78893-37-5; **16a**, 77618-26-9; **16b**, 68301-94-0; **16c**, 68301-99-5; **16d**, 94978-88-8; **16e**, 68302-00-1; **16f**, 68301-95-1; **16g**, 68302-16-9; **17a**, 61424-79-1; **17b**, 68302-25-0; **17c**, 68302-24-9; **17d**, 94978-89-9; **17e**, 68302-27-2; **17f**, 68377-76-4; **18**, 68302-36-3; **19**, 94978-90-2; **20**, 79052-79-2; **21a**, 79052-81-6; **21b**, 79052-83-8; **21c**, 79052-84-9; **21d**, 79052-82-7; **22**, 94978-91-3; **23a**, 68302-43-2; **23b**, 68302-61-4; **23c**, 68302-64-7; **23d**, 77618-27-0; **23e**, 68302-58-9; **23f**, 68302-51-2; **23g**, 68302-57-8; **23h**, 94978-92-4; **23i**, 68302-75-0; **23j**, 68302-71-6; **23k**, 68302-72-7; **23l**, 68302-70-5; **23m**, 94978-93-5; **23n**, 68302-74-9; **23o**, 68302-73-8; **23p**, 68302-77-2; **23q**, 94978-94-6; **23r**, 79052-92-9; **23s**, 79052-94-1; **23t**, 79052-95-2; **23u**, 79052-93-0; **23v**, 68302-68-1; **24a**, 70529-16-7; **24b**, 70529-17-8; **24c**, 70529-15-6; **24d**, 70529-21-4; **24e**, 70529-20-3; **24f**, 70529-24-7; **24g**, 70529-18-9; **24h**, 94978-95-7; ethyl propiolate, 623-47-2; cyanoacetylene, 1070-71-9; α-chloroacrylonitrile, 920-37-6; cyanoacetyl chloride, 16130-58-8; monomethyl malonate, 16695-14-0; cyanoacetic acid, 372-09-8; malonaldehyde bis(dimethyl acetal), 102-52-3; malononitrile, 109-77-3; ethyl acetoacetate, 141-97-9; ethyl cyanoacetate, 105-56-6; diethyl acetylenedicarboxylate, 762-21-0; diethyl malonate, 105-53-3; *O*-methylhydroxylamine hydrochloride, 593-56-6; sodium azide, 26628-22-8; *O*-ethylhydroxylamine, 624-86-2; *O*-butylhydroxylamine, 5622-77-5; hydroxylamine hydrochloride, 5470-11-1.

Studies on 4(1*H*)-Quinazolinones. 5.[1] Synthesis and Antiinflammatory Activity of 4(1*H*)-Quinazolinone Derivatives

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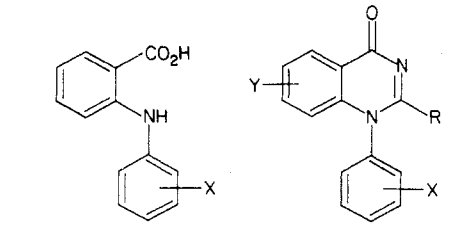
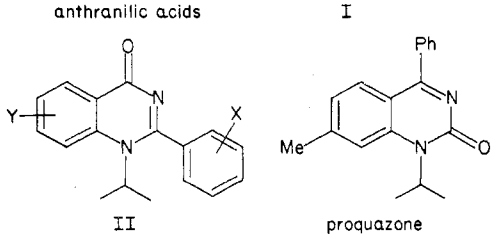
A number of new 4(1*H*)-quinazolinones were synthesized and evaluated in the carrageenin-induced paw edema test. Most of the compounds were obtained by the cyclization of the appropriately substituted anthranilamides with acid chlorides, followed by further chemical transformation. Structure–activity data suggest that 2-isopropyl-1-phenyl-, 2-cyclopropyl-1-phenyl-, and 1-isopropyl-2-phenyl-4(1*H*)-quinazolinones afford optimal potency and the presence of a halogen atom is preferred for activity. Adrenalectomy does not affect the antiinflammatory test results. The best result taking into account both efficacy and side effects was displayed by 1-isoproyl-(2-fluorophenyl)-4-(1*H*)-quinazolinone (**50**).

Various kinds of nonsteroidal antiinflammatory agents have been clinically used. However, most of these agents have gastrointestinal toxicity as a side effect. In order to search for a new drug without this characteristic side effect, we prepared 1-phenyl-4(1*H*)-quinazolinones I, because these were considered to be cyclic analogues of *N*-phenylanthranilic acids, which are known to possess potent antiinflammatory activity. In the course of this study, 2-isopropyl-1-phenyl-4(1*H*)-quinazolinones (I, R = isopropyl) were found to have marked antiinflammatory activity. We recognized the structural resemblance between I (R = isopropyl) and proquazone.[2] As a result of our continuing study, it was found that 1-isopropyl-2-phenyl-4(1*H*)-quinazolinones II also showed a good level of activity. In this paper, we report the synthesis and antiinflammatory activity of these 4(1*H*)-quinazolinones.





Chemistry. Most of the quinazolinone derivatives in Tables I–III were prepared by the methods illustrated in Schemes I–III. Scheme I shows the synthetic route to I and the dihydro derivative VII (Table II, **47**). Schemes II and III show the syntheses of 4-isopropyl-1-phenyl-2-(1*H*)-quinazolinone (IX, Table II, **44**), II, and the dihydro compounds XIII.

The starting *N*-phenylanthranilic acids were prepared by the Ullmann reaction. The anthranilic acids III were allowed to react with thionyl chloride (method A) or phosgene (method B), followed by treatment with aqueous ammonia to afford the corresponding 2-anilinobenzamides IV. Alternatively, two of the amides, 2-(2-toluidino)- and 2-anilino-5-methoxybenzamide (IVd and IVn, respectively), were prepared from the methyl *N*-phenylanthranilates VI (method C). Compounds I were generally obtained in moderate yield from IV by our reported method[1a] using an acyl chloride in chloroform (*N*,*N*-dimethylformamide was used as a solvent in those cases where solubility of IV in chloroform was low). The reaction of 2-(4-nitroanilino)benzamide (IVh) with cyclopropanecarbonyl chloride or cyclobutanecarbonyl chloride gave a mixture of intermediate *N*-(2-carbamoylphenyl)-*N*-(4-nitrophenyl)acylamide V and the cyclized 4(1*H*)-quinazolinone **27** or **29**. Without purification, each mixture was refluxed in acetic acid containing boron trifluoride etherate to afford

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[‡]Biological Research Laboratory.

(1) (a) Ozaki, K.; Yamada, Y.; Oine, T. *Chem. Pharm. Bull.* **1980**, *28*, 702. (b) Ozaki, K.; Yamada, Y.; Oine, T. *J. Org. Chem.* **1981**, *46*, 1571. (c) Ozaki, K.; Yamada, Y.; Oline, T. *Chem. Pharm. Bull.* **1983**, *31*, 2234. (d) Ozaki, K.; Yamada, Y.; Oline, T. *Ibid.* **1984**, *32*, 2160.
(2) (a) Coombs, R. V.; Danna, R. P.; Denzer, M.; Hardtmann, G. E.; Huegi, B.; Koletar, G.; Koletar, J.; Ott, H.; Jukniewicz, E.; Perrine, J. W.; Takesue, E. I.; Trapold, J. H. *J. Med. Chem.* **1973**, *16*, 1237. (b) Takesue, E. I.; Perrine, J. W.; Trapold, J. H. *Arch. Int. Pharmacodyn.* **1976**, *221*, 122.
(3) Hardtmann, G. E.; Koletar, G.; Pfister, O. R. *J. Heterocycl. Chem.* **1975**, *12*, 565.

