amidine Hydrochloride (11). The amino compound 8 (154 mg, 0.5 mmol) was dissolved in absolute ethanol (3 mL), *N*-ethylmorpholine (64 μL, 0.5 mmol) was added, and the mixture was cooled to −10 °C. Then, 4-chlorobutyryl chloride (70.5 mg, 0.5 mmol) was added slowly. After 15 min at room temperature, the solvent was evaporated, and the residue was triturated with acetonitrile to remove the morpholine hydrochloride. The residue was dissolved in absolute ethanol (1 mL) and precipitated with ethyl acetate to give 170 mg of crude product. Flash chromatography on silica gel with methanol afforded 70 mg (30% yield) of a very hygroscopic 11: mp 62–65 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.02 (m, 2 H), 2.43 (t, 2 H), 2.63 (t, 2 H), 3.52 (q, 2 H), 3.69 (t, 2 H), 3.82 and 3.83 (2 s, 6 H), 6.89 and 6.95 (2 d, 2 H), 7.17 and 7.21 (2 d, 2 H), 8.26 (t, 1 H), 8.71 (s, 2 H), 9.02 (s, 2 H), 9.93 and 9.98 (2 s, 2 H); IR (Nujol) ν_{max} 1269, 1377, 1405, 1445, 1464, 1534, 1582, 1641, 1690, 3100, 3124, 3275 cm^{-1}; MS-FAB, *m/z* (relative intensity) 436 (100) for ^{35}Cl, 438 (37) for ^{37}Cl.

Cytostatic Activity. Mouse leukemic cells (i.e., L1210 and P388D1) were obtained from American Type Tissue Collection (Rockville, MD) and were grown in either McCoy's 5A (L1210) or Fischer's (P388D1) medium supplemented with 10% fetal calf serum (Grand Island Biological Co., Grand Island, NY). Compounds to be tested were dissolved in water; compounds that were poorly water soluble were sonicated and administered as a suspension. Stock solutions were prepared at constant ratios up to 500 times that required in the growth medium so that 10 μL of stock solution could be added to 160 μL of growth medium. Cells were seeded onto 96-well microtiter plates at a concentration of 1×10^5 cells per well and allowed to grow for 72 h in 5% CO_2 at 37 °C in humidified incubator. The cytostatic activity of the drugs was determined by use of a methylenetetrazolium dye (MTT) assay as described by Mossmann.[24] Cell viability was measured as a function of the ability of cells to form a blue formazan product, the optical density of which was determined by a Dynatech Microplate (Model 600) Reader (570 nm; reference set at 630 nm).

The other anticancer assays were performed according to previously established procedures.[25,26]

Antiviral assays were performed as reported previously.[27,28]

Acknowledgment. This research was supported by grants (to J.W.L.) from DHHS Grant 2-R01 CA21488-10 of the U.S. PHS and from the Biotechnology Strategic Grants Programme of the Natural Sciences and Engineering Research Council of Canada, by Grant 3.0040.83 (to E.D.C.) from the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek, and by Grant GM 21749-3 (to R.A.N.). We thank Lizette van Berckelaer, Frieda De Meyer, and Anita Van Lierde for Excellent technical assistance.

Registry No. 1, 97950-71-5; 2, 101772-47-8; 3, 111770-96-8; 4, 111770-97-9; 5, 111770-98-0; 5 (free base), 111771-03-0; 6, 111770-99-1; 6 (free base), 111771-04-1; 7, 111771-00-7; 7 (free base), 111771-05-2; 8, 97950-75-9; 9, 111793-70-5; 9 (free base), 111771-06-3; 10, 111771-01-8; 10 (free base), 107580-63-2; 11, 111771-02-9; 11 (free base), 111771-07-4; $Cl_2CHCOCl$, 79-36-7; Cl_3CCOCl, 76-02-8; FCH_2COCl, 359-06-8; *c*-PrCOCl, 4023-34-1; $Cl(CH_2)_3COCl$, 4635-59-0.

(24) Mossmann, T. *J. Immunol. Methods* **1983**, *65*, 55.

(25) De Clercq, E.; Balzarini, J.; Torrence, P. F.; Mertes, M. P.; Schmidt, C. L.; Shugar, D.; Barr, P. J.; Jones, A. S.; Verhelst, G.; Walter, R. T. *Mol. Pharmacol.* **1981**, *19*, 321.

(26) Balzarini, J.; De Clercq, E.; Torrence, P. F.; Mertes, M. P.; Park, J. S.; Schmidt, C. L.; Shugar, D.; Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. *Biochem. Pharmacol.* **1982**, *31*, 1089.

(27) De Clercq, E.; Montgomery, J. A. *Antiviral Res.* **1983**, *3*, 17.

(28) De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. J. *Infect. Dis. Rev.* **1980**, *5*, 563.

Design and Synthesis of a Series of Combined Vasodilator/β-Adrenoceptor Antagonists Based on 6-Arylpyridazinones

R. A. Slater,* W. Howson, G. T. G. Swayne, E. M. Taylor, and D. R. Reavill

Smith Kline & French Research Ltd., The Frythe, Welwyn, Hertfordshire, AL6 9AR U.K. *Received April 27, 1987*

A series of new 6-[4-[[(aryloxy)acyl]amino]phenyl]-4,5-dihydropyridazinones have been synthesized and evaluated as combined vasodilator/β-adrenoceptor antagonists and potential antihypertensive agents. Many of the early compounds displayed an unacceptably high level of intrinsic sympathomimetic activity (ISA) and a relatively short duration of action. Disubstitution in the 2,3-positions or in the 4-position of the aryloxy ring gave compounds with low ISA levels and, in some instances, improved duration of action. All of the compounds were vasodilators, but the 5-methylpyridazinone derivatives showed consistently greater antihypertensive activity than their 5-H lower homologues. Further detailed pharmacological investigations led to the selection of 6-[4-[3-[[2-hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (4t) (SK&F 95018) as a development candidate.

