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.

Acknowledgment. This work was supported by American Cancer Society Grant CH1-F. The NMR spectra were obtained at the Southern California Regional NMR facility, which is supported by National Science Foundation Grant CHE 79-16324.

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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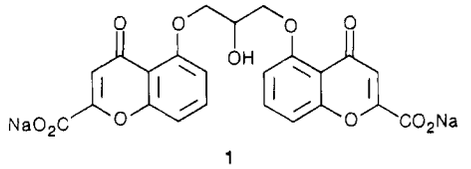
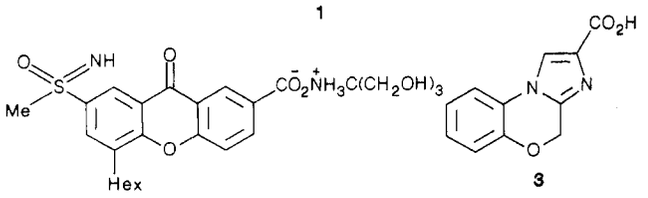
Roussel Laboratories Ltd., Covingham, Swindon, Wilts SN3 5BT, United Kingdom. *Received June 22, 1987*

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 10^3 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[8]).



1



2 **3**

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 (ED_{50} = 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).

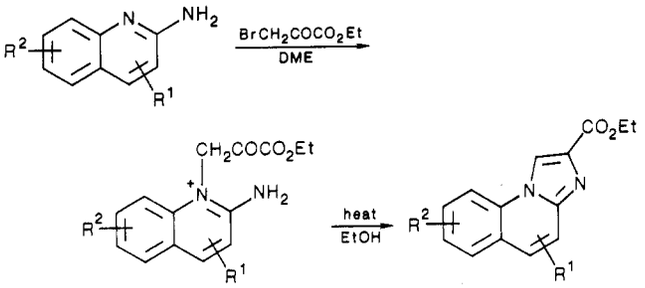
(a) Imidazo[2,1-*c*][1,4]benzoxazines (3, 11–39; Table I). The basic method of preparation of this system was described earlier,[9] and the derivatives studied are listed in Table I along with their pharmacological properties.

(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 reported[11] to give the imidazolidine **41**, but the

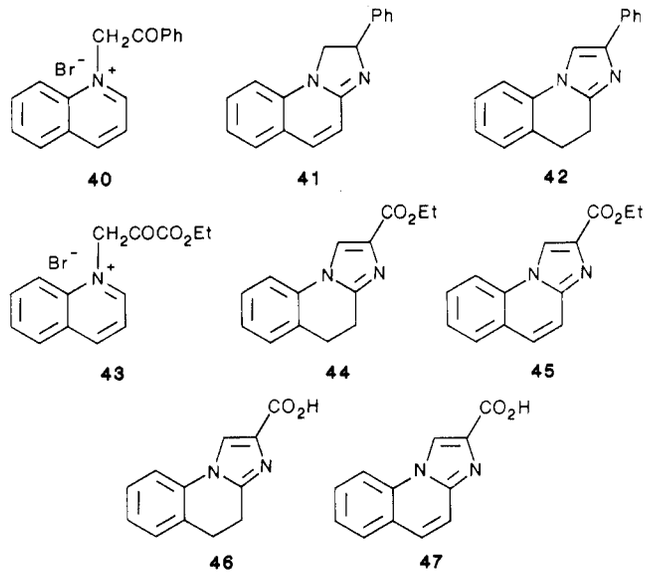
(1) Patterson, R. In *Current Perspectives in Allergy*; Goetzl, E. J., Kay, A. B., Eds.; Churchill Livingstone: New York, 1982; p 17.
(2) Cox, J. S. G.; Beach, J. E.; Blair, A. M. J. N.; Clarke, A. J.; King, J.; Lee, T. B.; Loveday, D. E. E.; Moss, G. F.; Orr, T. S. C.; Richie, J. T.; Sheard, P. *Adv. Drug. Res.* **1970**, *5*, 115.
(3) Turner-Warwick, M. in ref 1, p 153.
(4) Bernstein, I. L. *J. Allergy Clin. Immunol.* **1981**, *68*, 247.
(5) Church, M. K. *Med. Actual/Drugs Today* **1978**, *14*, 281.
(6) Barnes, A. C.; Hairsine, P. W.; Matharu, S. S.; Ramm, P. J.; Taylor, J. B. *J. Med. Chem.* **1979**, *22*, 418.
(7) Miller, P.; James, G. W. L. *Arch. Int. Pharmacodyn.* **1978**, *231*, 328.
(8) Proposed INN, *WHO Chron.* **1980**, *34* (Suppl. to 9), 21.
(9) Danswan, G. W.; Hairsine, P. W.; Rowlands, D. A.; Taylor, J. B.; Westwood, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1049.

0022-2623/88/1831-1098$01.50/0

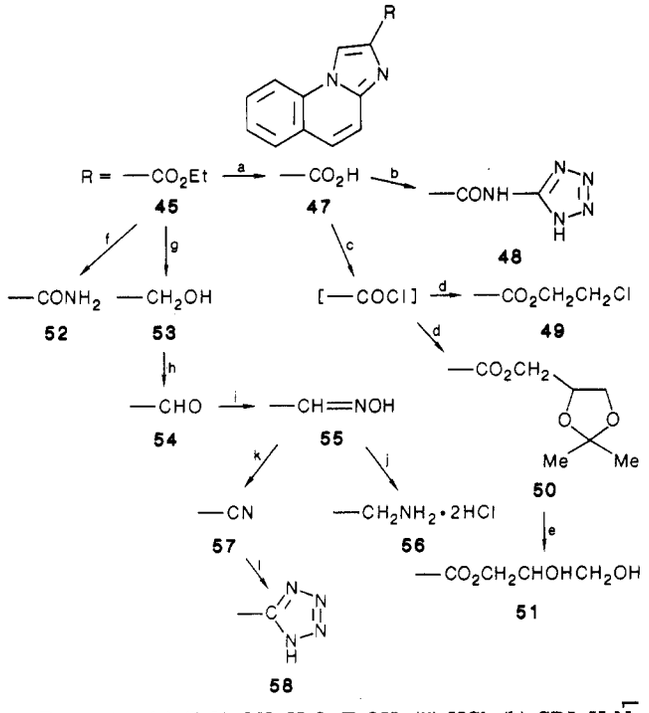
Scheme I



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 hydrochloride[14] 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 po, 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]

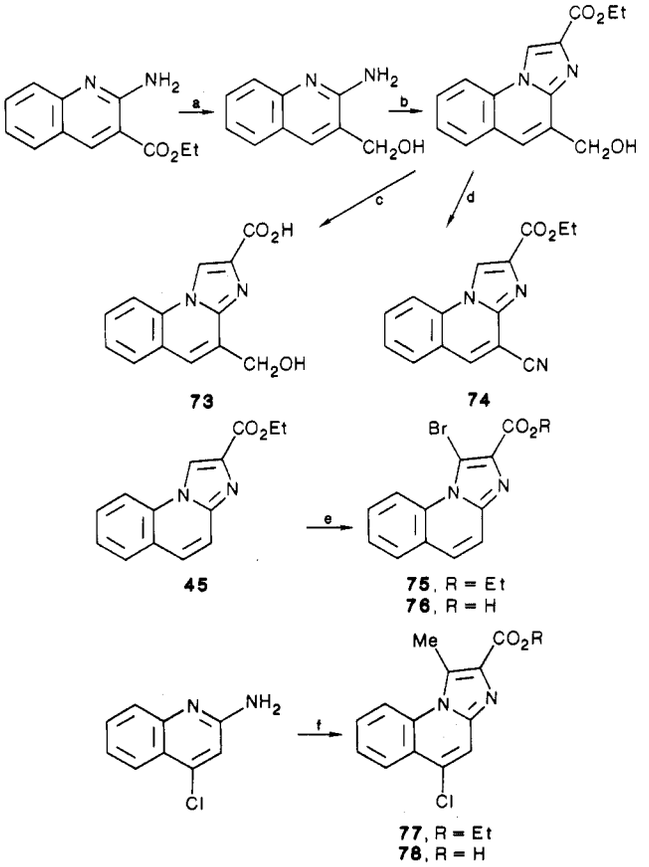


Scheme II[a]



[a] Reagents: (a) (i) NaOH; H_2O, EtOH, (ii) HCl; (b) CDI, H_2N-C=N-N=NH; (c) $SOCl_2$; (d) NEt_3, glycerol acetonide; $ClCH_2CH_2Cl$; (e) citric acid; H_2O; (f) Na, NH_3; EtOH; (g) $LiBH_4$; THF; (h) MnO_2; $CHCl_3$; (i) NH_2OH·HCl, NaOAc; H_2O, EtOH; (j) H_2, Pd/C; MeOH, HCl; (k) Ac_2O; (l) NaN_3, NH_4Cl; DMF.