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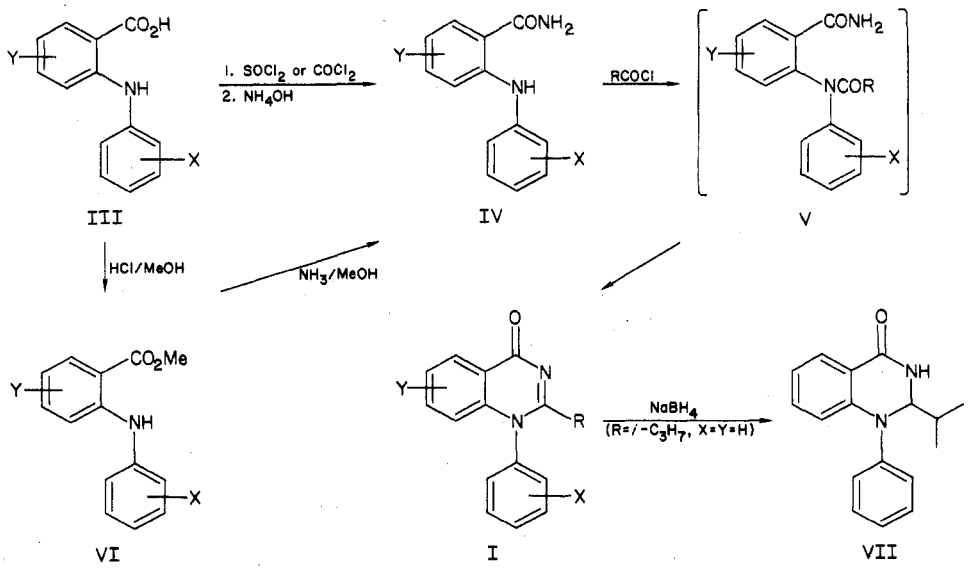
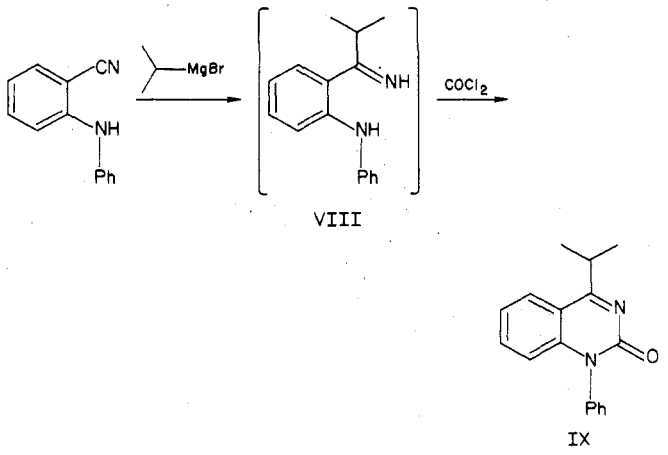
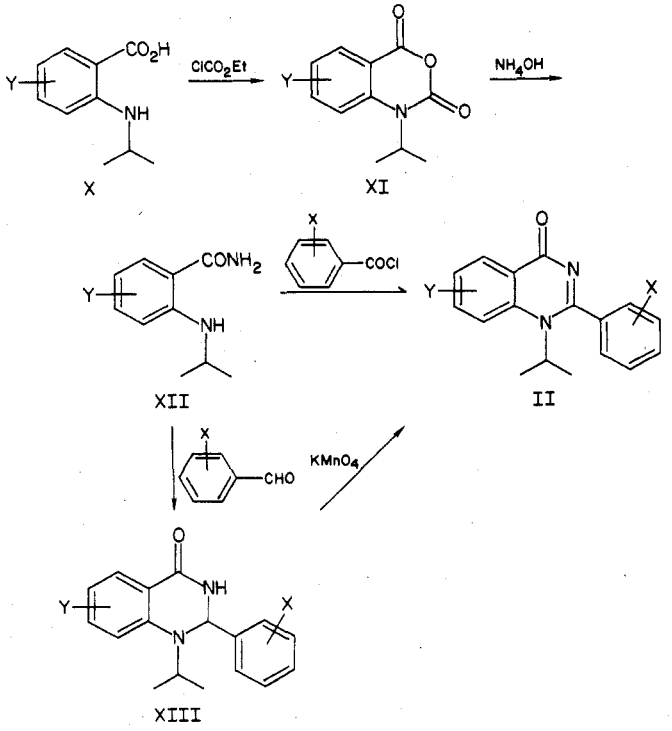
Scheme I



Scheme II



Scheme III



the desired **27** and **29** (Table I).

2,3-Dihydro-2-isopropyl-1-phenyl-4(1*H*)-quinazolinone (VII, Table II, **47**) was obtained by the reduction of 2-isopropyl-1-phenyl-4(1*H*)-quinazolinone (**3**, Table I) with sodium borohydride.

The reaction of 2-anilinobenzonitrile with isopropylmagnesium bromide, followed by careful quenching with water, gave the ketimine VIII, which was converted to 4-isopropyl-1-phenyl-2(1*H*)-quinazolinone (IX, Table II, **44**) by cyclization using phosgene.

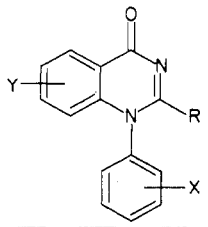
N-Isopropylanthranilic acids X were prepared by the reaction of 2-bromobenzoic acids with isopropylamine in the presence of copper powder (method D) or by the reaction of anthranilic acids with isopropyl iodide (method E). 2-(Isopropylamino)benzamides XII were obtained via the isatoic anhydrides XI. Thus compounds X were allowed to react with ethyl chlorocarbonate,[4] followed by treatment with aqueous ammonia to give XII. Transformation of XII to 1-isopropyl-4(1*H*)-quinazolinones II was accomplished by the following two methods. In a similar manner for the preparation of I, reaction of XII with benzoyl chlorides gave II in one step (method F). Alternatively, condensation of XII and benzaldehydes gave the dihydroquinazolinones XIII, which were converted to II by oxidation with potassium permanganate ($KMnO_4$) (method G). 4(3*H*)-Quinazolinones **45** and **46** (Table II) were also prepared from the corresponding 2-aminobenzamides in the same manner with method G. Reduction of 2-(2-chlorophenyl)-1-isopropyl-4(1*H*)-quinazolinone (**51**, Table III) with sodium borohydride gave 2-(2-chlorophenyl)-2,3-dihydro-1-isopropyl-4(1*H*)-quinazolinone (**48**, Table II).

Pharmacology and Structure–Activity Relationships. The quinazolinone derivatives summarized in Tables I–III were evaluated for antiinflammatory activity in the carrageenin-induced rat paw edema assay.[5] The more interesting compounds were tested for analgesic activity by using a modification of the method of Randall and Sellitto[20] and for their propensity to cause gastrointestinal ulceration by using the method of Senay and Levine.[21] Acute toxicity was also determined, and the

(4) Coppola, G. M. *Synthesis* **1980**, 505.

(5) Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.

Table I. 1-Phenyl-4(1*H*)-quinazolinones I



no.	R	X	Y	yield, %	mp, °C	recryst[a] solvent	anal.	act.[b]
1	CH_3	H	H	79[c]	226–228	B		–
2	CH_3	3-CF_3	H	49	227–228	C	C, H, N	–
3	isopropyl	H	H	72	228–230	C	C, H, N	++
4	isopropyl	3-CF_3	H	60	161–162	E–G	C, H, N	+
5	cyclopropyl	H	H	68[c]	241–242	C		++++
6	cyclopropyl	3-CF_3	H	67	220–222	C	C, H, N	–
7	CH_2Cl	H	H	88[c]	212–213	C–G		–
8	CH_2Cl	3-CF_3	H	69	194–195	B	C, H, N	–
9	$CH_2N(C_2H_5)_2$	H	H	47[c]	101–103	G		–
10	$CH_2N(C_2H_5)_2$	3-CF_3	H	70[d]	175–176	C	C, H, N	+
11	*n*-butyl	H	H	85	177–179	F	C, H, N	–
12	isobutyl	H	H	81	157–159	F–G	C, H, N	+
13	*tert*-butyl	H	H	66	220–223	C	C, H, N	–
14	cyclobutyl	H	H	67	230–232	C	C, H, N	+
15	cycloheptyl	H	H	71	247–250	D	C, H, N	–
16	$CH(CH_3)CO_2C_2H_5$	H	H	84	186–188	C	C, H, N	+
17	$CH_2CH_2CO_2CH_3$	H	H	70	157–158	F–H	C, H, N	–
18	$CH_2CH_2CO_2H$	H	H	59[d]	198–200	C–G	C, H, N	–
19	CF_3	H	H	64[e]	235–237	D	C, H, N	–
20	$N(CH_3)_2$	H	H	78[g]	209–210	C	C, H, N	–
21	isopropyl	4-F	H	87	237–240	B–G	C, H, N	+++
22	isopropyl	4-Cl	H	75	227–229	C	C, H, N	++++
23	isopropyl	4-NO_2	H	76	249–252	B–D	C, H, N	++
24	isopropyl	H	7-Cl	47	240–243	C	C, H, N	++++
25	cyclopropyl	4-F	H	53	250–252	B	C, H, N	++++
26	cyclopropyl	4-Cl	H	55	259–261	D	C, H, N	–
27	cyclopropyl	4-NO_2	H	25	276–280	B–D	C, H, N	–
28	cyclobutyl	4-Cl	H	74	209–211	B	C, H, N	+
29	cyclobutyl	4-NO_2	H	22	246–247	B–G	C, H, N	–
30	isopropyl	2-Cl	H	70	238–239	C	C, H, N	±
31	isopropyl	2-CH_3	H	87	214–216	C–G	C, H, N	++
32	isopropyl	2-CO_2H	H	53[d]	>280	B–D	C, H, N	±
33	isopropyl	2-$CONH_2$	H	78	>280	D	C, H, N	–
34	isopropyl	4-NH_2	H	56[f]	276–279	D	C, H, N	+
35	isopropyl	4-$COCH_3$	H	80	220–222	E–I	C, H, N	+
36	isopropyl	4-CH_2CO_2H	H	41[d]	265–267	A–G	C, H, N	±
37	isopropyl	H	6-CH_3	79	251–255	B	C, H, N	+
38	isopropyl	H	6-OCH_3	81	191–192	F–C	C, H, N	++++
39	isopropyl	H	6-$COCH_3$	54	206–208	B	C, H, N	–
40	isopropyl	H	6-CH_2CO_2H	36[d]	254–255	A–G	C, H, N	–
41	isopropyl	H	7-CH_3	74	235–238	F–H	C, H, N	+
42	isopropyl	H	7-NO_2	81	270–278	D	C, H, N	–
43	isopropyl	H	7-NH_2	56[f]	>280	D	C, H, N	±