Essential hypertension is characterized by elevated total peripheral resistance which maintains a raised systemic arterial blood pressure while cardiac output and heart rate remain within the normal range.[1] Although the etiology of elevated vascular resistance is unclear, clinical studies have shown that peripheral vasodilators can be used effectively to lower blood pressure. The therapeutic use of vasodilators alone is limited, however, by side effects arising directly from the vasodilator activity of these agents. Thus, reduction in blood pressure following administration of vasodilator agents initiates baroreceptor reflex changes which lead to increased sympathetic drive and activation of β-adrenoceptors in the heart, with a resultant undesirable increase in heart rate and activation of the renin/angiotensin system leading to vasoconstriction and fluid retention.[2] It has been shown that β-adrenoceptor antagonists will inhibit these undesirable effects of vasodilators, with the result that the combined use of vasodilators and β-blockers has been widely adopted for the treatment of hypertension.[3]

(1) Frohlich, E. D. In *Hypertension*; Crenest, J., Koiw, E., Kuchel, O., Eds.; McGraw-Hill: New York, 1977; Chapter 3.

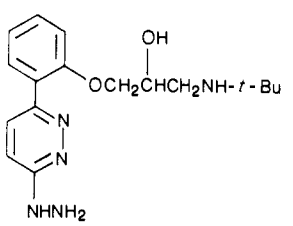
(2) Jund-Johansen, P. In *Handbook of Hypertension*; Doyle, A. E., Ed.; Elsevier: New York, 1984; Vol. 5, Chapter 2.

0022-2623/88/1831-0345$01.50/0

The underlying mechanism of vasodilatation is an important factor in selecting an appropriate vasodilator for use in therapy. Thus, agents which inhibit sympathetic vasoconstrictor function (e.g., α-adrenoceptor antagonists) impair normal hemodynamic reflexes, particularly during exercise or changes in posture. The vasodilator effects of agents which stimulate β-receptors in the peripheral vasculature may be largely attenuated by the β-adrenoceptor antagonism required for blockade of reflex-induced cardiac stimulation, unless they act selectively as β_2-adrenoceptor agonists and β_1-adrenoceptor antagonists. Furthermore, β-agonists will elicit their agonist actions in noncardiovascular tissue, e.g., skeletal muscle tremor. For these reasons vasodilators which act directly on vascular smooth muscle to reduce peripheral resistance are considered to be preferable to agents which act either by impairment of the sympathetic nervous system or as local sympathomimetics.

The successful treatment of hypertension with a combination of a direct-acting vasodilator (e.g., hydralazine) and a β-adrenoceptor antagonist (e.g., propranolol)[3] prompted our studies aimed at designing single chemical entities possessing both pharmacological properties. The advantage of a compound with dual activity over a combination of drugs should derive from the fact that a single compound could be absorbed, metabolized, and excreted at one rate in a given subject, thus increasing the likelihood that the two main biological activities would remain in balance during the course of drug action.

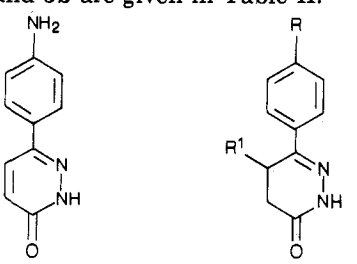
Prizidilol (**1**),[4] a hydrazinopyridazine carrying a β-blocking side chain, was the first candidate drug to emerge from this work and was shown to be an effective agent in the treatment of hypertension in humans.[5] The therapeutic profile of activity shown for prizidilol, namely, a sustained reduction in blood pressure due to peripheral vasodilatation and normal cardiac output, coupled with a physiologically responsive cardiovascular system, e.g., during exercise or change in posture, proved to be close to ideal for an antihypertensive agent.[6] Although adverse findings with prizidilol in long-term toxicological studies prevented completion of development, the substantial and favorable clinical data obtained with this drug established the potential therapeutic importance for the combination, in the same molecular entity, of direct-acting-vasodilator activity with β-adrenoceptor-antagonist activity. With the possible exception of carvedilol,[7] no other antihypertensive agents with the profile of activity of prizidilol have been reported. Thus, although many drugs in current development can be classified as vasodilator/β-blockers, their vasodilator activity is largely derived from either α_1-adrenoceptor-antagonist activity or β_2-adrenoceptor-agonist activity, and there still remains a need for novel agents possessing a combination of direct vasodilator activity and β-adrenoceptor-antagonist activity.



1

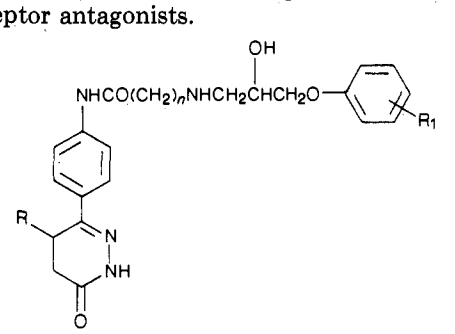
In seeking alternative antihypertensive agents, possessing both vasodilator and β-adrenoceptor-antagonist activities, we chose to focus on non-hydrazino derivatives, since the hydrazino group in prizidilol was implicated as a causative factor in its adverse toxicity. However, simple replacement of the hydrazine function in prizidilol with other groups led to a loss of vasodilator activity,[8] and it was therefore necessary to select a different structural class of vasodilator for combination with β-blocking activity.

Our existing interest in 6-aryl-3(2*H*)-pyridazinones as intermediates to hydrazinopyridazinones alerted our attention to the reported antihypertensive activities of 6-arylpyridazinones,[9a,b] and having established that certain members of this class were direct-acting vasodilators,[10] we selected the 4-aminophenyl and 4-acetamidophenyl derivatives **2**[9c] and **3**[9a,b] for combination with a β-blocking moiety. The antihypertensive and vasodilator activities of **2**, **3a**, and **3b** are given in Table II.



