which may be predictive of clinical antiallergic activity. Compared to disodium cromoglycate (DSCG, **1**), **3** was less active following iv administration but unlike DSCG showed very significant oral activity. To explore the structural requirements for this activity, a range of tricyclic compounds was prepared and their activities were measured. Individual 2-carboxylic acids derived from imidazo[1,2-*a*]quinolines, imidazo[1,2-*a*]quinoxalines, imidazo[1,2-*a*]quinoxalinones, pyrrolo[1,2-*a*]quinoxalinones, pyrrolo[2,3-*a*]quinoxalinones, and imidazo[2,1-*b*]benzothiazoles showed iv activities up to 10³ times as potent as DSCG and many of them showed significant oral activity. From these, imidazo[1,2-*a*]quinoxaline-2-carboxylic acid **114** has been chosen for further development.

Asthma is a disease of uncertain etiology primarily involving the small bronchi and manifested clinically by intermittent wheezing and dyspnea of varying intensity.¹ Treatment for the condition has involved use of bronchodilators, e.g., β -adrenergic agonists and theophylline and corticosteroids, but a major step forward was made with the introduction of disodium cromoglycate (DSCG, **1**)² as a prophylactic agent against the disease. Subsequent clinical trials have shown the efficacy of DSCG in suitable patients,^{3,4} but it is not active orally and has to be insufflated as a powder. The discovery of an oral, prophylactic antiasthmatic agent remains a goal of a number of laboratories,⁵ and we have previously reported one such compound,^{6,7} **2** (RU 31156, Sudexanox[®]).

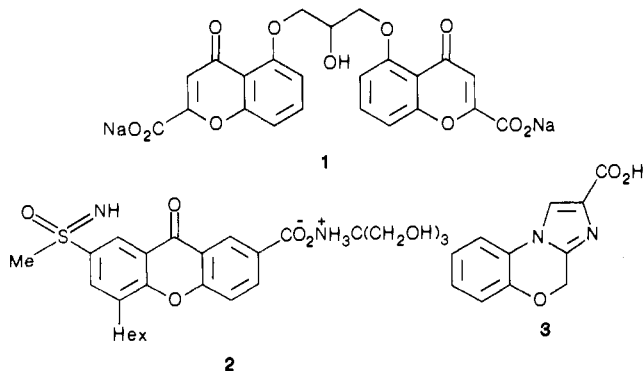
The origin of the work described in this paper was the unexpected rearrangement which gave 4*H*-imidazo[2,1-*c*][1,4]benzoxazines as previously described.⁹ 4*H*-Imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylic acid (**3**) was found to possess significant activity in the rat IgE-mediated passive cutaneous anaphylaxis test (ED₅₀ = 2.89 mg/kg iv, Table I), a possible but not unequivocally predictive model for clinical efficacy.⁵ This result led us to undertake a more systematic examination of structure-activity requirements for PCA activity in related tricyclic heterocyclic systems. Initial approaches retained the imidazole ring of **3** and varied the 4,5-positions to give series **4a-e**, **4h**, **5**, and **6**, and then retaining the quinoxalin-4-(5*H*)-one system, the five-membered ring was varied to give pyrrole **4f**, pyrazole **4g**, and triazole **4i**. Subsequent work produced ring systems **7-10** in order to observe the effects of a wider variety of modifications.

Chemistry

Structures **4a-j** and **5-10** show the variety of ring systems synthesized (Chart I).

(a) Imidazo[2,1-*c*][1,4]benzoxazines (**3**, **11-39**; Table I). The basic method of preparation of this system was described earlier,⁹ and the derivatives studied are listed in Table I along with their pharmacological properties.

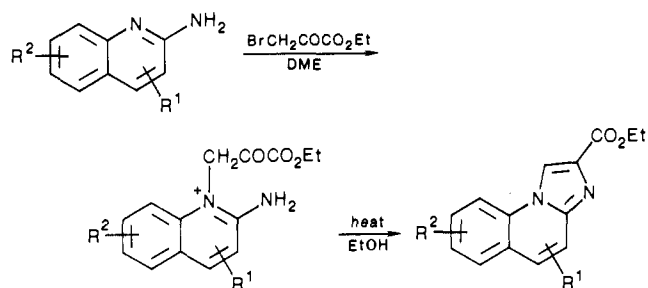
(b) Imidazo[1,2-*a*]quinolines (**46-113**; Tables II and III). Treatment of the quinolinium quaternary salt **40** with ammonium acetate in glacial acetic acid heated under reflux was reported¹¹ to give the imidazolidine **41**, but the



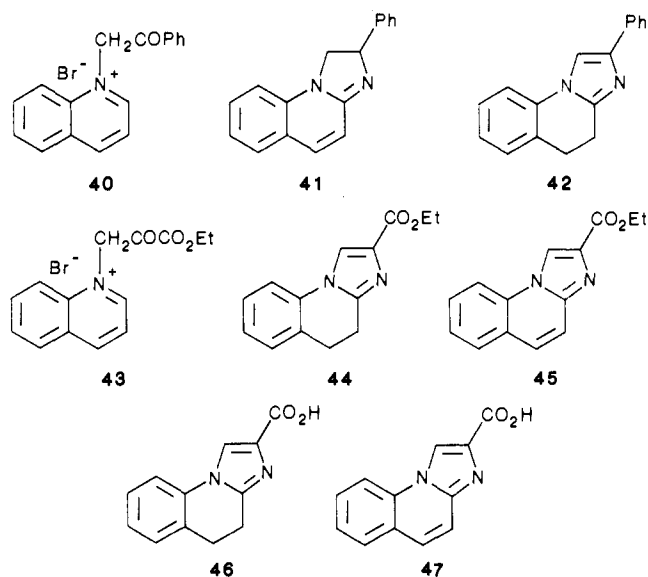
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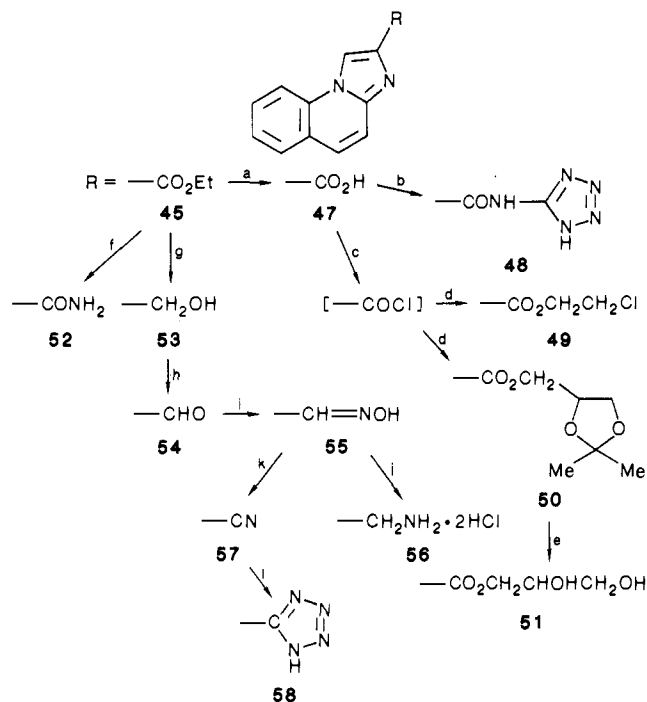
Scheme I



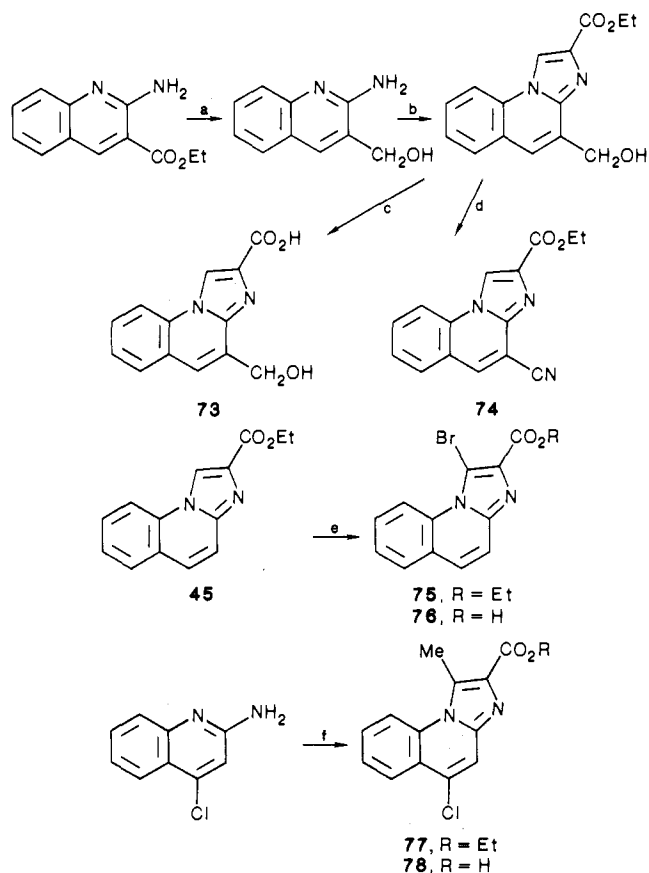
structure was subsequently amended^{12,13} to **42**, formed by double bond migration. We reasoned that, by using ethyl bromopyruvate instead of phenacyl bromide as the quaternizing agent to give **43**, then the equivalent reaction should give the dihydroimidazo[1,2-*a*]quinoline ester **44**. The product isolated from this reaction was a mixture of esters **44** and **45**, which were separated by chromatography and hydrolyzed to the respective acids **46** and **47**. The use of hydroxylamine hydrochloride¹⁴ instead of ammonium acetate as the nitrogen source in the cyclization step gave the ester **45** free from **44** but only in low yield. Since both acids **46** and **47** were more active in the rat PCA screen than **3**, but **46** was much less active, it was decided to concentrate on the series derived from ester **45**; therefore an improved synthetic route was required. This was achieved by reacting 2-aminoquinoline with ethyl bromopyruvate, giving a product which on heating in ethanol followed by basification yielded a compound identical in all respects with ester **45**. That the product from both routes is **45** confirms that quaternization of 2-aminoquinoline takes place on the 1-nitrogen prior to cyclization. An analogous preparation of imidazopyridines from 2-aminopyridine has been reported.¹⁵



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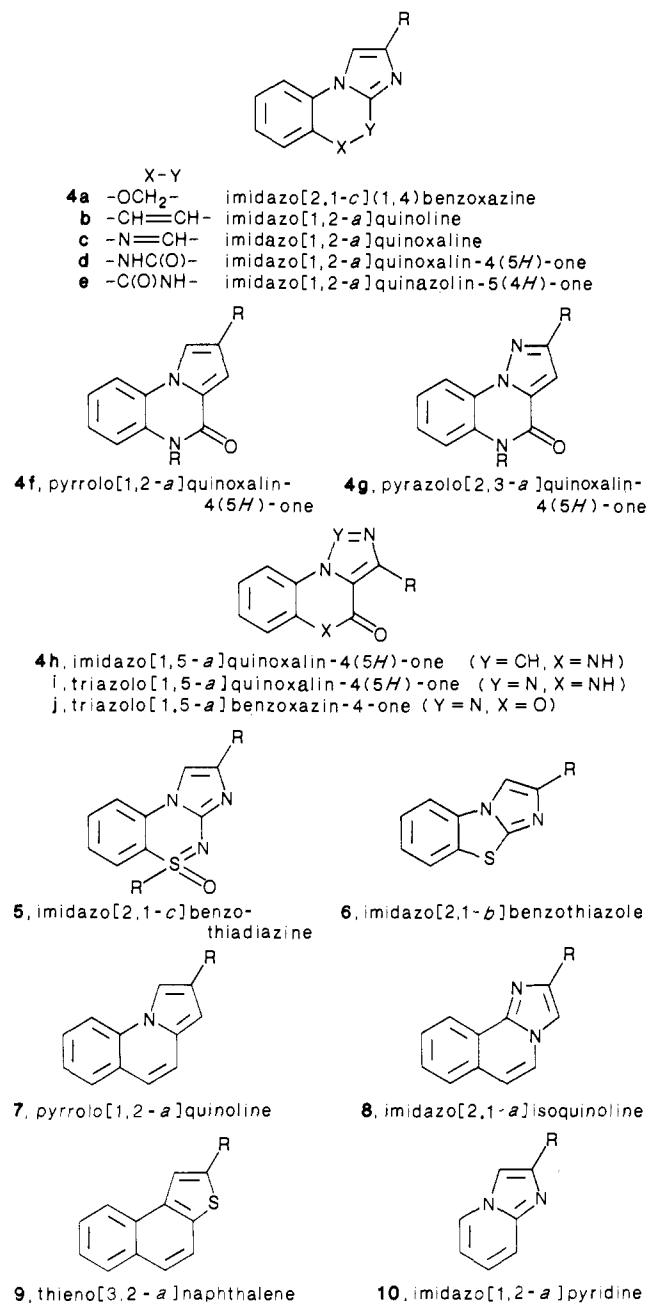
Scheme II^a

^a Reagents: (a) (i) NaOH; H₂O, EtOH, (ii) HCl; (b) CDI, H₂N⁻C=N-N=NH; (c) SOCl₂; (d) NEt₃, glycerol acetonide; ClCH₂C-H₂Cl; (e) citric acid; H₂O; (f) Na, NH₃; EtOH; (g) LiBH₄; THF; (h) MnO₂; CHCl₃; (i) NH₂OH·HCl, NaOAc; H₂O, EtOH; (j) H₂, Pd/C; MeOH, HCl; (k) Ac₂O; (l) NaN₃, NH₄Cl; DMF.

Scheme III^a

^a Reagents: (a) LiAlH₄; THF; (b) (i) BrCH₂COCO₂Et; DME, (ii) Δ; EtOH; (c) (i) NaOH; H₂O, EtOH, (ii) HCl; (d) (i) MnO₂; CHCl₃, (ii) NaOAc, NH₂OH·HCl; H₂O, EtOH, (iii) Ac₂O; (e) Br₂; AcONa, AcOH; (f) (i) MeCHBrCOCO₂Et; DME, (ii) Δ; EtOH.

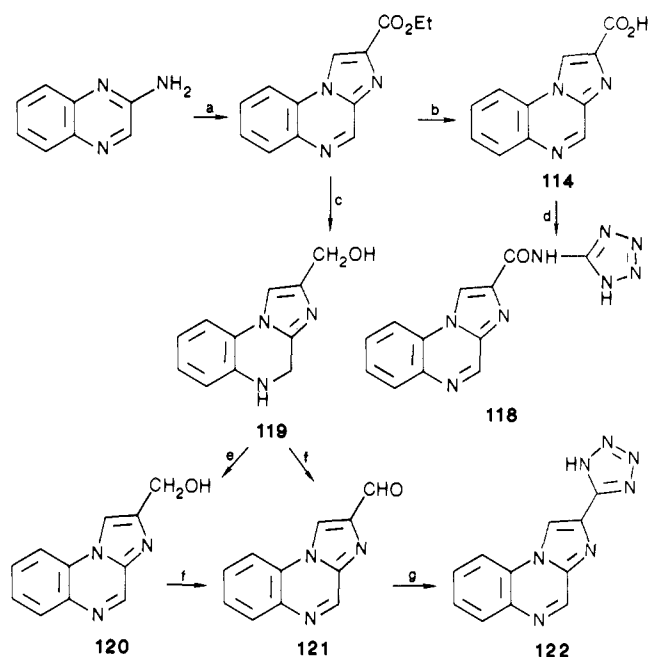
Chart I



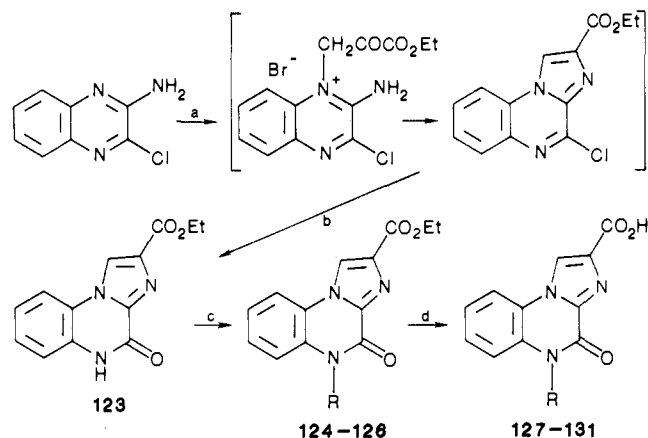
A variety of substituted 2-aminoquinolines were prepared and subjected to the same quaternization process (Scheme I). Substituents on the ring nucleus were also modified (Schemes II and III and the Experimental Section).

(c) **Imidazo[1,2-*a*]quinoxalines (114-122; Table IV)**. The reaction of 2-aminoquinoxalines with ethyl bromopyruvate as in the preparation of **45** followed by modification of the ester group (Scheme IV) gave a series of imidazo[1,2-*a*]quinoxalines.

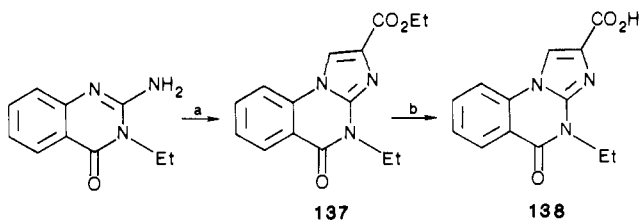
(d) **Imidazo[1,2-*a*]quinoxalin-4(5*H*)-ones (123-136; Table V)**. The reaction of 2-amino-3-chloroquinoxaline or 2-amino-3-methoxyquinoxaline¹⁶ with ethyl bromopyruvate was found to be accompanied by hydrolysis of the 3-substituent to give the imidazo[1,2-*a*]quinoxalin-4(5*H*)-one ester **123**. The 5-nitrogen atom was readily alkylated, and the resulting esters were then hydrolyzed to the corresponding acids (Scheme V). Modification of the

Scheme IV^a

^a Reagents: (a) (i) BrCH₂COCO₂Et; DME, (ii) Δ; EtOH; (b) (i) NaOH; H₂O, EtOH, (ii) HCl; (c) LiBH₄; THF; (d) CDI, NH₂C≡N—N=N—NH; DMF; (e) MnO₂; CHCl₃, room temperature; (f) MnO₂; CHCl₃, Δ; (g) (i) NH₂OH·HCl, NaOAc; EtOH, H₂O, (ii) Ac₂O, (iii) NaN₃, NH₄Cl; DMF.