[a] A = MeOH, B = EtOH, C = 2-propanol, D = DMF, E = THF, F = benzene, G = diisopropyl ether, H = hexane, I = petroleum ether, J = H_2O. [b] Percent inhibition of the carrageenin-induced rat paw edema (50 mg/kg po) 0–10% (–), 11–20% (±), 21–30% (+), 31–40% (++), 41–50% (+++), ≥51% (++++). [c] See ref 1a. [d] Prepared from **8**, **17**, **33**, **35**, and **39**. [e] Prepared by the reaction of IVa with $(CF_3CO)_2O$. [f] Prepared by reduction of **23** and **42**. [g] Prepared from 2-cyano-1-phenyl-4(1*H*)-quinazolinone by our reported method[1c] (see Experimental Section).

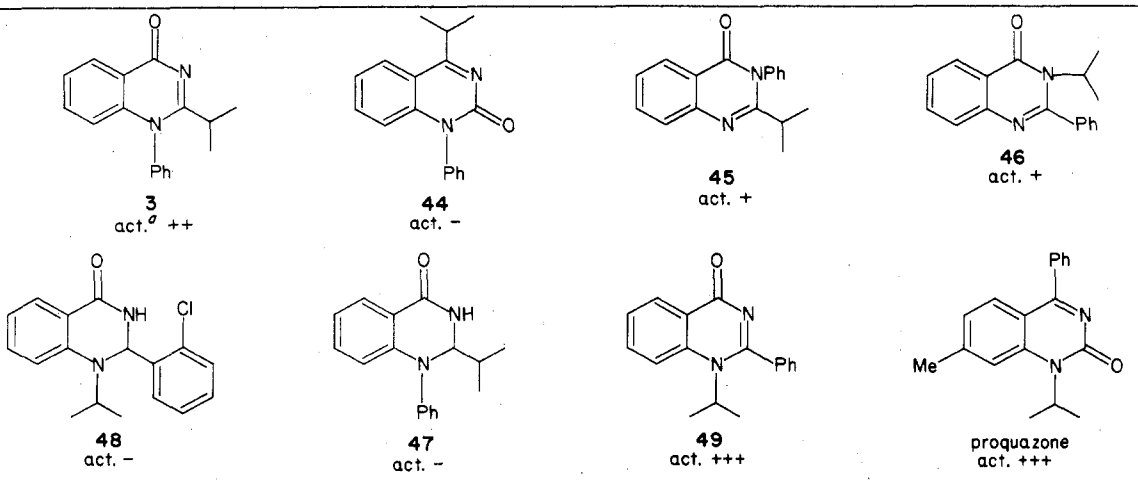
results, tabulated in Table IV, are compared with proquazone as a reference.

In the series of 1-phenyl- and 1-[3-(trifluoromethyl)-phenyl]-4(1*H*)-quinazolinones **1–10** having various substituents at position 2, two compounds **3** and **5** showed significantly potent antiinflammatory activity. In contrast to flufenamic acid,[6] one of the most active *N*-phenylanthranilic acids, the presence of the trifluoromethyl function on the 1-phenyl group of 4-(1*H*)-quinazolinones generally caused a decrease of activity. This result led us to continue the study on the structure–activity relationships from a different point of view.

While the phenyl substituent at position 1 was kept constant, the effects of additional substituents at position 2 on activity were examined (**11–20**). The results suggested that secondary lower alkyl and cycloalkyl groups were optimal for activity. Derivatives containing an isopropyl, cyclopropyl, or cyclobutyl group at position 2 were selected for further modification to examine the effect on activity of a substituent on the phenyl group or quinazolinone ring (**21–29**). The cyclobutyl derivatives **28** and **29** showed relatively weak activity. Among the 2-cyclopropyl derivatives, only compound **25** exhibited potent antiinflammatory activity, whereas compounds **26** and **27** were totally inactive. In contrast, derivatives **21–24** containing a 2-

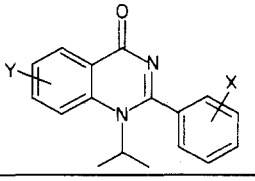
(6) Winder, C. V.; Wax, J.; Querubin, B. S.; Jones, E. M.; Mcphee, M. L. *Arthritis Rheum.* **1963**, *6*, 36.

Table II



[a] See footnote *b* of Table I.

Table III. 1-Isopropyl-2-phenyl-4(1*H*)-quinazolinones II



no.	X	Y	yield, %	method	mp, °C	recryst[a] solvent	anal.	act.[b]
49	H	H	68	F	223–226	B–G	C, H, N	+++
50	2-F	H	62	G	216–217	B–G	C, H, N	++++
51	2-Cl	H	77	F	203–205	B–G	C, H, N	+++
52	2-Br	H	78	G	217–219	B	C, H, N	-
53	2-OCH_3	H	78	G	199–201	B–D	C, H, N	-
54	3-Cl	H	57	F	214–216	B	C, H, N	+++
55	4-F	H	85	F	215–216	B–G	C, H, N	+++
56	4-Cl	H	87	F	231–233	A–G	C, H, N	+++
57	4-Br	H	55	F	232–234	B–D	C, H, N	+++
58	4-CH_3	H	65	F	242–244	B	C, H, N	-
59	4-NO_2	H	81	F	>280	D	C, H, N	-
60	4-NH_2	H	60	*c*	255–257	A	C, H, N	-
61	3,4-Cl_2	H	75	F	223–224	B	C, H, N	+++
62	H	5-Cl	47	G	222–224	B	C, H, N	±
63	H	5-OCH_3	69	G	178–180	C–G	C, H, N	±
64	H	6-F	65	F	232–234	B	C, H, N	++
65	H	6-Cl	66	F	273–274	D	C, H, N	+++
66	H	6-Br	54	G	>280	D	C, H, N	+
67	H	6-OCH_3	37	F	190–192	C–G	C, H, N	++
68	H	7-Cl	75	G	148–150	F–G	C, H, N	+++
69	H	7-CH_3	53	F	165–167	F–G	C, H, N	-
70	2-F	6-OCH_3	50	F	183–185	C–G	C, H, N	+
71	2-Cl	6-F	45	F	197–200	F	C, H, N	+
72	2-F	6-Cl	66	F	255–258	B–D	C, H, N	±
73	2-Cl	6-Cl	30	F	248–250	B	C, H, N	+++
74	4-F	6-Cl	41	F	249–251	B–D	C, H, N	+++
75	4-Cl	6-Cl	42	F	255–257	D	C, H, N	-
76	2-F	7-Cl	63	F	170–172	F–G	C, H, N	++
77	4-F	7-Cl	54	G	214–217	C	C, H, N	+
78	4-Cl	7-Cl	54	F	201–203	B	C, H, N	+

[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] Prepared by reduction of **59**.

isopropyl group showed good activity.

Furthermore, 2-isopropyl derivatives, which could readily be prepared, were tested. Among them, 6-methoxy and 1-(2-tolyl) derivatives **38** and **31** showed potent activity. Introduction of an acidic or a basic function generally caused a marked decrease of the potency, similar to side-chain substituents at position 2 (**9**, **10**, **18**, **20**, **34**, **36**, **40**, and **43**).