2 **3a**, R = NHAc, R^1 = H
b, R = NHAc, R^1 = CH_3
c, R = $NHCOCH_2CH_2NH_2$, R^1 = CH_3

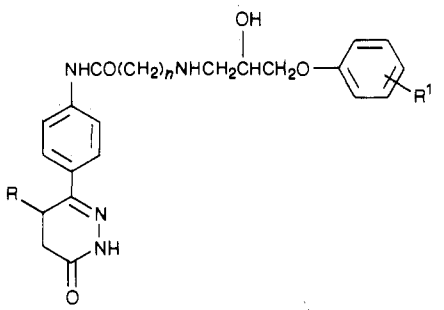
In this paper we describe the design, synthesis, and pharmacological activities of a series of novel antihypertensive agents, encompassed by the general formula **4**. These compounds, one of which, **4t** (R = CH_3, R^1 = 4-$CH_2CH_2OCH_2$-c-C_3H_5, n = 2), was selected as a development candidate, are direct-acting vasodilators and β-adrenoceptor antagonists.



4

(3) (a) Gottlieb, T. B.; Katz, F. H.; Chidsey, C. A. *Circulation* **1972**, *45*, 571–572. (b) Zacest, R.; Gilmore, E.; Koch-Weser, J. *N. Engl. J. Med.* **1972**, *286*, 617–622.
(4) (a) Taylor, E. M.; Cameron, D.; Eden, R. J.; Fielden, R.; Owen, D. A. A. *J. Cardiovasc. Pharmacol.* **1981**, *3*, 337–354. (b) Taylor, E. M.; Roe, A. M.; Slater, R. A. *Clin. Sci.* **1979**, *57*, 433S–436S.
(5) (a) Bell, A.; Boyce, M. J.; Burland, W. L.; Underwood, D. D. *Br. J. Clin. Pharmacol.* **1980**, *9*, 299P–300P. (b) Pitcher, D. W.; Curry, P. V. L.; Trounce, J. R. *Br. J. Clin. Pharmacol.* **1980**, *9*, 300P–301P.
(6) Lund-Hohansen, P.; Omvik, P. *J. Cardiovasc. Pharmacol.* **1982**, *4*, 1012–1017.
(7) Kaski, J. C.; Rodriguez-Plaza, L.; Brown, J.; Maseri, A. *Am. J. Cardiol.* **1985**, *56*, 35–40.
(8) Slater, R. A., et al., al., unpublished results.
(9) (a) Curran, W. V.; Ross, A. *J. Med. Chem.* **1974**, *17*, 273–281. (b) McEvoy, F. J.; Allen, G. R. *J. Med. Chem.* **1974**, *17*, 281–286. (c) Steck, E. A.; Brundage, R. P.; Fletcher, L. T. *J. Heterocycl. Chem.* **1974**, *11*, 755–761. (d) Thyes, M.; Lehmonn, H. D.; Gries, J.; Konig, H.; Kretzschmar, R.; Kunze, J.; Lebkucher, R.; Leuke, D. *J. Med. Chem.* **1983**, *26*, 800–807.
(10) Gristwood, R. W.; Eden, R. J.; Owen, D. A. A.; Coates, W. J.; Emmett, J. C.; Slater, R. A.; Warrington, B. H. 10th International Congress of Pharmacology, 1987; abstract.

Table I. Properties of 6-[4-[[(Aryloxy)acyl]amino]phenyl]-4,5-dihydropyridazinones



no.	*n*	R	R^1	mp, °C	salt	solvent	yield, %	formula	anal.
4a	1	H	2-CH_3	241–242	toluenesulfonate	EtOH/Et_2O	95	$C_{22}H_{26}N_4O_4 \cdot C_7H_8O_3S$	C, H, N, S
4b	1	CH_3	2-CH_3	221–226	toluenesulfonate	aq[a] EtOH/Et_2O	64	$C_{23}H_{28}N_4O_4 \cdot 1.1C_7H_8O_3S \cdot H_2O$	C, H, N, s
4c	1	H	2-OCH_3	210–211	toluenesulfonate	aq EtOH/Et_2O	88	$C_{22}H_{26}N_4O_5 \cdot C_7H_8O_3S$	C, H, N, S
4d	1	CH_3	2-OCH_3	195–202	toluenesulfonate	EtOH/Et_2O	88	$C_{23}H_{28}N_4O_5 \cdot 1.2C_7H_8O_3S \cdot H_2O$	C, H, N, S
4e	1	H	2-CN	215–217	toluenesulfonate	aq EtOH/Et_2O	92	$C_{22}H_{23}N_5O_4 \cdot C_7H_8O_3S \cdot 0.5h_2O$	C, H, N, S
4f	1	CH_3	2-CN	160–165	toluenesulfonate	EtOH/Et_2O	48	$C_{23}H_{25}N_5O_4 \cdot 1.35C_7H_8O_3S \cdot 0.75H_2O$	C, H, N, S
4g	2	CH_3	2-H	162–165	bromide	EtOH	65	$C_{23}H_{28}N_4O_4 \cdot HBr \cdot 0.8H_2O$	C, H, N, Br
4h	2	H	2-CH_3	207–208	toluenesulfonate	aq etOH/Et_2O	58	$C_{23}H_{28}N_4O_4 \cdot C_7H_8O_3S \cdot 0.5H_2O$	C, H, N, S
4i	2	CH_3	2-CH_3	168–172	toluenesulfonate	EtOH/Et_2O	27	$C_{24}H_{30}N_4O_4 \cdot 1.1C_7H_8O_3S \cdot H_2O$	C, H, N, S
4j	2	H	2-OCH_3	172–180	toluenesulfonate	EtOH/Et_2O	50	$C_{23}H_{28}N_4O_5 \cdot C_7H_8O_3S \cdot 0.5H_2O$	C, H, N, S
4k	2	CH_3	2-OCH_3	125–126	toluenesulfonate	EtOH/Et_2O	31	$C_{24}H_{30}N_4O_5 \cdot C_7H_8O_3S \cdot 0.5H_2O$	C, H, N, S
4l	2	H	2-CN	180–185	acetate		51	$C_{23}H_{25}N_5O_4 \cdot 0.75C_2H_4O_2$	C, H, N
4m	2	CH_3	2-CN	172–175	toluenesulfonate	EtOH/Et_2O	54	$C_{24}H_{27}N_5O_4 \cdot C_7H_8O_3S$	C, H, N, S
4n	2	CH_3	2-SO_2CH_3	219–222	chloride	MeOH/Et_2O	80	$C_{24}H_{30}N_4O_6S \cdot 1.09HCl \cdot H_2O$	C, H, N, Cl
4o	2	CH_3	2-c-$N(CH_2)_2O$-$(CH_2)_2$	168–172	toluenesulfonate	EtOH/Et_2O	86	$C_{27}H_{35}N_5O_5 \cdot 1.1C_7H_8O_3S \cdot 1.6H_2O$	C, H, N, S
4p	1	H		234–238	toluenesulfonate	aq EtOH/Et_2O	53	$C_{25}H_{26}N_4O_4 \cdot C_7H_8O_3S$	C, H, N, S
4q	2	CH_3		126–130	chloride	EtOH/Et_2O	62	$C_{25}H_{29}N_5O_4 \cdot 0.7HCl \cdot H_2O$	C, H, N
4r	2	CH_3	2,3-$(CH_3)_2$	159–164	toluenesulfonate	EtOH/Et_2O	80	$C_{25}H_{32}N_4O_4 \cdot C_7H_8O_3S$	C, H, N, S
4s	2	CH_3	4-$CH_2CH_2OCH_3$	166–168	toluenesulfonate	EtOH/Et_2O	69	$C_{26}H_{34}N_4O_5 \cdot C_7H_8O_3S \cdot 0.4H_2O$	C, H, N, S
4t	2	CH_3	4-$CH_2CH_2OCH_2$-c-C_3H_5	176–178	methanesulfonate	CH_2Cl_2/Et_2O	90	$C_{29}H_{38}N_4O_5 \cdot 1.05CH_4O_3S$	C, H, N, S