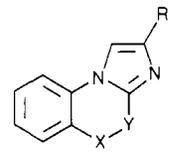
Scheme III[a]



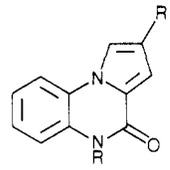
[a] Reagents: (a) $LiAlH_4$; THF; (b) (i) $BrCH_2COCO_2Et$; DME, (ii) Δ; EtOH; (c) (i) NaOH; H_2O, EtOH, (ii) HCl; (d) (i) MnO_2; $CHCl_3$, (ii) NaOAc, NH_2OH·HCl; H_2O, EtOH, (iii) Ac_2O; (e) Br_2; AcONa, AcOH; (f) (i) $MeCHBrCOCO_2Et$; DME, (ii) Δ; EtOH.

(10) Goose, J.; Blair, A. M. J. N. *Immunology* **1969**, *16*, 749.
(11) Krohnke, K.; Zecher, W. *Chem. Ber.* **1962**, *95*, 1128. Krohnke, K. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 225.
(12) Cookson, R. F.; Nowotnik, D. P.; Parfitt, R. T. *J. Chem. Soc., Chem. Commun.* **1974**, 911. Airey, J. E.; Cookson, R. F.; Kende, A. S.; Nowotnik, D. P.; Parfitt, R. T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 201.
(13) Habermalz, U.; Krohnke, F.; Reinshagen, B. *Chem. Ber.* **1975**, *108*, 984.
(14) Sale, A. O.; Toja, E.; Galliani, G.; Lemer, L. J. U. K. Patent 1 484 615, 23 Nov. 1974.
(15) Lombordino, J. G. *J. Org. Chem.* **1965**, *30*, 2403. Smakula Hand, E.; Paudler, W. W. *Tetrahedron* **1982**, *38*, 49.

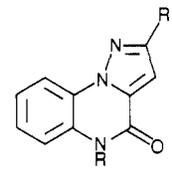
Chart I



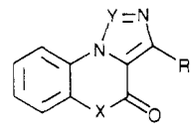
	X-Y	
4a	$-OCH_2-$	imidazo[2,1-*c*](1,4)benzoxazine
b	-CH=CH-	imidazo[1,2-*a*]quinoline
c	-N=CH-	imidazo[1,2-*a*]quinoxaline
d	-NHC(O)-	imidazo[1,2-*a*]quinoxalin-4(5*H*)-one
e	-C(O)NH-	imidazo[1,2-*a*]quinazolin-5(4*H*)-one



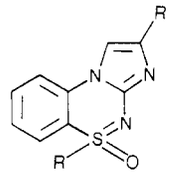
4f, pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one



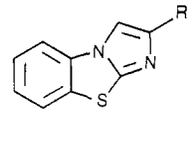
4g, pyrazolo[2,3-*a*]quinoxalin-4(5*H*)-one



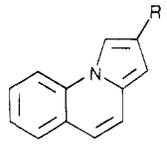
4h, imidazo[1,5-*a*]quinoxalin-4(5*H*)-one (Y = CH, X = NH)
i, triazolo[1,5-*a*]quinoxalin-4(5*H*)-one (Y = N, X = NH)
j, triazolo[1,5-*a*]benzoxazin-4-one (Y = N, X = O)



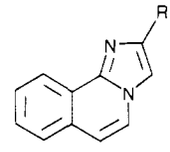
5, imidazo[2,1-*c*]benzothiadiazine



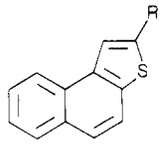
6, imidazo[2,1-*b*]benzothiazole



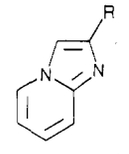
7, pyrrolo[1,2-*a*]quinoline



8, imidazo[2,1-*a*]isoquinoline



9, thieno[3,2-*a*]naphthalene



10, imidazo[1,2-*a*]pyridine

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).

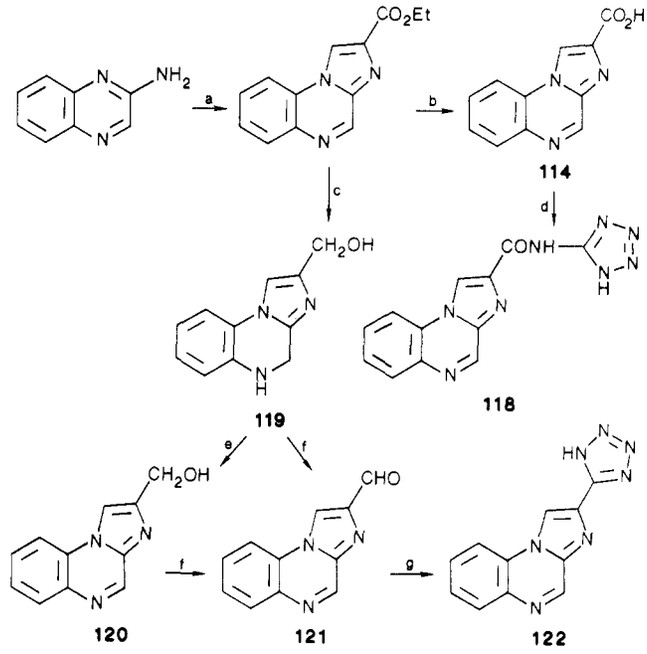
(c) Imidazo[1,2-*a*]quinoxalines (114–122; Table IV). The reaction of 2-aminoquinoxalines with ethyl bromopyruvate as in the preparation of **45** followed by modification of the ester group (Scheme IV) gave a series of imidazo[1,2-*a*]quinoxalines.

(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-methoxyquinoxaline[16] 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 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(3H)-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).

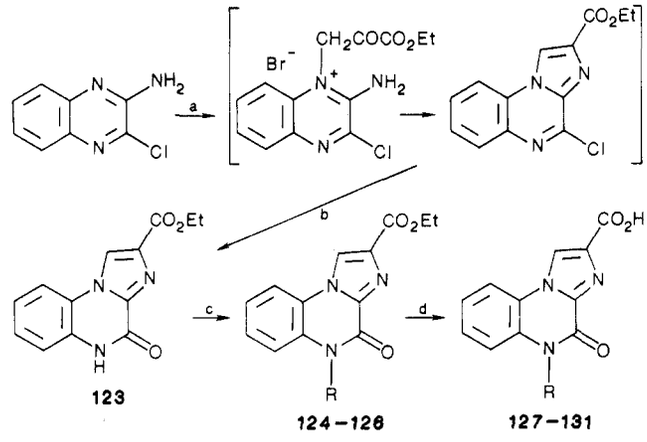
(16) Cheeseman, G. W. H. *J. Chem. Soc.* **1955**, 1804.

Scheme IV[a]



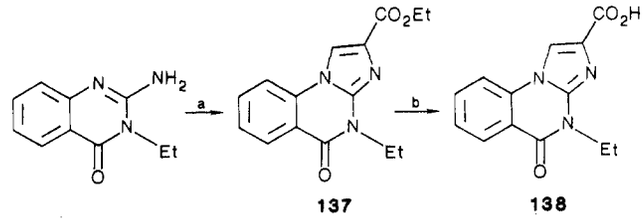
[a] Reagents: (a) (i) $BrCH_2COCO_2Et$; DME, (ii) Δ; EtOH; (b) (i) NaOH; H_2O, EtOH, (ii) HCl; (c) $LiBH_4$; THF; (d) CDI, $NH_2C(=N-N=N-NH)$; DMF; (e) MnO_2; $CHCl_3$, room temperature; (f) MnO_2; $CHCl_3$, Δ; (g) (i) $NH_2OH{\cdot}HCl$, NaOAc; EtOH, H_2O, (ii) Ac_2O, (iii) NaN_3, NH_4Cl; DMF.

Scheme V[a]



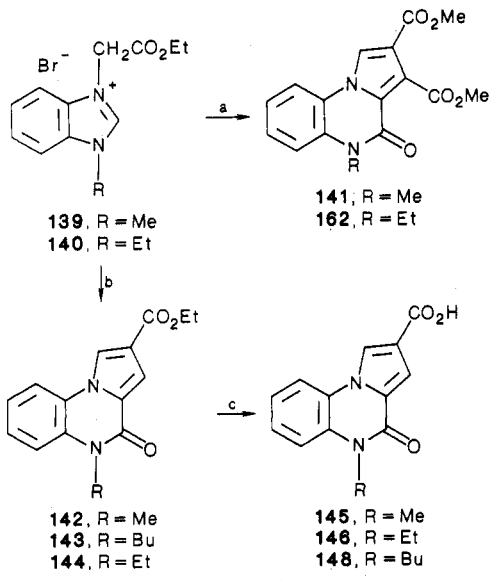
[a] Reagents: (a) $BrCH_2COCO_2Et$; DME; (b) Δ; EtOH; (c) NaH, RI; DMF; (d) (i) NaOH; H_2O, EtOH, (ii) HCl.

