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Synthesis and Antiinflammatory Activity of 1-Alkyl-4-aryl-2(1*H*)-quinazolinones and Quinazolinethiones

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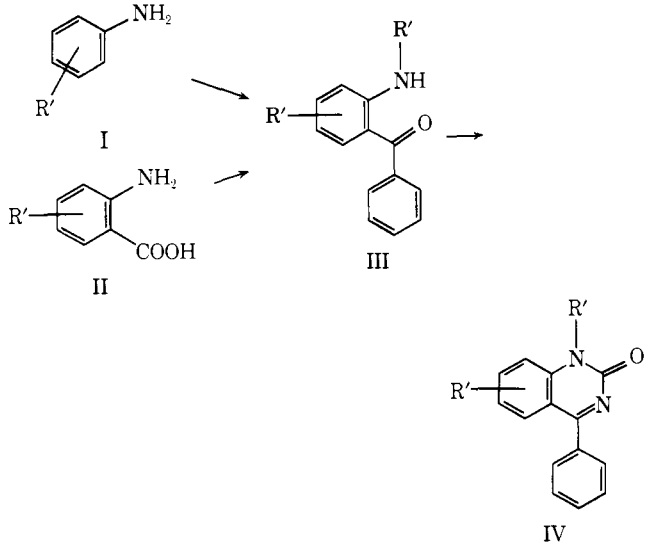
Several routes for the preparation of 1-alkyl-4-aryl-2(1*H*)-quinazolinones, a new class of potent antiinflammatory agents, are described. Two procedures for the synthesis of their sulfur analogs are discussed as is the antiinflammatory evaluation of these compounds.

In the course of our investigations into the chemistry and pharmacology of quinazoline derivatives we discovered a new reaction sequence leading to 1-alkyl-4-aryl-2(1*H*)-quinazolinones.[1] When these compounds were evaluated pharmacologically they were found to possess an interesting level of antiinflammatory activity and we therefore set out to undertake an intensive variation program in the hope of developing a compound of sufficient activity to warrant clinical investigation. This publication will describe only that fraction of the compounds prepared by us (approximately one-fourth) which we feel best illustrates our current thinking concerning the chemistry and structure–activity relationships in this series.

Chemistry. Apart from some early examples prepared by the sequence reported previously,[1] the majority of the quinazolinones IV was prepared by the ring closure of appropriately substituted *o*-aminobenzophenones III which were in turn prepared either from the corresponding anthranilic acids II or anilines I.



Scheme I shows the sequences employed to prepare the anthranilic acid derivatives and Scheme II those leading to the *o*-aminobenzophenones. Schemes III and IV continue the synthetic sequence and outline the preparation of the quinazolinones and their subsequent chemical modifications.

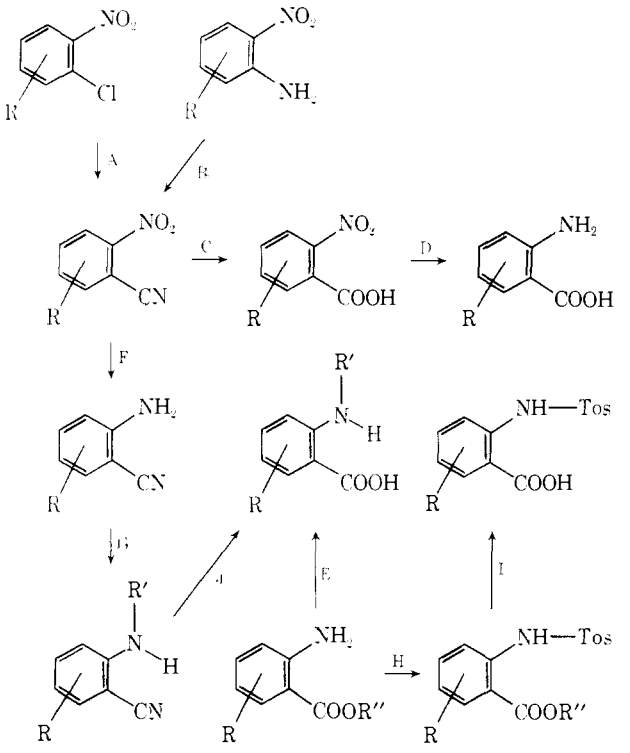
Many of the reactions are either described directly themselves in the literature or are very closely related to well-known procedures and therefore need no further discussion or amplification here, the particular sequence chosen in any one instance depending simply on the availabilities of the several possible starting materials. However, perhaps some synthetic aspects deserve brief comment, particularly the mono-N-alkylation of the various intermediates and end products.

For simple primary alkyl groups such as ethyl or propargyl, the most efficient method of introduction proved to be the alkylation of the sodio derivatives of the 1-unsubstituted quinazolinones (reaction CC, Scheme III). However, with alkyl halides of increasing chain length the yield of N-alkylated product dropped rapidly, much O-alkylation occurring, and secondary alkyl groups were also much less readily introduced in this way for a similar reason. Not unexpectedly, attempts with tertiary halides did not usefully lead to alkylated products.

It therefore became desirable to introduce these types of alkyl groups at an earlier stage of the synthesis. Preparation of the tosyl derivatives of the *o*-aminobenzophenones followed by alkylation was unexceptional with primary and secondary halides (reactions V and W, Scheme II). Subsequently it was found that *o*-aminobenzophenones and *o*-aminobenzonitriles could be alkylated directly with secondary halides, such as 2-iodopropane, to yield essentially monoalkyl derivatives, and this proved to be a general and efficient reaction (reactions G and Z, Schemes I and II).

The synthesis of *tert*-alkyl derivatives remained and a few specific examples were prepared [*i.e.*, 1-*tert*-butyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone] using the exchange reaction of an *o*-chlorobenzophenone with *tert*-alkylamines (reaction X, Scheme II), but this method is not a general one, being only practical for those compounds bearing substituents which activate the halogen grouping. A more general synthesis of *tert*-butylaminobenzophenones *via* 2,1-benzisoxazoles was therefore developed by us and this has been described elsewhere.[2]

Scheme I



R = one or two aromatic substituents
R′ = H, alkyl
R″ = Et or Me
Tos = *p*-toluenesulfonyl

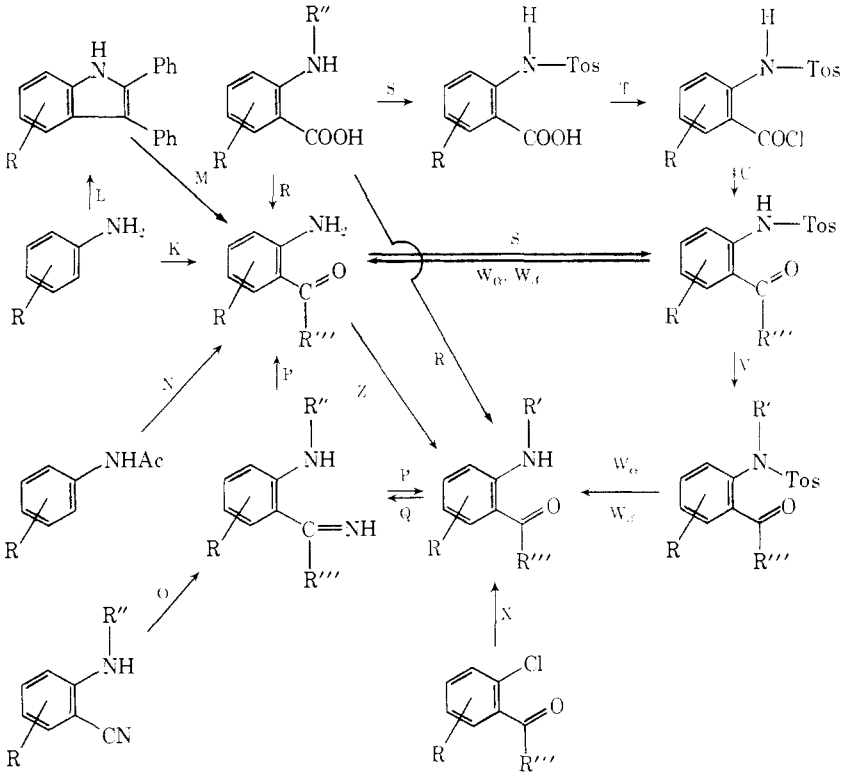
In Scheme III the pathways for obtaining the quinazolinones and thiones are outlined. Four methods were used interchangeably for the cyclization of the aminobenzophenones, all using derivatives of carbamic acid, namely urea, ethyl carbamate, potassium cyanate-acetic acid, and ammonium thiocyanate (reactions AA, BB, DD,[3] and GG, respectively).