Scheme V^a

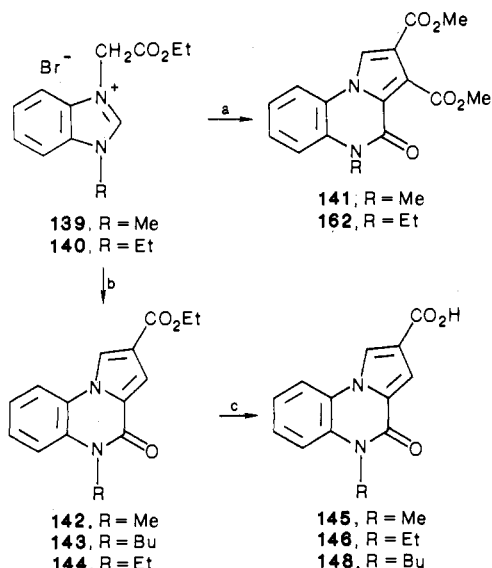
^a Reagents: (a) BrCH₂COCO₂Et; DME; (b) Δ; EtOH; (c) NaH, RI; DMF; (d) (i) NaOH; H₂O, EtOH, (ii) HCl.

Scheme VI^a

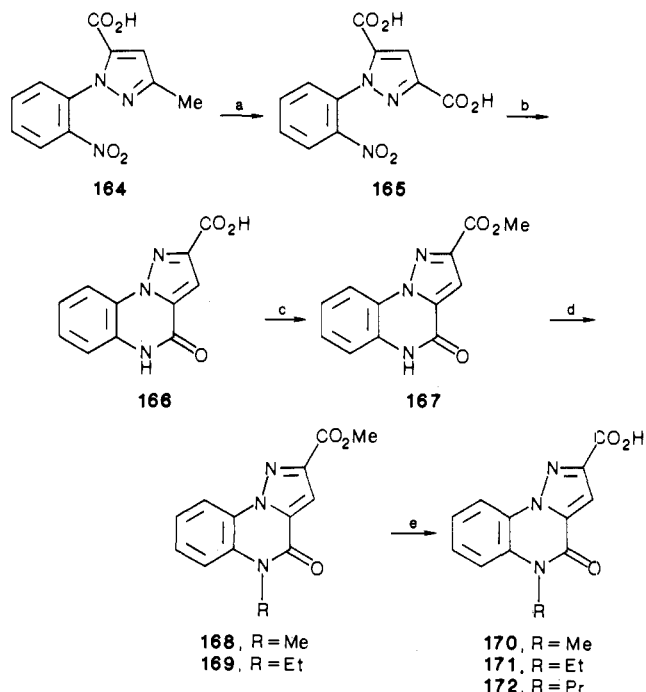
^a Reagents: (a) (i) BrCH₂COCO₂Et; DME, (ii) Δ, EtOH; (b) (i) NaOH; H₂O, EtOH, (ii) HCl.

ester group of **124** yielded derivatives **134-136**.

(e) **Imidazo[1,2-*a*]quinazolin-5(4*H*)-ones (137,138; Table VI)**. The reaction of 2-amino-3-ethylquinazolin-4(3*H*)-one with ethyl bromopyruvate as in the preparation of **45** gave the ester **137**, which was hydrolyzed by base to the acid **138** (Scheme VI).

Scheme VII^a

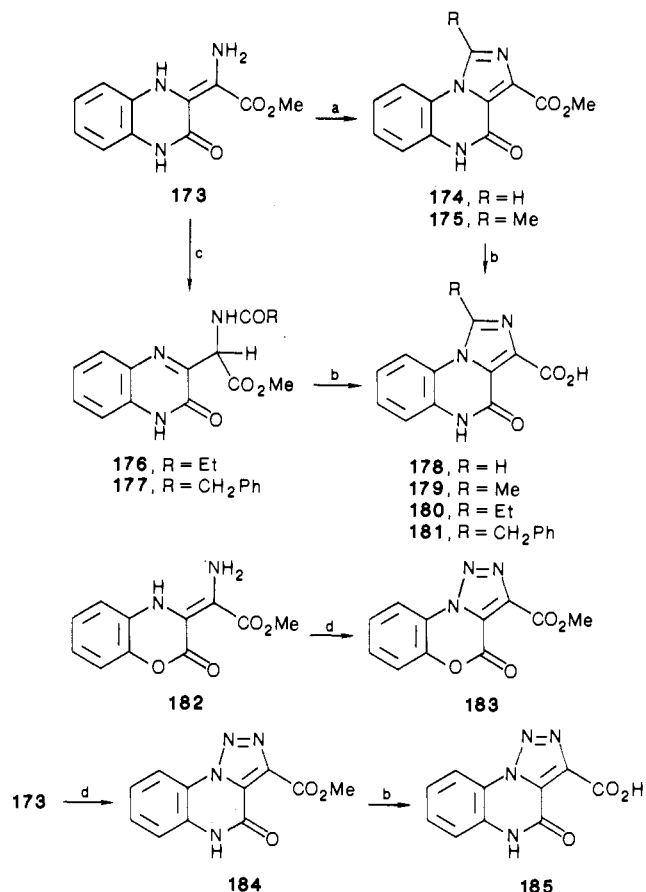
^a Reagents: (a) $\text{MeO}_2\text{C}\equiv\text{CCO}_2\text{Me}$, Et_3N ; DMF; (b) $\text{HC}\equiv\text{CCO}_2\text{Et}$, Et_3N ; DMF; (c) (i) NaOH ; H_2O , EtOH , (ii) HCl .

Scheme VIII^a

^a Reagents: (a) (i) KMnO_4 ; aqueous NaOH , (ii) concentrated HCl ; (b) (i) PtO_2 + 5% Pd-C , H_2 ; aqueous NaOH , (ii) concentrated HCl ; (c) MeOH , dry HCl ; (d) RI , NaH ; DMF; (e) (i) NaOH ; H_2O , EtOH , (ii) concentrated HCl .

(f) **Pyrrolo[1,2-a]quinoxalin-4(5H)-ones (141–163; Table VII).** The reaction of the benzimidazole quaternary salt 139 with dimethyl acetylene dicarboxylate was shown¹⁷ to give the pyrrolo[1,2-a]quinoxalin-4(5H)-one diester 141. We found that the use of methyl propiolate gave the corresponding monoester 142 (Scheme VII). With use of this method, a series of acids, 145–157, were prepared, and then a number of 5-ethyl derivatives, 158–163, were synthesized for comparison.

(g) **Pyrazolo[2,3-a]quinoxalin-4(5H)-ones (166–172; Table VIII).** An analogous series of pyrazolo[2,3-a]quinoxalin-4(5H)-one acids and esters were prepared as

Scheme IX^a

^a Reagents: (a) RC(OEt)_3 ; (b) (i) NaOH ; H_2O , EtOH , (ii) HCl ; (c) RCOCl ; (d) $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{ONO}$.

shown in Scheme VIII following literature precedents.¹⁸ Thus (*o*-nitrophenyl)hydrazine was condensed with ethyl acetylpyruvate¹⁹ to give, after hydrolysis, the pyrazole acid 164. Oxidation of the pyrazole methyl group using potassium permanganate gave the diacid 165, catalytic reduction of the nitro group of which converted it to the cyclized acid amide 166.

Esterification of 166 gave the ester 167, which was alkylated on nitrogen to produce esters 168 and 169, hydrolysis of which gave the acids 170 and 171. Acid 172 was prepared directly from 167 by alkylation and in situ hydrolysis.

(h) **Imidazo[1,5-a]quinoxalinones, Triazolo[1,5-a]quinoxalinones, and Triazolo[1,5-a]benzoxazinones (Scheme IX; Table IX).** A number of compounds were also prepared in related ring systems containing a 3-position (rather than 2-position) carboxyl group. Treatment of the diamine^{9,20} 173 with triethyl orthoformate or triethyl orthoacetate gave the imidazo[1,5-a]quinoxalinone esters 174 and 175, respectively. Reaction of 173 with acid chlorides gave the amides 176 and 177. Hydrolysis of 174 and 175 gave the acids 178 and 179, respectively. Similar base treatment of 176 and 177 caused cyclization followed by hydrolysis to give the respective acids 180 and 181. The diamine^{9,21} 182 was treated with isopentyl nitrite to give the triazole ester 183, and diamine 173 likewise yielded 184,

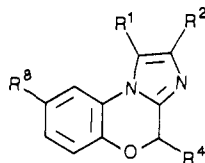
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Table I. 4*H*-Imidazo[2,1-*c*][1,4]benzoxazines

compd	R ¹	R ²	R ⁴	R ⁸	preparation ^d	antiallergic activity, IgE, rat PCA: ED ₅₀ ^a , mg/kg	
						iv	po
1		DSCG				1.21 (1.04–1.42)	inactive
2		Sudexanox				0.005 (0.004–0.006)	0.19 (0.07–0.030)
3	H	CO ₂ H	H	H	A	2.89 (2.22–3.63)	3.20 (2.47–3.45)
11	H	CO ₂ Me	H	H	A		10.8 (7.73–15.31)
12	H	CH ₂ OH	H	H	A		2.73 (0.29–6.49)
13	H	CHO	H	H	A	4.79 (1.73–30.03)	4.27 (2.71–7.46)
14	H	CH=NOH	H	H	A		inactive ^b
15	H	CN	H	H	A		inactive ^c
16	H		H	H	A	0.33 (0.21–0.51)	inactive ^c
17	H	CH ₂ CO ₂ H	H	H	A	inactive ^c	
18	H		H	H	A	inactive ^c	
19	CO ₂ H	CO ₂ Me	H	H	A	inactive ^c	
20	CO ₂ Et	CO ₂ Me	H	H	A	inactive ^c	
21	CO ₂ H	CO ₂ H	H	H	A	inactive ^c	
22		CO ₂ H	H	H	A	inactive ^c	
23	CO ₂ H	H	H	H	A	inactive ^c	
24	H		H	H	B	0.58 (0.43–0.74)	inactive ^c
25	H		H	H	B	0.33 (0.12–1.07)	inactive ^c
26	H		H	H	B	inactive ^c	
27	CH ₂ OH	CO ₂ Me	H	H	B		inactive ^c
28	CH ₂ OH	CO ₂ H	H	H	B		inactive ^c
29	H	CO ₂ H	H	NO ₂	A	2.22 (1.31–4.63)	
30	H	CO ₂ Me	H	NHAc	A		3.48 (2.89–3.99)
31	H	CO ₂ H	H	NHAc	A	0.073 (0.047–0.108)	inactive
32	H	CO ₂ Me	H	NHCOCO ₂ Et	A		0.50 (0.37–0.65)
33	H	CO ₂ H	H	NHCOCO ₂ H	A	0.0172 (0.0103–0.0214)	3.85 (2.71–5.46)
34	H	CO ₂ H	H	Cl	B	0.42 (0.34–0.44)	0.13 (0.04–0.45)
35	H	CO ₂ Me	H	Cl	B		2.79 (1.75–4.06)
36	H	CO ₂ Me	H	Me	B		1.46 (0.66–3.33)
37	H	CO ₂ H	H	Me	B	0.35 (0.26–0.50)	0.37 (0.11–1.43)
38	H	CO ₂ H	Me	H	B	1.76 (0.91–3.86)	8.46 (4.38–21.4)
39	H	CO ₂ H	Et	H	B	2.6 (1.61–7.0)	

^a 95% confidence limits in parentheses. ^b 42% inhibition at 10 mg/kg. ^c Inactive at 1 and 10 mg/kg. ^d A, ref 9; B, see the Experimental Section.

hydrolysis of which produced the acid 185.

(i) **Miscellaneous Ring Systems (Table X).** Schemes X and XI show the routes used to synthesize imidazo[1,2-*a*]pyridine²² 186, pyrrolo[1,2-*a*]quinolines 187 and 188, imidazo[2,1-*a*]isoquinolines 189 and 190,²³ thieno[3,2-*a*]naphthalene 191,²⁴ imidazo[2,1-*c*]benzothiadiazines 194–197, and imidazo[2,1-*b*]benzothiazoles 198–205.²⁵

Biological Results and Discussion

All compounds were tested for their ability to inhibit the IgE-mediated passive cutaneous anaphylaxis (PCA) reaction in rats passively sensitized to ovalbumen.^{6,7,10}

(a) **Imidazo[1,2-*c*][1,4]benzoxazines.** Table I shows that significant PCA activity resides in the acid 3 by both the iv and po dosing schedules. The latter result is of course of great interest in view of the lack of oral activity of DSCG. Further, the level of oral activity is surprisingly close to that of the iv result. Significant activity is shown by 2-substituents which could be metabolized to the acid (e.g., 11–13, 24, 25) or which mimic this group (e.g., 16). The presence of 1-substituents or even the movement of the acid group to this position (23) completely abolishes activity. Activity is enhanced by the presence of both

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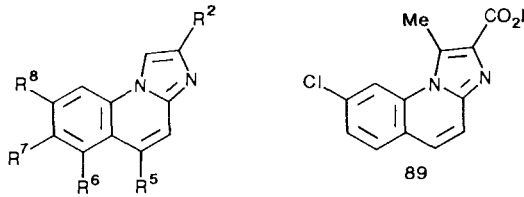
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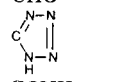
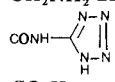
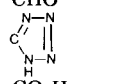
Table II. (Benzo unsubstituted)imidazo[1,2-a]quinoline-2-carboxylic Acids and Derivatives

compd	R ⁵	R ⁴	R ²	R ¹	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ , ^a mg/kg	
										iv	po
DSCG											
46		dihydro	CO ₂ H		274-278 ^c	EtOH/H ₂ O	85	C ₁₂ H ₁₀ N ₂ O ₂ ·2HCl	C, H, N, Cl	1.21 (1.04-1.42)	inactive ^b
47	H	H	CO ₂ H	H	234-236	EtOH/H ₂ O	90	C ₁₂ H ₈ N ₂ O ₂ ·H ₂ O	C, H, N	0.39 (0.34-0.45)	6.14 (5.21-7.35)
48	H	H		H	266-268	EtOAc/DMF	95	C ₁₃ H ₈ N ₂ O	C, H, N	0.30 (0.24-0.39)	0.34 (0.29-0.40)
49	H	H	CO ₂ CH ₂ CH ₂ Cl	H	162-164	EtOAc	13	C ₁₄ H ₁₁ N ₂ O ₂ Cl	C, H, N, Cl		3.5 (2.51-4.1)
50	H	H		H	156-158	CHCl ₃ /Et ₂ O	14	C ₁₈ H ₁₈ N ₂ O ₄	C, H, N		1.70 (0.65-6.05)
51	H	H	CO ₂ CH ₂ CHOHCH ₂ OH	H	217-220	CHCl ₃ /Et ₂ O	91	C ₁₅ H ₁₄ N ₂ O ₄	C, H, N		inactive ^d
52	H	H	CONH ₂	H	263-265	CHCl ₃ /MeOH/Et ₂ O	64	C ₁₂ H ₉ N ₃ O	C, H, N		inactive ^b
53	H	H	CH ₂ OH	H	158-159	EtOAc/Et ₂ O	92	C ₁₂ H ₁₀ N ₂ O	C, H, N		0.36 (0.21-0.53)
54	H	H	CHO	H	184-185	EtOAc/Et ₂ O	82	C ₁₂ H ₈ N ₂ O	C, H, N		0.093 (0.026-0.31)
56	H	H	CH ₂ NH ₂ ·2HCl	H	320-325	MeOH/Et ₂ O	64	C ₁₂ H ₁₁ N ₃ ·2HCl·0.5H ₂ O	C, H, N, Cl	0.11 (0.039-0.332)	0.976 (0.4-2.34)
58	H	H		H	300-301	CHCl ₃ /MeOH	75	C ₁₂ H ₈ N ₆	C, H, N	0.026 (0.019-0.032)	0.105 (0.037-0.38)
59	MeO	H	CO ₂ H	H	244-247	EtOH/H ₂ O	86	C ₁₃ H ₁₀ N ₂ O ₃	C, H, N	0.57 (0.48-0.67)	3.74 (3.26-4.31)
60	Me ₂ CHO	H	CO ₂ H	H	247-249	EtOH/H ₂ O	85	C ₁₅ H ₁₄ N ₂ O ₃ ·H ₂ O	C, H, N	0.12 (0.08-0.17)	1.13 (0.84-1.55)
61	Cl	H	CO ₂ Et	H	169-170	MeOH	29	C ₁₄ H ₁₁ N ₂ O ₂ Cl	C, H, N, Cl		0.096 (0.065-0.14)
62	Cl	H	CO ₂ H·HCl	H	263-265	MeOH	66	C ₁₂ H ₇ N ₂ O ₂ Cl·HCl	C, H, N, Cl	0.0075 (0.0062-0.0089)	0.47 (0.39-0.55)
63	Br	H	CO ₂ H	H	288-290	CHCl ₃ /MeOH	80	C ₁₂ H ₇ N ₂ O ₂ Br·CH ₃ OH	C, H, N, Br	0.046 (0.032-0.067)	0.14 (0.09-0.25)
64	SMe	H	CO ₂ H	H	273-274	CHCl ₃ /MeOH	89	C ₁₃ H ₁₀ N ₂ O ₂ S·0.5H ₂ O	C, H, N, S	0.046 (0.023-0.11)	
65	SOMe	H	CO ₂ H	H	266-268	EtOH/H ₂ O	86	C ₁₃ H ₁₀ N ₂ O ₂ S	C, H, N, S	0.29 (0.18-0.41)	
67	SO ₂ Me	H	CO ₂ H	H	276-278	DMSO	84	C ₁₃ H ₁₀ N ₂ O ₄ S	C, H, N, S	0.047 (0.025-0.11)	1.64 (0.51-7.81)
69	SO(=NH)Me	H	CO ₂ H	H	273-275	CHCl ₃ /MeOH	75	C ₁₃ H ₁₁ N ₃ O ₂ S	C, H, N, S	0.35 (0.22-0.59)	
71	Ph	H	CO ₂ H	H	272-273	MeOH/H ₂ O	80	C ₁₈ H ₁₂ N ₂ O ₂	C, H, N		inactive ^b
72	H	Ph	CO ₂ H	H	230-240 ^e	EtOH	75	C ₁₈ H ₁₂ N ₂ O ₂	C, H, N	inactive ^b	
73	H	CH ₂ OH	CO ₂ H	H	298-300	EtOH/H ₂ O	75	C ₁₃ H ₁₀ N ₂ O ₂ ·H ₂ O	C, H, N	inactive ^b	
74	H	CN	CO ₂ Et	H	221-222	EtOH/EtOAc	78	C ₁₅ H ₁₁ N ₃ O ₂	C, H, N		inactive ^b
76	H	H	CO ₂ H	Br	209-210	EtOH/H ₂ O	95	C ₁₂ H ₇ N ₂ O ₂ Br	C, H, N, Br	4.19 (2.74-6.94)	
78	Cl	H	CO ₂ H	Me	280-281	EtOH/H ₂ O	90	C ₁₃ H ₉ N ₂ O ₂ Cl·0.33H ₂ O	C, H, N, Cl		inactive ^b

^a 95% confidence limits in parentheses. ^b Inactive at 1 and 10 mg/kg. ^c As dihydrochloride. ^d 47% inhibition at 10 mg/kg. ^e As Na salt.