Scheme VI[a]



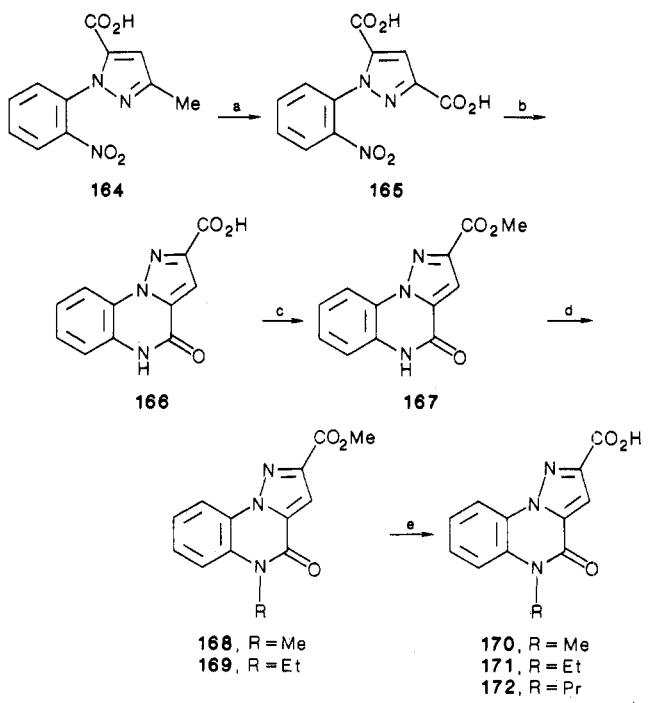
[a] Reagents: (a) (i) $BrCH_2COCO_2Et$; DME, (ii) Δ, EtOH; (b) (i) NaOH; H_2O, EtOH, (ii) HCl.

Scheme VII[a]



[a] Reagents: (a) $MeO_2CC{\equiv}CCO_2Me$, Et_3N; DMF; (b) $HC{\equiv}CCO_2Et$, Et_3N; DMF; (c) (i) NaOH; H_2O, EtOH, (ii) HCl.

Scheme VIII[a]



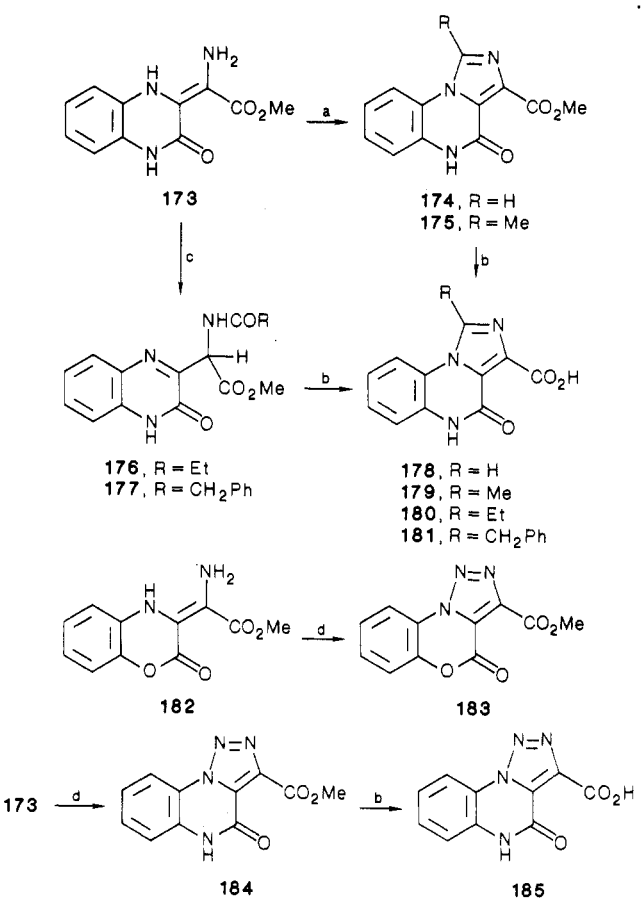
[a] Reagents: (a) (i) $KMnO_4$; aqueous NaOH, (ii) concentrated HCl; (b) (i) PtO_2 + 5% Pd–C, H_2; aqueous NaOH, (ii) concentrated HCl; (c) MeOH, dry HCl; (d) RI, NaH; DMF; (e) (i) NaOH; H_2O, EtOH, (ii) concentrated HCl.

(f) Pyrrolo[1,2-*a*]quinoxolin-4(5*H*)-ones (141–163; Table VII). The reaction of the benzimidazole quaternary salt **139** with dimethyl acetylene dicarboxylate was shown[17] to give the pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-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(5*H*)-ones (166–172; Table VIII). An analogous series of pyrazolo[2,3-*a*]-quinoxalin-4(5*H*)-one acids and esters were prepared as shown in Scheme VIII following literature precedents.[18] Thus (*o*-nitrophenyl)hydrazine was condensed with ethyl acetopyruvate[19] 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.

Scheme IX[a]



[a] Reagents: (a) $RC(OEt)_3$; (b) (i) NaOH; H_2O, EtOH, (ii) HCl; (c) RCOCl; (d) $(CH_3)_2CHCH_2CH_2ONO$.

(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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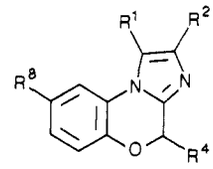
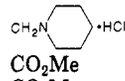
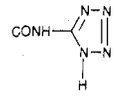
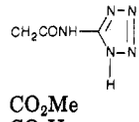
(21) Biekert, E.; Koessel, H. *Justus Leibigs. Ann. Chem.* **1963**, *662*, 83.

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_2H	H	H	A	2.89 (2.22–3.63)	3.20 (2.47–3.45)
11	H	CO_2Me	H	H	A		10.8 (7.73–15.31)
12	H	CH_2OH	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_2CO_2H	H	H	A	inactive[c]	
18	H		H	H	A	inactive[c]	
19	CO_2H	CO_2Me	H	H	A	inactive[c]	
20	CO_2Et	CO_2Me	H	H	A	inactive[c]	
21	CO_2H	CO_2H	H	H	A	inactive[c]	
22		CO_2H	H	H	A	inactive[c]	
23	CO_2H	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_2OH	CO_2Me	H	H	B		inactive[c]
28	CH_2OH	CO_2H	H	H	B		inactive[c]
29	H	CO_2H	H	NO_2	A	2.22 (1.31–4.63)	
30	H	CO_2Me	H	NHAc	A		3.48 (2.89–3.99)
31	H	CO_2H	H	NHAc	A	0.073 (0.047–0.108)	inactive
32	H	CO_2Me	H	$NHCOCO_2Et$	A		0.50 (0.37–0.65)
33	H	CO_2H	H	$NHCOCO_2H$	A	0.0172 (0.0103–0.0214)	3.85 (2.71–5.46)
34	H	CO_2H	H	Cl	B	0.42 (0.34–0.44)	0.13 (0.04–0.45)
35	H	CO_2Me	H	Cl	B		2.79 (1.75–4.06)
36	H	CO_2Me	H	Me	B		1.46 (0.66–3.33)
37	H	CO_2H	H	Me	B	0.35 (0.26–0.50)	0.37 (0.11–1.43)
38	H	CO_2H	Me	H	B	1.76 (0.91–3.86)	8.46 (4.38–21.4)
39	H	CO_2H	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*] pyridine[22] **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]

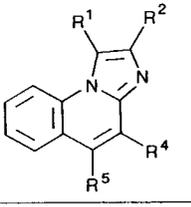
(22) Lombardino, J. G. *J. Org. Chem.* **1965**, *30*, 2403.
(23) Kuzmenko, T. A.; Kuzmenko, V. V.; Simonov, A. M.; Simkin, B. Y. *Khim. Geterotsikl. Soedin.* **1980**, *12*, 1656.
(24) Campaigne, E.; Cline, R. E. *J. Org. Chem.* **1956**, *21*, 32. Grunhaus, H.; Pailer, M.; Stof, S. J. *Heterocycl. Chem.* **1976**, *13*, 1161.
(25) Abignente, E.; Arena, F.; De Caprariis, P.; Parent, L. *Farmaco, Ed. Sci.* **1977**, *32*, 735.

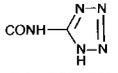
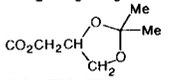
Biological Results and Discussion

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

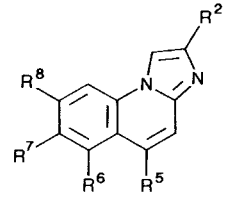
Table II. (Benzo unsubstituted)imidazo[1,2-*a*]quinoline-2-carboxylic Acids and Derivatives