[a] Aqueous.

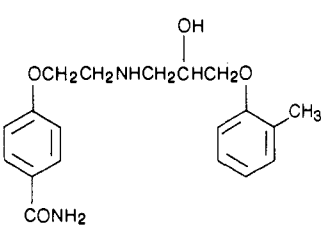
Chemistry

The compounds synthesized and tested in this study are listed in Table I, and their relevant biological activity is tabulated in Table II. A standard procedure, used for the synthesis of the novel vasodilator/β-blockers **4**, is summarized in Scheme I. This was as follows. The 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone[9a,d] **5** was treated with the appropriate acid chloride to give the amide **6**. Subsequent reaction with benzylamine yielded a key intermediate, the secondary amine **7**.

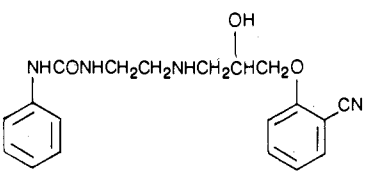
Selected phenols **8** were either purchased or prepared by standard methods and reacted with epibromohydrin or epichlorohydrin to give the required epoxide **9**, which was coupled with the appropriate amine **7** to provide the protected benzyl derivative **10**. This was then deprotected to yield the desired product **4**.

Results and Discussion

The first approach to the design of novel pyridazinone vasodilator/β-blockers involved the incorporation of a conventional oxypropanolamine side chain into vasodilators such as **2**, **3**, and related derivatives. However, in the few examples synthesized this led to a loss of vasodilator activity.[11] The subsequent observation that vasodilator activity is retained when the acetamido group in **3b** is replaced by the larger aminopropionamido group (see **3c** in Table II) suggested that an (aryloxy)propanolamine group attached through a spacer link to the amide function may furnish a compound with dual activity. The precedent for the β_1-adrenoceptor-antagonist activity of an (aryloxy)propanolamine, linked to a substituted aryl function through a polar spacer chain, was suggested to us by the reported activities of tolamolol (**11**)[12] and ICI 89406 (**12**).[13]



11, tolamolol



12, ICI 89406

Initially, a series of ortho-substituted (phenyloxy)propanolamine analogues of the vasodilator **3c** were synthesized following the finding that the first member of the series, **4a**, is a vasodilator with weak β-blocking activity.

(11) Coates, W. J.; Slater, R. A.; Warrington, B. H., unpublished results.

(12) Adam, K. R.; Baird, J. R. C.; Burgess, R. A.; Linnell, J. *Eur. J. Pharmacol.* **1974**, *25*, 170–175.

(13) Large, M. S.; Smith, L. H. *J. Med. Chem.* **1982**, *25*, 1286–1292.

Table II. Biological Activities of 6-[4-[[(Aryloxy)acyl]amino]phenyl]-4,5-dihydropyridazinones

no.	rat blood pressure:[a] ED_{40}, μmol kg^{-1}	rat hindqtr blood flow:[b] ED_{50}, μmol kg^{-1}	β_1-adrenoceptor antag:[c] ID_{50}, μmol kg^{-1}	ISA,[d] units
2	1[e]	20		
3a	1	4		
3b	0.18 (0.08–0.3)[f]	0.1		
3c	0.2	0.2		
4a	6 (4–20)	2 (0.4–4)	9 (6–17)	0.55
4b	<2	2.7 (0.6–12)	>5	
4c	11.5 (9–17)	4.6 (2–7)	10	0.42
4d	<4	3	2.6 (2.3–2.9)	0.37
4e	30	14	*g*	0.55
4f	2 (1–3)	0.9 (0.7–1)	>8	0.53
4g	0.6	1.5 (1–20)	*g*	0.86
4h	9.4 (6–13)	6	1.4 (1–2.5)	0.14
4i	0.5	2	*g*	0.59
4j	11	4.3 (2.6–7.7)	0.7 (0.5–0.9)	0.60
4k	2.0 (1.3–2.8)	3.0	0.7	0.48
4l	3.5 (2.5–6.8)	1.7 (1.3–2.3)	>1	
4m	1	2.3 (1.8–3.8)	*g*	0.63
4n	3.9 (2.2–5.2)	2.4 (1.9–2.9)	4 (3–5.5)	<0.3
4o	3.6 (2.2–7.5)	1.8 (1.3–2.3)	0.5 (0.3–4)	0.24
4p	28	1.4 (0.6–2)	30% at 10	0.1
4q	2.9 (2.4–3.7)	4.4 (3.2–5.7)	0.09 (0.07–0.1)	0.46
4r	2.5 (1.6–6)	2.4 (1.8–3.3)	0.6 (0.5–0.8)	0.14
4s	3	6	2 (1.3–3.6)	0.04
4t	2.4 (1.2–3.6)	1.6 (1–2.1)	1.0 (0.8–1.1)	0.05
hydralazine	1	0.6[h]		
prizidilol	14	10[h]	0.06	0.2
propranolol			0.08	
pindolol				0.7
oxprenolol			0.04	0.2