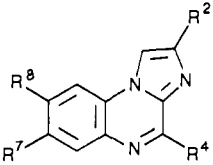
Table III. (Benzo substituted)imidazo[1,2-a]quinoline-2-carboxylic Acids and Derivatives

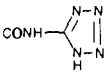



compd	R ⁸	R ⁷	R ⁶	R ⁵	R ²	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ , mg/kg	
											iv	po
79	Cl	H	H	H	CO ₂ Et	221-222	CHCl ₃ /Et ₂ O	50	C ₁₄ H ₁₁ N ₂ O ₂ Cl	C, H, N, Cl		1.72 (0.97-3.45)
80	Cl	H	H	H	CO ₂ H	288-289	EtOH/H ₂ O	64	C ₁₂ H ₇ N ₂ O ₂ Cl	C, H, N, Cl	0.069 (0.046-0.095)	0.11 (0.091-0.135)
81	MeO	H	H	H	CO ₂ H	272-273	AcOH	63	C ₁₃ H ₁₀ N ₂ O ₃	C, H, N	0.038 (0.026-0.058)	0.14 (0.07-0.30)
82	Et	H	H	H	CO ₂ H	241-244	EtOH	72	C ₁₄ H ₁₂ N ₂ O ₂	C, H, N	0.16 (0.08-0.37)	
83	SMe	H	H	H	CO ₂ H	262-264	EtOH/H ₂ O	81	C ₁₃ H ₁₀ N ₂ O ₂ S·H ₂ O	C, H, N, S	0.095 (0.058-0.15)	
85	SOMe	H	H	H	CO ₂ H	261-263	EtOH/H ₂ O	86	C ₁₃ H ₁₀ N ₂ O ₃ S	C, H, N, S	0.076 (0.043-0.12)	
87	SO ₂ Me	H	H	H	CO ₂ H	261-265	EtOH/H ₂ O	81	C ₁₃ H ₁₀ N ₂ O ₄ S	C, H, N, S	0.028 (0.021-0.03)	inactive ^b
88	SO(=NH)Me	H	H	H	CO ₂ H	235-237	EtOH/H ₂ O	76	C ₁₃ H ₁₁ N ₃ O ₃ S·0.5H ₂ O	C, H, N, S	0.095 (0.058-0.15)	
89						290-292	EtOH/H ₂ O	84	C ₁₃ H ₉ N ₂ O ₂ Cl·H ₂ O	C, H, N, Cl	1.99 (1.14-3.89)	
90	CF ₃	H	H	H	CO ₂ H	264-266	EtOH/H ₂ O	91	C ₁₃ H ₇ N ₂ O ₂ F ₃	C, H, N	0.070 (0.04-0.154)	
91	MeO	H	H	H	CH ₂ OH	173-175	THF/H ₂ O	89	C ₁₃ H ₁₂ N ₂ O ₂	C, H, N	0.27 (0.18-0.36)	0.24 (0.03-22.6)
92	MeO	H	H	H	CHO	190-193	EtOAc/Et ₂ O	80	C ₁₃ H ₁₀ N ₂ O ₂	C, H, N	0.12 (0.05-0.37)	0.40 (0.24-0.76)
93	MeO	H	H	H		305-306	DMSO	88	C ₁₃ H ₁₀ N ₆ O	C, H, N	0.01 (0.003-0.028)	0.12 (0.002-24.1)
94	MeO	H	H	H	CONH ₂	273-276	EtOH	40	C ₁₃ H ₁₁ N ₃ O ₂	C, H, N		inactive ^c
95	MeO	H	H	H	CH ₂ NH ₂ ·2HCl	274-277	MeOH/Et ₂ O	74	C ₁₃ H ₁₃ N ₃ O·2HCl·1.5H ₂ O	C, H, N, Cl	3.39 (2.22-5.31)	
96	MeO	H	H	H		298-301	DMF/EtOAc	95	C ₁₄ H ₁₁ N ₂ O ₂ ·0.5H ₂ O	C, H, N	inactive ^c	
97	H	Cl	H	H	CO ₂ H	278-279	EtOH/H ₂ O	93	C ₁₂ H ₇ N ₂ O ₂ Cl·H ₂ O	C, H, N, Cl	0.29 (0.22-0.36)	
98	H	NO ₂	H	H	CO ₂ H	311-313	EtOH/H ₂ O	90	C ₁₂ H ₇ N ₂ O ₄	C, H, N	0.28 (0.20-0.35)	
99	H	MeO	H	H	CO ₂ H	265-266	EtOH/H ₂ O	79	C ₁₃ H ₁₀ N ₂ O ₃	C, H, N	0.03 (0.003-0.48)	
100	Cl	H	H	Cl	CO ₂ Et	229-230	CHCl ₃ /Et ₂ O	79	C ₁₄ H ₁₀ N ₂ O ₂ Cl ₂	C, H, N, Cl		1.49 (0.30-10.04)
101	Cl	H	H	Cl	CH ₂ OH	207-210	EtOAc/Et ₂ O	47	C ₁₂ H ₈ N ₂ OCl ₂	C, H, N, Cl	0.16 (0.02-0.38)	
102	Cl	H	H	Cl	CHO	280-285	CHCl ₃ /Et ₂ O	50	C ₁₂ H ₆ N ₂ OCl ₂	C, H, N, Cl		0.5 (0.21-7.6)
103	Cl	H	H	Cl		322-324	DMF	70	C ₁₂ H ₆ N ₆ Cl ₂	<i>d</i>	0.016 (0.007-0.049)	0.5 (0.07-22.7)
104	H	H	Cl	H	CO ₂ H	288-289	EtOH/H ₂ O	82	C ₁₂ H ₇ N ₂ O ₂ Cl·H ₂ O	C, H, N	3.74 (2.91-4.95)	
105	Cl	H	H	Me ₂ CHO	CO ₂ H	283-285	EtOH/H ₂ O	85	C ₁₅ H ₁₃ N ₂ O ₃ Cl	C, H, N, Cl	0.027 (0.021-0.033)	0.34 (0.07-0.40)
106	MeO	H	H	MeO	CO ₂ H	248-250	MeOH/Et ₂ O	83	C ₁₄ H ₁₂ N ₂ O ₄	C, H, N	1.22 (0.85-1.74)	inactive ^c
107	MeO	H	H	Me ₂ CHO	CO ₂ H	259-261	MeOH/Et ₂ O	87	C ₁₆ H ₁₄ N ₂ O ₄ ·0.5H ₂ O	C, H, N	0.091 (0.064-0.127)	inactive ^b
108	Et	H	H	Cl	CO ₂ H	282-285	EtOH/H ₂ O	83	C ₁₄ H ₁₁ N ₂ O ₂ Cl	C, H, N, Cl	0.09 (0.05-0.15)	
109	Br	H	H	Cl	CO ₂ H	300-303	EtOH/H ₂ O	91	C ₁₂ H ₆ N ₂ O ₂ BrCl·H ₂ O	C, H, N, Br, Cl	0.025 (0.011-0.039)	0.08 (0.04-0.12)
110	Cl	H	H	Cl	CO ₂ H	304-305	EtOH/H ₂ O	92	C ₁₂ H ₆ N ₂ O ₂ Cl ₂	C, H, N, Cl	0.023 (0.019-0.026)	0.033 (0.010-0.035)
111	MeO	H	H	Cl	CO ₂ Et	215-216	CHCl ₃ /Et ₂ O	30	C ₁₅ H ₁₃ N ₂ O ₃ Cl	C, H, N, Cl		8.0 (4.65-18.7)
112	MeO	H	H	Cl	CO ₂ H	277-278	EtOH/H ₂ O	87	C ₁₃ H ₉ N ₂ O ₃ Cl	C, H, N, Cl	0.027 (0.021-0.033)	0.34 (0.07-0.40)
113	H	Cl	H	Ph	CO ₂ H	307-309	EtOH/H ₂ O	92	C ₁₈ H ₁₁ N ₂ O ₂ Cl	C, H, N, Cl		inactive ^c

^a 95% confidence limits in parentheses. ^b 50% inhibition at 10 mg/kg. ^c Inactive at 1 and 10 mg/kg. ^d Accurate mass; M⁺ requires 304.0031, found M⁺ 304.0015 ± 5 mmu.

Table IV. Imidazo[1,2-a]quinoxalines

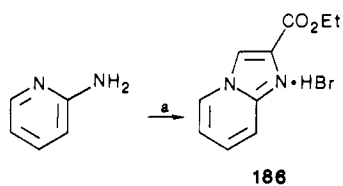


compd	R ²	R ⁴	R ⁷	R ⁸	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ ^a , mg/kg	
										iv	po
114	CO ₂ H	H	H	H	274–275	EtOH/H ₂ O	95	C ₁₁ H ₇ N ₃ O ₂	C, H, N	0.073 (0.057–0.091)	0.13 (0.54–0.90)
115	CO ₂ Et	H	Cl	Cl	297–299	EtOH	40	C ₁₃ H ₉ N ₃ O ₂ Cl ₂	C, H, N, Cl		inactive ^b
116	CO ₂ H	H	Cl	Cl	>350	EtOH/H ₂ O	88	C ₁₁ H ₅ N ₃ O ₂ Cl ₂	C, H, N, Cl	0.2 (0.12–0.35)	inactive ^b
117	CO ₂ H	CONH ₂	H	H	238–240	EtOH/H ₂ O	95	C ₁₂ H ₈ N ₄ O ₃ ·H ₂ O	C, H, N	3.13 (2.48–3.45)	
118		H	H	H	280–281	DMF	91	C ₁₂ H ₈ N ₈ O	C, H, N	0.45 (0.24–1.05)	inactive ^b
120	CH ₂ OH	H	H	H	217–220	CHCl ₃ / Et ₂ O	53	C ₁₁ H ₉ N ₃ O	C, H, N	0.156 (0.066–0.453) ^c	0.061 (0.021–0.089)
121	CHO	H	H	H	214–216	CHCl ₃ / Et ₂ O	89	C ₁₁ H ₇ N ₃ O	C, H, N	0.137 (0.052–0.43) ^c	0.073 (0.031–0.15)
122		H	H	H	320–322	DMF/H ₂ O	53	C ₁₁ H ₇ N ₇	C, H, N ^d	0.012 (0.005–0.033)	0.089 (0.025–0.282)

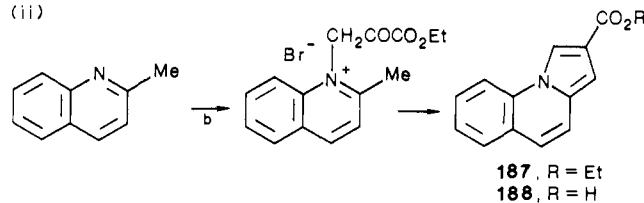
^a95% confidence limits in parentheses. ^bInactive at 1 and 10 mg/kg. ^cTested iv as HCl salts. ^dN: calcd, 41.33; found, 40.83.

Scheme X. Miscellaneous Analogues^a

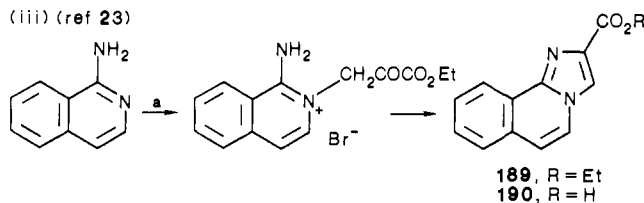
(i) (ref 22)



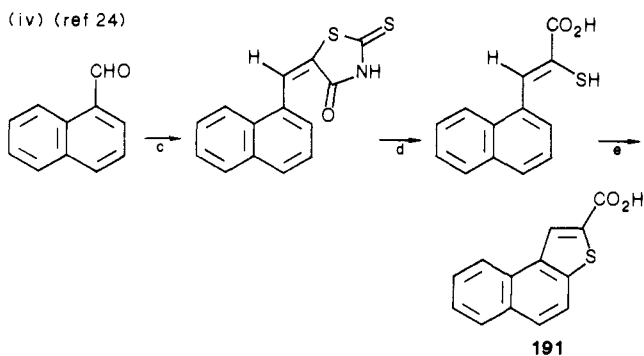
(ii)



(iii) (ref 23)



(iv) (ref 24)

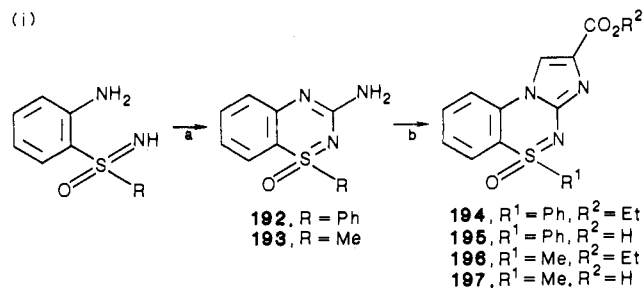


^aReagents: (a) (i) BrCH₂COCO₂Et; DME, (ii) Δ; EtOH; (b) BrCH₂COCO₂Et; EtOH, Δ; (c) rhodanine, NaOAc, Ac₂O, Δ; (d) NaOH; H₂O, EtOH, (ii) HCl; (e) I₂; dioxane.

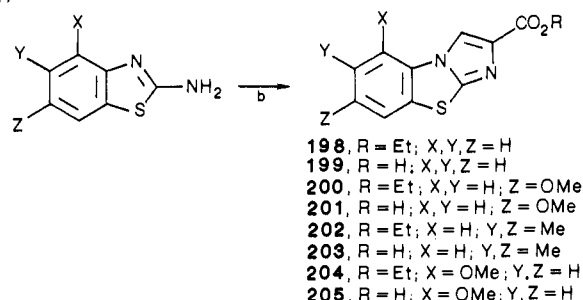
electron-withdrawing groups at position 8 (29–35) and electron-donating groups (36 and 37) although the iv/po ratio does vary. Also, alkyl groups in position 4 (38, 39)

Scheme XI^a

(i)



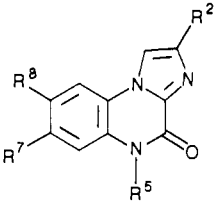
(ii)

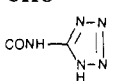


^aReagents: (a) BrCN; aqueous MeOH; (b) (i) BrCH₂COCO₂Et; DME, (ii) Δ; EtOH (hydrolysis: (i) NaOH; H₂O, EtOH, (ii) HCl).

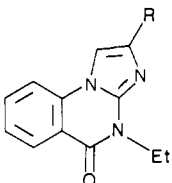
increase the activity. Overall, the conclusion seems to be that the parent 2-carboxylic acid possesses a good level of activity which is increased in a not easily accountable manner by substituents in the 4- and 8-positions.