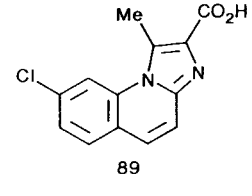


compd	R^5	R^4	R^2	R^1	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED_{50},[a] mg/kg iv	antiallergic activity, IgE, rat PCA: ED_{50},[a] mg/kg po
DSCG										1.21 (1.04–1.42)	inactive[b]
46	dihydro		CO_2H		274–278[c]	$EtOH/H_2O$	85	$C_{12}H_{10}N_2O_2 \cdot 2HCl$	C,H,N,Cl	0.39 (0.34–0.45)	6.14 (5.21–7.35)
47	H	H	CO_2H	H	234–236	$EtOH/H_2O$	90	$C_{12}H_8N_2O_2 \cdot H_2O$	C,H,N	0.30 (0.24–0.39)	0.34 (0.29–0.40)
48	H	H		H	266–268	EtOAc/DMF	95	$C_{13}H_9N_7O$	C,H,N	0.31 (0.20–0.50)	0.54 (0.20–0.83)
49	H	H	$CO_2CH_2CH_2Cl$	H	162–164	EtOAc	13	$C_{14}H_{11}N_2O_2Cl$	C,H,N,Cl		3.5 (2.51–4.1)
50	H	H		H	156–158	$CHCl_3/Et_2O$	14	$C_{18}H_{18}N_2O_4$	C,H,N		1.70 (0.65–6.05)
51	H	H	$CO_2CH_2CHOHCH_2OH$	H	217–220	$CHCl_3/Et_2O$	91	$C_{15}H_{14}N_2O_4$	C,H,N		inactive[d]
52	H	H	$CONH_2$	H	263–265	$CHCl_3/MeOH/Et_2O$	64	$C_{12}H_9N_3O$	C,H,N		inactive[b]
53	H	H	CH_2OH	H	158–159	$EtOAc/Et_2O$	92	$C_{12}H_{10}N_2O$	C,H,N		0.36 (0.21–0.53)
54	H	H	CHO	H	184–185	$EtOAc/Et_2O$	82	$C_{12}H_8N_2O$	C,H,N		0.093 (0.026–0.31)
56	H	H	$CH_2NH_2 \cdot 2HCl$	H	320–325	$MeOH/Et_2O$	64	$C_{12}H_{11}N_3 \cdot 2HCl \cdot 0.5H_2O$	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	$C_{12}H_8N_6$	C,H,N	0.026 (0.019–0.032)	0.105 (0.037–0.38)
59	MeO	H	CO_2H	H	244–247	$EtOH/H_2O$	86	$C_{13}H_{10}N_2O_3$	C,H,N	0.57 (0.48–0.67)	3.74 (3.26–4.31)
60	Me_2CHO	H	CO_2H	H	247–249	$EtOH/H_2O$	85	$C_{15}H_{14}N_2O_3 \cdot H_2O$	C,H,N	0.12 (0.08–0.17)	1.13 (0.84–1.55)
61	Cl	H	CO_2Et	H	169–170	MeOH	29	$C_{14}H_{11}N_2O_2Cl$	C,H,N,Cl		0.096 (0.065–0.14)
62	Cl	H	$CO_2H \cdot HCl$	H	263–265	MeOH	66	$C_{12}H_7N_2O_2Cl \cdot HCl$	C,H,N,Cl	0.0075 (0.0062–0.0089)	0.47 (0.39–0.55)
63	Br	H	CO_2H	H	288–290	$CHCl_3/MeOH$	80	$C_{12}H_7N_2O_2Br \cdot CH_3OH$	C,H,N,Br	0.046 (0.032–0.067)	0.14 (0.09–0.25)
64	SMe	H	CO_2H	H	273–274	$CHCl_3/MeOH$	89	$C_{13}H_{10}N_2O_2S \cdot 0.5H_2O$	C,H,N,S	0.046 (0.023–0.11)	
65	SOMe	H	CO_2H	H	266–268	$EtOH/H_2O$	86	$C_{13}H_{10}N_2O_3S$	C,H,N,S	0.29 (0.18–0.41)	
67	SO_2Me	H	CO_2H	H	276–278	DMSO	84	$C_{13}H_{10}N_2O_4S$	C,H,N,S	0.047 (0.025–0.11)	1.64 (0.51–7.81)
69	SO(=NH)Me	H	CO_2H	H	273–275	$CHCl_3/MeOH$	75	$C_{13}H_{11}N_3O_3S$	C,H,N,S	0.35 (0.22–0.59)	
71	Ph	H	CO_2H	H	272–273	$MeOH/H_2O$	80	$C_{18}H_{12}N_2O_2$	C,H,N		inactive[b]
72	H	Ph	CO_2H	H	230–240[e]	EtOH	75	$C_{18}H_{12}N_2O_2$	C,H,N	inactive[b]	
73	H	CH_2OH	CO_2H	H	298–300	$EtOH/H_2O$	75	$C_{13}H_{10}N_2O_3 \cdot H_2O$	C,H,N	inactive[b]	
74	H	CN	CO_2Et	H	221–222	EtOH/EtOAc	78	$C_{15}H_{11}N_3O_2$	C,H,N		inactive[b]
76	H	H	CO_2H	Br	209–210	$EtOH/H_2O$	95	$C_{12}H_7N_2O_2Br$	C,H,N,Br	4.19 (2.74–6.94)	
78	Cl	H	CO_2H	Me	280–281	$EtOH/H_2O$	90	$C_{13}H_9N_2O_2Cl \cdot 0.33H_2O$	C,H,N,Cl		inactive[b]

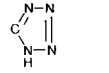
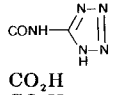
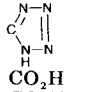
[a] 95% confidence limits in parentheses. [b] Inactive at 1 and 10 mg/kg. [c] As dihydrochloride. [d] 47% inhibition at 10 mg/kg. [e] As Na salt.

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



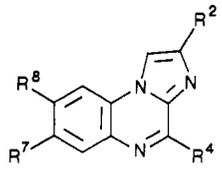


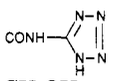
89

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	antiallergic activity, IgE, rat PCA: ED_{50}, mg/kg po
79	Cl	H	H	H	CO_2Et	221-222	$CHCl_3/Et_2O$	50	$C_{14}H_{11}N_2O_2Cl$	C,H,N,Cl		1.72 (0.97-3.45)
80	Cl	H	H	H	CO_2H	288-289	$EtOH/H_2O$	64	$C_{12}H_7N_2O_2Cl$	C,H,N,Cl	0.069 (0.046-0.095)	0.11 (0.091-0.135)
81	MeO	H	H	H	CO_2H	272-273	AcOH	63	$C_{13}H_{10}N_2O_3$	C,H,N	0.038 (0.026-0.058)	0.14 (0.07-0.30)
82	Et	H	H	H	CO_2H	241-244	EtOH	72	$C_{14}H_{12}N_2O_2$	C,H,N	0.16 (0.08-0.37)	
83	SMe	H	H	H	CO_2H	262-264	$EtOH/H_2O$	81	$C_{13}H_{10}N_2O_2S\cdot H_2O$	C,H,N,S	0.095 (0.058-0.15)	
85	SOMe	H	H	H	CO_2H	261-263	$EtOH/H_2O$	86	$C_{13}H_{10}N_2O_3S$	C,H,N,S	0.076 (0.043-0.12)	
87	SO_2Me	H	H	H	CO_2H	261-265	$EtOH/H_2O$	81	$C_{13}H_{10}N_2O_4S$	C,H,N,S	0.028 (0.021-0.03)	inactive[b]
88	SO(=NH)Me	H	H	H	CO_2H	235-237	$EtOH/H_2O$	76	$C_{13}H_{11}N_3O_3S\cdot 0.5H_2O$	C,H,N,S	0.095 (0.058-0.15)	
89						290-292	$EtOH/H_2O$	84	$C_{13}H_9N_2O_2Cl\cdot H_2O$	C,H,N,Cl	1.99 (1.14-3.89)	
90	CF_3	H	H	H	CO_2H	264-266	$EtOH/H_2O$	91	$C_{13}H_7N_2O_2F_3$	C,H,N	0.070 (0.04-0.154)	
91	MeO	H	H	H	CH_2OH	173-175	THF/H_2O	89	$C_{13}H_{12}N_2O_2$	C,H,N	0.27 (0.18-0.36)	0.24 (0.03-22.6)
92	MeO	H	H	H	CHO	190-193	$EtOAc/Et_2O$	80	$C_{13}H_{10}N_2O_2$	C,H,N	0.12 (0.05-0.37)	0.40 (0.24-0.76)
93	MeO	H	H	H		305-306	DMSO	88	$C_{13}H_{10}N_6O$	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	$C_{13}H_{11}N_3O_2$	C,H,N		inactive[c]
95	MeO	H	H	H	$CH_2NH_2\cdot 2HCl$	274-277	$MeOH/Et_2O$	74	$C_{13}H_{13}N_3O\cdot 2HCl\cdot 1.5H_2O$	C,H,N,Cl	3.39 (2.22-5.31)	
96	MeO	H	H	H		298-301	DMF/EtOAc	95	$C_{14}H_{11}N_7O_2\cdot 0.5H_2O$	C,H,N	inactive[c]	
97	H	Cl	H	H	CO_2H	278-279	$EtOH/H_2O$	93	$C_{12}H_7N_2O_2Cl\cdot H_2O$	C,H,N,Cl	0.29 (0.22-0.36)	
98	H	NO_2	H	H	CO_2H	311-313	$EtOH/H_2O$	90	$C_{12}H_7N_3O_4$	C,H,N	0.28 (0.20-0.35)	
99	H	MeO	H	H	CO_2H	265-266	$EtOH/H_2O$	79	$C_{13}H_{10}N_2O_3$	C,H,N	0.03 (0.003-0.48)	
100	Cl	H	H	Cl	CO_2Et	229-230	$CHCl_3/Et_2O$	79	$C_{14}H_{10}N_2O_2Cl_2$	C,H,N,Cl		1.49 (0.30-10.04)
101	Cl	H	H	Cl	CH_2OH	207-210	$EtOAc/Et_2O$	47	$C_{12}H_8N_2OCl_2$	C,H,N,Cl	0.16 (0.02-0.38)	
102	Cl	H	H	Cl	CHO	280-285	$CHCl_3/Et_2O$	50	$C_{12}H_6N_2OCl_2$	C,H,N,Cl		0.5 (0.21-7.6)
103	Cl	H	H	Cl		322-324	DMF	70	$C_{12}H_6N_6Cl_2$	*d*	0.016 (0.007-0.049)	0.5 (0.07-22.7)
104	H	H	Cl	H	CO_2H	288-289	$EtOH/H_2O$	82	$C_{12}H_7N_2O_2Cl\cdot H_2O$	C,H,N	3.74 (2.91-4.95)	
105	Cl	H	H	Me_2CHO	CO_2H	283-285	$EtOH/H_2O$	85	$C_{15}H_{13}N_2O_3Cl$	C,H,N,Cl	0.027 (0.021-0.033)	0.34 (0.07-0.40)
106	MeO	H	H	MeO	CO_2H	248-250	$MeOH/Et_2O$	83	$C_{14}H_{12}N_2O_4$	C,H,N	1.22 (0.85-1.74)	inactive[c]
107	MeO	H	H	Me_2CHO	CO_2H	259-261	$MeOH/Et_2O$	87	$C_{16}H_{16}N_2O_4\cdot 0.5H_2O$	C,H,N	0.091 (0.064-0.127)	inactive[b]
108	Et	H	H	Cl	CO_2H	282-285	$EtOH/H_2O$	83	$C_{14}H_{11}N_2O_2Cl$	C,H,N,Cl	0.09 (0.05-0.15)	
109	Br	H	H	Cl	CO_2H	300-303	$EtOH/H_2O$	91	$C_{12}H_6N_2O_2BrCl\cdot H_2O$	C,H,N,Br,Cl	0.025 (0.011-0.039)	0.08 (0.04-0.12)
110	Cl	H	H	Cl	CO_2H	304-305	$EtOH/H_2O$	92	$C_{12}H_6N_2O_2Cl_2$	C,H,N,Cl	0.023 (0.019-0.026)	0.033 (0.010-0.035)
111	MeO	H	H	Cl	CO_2Et	215-216	$CHCl_3/Et_2O$	30	$C_{15}H_{13}N_2O_3Cl$	C,H,N,Cl		8.0 (4.65-18.7)
112	MeO	H	H	Cl	CO_2H	277-278	$EtOH/H_2O$	87	$C_{13}H_9N_2O_3Cl$	C,H,N,Cl	0.027 (0.021-0.033)	0.34 (0.07-0.40)
113	H	Cl	H	Ph	CO_2H	307-309	$EtOH/H_2O$	92	$C_{18}H_{11}N_2O_2Cl$	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.