[a] Dose (μmol kg^{-1} iv) required to produce a fall in blood pressure of 40 mmHg in the anesthetized normotensive rat, derived from a dose–response curve. [b] Dose (μmol kg^{-1} iv) required to produce a 50% increase in blood flow to the autoperfused hindquarters of the anesthetized normotensive rat, derived from a dose–response curve. [c] Dose (μmol kg^{-1} iv) required to induce 50% inhibition of isoprenaline-induced tachycardia in the ganglion-blocked anesthetized cat. [d] ISA determined from the ratio of the maximal compound and isoprenaline induced tachycardia in anesthetized ganglion-blocked cats following intravenous administration. [e] Estimate only, due to large confidence intervals. [f] Numbers in parenthesis refer to lower and higher confidence interval at 95% limit (see Experimental Section for details). [g] ISA seen at high doses required to obtain an ID_{50} value for β_1-adrenoceptor antagonism. [h] Dose given ia.

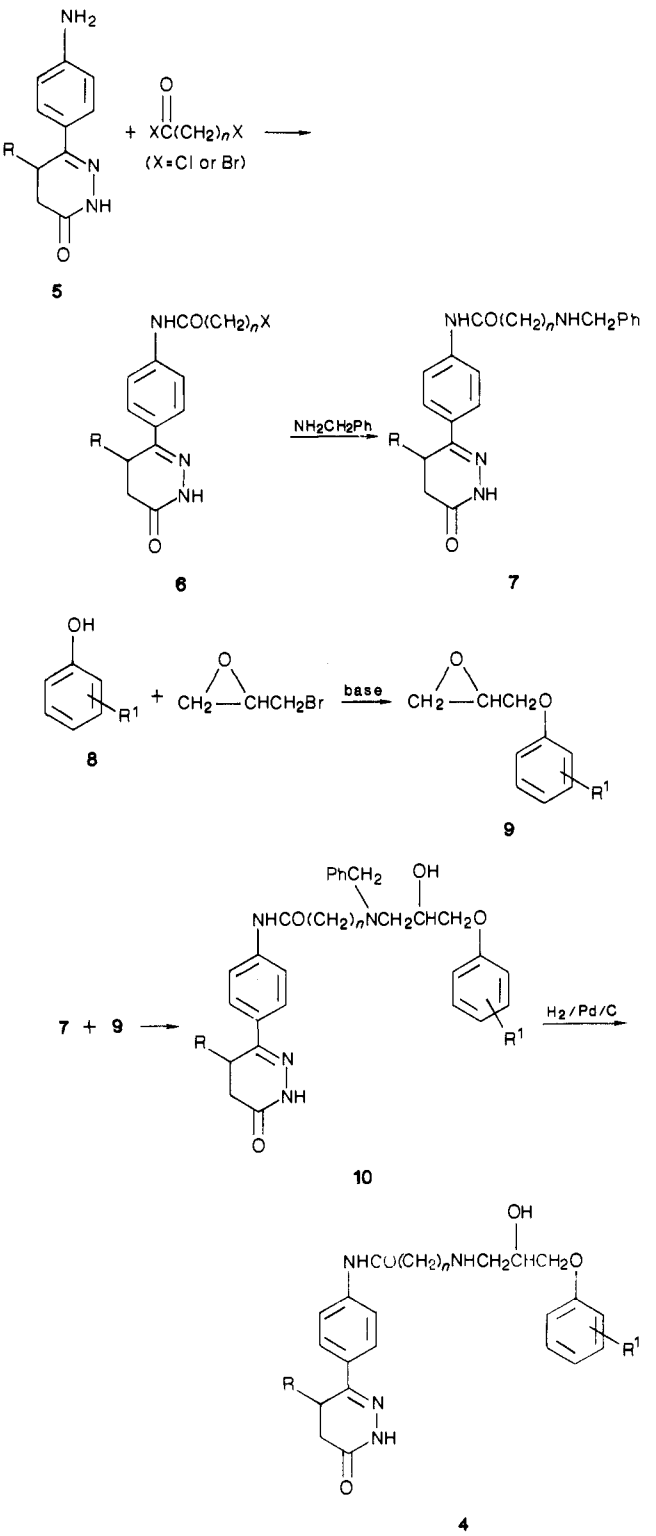
The following broad observations may be made on inspection of results for the compounds **4a–m** in Table II. Except for **4h**, all compounds either are weak β-blockers or have a high level of intrinsic sympathomimetic activity (ISA). Compounds in which $n = 2$ are more active β-adrenoceptor antagonists than compounds in which $n = 1$. All compounds are reasonably active vasodilators and antihypertensive agents, but 5-methylpyridazinone analogues are more active than 5-H analogues as antihypertensive agents and at least as active as vasodilators.