Many compounds with potent antiinflammatory activity were found among the 2-isopropyl derivatives. Most interestingly, their structural features are similar to those of proquazone in spite of our independent structure–activity optimization: the phenyl, isopropyl, and carbonyl groups on the quinazolinone nucleus are just arranged in a different manner. Therefore, our efforts were extended to search for new lead compounds. Six compounds as shown in Table II were prepared, including three possible quinazolinone ring systems (4(1*H*)-, 4(3*H*)-, and 2(1*H*)-quinazolinone) and reduced derivatives (2,3-dihydro-4-(1*H*)-quinazolinones). Of interest, compounds **45** and **46** showed weak but clear activity, but unexpectedly, activity was not observed for compounds **44**, **47**, and **48**. On the

Table IV. Pharmacological Activities of Some Quinazolinone Derivatives

compd	type	X	Y	antiinflam[a] ED30, mg/kg	analgesic[a] ED30, mg/kg	ulcerogenicity dose[c]	ulcerogenicity N^d	ulcerogenicity ulcer index	acute toxicity[e]
3	I	H	H	30	70				
21	I	4-F	H	30	76				
24	I	H	7-Cl	21	80				
50	II	2-F	H	20	65	60	1/5	0.1 ± 0.1	1/5
56	II	4-Cl	H	15	44	45	0/5	0.0	5/5
68	II	H	7-Cl	16	neg[b]	48	3/5	0.2 ± 0.08	0/5
74	II	4-F	6-Cl	18	100				
proquazone				10	20	30	4/5	0.3 ± 0.12	0/5

[a] Oral 30% effective dose. [b] Not effective at 200 mg/kg. [c] Oral dose (mg/kg) = (antiinflammatory ED30) × 3. [d] (Number of mice bearing ulcer)/(number of mice used). [e] Oral acute toxicity at 500 mg/kg, (number of mice dead)/(number of mice used).

other hand, 1-isopropyl-2-phenyl-4(1*H*)-quinazolinone (**49**) was very active.

We selected **49** as another lead compound for optimization. From the results summarized in Table III, it is difficult to find a definite relationship between the substituents on the phenyl group or quinazolinone nucleus and the activity. However, the activity appears to depend more on the nature of the substituent than on its position. Most of the compounds having a halogen atom showed potent activity, whereas disubstituted derivatives were relatively less active.

The more potent quinazolinones (**3**, **21**, **24**, **50**, **56**, **68**, **74**)[22] in the preliminary screening test were evaluated by dose–response studies for antiinflammatory and analgesic activity. As shown in Table IV, potencies of most of the compounds were in the range of $^1/_2$–$^1/_5$ times that of proquazone. Compound **56** produced behavioral changes such as salivation at 100 mg/kg po. The antiinflammatory activity of these compounds is, presumably, not mediated through activation of adrenals since compound **50** chosen as a representative retained antiedema activity when tested in adrenalectomized animals. In Table IV, the ulcerogenic property and the acute toxicity of some compounds are also shown. The data suggest that this series of compounds show less gastrointestinal irritation but in contrast have somewhat stronger acute toxicity compared with that of proquazone.

In summary, 1-isopropyl-2-(2-fluorophenyl)-4(1*H*)-quinazolinone (**50**) showed the most interesting results in this series.

Experimental Section

Chemistry. All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-27G spectrometer. NMR spectra were recorded on a Hitachi Perkin-Elmer R-20A instrument using tetramethylsilane as internal standard. MS were measured with a Hitachi M-60 mass spectrometer. The results of elemental analyses were within ±0.4% of the theoretical values. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063–0.200 mm, E. Merck).

N-Phenylathranilic acids III were prepared as follows: *N*-phenylanthranilic acid (IIIa),[7] *N*-[3-(trifluoromethyl)phenyl]-anthranilic acid (IIIb),[8] *N*-(2-chlorophenyl)anthranilic acid (IIIc),[9] *N*-(2-tolyl)anthranilic acid (IIId),[10] *N*-(2-carboxyphenyl)anthranilic acid (IIIe),[10] *N*-(4-fluorophenyl)anthranilic acid (IIIf),[11] *N*-(4-chlorophenyl)anthranilic acid (IIIg),[9] *N*-(4-nitrophenyl)anthranilic acid (IIIh),[12] 4-chloro-*N*-phenylanthranilic acid (IIIj),[13] 4-methyl-*N*-phenylanthranilic acid (IIIk),[14] and 4-nitro-*N*-phenylanthranilic acid (IIIl)[13] were prepared by reported methods. Other anthranilic acids (IIIi and IIIm–IIIo) were prepared as described in this section.

***N*-(4-Acetylphenyl)anthranilic Acid (IIIi).** A mixture of potassium anthranilate (122.5 g, 0.7 mol) and 4-acetylbromobenzene (69 g, 0.347 mol) in isoamyl alcohol (300 mL) was refluxed for 21 h in the presence of copper powder (0.5 g). The solvent was removed by steam distillation and K_2CO_3 (138 g, 1 mol) was added to the residual aqueous layer. The mixture was treated with Norit and filtered. The filtrate was acidified (pH 4–5) with 10% HCl to give 74 g of precipitate. Recrystallization from MeOH–ether gave 46 g (56.4%) of IIIi, mp 171–175 °C (lit.[15] mp 175–176 °C).

5-Methyl-*N*-phenylanthranilic Acid (IIIm). A mixture of 5-methylanthranilic acid (12.08 g, 0.08 mol), bromobenzene (15.7 g, 0.1 mol), and K_2CO_3 (10.24 g, 0.08 mol) in isoamyl alcohol (50 mL) was refluxed for 18 h in the presence of copper powder (0.4 g). The reaction mixture was worked up as described for the preparation of IIIi. The product was subjected to silica gel (400 g) column chromatography using $CHCl_3$ as an eluent to give 15.0 g (82.6%) of IIIm, mp 184–186 °C. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

5-Methoxy-*N*-phenylanthranilic Acid (IIIn). By a procedure similar to that described for the preparation of IIIi, reaction of potassium 2-chloro-5-methoxybenzoate (18 g, 0.08 mol) and aniline (54 g, 0.58 mol) provided 15.1 g of crude product. Recrystallization from benzene gave 10.7 g (55.0%) of IIIn, mp 137–140 °C. Anal. ($C_{14}H_{13}NO_3$) C, H, N.

5-Acetyl-*N*-phenylanthranilic Acid (IIIo). A mixture of potassium 5-acetyl-2-chlorobenzoate (2.0 g, 0.0084 mol) and aniline (2.0 g, 0.022 mol) in isoamyl alcohol (20 mL) was refluxed for 3.5 h in the presence of copper powder (0.5 g). The solvent was removed by steam distillation. The residue was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to give 2.4 g of IIIo as a syrup, which was used in the next reaction without purification.

Methyl *N*-(2-Tolyl)anthranilate (VId). A suspension of IIId (6.81 g, 0.03 mol) in MeOH (75 mL) was saturated with HCl. The mixture was refluxed for 16 h and then concentrated. The residue was dissolved in MeOH (75 mL) and resaturated with HCl. The mixture was refluxed for 7 h and the solvent was again evaporated. The residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated. The residue was subjected to silica gel column chromatography (20 g) using benzene as eluent to give 6.1 g (84.4%) of VId, mp 57–60 °C. Recrystallization from MeOH gave 4.0 g of VId: mp 61–62 °C; NMR ($CDCl_3$) δ 2.27 (3 H, s), 3.86 (3 H, s), 6.45–8.05 (8 H, m), 9.28 (1 H, br s). Anal. ($C_{15}H_{15}NO_2$) C, H, N.

Methyl 5-Methoxy-*N*-phenylanthranilate (VIn). A solution of IIIn (6.1 g, 0.025 mol) in MeOH (75 mL) was saturated with HCl. The mixture was refluxed for 24 h and then concentrated in vacuo. The residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column

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chromatography (16 g) using benzene–hexane as eluent to give 3.0 g (46.5%) of VIn: mp 47–50 °C; NMR ($CDCl_3$) δ 3.74 (3 H, s), 3.86 (3 H, s), 6.8–7.6 (8 H, m), 9.05 (1 H, br s). Anal. ($C_{15}H_{15}NO_3$) C, H, N.

2-Anilinobenzamides IV were prepared as follows: 2-anilinobenzamide (IVa), 2-[3-(trifluoromethyl)anilino]benzamide (IVb), 2-(2-chloroanilino)benzamide (IVc), 2-(4-fluoroanilino)benzamide (IVf), 2-(4-chloroanilino)benzamide (IVg), and 2-(2-carbamoylanilino)benzamide (IVp) were prepared by a reported method.[1b,16] Other (arylamino)benzamides (IVd and IVh–IVo) were prepared as described in this section.

General Procedures for the Preparation of 2-Anilinobenzamides IV (Table V). Method A. 2-(4-Acetylanilino)benzamide (IVi). A mixture of IIIi (35 g, 0.137 mol) and $SOCl_2$ (24.5 g, 0.20 mol) in benzene (300 mL) was stirred under reflux for 30 min and concentrated in vacuo. The residue was poured into ice-cooled 25% NH_4OH (50 mL). The mixture was stirred at room temperature for 15 h to give 32.3 g (92.3%) of almost pure IVi, mp 170–171 °C. Recrystallization from EtOH gave pure IVi as pale yellow prisms: mp 171–173 °C; NMR (Me_2SO-d_6) δ 2.50 (3 H, s), 6.80–8.30 (10 H, m), 10.30 (1 H, s). Anal. ($C_{15}H_{14}N_2O_2$) C, H, N.