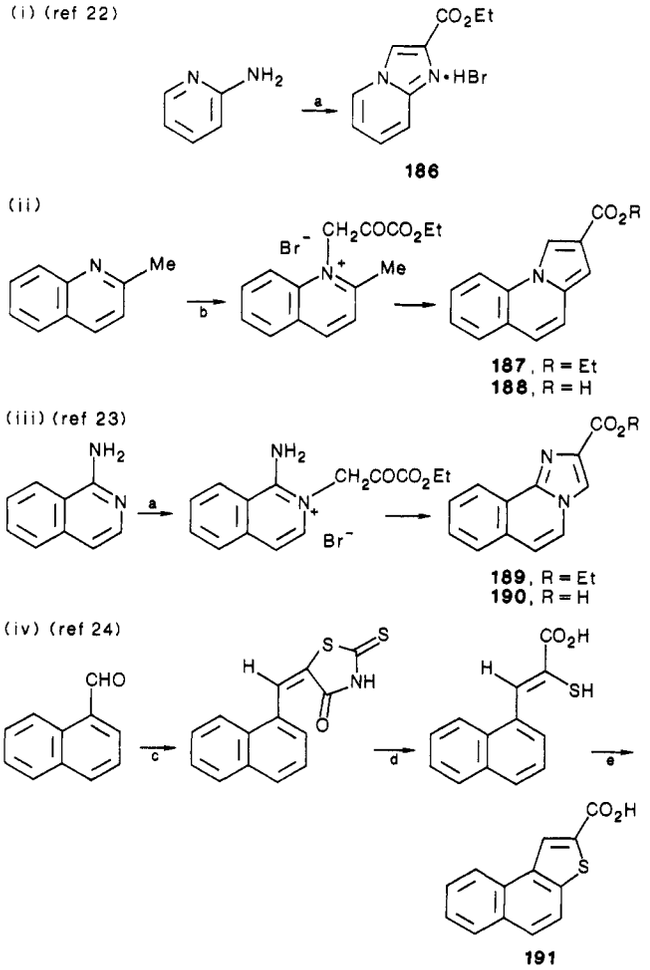
Table IV. Imidazo[1,2-*a*]quinoxalines



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_2H	H	H	H	274–275	EtOH/H_2O	95	$C_{11}H_7N_3O_2$	C,H,N	0.073 (0.057–0.091)	0.13 (0.54–0.90)
115	CO_2Et	H	Cl	Cl	297–299	EtOH	40	$C_{13}H_9N_3O_2Cl_2$	C,H,N,Cl		inactive[b]
116	CO_2H	H	Cl	Cl	>350	EtOH/H_2O	88	$C_{11}H_5N_3O_2Cl_2$	C,H,N,Cl	0.2 (0.12–0.35)	inactive[b]
117	CO_2H	$CONH_2$	H	H	238–240	EtOH/H_2O	95	$C_{12}H_8N_4O_3 \cdot H_2O$	C,H,N	3.13 (2.48–3.45)	
118		H	H	H	280–281	DMF	91	$C_{12}H_8N_8O$	C,H,N	0.45 (0.24–1.05)	inactive[b]
120	CH_2OH	H	H	H	217–220	$CHCl_3$/Et_2O	53	$C_{11}H_9N_3O$	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_2O	89	$C_{11}H_7N_3O$	C,H,N	0.137 (0.052–0.43)[c]	0.073 (0.031–0.15)
122		H	H	H	320–322	DMF/H_2O	53	$C_{11}H_7N_7$	C,H,N[d]	0.012 (0.005–0.033)	0.089 (0.025–0.282)

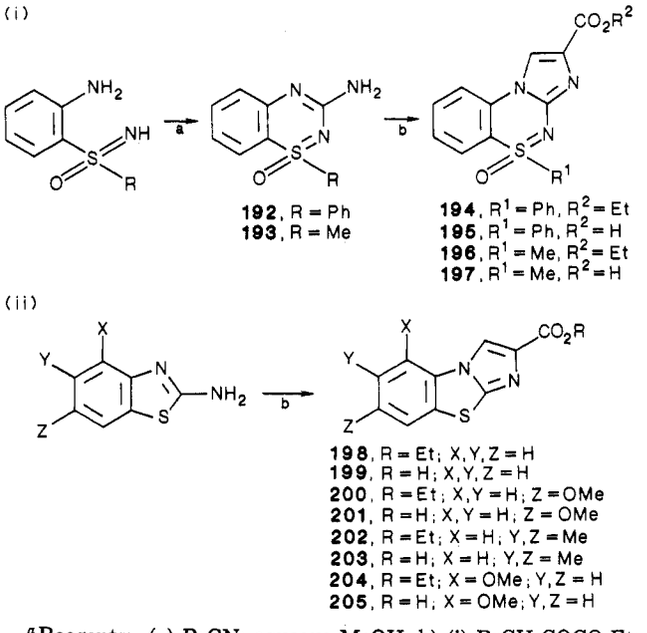
[a] 95% confidence limits in parentheses. [b] Inactive at 1 and 10 mg/kg. [c] Tested iv as HCl salts. [d] N: calcd, 41.33; found, 40.83.

Scheme X. Miscellaneous Analogues[a]



[a] Reagents: (a) (i) $BrCH_2COCO_2Et$; DME, (ii) Δ; EtOH; (b) $BrCH_2COCO_2Et$; EtOH, Δ; (c) rhodanine, NaOAc, Ac_2O, Δ; (d) (i) NaOH; H_2O, EtOH, (ii) HCl; (e) I_2; dioxane.

Scheme XI[a]

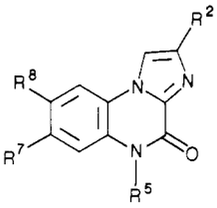


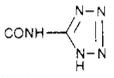
[a] Reagents: (a) BrCN; aqueous MeOH; b) (i) $BrCH_2COCO_2Et$; DME, (ii) Δ; EtOH (hydrolysis: (i) NaOH; H_2O, EtOH, (ii) HCl).

