112888-05-8; 11e, 112888-06-9; 11f, 112888-07-0; 11g, 112888-08-1; 11h, 112888-09-2; 12a, 112888-63-8; 12b, 112888-68-3; 12d, 112888-65-0; 12e, 112888-66-1; 13a, 112888-64-9; 13b, 112888-69-4; 13e, 112888-67-2; 14a, 118111-62-9; 14b, 118111-84-5; 14c, 118111-85-6; 14e, 118111-87-8; 15a, 112888-14-9; 15b, 112888-17-2; 15c, 112888-15-0; 15d, 112888-16-1; 16a, 118111-63-0; 16b, 112888-79-6; 17a, 112888-82-1; 17b, 112888-23-0; 18, 112887-93-1; methylamine, 74-89-5; 2-bromoethyl acetate, 927-68-4; 2,4-dichloro-6-methylquinazoline, 39576-82-4; phenol, 108-95-2; 2-methoxyethanol, 109-86-4; ethylamine, 75-04-7; ethylenediamine, 107-15-3; *N,N*-dimethylethylenediamine, 108-00-9; ethanolamine, 141-43-5; glycine ethyl ester hydrochloride, 623-33-6; dimethylamine, 124-40-3; imidazole, 288-32-4; thymidylate synthase, 9031-61-2.

2(1*H*)-Quinolinones with Cardiac Stimulant Activity. 2. Synthesis and Biological Activities of 6-(N-Linked, Five-Membered Heteroaryl) Derivatives

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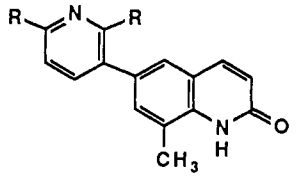
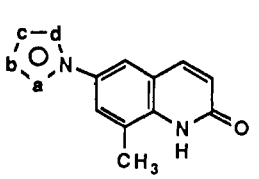
Received June 20, 1988

A series of 6-(N-linked, five-membered heteroaryl)-2(1*H*)-quinolinone derivatives was synthesized and evaluated for cardiotonic activity. Most compounds were prepared by sulfuric acid catalyzed cyclization of an *N*-(4-heteroarylphenyl)-3-ethoxypropenamide or by condensation of a 2-amino-5-heteroarylbenzaldehyde or -acetophenone derivative with the ylide derived from triethyl phosphonoacetate. In anesthetized dogs, 6-imidazol-1-yl-8-methyl-2(1*H*)-quinolinone (**3**; 25 μg/kg) produced a greater increase in cardiac contractility (percentage increase in d*P*/d*t* max) than alternative 6-(five-membered heteroaryl)-substituted analogues (**4–8**). Introduction of 4-methyl (**10**) or 2,4-dimethyl (**13**) substituents into the imidazole ring of **3** produced a marked increase in inotropic activity, and these compounds were some 10 and 5 times more potent than milrinone. Most of these quinolinones also displayed positive inotropic effects (decrease in QA interval) in conscious dogs after oral administration (0.0625–1 mg/kg) and in many cases (**3**, **5–7**, **9**, **11**, **13**, **16**) there was little difference in activities at both the 1- and 3-h time points. Compound **13** (62.5, 125, 250 μg/kg po) demonstrated dose-related cardiac stimulant activity which, in contrast to milrinone, was maintained over the whole 7-h test period. No changes in heart rate were detected at any dose level and compounds **3**, **9**, **10**, and **13** also displayed high selectivity for the stimulation of cardiac contractile force rather than heart rate in the Starling dog heart–lung preparation. Increases in d*P*/d*t* max of approximately 50% were accompanied by heart rate changes of less than 10 beats/minute. Physicochemical measurements gave a log *P* of 1.64 for **13** with pK_a values of 7.13 ± 0.04 and 11.5 ± 0.2 for the imidazole and quinolinone moieties, respectively. X-ray structural analysis of **13** showed the imidazole and quinolinone rings at 52° to one another in close agreement with the minimum-energy conformation (30°) suggested by PCILO calculations. 6-(2,4-Dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**13**, UK-61,260) is currently undergoing phase II clinical evaluation in congestive heart failure patients.

In a previous paper,[1] the synthesis and cardiac stimulant activities of a series of 2(1*H*)-quinolinone derivatives incorporating six-membered, heteroaryl substituents were described. These structure–activity relationship (SAR) studies identified the quinolinone 6-position as the preferred location for the heteroaryl moiety and also demonstrated the beneficial effects of an 8-methyl substituent. Two compounds from this series (**1a**, **1b**) showed greater



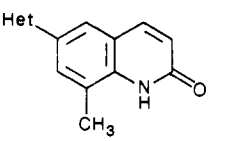
1a, R = H
1b, R = CH_3



2, a - d = N or C

intrinsic inotropic potency than milrinone and also improved duration of action after oral administration to conscious dogs. Moreover, **1a** and **1b** and related analogues had barely any effect on heart rate. In order to define the individual structural features that influence this favorable hemodynamic profile, a series of 8-methyl-2(1*H*)-quinolinones (**2**) incorporating various N-linked, five-membered heteroaryl moieties at the 6-position has been synthesized[2] and SARs for cardiac stimulant activity determined. Manipulation of the location and number of nitrogen atoms in these heteroaryl systems allows the electron-withdrawing capacity of the 6-substituent to be varied in a controlled manner and its effects on cardiac stimulant activity determined. Moreover, five-membered di- and triaza heterocycles are less susceptible to metabolic

Table I. Synthetic Routes and Physicochemical Data for 6-Heterocyclic 8-Methyl-2(1*H*)-quinolinone Derivatives



no.	Het	route	mp, °C	formula	anal.
3	imidazol-1-yl	A	259–262	$C_{13}H_{11}N_3O$	C, H, N
4	pyrazol-1-yl	A	229–231	$C_{13}H_{11}N_3O$	C, H, N
5	1,2,4-triazol-1-yl	A	318–321	$C_{12}H_{10}N_4O$	C, H, N
6	1,2,4-triazol-4-yl	A	365–369	$C_{12}H_{10}N_4O \cdot H_2O$	C,[a] H, N[b]
7	tetrazol-1-yl	A	267–268	$C_{11}H_9N_5O \cdot 0.5H_2O$	C, H, N
8	tetrazol-2-yl	B	264–266	$C_{11}H_9N_5O \cdot 0.25H_2O$	C, H, N

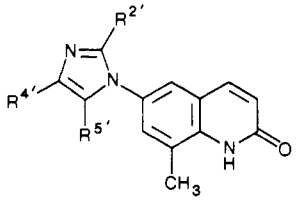
[a] C: calcd, 59.0; found, 59.7. [b] N: calcd, 23.0; found, 22.5.

(1) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1988**, *31*, 2048.

(2) Campbell, S. F.; Roberts, D. A. European Patent 0166533, 1986; *Chem. Abstr.* **1986**, *105*, 115061z.

0022-2623/89/1832-0575$01.50/0

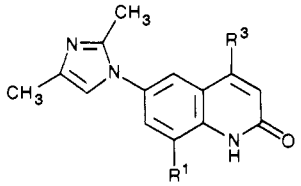
Table II. Synthetic Routes and Physicochemical Data for 6-Imidazol-1-yl-8-methyl-2(1*H*)-quinolinone Derivatives



no.	$R^{2'}$	$R^{4'}$	$R^{5'}$	route	mp, °C	formula	anal.
9	CH_3	H	H	A	295	$C_{14}H_{13}N_3O$	C, H, N
10	H	CH_3	H	A	292–295	$C_{14}H_{13}N_3O$	C,[a] H, N
11	H	H	CH_3	A	255–259	$C_{14}H_{13}N_3O$	C, H, N
12	H	CF_3	H	A	294	$C_{14}H_{10}F_3N_3O{\cdot}0.25H_2O$	C, H, N
13	CH_3	CH_3	H	A	323–325	$C_{15}H_{15}N_3O$	C, H, N

[a] C: calcd, 70.3; found, 69.8.