Method B. 5-Methyl-2-anilinobenzamide (IVm). A solution of $COCl_2$ (5 g, 0.051 mol) in benzene (20 mL) was slowly added to a stirred ice-cooled solution of IIIm (2.27 g, 0.01 mol) and NaOH (0.8 g, 0.02 mol) in H_2O (40 mL). The mixture was stirred at room temperature for 1 h. The benzene solution was dried over $MgSO_4$ and concentrated. The residue was added to 10% NH_4OH (50 mL) and the mixture was stirred at room temperature for 2.5 h. The solution was evaporated to give 1.2 g of IVm, mp 158–163 °C. Recrystallization from benzene gave 1.1 g (48.7%) of IVm as colorless needles: mp 163—165 °C; NMR (Me_2SO-d_6) δ 2.25 (3 H, s), 6.5–8.3 (10 H, m), 9.75 (1 H, s). Anal. ($C_{14}H_{14}N_2O$) C, H, N.

Method C. 5-Methoxy-2-anilinobenzamide (IVn). A solution of VIn (2.58 g, 0.01 mol) and NaOMe (0.6 g, 0.011 mol) in MeOH (200 mL) was saturated with NH_3. The mixture was allowed to stand at room temperature for 11 days. During this time the mixture was resaturated with NH_3 after 5, 7, and 9 days. The solvent was evaporated in vacuo. The residue was washed with H_2O and diisopropyl ether to give 1.76 g (72.7%) of IVn, mp 143–146 °C. Recrystallization from 2-propanol gave pure IVn, mp 144–147 °C, as colorless prisms: NMR (Me_2SO-d_6) δ 3.78 (3 H, s), 6.7–8.3 (10 H, m), 9.37 (1 H, s). Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

General Procedure for the Preparation of 1-Phenyl-4(1*H*)-quinazolinones I (Table I). 2-Isopropyl-1-phenyl-4(1*H*)-quinazolinone (3). Isobutyryl chloride (2.25 g, 0.021 mol) was added to a solution of IVa (1.5 g, 0.0071 mol) in $CHCl_3$ (25 mL) with ice cooling. After being refluxed for 1.5 h, the mixture was neutralized with aqueous $NaHCO_3$ with cooling. The $CHCl_3$ layer was concentrated in vacuo to give 1.84 g of **3**, mp 225–229 °C. Recrystallization from 2-propanol gave 1.35 g (72.0%) of **3** as colorless leaflets: mp 228–230 °C; IR (Nujol) 1650, 1598 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (6 H, d, J = 7 Hz), 2.35–2.95 (1 H, m), 6.45–6.7 (1 H, m), 7.2–7.9 (7 H, m), 8.25–8.5 (1 H, m). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

2-(2-Carboxyethyl)-1-phenyl-4(1*H*)-quinazolinone (18). A mixture of **17** (2.16 g, 0.007 mol) and KOH (0.392 g, 0.007 mol) in MeOH (30 mL) containing 5% H_2O was refluxed for 6 h. The solvent was evaporated in vacuo and the residue was acidified to pH 3 with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to give 1.4 g of **18**, mp 197–199 °C. Recrystallization from 2-propanol–diisopropyl ether gave 1.21 g (58.8%) of **18** as colorless needles: mp 199–201 °C; IR (Nujol) 1730, 1725 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.25–3.10 (4 H, m), 6.50–6.80 (1 H, m), 7.30–7.90 (7 H, m), 8.20–8.50 (1 H, m), 8.50–9.70 (1 H, br). Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

1-Phenyl-2-(trifluoromethyl)-4(1*H*)-quinazolinone (19). A mixture of IVa (2.12 g, 0.01 mol) and trifluoroacetic anhydride ($(CF_3CO)_2O$ (5 g, 0.022 mol) in $CHCl_3$ (30 mL) was stirred for 3 h with ice cooling. An additional 2.5 g of $(CF_3CO)_2O$ was added to the mixture. After stirring for 1 h with ice cooling, the mixture was concentrated in vacuo. The residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated in vacuo to give 2.5 g of **19**, mp 234–236 °C. Recrystallization from DMF gave 1.85 g (63.8%) of **19** as colorless prisms: IR (Nujol) 1655, 1603 cm^{-1}; NMR (Me_2SO-d_6) δ 6.5–6.75 (1 H, m), 7.5–7.9 (7 H, m), 8.1–8.3 (1 H, m). Anal. ($C_{15}H_9F_3N_2O$) C, H, N.

Preparation of 2-(Dimethylamino)-1-phenyl-4(1*H*)-quinazolinone (20). (a) 2-Carbamoyl-1-phenyl-4(1*H*)-quinazolinone (XIV). A solution of 2-(ethoxycarbonyl)-1-phenyl-4(1*H*)-quinazolinone[1a] (5.0 g, 0.017 mol) and NH_3 (10 g) in EtOH (100 mL) was stirred for 6 h at 80 °C in a pressure bottle. The mixture was concentrated to give 3.9 g (86.5%) of XIV, 230–233 °C dec. Recrystallization from DMF–H_2O gave pure XIV as colorless needles: mp 231–233 °C dec; NMR (Me_2SO-d_6) δ 6.56 (1 H, m), 7.25–8.43 (10 H, m). Anal. ($C_{15}H_{11}N_3O_2$) C, H, N.

(b) 2-Cyano-1-phenyl-4(1*H*)-quinazolinone (XV). A mixture of XIV (2.0 g, 0.0076 mol) and pyrophosphoryl chloride[1c] (10 mL) was stirred for 10 h at 50 °C. The mixture was poured into ice–water (50 mL). The crystalline product was collected by filtration to give 4 g (75.1%) of XV, mp >280 °C. Recrystallization from THF gave XV as colorless needles: mp >280 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 6.65–6.89 (1 H, m), 7.40–7.99 (7 H, m), 8.10–8.40 (1 H, m). Anal. ($C_{15}H_9N_3O$) C, H, N.

(c) 2-(Dimethylamino)-1-phenyl-4(1*H*)-quinazolinone (20). A mixture of XV (1.2 g, 0.0049 mol) and 40% Me_2NH (10 mL) was stirred for 2 h to give 1.0 g (77.7%) of **20**, mp 209–210 °C. Recrystallization from 2-propanol gave **20** as colorless prisms: mp 209–210 °C; NMR (Me_2SO-d_6) δ 2.74 (6 H, s), 6.88–7.80 (8 H, m), 7.95–8.17 (1 H, m). Anal. ($C_{16}H_{15}N_3O$) C, H, N.

1-(4-Nitrophenyl)-4(1*H*)-quinazolinones. Compounds **27** and **29** were prepared by a procedure similar to that described for 2-cyclobutyl-1-(4-nitrophenyl)-4(1*H*)-quinazolinone (**29**) as follows. Cyclobutanecarbonyl chloride (1.4 g, 0.012 mol) was added to a suspension of IVl (1.03 g, 0.004 mol) in DMF (15 mL) with ice cooling. The mixture was stirred for 26 h at room temperature and then poured into aqueous $NaHCO_3$. The precipitate was collected by filtration and dissolved in AcOH (10 mL) containing BF_3·Et_2O (0.5 g). The mixture was refluxed for 1 h. After cooling, the product was filtered and washed with aqueous $NaHCO_3$. Recrystallization from DMF–EtOH gave 0.28 g (21.8%) of **29** as pale yellow prisms: mp 246–247 °C; IR (Nujol) 1655, 1642, 1602 cm^{-1}; NMR ($CDCl_3$) δ 1.57–3.33 (7 H, m), 6.34–6.65 (1 H, m), 7.10–7.80 (4 H, m), 8.18–8.71 (3 H, m). Anal. ($C_{18}H_{15}N_3O_3$) C, H, N.