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**) 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

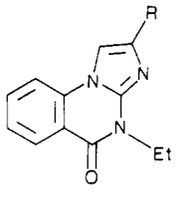
Table V. Imidazo[1,2-*a*]quinoxalinones



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	antiallergic activity, IgE, rat PCA: ED_{50},[a] mg/kg po
124	H	H	Et	CO_2Et	216–218	EtOH	63	$C_{15}H_{15}N_3O_3$	C,H,N		0.16 (0.05–0.64)
125	H	H	Pr	CO_2Et	212–214	EtOH	65	$C_{16}H_{17}N_3O_3$	C,H,N		1.21 (0.74–2.02)
126	H	H	CH_2Ph	CO_2Et	259–260	DMF/EtOH	89	$C_{20}H_{17}N_3O_3$	C,H,N		inactive[c]
127	H	H	H	CO_2H	272–275	EtOH/H_2O	95	$C_{11}H_7N_3O_3 \cdot 0.25H_2O$	C,H,N	0.16 (0.11–0.25)	2.0 (0.97–4.61)
128	H	H	Me	CO_2H	267–268	EtOH/H_2O	95	$C_{12}H_9N_3O_3$	C,H,N	0.031 (0.024–0.041)	1.28 (0.67–2.51)
129	H	H	Et	CO_2H	260–262	EtOH/H_2O	79	$C_{13}H_{11}N_3O_3$	C,H,N	0.01 (0.007–0.014)	0.45 (0.29–0.58)
130	H	H	Pr	CO_2H	232–234	EtOH/H_2O	95	$C_{14}H_{13}N_3O_3 \cdot H_2O$	C,H,N	0.01 (0.006–0.021)	0.24 (0.12–0.32)
131	H	H	Bu	CO_2H	220–222	EtOH/H_2O	95	$C_{15}H_{15}N_3O_3 \cdot H_2O$	C,H,N	0.023 (0.058–0.12)	0.59 (0.46–0.73)
133	Cl	Cl	H	CO_2H	>330	EtOH/H_2O	95	$C_{11}H_5Cl_2N_3O_3 \cdot H_2O$	C;[b]H,N		inactive[c]
134	H	H	Et	CH_2OH	215–218	EtOH	43	$C_{13}H_{13}N_3O_2$	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	$C_{13}H_{11}N_3O_2$	C,H,N		0.077 (0.028–0.149)
136	H	H	Et		>310	DMF	90	$C_{14}H_{12}N_8O_2 \cdot (C_3H_7NO)$[e]	C,H,N	0.32 (0.25–0.41)	

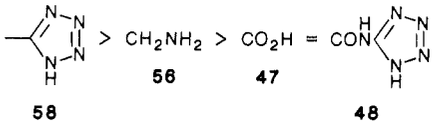
[a] 95% confidence limits in parentheses. [b] C: calcd, 41.80; found, 42.35. [c] Inactive at 10 mg/kg. [d] Tested as HCl salt. [e] One mole of DMF of crystallization.

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

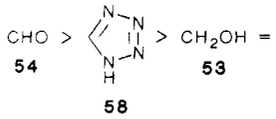


compd	R	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED_{50}, mg/kg iv	antiallergic activity, IgE, rat PCA: ED_{50}, mg/kg po
137	CO_2Et	215–217	Et_2O	49	$C_{15}H_{15}N_3O_3$	C,H,N		inactive
138	CO_2H	279–282	EtOH/H_2O	82	$C_{13}H_{11}N_3O_3 \cdot 0.75H_2O$	C,H,N	inactive	

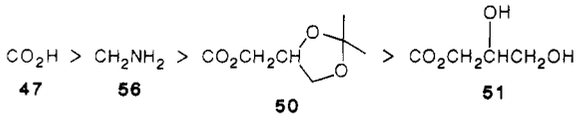
administration for compounds substituted only in the 2-position is as follows:



58 **56** **47** **48**



54 **58** **53**



47 **56** **50** **51**

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

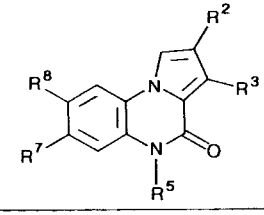
Cl > Br = SMe = SO_2Me > $OCHMe_2$ > SOMe = H = SONHMe > OMe

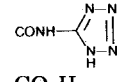
62 **63** **64** **67** **60** **65** **47** **69** **59**

By po administration only the 4-Br compound **63** is more active than **47**. Substituents in the 3-position such as Ph (**72**), CH_2OH (**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

(26) Kadin, S. B. U.S. Patent 4 075 343 21 Feb. 1978.

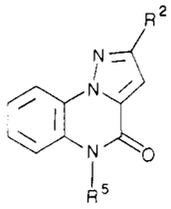
Table VII. Pyrrolo[1,2-*a*]quinoxalinones



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_2Et	197-198	EtOAc	41	$C_{15}H_{14}N_2O_3$	C,H,N		7.0 (3.55-11.7)
143	H	H	Bu	H	CO_2Et	146-148	Et_2O	44	$C_{18}H_{20}N_2O_3$	C,H,N		4.1 (1.95-11.5)
145	H	H	Me	H	CO_2H	330-333	$EtOH/H_2O$	95	$C_{13}H_{10}N_2O_3$	C,H,N	0.089 (0.063-0.125)	0.54 (0.45-0.63)
146	H	H	Et	H	CO_2H	314-316	$EtOH/H_2O$	94	$C_{14}H_{12}N_2O_3$	C,H,N	0.026 (0.019-0.035)	0.035 (0.024-0 053)
147	H	H	Pr	H	CO_2H	260-262	$EtOH/H_2O$	96	$C_{15}H_{14}N_2O_3$	C,H,N	0.019 (0.015-0.023)	0.032 (0.023-0.047)
148	H	H	Bu	H	CO_2H	212-214	$EtOH/H_2O$	89	$C_{16}H_{16}N_2O_3$	C,H,N	0.019 (0.014-0.024)	0.058 (0.039-0.063)
149	H	H	Pent	H	CO_2H	184-186	$EtOH/H_2O$	95	$C_{17}H_{18}N_2O_3$	C,H,N	0.087 (0.036-0.43)	0.31 (0.21-0.46)
150	H	H	Ph	H	CO_2H	304-306	EtOH	65	$C_{18}H_{12}N_2O_3$	C,H,N	1.57 (1.14-2.28)	18.9 (12.3-33.8)
151	H	H	cyclopentyl	H	CO_2H	215-216	$EtOH/H_2O$	95	$C_{17}H_{16}N_2O_3 \cdot 0.5H_2O$	C,H,N	0.037 (0.30-0.46)	1.96 (1.22-2.52)
152	H	H	isopropyl	H	CO_2H	238-240	$EtOH/H_2O$	94	$C_{15}H_{14}N_2O_3 \cdot 0.5H_2O$	C,H,N	0.85 (0.49-1.41)	
153	H	H	allyl	H	CO_2H	306-308	$EtOH/H_2O$	96	$C_{15}H_{12}N_2O_3$	C,H,N	0.035 (0.024-0.053)	0.28 (0.21-0.37)
154	Me	Me	Et	H	CO_2H	313-316	$EtOH/H_2O$	89	$C_{16}H_{16}N_2O_3 \cdot 0.5H_2O$	C,H,N	0.030 (0.022-0.040)	
155	Cl	Cl	Bu	H	CO_2H	281-283	$EtOH/H_2O$	92	$C_{16}H_{14}Cl_2N_2O_3$	C,H,Cl,N	0.014 (0.009-0.024)	0.117 (0.044-0.288)
156	Cl	H	Et	H	CO_2H	322-326	$EtOH/H_2O$	91	$C_{14}H_{11}ClN_2O_3$	C,H,N	0.035 (0.028-0.045)	0.29 (0.24-0.35)
157	H	Cl	Bu	H	CO_2H	275-276	EtOH	93	$C_{16}H_{15}ClN_2O_3$	C,H,Cl,N	0.019 (0.013-0.023)	0.114 (0.060-0.199)
158	H	H	Et	H	CH_2OH	171-173	EtOAc	88	$C_{14}H_{14}N_2O_2$	C,H,N		0.045 (0.032-0.069)
159	H	H	Et	H	CHO	252-255	$EtOAc/Et_2O$	82	$C_{14}H_{12}N_2O_2$	C,H,N		2.53 (1.88-2.85)
160	H	H	Et	H		295-297	DMF/EtOAc	48	$C_{14}H_{12}N_6O$	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	$C_{15}H_{13}N_7O_2$	C,H,N	0.18 (0.13-0.26)	
163	H	H	Et	CO_2Me	CO_2H	290-293	$EtOH/H_2O$	96	$C_{16}H_{14}N_2O_5$	C,H,N	inactive	

[a] 95% confidence limits in parentheses.

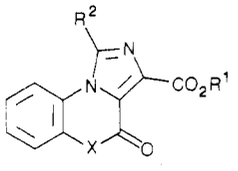
Table VIII. Pyrazolo[2,3-*a*]quinoxalinones



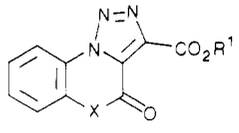
compd	R^5	R^2	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED_{50},[a] mg/kg iv	po
166	H	CO_2H	333–334[b]	$EtOH/H_2O$	93	$C_{11}H_7N_3O_3$	C,H,N	0.33 (0.08–1.71)	
170	Me	CO_2H	309–312	$EtOH/H_2O$	54	$C_{12}H_9N_3O_3$	C,H,N	0.19 (0.10–0.44)	
171	Et	CO_2H	242–244	$EtOH/H_2O$	66	$C_{13}H_{11}N_3O_3$	C,H,N	0.11 (0.06–0.22)	
172	Pr	CO_2H	228–229	$EtOH/H_2O$	51	$C_{14}H_{13}N_3O_3 \cdot H_2O$	C,H,N	0.023 (0.014–0.029)	

[a] 95% confidence limits in parentheses. [b] Reference 18, mp >315 °C.