On the basis of this primary screening data, **4h** was selected for a more detailed pharmacological evaluation. However, this compound was shown to be too short acting (60 min) in conscious animals to be potentially useful as an antihypertensive agent. These results emphasized the necessity for us to modify structure in order to obtain a compound with a low level of ISA, i.e., <0.2, as defined in the Experimental Section, equivalent or improved vasodilator activity compared with **4h**, sufficient β-adrenoceptor-antagonist activity to counteract reflex tachycardia, and increased duration of action compared with **4h**.

The high levels of ISA observed for many of the compounds discussed so far prevented them from being considered as potential therapeutic agents. This problem was addressed by modifying substitution in the β-adrenoceptor phenoxy ring, with the object of obtaining compounds with an ISA index of ≤0.2, by the use of either bulky 2-substituents, disubstitution in the 2,3-positions, or selective substitution in the 4-position.

Main[14] has shown that, for a series of chosen β-blockers, heart rate (as an index of ISA) decreased with increasing size of the 2-substituent as expressed by the Taft steric parameter E_S. In our series, two compounds with bulky 2-substituents were prepared: the methanesulfonyl de-

Scheme I



(14) Main, B. G. *J. Chem. Technol. Biotechnol.* **1982**, *32*, 617–626.

Table III. Comparison of the Size of the 2-Substituent in the β-Adrenoceptor Phenoxy Ring with ISA

no.	R^1	ISA, units	van der Waals vol of PhR^1,[a] Å^3
4g	2-H	0.86	80.4
4m	2-CN	0.63	99.5
4i	2-CH_3	0.59	96.6
4k	2-OCH_3	0.48	102.8
4n	2-SO_2CH_3	<0.3	114.6
4o	2-c-$N(CH_2)_2O(CH_2)_2$	0.24	153.3

[a] Determined by the molecular graphics system at SK&F.

rivative **4n** (R = CH_3SO_2) and the morpholine analogue **4o** [R = c-$N(CH_2)_2O(CH_2)_2$]. Both of these compounds had low ISA. Thus, a similar trend to that described by Main is observed, i.e., ISA decreases as the size of the 2-substituent as measured by its van der Waals volume is increased (see Table III). Unfortunately, **4n** was only a moderate β-adrenoceptor antagonist, and although **4o** was a more potent antagonist, it was too short acting.

Our interest in the use of 2,3-disubstitution lay initially in the lack of ISA shown by propranolol; however, the naphthyl analogue **4p** was both a weak β-adrenoceptor antagonist and vasodilator. Like pindolol, the indole **4q** possessed significant ISA but was also a potent antagonist. In contrast, the 2,3-dimethyl compound **4r**, although a little less active as a β-antagonist, was almost devoid of ISA. As may be seen from Table II, **4r** was both a vasodilator and a β-adrenoceptor antagonist, but its duration of action was too short.

The third option for limiting partial agonist activity appeared to lie in the choice of a suitable 4-substituent. Although interest in this type of substitution in β-blockers has primarily centered on the development of highly cardioselective compounds,[15] the additional properties offered by (alkyloxy)methyl groups appeared to be more relevant to our problems. Metoprolol is known to be devoid of ISA, and its cyclopropyl analogue betzxolol is reported to have a long duration of action in humans.[16] Accordingly, the corresponding analogues in our series were prepared, **4s** and 4t. Although both compounds were only modest β-adrenoceptor antagonists, they possessed minimal ISA, and the duration of the betaxolol analogue 4t was indeed prolonged. Moreover, further evaluation of 4t in the conscious cat model demonstrated that the compound caused a prolonged fall in blood pressure (≫120 min) without accompanying reflex tachycardia, consistent with a balance between vasodilatation and β-adrenoceptor activity, coupled with a satisfactory duration of action. In addition, 4t produced statistically significant ($P < 0.001$) falls in blood pressure in conscious genetically hypertensive rats, in the dose range 13–103 μmol kg^{-1}, following oral administration up to 5 h after dosing.[17] This promising profile of activities in the novel vasodilator/β-blocker 4t led to its selection as a candidate for development as an antihypertensive agent. The accompanying paper[18] describes the synthesis and biological activities of all four stereoisomers of 4t, while a further paper will describe the pharmacology of the racemic mixture.[17]

Experimental Section

Pharmacological Methods. Statistical Analysis. Each compound was tested in at least three animals at a minimum of three doses, from which the end points described in Table II were derived.

Responses were assumed to be on the middle portion of the sigmoidal log dose–response curve, where data are normally distributed and have similar variances and the relationship between dose and response can be adequately approximated by a straight line. An ordinary least-squares regression line was fitted to the data from which the ED_{50} was estimated. Ninety-five percent confidence intervals for the ED_{50} were calculated by using Fieller's theorem. As the β_1-adrenoceptor activity was measured by the percent inhibition of a standard isoprenaline-induced tachycardia in the anesthetized cat, the scale between 0% and 100% was transformed by using a logit transformation (see below) before the above method of analysis was applied.

$$\text{response} = \log_{10}[(100 - \%)/\%]$$

Hypotensive effect, anesthetized rat:[17] dose required to produce a fall in blood pressure of 40 mmHg in anesthetized normotensive rats, derived from a dose–response curve. Doses were administered by intravenous injection. Results are reported in Table II as rat blood pressure (ED_{40}, μmol kg^{-1}).

Hypotensive Effect, Conscious Normotensive Cat.[4a] Normotensive cats were surgically prepared with indwelling aortic and superior vena cava cannulae exterioized at the nape of the neck. Mean arterial blood pressure, from which heart rate was derived, was measured directly via a physiological pressure transducer. Doses were administered by intravenous injection, and the effects on blood pressure and heart rate were monitored for up to 2 h following dosing. This model allowed the assessment of β-adrenoceptor antagonism, measured by the absence of a reflex tachycardia and the presence of a sustained hypotensive effect. The duration of both β-adrenoceptor and hypotensive activities could also be obtained.

Vasodilator effect:[4a] dose, derived from a dose–response curve, required to produce a 50% increase in blood flow to the autoperfused hindquarters of anesthetized normotensive rats. Intravenous bolus doses were administered. Results are reported in Table II as rat hindquarter blood flow (ED_{50}, μmol kg^{-1}).