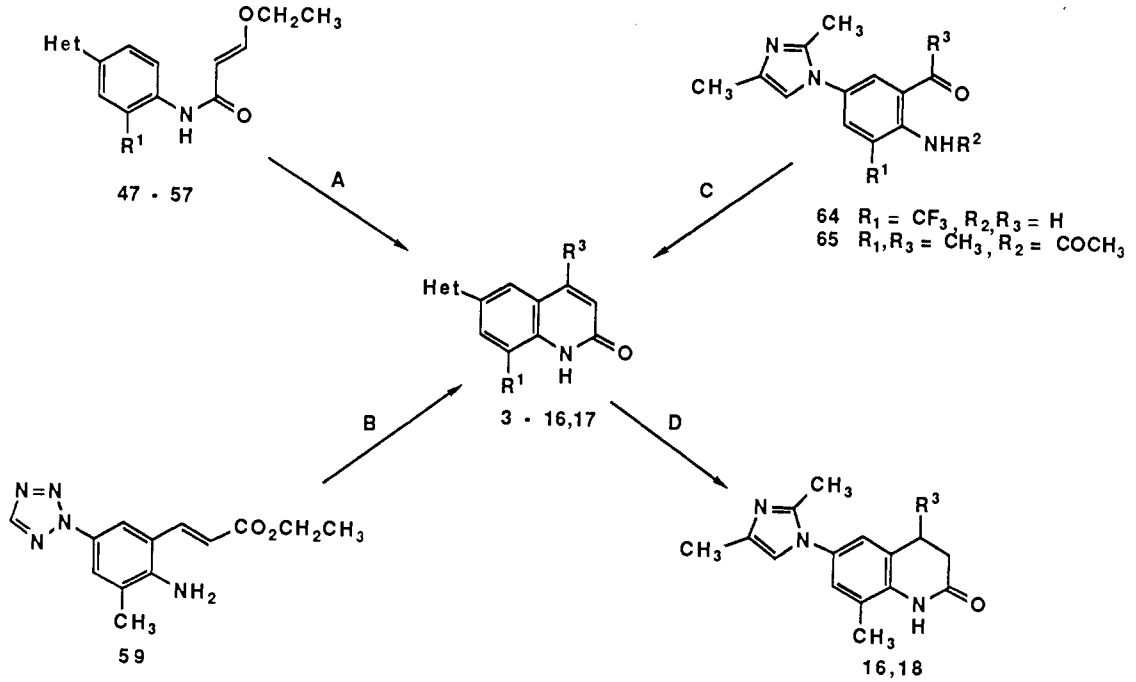
Table III. Synthetic Routes and Physicochemical Data for 6-(2,4-Dimethylimidazol-1-yl)-2(1*H*)-quinolinone Derivatives



no.	R^1	R^3	route	mp, °C	formula	anal.
14	H	H	A	297–300	$C_{14}H_{13}N_3O$	C, H, N
15	CF_3	H	C	230–233	$C_{15}H_{12}F_3N_3O$	C, H, N
16	CH_3	H[a]	D	260–262	$C_{15}H_{17}N_3O$	C, H, N
17	CH_3	CH_3	C	291–293	$C_{16}H_{17}N_3O{\cdot}0.25H_2O$	C, H, N
18	CH_3	CH_3[a]	D	243–246	$C_{16}H_{19}N_3O$	C, H, N

[a] 3,4-Dihydro.

Scheme I

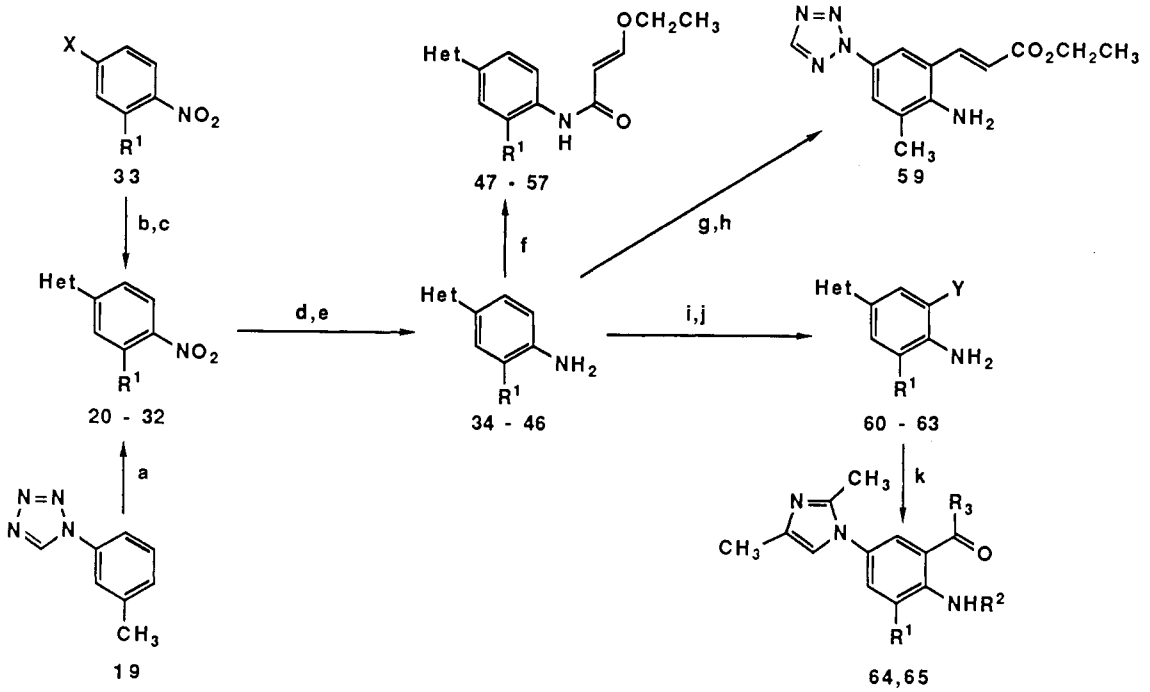


N-oxidation than the pyridyl systems in series 1 and improved in vivo performance might be expected. As a result of these studies, **13** (UK-61,260) was selected for further development[3,4] and is currently undergoing phase II clinical evaluation for the treatment of congestive heart failure.

Chemistry. All of the compounds in Tables I–III, which were evaluated for cardiac stimulant activity, were prepared by the synthetic routes A–D, as summarized in Scheme I. Thus, sulfuric acid catalyzed cyclization of the *N*-(4-heteroarylphenyl)-3-ethoxypropenamides (**47–57**) provided quinolinones (**3–7, 9–14**) (route A).[1] In situ isomerization of the *trans*-cinnamate **59** with hydrochloric acid followed by subsequent ring closure gave **8** (route B). Attempted synthesis of the 8-(trifluoromethyl)quinolinone

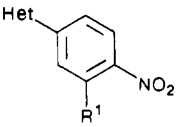
(3) Ellis, P.; Henderson, C. G.; Samuels, G. M. R. *Br. J. Pharmacol.* **1987**, *91*, 392P.
(4) Alabaster, C. T.; Rance, D. J. *Br. J. Pharmacol.* **1987**, *91*, 391P.

Scheme II[a]



[a] Reagents: (a) HNO_3; (b) heterocycle/Na_2CO_3/DMF; (c) HCONHNHCHO; (d) $SnCl_2.2H_2O/C_2H_5OH$; (e) H_2/Pd or H_2/RaNi; (f) $C_2H_5OCH{=}CHCOCl$/pyridine; (g) ICl; (h) $CH_2{=}CHCO_2C_2H_5/(CH_3CO_2)_2Pd/(C_2H_5)_3N$; (i) Br_2; (j) CuCN; (k) $[(CH_3)_2CHCH_2]AlH$ or CH_3Li followed by CH_3COCl.