No attempt was made by us to optimize the yields in these multistep sequences and in the Experimental Section only a representative example of each of the reactions in Schemes I-IV is described. All the 2(1*H*)-quinazolinones under discussion are listed in Tables I and II of this paper but new intermediates are omitted here (see Supplementary Material Available paragraph).

Pharmacology. The antiinflammatory effects were tested against the acute inflammatory condition induced by carrageenin and the compounds are listed in Tables I and II.

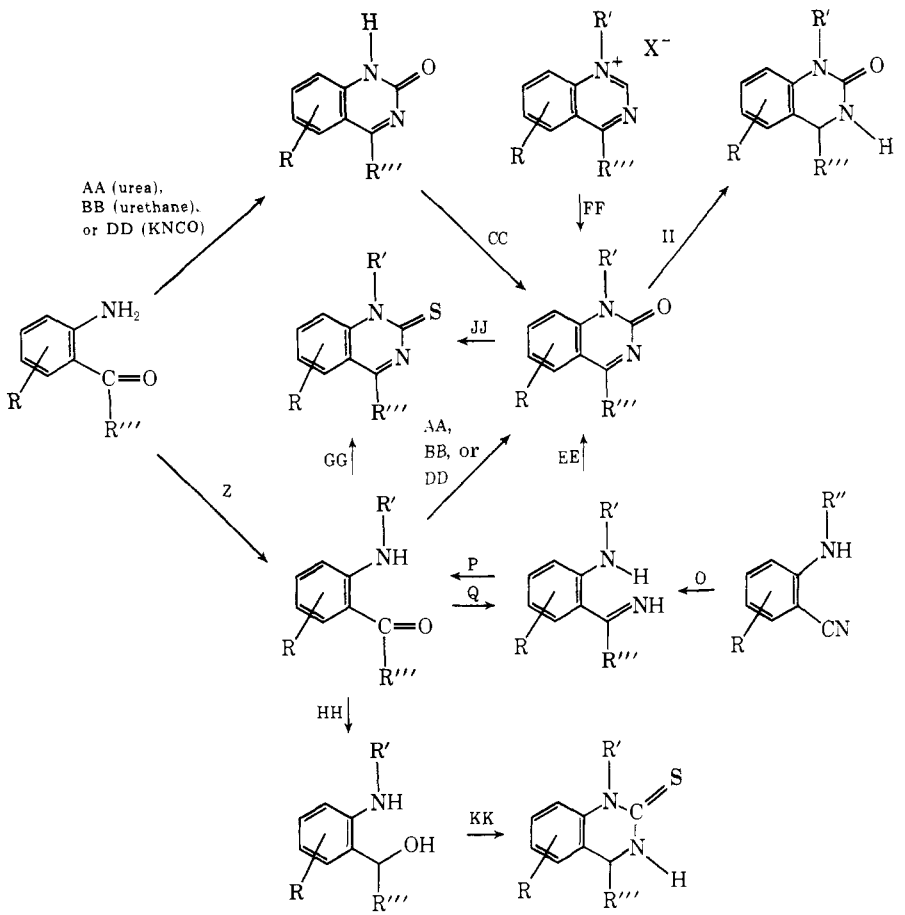
Arbitrarily, the more active compounds, that is, any compound exhibiting activity at 10 mg/kg or less orally, were selected for further evaluation and compared to two standard nonsteroidal antiinflammatory agents. The evaluation listed in Table III consisted of testing the compounds against carrageenin-induced edema in normal and adrenalectomized rats (one week postsurgical extripation). The oral effectiveness was also tested against the hyperesthetic rat paw[4] and against the adjuvant arthritis in

Scheme II



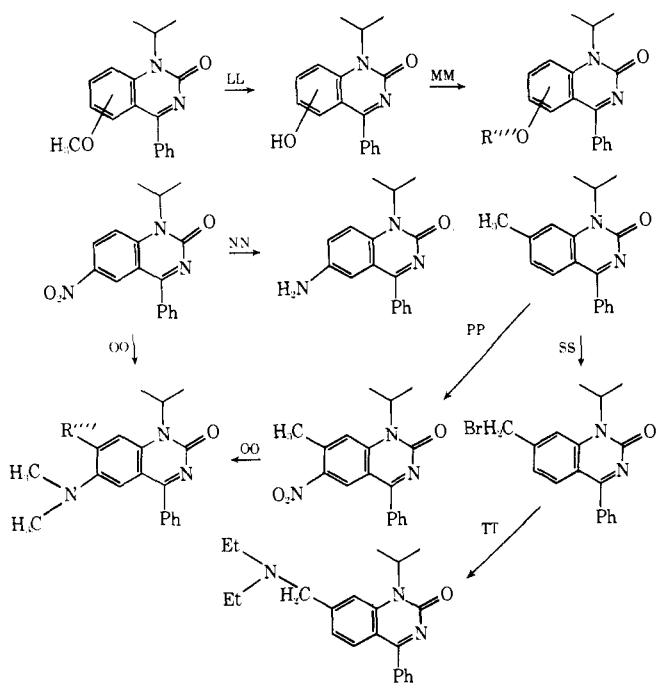
R = one or two aromatic substitutents
R′ = alkyl, alkenyl
R″ = H or alkyl, alkenyl
R‴ = heteroaryl, aryl, or alkyl

Scheme III



R = one or two aromatic substituents
R′ = alkyl, alkenyl
R″ = H or alkyl, alkenyl
R‴ = heteroaryl, aryl, or alkyl

Scheme IV



R⁗ = H, CH_3, or *n*-propyl

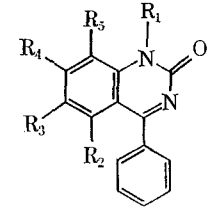
rats and tested between days 12–16 after administration of the mycobacterium butyricum plus adjuvant in the distal position of the tail,[5] The compounds were administered intravenously and tested against the bradykinin-induced bronchoconstriction in guinea pigs.[6]

The results are found in Table III. The numbers represent doses in milligrams per kilogram and are the "effective doses" 50 (ED_{50}) except for the Randall-Selitto test where the number represents the minimum effective dose, that is, the response at that dose which is significantly different ($p > 0.05$) from the control group. The ED_{50} is the milligram per kilogram dose which effectively reduces the foot volume by 50% in the carrageenin edema and adjuvant arthritis tests or reduces the bronchoconstrictive activity of bradykinin by 50% in defining antiinflammatory or antibradykinin properties of these compounds. Since the compounds were examined in the various tests with unequal frequencies, *i.e.*, in proportion to interest of activity rather than in structure, the values represent means of three to ten experiments (six animals each) per individual test procedures.

Structure–Activity Relationship. In a variation of the alkyl substituent in position 1 (**1**, **3**, **8**, **13–17**, **19**, **20**, and **22–24**), those having two or three carbon atoms led to the highest levels of activity in the carrageenin edema assay. Further work indicated that the isopropyl group was the most consistent in its effect on activity and this structural feature was therefore incorporated into subsequent variations.