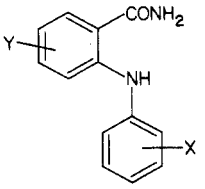
1-(2-Carboxyphenyl)-2-isopropyl-4(1*H*)-quinazolinone (32). A solution of $NaNO_2$ (1.62 g, 0.024 mol) in H_2O (3 mL) was added to concentrated H_2SO_4 (16 mL) solution of **33** (2.46 g, 0.008 mol) at 10–20 °C. The mixture was stirred at room temperature for 17 h and poured into ice–water (50 mL). The mixture was neutralized with 10% NaOH to give 2.2 g of **32**, mp >280 °C. Recrystallization from DMF–EtOH gave 1.3 g (53.1%) of pure **32**: mp >280 °C; IR (Nujol) 1710 cm^{-1}; NMR (Me_2SO-d_6) δ 2.15 (6 H, d, J = 7 Hz), 2.20–2.90 (1 H, m), 6.31–6.70 (1 H, m), 7.22–8.41 (7 H, m). Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

1-(4-Aminophenyl)-2-isopropyl-4(1*H*)-quinazolinone (34). A suspension of **23** (2.16 g, 0.07 mol) in 10% HCl (100 mL) was hydrogenated at room temperature for 4 h in the presence of 5% Pd–C (0.3 g). The catalyst was filtered off and the filtrate was neutralized with aqueous $NaHCO_3$. The precipitate was collected by filtration to give 1.6 g of **34**, mp 268–273 °C. Recrystallization from DMF gave 1.1 g (55.7%) of **34**: mp 272–275 °C; IR (Nujol) 3450–3200, 1648, 1601 cm^{-1}; NMR (Me_2SO-d_6) δ 1.15 (6 H, d, J = 7 Hz), 2.50–3.10 (1 H, m), 5.70 (2 H, s), 6.60–7.85 (7 H, m), 8.00–8.25 (1 H, m). Anal. ($C_{17}H_{17}N_3O$) C, H, N.

Preparation of 2-Isopropyl-1-phenyl-4(1*H*)-quinazolinones with Carboxymethyl Group. Compound **36** and **40** were prepared by a procedure similar to that described for 1-(4-carboxymethylphenyl)-2-isopropyl-4(1*H*)-quinazoline (**36**) as follows.

(a) 2-Isopropyl-1-[4-[(morpholinothiocarbonyl)methyl]-phenyl]-4(1*H*)-quinazolinone (XVIa). A mixture of **35** (7.65 g, 0.025 mol), sulfur (2.4 g), and morpholine (12 g) was refluxed for 4 h. After cooling, the mixture was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (50 mL × 2). The $CHCl_3$ layer was washed with H_2O (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give 7.0 g of crude XVIa, mp 243–250 °C. Recrystallization from $CHCl_3$–diisopropyl ether (twice) gave 4.2 g (41.2%)

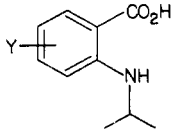
Table V. 2-Anilinobenzamides IV



no.	X	Y	yield, %	method	mp, °C	recryst[a] solvent	anal.
IVd	2-CH_3	H	48	C	117–118	F–H	C, H, N
IVh	4-NO_2	H	80	A	193–195	B–D	C, H, N
IVi	4-$COCH_3$	H	92	A	171–173	B	C, H, N
IVj	H	4-Cl	29	A	135–137	F–I	C, H, N
IVk	H	4-CH_3	49	B	138–140	F–H	C, H, N
IVl	H	4-NO_2	55	A	168–170	C	C, H, N
IVm	H	5-CH_3	52	B	163–165	F	C, H, N
IVn	H	5-OCH_3	73	C	144–147	C	C, H, N
IVo	H	5-$COCH_3$	56[b]	A	216–219	B	C, H, N

[a] See footnote *a* of Table I. [b] Overall yield from potassium 5-acetyl-2-chlorobenzoate.

Table VI. *N*-Isopropylanthranilic Acids X



no.	Y	yield, %	method	mp, °C	recryst[a] solvent	anal.
Xa	H	30 (49)	D (E)	86–90[b]		
Xb	4-Cl	39	E	160–164	A–J	C, H, N
Xc	4-CH_3	72	D	158–159	A	C, H, N
Xd	5-F	55	E	144–146	A–J	C, H, N
Xe	5-Cl	55	E	171–172	A–J	C, H, N
Xf	5-Br	25	E	184–186	B–J	C, H, N
Xg	5-OCH_3	46	E	130–132	G	C, H, N
Xh	6-Cl	*c*	E			

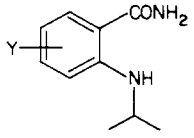
[a] See footnote *a* of Table I. [b] Not purified (ref 3). [c] Used in text reaction with purification.

of XVIa as yellow prisms: mp 268–270 °C dec; IR (Nujol) 1647, 1620, 1598 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (6 H, d, J = 7 Hz), 2.20–2.93 (1 H, m), 3.30–4.10 (6 H, m), 3.15–4.68 (4 H, m), 6.34–6.70 (1 H, m), 7.08–7.90 (6 H, m), 8.10–8.42 (1 H, m). Anal. ($C_{33}H_{25}N_3O_2S$) C, H, N.

(b) 1-[4-(Carboxymethyl)phenyl]-2-isopropyl-4(1*H*)-quinazolinone (36). H_2SO_4 (50%, v/v, 10 mL) was added to a solution of XVIa (4 g, 0.0098 mol) in AcOH (20 mL). After stirring at reflux for 1.5 h, the mixture was poured into ice–water (20 mL) and neutralized with aqueous $NaHCO_3$ to give 2.6 g of crude product. Recrystallization from MeOH–diisopropyl ether gave 1.3 g (41.1%) of **36** as yellow needles: mp 261–265 °C dec; IR (Nujol) 1725, 1655, 1603 cm^{-1}; NMR (Me_2SO-d_6) δ 1.18 (6 H, d, J = 7 Hz), 2.20–2.95 (1 H, m), 3.80 (2 H, s), 6.40–6.55 (1 H, s), 7.20–7.90 (6 H, m), 8.00–8.25 (1 H, s). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

4-Isopropyl-1-phenyl-2(1*H*)-quinazolinone (IX). A solution of 2-anilinobenzonitrile (2.0 g, 0.0103 mol) in ether (15 mL) was added to an ether solution of freshly prepared isopropylmagnesium bromide [from isopropyl bromide (7.8 g, 0.06 mol) and magnesium (1.5 g, 0.063 mol)] at −20 °C under a stream of nitrogen. After stirring at room temperature for 1 h, the mixture was poured in small portions into ice–water (100 mL). A solution of $COCl_2$ (1.1 g, 0.012 mol) in $CHCl_3$ (30 mL) was added to the above mixture with ice cooling. After stirring at room temperature for 1 h, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was triturated with diisopropyl ether. The precipitate was collected by filtration to give 1.2 g (32.0%) of IX, mp 195–196 °C. Recrystallization from $CHCl_3$–diisopropyl ether gave 1 g of yellow prisms: mp 196–197 °C; IR (Nujol) 1665, 1615, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (6 H, d, J = 7 Hz), 3.85 (1 H, m), 6.60–6.83 (1 H, m), 7.15–7.80 (7 H, m), 7.98–8.24 (1 H, m). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

Table VII. 2-(Isopropylamino)benzamides XII



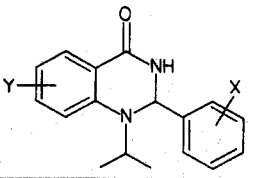
no.	Y	yield, %	mp, °C	recryst[a] solvent	anal.
XIIa	H	68	100–103	F–I	C, H, N
XIIb	4-Cl	75	136–138	G	C, H, N
XIIc	4-CH_3	56	152–155	F	C, H, N
XIId	5-F	65	113–116	G–I	C, H, N
XIIe	5-Cl	59	120–122	G	C, H, N
XIIf	5-Br	54	121–124	G	C, H, N
XIIg	5-OCH_3	51	96–98	G–H	C, H, N
XIIh	6-Cl	13[b]	125–127	F–H	C, H, N
XIIi	6-OCH_3	58[c]	115–117	C–G	C, H, N

[a] See footnote *a* of Table I. [b] Overall yield from 6-chloroanthranilic acid. [c] Prepared from 2-amino-6-methoxybenzamide and isopropyl iodide.

2,3-Dihydro-2-isopropyl-1-phenyl-4(1*H*)-quinazolinone (47). A mixture of **3** (1.7 g, 0.0064 mol) and $NaBH_4$ (0.27 g, 0.0071 mol) in 2-propanol (30 mL) was refluxed for 1 h. The solvent was evaporated in vacuo and the residue was triturated with H_2O to give 1.7 g of **47**. Recrystallization from 2-propanol gave 1.1 g (64.2%) of **47** as colorless needles: mp 168–170 °C; NMR ($CDCl_3$) δ 1.02 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 2.08 (1 H, m), 4.72 (1 H, dd, J = 8 Hz, J = 4.5 Hz), 6.90–7.60 (8 H, m), 7.95–8.50 (2 H, m). Anal. ($C_{17}H_{18}N_2O$) C, H, N.

2-(2-Chlorophenyl)-2,3-dihydro-1-isopropyl-4(1*H*)-quinazolinone (48). By a procedure similar to that described above, **48** (mp 178–180 °C from 2-propanol) was obtained from

Table VIII. 2,3-Dihydro-1-isopropyl-2-phenyl-4(1*H*)-quinazolinones XIII



no.	X	Y	yield, %	mp, °C	recryst[a] solvent	anal.
XIIIa	2-Br	H	78	174–176	C	C, H, N
XIIIb	2-OCH_3	H	84	169–171	B–G	C, H, N
XIIIc	H	5-Cl	63	142–145	F–G	C, H, N
XIIId	H	5-OCH_3	62[b]	204–206	C–G	C, H, N
XIIIe	H	6-Br	87	197–200	B	C, H, N
XIIIf	H	7-Cl	77	204–206	C	C, H, N
XIIIg	4-F	7-Cl	74	150–151	C	C, H, N

[a] See footnote *a* of Table I. [b] Carried out at 135 °C for 24 h in a pressure bottle.