Table IV. Physicochemical Properties for 2,4-Disubstituted-nitrobenzene Derivatives



no.	Het	R^1	mp, °C	formula	anal.
20	imidazol-1-yl	CH_3	112–115	$C_{10}H_9N_3O_2$	C, H, N
21	pyrazol-1-yl	CH_3	87–88	$C_{10}H_9N_3O_2{\cdot}0.66H_2O$	C, H, N
22	1,2,4-triazol-1-yl	CH_3	116–117	$C_9H_8N_4O_2$	C, H, N
23	1,2,4-triazol-4-yl	CH_3	208–210	$C_9H_8N_4O_2$	C, H, N
24	tetrazol-1-yl	CH_3	166–168	$C_8H_7N_5O_2$	C, H, N
25	tetrazol-2-yl	CH_3	107–110	$C_8H_7N_5O_2$	C, H, N
26	2-methylimidazol-1-yl	CH_3	135	$C_{11}H_{11}N_3O_2$	C, H, N
27	4-methylimidazol-1-yl	CH_3	144–147	$C_{11}H_{11}N_3O_2$	C, H, N
28[a]	5-methylimidazol-1-yl	CH_3		$C_{11}H_{11}N_3O_2$	
29	4-trifluoromethylimidazol-1-yl	CH_3	147	$C_{11}H_8F_3N_3O_2$	C, H, N
30	2,4-dimethylimidazol-1-yl	CH_3	135–138	$C_{12}H_{13}N_3O_2$	C, H, N
31	2,4-dimethylimidazol-1-yl	H	189	$C_{11}H_{11}N_3O_2$	C, H, N
32	2,4-dimethylimidazol-1-yl	CF_3	169–171	$C_{12}H_{10}F_3N_3O_2$	C, H, N

[a] Impure mixture with **27**.

15 was unsuccessful via route A due to acid-catalyzed fragmentation of the propenamide intermediate to the corresponding aniline (**46**). Presumably, the combined electron-withdrawing effects of the trifluoromethyl group and the protonated imidazolyl system deactivate the aromatic ring toward electrophilic attack. Similarly, treatment of *N*-[4-(2,4-dimethylimidazol-1-yl)-2-methylphenyl]-3-oxobutanamide with sulfuric acid also resulted in hydrolysis, although related cyclizations in systems lacking the additional heterocyclic substituent proceed satisfactorily.[5] However, reaction of the benzaldehyde **64** or the acetophenone **65** with the ylide derived from triethyl phosphonoacetate provided **15** and **17** directly (route C), albeit in low yield. Finally, catalytic hydrogenation of **13** and **17** in the presence of palladium gave the 3,4-dihydro derivatives (**16**, **18**) (route D).

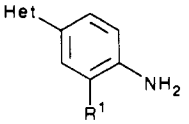
Synthesis of the intermediates required for the preparation of the 2(1*H*)-quinolinone derivatives in Tables I–III are summarized in Scheme II. Nitration of 1-(3-methylphenyl)tetrazole (**19**) gave **24** while reaction of 4-fluoro-2-methylnitrobenzene (**33**, $R^1 = CH_3$, X = F) with an appropriate heterocycle in DMF/sodium carbonate at 100–150 °C provided **20–22** and **25–32**. In the case of **22** and **25**, nucleophilic aromatic substitution proceeded regioselectively at the triazole N-1 and tetrazole N-2 centers, respectively.[6,7] Reaction of **33** ($R^1 = CH_3$, X = F) with 4-methylimidazole gave a 9:1 mixture of **27** and **28** from

(5) Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1986**, *29*, 2427.

(6) Jacquier, R.; Roumestant, M.-L.; Viallefont, P. *Bull. Soc. Chim. Fr.* **1967**, 2634.

(7) Katritzky, A. R.; Lagowski, J. M. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; p 39.

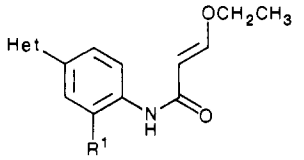
Table V. Physicochemical Properties for 2,4-Disubstituted Aniline Derivatives



no.	Het	R^1	mp, °C	formula	anal.
34	imidazol-1-yl	CH_3	131–134	$C_{10}H_{11}N_3$	C, H, N
35	pyrazol-1-yl	CH_3	263–266	$C_{10}H_{11}N_3 \cdot HCl \cdot 0.25H_2O$	C, H, N
36	1,2,4-triazol-1-yl	CH_3	122–125	$C_9H_{10}N_4$	C, H, N
37	1,2,4-triazol-4-yl	CH_3	152–154	$C_9H_{10}N_4$	C, H, N
38	tetrazol-1-yl	CH_3	100–103	$C_8H_9N_5$	C, H, N
39	tetrazol-2-yl	CH_3	110–112	$C_8H_9N_5$	C, H, N
40	2-methylimidazol-1-yl	CH_3	166	$C_{11}H_{13}N_3 \cdot 0.25H_2O$	C, H, N
41	4-methylimidazol-1-yl	CH_3	109–112	$C_{11}H_{13}N_3$	C, H, N
42	5-methylimidazol-1-yl	CH_3	162–166	$C_{11}H_{13}N_3$	C, H, N
43	4-(trifluoromethyl)imidazol-1-yl	CH_3	230	$C_{11}H_{10}F_3N_3 \cdot HCl$	C, H, N
44	2,4-dimethylimidazol-1-yl	CH_3	118–120	$C_{12}H_{15}N_3$	C,[a] H, N
45[22]	2,4-dimethylimidazol-1-yl	H	120	$C_{11}H_{13}N_3$	C, H, N[b]
46	2,4-dimethylimidazol-1-yl	CF_3	126–127	$C_{12}H_{12}F_3N_3$	C, H, N

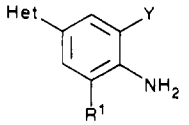
[a] C: found, 71.0; calcd, 71.6. [b] N: found, 21.8; calcd, 22.4.

Table VI. Physicochemical Data for *N*-(2,4-Disubstituted aryl)-3-ethoxypropenamide Derivatives



no.	Het	R^1	mp, °C	formula	anal.
47	imidazol-1-yl	CH_3	141–144	$C_{15}H_{17}N_3O_2$	C, H, N
48	pyrazol-1-yl	CH_3	159–160	$C_{15}H_{17}N_3O_2$	C, H, N
49	1,2,4-triazol-1-yl	CH_3	163–165	$C_{14}H_{16}N_4O_2$	C, H, N
50	1,2,4-triazol-4-yl	CH_3	207–209	$C_{14}H_{16}N_4O_2$	C, H, N
51	tetrazol-1-yl	CH_3	179–181	$C_{13}H_{15}N_5O_2$	C, H, N
52	2-methylimidazol-1-yl	CH_3	260	$C_{16}H_{19}N_3O_2 \cdot HCl$	C, H, N
53	4-methylimidazol-1-yl	CH_3	181–183	$C_{16}H_{19}N_3O_2$	C, H, N
54	5-methylimidazol-1-yl	CH_3	131–133	$C_{16}H_{19}N_3O_2$	C, H, N
55	4-(trifluoromethyl)imidazol-1-yl	CH_3	194	$C_{16}H_{16}F_3N_3O_2$	C, H, N
56	2,4-dimethylimidazol-1-yl	CH_3	143–145	$C_{17}H_{21}N_3O_2$	C, H, N
57	2,4-dimethylimidazol-1-yl	H	267	$C_{16}H_{19}N_3O_2 \cdot HCl$	C, H, N

Table VII. Physicochemical Data for 2,4,6-Trisubstituted Aniline Derivatives



no.	Het	R^1	Y	mp, °C	formula	anal.
58	tetrazol-2-yl	CH_3	I	196–199	$C_8H_8IN_5$	C, H, N
60	2,4-dimethylimidazol-1-yl	CH_3	Br	176–181	$C_{12}H_{14}BrN_3 \cdot 0.5H_2O$	C, H, N
61	2,4-dimethylimidazol-1-yl	CF_3	Br	149	$C_{12}H_{11}BrF_3N_3$	C, H, N
62	2,4-dimethylimidazol-1-yl	CH_3	CN	209–214	$C_{13}H_{14}N_4$	C,[a] H, N
63	2,4-dimethylimidazol-1-yl	CF_3	CN	208–210	$C_{13}H_{11}F_3N_4$	C, H, N

[a] C: found, 68.3; calcd, 69.0.

which **27** could be isolated,[8] but **28** was contaminated with isomeric product. For **30**, the 2,4-dimethyl substituents exerted more pronounced steric control, and less than 3% of the 2,5-isomer was detected. Similar high regioselectivity was observed in the synthesis of **31** and **32** from **33** (X = F, R^1 = H or CF_3). Finally, reaction of 3-methyl-4-nitroaniline (**33**, $R^1 = CH_3$, X = NH_2) with 1,2-diformylhydrazine gave **23**.