The placing of substituents in positions 5–8 of the quinazolinone nucleus (**25–48**) was less clear in revealing a structure–activity correlation. Whereas one or two methyl groups in positions 5 and 7 (**25**, **27**, and **29**) increased ac-

Table I

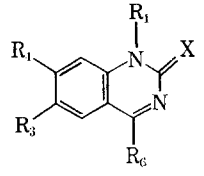


No.	R_1	R_2	R_3	R_4	R_5	Method[a]	Mp, °C	Solvent	Empirical formula	Analyses	Carr. edema,[b] mg/kg[c]
1	H	H	H	H	H	AA[d]	255–256[e]	EtOH	$C_{14}H_{10}N_2O$	C, H, O	>50
2	H	H	H	CH_3	H	L, M, AA[f]	282–284	MeOH	$C_{15}H_{12}N_2O$	C, H, N	>50
3	CH_3	H	H	H	H	FF[g]	142–143[g]	EtOAc	$C_{15}H_{12}N_2O$	C, H, N, O	30
4	CH_3	H	H	CH_3	H	L, M, S, V, W_α, BB[f]	171–172	EtOAc	$C_{16}H_{14}N_2O$	C, H, N	>50
5	CH_3	H	CH_3	H	H	K, BB, CC[h,y]	146–147	EtOAc	$C_{16}H_{14}N_2O$	C, H, N	>50
6	CH_3	H	H	Cl	H	S, T, U, W_α, DD, CC[i]	188–190[j]	EtOAc	$C_{15}H_{11}N_2OCl$	C, H	>50
7	CH_3	H	Cl	H	H	AA, CC[k]	222–223[j]	EtOAc	$C_{15}H_{11}N_2OCl$	C, H, N, O	30
8	CH_3CH_2	H	H	H	H	AA, CC[d]	182–183	EtOAc	$C_{16}H_{14}N_2O$	C, H, O	25
9	CH_3CH_2	H	H	CH_3	H	L, M, AA, CC[f]	157–158	EtOAc	$C_{17}H_{16}N_2O$	C, H, N	40
10	CH_3CH_2	H	CH_3	H	H	K, BB, CC[h]	178–180	Et_2O	$C_{17}H_{16}N_2O$	C, H, N	25
11	CH_3CH_2	H	H	Cl	H	S, T, U, W_α, DD, CC[i]	187–188	EtOAc	$C_{16}H_{13}ClN_2O$	C, H, N	40
12	CH_3CH_2	H	Cl	H	H	AA, CC[k]	167–168[j]	EtOAc	$C_{16}H_{14}ClN_2O$	C, H, N, Cl	18
13	$CH_3CH_2CH_2$	H	H	H	H	CC*	130–131	EtOAc	$C_{17}H_{16}N_2O$	C, H, N, O	40
14	Isopropyl	H	H	H	H	S, V, W_α, BB[d]	119–121	EtOAc	$C_{17}H_{16}N_2O$	C, H, N	20
15	*n*-Butyl	H	H	H	H	S, V, W_α, BB[d]	102–103	Et_2O	$C_{18}H_{16}N_2O$	C, H, N	45
16	Isobutyl	H	H	H	H	S, V, W_α, BB[d]	121–122	EtOAc	$C_{18}H_{18}N_2O$	C, H, N	>50
17	*tert*-Butyl	H	H	H	H	Q, EE[l]	128–132	Et_2O–pentane	$C_{18}H_{18}N_2O$	C, H, N	>50
18	*tert*-Butyl	H	H	CH_3	H	Q, EE[l]	141–143	Et_2O	$C_{19}H_{20}N_2O$	C, H, N	36
19	$CH_2(CH_2)_4$	H	H	H	H	S, V, W_α, BB[d]	121–122	Et_2O	$C_{19}H_{20}N_2O$	C, H, N	45
20	$CH_2CH{=}CH_2$	H	H	H	H	CC	159–160	MeOH	$C_{17}H_{14}N_2O$	C, H, N, O	33
21	$CH_2CH{=}CH_2$	H	H	CH_3	H	L, M, S, V, W_α, BB[f]	153–155	EtOH	$C_{18}H_{16}N_2O$	C, H, N	55
22	$CH_2C{\equiv}CH$	H	H	H	H	CC	181	CH_2Cl_2	$C_{17}H_{13}N_2O$	C, H, N	26
23	$CH_2CH_2N(CH_3)_2$	H	H	H	H	CC	108–109	Et_2O	$C_{18}H_{19}N_3O$	C, H, N	>50
24	Cyclohexyl	H	H	H	H	Z, BB[d]	147–148	EtOAc	$C_{20}H_{20}N_2O$	C, H, N	>50
25	Isopropyl	CH_3	H	H	H	B, C, D, S, T, U, W_α, Z, BB[m]	153–154	Et_2O	$C_{18}H_{18}N_2O$	C, H, N	10
26	Isopropyl	H	CH_3	H	H	K, Z, BB[h]	170–171	EtOH–Et_2O	$C_{18}H_{18}N_2O$	C, H, N	60
27	Isopropyl	H	H	CH_3	H	L, M, Z, BB[f]	137–138	EtOAc	$C_{18}H_{18}N_2O$	C, H, N, O	5
28	Isopropyl	H	H	H	CH_3	S, T, U, V, W_β, BB*[n]	165–166	EtOAc	$C_{18}H_{18}N_2O$	C, H	60
29	Isopropyl	CH_3	H	CH_3	H	L, M, Z, BB[o]	145–147	MeOH–H_2O	$C_{19}H_{20}N_2O$	C, H, N, O	5
30	Isopropyl	H	CH_3	H	CH_3	K, Z, BB[p]	168–169	Et_2O–pentane	$C_{19}H_{20}N_2O$	C, H, N	>50
31	Isopropyl	H	CH_3	CH_3	H	N, Z, BB[w]	135–137	Et_2O	$C_{19}H_{20}N_2O$	C, H, N	20
32	Isopropyl	H	H	F	H	D, R, Z, BB*[q]	142–143	Et_2O	$C_{17}H_{15}FN_2O$	N, F	13
33	Isopropyl	H	Cl	H	H	Z, BB[k]	149–150	$(CH_3)_2CO$, Et_2O	$C_{17}H_{15}N_2OCl$	C, H, N, Cl	23
34	Isopropyl	H	H	Cl	H	R, Z, BB[s]	165–168	EtOAc	$C_{17}H_{15}N_2OCl$	C, H, N	15
35	Isopropyl	H	CH_3	Cl	H	K, Z, BB[r]	190–191	CH_2Cl_2–Et_2O	$C_{18}H_{17}ClN_2O$	C, H, Cl	27
36	Isopropyl	H	OCH_3	H	H	D, R, Z, BB[s]	140–143	CH_2Cl_2–Et_2O	$C_{18}H_{18}N_2O_2$	C, H, N, O	9
37	Isopropyl	H	H	OCH_3	H	B, F, G, O, P, BB[t,x]	133–137	CH_2Cl_2–Et_2O	$C_{18}H_{18}N_2O$	C, H, N, O	4
38	Isopropyl	H	OCH_3	OCH_3	H	H, I, T, U, W_β, Z, BB[x]	148–150	Me_2CO–pentane	$C_{19}H_{20}N_2O_3$	C, H, N	70
39	Isopropyl	H	OH	H	H	LL	285–288	MeOH	$C_{17}H_{16}N_2O_2$	C, H	>50
40	Isopropyl	H	H	OH	H	LL	266–267	MeOH	$C_{17}H_{16}N_2O_2$	C, H, N	>50
41	Isopropyl	H	H	OEt	H	MM	117–120	Et_2O–pentane	$C_{19}H_{20}N_2O_2$	C, H, O	14
42	Isopropyl	H	H	OPr	H	MM	142–143	Et_2O	$C_{20}H_{22}N_2O_2$	C, H, N	>50

43	Isopropyl	H	NO_2	H	H	X, BB[u]	190–192	EtOAc	$C_{17}H_{15}N_3O_3$	C, H, N	22
44	Isopropyl	H	NH_2	H	H	X, BB, NN[u]	252	EtOAc	$C_{17}H_{17}N_3O$	C, H, N	50
45	Isopropyl	H	$N(CH_3)_2$	H	H	X, BB, OO[u]	167–168	Et_2O	$C_{19}H_{21}N_3O$	C, H, N	10
46	Isopropyl	H	H	$N(CH_3)_2$	H	A, F, G, O, EE[v]	181–183	EtOAc	$C_{19}H_{21}N_3O$	C, H, N, O	10
47	Isopropyl	H	$N(CH_3)_2$	CH_3	H	PP, OO	184–186	EtOAc	$C_{20}H_{23}N_3O$	C, H, N	8
48	Isopropyl	H	H	$CH_2N(Et)_2$	H	SS, TT	174–176	Me_2CO	$C_{22}H_{27}N_3O$ $C_4H_4O_4$	C, H, N, O	15