(b) **Imidazo[1,2-a]quinolines.** Tables II and III list the results of testing compounds in the PCA test in comparison to DSCG. Table II lists the screening results of the benzo-unsubstituted imidazo[1,2-a]quinoline-2-carboxylic acids and derivatives while Table III lists the screening results of the benzo-substituted members of the same series. In general, among all the compounds in Tables II and III, it can be seen that high levels of iv activity are present (up to 160 times that of DSCG), and furthermore, certain compounds such as 47, 91, and 110 are equiactive following iv or po dosing. In particular, concentrating on Table II, the rank order of activity for iv

Table V. Imidazo[1,2-*a*]quinoxalinones


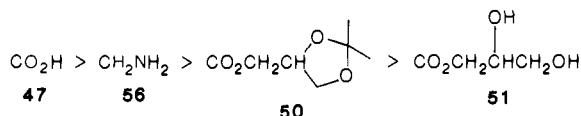
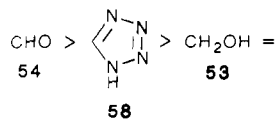
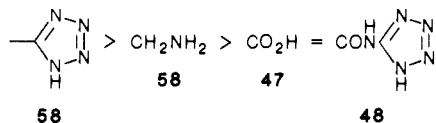
compd	R ⁸	R ⁷	R ⁵	R ²	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ ^a mg/kg	
										iv	po
124	H	H	Et	CO ₂ Et	216–218	EtOH	63	C ₁₅ H ₁₅ N ₃ O ₃	C,H,N		0.16 (0.05–0.64)
125	H	H	Pr	CO ₂ Et	212–214	EtOH	65	C ₁₆ H ₁₇ N ₃ O ₃	C,H,N		1.21 (0.74–2.02)
126	H	H	CH ₂ Ph	CO ₂ Et	259–260	DMF/EtOH	89	C ₂₀ H ₁₇ N ₃ O ₃	C,H,N		inactive ^c
127	H	H	H	CO ₂ H	272–275	EtOH/H ₂ O	95	C ₁₁ H ₇ N ₃ O ₃ ·0.25H ₂ O	C,H,N	0.16 (0.11–0.25)	2.0 (0.97–4.61)
128	H	H	Me	CO ₂ H	267–268	EtOH/H ₂ O	95	C ₁₂ H ₉ N ₃ O ₃	C,H,N	0.031 (0.024–0.041)	1.28 (0.67–2.51)
129	H	H	Et	CO ₂ H	260–262	EtOH/H ₂ O	79	C ₁₃ H ₁₁ N ₃ O ₃	C,H,N	0.01 (0.007–0.014)	0.45 (0.29–0.58)
130	H	H	Pr	CO ₂ H	232–234	EtOH/H ₂ O	95	C ₁₄ H ₁₃ N ₃ O ₃ ·H ₂ O	C,H,N	0.01 (0.006–0.021)	0.24 (0.12–0.32)
131	H	H	Bu	CO ₂ H	220–222	EtOH/H ₂ O	95	C ₁₅ H ₁₅ N ₃ O ₃ ·H ₂ O	C,H,N	0.023 (0.058–0.12)	0.59 (0.46–0.73)
133	Cl	Cl	H	CO ₂ H	>330	EtOH/H ₂ O	95	C ₁₁ H ₅ Cl ₂ N ₃ O ₃ ·H ₂ O	C, ^b H,N		inactive ^c
134	H	H	Et	CH ₂ OH	215–218	EtOH	43	C ₁₃ H ₁₃ N ₃ O ₂	C,H,N	0.071 (0.05–0.11) ^d	0.062 (0.020–0.116)
135	H	H	Et	CHO	302–306	EtOH/CHCl ₃	62	C ₁₃ H ₁₁ N ₃ O ₂	C,H,N		0.077 (0.028–0.149)
136	H	H	Et		>310	DMF	90	C ₁₄ H ₁₂ N ₃ O ₂ ·(C ₃ H ₇ NO) ^e	C,H,N	0.32 (0.25–0.41)	

^a95% confidence limits in parentheses. ^bC: calcd, 41.80; found, 42.35. ^cInactive at 10 mg/kg. ^dTested as HCl salt. ^eOne mole of DMF of crystallization.

Table VI. Imidazo[1,2-*a*]quinazolinones and Derivatives


compd	R	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ , mg/kg	
							iv	po
137	CO ₂ Et	215–217	Et ₂ O	49	C ₁₅ H ₁₅ N ₃ O ₃	C,H,N		inactive
138	CO ₂ H	279–282	EtOH/H ₂ O	82	C ₁₃ H ₁₁ N ₃ O ₃ ·0.75H ₂ O	C,H,N	inactive	

administration for compounds substituted only in the 2-position is as follows:



The activity of the primary amine **56** is surprising since this is not a group usually associated with PCA inhibitory activity. Additionally, good levels of po activity are seen for the alcohol **53** and the aldehyde **54** but, whether this is due to metabolism to the acid is unknown. It will be seen in later series that alcohols and aldehydes can show

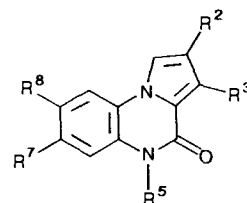
significant levels of activity (see **120**, **121**, **134**, and **135**). For compounds with a range of substituents in the 4-position and retaining carboxyl in the 2-position, all except the 4-MeO and 4-SONHMe compounds, **59** and **69**, respectively, are more active than **47**, and the rank order of activity for iv administration is


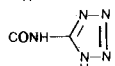
Cl > Br = SMe = SO₂Me > OCHMe₂ > SOMe = H = SONHMe > OMe

62 63 64 67 80 65 47 69 59

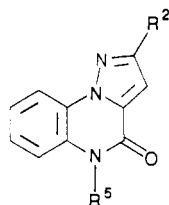
By po administration only the 4-Br compound **63** is more active than **47**. Substituents in the 3-position such as Ph (**72**), CH₂OH (**73**), and CN (**74**) and those in the 1-position such as Br (**76**) and Me (**78**) (while retaining the 2-carboxy group) caused a loss of activity. Therefore, as in the imidazo[2,1-*c*][1,4]benzoxazine series, PCA inhibitory activity seems to be restricted to those tricyclics with a 2-carboxylic acid substituent or equivalent. It should be noted that Pfizer have described the PCA inhibitory activity of a series of 4-alkoxyimidazo[1,2-*a*]quinoline-2-carboxylic acids.²⁶ The only compound common to our work and

Table VII. Pyrrolo[1,2-a]quinoxalinones



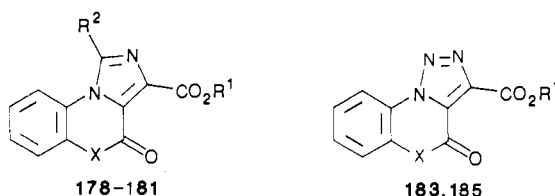
compd	R ⁸	R ⁷	R ⁵	R ³	R ²	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ , ^a mg/kg	
											iv	po
DSCG											1.21 (1.04-1.42)	inactive
142	H	H	Me	H	CO ₂ Et	197-198	EtOAc	41	C ₁₅ H ₁₄ N ₂ O ₃	C,H,N		7.0 (3.55-11.7)
143	H	H	Bu	H	CO ₂ Et	146-148	Et ₂ O	44	C ₁₈ H ₂₀ N ₂ O ₃	C,H,N		4.1 (1.95-11.5)
145	H	H	Me	H	CO ₂ H	330-333	EtOH/H ₂ O	95	C ₁₃ H ₁₀ N ₂ O ₃	C,H,N	0.089 (0.063-0.125)	0.54 (0.45-0.63)
146	H	H	Et	H	CO ₂ H	314-316	EtOH/H ₂ O	94	C ₁₄ H ₁₂ N ₂ O ₃	C,H,N	0.026 (0.019-0.035)	0.035 (0.024-0.053)
147	H	H	Pr	H	CO ₂ H	260-262	EtOH/H ₂ O	96	C ₁₅ H ₁₄ N ₂ O ₃	C,H,N	0.019 (0.015-0.023)	0.032 (0.023-0.047)
148	H	H	Bu	H	CO ₂ H	212-214	EtOH/H ₂ O	89	C ₁₆ H ₁₆ N ₂ O ₃	C,H,N	0.019 (0.014-0.024)	0.058 (0.039-0.063)
149	H	H	Pent	H	CO ₂ H	184-186	EtOH/H ₂ O	95	C ₁₇ H ₁₈ N ₂ O ₃	C,H,N	0.087 (0.036-0.43)	0.31 (0.21-0.46)
150	H	H	Ph	H	CO ₂ H	304-306	EtOH	65	C ₁₈ H ₁₂ N ₂ O ₃	C,H,N	1.57 (1.14-2.28)	18.9 (12.3-33.8)
151	H	H	cyclopentyl	H	CO ₂ H	215-216	EtOH/H ₂ O	95	C ₁₇ H ₁₆ N ₂ O ₃ ·0.5H ₂ O	C,H,N	0.037 (0.30-0.46)	1.96 (1.22-2.52)
152	H	H	isopropyl	H	CO ₂ H	238-240	EtOH/H ₂ O	94	C ₁₅ H ₁₄ N ₂ O ₃ ·0.5H ₂ O	C,H,N	0.85 (0.49-1.41)	
153	H	H	allyl	H	CO ₂ H	306-308	EtOH/H ₂ O	96	C ₁₅ H ₁₂ N ₂ O ₃	C,H,N	0.035 (0.024-0.053)	0.28 (0.21-0.37)
154	Me	Me	Et	H	CO ₂ H	313-316	EtOH/H ₂ O	89	C ₁₆ H ₁₆ N ₂ O ₃ ·0.5H ₂ O	C,H,N	0.030 (0.022-0.040)	
155	Cl	Cl	Bu	H	CO ₂ H	281-283	EtOH/H ₂ O	92	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₃	C,H,Cl,N	0.014 (0.009-0.024)	0.117 (0.044-0.288)
156	Cl	H	Et	H	CO ₂ H	322-326	EtOH/H ₂ O	91	C ₁₄ H ₁₁ ClN ₂ O ₃	C,H,N	0.035 (0.028-0.045)	0.29 (0.24-0.35)
157	H	Cl	Bu	H	CO ₂ H	275-276	EtOH	93	C ₁₆ H ₁₅ ClN ₂ O ₃	C,H,Cl,N	0.019 (0.013-0.023)	0.114 (0.060-0.199)
158	H	H	Et	H	CH ₂ OH	171-173	EtOAc	88	C ₁₄ H ₁₄ N ₂ O ₂	C,H,N		0.045 (0.032-0.069)
159	H	H	Et	H	CHO	252-255	EtOAc/Et ₂ O	82	C ₁₄ H ₁₂ N ₂ O ₂	C,H,N		2.53 (1.88-2.85)
160	H	H	Et	H		295-297	DMF/EtOAc	48	C ₁₄ H ₁₂ N ₆ O	C,H,N	0.011 (0.004-0.041)	0.44 (0.182-1.56)
161	H	H	Et	H		315-318	DMF/EtOAc	95	C ₁₅ H ₁₃ N ₇ O ₂	C,H,N	0.18 (0.13-0.26)	
163	H	H	Et	CO ₂ Me	CO ₂ H	290-293	EtOH/H ₂ O	96	C ₁₆ H ₁₄ N ₂ O ₅	C,H,N	inactive	

^a 95% confidence limits in parentheses.

Table VIII. Pyrazolo[2,3-*a*]quinoxalinones

compd	R ⁵	R ²	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ ^a mg/kg	
								iv	po
166	H	CO ₂ H	333-334 ^b	EtOH/H ₂ O	93	C ₁₁ H ₇ N ₃ O ₃	C,H,N	0.33 (0.08-1.71)	
170	Me	CO ₂ H	309-312	EtOH/H ₂ O	54	C ₁₂ H ₉ N ₃ O ₃	C,H,N	0.19 (0.10-0.44)	
171	Et	CO ₂ H	242-244	EtOH/H ₂ O	66	C ₁₃ H ₁₁ N ₃ O ₃	C,H,N	0.11 (0.06-0.22)	
172	Pr	CO ₂ H	228-229	EtOH/H ₂ O	51	C ₁₄ H ₁₃ N ₃ O ₃ ·H ₂ O	C,H,N	0.023 (0.014-0.029)	

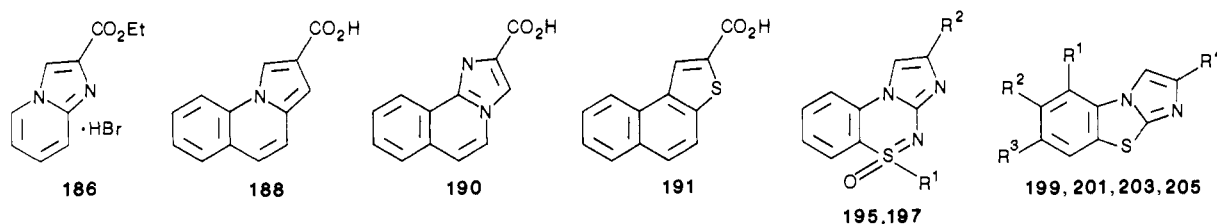
^a95% confidence limits in parentheses. ^bReference 18, mp >315 °C.

Table IX. Imidazo[1,5-*a*]quinoxalinones, Triazolo[5,1-*c*][1,4]benzoxazinones, and Triazolo[1,5-*a*]quinoxalinones

compd	X	R ¹	R ²	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ ^a mg/kg	
									iv	po
178	NH	H	H	>320	EtOH/H ₂ O	91	C ₁₁ H ₇ N ₃ O ₃	C,H,N	0.104 (0.073-0.151)	inactive ^b
179	NH	H	Me	302-305	EtOH/H ₂ O	81	C ₁₂ H ₉ N ₃ O ₃	C,H,N	0.37 (0.31-0.45)	
180	NH	H	Et	214-216	EtOH/H ₂ O	60	C ₁₃ H ₁₁ N ₃ O ₃	C,H,N	inactive ^c	
181	NH	H	CH ₂ Ph	181-183	EtOH/H ₂ O	47	C ₁₈ H ₁₃ N ₃ O ₃	C,H,N		inactive ^c
183	O	Me		205-207	EtOAc	54	C ₁₁ H ₇ N ₃ O ₄	C,H,N		inactive ^d
185	NH	H		>320	EtOH/H ₂ O	76	C ₁₀ H ₆ N ₂ O ₃	C,H,N	0.084 (0.058-0.12)	inactive ^e

^a95% confidence limits in parentheses. ^bInactive at 20 mg/kg. ^cInactive at 1 and 10 mg/kg. ^d50% inhibition at 10 mg/kg. ^e45% inhibition at 20 mg/kg.

Table X. Related Ring Systems



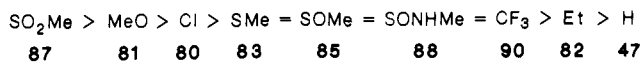
compd	R ¹	R ²	R ³	R ⁴	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED ₅₀ ^a mg/kg	
										iv	po
186					175-178 ^b	EtOH/Et ₂ O	31	C ₁₀ H ₁₁ N ₂ O ₂ Br		inactive ^c	
188					242-247	EtOH/H ₂ O	82	C ₁₃ H ₉ NO ₂	C,H,N	inactive ^c	
190					>370 ^d	EtOH/H ₂ O	80	C ₁₂ H ₈ N ₂ O ₂	C,H,N	inactive ^c	
191					281-284 ^e	EtOH/H ₂ O	66	C ₁₃ H ₉ O ₂ S	C,H,S	inactive ^c	
195	Ph	CO ₂ H			181-183	MeOH/Et ₂ O	96	C ₁₆ H ₁₁ N ₃ O ₃ S·0.5H ₂ O	C,H,N,S	1.92 (1.07-3.93)	
197	Me	CO ₂ H			196-200	DMF/EtOAc	85	C ₁₁ H ₉ N ₃ O ₃ S·0.5H ₂ O	C,H,N,S	2.59 (2.20-3.00)	
199	H	H	H	CO ₂ H	254-255 ^f	EtOH/H ₂ O	91	C ₁₀ H ₆ N ₂ O ₂ S	C,H,N,S	0.33 (0.19-0.59)	
201	H	H	MeO	CO ₂ H	270-273	EtOH/H ₂ O	86	C ₁₁ H ₈ N ₂ O ₃ S·1.25H ₂ O	C,H,N,S	0.62 (0.39-0.96)	
203	H	Me	Me	CO ₂ H	307-308	EtOH/H ₂ O	82	C ₁₂ H ₁₀ N ₂ O ₂ S·0.33H ₂ O	C,H,N,S	0.30 (0.22-0.38)	
205	MeO	H	H	CO ₂ H	288-290	EtOH/H ₂ O	85	C ₁₁ H ₈ N ₂ O ₃ S	C,H,N,S	0.16 (0.072-0.41)	

^a95% confidence limits in parentheses. ^bReference 22, mp 174.5-175.5 °C. ^cInactive at 1 and 10 mg/kg. ^dReference 23. ^eReference 24, mp 277-278 °C. ^fReference 25, mp 263-265 °C.

theirs is 59 for which we find very similar levels of activity, i.e., 78% inhibition at 0.3 mg/kg iv and 90% inhibition at 3.0 mg/kg po against ED₅₀s of 0.57 and 3.74, respectively (Table II). While some 4-chloro compounds were described

in the patent, their activities were not given, and so our finding that compounds with 4-Cl (62), 4-Br (63), and 4-SMe (64) substituents are more active than the 4-MeO-substituted compound is not corroborated.

Table III lists the activities of compounds with substituents in the benzo ring. Substituents in the 7- and especially 8-positions enhance activities, the rank order for the 8-position for iv administration being:



Disubstitution, especially in the 5,8-positions, also increased iv and po activities and compounds 109 and 110 have the best overall combined iv and po activities of this series.

(c) **Imidazo[1,2-*a*]quinoxalines.** The best results (Table IV) in this limited series were again found with acid and tetrazole groups in the 2-position. Substitution in the benzene ring (115, 116) or in the 4-position (117) reduced activity.

(d) **Imidazo[1,2-*a*]quinoxalinones.** The esters were too insoluble to be tested by iv administration (Table V), but in the acid series the iv activity increases with *N*-alkyl chain length to a maximum at *n*-propyl (130). However, the oral activity was not as good as in some of the other series.

(e) **Imidazo[1,2-*a*]quinazolinones.** The "reverse amide" analogues (137, 138) were inactive (Table VI), indicating the limits to change allowed in the 4,5-positions.

(f) **Pyrrolo[1,2-*a*]quinoxalinones.** Table VII shows that all compounds of this series (other than the acid ester 163) show significant activity in the PCA test following either, and in some cases both, iv or po dosing.