51 in 72.8% yields: NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 7 Hz), 1.39 (3 H, d, J = 7 Hz), 4.25 (1 H, m), 6.21 (1 H, d, J = 4 Hz), 6.80–7.73 (8 H, m), 7.92–8.13 (1 H, m). Anal. ($C_{17}H_{17}ClN_2O$) C, H, N.

General Procedures for the Preparation of *N*-Isopropylanthranilic Acids X (Table VI). Method D. *N*-Isopropyl-4-methylanthranilic Acid (Xc). A mixture of 2-bromo-4-methylbenzoic acid (16.5 g, 0.077 mol) and isopropylamine (30 g, 0.5 mol) in dioxane (100 mL) was stirred at 100 °C for 16 h in the presence of copper powder (0.5 g) in a pressure bottle. The solvent was evaporated in vacuo and the residue was dissolved in 10% HCl. The acid layer was treated with Norit and neutralized with aqueous $NaHCO_3$ to give 10.7 g of crude Xc, mp 149–151 °C. Recrystallization from MeOH–H_2O gave 8.4 g (56.5%) of Xc as colorless needles: 158–159 °C; IR (Nujol) 3360, 1660, 1616 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (6 H, d, J = 7 Hz), 2.33 (3 H, s), 3.40–4.09 (1 H, m), 6.30–6.67 (2 H, m), 7.89 (1 H, d, J = 8 Hz), 8.70–10.32 (2 H, br). Anal. ($C_{11}H_{15}NO_2$) C, H, N.

Method E. 5-Fluoro-*N*-isopropylanthranilic Acid (Xd). A mixture of 5-fluoroanthranilic acid (10.0 g, 0.0065 mol), isopropyl iodide (50 mL), and pyridine (5.6 g, 0.07 mol) was refluxed for 4 h. The precipitate was filtered off and washed with $CHCl_3$. The filtrate and the washings were mixed, and then concentrated in vacuo. The residue was shaken with benzene (200 mL)–10% HCl (200 mL). The acid layer was neutralized with K_2CO_3 to give 8.5 g of **Xd**, mp 132–137 °C. Recrystallization from MeOH–H_2O gave 7.0 g (54.6%) of Xd as yellow prisms: mp 144–146 °C; IR (Nujol) 3370, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (6 H, d, J = 7 Hz), 3.30–4.05 (1 H, m), 6.45–7.86 (3 H, m), 9.42 (2 H, br). Anal. ($C_{10}H_{12}FNO_2$) C, H, N.

General Procedure for the Preparation of 2-(Isopropylamino)benzamides XII (Table VII). 5-Fluoro-2-(isopropylamino)benzamide (XIId). A mixture of Xd (7.0 g, 0.036 mol) and $ClCO_2Et$ (120 mL) was refluxed for 7 h. The precipitate was collected by filtration and then poured into 10% NH_4OH (50 mL). The mixture was stirred at room temperature for 15 h and extracted with $CHCl_3$. The extract was concentrated in vacuo to give 5.0 g of XIId. Recrystallization from diisopropyl ether–petroleum ether gave 4.5 g (64.6%) of XIId: mp 113–116 °C; IR (Nujol) 3480–3335, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (6 H, d, J = 7 Hz), 3.26–3.98 (1 H, m), 6.14 (2 H, br s), 6.42–7.60 (4 H, m). Anal. ($C_{10}H_{13}FN_2O$) C, H, N.

2-(Isopropylamino)-6-methoxybenzamide (XIIi). A mixture of 2-amino-6-methoxybenzamide (1.66 g, 0.01 mol), isopropyl iodide (5 mL), and pyridine (1.6 g, 0.02 mol) was refluxed for 1 h. The mixture was shaken with $CHCl_3$ and aqueous $NaHCO_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated in vacuo to give 1.2 g (57.7%) of XIIi, mp 114–116 °C. Recrystallization from 2-propanol–diisopropyl ether gave XIIi as colorless prisms: mp 115–117 °C; NMR (Me_2SO-d_6) δ 1.13 (6 H, d, J = 7 Hz), 3.57 (1 H, m), 3.78 (3 H, s), 6.22 (1 H, d, J = 9 Hz), 6.28 (1 H, d, J =9 Hz), 7.13 (1 H, t, J = 9 Hz), 7.28 (1 H, br), 7.55 (2 H, br). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

General Procedures for the Preparation of 2,3-Dihydro-1-isopropyl-2-phenyl-4(1*H*)-quinazolinones XIII (Table VIII). 7-Chloro-2,3-dihydro-1-isopropyl-2-phenyl-4(1*H*)-quinazolinone (XIIIf). A solution of **XIIb** (6.39 g, 0.03 mol), benzaldehyde (3.5 g, 0.033 mol), and piperidine (1 mL) in EtOH (50 mL) was refluxed for 18 h. The solvent was evaporated in vacuo. The residue was again refluxed with benzaldehyde (2.0 g) and piperidine (1 mL) in EtOH (50 mL) for 31 h. The solvent was evaporated in vacuo and the residue was triturated with diisopropyl ether to give 7.3 g (77.4%) of XIIIf, mp 200–205 °C. Recrystallization from 2-propanol gave pure XIIIf as colorless prisms: mp 204–206 °C; NMR ($CDCl_3$) δ 1.30 (6 H, d, J = 7 Hz), 3.82–4.33 (1 H, m), 5.81 (1 H, d, J = 4 Hz), 6.70–7.48 (7 H, m), 7.82 (1 H, d, J = 8 Hz), 8.41–8.77 (1 H, br). Anal. ($C_{17}H_{17}ClN_2O$) C, H, N.

2,3-Dihydro-3-isopropyl-2-phenyl-4(1*H*)-quinazolinone (XVII). A mixture of 2-amino-*N*-isopropylbenzamide[17] (3.56 g, 0.020 mol), benzaldehyde (2.54 g, 0.024 mol), 10% aqueous NaOH (5 mL) in EtOH (30 mL) was refluxed for 1 h. The solvent was evaporated in vacuo to give 4.6 g of XVII, mp 190–195 °C. Recrystallization from 2-propanol–diisopropyl ether gave 1.65 g (79.2%) of XVII as colorless prisms: mp 196–198 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.96 (3 H, *d*, J = 7 Hz), 1.28 (3 H, d, J = 7 Hz), 4.50–5.10 (1 H, m), 5.76 (1 H, d, J = 2 Hz), 6.44–7.95 (10 H, m). Anal. ($C_{17}H_{18}N_2O$) C, H, N.

General Procedures for the Preparation of 1-Isopropyl-2-phenyl-4(1*H*)-quinazolinones II (Table III). Method F. 1-Isopropyl-2-phenyl-4(1*H*)-quinazolinone (49). A mixture of XIIa (1.6 g, 0.009 mol) and benzoyl chloride (3.8 g, 0.027 mol) in $CHCl_3$ (25 mL) was refluxed for 24 h. The solvent was evaporated in vacuo and the residue was triturated with diisopropyl ether. The precipitate was collected by filtration and then neutralized with aqueous $NaHCO_3$ to give 2.4 g of **49**. Recrystallization from EtOH–diisopropyl ether gave 1.62 g (68.2%) of **49** as colorless needles: mp 223–226 °C; IR (Nujol) 1650, 1609 cm^{-1}; NMR ($CDCl_3$) δ 1.65 (6 H, d, J = 7 Hz), 4.55–5.10 (1 H, m), 7.25–8.50 (9 H, m). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

Method G. 7-Chloro-1-isopropyl-2-phenyl-4(1*H*)-quinazolinone (68). A mixture of XIIIf (7.0 g, 0.023 mol) and potassium permanganate (7.9 g, 0.05 mol) in acetone (200 mL) was refluxed for 1.5 h. Thereafter potassium permanganate (2.0 g) was added and the mixture was refluxed for a further 1.5 h. The MnO_2 was filtered off and washed with $CHCl_3$. The filtrate and the washings were mixed and concentrated in vacuo to give 5.8 g of **68**, mp 145–147 °C. Recrystallization from 2-propanol–diisopropyl ether gave 5.2 g (74.8%) as colorless prisms: mp 148–150 °C; NMR ($CDCl_3$) δ 1.64 (6 H, d, J = 7 Hz), 4.38–5.10 (1 H, m), 7.28–8.00 (7 H, m), 8.28 (1 H, d, J = 9 Hz). Anal. ($C_{17}H_{15}ClN_2O$) C, H, N.