[a]Methods: Actual sequence is given; some intermediates are known. The melting points of known compounds agreed with the reported values within narrow limits (5°); * indicates a low (<15%) yield reaction. [b]C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111,** 544 (1962). [c]ED_{50} = effective dose (in mg/kg) to reduce edema by 50%. [d]From 2-aminobenzophenone. [e]K. Schofield, *J. Chem. Soc.*, 192 (1952). [f]2-Amino-4-methylbenzophenone intermediate; see ref 11. [g]See ref 1. [h]2-Amino-5-methylbenzophenone intermediate: D. A. Denton and H. Suschitsky, *J. Chem. Soc.*, 4741 (1963). [i]2-Amino-4-chlorobenzophenone described by E. Reeder and L. Sternbach, U. S. Patent 3,136,815 (1964) (see also footnote *s*). [j]See ref 3. [k]2-Amino-5-chlorobenzophenone. [l]For respective 2-*tert*-butylaminobenzophenones, see ref 2. [m]From 6-methyl-2-nitroaniline. [n]From 3-methylanthranilic acid. [o]From 3,5-dimethylaniline. [p]3,5-Dimethylbenzophenone intermediate described by L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26,** 4488 (1961). [q]4-Fluoroanthranilic acid: E. Steck and L. Fletcher, *J. Amer. Chem. Soc.*, **70,** 439 (1948). [r]From 3-chloro-4-methylaniline. [s]2-Amino-5-methoxybenzophenone: L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sachs, and A. Stempel, *J. Org. Chem.*, **27,** 3781 (1962). [t]2-Amino-*p*-anisonitrile; see ref 8. [u]From 2-chloro-5-nitrobenzophenone. [v]From 4-chloro-3-nitro-*N,N*,-dimethylaniline; see ref 7. [w]2-Amino-4,5-dimethylbenzophenone: G. Kränzlein and T. Meissner, German Patent 630,021 (1936); *Chem. Abstr.*, **30,** 5591 (1936). [x]For 2-amino-4-methoxybenzophenone see M. Lachen and A. Wichen, *J. Chem. Soc.*, 2779 (1959). 2-Amino-4,5-dimethoxybenzophenone has been mentioned in two patents, Japanese Patent 27019 (1969) and U. S. Patent 3,428,644 (1969), but was not specifically exemplified. [y]H. Ott, Ger. Offen. 1,909,110 (1969); *Chem. Abstr.*, **72,** 43720p (1970).

Table II



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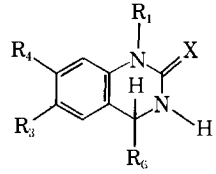

type "B"

No.	Type	X	R_1	R_3	R_4	R_6	Method	Mp, °C	Solvent	Empirical formula	Analyses	Carr, edema
49	A	O	Isopropyl	H	H	*p*-Tolyl	Z, BB	138–140	Et_2O	$C_{18}H_{18}N_2O$	C, H, N	>50
50	A	O	Isopropyl	H	CH_3	*p*-Methoxyphenyl	S, T, U, W_α, Z, BB[a]	159–162	EtOAc	$C_{19}H_{20}N_2O_2$	C, H, N	25
51	A	O	Isopropyl	H	CH_3	*p*-Chlorophenyl	A, F, G, O, P, BB[b]	193–196	EtOAc	$C_{18}H_{17}N_2OCl$	C, H, N	>50
52	A	O	Isopropyl	Cl	H	*o*-Chlorophenyl	Z, BB	147–149	Et_2O	$C_{17}H_{15}Cl_2N_2O$	C, H, N, Cl	>50
53	A	O	Isopropyl	H	CH_3	*m*-Chlorophenyl	A, F, O, P, Z, BB[b]	142–143	EtOAc	$C_{18}H_{17}N_2OCl$	C, H, N, Cl	>50
54	A	O	Isopropyl	H	H	2-Pyridyl	E, R, BB[w]	98–99	Et_2O	$C_{16}H_{15}N_3O$	C, H, N	58
55	A	O	Isopropyl	H	H	2-Thienyl	S, T, U, V, W_α, BB	148–150	EtOAc	$C_{15}H_{14}N_2OS$	C, H, N	25
56	A	O	Isopropyl	H	CH_3	2-Thienyl	S, T, U, W_α, Z, BB[a]	154–157	EtOAc	$C_{16}H_{16}N_2OS$	C, H, N, S	20
57	A	O	Isopropyl	H	CH_3	2-Furyl	A, F, G, J, R, DD[b]	184–187	EtOAc	$C_{16}H_{16}N_2O_2$	C, H, N	>50
58	A	O	Isopropyl	H	CH_3	Methyl	A, F, G, O, P, BB[b]	209–212	EtOAc	$C_{13}H_{16}N_2O$	C, H, N	>50
59	A	O	Isopropyl	H	CH_3	*n*-Butyl	A, F, G, O, EE[b]	82–85	Et_2O	$C_{16}H_{22}N_2O$	C, H, N	>50
60	B	O	Isopropyl	H	H	Phenyl	II	145–146	EtOAc–pentane	$C_{17}H_{18}N_2O$	C, H, N	>50
61	B	O	Isopropyl	H	CH_3	Phenyl	II	159–162	EtOAc	$C_{18}H_{20}N_2O$	C, H	>50
62	B	S	Isopropyl	H	H	Phenyl	Z, HH, KK[c]	185–186	CH_2Cl_2–Et_2O	$C_{17}H_{18}N_2S$	C, H, N, S	25
63	B	S	Isopropyl	H	CH_3	Phenyl	Z, HH, KK[d]	125–127	Et_2O–pentane	$C_{18}H_{20}N_2S$	C, H, S	>50
64	A	S	Isopropyl	H	H	Phenyl	JJ	214–216	EtOAc	$C_{17}H_{16}N_2S$	C, H, N, S	33
65	A	S	Isopropyl	H	CH_3	Phenyl	JJ or GG	194–198	CH_2Cl_2–Et_2O	$C_{18}H_{18}N_2S$	C, H, N, S	21

[a]From 4-methylanthranilic acid. [b]From 4-chloro-2-nitrotoluene. [c]See footnote *a*, Table I. [d]See footnote *f*, Table I.

Table III. Evaluation of the Antiinflammatory Activity of 1-Alkyl-4-aryl-2(1*H*)-quinazolinones[a]

No.	Carrageenin edema: Normal	Carrageenin edema: Adrex[b]	Antibradykinin[c]	Randall-Selitto	Adjuvant arthritis
25	10	50	0.15	2	NT[e]
27	5	6	0.008	1	1
29	5	40	>1.0	12	8
36	9	12	NT	4	50
37	4	19	0.07	<1	18
45	10	30	>1.0	7	29
46	10	22	0.35	2	2
47	9	87	>1.0	6	3
65	21[d]	45	NT	1	2
Indomethacin	5	6	0.3	4	0.1
Phenylbutazone	25	30	>1.0	9	5

[a] Numbers under columns represent dosage in mg/kg (ED_{50}'s, except Randall-Selitto, minimum effective dose). [b] Adrex = bilateral adrenalectomized rats. [c] Compound administered intravenously. [d] Falls to 6 if drug is given 1 hr earlier. [e] NT = not tested.

tivity, and in 6 and 8 (**26**, **28**, and **30**) decreased it, for chloro and methoxy groups both 6 and 7 (**33**, **34**, **36**, and **37**) proved favorable although now disubstitution (**38**) was unfavorable. Noteworthy also is the high activity of the dimethylamino substituents in positions 6 and 7 (**45-47**).

In considering position 4 (**49-59**) departure from the unsubstituted phenyl ring generally led to a lowering in activity. The main exception to this generalization was the 2-thienyl group (**55** and **56**) where significant activity was retained.

The exchange of the carbonyl group by a thiocarbonyl group (**64** and **65**) preserved the potency whereas reduction of the C-N double bond (**60-63**) was almost always accompanied by a corresponding reduction in activity.

The spectrum of activity of the more interesting compounds, as shown in Table III, demonstrates that they often compare favorably with the two nonsteroidal antiinflammatory agents used as standards (except in the adjuvant arthritis test for one of these) and their use in humans is under active investigation.

Experimental Section

All compounds gave satisfactory elemental analyses and their spectra (ir, obtained on a Perkin-Elmer Model 137 spectrophotometer, and nmr, on a Varian Model A-60) were in full accord with the proposed structures. Melting points, obtained on a Hoover melting point apparatus, are uncorrected. By a "usual work-up" is meant: the organic solution of the crude product was washed with H_2O and then brine before being dried over Na_2SO_4, filtered, and concentrated *in vacuo* using a Büchi rotavapor.