β_1-Adrenoceptor antagonist effect:[4a] dose required to induce a 50% inhibition of an isoprenaline-induced tachycardia in ganglion-blocked anesthetized cats. Doses were administered by intravenous injection. Results are reported in Table II as β_1-adrenoceptor antagonism (ID_{50}, μmol kg^{-1}).

Intrinsic Sympathomimetic Activity (ISA). Male or female cats (2.5–3.5 kg) were anesthetized with sodium pentobarbitone (60 mg kg^{-1} ip) and maintained with subsequent intravenous doses as required. The trachea was cannulated and blood pressure recorded from a carotid or femoral artery. The cephalic vein was cannulated for the administration of drugs. Temperature was measured by rectal thermometer and maintained at 37 °C either by a thermistor-controlled infrared lamp or by the heated operating table. Instantaneous heart rate was derived from the blood pressure pulse. The animals were treated with the ganglion-blocking drug pempidine, 5 mg kg^{-1} iv, and left until the blood pressure and heart rate had stabilized. A full dose–response curve to isoprenaline (0.01–10 μg kg^{-1}) induced tachycardia was obtained, after which the cannula was washed with saline before a cumulative dose–response curve was determined for each compound in separate animals. The dose was increased until a maximum increase in heart rate was achieved. Because of the high doses sometimes requires to obtain a maximal tachycardia, the compounds were routinely dissolved in 50% polyethylene glycol (PEG) 400. In five animals, the dose–response to the compound was preceded by a cumulative volume–response curve to 50% PEG, equivalent to the total volume administered with the compound, which produced an increase in heart rate of 6 beats/min at the largest administered volume. The ISA index indicates the degree of intrinsic sympathomimetic agonist activity relative to isoprenaline-induced tachycardia = 1.0. ISA was estimated either

(15) (a) Smith, L. H. *J. Appl. Chem. Biotechnol.* 1978, *28*, 201–212. (b) Machin, P. J.; Hurst, D. N.; Bradshaw, R. M.; Blaber, L. C.; Burden, D. T.; Melrange, R. A. *J. Med. Chem.* 1984, *27*, 503–509.

(16) Guidicelli, J. F.; Charin, M.; Thuillez, C.; Richer, C.; Bianchetti, G.; Gomeni, R.; Morselli, P. L. *Br. J. Clin. Pharmacol.* 1980, *10*, 41–49.

(17) Swayne, G. T. G.; Owen, D. A. A.; Taylor, E. M.; Eden, R. J.; Slater, R. A.; Howson, W. *Arch. Int. Pharmacodyn.* 1987, *289*, 251–266.

(18) Howson, W.; Kitteringham, J.; Mistry, J.; Mitchell, M. B.; Novelli, R.; Slater, R. A.; Swayne, G. T. G. *J. Med. Chem.*, following paper in this issue.

from the compound-induced tachycardia in anesthetized cats at three doses or from full cumulative dose–response curves compared to a maximum isoprenaline tachycardia.

Chemistry. Synthesis. Melting points were determined on a Büchi 510 apparatus and were uncorrected. NMR spectra were recorded on JEOL PFT 100P (100 MHz) and Brucker AN 250 and 360 (250 and 360 MHz) instruments with $(CH_3)_4Si$ as the internal reference. The various splitting patterns were designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet or quintuplet; m, multiplet.

Microanalyses for elements indicated are within ±0.4% of the theoretical values. Purity of compounds was checked by TLC analysis on silica gel 60_{F254} plates, and components were visualized by a UV fluorescent lamp or by spraying with potassium iodine platinate solution. HPLC assays were performed by using an analytical pump coupled to an HPLC column (300 × 4 mm) prepacked with 5-μm octadecyl-bonded silica and a detector set at 280 nm; elution was carried out at a flow rate of 2 mL/min with a mixture of acetonitrile/pentanesulfonic acid (0.005 M, pH 2).

The syntheses of **4h** and 4t are given as examples. The other vasodilator/β-adrenoceptor antagonists were prepared according to these procedures from appropriate starting materials. The epoxides **9** were prepared according to published procedures[19] except for compounds **9**, R = 2-SO_2CH_3 and 2,3-$(CH_3)_2$); preparation of these compounds is described below. The final compounds 4 are tabulated in Table I with appropriate analytical data.

Preparation of 4h. 6-[4-(3-Bromopropionamido)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (6, *n* = 2, R = H, X = Br). A stirred mixture of 6-(4-aminophenyl)-4;5-dihydro-3-(2*H*)-pyridazinone (**5**, R = H)[9a] (170 g, 0.903 mol), 3-bromopropionyl chloride (155 g, 0.903 mol), and dry toluene (1 L) was heated under reflux for 16 h. The cooled mixture was then filtered and the yellow solid washed throroughly, by stirring with water, collected, and dried: yield, 267 g (91%); mp 222–224 °C; MS, *m/e* 323/5 (M^+); NMR (DMSO-d_6, 100 MHz) δ 7.68 (m, 4 H, Ar H), 3.74 (m, 2 H, CH_2Br), 2.91 (m, 4 H, $COCH_2$), 2.42 (m, 2 H, $CH_2C{=}N$).

6-[4-[3-(Benzylamino)propionamido]phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (7, *n* = 2, R = H). A stirred mixture of **6** (*n* = 2, R = H, X = Br) (267 g, 0.824 mol), benzylamine (267 g, 2.5 mol), and *n*-PrOH (2 L) was heated under reflux for 16 h. The solution was then filtered hot, reduced by evaporation to about 1.5 L, and allowed to cool. The resulting crystalline solid was collected, washed with ether, and dried: yield, 151 g (42%); mp 201–202 °C; MS, *m/e* 350 (M^+); NMR (DMSO-d_6, 100 MHz) δ 7.65 (br s, 4 H, Ar H), 7.3 (br s, 5 H, Ar H), 3.71 (s, 2 H, $NHCH_2Ph$), 3–2.3 (2 m, 8 H, CH_2CO, CH_2NH, $CH_2C{=}N$).