Indeed many compounds show activity of the order of 100 times that of DSCG. In the 2-carboxylic acid series, the activity peaks after iv administration with the 5-Pr and 5-Bu substituents (147, 148) and after po dosing with the 5-Et and 5-Pr groups (146, 147). Maximal activity is restricted to straight-chain alkyl or alkenyl substituents on the 5-nitrogen atom, and the presence of branched chains as in 151 and 152 or a phenyl ring as in 150 in this position causes a dramatic loss of activity, perhaps indicating a subtle balance of steric and lipophilic effects. Surprisingly, the esters 142 and 143 show little po activity compared to the corresponding acids 145 and 148. The introduction of substituents in the aromatic ring, e.g., 154–157, has little effect on iv activities but generally causes a slight drop in po activities.

(g) **Pyrrolo[2,3-*a*]quinoxalin-4(5*H*)-ones.** As shown in Table VIII, the compounds were inactive orally and were less active following iv administration than their imidazo[1,2-*a*]quinoxalinone counterparts (compare 170 and 145; 171 and 146; 172 and 147).

(h) **Imidazo[1,5-*a*]quinoxalinones, Triazolo[1,5-*a*]quinoxalinones, and Triazolo[1,5-*a*]benzoxazinones.** Table IX shows the activities found in these compound in which the acid or ester group is now in the 3-position. While 178, 179, and 185 showed reasonable intravenous activity, none of the compounds showed any oral activity.

(i) **Miscellaneous Ring Systems.** The results from the screening of compounds from related ring systems are shown in Table X. No activity was found for compounds 186, 188, 190, and 191. The two cyclic sulfoximide acids 195 and 196 showed moderate levels of iv activity and slightly better were the imidazobenzothiazoles 199, 201, 203, and 205.

Conclusions

In summary, very good levels of activity in the IgE-mediated PCA test following either iv or po doses (or in some cases both) have been found in 2-carboxylic acids derived from 4*H*-imidazo[2,1-*c*][1,4]benzoxazines (Table I), imidazo[1,2-*a*]quinolines (Table II and III), imidazo-

[1,2-*a*]quinoxalines (Table IV), imidazo[1,2-*a*]quinoxalinones (Table V), pyrrolo[1,2-*a*]quinoxalinones (Table VII), pyrazolo[2,3-*a*]quinoxalinones (Table VIII), imidazo[1,5-*a*]quinoxalinones (Table IX), triazolo[1,5-*a*]quinoxalinones (Table IX), imidazo[1,2-*c*][1,2,4]benzothiadiazines (Table X), and imidazo[1,2-*a*]benzothiazoles (Table X). In addition, it is possible to replace the carboxylic acid group by alcohol, aldehyde, tetrazoyl, tetrazoylamide, and aminomethyl. Within an active series, a certain number of benzo substituents are allowed without destroying the activity, but the effects are not easily explicable in terms of lipophilicity or electronic effects. Of these series, the two belonging to the imidazo[1,2-*a*]quinoline²⁷ and imidazo[1,2-*a*]quinoxalines²⁸ show the best activities, and the acid 114 has been chosen for further development both on the basis of the results described here and the lack of cross tachyphylaxis with DSCG.²⁹

Experimental Section

Melting points were determined with an Electrothermal open-ended capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Unicam SP1000 infrared spectrophotometer as KBr disks. ¹H NMR spectra were recorded in either CDCl₃ or Me₂SO-*d*₆ with a Perkin-Elmer R12A spectrometer (60 MHz) with Me₄Si as internal standard. All OH and NH peaks were exchanged on D₂O shake. IR and NMR spectra were run on all compounds and were fully in accord with the assigned structures. Elemental analyses (determined by CHN Analysis Ltd., Leicester, England) were carried out on all new compounds and results were within 0.4% of the expected values, except where noted. All organic extracts were dried over magnesium sulfate and solid products were dried under vacuum over P₂O₅.

(a) **Imidazo[2,1-*c*][1,4]benzoxazines.** *N*-(1*H*-Tetrazol-5-yl)-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-acetamide (26). 1,1'-Carbonyldiimidazole (0.90 g, 55 mmol) was added to a stirred solution of the acetic acid 17⁹ (1.15 g, 50 mmol) in DMF (20 mL) and the mixture was stirred at room temperature for 5 h. Anhydrous 5-aminotetrazole (0.5 g, 59 mmol) was added and stirring was continued overnight. The mixture was then concentrated by evaporation in vacuo (air-bleed) and triturated with CHCl₃ to give 26 (750 mg, 44%) as pale pink crystals, mp 282–284 °C (from DMF–CHCl₃). Anal. (C₁₃H₁₁N₇O₂) C, H, N.

2-[(1*H*-5-Aminotetrazol-1-yl)carbonyl]-4*H*-imidazo[2,1-*c*][1,4]benzoxazine (24) and *N*-(1*H*-Tetrazol-5-yl)-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxamide (25). Reaction of the carboxylic acid 3⁹ with 5-aminotetrazole as in the preparation of 26 gave the carboxamide 25, mp 296–297 °C; IR 740, 1257, 1516, 1537, 1570, 1609, 1700, 3140, and 2500–3250 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 5.33 (2 H, s, 4-H), 6.8–7.2 (3 H, m, Ar H), 7.6–7.95 (1 H, m, 9-H), 8.72 (1 H, s, 1-H). Anal. (C₁₂H₉N₇O₂) C, H, N.

Reaction of the acid chloride of 3 with 5-aminotetrazole under azeotropic conditions in DMF–benzene yielded a mixture of 25 and a similar compound separated by fractional crystallization from MeOH and tentatively assigned structure 24: mp 300–301 °C; IR 750, 1242, 1506, 1560, 1603, 1690, 3130, 3280, and 3395 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 5.30 (2 H, s, 4-H), 6.95–7.2 (3 H, m, Ar H), 7.5–7.8 (1 H, m, 9-H), 8.60 (1 H, s, 1-H). Anal. (C₁₂H₉N₇O₂) C, H, N.

Methyl 1-(Hydroxymethyl)-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylate (27). Sodium borohydride (1.0 g, 26 mmol) was added slowly over a 2-h period to a solution of the acid chloride of 19⁹ (0.85 g, 2.9 mmol) in dimethoxyethane (20 mL) at room temperature. Stirring of the reaction mixture was continued for a further 4 h. The mixture was then poured into water (100 mL)–CHCl₃ (100 mL). The CHCl₃ layer was removed and the aqueous layer was further extracted with CHCl₃ (2 × 50 mL). The combined CHCl₃ extract was washed once with water, dried, and evaporated. Trituration with Et₂O gave 27 as colorless

(27) Ager, I. R.; Ramm, P. J. U.K. Patent 1 596 652, 20 Jan. 1977.

(28) Barnes, A. C.; Ramm, P. J. U.K. Patent 2027 707, 31 July 1979.

(29) Miller, P., unpublished results.

needles (0.35 g, 46%), mp 209–210 °C (from Et₂O). Anal. (C₁₃H₁₂N₂O₄) C, H, N.

1-(Hydroxymethyl)-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylic Acid (28). Ester 27 was hydrolyzed as for the preparation of 47 to give acid 28 (78%), mp 232–233 °C (from EtOH–H₂O). Anal. (C₁₂H₁₀N₂O₄·0.5H₂O) C, H, N.

The following compounds were prepared in the same way as 3⁹ in yields of 75–95%.

8-Chloro-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylic acid (34), mp 276–278 °C (from EtOH). Anal. (C₁₁H₇ClN₂O₃) C, H, Cl, N.

Methyl 8-chloro-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylate (35), mp 239–240 °C (from EtOH–Et₂O). Anal. (C₁₂H₉ClN₂O₃) C, H, N.

Methyl 8-methyl-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylate (36), mp 195–197 °C (from Et₂O). Anal. (C₁₃H₁₂N₂O₃) C, H, N.

8-Methyl-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylic acid (37), mp 221–223 °C (from EtOH–H₂O). Anal. (C₁₂H₁₀N₂O₃) C, H, N.

4-Methyl-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylic acid (38), mp 210–211 °C (from EtOH–H₂O). Anal. (C₁₂H₁₀N₂O₃) C, H, N.

4-Ethyl-4H-imidazo[2,1-c][1,4]benzoxazine-2-carboxylic acid (39), mp 172–174 °C (from EtOH–H₂O). Anal. (C₁₃H₁₂N₂O₃·0.5H₂O) C, H, N.

(b) **Imidazo[1,2-a]quinolines.** The following substituted 2-aminoquinolines were prepared according to the routes described in the literature; 4-hydroxy,³⁰ 4-methoxy,^{26,31} 4-isopropoxy,^{26,31} 4-chloro,³² 4-bromo,³³ 6-chloro-4-phenyl,³⁴ 3-phenyl,³⁵ 3-ethoxy-carbonyl,³⁶ 7-chloro,³⁷ 7-methoxy,³⁷ 4-chloro-7-ethyl,²⁶ 7-methylthio,²⁶ 6-chloro,³⁸ 6-nitro,³⁹ 7-ethyl-4-hydroxy,²⁶ 7-bromo-4-hydroxy,²⁶ 7-chloro-4-hydroxy,³² 4-hydroxy-7-methoxy,³² 7-chloro-4-isopropoxy,^{26,30} 4,7-dimethoxy,²⁶ 4-isopropoxy-7-methoxy,²⁶ 7-bromo-4-chloro,²⁶ 4,7-dichloro,³² and 4-chloro-7-methoxy.²⁶

2-Amino-4-(methylthio)quinoline. A solution of sodium (2.0 g, 87 mg-atom) dissolved in EtOH (500 mL) was cooled in an ice bath and treated with a slow stream of MeSH for 0.5 h. 2-Amino-4-chloroquinoline (5.0 g, 28 mmol) was added and the mixture was refluxed for 36 h (passing the effluent gases through acidic KMnO₄ solution). The solution was then distilled under a stream of nitrogen, reducing the volume to 50 mL. The mixture was treated with ice/water (700 mL) and allowed to stand 1 h to crystallize buff crystals of the (methylthio)quinoline (5.0 g, 94%), mp 173–175 °C (from CHCl₃–Et₂O). Anal. (C₁₀H₁₀N₂S) C, H, N, S.

2-Amino-4-(methylsulfinyl)quinoline. A solution of 2-amino-4-(methylthio)quinoline (12.0 g, 63 mmol) in EtOH (1500 mL) was stirred vigorously while being heated under reflux, and NaIO₄ (18 g, 84 mmol) in water (250 mL) was added in portions over 24 h. The solution was then cooled and evaporated to a small volume. Water (600 mL) was added and the solution stood for 1 h to crystallize the (methylsulfinyl)quinoline (8.6 g, 66%), as light brown crystals, mp 238–240 °C (from CHCl₃–MeOH–Et₂O). Anal. (C₁₀H₁₀N₂OS) C, H, N, S.

2-Amino-3-(hydroxymethyl)quinoline. Ethyl 2-aminoquinoline-3-carboxylate³⁶ (8 g, 30 mmol) was dissolved in dry THF

(200 mL) and added dropwise to LiAlH₄ (4 g, 105 mmol) in dry THF (200 mL) heated under reflux. Heating was continued for 1 h, and then the mixture was cooled to room temperature and water (200 mL) was added dropwise. The solution was extracted with EtOAc (2 × 300 mL) and the combined EtOAc extract was washed once with water, dried, and evaporated to give the (hydroxymethyl)quinoline (4.3 g, 68%), as off-white crystals, mp 197–199 °C (from MeOH–Et₂O). Anal. (C₁₀H₁₀N₂O) C, H, N.

2-Amino-7-(trifluoromethyl)quinoline. 2-Chloro-7-(trifluoromethyl)quinoline (6.5 g, 28 mmol) [prepared⁴⁰ from 3-(trifluoromethyl)aniline] was suspended in aqueous ammonia (*d* 0.88, 75 mL) in a pressure vessel containing a small quantity of Cu₂Cl₂ (250 mg). The vessel was shaken and heated to 150 °C, with the pressure reaching 18 atm. After 6 h, the vessel was allowed to cool and the ammonia solution was reduced in volume and cooled. The crude precipitated product was filtered, dissolved in CHCl₃ (200 mL), and extracted with 2 N HCl (2 × 100 mL). The acid extract was made basic with Na₂CO₃ and extracted with CHCl₃ (2 × 100 mL). The combined CHCl₃ extract was dried and evaporated and the residue was triturated with CHCl₃–Et₂O to give the (trifluoromethyl)quinoline (2.56 g, 41%), mp 174–177 °C (from CHCl₃–Et₂O). Anal. (C₁₀H₇F₃N₂) C, H, N.

2-Amino-5-chloroquinoline. 2-Chloro-6-nitroaniline⁴¹ (8.6 g, 50 mmol) suspended in concentrated HCl (10.8 mL) and AcOH (30 mL) was stirred at –2 to 2 °C during the addition of NaNO₂ (3.5 g, 50.8 mmol) in water (10 mL) over 2 h. A further quantity of NaNO₂ (200 mg, 2.9 mmol) in water (1 mL) was added and the mixture was stirred for a further 1 h and then treated with urea (to destroy any remaining nitrous acid). After filtration (cold) through Celite, the filtrate was slowly added to acrylonitrile (13.9 g, 262 mmol) in Me₂CO (100 mL) at 0–4 °C. A suspension of CuCl (0.5 g, 5.05 mmol) and LiCl (0.3 g, 7.1 mmol) in Me₂CO (30 mL) was then added, while the temperature was maintained at 0 °C. After the mixture was allowed to warm up to room temperature, the Me₂CO was removed under reduced pressure and the residue was dissolved in Et₂O (300 mL). The Et₂O solution was washed with water, dilute Na₂CO₃ solution, and water and then dried and evaporated. Chromatography of the red oil so obtained (SiO₂; 10% EtOAc–60–80 °C petroleum ether) gave 2-chloro-6-nitrodihydrocinnamonitrile as a pale yellow oil (1.7 g, 14%).

The yellow oil (1.7 g, 6.95 mmol) was heated under reflux for 5 h in benzene (50 mL) in the presence of iron powder (8 g, 143 mmol) while concentrated HCl (0.4 mL) and water (1 mL) were added slowly. The solution was then filtered hot and the residue was made basic with Na₂CO₃ solution before being extracted with benzene (2 × 100 mL). The benzene solutions were combined and washed with 2 N HCl (4 × 50 mL). The aqueous acid extract was washed with EtOAc (100 mL), basified with Na₂CO₃, and extracted with CH₂Cl₂ (2 × 100 mL). The CH₂Cl₂ solution was washed with water, dried, and evaporated to give a pale brown solid (440 mg) after trituration with Et₂O–40–60 °C petroleum ether. The solid was chromatographed (SiO₂; CHCl₃) to give 2-amino-5-chloroquinoline (180 mg, 14.5%) as off-white needles, mp 176–178 °C (from EtOAc–Et₂O). Anal. (C₉H₇N₂Cl) H, N, Cl; C: calcd, 60.6; found, 59.9

1-(Ethoxalylmethyl)quinolinium Bromide (43). Quinoline (5.0 g, 39 mmol) was dissolved in a mixture of dimethoxyethane (DME) (25 mL)–Et₂O (25 mL) and ethyl bromopyruvate (8.0 g, 40 mmol) was added. The solution was kept at room temperature for 16 h to crystallize the quaternary salt 43 (4.9 g, 38%), mp 128–130 °C (from EtOH–Et₂O); IR 783, 1147, 1537, 1654, and 2900–3250 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 0.93 and 1.18 (2 × 3 H, 2 × *t*, *J* = 7 Hz, ester CH₃ and ethanol CH₃), 3.39 and 4.16 (2 × 2 H, 2 × *q*, *J* = 7 Hz, ester CH₂ and ethanol CH₂), 5.49 (2 H, br s, NCH₂), 7.9–8.8 (5 H, m, Ar H), and 9.45 (2 H, br d, 2-H). Anal. (C₁₄H₁₄BrNO₃·C₂H₅OH) C, H, Br, N.

Ethyl 4,5-Dihydroimidazo[1,2-*a*]quinoline-2-carboxylate (44) and Ethyl Imidazo[1,2-*a*]quinoline-2-carboxylate (45). The quaternary salt 43 (3.5 g, 10.8 mmol) was dissolved in AcOH (30 mL) and NH₄OAc (6 g, 78 mmol) was added. After the mixture had been heated under reflux for 4 h, the solution was

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poured into water (200 mL), basified to pH 9–10 (Na_2CO_3), and extracted with CHCl_3 (3×100 mL). The combined CHCl_3 extract was washed with water (100 mL), dried, and evaporated. The oil so obtained was chromatographed (SiO_2 ; EtOAc) to give 44, as the lower R_f product (0.65 g, 25%): mp 134–135 °C (from $\text{EtOAc-Et}_2\text{O}$) IR 753, 1252, 1559, 1706, and 3145 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 1.40 (3 H, t, ester CH_3), 3.0–3.25 (4 H, br m, 4-H and 5-H) 4.40 (2 H, q, ester CH_2), 7.25–7.50 (4 H, br m, Ar H), and 8.05 (1 H, s, 1-H). Anal. ($\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$) C, H, N. The higher R_f product was 45 (0.92 g, 35%): mp 175–177 °C (from $\text{EtOAc-Et}_2\text{O}$); IR 745, 1249, 1538, 1571, 1702, and 3145 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 1.45 (3 H, t, ester CH_3), 4.49 (2 H, q, ester CH_2), 7.45–8.10 (6 H, m, Ar H), and 8.69 (1 H, s, 1-H). Anal. ($\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2$) C, H, N.