Reaction A. 4-Dimethylamino-2-nitrobenzonitrile. A solution of 4-chloro-3-nitro-*N*,*N*-dimethylaniline[7] (4 g, 19.9 mmol) in dimethylacetamide (20 ml) was treated with CuCN (2.1 g, 23.0 mmol) and the mixture was then stirred and refluxed for 4 hr. After this time it was poured onto ice-H_2O and the resulting precipitate isolated by filtration. This solid crude complex was decomposed by refluxing in CH_2Cl_2-MeOH. Insoluble material was filtered off (Celite) and the filtrate worked up as usual. The residue obtained on evaporation of the solvent was crystallized from EtOH to give the product, 2.0 g (52%), mp 182-185° after one further recrystallization from EtOH.

Reaction B. See ref 8.

Reaction C. See ref 9.

Reaction D. 4-Fluoroanthranilic Acid. A solution of 4-fluoro-2-nitrobenzoic acid (10 g, 54.0 mmol) in absolute EtOH (75 ml) was hydrogenated at atmospheric pressure in the presence of Pt (from 0.1 g of PtO_2). When the theoretical amount of H_2 had been absorbed, a crystalline precipitate was present. This was redissolved by the addition of more EtOH and the solution was then filtered (Celite). The filtrate was evaporated *in vacuo* and the residue was crystallized from Et_2O-pentane to give the product, 7.9 g (93%), mp 192-194°.

Reaction E. *N*-Isopropylanthranilic Acid. A mixture of methyl anthranilate (50 ml, 0.33 mol) and Na_2CO_3 (50 g) in 2-iodopropane (100 ml) was heated under reflux for 4 days. It was then cooled and the solids were removed by filtration. The filtrate was distributed between CH_2Cl_2 and H_2O, the aqueous phase was extracted with CH_2Cl_2, and the organic solutions were combined and evaporated. The oily residue was dissolved in Et_2O and extracted ten times with 2 *N* HCl to remove unreacted starting material (the combined aqueous phases did, however, contain a considerable amount of isopropylated ester which could be isolated by repeatedly extracting with Et_2O, evaporating the Et_2O, and chromatographing the crude residue). The Et_2O layer was worked up in the usual manner yielding methyl *N*-isopropylanthranilate (10 g) as an oil. This was dissolved in EtOH (130 ml) and heated under reflux with 2 *N* NaOH (100 ml) for 2 hr. The clear solution was concentrated *in vacuo*, cooled, and neutralized with HCl. The precipitate of the product which formed was filtered off (9.2 g, 10.4%) and recrystallized from Et_2O-petroleum ether, mp 106-107°.

Reaction F. 4-Dimethylaminoanthranilonitrile. A solution of 4-dimethylamino-2-nitrobenzonitrile (30 g, 0.16 mol) in EtOH (500 ml), dioxane (60 ml), and concentrated HCl (80 ml) was treated with iron filings (30 g) added in portions and then refluxed for 1 hr. After cooling, the reaction mixture was filtered and the filtrate made basic by the addition (ice cooling) of 2 *N* NaOH. A thick semicrystalline precipitate formed which was filtered off. This was then stirred with a MeOH-CH_2Cl_2 (1/1) mixture and the cloudy solution was filtered (Celite). The filtrate was evaporated and the residue was dissolved in Et_2O and worked up in the usual manner. The crude crystalline product was recrystallized from CH_2Cl_2 to yield 19 g (75%), mp 110-112°.

Reaction G. (a) 2-Isopropylamino-*p*-anisonitrile. A mixture of 2-amino-*p*-anisonitrile (60 g, 0.40 mol) and K_2CO_3 (60 g) suspended in 2-iodopropane (200 ml) was heated for 72 hr in a sealed steel cylinder at 130-140°. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and filtered through a short column of silica gel. The eluate was evaporated and the residue crystallized from CH_2Cl_2-Et_2O to give the product, 31 g (40%), mp 68-73°.

(b) 4-Dimethylamino-*N*-isopropylanthranilonitrile. A mixture of 4-dimethylaminoanthranilonitrile (10 g, 62.1 mmol), Na_2CO_3 (10 g), and Cu powder (0.2 g) in 2-iodopropane (35 ml) was heated under reflux for 30 hr. After cooling, the reaction mixture was filtered and the filtrate diluted with Et_2O and worked up in the usual way. The residue obtained on evaporation of the solvent was dissolved in $CHCl_3$ and filtered through a short column of silica gel. The first few fractions yielded the product as an oil, 8.9 g (70%), whereas later fractions consisted mainly of starting material.

Reactions H and I. 4,5-Dimethoxy-2-*p*-toluenesulfonamidobenzoic Acid. To a solution of methyl 4,5-dimethoxyanthranilate (53 g, 0.25 mol) in dioxane (250 ml)-pyridine (50 ml) was added TsCl (60 g, 0.31 mol) and the mixture was then heated at 70° for 4 hr. After cooling it was filtered and the filtrate concentrated *in vacuo*. The residue was distributed between CH_2Cl_2 and H_2O and the organic phase was washed with ice-cold dilute HCl (twice) and ice cold 1 *N* NaOH (twice). Work-up in the usual manner yielded 85 g of a solid which was dissolved in dioxane (500 ml) and stirred at room temperature with 2 *N* NaOH (250 ml). Since the hydrolysis was not complete after 20 hr, 50% NaOH (30 ml) was added and the mixture was stirred and heated at 100° for 2 hr. It was then poured onto ice and made acidic with concentrated HCl. The precipitate which formed was filtered off, washed with H_2O, and dried. Recrystallization from Me_2CO yielded the product, 70 g (79%), mp 220°.

Reaction J. 2-Isopropylamino-*p*-toluic Acid. A suspension of 2-isopropylamino-*p*-tolunitrile (50 g, 0.29 mol) in concentrated H_2SO_4 (200 ml) was stirred at room temperature until the solid dissolved and the solution was then maintained at 60° for 1 hr. It was next cooled and poured onto ice. The mixture was made basic with 50% NaOH and the resulting precipitate (the intermediate amide) was filtered off and added to concentrated HCl (250 ml). The solution so obtained was refluxed for 8 hr and then, after cooling, was made basic again and extracted with Et_2O (the Et_2O phase contained 14 g of 2-isopropylamino-*p*-toluamide). The H_2O phase was carefully neutralized when the product crystallized out, 34 g (61%), mp 153-158°.

Reaction K. Our reaction K is essentially the same as method A in ref 10.

Reaction L. 4,6-Dimethyl-2,3-diphenylindole.[11] A mixture of 3,5-dimethylaniline (30 g, 0.25 mol), benzoin (45 g, 0.21 mol), and concentrated HCl (3.6 ml) was slowly stirred and heated to 90°, when a clear solution was obtained. On further heating to 120° water was evolved and a crystalline solid formed, which melted again at 160°. Finally, the mixture was heated to 210° (foaming) and kept at this temperature for 1 hr. After cooling, $CHCl_3$ was added and the solution was washed twice with 2 *N* HCl and worked up in the usual manner. The resulting crude dark oil was dissolved in CH_2Cl_2 and filtered through a bed of aluminum oxide. The filtrate was concentrated and the residue was crystallized from Et_2O-petroleum ether to give the product, 51 g (81%), mp 131-132°.

Reaction M.[12] **2'-Benzoylbenzo-3',5'-xylidide.** An excess of ozone was passed through a solution of 4,6-dimethyl-2,3-diphenylindole (1.0 g, 3.4 mmol) in 90% AcOH (30 ml). H_2O (10 ml) was added and the resulting suspension was treated with Zn dust (3.0 g) and stirred at 25° for 1 hr. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in CH_2Cl_2-H_2O and the organic phase was washed first with $NaHCO_3$ solution and then with H_2O (three times). The residue obtained on work-up was crystallized from Et_2O-pentane to give the product, 0.7 g (63%), mp 95-99°.

2-Amino-4,6-dimethylbenzophenone. A solution of the 2'-benzoylbenzo-3',5'-xylidide (0.5 g, 1.5 mmol) in AcOH (2 ml) and concentrated HCl (2 ml) was refluxed for 18 hr. After cooling, the mixture was poured onto ice and the oil which formed was taken up in Et_2O. The organic phase was then washed with 2 *N* NaOH and worked up in the usual manner, yielding the product, 0.15 g (44%), mp 47-48°, crystallized from pentane.