Reduction of the nitro compounds in Table IV with stannous chloride in ethanol (**20–22**, **24–29**, **31**) or by catalytic hydrogenation using Raney nickel (**23**) or palladium (**30**, **32**) gave the aniline derivatives (**34–46**) in Table V. Reduction of impure **28**, which also contained **27**, gave a mixture of **41** and **42** from which the latter compound was isolated by chromatography. Acylation of **34–38** and **40–45** with *trans*-3-ethoxyprop-2-enoyl chloride then provided the intermediate propenamides (**47–57**, Table VI) for use in route A. Alternatively, iodination of **39** gave **58** (Table VII), which on treatment with ethyl acrylate under Heck conditions[9] gave **59** for use in route B. Bromination, under acid conditions, of **44** or **46**[10] ortho to the amino

(8) Imbach, J.-L.; Jacquier, R. *C. R. Hebd. Seances Acad. Sci.* **1963**, *257*, 2683.

(9) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

Table VIII. Inotropic Activity for Quinolinone Derivatives (2) following Intravenous and Oral Administration to Dogs

no.	% increase in dP/dt max[a]	dose, μg/kg, iv	rel inotropic potency[b]	decrease in QA interval (ms ± SEM)[c] 1 h	3 h	dose, mg/kg, po
3	139	25	4.5	20 ± 2	15 ± 3	0.25
4	79	50	1.7	-	-	-
5	67	25	3.6	21 ± 1	21 ± 1	0.5
6	68	50	2.3	15 ± 2	17 ± 2	0.25
7	117	25	3.4	15 ± 2	16 ± 2	0.25
8	24	50	1.1	-	-	-
9	50	12.5	5.5	14 ± 3	13 ± 2	0.125
10	59	6.25	16.3	12 ± 1	7 ± 2	0.0625
11	55	12.5	4.9	14 ± 2	11 ± 2	0.125
12	82	12.5	4.5	11 ± 2	5 ± 1	0.125
13	40	12.5	7.6	16 ± 1	17 ± 1	0.25
14	29	250	0.2	-	-	-
15	22	250	0.2	-	-	-
16	52	50	0.9	12 ± 2	13 ± 1	1.0
17	10	10	1.2	-	-	-
18	20	10	1.9	-	-	-
milrinone	46	25	1.6	13 ± 4	7 ± 3	0.25
CI-930	100	50	1.6	-	-	-

[a] Anesthetized dog. [b] Compared to the percentage increase in dP/dt max observed with 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline (50 μg/kg) in the same dog (see the Experimental Section). [c] Conscious dog (n = 4).

function provided **60** and **61**, which on treatment with cuprous cyanide in 1-methyl-2-pyrrolidinone at 150 °C gave the 3,5-disubstituted anthranilonitriles (**62**, **63**) (Table VII). The intermediates (**64**, **65**) required for route C were then obtained by reduction of **63** with diisobutylaluminum hydride and by reaction of **62** with methyllithium followed by N-acetylation, respectively.

SARs for Inotropic Activity. All of the quinolinone derivatives listed in Tables I–III were administered intravenously to anesthetized dogs in order to assess positive inotropic activity.[11] Changes in cardiac contractility are expressed as percentage increases in dP/dt_{max} and also as inotropic potencies relative to the response observed in the same animal with 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)-ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline[1] (Table VIII). Comparison of quinolinones **3**–**8** indicated improved inotropic activity for **3**, **5**, and **7** and the 6-imidazol-1-yl-8-methyl-2(1*H*)-quinolinone nucleus (**3**) was chosen for more detailed SAR studies. Introduction of a 2- or 5-methyl substituent (**9** and **11**, respectively) into the imidazole ring maintained inotropic potency similar to that of **3** whereas the 4-methyl derivative (**10**) displayed a marked increase in activity and was some 10 times more active than milrinone. By contrast, the corresponding 4-trifluoromethyl analogue (**12**) was only as active as **3**, which may suggest that increasing electron density at the imidazole 3-nitrogen center in **10** is beneficial for inotropic potency. Combination of a 2- and 4-methyl substituent (**13**) did not maintain activity at the exceptional level displayed by **10** but, even so, this 2,4-dimethylimidazolyl derivative was still some 5 times more potent than milrinone or CI-930.[12] Various structural modifications of the quinolinone nucleus of **13** were examined, but none provided any improvement. Thus, removal of the 8-methyl substituent (**14**) led to a marked drop in inotropic activity, which is consistent with previous observations in this quinolinone series.[1] An 8-methyl moiety appears to be particularly beneficial for increasing intrinsic inotropic activity and also for improving in vivo performance possibly by protecting the quinolinone system from oxidative metabolism.[13] The poor activity of the trifluoromethyl analogue (**15**) again underlines the restricted scope for structural manipulation at the 8-position. Reduction of the 3,4-double bond (**16**), introduction of a 4-methyl substituent (**17**), or combination of both structural modifications (**18**) also reduced inotropic activity in this series.

Most of the compounds in Table VIII were also examined for effects on cardiac contractility (decrease in QA interval) after oral administration to conscious dogs. Thus, the relative positive inotropic activities displayed by **3** and **5**–**7** were roughly comparable to those obtained in anesthetized animals with **3** showing slight superiority. Similar maximum effects on cardiac contractility were obtained with **9**, **11**, and **13**, and there was little difference in activities at both the 1- and 3-h time points. Thus, a prolonged duration of positive inotropic action appears to be characteristic of several members of this novel quinolinone series. By contrast, the response to **10** was shorter lived, although the compound did display substantial activity at extremely low dose level (62 μg/kg) and was some 4 times more potent than milrinone.

More extensive studies were undertaken with **13**, and dose-related increases in inotropic activity were observed (Figure 1) following oral administration of 62, 125, and 250 μg/kg. Moreover, in all cases increases in cardiac contractility were well maintained over the whole 7-h test period. By contrast, the positive inotropic response to milrinone was maximum at 1–2 h postdose, but then decayed rapidly over the rest of the experimental time course.

The maximum decrease in QA interval observed with **13** at the top dose level (250 μg/kg, po) corresponds approximately to a 60% increase in dP/dt_{max}. However, despite such a marked enhancement of cardiac contractility, heart rate changed by less than 5 beats/min over the whole of the experimental period (data not presented). Moreover, evaluation of **3**, **9**, **10**, and **13** in the Starling heart–lung preparation confirmed high selectivity for stimulation of cardiac contractile force rather than heart rate (Figure 2). Indeed, for **3**, **9**, and **13** increases in dP/dt_{max} of approximately 50% were accompanied by

(10) Bromination of **46** under any other conditions than those described in the Experimental Section led to reaction at the 5-position of the imidazole ring.

(11) In these experiments, none of the compounds had any significant effect on blood pressure or heart rate.

(12) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099.

(13) Mori, H.; Kido, M.; Murakami, N.; Morita, S.; Korhi, H.; Nakagawa, K.; Uno, T.; Ishihara, T. *Yakugaku Zasshi* **1977**, *97*, 350.

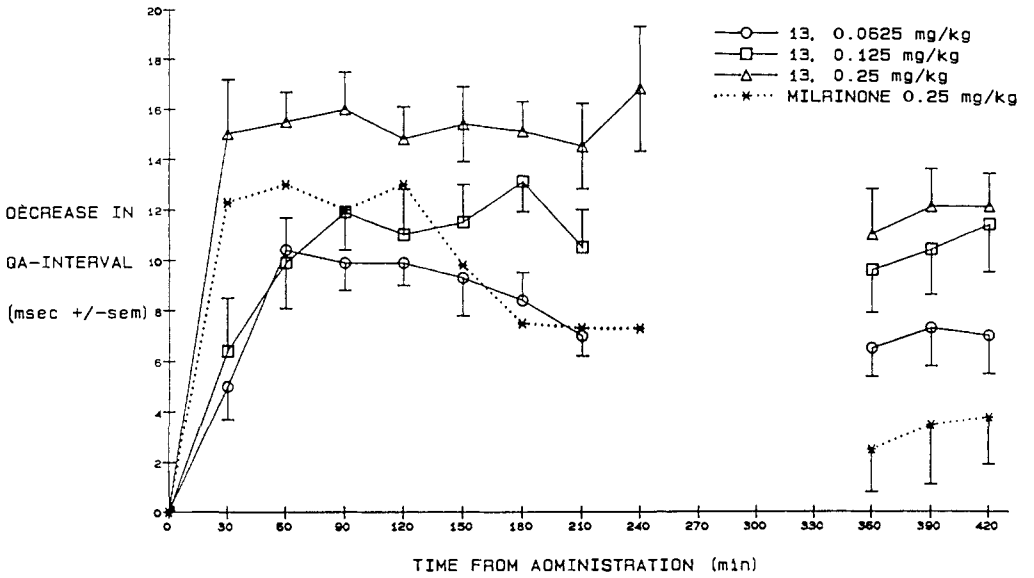


Figure 1. Effects of **13** (n = 8) and milrinone (n = 4) on QA interval in conscious dogs following oral administration.