Alternatively, 2-aminoquinoline (30 g, 0.208 mol) was dissolved in DME (300 mL) with warming and a solution of ethyl bromopyruvate (50 g, 0.256 mol) in DME (50 mL) was added. The solution was cooled in an ice bath for 1 h and the yellow precipitate was filtered and washed well with Et_2O . A suspension of the salt (45 g) in EtOH (200 mL) was heated under reflux for 2 h, reduced in volume on a rotary evaporator, and triturated with Et_2O . The resulting HBr salt of 45 was filtered and dissolved in water (250 mL). The solution was basified with dilute Na_2CO_3 solution and extracted with CHCl_3 (3×100 mL). The combined CHCl_3 extract was decolorized (charcoal) and evaporated. Trituration with Et_2O gave 45 (26.8 g, 55% overall from 2-aminoquinoline) identical in all respects with that prepared from 43. In this way substituted 2-aminoquinolines were used to prepare the imidazo[1,2-*a*]quinoline-2-carboxylates, including 61, 79, 100, and 111.

Imidazo[1,2-*a*]quinoline-2-carboxylic Acid (47). Ester 45 (2.0 g, 8.3 mmol) was suspended in EtOH (40 mL)–water (20 mL) and 1 N NaOH (9 mL) was added. The mixture was heated under reflux for 0.5 h and the hot solution was acidified with 1 N HCl (9.5 mL). The mixture was cooled in an ice bath to crystallize the acid 47 (Table II); IR 1710, 3140, 2100–3000, and 3200–3750 cm^{-1} . Acid 46 (Table II) was prepared in the same way from ester 44.

The following acids were prepared in a similar manner from the esters obtained from the corresponding 2-quinolinamines: compounds 59, 60, 62–65, 72, 73, 80–83, 90, 97–99, 104–110, 112, and 113 with yields in the range 63–96% (Tables II and III).

***N*-(1*H*-Tetrazol-5-yl)imidazo[1,2-*a*]quinoline-2-carboxamide (48) and 8-methoxy-*N*-(1*H*-tetrazol-5-yl)imidazo[1,2-*a*]quinoline-2-carboxamide (96)** were synthesized from the corresponding acids 47 and 81 as for the preparation of 26 (Tables II and III).

2-Chloroethyl Imidazo[1,2-*a*]quinoline-2-carboxylate (49) and (2,2-Dimethyl-1,3-dioxolan-4-yl)methyl Imidazo[1,2-*a*]quinoline-2-carboxylate (50). Dried acid 47 (5 g, 23.6 mmol) was added to SOCl_2 (90 mL) containing DMF (10 drops) and the mixture was heated under reflux for 3 h. The excess SOCl_2 was removed in vacuo by azeotrope with toluene and trituration with Et_2O to give the crude acid chloride. This solid (3 g, 13 mmol) was added to a solution of glycerol acetonide (1.8 g, 13.6 mmol) and NEt_3 (1.46 g, 14.5 mmol) in $\text{C}_2\text{H}_4\text{Cl}_2$ (100 mL) and the mixture obtained was heated under reflux overnight. The solution was then evaporated and the residue was chromatographed (SiO_2 ; CHCl_3) to give two products. The less polar material was recrystallized from EtOAc to give the chloroethyl ester 49 (Table II). The more polar material was recrystallized from $\text{CHCl}_3\text{-Et}_2\text{O}$ to give 50 (Table II).

2,3-Dihydroxypropyl Imidazo[1,2-*a*]quinoline-2-carboxylate (51). A suspension of glycerol acetonide ester 50 (0.45 g, 1.38 mmol) in water (90 mL) containing citric acid monohydrate (0.48 g, 2.3 mmol) was heated under reflux for 4 h. After cooling, saturated Na_2CO_3 solution was added to precipitate the ester 51 (Table II).

Imidazo[1,2-*a*]quinoline-2-carboxamide (52). The ester 45 (0.5 g, 2.1 mmol) was dissolved in EtOH (200 mL) and sodium (25 mg, 1.1 mg-atom) was added. NH_3 gas was bubbled through the solution for 5 h. Stirring was continued for 24 h and then more NH_3 gas was bubbled through for 3 h. The solution was concentrated, cooled in an ice bath, acidified with dilute HCl , and then basified with NaHCO_3 solution. The solution was extracted with CHCl_3 (2×100 mL), the combined CHCl_3 extract was evaporated, and the residue was triturated with Et_2O to give the

the amide 52 (Table II). Amide 94 (Table III) was prepared in the same way from the ester precursor of acid 81.

Imidazo[1,2-*a*]quinoline-2-methanol (53). Ester 45 (7.2 g, 30 mmol) was dissolved in dry THF (140 mL) and stirred while being heated under reflux with LiBH_4 (1.0 g, 46 mmol) for 20 h. On cooling the solution was acidified with 2 N HCl , stirred for 1 h, basified with saturated Na_2CO_3 solution, and evaporated. Water (500 mL) was added and the solution was extracted with CHCl_3 (2×200 mL). The combined CHCl_3 extract was washed once with water and evaporated. Addition of $\text{EtOAc-Et}_2\text{O}$ gave the alcohol 53 (Table II). Methanol 91 was prepared in the same way from the ester precursor of acid 81 and likewise 101 from 100 (Table III).

Imidazo[1,2-*a*]quinoline-2-carboxaldehyde (54). The alcohol 53 (4.2 g, 21.2 mmol) in CHCl_3 (500 mL) was heated under reflux with activated MnO_2 (16 g, 184 mmol) for 4 h and then stirred at room temperature overnight. The mixture was filtered through a Celite pad and the pad was washed with CHCl_3 . The CHCl_3 filtrate was evaporated and the residue was triturated with Et_2O to give the aldehyde 54 (Table II). Aldehyde 92 was prepared in the same way from methanol 91, and likewise 102 from 101 (Table III).

Imidazo[1,2-*a*]quinoline-2-methanamine Dihydrochloride (56). The aldehyde 54 (2.4 g, 12.2 mmol) in EtOH (60 mL) was treated with a solution of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.0 g, 14.4 mmol) and NaOAc (1.35 g, 16.5 mmol) in water (20 mL). The mixture was heated under reflux for 2 h and then concentrated under reduced pressure. Water (50 mL) was added to crystallize imidazo[1,2-*a*]quinoline-2-carboxaldehyde oxime (55) (2.55 g, 98%), mp 224–226 °C (from $\text{CHCl}_3\text{-MeOH}$). A solution of 55 (1.0 g, 4.74 mmol) in 0.25 N methanolic HCl (100 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd/C (100 mg). After 4 h absorption of hydrogen ceased (125 mL used), further portion of catalyst (200 mg) was added and hydrogenation was continued at 50 °C for 2 h (62 mL further used). The mixture was then filtered through Celite and evaporated. Trituration with dry Et_2O gave 56 (Table II). Methanamine 95 was prepared in the same way from aldehyde 92 (Table III).

2-(1*H*-Tetrazol-5-yl)imidazo[1,2-*a*]quinoline (58). The oxime 55 (2.0 g, 9.5 mmol) in Ac_2O (20 mL) was stirred while being heated under reflux for 3 h and then allowed to stand overnight at room temperature. The solution was poured into saturated Na_2CO_3 solution (200 mL) and extracted with CHCl_3 (3×100 mL). The combined CHCl_3 extract was washed with dilute Na_2CO_3 solution (100 mL) and water (100 mL) and then evaporated. Trituration with Et_2O gave imidazo[1,2-*a*]quinoline-2-carbonitrile (57) (1.3 g, 71%) as pale yellow crystals, mp 244–246 °C (from $\text{CHCl}_3\text{-Et}_2\text{O}$). The nitrile 57 (1.0 g, 5.2 mmol) in DMF (50 mL) was stirred at 40 °C during the addition of NH_4Cl (0.4 g, 7.5 mmol) and NaN_3 (0.45 g, 6.9 mmol). The temperature was raised to 100 °C and stirring was continued for 16 h. The mixture was treated with NH_4Cl (0.2 g, 3.75 mmol) and NaN_3 (0.225 g, 3.45 mmol) and stirred for a further 6 h at 120 °C. A final addition of NH_4Cl (0.2 g, 3.75 mmol) and NaN_3 (0.225 g, 3.45 mmol) was made, and the resultant mixture was stirred for 16 h at 100 °C, then cooled to room temperature, and treated dropwise with water (50 mL) to precipitate 58 (Table II). Compounds 93 and 103 were prepared in the same way from the oximes of aldehydes 92 and 102 (Table III).

5-(Methylsulfonyl)imidazo[1,2-*a*]quinoline-2-carboxylic Acid (67). 2-Amino-4-(methylsulfinyl)quinoline was reacted with ethyl bromopyruvate as in the preparation of 45 to give ethyl 5-(methylsulfinyl)imidazo[1,2-*a*]quinoline-2-carboxylate. This ester (1.5 g, 5 mmol) was stirred in AcOH (50 mL) containing 30% H_2O_2 (5 mL, 44 mmol) for 1 week at room temperature. The solution was then basified with saturated Na_2CO_3 solution to give ethyl 5-(methylsulfonyl)imidazo[1,2-*a*]quinoline-2-carboxylate (66) (1.26 g, 80%), mp 246–247 °C (from $\text{CHCl}_3\text{-Et}_2\text{O}$). Anal. ($\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$) C, H, N, S. Hydrolysis of the ester as in the preparation of 47 gave the acid 67 (Table II).

5-(Methylsulfonimidoyl)imidazo[1,2-*a*]quinoline-2-carboxylic Acid (69). Ethyl 5-(methylsulfonyl)imidazo[1,2-*a*]quinoline-2-carboxylate (66) (1.5 g, 5 mmol) was stirred in PPA (40 mL) at 60 °C during the addition of NaN_3 (400 mg, 6.2 mmol) over a 2-h period. Stirring and heating were continued for a further 6 h while two further portions of NaN_3 (2×150 mg, 2

$\times 2.3$ mmol) were added. The mixture was cooled and poured into ice-water (250 mL), basified with Na_2CO_3 solution, and extracted with EtOAc (2×300 mL). The combined EtOAc extract was washed once with water, dried, and evaporated. Trituration with Et_2O gave ethyl 5-(methylsulfonimidoyl)imidazo[1,2-*a*]-quinoline-2-carboxylate (68) (1.1 g, 70%), mp 226–228 °C (from EtOAc). Anal. ($\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$) C, H, N. Hydrolysis of the ester as in the preparation of 47 gave the acid 69 (Table II).

5-Phenylimidazo[1,2-*a*]quinoline-2-carboxylic Acid (71). 2-Amino-6-chloro-4-phenylquinoline was reacted with ethyl bromopyruvate as in the preparation of 45 to give ethyl 7-chloro-5-phenylimidazo[1,2-*a*]quinoline-2-carboxylate. A mixture of this ester (2.1 g, 6 mmol), NaOAc (1.0 g, 12.2 mmol), Pd/C (5%, 250 mg), DME (75 mL), and EtOH (75 mL) was stirred under H_2 at atmospheric pressure for 2 h. After being filtered through Celite, the solution was evaporated and the residue was dissolved in CHCl_3 (200 mL). After the mixture was washed with water (100 mL), the solvent was removed under reduced pressure and the residue triturated with Et_2O to give ethyl 5-phenylimidazo[1,2-*a*]quinoline-2-carboxylate (70) (1.82 g, 98%), mp 144–145 °C (from CHCl_3 -Et₂O). Anal. ($\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_2$) H, N; C: calcd, 56.5; found, 57.8. Hydrolysis of the ester as in the preparation of 47 gave the acid 71 (Table II).

Ethyl 4-Cyanoimidazo[1,2-*a*]quinoline-2-carboxylate (74). 2-Amino-3-(hydroxymethyl)quinoline was reacted with ethyl bromopyruvate as in the preparation of 45 to give ethyl 4-(hydroxymethyl)imidazo[1,2-*a*]quinoline-2-carboxylate. The hydroxymethyl group was converted into a cyano group via the aldehyde and oxime, as in the preparation of 57 from 53, to give 74 (Table II).

1-Bromoimidazo[1,2-*a*]quinoline-2-carboxylic Acid (76). A solution of Br_2 in AcOH (10% w/v, 17.6 mL, 11 mmol) was added dropwise to a stirred solution of 45 (2.4 g, 10 mmol) and NaOAc (1 g, 12.2 mmol) in AcOH (50 mL). The mixture was warmed on a water bath for 1 h and poured into aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (1%, 200 mL). The precipitate was filtered and dissolved in CHCl_3 (100 mL). The solution was washed with aqueous Na_2CO_3 and evaporated to give ethyl 1-bromoimidazo[1,2-*a*]quinoline-2-carboxylate (75) (2.85 g, 90%), mp 132–133 °C (from CHCl_3 -Et₂O). Anal. ($\text{C}_{14}\text{H}_{11}\text{BrN}_2\text{O}_2$) C, H, Br, N. Hydrolysis of 75 as in the preparation of 47 gave 76 (Table II).

5-Chloro-1-methylimidazo[1,2-*a*]quinoline-2-carboxylic acid (78) (Table II) was prepared by reacting 2-amino-4-chloroquinoline with ethyl 3-bromo-2-oxobutanoate as in the synthesis of 45 and hydrolyzing the resulting ester 77 as in the preparation of 47. Acid 89 (Table III) was prepared in the same way from 2-amino-7-chloroquinoline.

8-(Methylsulfinyl)imidazo[1,2-*a*]quinoline-2-carboxylic Acid (85). Ethyl 8-(methylthio)imidazo[1,2-*a*]quinoline-2-carboxylate (6 g, 21 mmol), obtained from 2-amino-7-(methylthio)quinoline, was dissolved in MeOH (300 mL) and a solution of NaOAc (6 g, 28 mmol) in water (30 mL) was added. The mixture was allowed to stand at room temperature for 65 h and then filtered and the filtrate was evaporated. The residue was dissolved in CHCl_3 (100 mL) and the organic solution was washed with water and evaporated to give a cream solid, which was chromatographed (SiO_2 ; 5% MeOH in CHCl_3) to give ethyl 8-(methylsulfinyl)imidazo[1,2-*a*]quinoline-2-carboxylate (84) (4.88 g, 77%), mp 225–227 °C (from MeOH). Anal. ($\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$) C, H, N, S. Hydrolysis of 84 as in the preparation of 47 gave the acid 85 (Table III).

8-(Methylsulfonyl)imidazo[1,2-*a*]quinoline-2-carboxylic Acid (87). The methylthio ester used in the preparation of 84 (2.5 g, 8.7 mmol) was suspended in AcOH (50 mL) and hydrogen peroxide (100 w/v, 5 mL) was added. The mixture was allowed to stand at room temperature for 3 days, then poured into water (300 mL), and extracted with CHCl_3 (2×150 mL). The combined CHCl_3 extract was washed with dilute Na_2CO_3 solution and water and evaporated to give a yellow solid, which was chromatographed (SiO_2 ; 5% MeOH in CH_2Cl_2) to give ethyl 8-(methylsulfonyl)imidazo[1,2-*a*]quinoline-2-carboxylate (86) (1.71 g, 62%), mp 249–251 °C, (from CHCl_3 -EtOAc). Anal. ($\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$) C, H, N, S. Hydrolysis of 86 as in the preparation of 47 gave the acid 87 (Table III).

8-(Methylsulfonimidoyl)imidazo[1,2-*a*]quinoline-2-carboxylic acid (88) (Table III) was prepared by hydrolysis of

the corresponding ethyl ester, which was obtained from reaction of 86 with NaN_3 as in the synthesis of 68.

(c) **Imidazo[1,2-*a*]quinoxalines.** 2-Aminoquinoxaline and 2-aminoquinoxaline-3-carboxamide were prepared as described.⁴²

2-Amino-6,7-dichloroquinoxaline. A solution of 4,5-dichloro-1,2-phenylenediamine (4 g, 22.6 mmol) in AcOH (50 mL) was added to a solution of alloxan hydrate (3.6 g, 22.4 mmol) and boric acid (0.6 g, 9.8 mmol) in AcOH (50 mL). The reaction mixture was stirred at room temperature overnight when a brown solid separated. The product was filtered, washed well with water, and dried to give the dichloroalloxazine (5.43 g, 85%), as a yellow crystalline solid, mp >370 °C (from EtOH).

The dichloroalloxazine (2 g, 7.1 mmol) was dissolved in concentrated H_2SO_4 (10 mL), heated gradually to 240 °C, and kept at this temperature for 10 min. The mixture was cooled, poured onto ice-water, and basified with aqueous NaOH (2 N, 100 mL). The aqueous solution was extracted with Et_2O (4×100 mL) and the ethereal solution so obtained was washed once with water (50 mL), dried, and evaporated. Trituration with Et_2O gave 2-amino-6,7-dichloroquinoxaline (0.73 g, 48%), as an orange crystalline solid, mp 220–222 °C (from EtOH). Anal. ($\text{C}_8\text{H}_5\text{Cl}_2\text{N}_3$) C, H, Cl, N.

Imidazo[1,2-*a*]quinoxaline-2-carboxylic acid (114) (Table IV) was prepared by reacting ethyl bromopyruvate with 2-aminoquinoxaline as in the synthesis of 45 and then hydrolyzing the ester as in the synthesis of 47. Compounds 115–117 were prepared in the same way from the corresponding quinoxalines.

N-(1*H*-Tetrazol-5-yl)imidazo[1,2-*a*]quinoxaline-2-carboxamide (118) (Table IV) was prepared from the acid 114 as for 26.

Imidazo[1,2-*a*]quinoxaline-2-methanol (120). Ethyl imidazo[1,2-*a*]quinoxaline-2-carboxylate (14 g, 98 mmol) obtained in the preparation of 114 was dissolved in dry THF (320 mL) and stirred and heated under reflux for 20 h with LiBH_4 (2 g, 92 mmol). The mixture was then cooled and poured into aqueous HCl (2 N, 200 mL). After 1 h the solution was made basic with Na_2CO_3 and extracted with EtOAc (2×200 mL). The combined EtOAc extract was dried and evaporated. Chromatography of the residue (SiO_2 ; 3% MeOH in CHCl_3) gave 4,5-dihydroimidazo[1,2-*a*]quinoxaline-2-methanol (119) (9.56 g, 82%), mp 172–174 °C (from EtOAc). A mixture of 119 (2.3 g, 11.5 mmol) in CHCl_3 (300 mL) and activated MnO_2 (4 g, 46 mmol) was stirred vigorously for 2 h at room temperature and then filtered through Celite. The filtrate was evaporated to a small volume and the solution was cooled in an ice bath to crystallize 120 (Table IV).