Reaction N. See ref 13.

Reaction O.[14,†] **1-(4-Dimethylamino-2-isopropylaminophenyl)-1-phenylmethylenimine.** A solution of phenyllithium was prepared from bromobenzene (20 g, 0.13 mol) in Et_2O (50 ml) and *n*-BuLi in hexane (80 ml of a 1.6 *M* solution) at 0-5°. To this was added a solution of 4-dimethylamino-*N*-isopropylanthranilonitrile (8.66 g, 0.04 mol) in Et_2O (150 ml) and the resulting reddish mixture was allowed to warm to room temperature, at which temperature it was stirred for 1 hr. It was then poured onto ice-2 *N* NaOH and the basic aqueous phase was extracted with Et_2O. The organic phases were combined and worked up in the usual way to yield the crude imine, 12 g (100%), as an oil which was used as such for the next step (EE).

Reactions O and P. 2-Amino-3'-chloro-4-methylbenzophenone. A solution of 1-bromo-3-chlorobenzene (80 g, 0.42 mol) in absolute Et_2O (300 ml) was slowly added to a stirred suspension of Mg turnings (12.3 g, 0.51 g-atom) in Et_2O (100 ml). The rate of addition was adjusted so as to keep the solution refluxing continuously. After the addition was complete the mixture was refluxed for a further 30 min. To this mixture was added dropwise a solution of 2-amino-*p*-tolunitrile (18.3 g, 0.14 mol) in Et_2O (300 ml) and the reaction was refluxed again for 1 hr. After cooling it was poured onto ice and excess 2 *N* HCl and then stirred at room temperature for 20 min. The organic phase was separated and the aqueous phase extracted with Et_2O. The organic solutions were combined and worked up in the usual manner. The residue obtained was crystallized from Et_2O-petroleum ether to give the product, 24 g (71%), mp 87-89°.

Reaction Q. 1-(2-*tert*-Butylamino-*p*-tolyl)-1-phenylmethyleneimine. A mixture of 4-methyl-2-*tert*-butylaminobenzophenone (1.6 g, 5.9 mmol), NH_3 (10 ml), and $ZnCl_2$ (0.05 g) was heated at 120° in a sealed tube for 4 days. After cooling, the NH_3 was allowed to evaporate and the residue was extracted with Et_2O. On evaporation of the Et_2O a yellow oil (1.5 g) was obtained which consisted of a mixture of the benzophenone and its imine. This material was used in the next step (EE) without further purification.

Reaction R. 2-Amino-4-fluorobenzophenone. A solution of bromobenzene (45 g, 0.29 mol) in Et_2O (50 ml) was slowly added dropwise at 0° to a solution of *n*-BuLi (155 ml, 1.6 *M* in Et_2O-hexane). The mixture was then stirred at 10° for 30 min after which time it was cooled to 0° and a solution of 4-fluoroanthranilic acid (7.8 g, 0.05 mol) in Et_2O (250 ml) was added at this temperature. Stirring was continued for a further 45 min after which time H_2O was added to the cold reaction until two clear layers were formed. The organic layer was separated and worked up in the usual manner. The residual oil was crystallized from Et_2O-pentane to yield the product, 4.6 g (41%), mp 100-102°.

† Aryllithium compounds and aryl Grignard compounds were used interchangeably. For preparations of alkyl derivatives, lithium reagents were selected.

In the same fashion, but at −30 to −40°, α-pyridyllithium was prepared and allowed to react with *N*-isopropylanthranilic acid.

Reaction S. (a) 6-*p*-Toluenesulfonamido-*o*-toluic Acid. To a solution of Na_2CO_3 (24 g) in H_2O (150 ml) at 50° was added in small portions 6-amino-*o*-toluic acid (15 g, 0.10 mol). To this clear dark solution was added also, portionwise, TsCl (22.8 g, 0.12 mol), the temperature being maintained at 55-60°. The mixture was then stirred at this temperature for an additional 1 hr. After cooling, it was poured onto ice-6 *N* HCl and the precipitate obtained was filtered off. This crude material was dissolved in EtOH and treated with charcoal. After filtration and removal of the EtOH the residue was dissolved in an excess of warm 2 *N* NaOH and reprecipitated with 6 *N* HCl. The low-melting precipitate was taken up in $CHCl_3$ and worked up in the usual manner. Attempts to crystallize the residual oil failed and this material (14.7 g, 48.0%) was therefore used as such in the next step.

(b) **2-*p*-Toluenesulfonamido-4-methylbenzophenone.** To a solution of 2-amino-4-methylbenzophenone (5.2 g, 2.5 mmol) in pyridine (30 ml) was added TsCl (7.5 g, 3.9 mmol). The temperature of the mixture rose slightly and the solution was then allowed to stand at room temperature for 2 hr, during which time crystals of pyridine hydrochloride were deposited. The reaction mixture was then poured onto ice-H_2O and the precipitate obtained was filtered off. Recrystallization from EtOH yielded the product, 8.2 g (85%), mp 114-115°.

Reaction T. *o*-(*p*-Toluenesulfonamido)benzoyl Chloride. A solution of *o*-(*p*-toluenesulfonamido)benzoic acid (100 g, 0.34 mol) in $SOCl_2$ (300 ml) was heated at reflux for 2 hr. After cooling, the excess $SOCl_2$ was removed *in vacuo* and the crystalline residue was dissolved in hot C_6H_6. The solution was filtered and the product precipitated by the addition of petroleum ether. The crystalline material was filtered off and washed with C_6H_6-pentane to give 92 g (86%), mp 123-125°.

Reaction U. *o*-(2-Thienoyl)-*p*-toluenesulfonanilide. To a stirred solution of *o*-(*p*-toluenesulfonamido)benzoyl chloride (150 g, 0.48 mol) in CS_2 (2 l.) and thiophene (80 ml, 1.0 mol) was added in portions $AlCl_3$ (150 g, 1.1 mol). A red oil precipitated and the mixture was left at room temperature with occasional swirling for 2 hr. The CS_2 was decanted from the red oil and discarded. The oil was treated with ice to give a precipitate which was filtered off, washed with ice H_2O, and dissolved in CH_2Cl_2. The solution was washed with NH_4OH and H_2O and worked up in the usual manner. The residue was crystallized from EtOH to yield the product, 125 g (72%), mp 110°. Charcoal treatment and recrystallization from EtOH raised the melting point to 120-122°.

Reaction V. 2-(*N*-Methyl-*p*-toluenesulfonamido)-4-methylbenzophenone. To a solution of 2-*p*-toluenesulfonamido-4-methylbenzophenone (8.2 g, 22.4 mmol) in dimethylacetamide (50 ml) was added NaH (1.3 g, 29.8 mmol, 55% dispersion in mineral oil). After the evolution of hydrogen had ceased the solution was left at room temperature for 90 min. MeI (5 ml, 80.5 mmol) was added and the mixture was left again at room temperature, this time overnight. The solution was diluted with H_2O and the solid produced was filtered off to give the crude product, 8.8 g. Recrystallization from EtOH gave 7.0 g (83%), mp 150-153°.

Reaction W_α. 2-Amino-6-methylbenzophenone. A suspension of 2-*p*-toluenesulfonamido-6-methylbenzophenone (4.2 g, 11.5 mmol) in concentrated H_2SO_4 (20 ml) was shaken for 20 hr at 25°. The resulting clear solution was poured onto ice and filtered and the filtrate was made basic with 50% NaOH (cooling). The precipitate which formed was extracted into Et_2O and the organic phase was worked up in the normal manner to give the product (1.45 g, 60%) as an oil which was used as such for the next step (*e.g.*, reaction Z).

Reaction W_β,[15] **2-Isopropylamino-3-methylbenzophenone.** To a solution of dry HBr (10 g) in AcOH (30 ml) were added 2-(*N*-isopropyl-*p*-toluenesulfonamido)-3-methylbenzophenone (2.03 g, 5.0 mmol) and phenol (0.85 g, 9.0 mmol), and the mixture was left at room temperature for 4 hr. The red-brown solution was then diluted with Et_2O (500 ml) and left at 0° for several days. Yellow crystals [0.85 g (56%), mp 180-183°] of the HBr salt were slowly deposited, filtered off, and dissolved in $NaHCO_3$ solution. The mixture was extracted with Et_2O and the organic phase worked up in the usual way to yield the product as an oil which was used as such in the next step (*e.g.*, reaction BB).