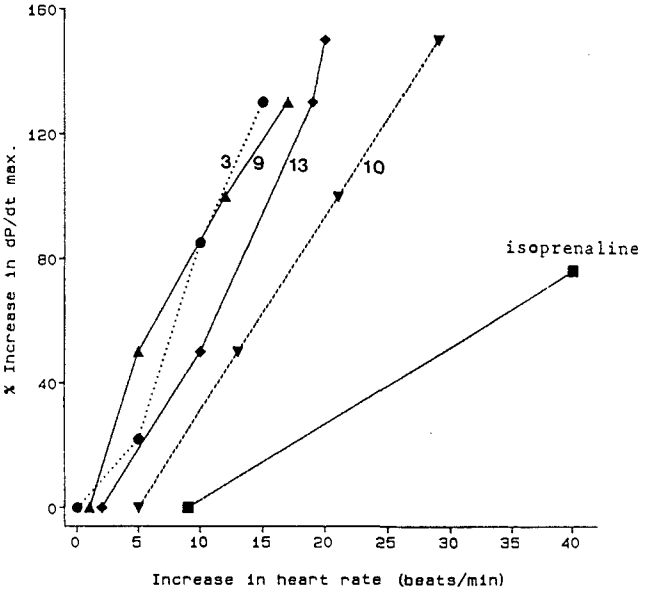


Figure 2. Effects of **3**, **9**, **10**, **13**, and isoprenaline on contractile force and heart rate in the dog heart–lung preparation (for dose levels see the Experimental Section).

heart-rate changes of less than 10 beats/min. By contrast, a similar degree of positive inotropism observed with isoprenaline was accompanied by a tachycardia of some 30 beats/min. Finally, it is also important to note that **13** has been shown to display direct vasodilator activity over the same dose range which produces physiologically relevant increases in cardiac contractility[3].

Physicochemical Data. A space-fill representation of the single-crystal X-ray structure[14] of **13** is presented in Figure 3. The individual imidazole and quinolinone rings are essentially planar but are twisted at 52° to one another in order to relieve steric interactions between the 2-methyl group and the 5,7 hydrogen atoms. PCILO molecular orbital calculations[15,16] suggest a minimum-energy conformation for **13** with a 30° torsion angle between the

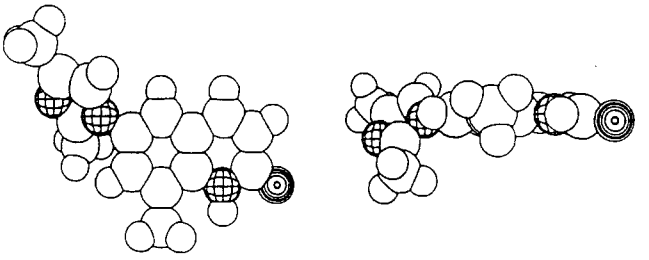


Figure 3. Space fill representation of the X-ray structure of **13**.

2,4-dimethylimidazole and 2(1*H*)-quinolinone systems, in close correspondence (<1.0 kcal/mol) with the X-ray structure. Physicochemical measurements indicate a log P of 1.64 for **13** with pK_a values of 7.13 ± 0.04 and 11.5 ± 0.2 for the imidazole and quinolinone moieties, respectively.[17] Thus, **13** will be approximately 35% protonated at physiological pH, although the current SAR studies suggest that ionization is not essential for cardiac stimulant activity.

In summary, this paper describes SARs for a novel series of 2(1*H*)-quinolinone cardiac stimulants that incorporate a range of N-linked, five-membered heterocyclic moieties at the 6-position. These studies identified the beneficial effects of a 6-imidazolyl and an 8-methyl substituent, and 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**13**, UK-61,260) was selected for detailed evaluation. This compound displayed marked positive inotropic activity after intravenous and oral administration to dogs, with a long duration of action and little effect on heart rate. Direct vasodilator activity has previously been demonstrated for **13**.[3] It would be expected that such a favorable pharmacological profile would address the underlying hemodynamic derangements characteristic of congestive heart failure, and **13** is now undergoing phase II clinical evaluation.

Experimental Section

Chemistry. Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin-Elmer 257 (IR), AEI MS 12 or VG 7070F (MS), Varian XL 100, Bruker WM250, and Nicolet QE300 (NMR) instruments and were consistent with

(14) We thank Dr. Jon Bordner (Pfizer Central Research. Groton, CT) for these data.
(15) Programme 221 from Quantum Chemistry Program Exchange Bloomington, IN.
(16) Rigid rotation around the imidazole quinolinone bond was undertaken in 10-deg steps.
(17) pK_a determined by UV spectrometry; apparent log P was determined by the conventional "shake-flask" method using octanol/water at pH 7.4.

assigned structures. NMR data are reported in ppm relative to external TMS (0.0 ppm) as standard, and are referenced to the solvent shift (DMSO-d_6, 2.49 ppm). Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

Route A. 6-Imidazol-1-yl-8-methyl-2(1*H*)-quinolinone (3). *trans*-1-[4-(3-Ethoxypropenamido)-3-methylphenyl]imidazole (**47**, 2.7 g, 10 mmol) was added portionwise with stirring to concentrated sulfuric acid (98% w/w, 20 mL) at 0 °C. After 24 h at room temperature, the mixture was poured carefully onto ice (200 g) and the resulting solution was adjusted to pH 8 with saturated sodium carbonate solution. The suspension was extracted with methanol/chloroform (1:4, 7 × 200 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica by eluting with methanol/chloroform (1:19) and the product was recrystallized from ethyl acetate/methanol to give 6-imidazol-1-yl-8-methyl-2(1*H*)-quinolinone (1.71 g, 76%): mp 259–262 °C; ^{1}H NMR (DMSO-d_6) δ 2.47 (3 H, s), 6.59 (1 H, d), 7.09 (1 H, s), 7.69 (1 H, s), 7.70 (1 H, s), 7.79 (1 H, s), 7.89 (1 H, d), 8.20 (1 H, s), 11.09 (1 H, s) ppm. Anal. ($C_{13}H_{11}N_3O$) C, H, N.

Route B. 8-Methyl-6-tetrazol-2-yl-2(1*H*)-quinolinone 0.25-Hydrate (8). Hydrochloric acid (5 M, 20 mL) was added to *trans*-ethyl 3-(2-amino-3-methyl-5-tetrazol-2-ylphenyl)prop-2-enoate (**59**, 0.45 g, 1.6 mmol) and the mixture was heated on a steam bath for 1 h. The mixture was cooled, adjusted to pH 7 (aqueous Na_2CO_3 solution), and extracted with dichloromethane/methanol (20:1, 3 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate/methanol (10:1) to give 8-methyl-6-tetrazol-2-yl-2(1*H*)-quinolinone 0.25-hydrate (0.08 g, 21%): mp 264–266 °C; ^{1}H NMR (DMSO-d_6) δ 2.54 (3 H, s), 6.63 (1 H, d), 8.08 (1 H, s), 8.10 (1 H, d), 8.32 (1 H, s), 9.24 (1 H, s) ppm. Anal. ($C_{11}H_9N_5O{\cdot}0.25H_2O$) C, H, N.