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



178–181

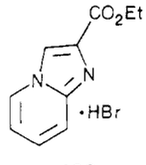


183, 185

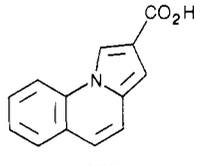
compd	X	R^1	R^2	mp, °C	recrystn solvent	yield, %	formula	anal.	antiallergic activity, IgE, rat PCA: ED_{50},[a] mg/kg iv	po
178	NH	H	H	>320	$EtOH/H_2O$	91	$C_{11}H_7N_3O_3$	C,H,N	0.104 (0.073–0.151)	inactive[b]
179	NH	H	Me	302–305	$EtOH/H_2O$	81	$C_{12}H_9N_3O_3$	C,H,N	0.37 (0.31–0.45)	
180	NH	H	Et	214–216	$EtOH/H_2O$	60	$C_{13}H_{11}N_3O_3$	C,H,N	inactive[c]	
181	NH	H	CH_2Ph	181–183	$EtOH/H_2O$	47	$C_{18}H_{13}N_3O_3$	C,H,N		inactive[c]
183	O	Me		205–207	EtOAc	54	$C_{11}H_7N_3O_4$	C,H,N		inactive[d]
185	NH	H		>320	$EtOH/H_2O$	76	$C_{10}H_6N_4O_3$	C,H,N	0.084 (0.058–0.12)	inactive[e]

[a] 95% confidence limits in parentheses. [b] Inactive at 20 mg/kg. [c] Inactive at 1 and 10 mg/kg. [d] 50% inhibition at 10 mg/kg. [e] 45% inhibition at 20 mg/kg.

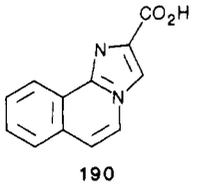
Table X. Related Ring Systems



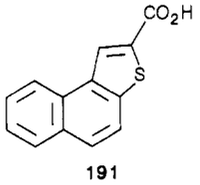
186



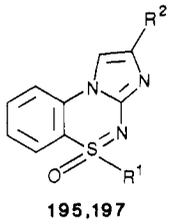
188



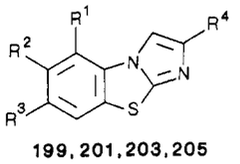
190



191



195, 197



199, 201, 203, 205

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]	$EtOH/Et_2O$	31	$C_{10}H_{11}N_2O_2Br$		inactive[c]	
188					242–247	$EtOH/H_2O$	82	$C_{13}H_9NO_2$	C,H,N	inactive[c]	
190					>370[d]	$EtOH/H_2O$	80	$C_{12}H_8N_2O_2$	C,H,N	inactive[c]	
191					281–284[e]	$EtOH/H_2O$	66	$C_{13}H_8O_2S$	C,H,S	inactive[c]	
195	Ph	CO_2H			181–183	$MeOH/Et_2O$	96	$C_{16}H_{11}N_3O_3S \cdot 0.5H_2O$	C,H,N,S	1.92 (1.07–3.93)	
197	Me	CO_2H			196–200	DMF/EtOAc	85	$C_{11}H_9N_3O_3S \cdot 0.5H_2O$	C,H,N,S	2.59 (2.20–3.00)	
199	H	H	H	CO_2H	254–255[f]	$EtOH/H_2O$	91	$C_{10}H_6N_2O_2S$	C,H,N,S	0.33 (0.19–0.59)	
201	H	H	MeO	CO_2H	270–273	$EtOH/H_2O$	86	$C_{11}H_8N_2O_3S \cdot 1.25H_2O$	C,H,N,S	0.62 (0.39–0.96)	
203	H	Me	Me	CO_2H	307–308	$EtOH/H_2O$	82	$C_{12}H_{10}N_2O_2S \cdot 0.33H_2O$	C,H,N,S	0.30 (0.22–0.38)	
205	MeO	H	H	CO_2H	288–290	$EtOH/H_2O$	85	$C_{11}H_8N_2O_3S$	C,H,N,S	0.16 (0.072–0.41)	

[a] 95% confidence limits in parentheses. [b] Reference 22, mp 174.5–175.5 °C. [c] Inactive at 1 and 10 mg/kg. [d] Reference 23. [e] Reference 24, mp 277–278 °C. [f] Reference 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 ED_{50}'s 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:

SO_2Me	>	MeO	>	Cl	>	SMe = SOMe = SONHMe = CF_3	>	Et	>	H
87		**81**		**80**		**83 85 88**		**90**		**82**		**47**

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) Imidazol1,2-*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) Pyrazolo[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*]quinoline[27] and imidazo[1,2-*a*]quinoxalines[28] 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 $CDCl_3$ or Me_2SO-d_6 with a Perkin-Elmer R12A spectrometer (60 MHz) with Me_4Si as internal standard. All OH and NH peaks were exchanged on D_2O 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 P_2O_5.

(a) Imidazo[2,1-*c*][1,4]benzoxazines.[9] ***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 **17**[9] (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 $CHCl_3$ to give **26** (750 mg, 44%) as pale pink crystals, mp 282–284 °C (from DMF–$CHCl_3$). Anal. ($C_{13}H_{11}N_7O_2$) 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 **3**[9] 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 (Me_2SO-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. ($C_{12}H_9N_7O_2$) C, H, N.

Reaction of the acid chloride of **3** with 5-aminotetrazole under azeotroping 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 (Me_2SO-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. ($C_{12}H_9N_7O_2$) 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 **19**[9] (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)–$CHCl_3$ (100 mL). The $CHCl_3$ layer was removed and the aqueous layer was further extracted with $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ extract was washed once with water, dried, and evaporated. Trituration with Et_2O gave **27** as colorless

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(29) Miller, P., unpublished results.

needles (0.35 g, 46%), mp 209–210 °C (from Et_2O). Anal. ($C_{13}H_{12}N_2O_4$) C, H, N.

1-(Hydroxymethyl)-4*H*-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–H_2O). Anal. ($C_{12}H_{10}N_2O_4 \cdot 0.5H_2O$) C, H, N.

The following compounds were prepared in the same way as **3**[9] in yields of 75–95%.

8-Chloro-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylic acid (34), mp 276–278 °C (from EtOH). Anal. ($C_{11}H_7ClN_2O_3$) C, H, Cl, N.

Methyl 8-chloro-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylate (35), mp 239–240 °C (from EtOH–Et_2O). Anal. ($C_{12}H_9ClN_2O_3$) C, H, N.

Methyl 8-methyl-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylate (36), mp 195–197 °C (from Et_2O). Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

8-Methyl-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylic acid (37), mp 221–223 °C (from EtOH–H_2O). Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.

4-Methyl-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylic acid (38), mp 210–211 °C (from EtOH–H_2O). Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.

4-Ethyl-4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylic acid (39), mp 172–174 °C (from EtOH–H_2O). Anal. ($C_{13}H_{12}N_2O_3 \cdot 0.5H_2O$) 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-ethoxycarbonyl,[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 $KMnO_4$ 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 $CHCl_3$–Et_2O). Anal. ($C_{10}H_{10}N_2S$) 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 $NaIO_4$ (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 $CHCl_3$–MeOH–Et_2O). Anal. ($C_{10}H_{10}N_2OS$) C, H, N, S.

2-Amino-3-(hydroxymethyl)quinoline. Ethyl 2-aminoquinoline-3-carboxylate[36] (8 g, 30 mmol) was dissolved in dry THF (200 mL) and added dropwise to $LiAlH_4$ (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–Et_2O). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

2-Amino-7-(trifluoromethyl)quinoline. 2-Chloro-7-(trifluoromethyl)quinoline (6.5 g, 28 mmol) [prepared[40] from 3-(trifluoromethyl)aniline] was suspended in aqueous ammonia (*d* 0.88, 75 mL) in a pressure vessel containing a small quantity of Cu_2Cl_2 (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 $CHCl_3$ (200 mL), and extracted with 2 N HCl (2 × 100 mL). The acid extract was made basic with Na_2CO_3 and extracted with $CHCl_3$ (2 × 100 mL). The combined $CHCl_3$ extract was dried and evaporated and the residue was triturated with $CHCl_3$–Et_2O to give the (trifluoromethyl)quinoline (2.56 g, 41%), mp 174–177 °C (from $CHCl_3$–Et_2O). Anal. ($C_{10}H_7F_3N_2$) C, H, N.