Imidazo[1,2-*a*]quinoxaline-2-carboxaldehyde (121). A solution of 119 (2.5 g, 12.5 mmol) in CHCl_3 (500 mL) was heated under reflux for 3 h with activated MnO_2 (12 g, 138 mmol). The mixture was then filtered through Celite and the filtrate was evaporated. Trituration with Et_2O gave 121 (Table IV).

2-(1*H*-Tetrazol-5-yl)imidazo[1,2-*a*]quinoxaline (122) (Table IV) was prepared from 121 as in the synthesis of 58 from 54.

(d) **Imidazo[1,2-*a*]quinoxalin-4(5*H*)-ones.** **Ethyl 4,5-Dihydro-4-oxoimidazo[1,2-*a*]quinoxaline-2-carboxylate (123).** 2-Amino-3-chloroquinoxaline¹⁶ (6.1 g, 34 mmol) and ethyl bromopyruvate (8.0 g, 41 mmol) in dimethoxyethane (120 mL) were stirred at room temperature overnight. A small amount of yellow crystalline solid was filtered and the filtrate was stood at room temperature. Over the next 2 weeks four further crops of quaternary salt were filtered (total yield 7.81 g, 61%); IR 1763 cm^{-1} (ester carbonyl). The quaternary salt (6.5 g, 17.5 mmol) was heated under reflux in EtOH (500 mL) for 2 h to give a clear yellow solution. The EtOH solution was concentrated to ca. 50 mL to crystallize 123 (3.75 g, 85%; 52% overall), mp 292–293 °C (from EtOH); IR 743, 1261, 1274, 1538, 1701 (br), and 3135 cm^{-1} ; ¹H NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.33 (3 H, t, CH_3), 3.40 (1 H, br s, 4-OH), 4.30 (2 H, q, CH_2), 7.0–7.45 (3 H, m, Ar H), 8.05 (1 H, m, 9-H), and 9.05 (1 H, s, 1-H). IR and NMR suggest it may exist in the tautomeric 4-OH form. Anal. ($\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$) C, H, N. Hydrolysis of 123 as in the preparation of 47 gave the acid 127 (Table V).

5-Alkyl-4,5-dihydro-4-oxoimidazo[1,2-*a*]quinoxaline-2-carboxylic Acids (128–131). A solution of 123 in DMF was treated with NaH (1 equiv) followed by an alkyl iodide (1.1 equiv) to yield the corresponding ethyl 5-alkyl-4,5-dihydro-4-oxoimidazo[1,2-*a*]quinoxaline-2-carboxylate, for example 5-ethyl (124), 5-propyl (125), and 5-benzyl (126) (Table V). Hydrolysis of these

esters as in the preparation of 47 gave the corresponding acids 128–131 (Table V).

7,8-Dichloro-4,5-dihydro-4-oxoimidazo[1,2-*a*]quinoxaline-2-carboxylic Acid (133). 2,3,6,7-Tetrachloroquinoxaline⁴³ (3.46 g, 13 mmol) was added to EtOH (30 mL) and the mixture was saturated with NH₃ gas at 0 °C. The reaction mixture was shaken under pressure (60 psi) at 80 °C overnight. The solution was then cooled, evaporated, and triturated with water to give a buff crystalline solid, which was purified by chromatography (SiO₂; 50% EtOAc in 40–60 °C petroleum ether) to give 2-amino-6,7-dichloro-3-ethoxyquinoxaline (1.36 g, 41%) as a pale yellow crystalline solid: mp 191–193 °C (from EtOAc–Et₂O); IR 882, 1033, 1231, 1281, 1471, 1660, and 3500 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 1.39 (3 H, t, CH₃), 4.43 (2 H, q, CH₂), 7.10 (2 H, br s, NH₂), and 7.52, 7.63 (2 × 1 H, 2 s, 5- and 8-H). Anal. (C₁₀H₈Cl₂N₃O) C, H, N. A solution of this amine (1.0 g, 3.9 mmol) and ethyl bromopyruvate (1.0 g, 5.1 mmol) in dimethoxyethane (50 mL) was stirred at room temperature for 1 week. A pinkish white solid was filtered and chromatographed (SiO₂; CHCl₃) to give ethyl 7,8-dichloro-4-ethoxyimidazo[1,2-*a*]quinoxaline-2-carboxylate (132) (0.15 g, 11%): mp 256–258 °C (from EtOH–Et₂O); IR 1700, 3130 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 1.37 (6 H, t, 2 CH₃), 4.40 (4 H, q, 2 CH₂), 7.82 (1 H, s, 6-H), 8.68 (1 H, s, 9-H), and 9.26 (1 H, s, 1-H). Anal. (C₁₅H₁₃Cl₂N₃O₃) C, H, N. To the ester 132 (0.14 g, 0.39 mmol) suspended in EtOH (10 mL) was added aqueous NaOH (1 N, 3 mL) and water (20 mL). The mixture so obtained was heated under reflux overnight and then cooled and acidified with concentrated HCl to pH 2–3 to precipitate 133 (Table V); IR 1700, 3130, and 3150–3410 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 7.42 (1 H, s, 6-H), 8.54 (1 H, s, 9-H), and 9.07 (1 H, s, 1-H).

5-Ethyl-4,5-dihydro-4-oxoimidazo[1,2-*a*]quinoxaline-2-methanol (134) (Table V) was prepared from 123 as for the synthesis of 53.

5-Ethyl-4,5-dihydro-4-oxoimidazo[1,2-*a*]quinoxaline-2-carboxaldehyde (135) (Table V) was prepared from 134 as for the synthesis of 54.

5-Ethyl-4,5-dihydro-4-oxo-*N*-(1*H*-tetrazol-5-yl)imidazo[1,2-*a*]quinoxaline-2-carboxamide (136) (Table V) was prepared from 129 as for the synthesis of 26.

(e) **Imidazo[1,2-*a*]quinazolin-5(4*H*)-ones. 4-Ethyl-4,5-dihydro-5-oxoimidazo[1,2-*a*]quinazolin-2-carboxylic Acid (138).** 2-Amino-3-ethylquinazolin-4(3*H*)-one⁴⁴ (2.90 g, 15.3 mmol) and ethyl bromopyruvate (4.5 g, 23 mmol) were dissolved in dimethoxyethane (50 mL), and the mixture was stirred for 3 h. EtOH (50 mL) was added and the mixture was heated under reflux for 3 h and then allowed to stand at room temperature for 2 days to crystallize ethyl 4-ethyl-4,5-dihydro-5-oxoimidazo[1,2-*a*]quinazolin-2-carboxylate (137) (Table VI); IR 1672, 1713, and 3135 cm⁻¹; ¹H NMR (CDCl₃) δ 1.40 (6 H, t, 2 CH₃), 4.38 (2 H, q, CH₂), 4.35 (2 H, q, CH₂), 7.3–8.0 (3 H, m, Ar H), 8.09 (1 H, s, 1-H), and 8.30 (1 H, m, 6-H). Hydrolysis of 137 as in the preparation of 47 gave the acid 138 (Table VI).

(f) **Pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones.** 1-Substituted benzimidazoles were prepared⁴⁵ by treating benzimidazoles with alkyl or alkenyl bromo or iodo compounds in the presence of base. Chromatography (Al₂O₃; CHCl₃) gave the 1-substituted benzimidazoles as crude oils, which were used without distillation. 1-Phenylbenzimidazole⁴⁶ was prepared from *N*-phenyl-*o*-phenylenediamine by cyclization with formic acid.

1-[(Ethoxycarbonyl)methyl]-3-ethylbenzimidazolium Bromide (140). Crude 1-ethylbenzimidazole (30.7 g, 0.21 mol) was dissolved in Et₂O (300 mL) and ethyl bromoacetate (39 g, 0.234 mol) was added. After the mixture was allowed to stand at room temperature for 3 days, a crystalline precipitate of 140 was formed (53.0 g, 57%); mp 119–121 °C (from MeOH–Et₂O); IR 760, 1231, 1570, 1753, 3415, and 3490 cm⁻¹; ¹H NMR (CDCl₃)

δ 1.27 (3 H, t, ester CH₃), 1.70 (3 H, t, 3-CH₂CH₃), 4.26 (2 H, q, ester CH₂), 4.60 (2 H, q, 3-CH₂CH₃), 5.65 (2 H, s, 1-CH₂), 7.4–8.0 (4 H, m, Ar H), and 10.93 (1 H, s, 2-H). Anal. (C₁₃H₁₇BrN₂O₂H₂O) C, H, Br, N.

Ethyl 5-Ethyl-4,5-dihydro-4-oxopyrrolo[1,2-*a*]quinoxaline-2-carboxylate (144). The quaternary salt 140 (20.0 g, 64 mmol) was dissolved in DMF (100 mL), and NEt₃ (7.4 g, 73 mmol) and ethyl propiolate (8.05 g, 83 mmol) were added. The mixture was allowed to stand at room temperature for 3 days, and then EtOAc (200 mL) and water (200 mL) were added. The EtOAc layer was separated and the aqueous layer was further extracted with EtOAc (3 × 100 mL). The combined EtOAc layer was washed with water (200 mL), dried, and evaporated. The reddish oil formed was triturated with Et₂O to give 144 (9.1 g, 50%) as buff needles: mp 184–186 °C (from Et₂O); IR 739, 747, 759, 1260, 1276, 1653, 1714, and 3125 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (3 H, t, 5-CH₂CH₃), 1.36 (3 H, t, ester CH₃), 4.22 (2 H, q, 5-CH₂CH₃), 4.28 (2 H, q, ester CH₂), 7.0–7.4 (3 H, m, Ar H), 7.45 (1 H, d, *J* = 1.5 Hz, 3-H), 7.5–7.75 (1 H, m, 9-H), 8.05 (1 H, d *J* = 1.5 Hz, 1-H). Anal. (C₁₆H₁₆N₂O₃) C, H, N. Esters 142 and 143 (Table VII) were prepared in the same way from the corresponding salts.

5-Ethyl-4,5-dihydro-4-oxopyrrolo[1,2-*a*]quinoxaline-2-carboxylic Acid (146). The ester 144 (6.5 g, 23 mmol) was suspended in EtOH (100 mL) and heated on a steam bath. A solution of NaOH (2.0 g, 50 mmol) in water (200 mL) was added and the mixture was heated until a clear solution was obtained. The solution was filtered hot and acidified to pH 2–3 (concentrated HCl). On cooling in an ice bath, crystallization gave 146 (Table VII); IR 738, 765, 1283, 1311, 1654, 1696, and 3140 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 1.22 (3 H, t, CH₃), 4.19 (2 H, q, CH₂), 7.21 (1 H, d, *J* = 1 Hz, 3-H), 7.1–7.6 (3 H, m, Ar H), 8.20 (1 H, dd, 9-H), and 8.60 (1 H, d, *J* = 1 Hz, 1-H). Acids 145 and 147–157 (Table VII) were prepared in the same way from the corresponding esters.

5-Ethyl-4,5-dihydro-4-oxopyrrolo[1,2-*a*]quinoxaline-2-methanol (158) (Table VII) was prepared from 150 as for the synthesis of 53.

5-Ethyl-4,5-dihydro-4-oxopyrrolo[1,2-*a*]quinoxaline-2-carboxaldehyde (159) (Table VII) was prepared from 158 as for the synthesis of 54.

5-Ethyl-2-(1*H*-tetrazol-5-yl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (160) (Table VII) was prepared from 159 as in the synthesis of 58 from 54.

5-Ethyl-4,5-dihydro-4-oxo-*N*-(1*H*-tetrazol-5-yl)pyrrolo[1,2-*a*]quinoxaline-2-carboxamide (161) (Table VII) was prepared from 146 as for the synthesis of 26.

Dimethyl 5-Ethyl-4,5-dihydro-4-oxopyrrolo[1,2-*a*]quinoxaline-2,3-dicarboxylate (162). The quaternary salt 140 (2.7 g, 8.6 mmol) was dissolved in DMF (50 mL), and NEt₃ (1.0 g, 10 mmol) and dimethyl acetylenedicarboxylate (1.5 g, 10.5 mmol) were added. The mixture was warmed on a water bath for 15 min and then allowed to stand at room temperature overnight. Workup as for 144 gave 162 (1.4 g, 50%) as buff crystals: mp 198–200 °C (from Et₂O); IR 742, 1261, 1278, 1660, 1722, 1749, and 3160 cm⁻¹; ¹H NMR (CDCl₃) δ 1.31 (3 H, t, CH₂CH₃), 3.80 (3 H, s, CH₃), 3.97 (3 H, s, CH₃), 4.21 (2 H, q, CH₂CH₃), 7.0–7.4 (3 H, m, Ar H), 7.5–7.8 (1 H, m, 9-H), and 8.02 (1 H, s, 1-H). Anal. (C₁₇H₁₆N₂O₅) C, H, N.

5-Ethyl-4,5-dihydro-3-(methoxycarbonyl)-4-oxopyrrolo[1,2-*a*]quinoxaline-2-carboxylic Acid (163). The diester 162 (0.85 g, 2.6 mmol) was suspended in EtOH (30 mL) and a solution of NaOH (0.5 g, 12.5 mmol) in water (10 mL) was added. The mixture was heated on a water bath for 2 h and then filtered and acidified (concentrated HCl) to pH 2–3 to precipitate 163 (Table VII).

(g) **Pyrazolo[2,3-*a*]quinoxalin-4(5*H*)-ones. 4,5-Dihydro-4-oxopyrazolo[2,3-*a*]quinoxaline-2-carboxylic Acid (166).** A suspension of the diacid¹⁸ 165 (7.65 g, 0.027 mol), platinum oxide (200 mg), and 10% Pd/C (200 mg) in aqueous NaOH (10%) was stirred under H₂ (4 atm) for 6 h. The mixture was filtered through Celite and acidified with concentrated HCl to pH 2–3 to give the acid 166 (Table VIII).

Methyl 4,5-Dihydro-4-oxopyrazolo[2,3-*a*]quinoxaline-2-carboxylate (167). A suspension of acid 166 (3.5 g, 15.3 mmol) in methanolic HCl (5%, 250 mL) was heated on a water bath for 3 h. On cooling, the ester 167 (3.4 g, 92%), mp 329–331 °C,

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crystallized as white needles (from EtOAc). Anal. (C₁₂H₉N₃O₃) C, H, N.

Methyl 4,5-Dihydro-5-methyl-4-oxopyrazolo[2,3-a]-quinoxaline-2-carboxylate (168). A solution of ester 167 (1.1 g, 4.5 mmol), NaH (60% dispersion in oil; 0.4 g, 10 mmol), and MeI (1.14 g, 8.0 mmol) in DMF (25 mL) was stirred at room temperature for 3 h and cooled, after which water (100 mL) and EtOAc (150 mL) were added. The EtOAc layer was separated, washed (H₂O), and evaporated to give 168 (0.75 g, 71%): mp 240–242 °C as colorless needles (from Et₂O); IR 742, 1272, 1348, 1660, 1725, and 3140 cm⁻¹; ¹H NMR (CDCl₃) δ 3.70 (3 H, s, 5-CH₃), 3.97 (3 H, s, ester CH₃), 7.1–7.6 (3 H, m, Ar H), 7.61 (1 H, s, 3-H), and 8.3–8.6 (1 H, m, 9-H). Anal. (C₁₃H₁₁N₃O₃) C, H, N.

Use of EtI in place of MeI gave methyl 4,5-dihydro-5-ethyl-4-oxopyrazolo[2,3-a]quinoxaline-2-carboxylate (169), mp 177–178 °C (from Et₂O) [anal. (C₁₄H₁₃N₃O₃) C, H, N], but when PrI was employed, the aqueous workup was carried out at 50 °C to hydrolyze the intermediate ester to acid 172 (Table VIII). Acids 170 and 171 were obtained from esters 168 and 169 as in the preparation of 47.

(h) **Imidazo[1,5-a]quinoxalinones, Triazolo[1,5-a]quinoxalinones, and Triazolo[1,5-a]benzoxazinones. Methyl 4,5-Dihydro-4-oxoimidazo[1,5-a]quinoxaline-3-carboxylate (174).** A solution of diamine 173^{10,25} (1.0 g, 4.3 mmol) and *p*-TsOH (5 mg) in triethyl orthoformate (5 g, 34 mmol) was refluxed for 2 h, cooled, and diluted with Et₂O to precipitate a red solid. This was filtered and chromatographed twice (SiO₂, EtOAc and 5% MeOH–CHCl₃) to give 174 (0.81 g, 85%): mp 270–271 °C (EtOAc–CHCl₃); IR 1445, 1485, 1520, 1565, 1630, 1680, 1735, 3000, 3110, 3270, and 3520 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.8 (3 H, s, ester CH₃), 7.1–7.4 (3 H, m, Ar H), 8.1–8.4 (1 H, m, 9-H), 9.0 (1 H, s, 1-H), 11.3 (1 H, br s, 5-H). Anal. (C₁₂H₉N₃O₃) C, H, N.

Methyl 4,5-Dihydro-1-methyl-4-oxoimidazo[1,5-a]quinoxaline-3-carboxylate (175). This was prepared in the same way as 174 but with triethyl orthoacetate (yield 62%): mp 255–252 °C; IR 1560, 1620, 1705, 1735, 2920, 3000, 3100, and 3450 cm⁻¹; ¹H NMR (CDCl₃) δ 2.85 (3 H, s, 1-CH₃), 3.75 (3 H, s, ester CH₃), 7.3–8.0 (4 H, m, Ar H), 11.6 (1 H, s, 5-H). Anal. (C₁₃H₁₁N₃O₃) C, H, N.