Route C. 8-(Trifluoromethyl)-6-(2,4-dimethylimidazol-1-yl)-2(1*H*)-quinolinone (15). Triethyl phosphonoacetate (0.38 g 1.7 mmol) was added to a stirred suspension of sodium hydride (0.076 g of a 50% dispersion in mineral oil, 1.6 mmol) in ethanol (4 mL). After 0.5 h, a solution of 1-[4-amino-3-formyl-5-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (**64**, 0.38 g, 1.3 mmol) in ethanol (6 mL) was added and the mixture was heated under reflux for 1.5 h. The mixture was cooled and partitioned between water (100 mL) and chloroform (100 mL), and the aqueous layer was extracted with chloroform (100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate/methanol (92:8). The first product eluted was *trans*-ethyl 3-[2-amino-3-(trifluoromethyl)-5-(2,4-dimethylimidazol-1-yl)phenyl]prop-2-enoate (0.27 g, 52%): mp 181–182 °C. Anal. ($C_{17}H_{18}F_3N_3O_2$) C, H, N. Further elution then provided 8-(trifluoromethyl)-6-(2,4-dimethylimidazol-1-yl)-2(1*H*)-quinolinone (0.05 g, 11%): mp 230–233 °C; ^{1}H NMR (DMSO-d_6) δ 2.08 (3 H, s), 2.25 (3 H, s), 6.83 (1 H, d), 7.07 (1 H, s), 7.90 (1 H, s), 8.11 (1 H, d), 8.13 (1 H, s), 11.25 (1 H, br s) ppm. Anal. ($C_{15}H_{12}F_3N_3O$) C, H, N.

Route D. 3,4-Dihydro-8-methyl-6-(2,4-dimethylimidazol-1-yl)-2(1*H*)-quinolinone (16). A suspension of 8-methyl-6-(2,4-dimethylimidazol-1-yl)-2(1*H*)-quinolinone (**13**, 0.7 g, 2.8 mmol) in ethanol (50 mL) was hydrogenated at 60 °C/60 psi over 10% palladized charcoal (0.35 g) for 72 h. The cooled mixture was filtered through Solkafloc and then was evaporated. The residue was chromatographed on silica by eluting with chloroform/methanol (49:1). Recrystallization of the product from ethyl acetate/methanol gave 3,4-dihydro-8-methyl-6-(2,4-dimethylimidazol-1-yl)-2(1*H*)-quinolinone (0.25 g, 35%): mp 260–262 °C; ^{1}H NMR (DMSO-d_6) δ 2.05 (3 H, s), 2.18 (3 H, s), 2.23 (3 H, s), 2.45 (2 H, t), 2.89 (2 H, t), 6.85 (1 H, s), 7.03 (1 H, s), 7.06 (1 H, s), 9.58 (1 H, s) ppm. Anal. ($C_{15}H_{17}N_3O$) C, H, N.

***trans*-1-[4-(3-Ethoxypropenamido)-3-methylphenyl]imidazole (47).** (a) A mixture of 4-fluoro-2-methylnitrobenzene (15.5 g, 100 mmol), imidazole (6.8 g, 100 mmol), and sodium carbonate (11.1 g, 105 mmol) was heated at 100 °C for 24 h in DMF (50 mL). The mixture was then concentrated, the residue adjusted to pH 1 with 4 N HCl, and the solution extracted with chloroform (2 × 25 mL). The aqueous phase was basified to pH 10 (NaOH solution, 2.5 M) and then was extracted with chloroform (3 × 100 mL). The dried organic extracts were evaporated, and the solid residue was recrystallized from ethyl acetate to give 1-(3-methyl-4-nitrophenyl)imidazole (**20**) (10.0 g, 59%): mp 112–115 °C. Anal. ($C_{10}H_9N_3O_2$) C, H, N.

(b) Stannous chloride dihydrate (55 g, 250 mmol) was added portionwise to a stirred suspension of **20** (10.0 g, 50 mmol) in absolute ethanol (100 mL). After heating under reflux for 4 h, the cooled mixture was basified to pH 8 (NaOH solution, 2.5 M) and then filtered. The filtrate was evaporated, the residue was partitioned between chloroform (100 mL) and water (50 mL), and the aqueous phase was further extracted with chloroform (3 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the solid residue was recrystallized from ethyl acetate to afford 1-(4-amino-3-methylphenyl)imidazole (**34**) (4.7 g, 84%): mp 131–134 °C. Anal. ($C_{10}H_{11}N_3$) C, H, N.

Imidazoles **41** and **42** were obtained as a mixture from impure **28** (which contained **27**) and were purified by column chromatography.

(c) *trans*-3-Ethoxy-2-propenoyl chloride (3.69 g, 27 mmol) was added dropwise to a stirred solution of the above product (4.33 g, 25 mmol) in pyridine (30 mL) at 0 °C. After stirring for 4 h at room temperature, the solution was evaporated and the residue was partitioned between chloroform (150 mL) and saturated sodium carbonate solution (20 mL). The aqueous phase was further extracted with chloroform (2 × 50 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica by eluting with chloroform/methanol (97:3). Trituration of the product with ethyl acetate/ether gave *trans*-1-[4-(3-ethoxypropenamido)-3-methylphenyl]imidazole (2.75 g, 41%): mp 141–144 °C. Anal. ($C_{15}H_{17}N_3O_2$) C, H, N.

4-(3-Methyl-4-nitrophenyl)-1,2,4-triazole (23). A mixture of 3-methyl-4-nitroaniline (2.0 g, 13 mmol) and 1,2-diformylhydrazine (1.3 g, 15 mmol) was heated under nitrogen at 200 °C for 1 h. The mixture was cooled, then chromatographed on silica by eluting with dichloromethane/methanol (19:1). The product was recrystallized from ethanol to give 4-(3-methyl-4-nitrophenyl)-1,2,4-triazole (1.03 g, 38%): mp 208–210 °C. Anal. ($C_9H_8N_4O_2$) C, H, N.

4-(4-Amino-3-methylphenyl)-1,2,4-triazole (37). A solution of **23** (1.0 g, 5 mmol) in acetic acid (25 mL) was hydrogenated at 25 °C/50 psi over Raney nickel (0.2 g) for 2 h. The mixture was filtered through Solkafloc and then evaporated, and the residue was partitioned between chloroform (100 mL) and sodium carbonate solution (20 mL). The aqueous phase was extracted with chloroform (3 × 50 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residual oil was chromatographed on silica by eluting with methanol/ethyl acetate (1:9), and the solid product was recrystallized from ethyl acetate/hexane to give 4-(4-amino-3-methylphenyl)-1,2,4-triazole (0.67 g, 78%): mp 152–154 °C. Anal. ($C_9H_{10}N_4$) C, H, N.

1-(3-Methyl-4-nitrophenyl)tetrazole (24). 1-(3-Methylphenyl)tetrazole[18] (11.3 g, 70 mmol) was added slowly with caution to ice-cooled fuming nitric acid (100 mL, sp gr 1.5) and then the solution was warmed on the steam bath for 0.1 h. The cooled solution was poured onto ice, and the solid product was collected and washed with water. The semidried product was taken up in ethanol, the solution was evaporated, and the residue was recrystallized from ethyl acetate to give 1-(3-methyl-4-nitrophenyl)tetrazole (9.4 g, 64%): mp 166–168 °C. Anal. ($C_8H_7N_5O_2$) C, H, N.

1-[4-Amino-3-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (46). A solution of 1-[4-nitro-3-(trifluoromethyl)-phenyl]-2,4-dimethylimidazole (**32**, 29.0 g, 100 mmol) in ethanol (300 mL) was hydrogenated at 50 °C/50 psi over 5% palladized charcoal (2 g) for 16 h. The mixture was then filtered through Solkafloc and evaporated to give a pale yellow solid (25.8 g, 99%). A sample was recrystallized from ethyl acetate/hexane to give 1-[4-amino-3-(trifluoromethyl)phenyl]-2,4-dimethylimidazole, mp 126–127 °C. Anal. ($C_{12}H_{12}F_3N_3$) C, H, N.