2-Amino-5-chloroquinoline. 2-Chloro-6-nitroanline[41] (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 $NaNO_2$ (3.5 g, 50.8 mmol) in water (10 mL) over 2 h. A further quantity of $NaNO_2$ (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 Me_2CO (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 Me_2CO (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 Me_2CO was removed under reduced pressure and the residue was dissolved in Et_2O (300 mL). The Et_2O solution was washed with water, dilute Na_2CO_3 solution, and water and then dried and evaporated. Chromatography of the red oil so obtained (SiO_2; 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 Na_2CO_3 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 Na_2CO_3, and extracted with CH_2Cl_2 (2 × 100 mL). The CH_2Cl_2 solution was washed with water, dried, and evaporated to give a pale brown solid (440 mg) after trituration with Et_2O–40–60 °C petroleum ether. The solid was chromatographed (SiO_2; $CHCl_3$) to give 2-amino-5-chloroquinoline (180 mg, 14.5%) as off-white needles, mp 176–178 °C (from EtOAc–Et_2O). Anal. ($C_9H_7N_2Cl$) 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)–Et_2O (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–Et_2O); IR 783, 1147, 1537, 1654, and 2900–3250 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.93 and 1.18 (2 × 3 H, 2 × t, J = 7 Hz, ester CH_3 and ethanol CH_3), 3.39 and 4.16 (2 × 2 H, 2 × q, J = 7 Hz, ester CH_2 and ethanol CH_2), 5.49 (2 H, br s, NCH_2), 7.9–8.8 (5 H, m, Ar H), and 9.45 (2 H, br d, 2-H). Anal. ($C_{14}H_{14}BrNO_3 \cdot C_2H_5OH$) 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 NH_4OAc (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 EtOAc–Et_2O) IR 753, 1252, 1559, 1706, and 3145 cm^{-1}; ^1H 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. ($C_{14}H_{14}N_2O_2$) C, H, N. The higher R_f product was **45** (0.92 g, 35%): mp 175–177 °C (from EtOAc–Et_2O); IR 745, 1249, 1538, 1571, 1702, and 3145 cm^{-1}; ^1H 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. ($C_{14}H_{17}N_2O_2$) 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 azeotroping 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 $C_2H_4Cl_2$ (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 $CHCl_3$–Et_2O 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 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 EtOAc–Et_2O 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 NH_2OH·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-carboxyaldehyde oxime (**55**) (2.55 g, 98%), mp 224–226 °C (from $CHCl_3$–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 $CHCl_3$–Et_2O). 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 $CHCl_3$–Et_2O). Anal. ($C_{15}H_{14}N_2O_4S$) 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

× 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. ($C_{15}H_{15}N_3O_3S$) 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 $CHCl_3$–Et_2O). Anal. ($C_{18}H_{12}N_2O_2$) 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 $Na_2S_2O_3$ (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 $CHCl_3$–Et_2O). Anal. ($C_{14}H_{11}BrN_2O_2$) 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 $NaIO_4$ (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. ($C_{15}H_{14}N_2O_3S$) 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. ($C_{15}H_{14}N_2O_4S$) 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. ($C_8H_5Cl_2N_3$) 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-chloroquinoxaline[16] (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 (Me_2SO-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. ($C_{13}H_{11}N_3O_3$) 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-oxo-imidazo[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-Tetrachloroquinoxaline[43] (3.46 g, 13 mmol) was added to EtOH (30 mL) and the mixture was saturated with NH_3 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 (SiO_2; 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–Et_2O); IR 882, 1033, 1231, 1281, 1471, 1660, and 3500 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.39 (3 H, t, CH_3), 4.43 (2 H, q, CH_2), 7.10 (2 H, br s, NH_2), and 7.52, 7.63 (2 × 1 H, 2 s, 5- and 8-H). Anal. ($C_{10}H_9Cl_2N_3O$) 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 (SiO_2; $CHCl_3$) 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–Et_2O); IR 1700, 3130 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.37 (6 H, t, 2 CH_3), 4.40 (4 H, q, 2 CH_2), 7.82 (1 H, s, 6-H), 8.68 (1 H, s, 9-H), and 9.26 (1 H, s, 1-H). Anal. ($C_{15}H_{13}Cl_2N_3O_3$) 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 (Me_2SO-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*]quinazoline-2-carboxylic Acid (138). 2-Amino-3-ethylquinazolin-4(3*H*)-one[44] (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*]quinazoline-2-carboxylate (**137**) (Table VI); IR 1672, 1713, and 3135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (6 H, t, 2 CH_3), 4.38 (2 H, q, CH_2), 4.35 (2 H, q, CH_2), 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 prepared[45] by treating benzimidazoles with alkyl or alkenyl bromo or iodo compounds in the presence of base. Chromatography (Al_2O_3; $CHCl_3$) gave the 1-substituted benzimidazoles as crude oils, which were used without distillation. 1-Phenylbenzimidazole[46] 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 Et_2O (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–Et_2O); IR 760, 1231, 1570, 1753, 3415, and 3490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3 H, t, ester CH_3), 1.70 (3 H, t, 3-CH_2CH_3), 4.26 (2 H, q, ester CH_2), 4.60 (2 H, q, 3-CH_2CH_3), 5.65 (2 H, s, 1-CH_2), 7.4–8.0 (4 H, m, Ar H), and 10.93 (1 H, s, 2-H). Anal. ($C_{13}H_{17}BrN_2O_2 \cdot H_2O$) 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 NEt_3 (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 Et_2O to give **144** (9.1 g, 50%) as buff needles: mp 184–186 °C (from Et_2O); IR 739, 747, 759, 1260, 1276, 1653, 1714, and 3125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, t, 5-CH_2CH_3), 1.36 (3 H, t, ester CH_3), 4.22 (2 H, q, 5-CH_2CH_3), 4.28 (2 H, q, ester CH_2), 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. ($C_{16}H_{16}N_2O_3$) 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 (Me_2SO-d_6) δ 1.22 (3 H, t, CH_3), 4.19 (2 H, q, CH_2), 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 NEt_3 (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 Et_2O); IR 742, 1261, 1278, 1660, 1722, 1749, and 3160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, CH_2CH_3), 3.80 (3 H, s, CH_3), 3.97 (3 H, s, CH_3), 4.21 (2 H, q, CH_2CH_3), 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. ($C_{17}H_{16}N_2O_5$) 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 diacid[18] **165** (7.65 g, 0.027 mol), platinum oxide (200 mg), and 10% Pd/C (200 mg) in aqueous NaOH (10%) was stirred under H_2 (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. ($C_{12}H_9N_3O_3$) 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 (H_2O), and evaporated to give **168** (0.75 g, 71%): mp 240–242 °C as colorless needles (from Et_2O); IR 742, 1272, 1348, 1660, 1725, and 3140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (3 H, s, 5-CH_3), 3.97 (3 H, s, ester CH_3), 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. ($C_{13}H_{11}N_3O_3$) 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 Et_2O) [anal. ($C_{14}H_{13}N_3O_3$) 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 Et_2O to precipitate a red solid. This was filtered and chromatographed twice (SiO_2; EtOAc and 5% MeOH–$CHCl_3$) to give **174** (0.81 g, 85%): mp 270–271 °C (EtOAc–$CHCl_3$); IR 1445, 1485, 1520, 1565, 1630, 1680, 1735, 3000, 3110, 3270, and 3520 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.8 (3 H, s, ester CH_3), 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. ($C_{12}H_9N_3O_3$) 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 ($CDCl_3$) δ 2.85 (3 H, s, 1-CH_3), 3.75 (3 H, s, ester CH_3), 7.3–8.0 (4 H, m, Ar H), 11.6 (1 H, s, 5-H). Anal. ($C_{13}H_{11}N_3O_3$) 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 **176**[9] (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 **177**[9] 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 **182**[21] (1.2 g, 5 mmol) in dioxane (5 mL) and Et_2O (10 mL) at 0 °C was treated with Cl_3CCO_2H (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 (SiO_2; $CHCl_3$) to give **183** (800 mg) (Table IX): IR 1510, 1610, 1620, 1740, 1770, and 3100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9 (3 H, s, CH_3), 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–$CHCl_3$); IR 1450, 1495, 1550, 1630, 1700, 1735, and 3320 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.95 (3 H, s, CH_3), 7.3–7.7 (3 H, m, Ar H), 8.4 (1 H, br d, 9-H). Anal. ($C_{11}H_8N_4O_3$) 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 $NaHCO_3$ 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 Na_2CO_3 solution and water, and evaporated to give a deep red oil, which was chromatographed (SiO_2; $CHCl_3$) to give **187** as lemon needles (3.41 g, 23%), mp 77–78 °C (Et_2O; petroleum ether). Anal. ($C_{15}H_{13}NO_2$) 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 (SiO_2; $CHCl_3$–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 $CHCl_3$–EtOAc). Anal. ($C_{18}H_{15}N_3O_3S$) 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. ($C_{13}H_{13}N_3O_3S$) 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-benzothiazolamine[48] with ethyl bromopyruvate in DME, evaporating the solvent, and refluxing the residue in EtOH, there were obtained after chromatography (SiO_2) the following esters: unsubstituted (**198**), mp 142–143 °C (lit.[25] mp 147–148 °C) [anal. ($C_{12}H_{10}N_2O_2S$) C, H, N, S]; 7-methoxy (**200**), mp 133–136 °C [anal. ($C_{13}H_{12}N_2O_3S$) C, H, N, S]; 6,7-dimethyl (**202**), mp 176–178 °C [anal. ($C_{14}H_{14}N_2O_2S$) C, H, N, S]; 5-methoxy (**204**), mp 145–148 °C [anal. ($C_{13}H_{12}N_2O_3S$) 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; $H_2C{=}CHCN$, 107-13-1; $BrCH_2COCO_2Et$, 10-23-1; $H_3CCHBrCOCO_2Et$, 57332-84-0; $BrCH_2CO_2Et$, 105-36-2; $H_3CC(OEt)_3$, 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-nitrodihydrocinnamonitrile, 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; glycerolacetonide, 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-chloroquinoxalinonium 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 propiolate, 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 (pentylenetetrazole 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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