2-Isopropyl-3-phenyl-4(3*H*)-quinazolinone (45).[18] By a procedure similar to that described above, **45** (mp 136–137 °C, colorless needles from benzene–diisopropyl ether) was obtained in 81.2% yield from 2,3-dihydro-2-isopropyl-3-phenyl-4(1*H*)-quinazolinone: NMR ($CDCl_3$) δ 1.22 (6 H, d, J = 7 Hz), 2.45–3.00

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(1 H, m), 7.10–7.80 (8 H, m), 8.15–8.40 (1 H, m). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

3-Isopropyl-2-phenyl-4(3*H*)-quinazolinone (46).[19] By a procedure similar to that described for the synthesis of II (method G), **46** (mp 132–135 °C, colorless prisms from benzene–diisopropyl ether) was obtained in 78.4% yield from XVII: NMR ($CDCl_3$) δ 1.60 (6 H, d, J = 7 Hz), 4.10–4.65 (1 H, m), 7.2–7.8 (8 H, m), 8.20–8.42 (1 H, m). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

2-(4-Aminophenyl)-1-isopropyl-4(1*H*)-quinazolinone (60). A mixture of **59** (2.5 g, 0.0081 mol) and 10% HCl (50 mL) in MeOH (50 mL) was hydrogenated at room temperature for 4 h in the presence of 5% Pd–C (0.1 g). The catalyst was filtered off. The filtrate was concentrated and neutralized with aqueous $NaHCO_3$ to give 2.0 g of **60**, mp 251–253 °C. Recrystallization from MeOH gave 1.35 g (59.8%) of **60** as yellow prisms: mp 255–257 °C; NMR (Me_2SO-d_6) δ 1.50 (6 H, d, J = 7 Hz), 4.60–5.13 (1 H, m), 5.75 (2 H, s), 6.72 (2 H, d, J = 8 Hz), 7.25–8.28 (6 H, m). Anal. ($C_{17}H_{17}N_3O$) C, H, N.

Pharmacology. (a) Antiinflammatory Activity. The carrageenin-induced rat paw edema assay was carried out by a modification of Winter's method.[5] Eight male Sprague–Dawley rats (Charles River) weighing between 160 and 180 g were fasted overnight. One hour after oral administration of the test compounds, carrageenin (0.05 mL of 1% solution in sterile saline) was injected subcutaneously into the subplanter surface of the left hind paw. Foot volumes were measured 4 h after the injection of the phlogistic agent. Edema was determined by the difference between left and right foot volumes. ED_{30} values (30% effective dose) were estimated graphically.

(b) Analgesic Activity. Ten male Sprague–Dawley rats (Charles River) weighing between 70 and 90 g were fasted overnight. The method used was a slight modification of that described by Randall and Selitto.[20] Immediately after oral administration of the test compounds, baker's yeast (0.1 mL of 20% suspension in sterile saline) was injected into the subplantar surface of the left hind paw. Two hours after the yeast injection, the pain threshold of both feet was measured by using a Analgesy Meter (Ugo Basile).

(c) Ulcerogenicity.[21] Five male mice of Slc:ddY, weighing 24–26 g, were fasted from 9 a.m. on the day of experiment. The mice were administered the test compounds orally at around noon and immobilized in each compartment of the stress cage immediately. The cage was then immersed vertically in a water bath kept at 23 ± 0.5 °C for 15 min to the height of their neck. After this acute stress period, they were returned to their home cage in the air-conditioned room (22–23 °C, 50–60%). Two hours after the compound administration, they were sacrificed by dislocation of the neck. The stomach was isolated and stretched out. The severity of the ulcer was assessed by an arbitrary scale of 0–4.

(d) Acute Toxicity. Five male Slc:ddY mice, weighing 18–22 g, were fasted from 9 a.m. on the day of the experiment. The compound, suspended in 0.25% CMC solution, was given orally at around 2 p.m., and the animals were kept under observation for 1 week.

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Registry No. 1, 1086-20-0; 2, 64445-31-4; 3, 70344-46-6; 4, 70344-49-9; 5, 66491-82-5; 6, 66491-86-9; 7, 66478-79-3; 8, 66491-81-4; 9, 66478-84-0; 10, 66478-82-8; 11, 95216-35-6; 12, 95216-36-7; 13, 75065-10-0; 14, 71567-80-1; 15, 71608-84-9; 16, 88267-71-4; 17, 66492-21-5; 18, 66491-80-3; 19, 95216-37-8; 20, 95216-38-9; 21, 70344-54-6; 22, 70344-47-7; 23, 70368-48-8; 24, 70344-60-4; 25, 95216-39-0; 26, 95216-40-3; 27, 95216-41-4; 28, 95216-42-5; 29, 95216-43-6; 30, 70344-52-4; 31, 70344-53-5; 32, 70344-56-8; 33, 70344-50-2; 34, 95216-44-7; 35, 95216-45-8; 36, 95216-46-9; 37, 70344-62-6; 38, 70344-48-8; 39, 95216-47-0; 40, 95216-48-1; 41, 70344-59-1; 42, 70344-61-5; 43, 95216-49-2; 44, 95216-50-5; 45, 32700-64-4; 46, 32700-71-3; 47, 95216-51-6; 48, 95216-52-7; 49, 81822-02-8; 50, 81822-04-0; 51, 81822-09-5; 52, 81822-08-4; 53, 95216-53-8; 54, 81822-10-8; 55, 81822-12-0; 56, 81822-11-9; 57, 81822-16-4; 58, 81822-13-1; 59, 95216-54-9; 60, 95216-55-0; 61, 81822-14-2; 62, 81822-05-1; 63, 81822-40-4; 64, 81822-26-6; 65, 81822-17-5; 66, 81822-29-9; 67, 81822-41-5; 68, 81822-21-1; 69, 81822-36-8; 70, 81822-43-7; 71, 81822-27-7; 72, 81822-19-7; 73, 81822-18-6; 74, 81835-15-6; 75, 81822-20-0; 76, 81822-07-3; 77, 81822-25-5; 78, 81822-24-4; IIId, 579-92-0; IIIi, 23600-82-0; IIIm, 95216-56-1; IIIn, 89224-95-3; IIIo, 95216-57-2; IVa, 13481-61-3; IVd, 95216-60-7; IVh, 95216-61-8; IVi, 95216-62-9; IVj, 64445-26-7; IVk, 95216-63-0; IVl, 95216-64-1; IVm, 95216-65-2; IVn, 95216-66-3; IVo, 95216-67-4; VId, 5509-39-7; VIn, 32082-97-6; Xa, 50817-45-3; Xb, 83389-06-4; Xc, 50817-48-6; Xd, 81822-46-0; Xe, 95216-71-0; Xf, 95216-72-1; Xg, 95216-73-2; Xh, 95216-74-3; XIIa, 5363-32-6; XIIb, 81822-50-6; XIIc, 81822-48-2; XIId, 81822-47-1; XIIe, 81822-51-7; XIIf, 81822-52-8; XIIg, 81822-53-9; XIIh, 95216-75-4; XIIi, 81822-54-0; XIIIa, 95216-76-5; XIIIb, 95216-77-6; XIIIc, 95216-78-7; XIIId, 95248-85-4; XIIIe, 95216-79-8; XIIIf, 95216-80-1; XIIIg, 95216-81-2; XIV, 95216-68-5; XV, 95216-69-6; XVIa, 95216-70-9; XVII, 95216-82-3; $ClCO_2Et$, 541-41-3; potassium anthranilate, 37960-65-9; 4-acetylbromobenzene, 99-90-1; 5-methylanthranilic acid, 2941-78-8; bromobenzene, 108-86-1; potassium 2-chloro-5-methoxybenzoate, 95216-58-3; aniline, 62-53-3; potassium 5-acetyl-2-chlorobenzoate, 95216-59-4; isobutyryl chloride, 79-30-1; trifluroacetic anhydride, 407-25-0; 2-(ethoxycarbonyl)-1-phenyl-4(1*H*)-quinazolinone, 66491-84-7; cyclobutanecarbonyl chloride, 5006-22-4; 2-anilinobenzonitrile, 17583-00-5; 2-bromo-4-methylbenzoic acid, 7697-27-0; 5-fluoroanthranilic acid, 446-08-2; 2-amino-6-methoxybenzamide, 1591-38-4; benzaldehyde, 100-52-7; 2-amino-*N*-isopropylbenzamide, 30391-89-0; benzoyl chloride, 98-88-4; 2,3-dihydro-2-isopropyl-3-phenyl-4(1*H*)-quinazolinone, 38511-64-7.

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(22) Compounds **5**, **22**, **25**, and **38** produced behavioral changes such as clonic convulsion at 100 mg/kg po; therefore these compounds were excluded.