***trans*-Ethyl 3-(2-Amino-3-methyl-5-tetrazol-2-ylphenyl)-prop-2-enoate 0.16-Hydrate (59).** (a) A solution of iodine monochloride (0.58 g, 3.6 mmol) in acetic acid (10 mL) was added dropwise to a stirred solution of 2-methyl-4-tetrazol-2-ylaniline (**38**, 0.50 g, 2.9 mmol) in acetic acid (5 mL). After 1.5 h, the

(18) Fallon, F. G.; Herbst, R. M. *J. Org. Chem.* **1957**, *22*, 933.

mixture was adjusted to pH 6 (Na_2CO_3 solution) and extracted with dichloromethane (30 mL). The dried ($MgSO_4$) organic phase was evaporated and the residue chromatographed on silica by eluting with toluene to give 2-(4-amino-3-iodo-5-methylphenyl)tetrazole (**58**, 0.21 g, 24%). Recrystallization of a small sample from dichloromethane/hexane gave mp 196–199 °C. Anal. ($C_8H_8IN_5$) C, H, N.

(b) Ethyl acrylate (0.96 g, 9.6 mmol), triethylamine (0.51 g, 9.6 mmol), and palladium acetate (0.1 g) were added to a solution of 2-(4-amino-3-iodo-5-methylphenyl)tetrazole (**58**, 2.42 g, 8 mmol) in acetonitrile (50 mL). The mixture was heated under reflux for 1.5 h, cooled, and then partitioned between water (50 mL) and dichloromethane (50 mL). The aqueous phase was reextracted with dichloromethane (2 × 50 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica by eluting with dichloromethane/ethanol (30:1), and the product was recrystallized from ethyl acetate/hexane to give *trans*-ethyl 3-(2-amino-3-methyl-5-tetrazol-2-ylphenyl)-prop-2-enoate 0.16-hydrate (0.7 g, 32%): mp 162–165 °C. Anal. ($C_{13}H_{15}N_5O_2 \cdot 0.16H_2O$) C, H, N.

1-(4-Amino-3-bromo-5-methylphenyl)-2,4-dimethylimidazole 0.5-Hydrate (60). A solution of bromine (56 mL, 110 mmol) in acetic acid (50 mL) was added dropwise at 20 °C to a solution of 1-(4-amino-3-methylphenyl)-2,4-dimethylimidazole (**44**, 20.3 g, 100 mmol) and sodium acetate (90 g, 110 mmol) in acetic acid (150 mL). The mixture was stirred at 20 °C for 0.5 h and then evaporated. The residue was basified (10% NaOH solution) and then extracted with chloroform (4 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with dichloromethane/methanol (25:1) to give 1-(4-amino-3-bromo-5-methylphenyl)-2,4-dimethylimidazole (17.3 g, 62%). Trituration of a sample with ether gave mp 176–181 °C. Anal. ($C_{12}H_{14}BrN_3 \cdot 0.5H_2O$) C, H, N.

1-[4-Amino-3-formyl-5-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (64). (a) A solution of hydrogen bromide in glacial acetic acid (45% w/w, 7.4 mL) was added to a solution of 1-[4-amino-3-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (**46**, 10 g, 39 mmol) in acetic acid (80 mL) followed by the dropwise addition of bromine (2.1 mL, 40 mmol) in glacial acetic acid (20 mL). The mixture was heated at 70 °C for 3 h, cooled, and evaporated. The residue was adjusted to pH 8 (Na_2CO_3 solution) and was extracted with chloroform (3 × 200 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate to give 1-[4-amino-3-bromo-5-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (**61**) (4.76 g, 36%). A sample was recrystallized from ethyl acetate/hexane and gave mp 149 °C. Anal. ($C_{12}H_{11}BrF_3N_3$) C, H, N.

(b) Cuprous cyanide (3.7 g, 41 mmol) was added to a stirred solution of the above product (4.61 g, 14 mmol) in 1-methyl-2-pyrrolidinone (50 mL) and the mixture was heated at 150 °C for 48 h. The cooled mixture was evaporated and then ammonia (sp gr 0.88, 100 mL) was added and the aqueous phase was extracted with chloroform/methanol (20:1, 3 × 100 mL). The combined, dried ($MgSO_4$) organic extracts were evaporated, and the residue was chromatographed on silica by eluting with chloroform/methanol (50:1). The product was recrystallized from ethyl acetate/methanol to give 1-[4-amino-3-cyano-5-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (**63**, 1.1 g, 28%): mp 208–210 °C. Anal. ($C_{13}H_{11}F_3N_4$) C, H, N.

(c) A solution of diisobutylaluminum hydride in toluene (3.5 mL, 1.5 M, 5.3 mmol) was added to a stirred solution of the above product (0.7 g, 2.5 mmol) in THF (10 mL) at 0 °C. The mixture was heated at 40 °C for 2 h and then cooled in ice and methanol (2 mL) was added. The mixture was evaporated, and the residue was treated with water (25 mL) and HCl (5 mL, 2 M) and then heated on a steam bath for 0.1 h. The solution was cooled, adjusted to pH 8 (Na_2CO_3 solution), and extracted with chloroform/methanol (20:1, 3 × 30 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate/methanol (50:1) to give 1-[4-amino-3-formyl-5-(trifluoromethyl)phenyl]-2,4-dimethylimidazole (0.39 g, 55%): mp 200–202 °C. Anal. ($C_{13}H_{12}F_3N_3O$) H, N; C: found, 54.6; calcd, 55.1.

1-(4-Acetamido-3-acetyl-5-methylphenyl)-2,4-dimethylimidazole (65). (a) Methyllithium (40 mL of 1.6 M solution in ether, 64 mmol) was added dropwise to a stirred suspension of 1-(4-amino-3-cyano-5-methylphenyl)-2,4-dimethylimidazole (**62**, 2.71 g, 12 mmol) in diethyl ether (20 mL), and the mixture was heated under reflux for 24 h. The cooled suspension was treated with saturated aqueous ammonium chloride solution (5 mL) and then acidified to pH 1 (2 N HCl) and heated under reflux for 0.5 h. The solution was basified to pH 9 (saturated Na_2CO_3 solution) and then extracted with dichloromethane (5 × 20 mL). The combined, dried ($MgSO_4$) extracts were evaporated and then chromatographed on silica by eluting with ethyl acetate/methanol (19:1) to afford 1-(3-acetyl-4-amino-5-methylphenyl)-2,4-dimethylimidazole (1.35 g, 46%): mp 150–155 °C. Recrystallization of a small sample from ethyl acetate gave mp 163–167 °C. Anal. ($C_{14}H_{17}N_3O$) C, H; N: found, 19.0; calcd, 17.3.

(b) Acetyl chloride (0.71 mL, 10 mmol) was added dropwise to a solution of the above product (1.3 g, 5 mmol) in pyridine (15 mL). After 1 h the mixture was evaporated and the residue partitioned between dichloromethane (40 mL) and sodium carbonate solution (10%, 20 mL). The organic phase was dried ($MgSO_4$), evaporated, and chromatographed on silica with dichloromethane/methanol (13:1) as eluent. The product was recrystallized from ethyl acetate/methanol to afford 1-(4-acetamido-3-acetyl-5-methylphenyl)-2,4-dimethylimidazole (0.5 g, 39%): mp 181–183 °C. Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

Biology. Measurement of Inotropic Activity. (a) Anesthetized Dogs. Dogs were anesthetized with intravenous sodium pentobarbitone (Sagatal, M & B; 30–40 mg/kg) and were intubated. The saphenous vein and femoral and carotid arteries were cannulated for compound injection and for the recording of blood pressure and left ventricular pressure (LVP), respectively. LVP was recorded with a Millar Mikso-tip catheter introduced to the left ventricle via the carotid artery. The signal was differentiated to give dP/dt max, which was used as the index of cardiac contractility. Following surgery, an equilibration period of 0.75 h was allowed. All compounds were administered intravenously in saline solution (4 mL, 0.9%) 0.5 h after the standard agent, 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline (50 μg/kg). This cycle was repeated when control levels were reestablished, with a minimum of 0.5 h between compound administration. Changes in dP/dt max (mmHg/s), blood pressure (mmHg), and heart rate (beats/min) were recorded. Inotropic activity, after a single administration of the test compound, is presented as both a percentage increase in dP/dt max and relative to 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline evaluated in the same dog. Thus

$$\text{relative inotropic potency} = \frac{\%\ \text{increase in } dP/dt \text{ max to drug}}{\%\ \text{increase in } dP/dt \text{ max to standard}} \times \frac{\text{dose standard}}{\text{dose drug}}$$

During a typical test run in which five quinolinone derivatives were evaluated, percentage increases in dP/dt max recorded for 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline (50 μg/kg) were 48, 42, 45, 48, and 46%.