Reaction X. 2-Isopropylamino-5-nitrobenzophenone. A mixture of 2-chloro-5-nitrobenzophenone (100 g, 0.38 mol), Cu powder (5 g), CuCl (5 g), EtOH (100 ml), and isopropylamine (100 ml) was stirred and heated under reflux for 15 hr. Insoluble material was removed by filtration (Celite) and the filtrate was concentrated *in vacuo*. The residue was crystallized from Et_2O-petroleum ether to

give the product, 100 g (92%), mp 154–155°.

Reaction Z. 2-Isopropylamino-6-methylbenzophenone. To a solution of 2-amino-6-methylbenzophenone (1.4 g, 6.6 mmol) in 2-iodopropane (20 ml) was added K_2CO_3 (2 g) and the mixture was stirred and refluxed for 72 hr. After cooling, CH_2Cl_2 was added and the mixture was filtered. The filtrate was evaporated to dryness and the residue was dissolved in C_6H_6 and filtered through a short column of aluminum oxide. The residue obtained as an oil on evaporation of the eluate (1.15 g, 69%) was essentially pure product.

Analogous alkylations were also carried out with Na_2CO_3 in place of K_2CO_3. All alkylation reactions were followed by tlc and were terminated when little starting material remained.

Reaction AA. 7-Methyl-4-phenyl-2(1*H*)-quinazolinone (2). A mixture of 4-methyl-2-aminobenzophenone (7 g, 33 mmol) and urea (3.6 g, 60.0 mmol) was heated at 180–200°. After 2 hr, additional urea (1.8 g, 30.0 mmol) was added and the heating continued for a total of 3.5 hr. The cooled, almost solid residue was powdered and extracted with MeOH and CH_2Cl_2. Insoluble material was filtered off and the filtrate was concentrated until crystallization occurred. The crude material was recrystallized from MeOH to yield **2**, 5 g (64%), mp 282–284°.

Reaction BB. 1,7-Dimethyl-4-phenyl-2(1*H*)-quinazolinone (4). A mixture of 2-methylamino-4-methylbenzophenone (4 g, 17.5 mmol), ethyl carbamate (4 g, 45 mmol), and $ZnCl_2$ (0.5 g) was heated at 190° for 2 hr. Further ethyl carbamate (4 g, 45 mmol) and $ZnCl_2$ (0.5 g) were then added and the heating was continued for a total of 3.5 hr. The mixture was then cooled and $CHCl_3$ was added. The resulting suspension was filtered and the filtrate washed with H_2O and worked up in the usual manner. The residue obtained on evaporation was crystallized from EtOAc to yield **4**, 2.6 g (58%), mp 171–172°.

Reaction CC. 1-Ethyl-6-methyl-4-phenyl-2(1*H*)-quinazolinone (10). A solution of 6-methyl-4-phenyl-2(1*H*)-quinazolinone (7 g, 29.6 mmol) in dimethylacetamide (80 ml) was treated with NaH (1.5 g, 35 mmol, 57% dispersion in mineral oil, washed with petroleum ether). The sodium salt of the starting material precipitated partially. The mixture was stirred for 15 min at room temperature and then an excess of EtI (20 ml) was added and the stirring continued for a further 6 hr. The residue obtained on evaporation of the solvent was dissolved in CH_2Cl_2–H_2O and the organic phase was separated and worked up in the usual manner to yield 5 g of **10** as a crude crystalline material. One recrystallization from Et_2O gave 4.1 g (54%), mp 178–180°.

Reaction DD,[3] 4-(2-Furyl)-1-isopropyl-7-methyl-2(1*H*)-quinazolinone (57). A solution of 2-furoyl-5-methyl-*N*-isopropylaniline (1 g, 4.1 mmol) in AcOH (30 ml) was stirred and KNCO (0.4 g, 4.9 mmol) was added. The mixture was heated at 56° for 6 hr. After cooling, the mixture was poured onto ice and the precipitate which formed was filtered off and dissolved in CH_2Cl_2. Work-up as usual yielded crude **57**, 1 g, which was crystallized from EtOAc–Et_2O, 0.5 g (46%), mp 184–187°.

Reaction EE. (a) **7-Dimethylamino-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (46).** To a cooled (ice bath), stirred solution of crude 1-(4-dimethylamino-2-isopropylaminophenyl)-1-phenylmethylenimine (12 g, 43 mmol) in a mixture of C_6H_6 (100 ml) and Et_3N (20 ml) was cautiously added a 12% solution of $COCl_2$ in C_6H_6 (52 ml, ~63 mmol). The mixture was then left at room temperature for 30 min after which time excess $COCl_2$ was removed by partial evaporation. The concentrated reaction mixture was poured onto ice–NaOH and the H_2O layer was extracted with C_6H_6. The organic phases were combined, washed with 2 *N* NaOH, and worked up in the usual way. The crude crystalline material obtained was recrystallized from EtOAc to give **46**, 7.4 g (57%), mp 181–183°.

(b) **1-*tert*-Butyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (18).** The crude imine (1.5 g, ~5.5 mmol) obtained in reaction Q was dissolved in C_6H_6 (30 ml) and treated with Et_3N (5 ml). To this solution was added $COCl_2$ (20 ml of a 12% solution in C_6H_6) and the mixture was kept at room temperature for 20 min. The solvent was then evaporated and the residue was dissolved in Et_2O–H_2O. The organic phase was worked up as usual and the residual oil obtained was chromatographed on silica gel. Using CH_2Cl_2 as the solvent, the initial fractions contained the starting benzophenone whereas the later ones contained the product, **18**, which was crystallized from Et_2O–pentane, 0.44 g (27%), mp 141–143°.

Reaction FF. See ref 1.

Reaction GG. 1-Isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinethione (65). To a stirred solution of NH_4SCN (35 g, 0.46 mol) in anhydrous Me_2CO (800 ml) benzoyl chloride (60 g, 0.43 mol) was added dropwise. The mixture was briefly (3–4 min) heated at reflux and then cooled and a solution of 2-isopropylamino-4-methylbenzophenone (96 g, 0.38 mol) in Me_2CO (500 ml) was added. The resulting mixture was heated at reflux for 1 hr. After cooling the precipitate which formed was filtered off; the residue was washed with Me_2CO and set aside (see below). The combined filtrate was evaporated and the residue dissolved in EtOH (800 ml). This solution mixed with aqueous NaOH (2 *N*, 750 ml) was heated for 10 min on the steam bath. On concentration of this solution to two-thirds of its volume and cooling, the product, **65**, began to crystallize out. This was filtered off, washed with H_2O, and dried (38 g, mp 184–188°). Further concentration of the filtrate yielded additional material, 4 g, mp 183–187°. The filtered residue, obtained originally (see above), consists of **1-benzoyl-3-isopropyl-3-(5-methyl-2-benzoylphenyl)thiourea** which on treatment with 2 *N* NaOH in THF–EtOH (1:1) can also be converted into the desired material (27 g, mp 184–189°). The combined fractions (69 g) were recrystallized from CH_2Cl_2–Et_2O–pentane, 66 g (58%), mp 194–198°.

Reactions HH and KK. 3,4-Dihydro-1-isopropyl-4-phenyl-2(1*H*)-quinazolinethione (62). To a solution of 2-isopropylaminobenzophenone (24 g, 0.1 mol) in 95% EtOH (200 ml) was added in portions $NaBH_4$ (8 g, 0.22 mol). The mixture was stirred at 60° for 3 hr. After cooling, 6 *N* HCl was added dropwise until the mixture was acidic and the solution was then neutralized with 2 *N* NaOH and extracted with CH_2Cl_2. Work-up in the usual fashion yielded 2-isopropylaminobenzohydrol (22 g, 91%) as an oil. This was dissolved in a mixture of dioxane (10 ml), H_2O (100 ml), and concentrated HCl (7.7 ml). To this stirred solution was added NH_4SCN (7 g, 0.09 mol) and the mixture was heated at 100° for 30 min. After cooling the crystalline precipitate which had formed was filtered off and recrystallized from CH_2Cl_2 to give **62**, 22 g (85%), mp 185°.