4,5-Dihydro-4-oxoimidazo[1,5-a]quinoxaline-3-carboxylic Acid (178). A suspension of 174 (1 g) in aqueous EtOH (50%, 20 mL) containing KOH (1 g) was refluxed until clear, cooled, acidified (concentrated HCl), and filtered to give 178 (Table IX).

4,5-Dihydro-1-methyl-4-oxoimidazo[1,5-a]quinoxaline-3-carboxylic acid (179) (Table IX) was prepared from 175 in the same way as 178.

4,5-Dihydro-1-ethyl-4-oxoimidazo[1,5-a]quinoxaline-3-carboxylic Acid (180). A suspension of 176⁹ (100 mg) in aqueous MeOH (50%; 10 mL) containing NaOH (100 mg) was refluxed for 2 h, cooled, and acidified to give 180 (Table IX).

4,5-Dihydro-1-benzyl-4-oxoimidazo[1,5-a]quinoxaline-3-carboxylic acid (181) (Table IX) was prepared from 177⁹ in the same way as 180.

Methyl 4-Oxo[1,2,3]triazolo[3,4-c][1,4]benzoxazine-3-carboxylate (183). A solution of 182²¹ (1.2 g, 5 mmol) in dioxane (5 mL) and Et₂O (10 mL) at 0 °C was treated with Cl₃CCO₂H (300 mg) and amyl nitrite (600 mg), left overnight at 0 °C, diluted with EtOH, and filtered. The filtrate was evaporated and the residue chromatographed (SiO₂; CHCl₃) to give 183 (800 mg) (Table IX): IR 1510, 1610, 1620, 1740, 1770, and 3100 cm⁻¹; ¹H NMR (CDCl₃) δ 3.9 (3 H, s, CH₃), 7.5 (3 H, m, Ar H), 8.3 (1 H, d, 9-H).

Methyl 4,5-dihydro-4-oxo[1,2,3]triazolo[1,5-a]quinoxaline-3-carboxylate (184) was prepared from 173^{10,25} in the same way as 183 (yield 60%): mp 232–234 °C (EtOAc–CHCl₃); IR 1450, 1495, 1550, 1630, 1700, 1735, and 3320 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.95 (3 H, s, CH₃), 7.3–7.7 (3 H, m, Ar H), 8.4 (1 H, br d, 9-H). Anal. (C₁₁H₈N₄O₃) C, H, N: calcd, 22.9; found, 24.6.

4,5-Dihydro-4-oxo[1,2,3]triazolo[1,5-a]quinoxaline-3-carboxylic acid (185) (Table IX) was prepared by refluxing a suspension of 184 and NaHCO₃ in aqueous MeOH followed by precipitation with concentrated HCl.

(i) **Miscellaneous Ring Systems. Ethyl Pyrrolo[1,2-a]quinoline-2-carboxylate (187).** To a refluxing solution of

quinaldine (9 g, 63 mmol) in EtOH (100 mL) was added over 0.5 h ethyl bromopyruvate (13 g, 67 mmol) in EtOH (50 mL). Heating was continued for a further 1.5 h, the solvent was evaporated, and the residue was partitioned between dilute HCl–EtOAc. The organic layer was separated, washed with dilute Na₂CO₃ solution and water, and evaporated to give a deep red oil, which was chromatographed (SiO₂; CHCl₃) to give 187 as lemon needles (3.41 g, 23%), mp 77–78 °C (Et₂O; petroleum ether). Anal. (C₁₅H₁₃NO₂) C, H, N.

Pyrrolo[1,2-a]quinoline-2-carboxylic Acid (188). A solution of 187 (1.2 g) in EtOH (10 mL) and aqueous NaOH (1 N, 1 mL) was refluxed for 4 h, cooled, and acidified (concentrated HCl) to give 188 (Table IX).

5-Oxo-5-phenylimidazo[3,4-b][1,2,4]benzothiadiazine-2-carboxylic Acid (195). Ethyl bromopyruvate (750 mg) was added to a solution of 1-oxo-1-phenylbenzothiadiazin-3-amine (192)⁴⁷ (800 mg) in THF (40 mL) at 0 °C. After the mixture was allowed to stand at room temperature overnight, more ethyl bromopyruvate (300 mg) was added and 4 h later the solvent was evaporated. The residue was refluxed in EtOH for 36 h, and after evaporation of the solvent, the residue was chromatographed (SiO₂; CHCl₃–EtOH) to give ethyl 5-oxo-5-phenylimidazo[3,4-*b*][1,2,4]benzothiadiazine-2-carboxylate (194) (600 mg, 47%), mp 167–169 °C (from CHCl₃–EtOAc). Anal. (C₁₈H₁₅N₃O₃S) H, N, S; C: calcd, 53.6; found 53.1. Hydrolysis of 194 as in the preparation of 188 gave the acid 195 (Table X).

5-Methyl-5-oxoimidazo[3,4-*b*][1,2,4]benzothiadiazine-2-carboxylic acid (197) (Table X) was prepared in the same way as 195 with 1-methyl-1-oxobenzothiadiazin-3-amine as the starting material via ethyl 5-methyl-5-oxoimidazo[3,4-*b*][1,2,4]benzothiadiazine-2-carboxylate (196), mp 270 °C. Anal. (C₁₃H₁₃N₃O₃S) H, N; C: calcd, 53.1; found, 53.6.

Ethyl Imidazo[2,1-*b*]benzothiazole-2-carboxylates (198, 200, 202, 204). By quaternizing the corresponding 2-benzothiazolamine⁴⁸ with ethyl bromopyruvate in DME, evaporating the solvent, and refluxing the residue in EtOH, there were obtained after chromatography (SiO₂) the following esters: unsubstituted (198), mp 142–143 °C (lit.²⁵ mp 147–148 °C) [anal. (C₁₂H₁₀N₂O₂S) C, H, N, S]; 7-methoxy (200), mp 133–136 °C [anal. (C₁₃H₁₂N₂O₃S) C, H, N, S]; 6,7-dimethyl (202), mp 176–178 °C [anal. (C₁₄H₁₄N₂O₂S) C, H, N, S]; 5-methoxy (204), mp 145–148 °C [anal. (C₁₃H₁₂N₂O₃S) C, H, N, S].

Imidazo[2,1-*b*]benzothiazole-2-carboxylic acids (199, 201, 203, 205) (Table X) were obtained by hydrolysis of the corresponding esters as in the preparation of 188.

Registry No. 1, 15826-37-6; 2, 58761-87-8; 3, 65565-73-3; 3 (acid chloride), 65565-75-5; 11, 65565-72-2; 12, 76577-75-8; 13, 76577-76-9; 14, 76577-77-0; 15, 76577-78-1; 16, 76577-79-2; 17, 82296-38-6; 18, 82296-36-4; 19, 65565-85-7; 19 (acid chloride), 82296-30-8; 20, 82296-10-4; 21, 82296-29-5; 22, 82296-32-0; 23, 82296-34-2; 24, 113508-03-5; 25, 113508-04-6; 26, 113508-05-7; 27, 113508-06-8; 28, 113508-07-9; 29, 65565-82-4; 30, 65565-80-2; 31, 65565-83-5; 32, 65565-81-3; 33, 65565-84-6; 34, 70917-73-6; 35, 70917-68-9; 36, 70917-72-5; 37, 70917-77-0; 38, 113508-08-0; 39, 113508-09-1; 43, 62235-41-0; 43 (2-amino), 113508-15-9; 44, 113508-14-8; 45, 68050-48-6; 45-HBr, 113508-16-0; 46, 113508-17-1; 46·2HCl, 113508-63-7; 47, 68050-43-1; 47 (acid chloride), 113508-54-6; 48, 76577-85-0; 49, 113508-18-2; 50, 68069-09-0; 51, 68050-41-9; 52, 76577-86-1; 53, 76577-48-5; 54, 76577-49-6; 55, 76577-50-9; 56, 113508-19-3; 56·2HCl, 113508-64-8; 57, 76577-51-0; 58, 76577-52-1; 59, 66491-26-7; 59 (ethyl ester), 66491-09-6; 60, 68050-47-5; 60 (ethyl ester), 68050-10-2; 61, 67817-46-3; 62, 113508-20-6; 62-HCl, 68050-08-8; 63, 68050-34-0; 63 (ethyl ester), 68050-33-9; 64, 113508-21-7; 64 (ethyl ester), 113508-43-3; 65, 113508-22-8; 65 (ethyl ester), 113508-44-4; 66, 113508-55-7; 67, 113508-23-9; 68, 113508-56-8; 69, 113508-24-0; 70, 113508-57-9; 71, 113508-25-1; 72, 113508-26-2; 72 (ethyl ester), 113508-45-5; 73, 113508-27-3; 73 (ethyl ester), 113508-46-6; 74, 113508-28-4; 75, 113508-58-0; 76, 113508-29-5; 77, 113508-59-1; 78, 113508-30-8; 79, 68050-12-4; 80, 68050-45-3; 81, 68050-27-1; 81 (ethyl ester), 68050-26-0; 82,

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113508-31-9; 82 (ethyl ester), 113508-47-7; 83, 113508-32-0; 83 (ethyl ester), 113508-48-8; 84, 113508-60-4; 85, 113508-33-1; 86, 113508-61-5; 87, 113508-34-2; 88, 113508-35-3; 88 (ethyl ester), 113508-62-6; 89, 113508-36-4; 90, 113508-37-5; 90 (ethyl ester), 113508-49-9; 91, 76577-59-8; 92, 76577-60-1; 92 (oxime), 76577-61-2; 93, 76577-63-4; 94, 76577-88-3; 95, 113508-38-6; 95-HCl, 76577-64-5; 96, 76577-87-2; 97, 68050-32-8; 97 (ethyl ester), 68050-31-7; 98, 113508-39-7; 98 (ethyl ester), 113508-50-2; 99, 68050-36-2; 99 (ethyl ester), 68050-35-1; 100, 68050-29-3; 101, 76577-54-3; 102, 76577-55-4; 102 (oxime), 76577-56-5; 103, 76577-58-7; 104, 113508-40-0; 104 (ethyl ester), 113508-51-3; 105, 68050-25-9; 105 (ethyl ester), 68050-24-8; 106, 68050-16-8; 106 (ethyl ester), 68050-15-7; 107, 68050-19-1; 107 (ethyl ester), 68050-18-0; 108, 113508-41-1; 108 (ethyl ester), 113508-52-4; 109, 68050-40-8; 109 (ethyl ester), 68050-39-5; 110, 68050-30-6; 110 (ethyl ester), 68050-29-3; 111, 68050-21-5; 112, 68050-46-4; 112 (ethyl ester), 68050-21-5; 113, 113508-42-2; 113 (ethyl ester), 113508-53-5; 114, 76002-75-0; 114 (ethyl ester), 76013-27-9; 115, 76002-76-1; 116, 76002-77-2; 117, 76002-86-3; 118, 76577-47-4; 119, 76577-41-8; 120, 76577-43-0; 121, 76577-42-9; 122, 76577-46-3; 123, 76002-83-0; 124, 76325-62-7; 125, 76325-51-4; 126, 113508-65-9; 127, 76325-47-8; 128, 76325-49-0; 129, 76325-50-3; 130, 76325-52-5; 131, 76325-54-7; 132, 76325-56-9; 133, 76325-55-8; 134, 76577-90-7; 134-HCl, 76577-80-5; 135, 76577-65-6; 136, 113508-66-0; 137, 113508-67-1; 138, 113508-68-2; 140, 69015-16-3; 142, 69015-14-1; 143, 69015-25-4; 144, 69015-24-3; 145, 69015-32-3; 146, 69015-34-5; 147, 69015-35-6; 147 (ethyl ester), 69040-91-1; 148, 69015-36-7; 149, 69015-37-8; 149 (ethyl ester), 69015-26-5; 150, 69015-33-4; 150 (ethyl ester), 69015-23-2; 151, 69015-40-3; 151 (ethyl ester), 69015-29-8; 152, 69015-38-9; 152 (ethyl ester), 69015-27-6; 153, 69015-39-0; 153 (ethyl ester), 69015-28-7; 154, 113508-69-3; 154 (ethyl ester), 113508-70-6; 155, 69015-42-5; 155 (ethyl ester), 69015-31-2; 156, 69015-54-9; 156 (ethyl ester), 69015-53-8; 157, 69015-41-4; 157 (ethyl ester), 69015-30-1; 158, 76577-69-0; 159, 76577-70-3; 160, 76577-73-6; 161, 76577-74-7; 162, 113508-75-1; 163, 113532-99-3; 165, 99867-03-5; 166, 113508-71-7; 167, 113508-76-2; 168, 113508-77-3; 169, 113508-78-4; 170, 113508-72-8; 171, 113508-73-9; 172, 113508-74-0;

173, 113508-79-5; 174, 113508-80-8; 175, 113508-81-9; 176, 82296-39-7; 177, 82296-41-1; 178, 90510-54-6; 179, 113508-82-0; 180, 82296-43-3; 181, 82296-45-5; 182, 65565-70-0; 183, 113508-83-1; 184, 113508-85-3; 185, 113508-84-2; 186, 38922-77-9; 186-HBr, 2549-17-9; 187, 76577-82-7; 188, 76577-83-8; 190, 77947-41-2; 191, 88220-27-3; 192, 60050-77-3; 193, 113508-91-1; 194, 113533-00-9; 195, 113508-86-4; 196, 113508-92-2; 197, 113508-87-5; 198, 64951-05-9; 199, 64951-09-3; 200, 81021-97-8; 201, 113508-88-6; 202, 113508-93-3; 203, 113508-89-7; 204, 113508-94-4; 205, 113508-90-0; H₂C=CHCN, 107-13-1; BrCH₂COCO₂Et, 10-23-1; H₃CCHBrCOCO₂Et, 57332-84-0; BrCH₂CO₂Et, 105-36-2; H₃CC-(OEt)₃, 78-39-7; 5-aminotetrazole, 4418-61-5; 2-amino-4-chloroquinoline, 20151-42-2; 2-amino-4-(methylthioquinoline), 113508-10-4; 2-amino-4-(methylsulfinyl)quinoline, 113508-11-5; ethyl 2-aminoquinoline-3-carboxylate, 36926-83-7; 2-amino-3-(hydroxymethyl)quinoline, 75353-55-8; 2-chloro-7-(trifluoromethyl)quinoline, 83183-56-6; 2-amino-7-(trifluoromethyl)quinoline, 113508-12-6; 2-chloro-6-nitroaniline, 769-11-9; 2-chloro-6-nitrodihydrocinnamitrile, 113508-13-7; 2-amino-5-chloroquinoline, 68050-37-3; quinoline, 91-22-5; 2-aminoquinoline, 580-22-3; 2-amino-7-chloroquinoline, 43200-95-9; 2-amino-4,7-dichloroquinoline, 68050-28-2; 2-amino-4-chloro-7-methoxyquinoline, 68050-20-4; glycerolacetone, 100-79-8; 2-amino-6-chloro-4-phenylquinoline, 51478-40-1; 4,5-dichloro-*o*-phenylenediamine, 5348-42-5; alloxan hydrate, 3237-50-1; dichloroalloxazine, 58590-56-0; 2-amino-6,7-dichloroquinoxaline, 76002-68-1; 2-aminoquinoxaline, 5424-05-5; 2-aminoquinoxaline-3-carboxamide, 67568-30-3; 2-amino-3-chloroquinoxaline, 34117-90-3; 2-amino-3-chloroquinoxalinium bromide, 76002-73-8; 2,3,6,7-tetrachloroquinoxaline, 25983-14-6; 2-amino-6,7-dichloro-3-ethoxyquinoxaline, 76325-57-0; 2-amino-3-ethylquinazolin-4(3*H*)-one, 2161-26-4; 1-ethylbenzimidazole, 7035-68-9; ethyl propionate, 623-47-2; 1-methylbenzimidazole, 1632-83-3; 1-butylbenzimidazole, 4886-30-0; quinaldine, 91-63-4; 2-aminobenzothiazole, 136-95-8; 2-amino-6-methoxybenzothiazole, 1747-60-0; 2-amino-5,6-dimethoxybenzothiazole, 29927-08-0; 2-amino-4-methoxybenzothiazole, 5464-79-9.

6-(Alkylamino)-3-aryl-1,2,4-triazolo[3,4-*a*]phthalazines. A New Class of Benzodiazepine Receptor Ligands[†]

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Some 6-(alkylamino)-3-aryl-1,2,4-triazolo[3,4-*a*]phthalazines have been shown to displace diazepam from rat brain specific binding sites, *in vitro*, with *K_i* (nM) values comparable to those of reference benzodiazepines and to have anticonvulsant (pentylentetrazole test, mice) and anticonflict activity (Vogel test, rat) *in vivo*. Separation between the doses causing anticonflict effects (Vogel test, rat) and those impairing motor coordination (rotarod test, rat) has been shown for *N,N*-bis(2-methoxyethyl)-3-(4-methoxyphenyl)-1,2,4-triazolo[3,4-*a*]phthalazin-6-amine (80). This compound, unlike diazepam, was inactive in counteracting the strychnine (mouse) and maximal electroshock (mouse) induced convulsions and in the "aggressive monkey" model. These differences from the classical benzodiazepines in the animal tests indicate that 80 may have some selective anxiolytic activity.

The search for antianxiety agents without nonspecific central nervous system (CNS) depressant side effects has led to the discovery of several classes of compounds chemically unrelated to the benzodiazepines (BZ). The

field has been recently reviewed,¹⁻⁵ and since then a few more examples of this type of compounds have been reported.⁶⁻¹⁰ All these compounds share the property of

[†]This work is dedicated to Prof. Valdo Mazzi, Institute of Comparative Anatomy, University of Torino (Italy) on occasion of his 70th birthday.

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