Dog Heart–Lung Preparation. A Starling dog heart–lung preparation was set up as previously described.[19] Cannulae were inserted via the inferior vena cava into the right atrium and via the left subclavian artery into the left ventricle to record right atrial and left intraventricular pressures, respectively. These cannulae were connected via Bell and Howell pressure transducers to a Devices 8-channel pen recorder. The first derivative of left ventricular pressure (dP/dt) was recorded and the maximum value was utilized as an index of myocardial contractility. ECG (lead II) was recorded conventionally with needle electrodes. The temperature of the blood was maintained at 37 °C and was adequately oxygenated. Control values were established for left ventricular end diastolic pressure, left ventricular dP/dt max, central venous pressure, circuit pressure, circuit flow, heart rate, and filling pressure. Drugs were injected via the venous inflow catheter and hemodynamic parameters remeasured. Force/rate selectivity is expressed graphically (Figure 2) by plotting percentage increases in dP/dt max against absolute increases in heart rate. All compounds were tested in two to four dogs and dose

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ranges employed were 5–320 μg for **3**, **9**, and **13**, 5–80 μg for **10**, and 50–500 ng for isoprenaline. Figure 2 is derived by drawing the best lines through the accumulated data points for increases in force and rate. All data points lie within 10% of the line for either dependent variable.

(b) **Conscious Dogs.**[20,21] Adult beagle dogs (Pfizer colony) were prepared, under aseptic recovery surgery, with a carotid artery loop and two subcutaneous titanium studs, designed to act as permanent ECG electrodes and placed, one each, in the dorsal neck and rump areas. Following adequate time for recovery and full wound healing, each dog was placed in a canvas support within the laboratory. A strain gauge was placed around the carotid loop and recording leads attached to the two electrodes. Recordings of both the arterial pulse and the ECG were made via appropriate interfacing onto a Grass polygraph. Measurements of QA interval (the time in milliseconds between the R wave of the ECG signal and the up-stroke of the arterial pressure pulse) were made by digital computer. To assess the activity of a test substance, recordings of QA interval were made every 0.16 h from 0.5 h before to up to 4 h after the oral administration, by gavage, of a solution of the test substance. Each value of QA interval, at a given time point, represents the mean of six consecutive sets of values, each set being the mean of the values recorded in an 8-s period. Results are expressed as the change in QA interval from the mean control (predose) value. In control animals ($n = 8$), changes in QA interval of 1.5 ± 2 and 0.5 ± 1.5 ms were observed at 1 and 3 h, respectively, after saline administration. Decreases in QA interval of 10, 15, and 20 ms correspond approximately to increases in dP/dt max of 20, 45, and 70%, respectively. A decrease in QA interval of 20 ms approaches the maximum change possible.

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(22) Yamanaka, M.; Saito, I.; Yamatsu, K.; Fujimoto, T. Belgian Patent 4,880,020; *Chem. Abstr.* **1980**, *93*, 220743.

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Registry No. **3**, 102791-36-6; **4**, 102791-49-1; **5**, 102791-44-6; **6**, 102791-50-4; **7**, 102791-51-5; **8**, 102791-60-6; **9**, 102791-39-9; **10**, 102791-41-3; **11**, 102791-42-4; **12**, 102791-48-0; **13**, 102791-47-9; **14**, 102791-45-7; **15**, 118111-92-5; **16**, 102791-55-9; **17**, 118111-93-6; **18**, 118111-94-7; **19**, 99584-29-9; **20**, 102791-92-4; **21**, 102792-12-1; **22**, 102791-96-8; **23**, 118111-95-8; **24**, 102792-31-4; **25**, 102792-14-3; **26**, 102791-93-5; **27**, 102791-94-6; **28**, 102791-95-7; **29**, 102792-11-0; **30**, 102792-10-9; **31**, 23309-18-4; **32**, 102792-15-4; **33**, 446-33-3; **34**, 118111-96-9; **35**, 102792-04-1; **36**, 102791-90-2; **37**, 102792-08-5; **38**, 102792-05-2; **39**, 102792-07-4; **40**, 102791-86-6; **41**, 102791-88-8; **42**, 102791-89-9; **43**, 102792-09-6; **44**, 102792-03-0; **45**, 102791-91-3; **46**, 102792-18-7; **47**, 102791-75-3; **48**, 102791-99-1; **49**, 102791-83-3; **50**, 102792-00-7; **51**, 102792-01-8; **52**, 102791-78-6; **53**, 102791-80-0; **54**, 102791-81-1; **55**, 102791-98-0; **56**, 102791-97-9; **57**, 102791-84-4; **58**, 102792-21-2; **59**, 102792-23-4; **60**, 108857-39-2; **61**, 102792-24-5; **62**, 108857-38-1; **63**, 102792-29-0; **64**, 102792-17-6; **65**, 118111-97-0; 4-methylimidazole, 822-36-6; 3-methyl-4-nitroaniline, 611-05-2; *trans*-3-ethoxyprop-2-enoyl chloride, 99471-66-6; triethyl phosphonoacetate, 867-13-0; *trans*-ethyl 3-[2-amino-3-(trifluoromethyl)-5-(2,4-dimethylimidazol-1-yl)phenyl]prop-2-enoate, 102791-70-8; 1,2-diformylhydrazine, 628-36-4; ethyl acrylate, 140-88-5; pyrazole, 288-13-1; 1,2,4-triazole, 288-88-0; 2*H*-tetrazole, 288-95-9; 2-methylimidazole, 693-98-1; 4-trifluoromethylimidazole, 33468-69-8; 2,4-dimethylimidazole, 930-62-1; 4-fluoronitrobenzene, 350-46-9; 4-fluoro-(2-trifluoromethyl)nitrobenzene, 393-09-9; 1-(3-acetyl-4-amino-5-methylphenyl)-2,4-dimethylimidazole, 118111-98-1.

Supplementary Material Available: X-ray data are available for 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**13**) (9 pages). Ordering information is given on any current masthead page.

Acrylamide Derivatives as Antiallergic Agents. 2.[1] Synthesis and Structure–Activity Relationships of *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides

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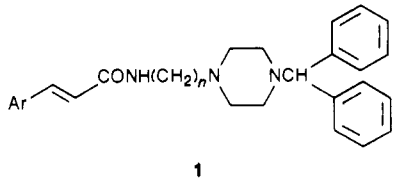
A new series of 3-(3-pyridyl)acrylamides **16**, **17**, **19**, and **26**, and 5-(3-pyridyl)-2,4-pentadienamides **20–25** were prepared and evaluated for their antiallergic activity. Several of these compounds exhibited more potent inhibitory activities than the parent compound **1a** [(*E*)-*N*-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamide] against the rat passive cutaneous anaphylaxis (PCA) reaction and the enzyme 5-lipoxygenase. Particularly, (*E*)-*N*-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridyl)acrylamide (**17p**) showed an ED_{50} value of 3.3 mg/kg po in the rat PCA test, which was one-fifth of ketotifen and oxatomide. As compared with ketotifen and oxatomide, compound **17p** (AL-3264) possessed a better balance of antiallergic properties due to inhibition of chemical mediator release, inhibition of 5-lipoxygenase, and antagonism of histamine.

The clinical success of disodium cromoglycate (DSCG)[2] as a therapeutic drug for the prophylactic treatment of asthma and allergic disease has stimulated a research interest that has led to the discovery of orally, more potent antiallergic agents with desirable biological properties. We have found new, orally active antiallergic compounds having (i) inhibitory activity against the enzyme 5-lipoxygenase, which catalyzes the generation of leukotrienes

Chart I



1

(LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4), from arachidonic acid, (ii) inhibitory activity against the release of chemical mediators such as histamine and slow reacting substance of anaphylaxis (SRS-A) (LTC_4, LTD_4, and LTE_4) and (iii) antihistamine activity as well. Our previous paper reported[1] that some of the β-aryl- and β-heteroarylacryl-

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