Reaction II. 3,4-Dihydro-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (60). To a solution of 1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (14, 7.9 g, 30 mmol) in 95% EtOH (150 ml) was added in portions, $NaBH_4$ (2 g, 54 mmol). The mixture was stirred at room temperature for 30 min after which time the excess $NaBH_4$ was destroyed with AcOH and the EtOH was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and H_2O, and sufficient $NaHCO_3$ solution was added to neutralize any acid present. The H_2O phase was extracted with CH_2Cl_2 (three times) and the CH_2Cl_2 solutions were combined and worked up in the usual manner. The residual oil was crystallized from EtOAc–pentane to give **60**, 7.7 g (96%), mp 145°.

Reaction JJ. 1-Isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinethione (65). To a solution of 1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (**27**, 2 g, 7.2 mmol) in pyridine (20 ml) was added P_2S_5 (4 g, 18 mmol) and the mixture was refluxed for 2.5 hr. After cooling, the reaction was poured onto ice and extracted with CH_2Cl_2. The organic phase was separated and washed several times with H_2O. The brown solid which was obtained by the usual work-up was dissolved in CH_2Cl_2 and chromatographed on aluminum oxide. The lead fractions contained the desired material **65** which was crystallized from CH_2Cl_2–Et_2O to give 0.67 g (32%), mp 194–198°.

Reaction LL. 6-Hydroxy-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (39). A mixture of 1-isopropyl-6-methoxy-4-phenyl-2(1*H*)-quinazolinone (**36**, 3.1 g, 10.5 mmol) and 48% HBr (40 ml) was heated at 130–140° for 16 hr. After cooling, the mixture was added to ice–H_2O and 2 *N* NaOH was added until the pH was 5. It was then extracted with $CHCl_3$ (three times) and the organic phase was worked up in the usual manner. The residue was crystallized from MeOH–Et_2O to give **39**, 2.0 g (70%), mp 280–283°. One recrystallization raised the melting point to 285–288°.

Reaction MM. 1-Isopropyl-4-phenyl-7-propoxy-2(1*H*)-quinazolinone (42). To a solution of 7-hydroxy-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (**40**, 1.4 g, 5 mmol) in CH_2Cl_2–MeOH, 1/1 (20 ml), was added a solution of NaOMe (0.3 g, 5.5 mmol) in MeOH (5 ml). The reaction mixture was stirred at room temperature for 10 min and then evaporated to dryness. The residue was dissolved in warm dimethylacetamide (15 ml) and 1-iodopropane (40 ml) was added. After heating at 80° for 45 min it was allowed to cool and H_2O (100 ml) was added. The organic phase was separated and worked up in the usual manner. The residual oil (1.5 g) was dissolved in Et_2O and the solution was washed with 2 *N* NaOH, H_2O, and brine. The resulting oil (1.3 g) obtained on the usual work-up was dissolved in CH_2Cl_2 and filtered through a column of silica gel. The eluate was evaporated and the residue crystallized from Et_2O to give **42**, 0.8 g (49%), mp 142–143°.

Reaction NN. 6-Amino-1-isopropyl-4-phenyl-2(1*H*)-quinazol-

inone (44). To a refluxing, stirred solution of 1-isopropyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone (43, 12 g, 39 mmol) in EtOH (240 ml) and H_2O (80 ml) was added Fe filings (16 g). To this suspension was added dropwise a solution containing EtOH (80 ml), H_2O (20 ml), and 2 *N* HCl (4 ml). The refluxing was then continued for a further 3 hr. To the hot reaction mixture was added 2 *N* NaOH (4 ml) and the resulting suspension was then filtered hot (Celite). The filtrate was evaporated and the residue extracted with 2 *N* HCl-Et_2O. The acidic aqueous solution was made basic with concentrated NH_4OH (cooling) and extracted with CH_2Cl_2. The usual work-up of the organic phase gave a residue which was crystallized from EtOAc to yield 44, 8.8 g (81%), mp 250–252°.

Reaction OO. 6-Dimethylamino-1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (47). A mixture of 1-isopropyl-7-methyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone (8 g, 25.8 mmol) and Raney Ni (*ca.* 8 g, wet with MeOH) in MeOH (200 ml) and dioxane (100 ml) containing HCHO (20 ml of a 37% solution in MeOH) was shaken under H_2 at room temperature and a pressure of 50 psi. After 2 hr no further uptake occurred and the mixture was filtered and the filtrate evaporated. The residue was crystallized from EtOAc to give 47, 7.2 g (87%), mp 184–186°.

Reaction PP.[16] **1-Isopropyl-7-methyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone.** To a cooled solution (0–5°) of 1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (13.9 g, 50 mmol) in concentrated H_2SO_4 (50 ml) was added dropwise over 10 min a solution of KNO_3 (6.07 g, 60 mmol) in concentrated H_2SO_4 (15 ml). The resulting solution was allowed to warm to room temperature and then stirred for a further 2 hr. It was next poured onto ice and the solid obtained was filtered off. After drying the crude product was crystallized from EtOAc to give 11.7 g (72%), mp 192–194°.

Reactions SS and TT. 7-Diethylaminomethyl-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (48). To a solution of 1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (27, 2.8 g, 10 mmol) in CCl_4 (250 ml) was added NBS (2 g, 20 mmol) and benzoyl peroxide (250 mg). The mixture was stirred and refluxed for 6 hr. It was then cooled, filtered, washed (H_2O), and dried (Na_2SO_4). A sample evaporated to dryness gave a residue which was shown by nmr to consist of 70% of the product, 7-bromomethyl-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone, and 30% of unreacted starting material. To the bulk of the solution obtained above was added Et_2NH (5 ml). A precipitate rapidly formed and after 1 hr at room temperature this was filtered off. The filtrate was extracted with 2 *N* HCl and the acidic aqueous extract basified with 2 *N* NaOH. Extraction with Et_2O and the usual work-up gave the product, 48 (2.1 g, 60%), as a brown oil. The maleate salt was prepared and crystallized from Me_2CO, mp 174–176°.

Supplementary Material Available. A listing of the new intermediates and their physical constants will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $3.00 for microfiche, referring to code number JMED-73-1237.

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β-Adrenoceptor Blocking Agents. 1. Cardioselective 1-Aryloxy-3-(aryloxyalkylamino)propan-2-ols

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A series of 1-aryloxy-3-(aryloxyalkylamino)propan-2-ols was synthesized and investigated for cardioselective β-adrenoceptor blocking activity. Several compounds exhibited potency comparable with that of propanolol, both *in vitro* and *in vivo*, and showed selectivity for cardiac *vs.* tracheal receptors. The cardiac depressant activity of the compounds was generally much less marked than that exhibited by propranolol. Compound **3** (tolamolol) has been shown to be a cardiac-selective β-adrenoceptor blocking agent in man.

Many β-adrenergic blocking agents have been described which antagonize the effects of catecholamines at β-adrenoceptors irrespective of whether the latter are β-1 or β-2 as classified by Lands and coworkers.[1] The discovery of practolol[2] showed that it is possible to develop blockers specific for the β-1 adrenoceptors and this prompted us to seek more potent cardioselective agents. We describe here the synthesis and biological activity of a new series of β-adrenoceptor blocking agents, some of which were more potent than practolol and exhibited comparable selectivity for myocardial receptors.

The compound which ultimately proved to be of greatest interest was 4-[2-(2-hydroxy-3-*o*-tolyloxypropylamino)ethoxy]benzamide hydrochloride (**3**, tolamolol,† Table I) a potent, orally active agent possessing selectivity for myocardial (β-1) *vs.* peripheral vascular (β-2) receptors in man.[3] In the dog heart–lung‡ and cat papillary muscle (Table I) preparations, **3** was appreciably less cardiac depressant than propranolol. These indications of negligible myocardial depression have been borne out in human studies.§ This compound is currently undergoing extensive clinical evaluation as a potential antianginal–antiarrhythmic agent.

Chemistry. The majority of the compounds listed in Tables I–III were synthesized *via* the two general routes illustrated in Scheme I. The epoxypropane derivatives **70** were obtained from the appropriate phenol and epichlorohydrin in essentially the manner described by Schwender.[4] The amines **71** and **72** were synthesized by catalytic

† British Pharmacopoeia Commission approved name.

‡ P. C. Sholfield, unpublished work, 1970.
§ A. R. Lorimer, *et al.*, to be published.