6-[4-[3-[Benzyl[2-hydroxy-3-(2-methylphenoxy)propyl]amino]propionamido]phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (10, *n* = 2, R = H, R′ = 2-CH_3). A stirred mixture of the above benzylamino compound **7** (*n* = 2, R = H) (10.0 g, 0.0284 mol), 2-(2,3-epoxypropoxy)toluene (**9**, R′ = 2-CH_3) (14.1 g, 0.0858 mol), and *n*-PrOH (200 mL) was heated at reflux for 16 h, charcoal was added, and the mixture was filtered while hot. Evaporation of the solvent under reduced pressure gave a viscous oil, which was washed several times with ether and then allowed to stand overnight under ether. The resulting solid was collected, washed with ether, and dried in vacuo: yield, 11.0 g (75%); mp 108–110 °C. This crude material was used in the subsequent reaction without further purification. Generally compounds **10** were not extensively purified or characterized.

6-[4-[3-[[2-Hydroxy-3-(2-methylphenoxy)propyl]amino]propionamido]phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (4h). A solution of the benzylamino precursor **10** (*n* = 2, R = H, R′ = 2-CH_3) (5.0 g, 0.01 mol) in glacial acetic acid (200 mL) was shaken in a hydrogen atmosphere at atmospheric pressure in the presence of palladium hydroxide on carbon (0.7 g) until the required volume had been taken up (about 12 h). The filtered solution was evaporated under reduced pressure, and the product was purified by elution from a silica gel column with $CHCl_3$/MeOH mixtures. The pure base was obtained as a pale yellow oil (3.1 g), which was dissolved in EtOH and treated with an ethanolic solution of *p*-toluenesulfonic acid (1.39 g, 0.0073 mol). The solution was evaporated to a small volume and the residue recrystallized from H_2O/EtOH/Et_2O to give the product as the *p*-toluenesulfonate salt: yield 2.5 g (43%); mp 207–208 °C; NMR (DMSO-d_6, 360 MHz) δ 10.76, 10.25 (2 s, 2 H, NH), 7.67 (m, 4 H, Ar H), 7.50 (m, 2 H, HSO_3-ArH), 7.1–7.2 (m, 4 H, HSO_3-ArH, OArH), 6.92, 6.85 (2 m, 2 H, OArH), 4.21 (m, 1 H, C*H*OH), 4.0 (m, 2 H, CH_2O), 3.1–3.4 (m, 4 H, NCH_2), 2.92 (m, 2 H, $CH_2C{=}N$), 2.84 (m, 2 H, $COCH_2$), 2.43 (m, 2 H, $COCH_2$), 2.28 (s, 3 H, CH_3 Ar), 2.19 (s, 3 H, CH_3 Ar).

Preparation of 4t. 6-[4-(3-Bromopropionamido)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (6, *n* = 2, R = CH_3, X = Br). 6-(4-Aminophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone[9a] (**5**, R = CH_3) (50 g, 0.246 mol) was dissolved in hot acetonitrile (1.2 L). To this was added 3-bromopropionyl chloride (65 g, 0.38 mol) in CH_3CN (200 mL) over several minutes. The reaction mixture was then heated at reflux for 3 h and cooled and the solid product collected by filtration and washed with H_2O and then Et_2O: yield, 82 g (99%); mp 220–221 °C; NMR (DMSO-d_6, 100 MHz) δ 10.77, 10.10 (2 s, 2 H, NH's), 7.69 (m, 4 H, Ar H), 3.74 (t, 2 H, CH_2Br), 3.35 (m, 1 H, C*H*CH_3), 2.97 (t, 2 H, CH_2CO), 2.68, 2.20 (2 m, 2 H, CH_2CO), 1.08 (d, 3 H, CH_3). Anal. ($C_{14}H_{16}BrN_3O_2$) C, H, N.

6-[4-(3-(Benzylamino)propionamido)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone Hydrobromide (7, *n* = 2, R = CH_3). Compound **6** (*n* = 2, R = CH_3, X = Br) (10 g, 0.0296 mol) was suspended in *n*-PrOH (100 mL). To the vigorously stirred mixture was added benzylamine (12 mL, 0.11 mol). The mixture was heated at reflux for 6 h, during which time some precipitation occurred. The solution was then allowed to cool and the product precipitated out. This was collected by filtration, washed with *n*-PrOH, and dried to give the product as the hydrobromide salt: yield, 10.7 g (81%); mp 275–280 °C; NMR (DMSO-d_6, 360 MHz) δ 10.82 (s, 1 H, NH), 10.32 (s, 1 H, NH), 8.87 (br s, 2 H, NH_2^+), 7.70 (m, 4 H, Ar H), 7.54, 7.44 (2 m, 5 H, Ar H), 4.22 (s, 2 H, CH_2Ph), 3.36 (m, 1 H, C*H*CH_3), 3.24 (m, 2 H, CH_2NH), 2.96 (m, 2 H, $COCH_2CH_2$), 2.68, 2.23 (2 m, 2 H, $COCH_2$), 1.06 (d, 3 H, CH_3). Anal. ($C_{21}H_{24}N_4O_2$·HBr·0.25H_2O) C, H, N.

6-[4-[3-[Benzyl[3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (10, *n* = 2, R = CH_3, R^1 = 4-$CH_2CH_2OCH_2$-c-C_3H_5). A mixture of **7** (*n* = 2, R = CH_3) (1.46 g, 0.004 mol), 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-2,3-epoxypropane **9**[20] (2.0 g, 0.008 mol), and *n*-PrOH (100 mL) was stirred and heated at reflux for 22 h. Evaporation of the solvent under reduced pressure gave an oily residue, which was purified by elution from a silica gel column with CH_2Cl_2/MeOH mixtures to give the free base as a foam: yield, 1.3 g, (38%); NMR ($CDCl_3$, 100 MHz) δ 9.95, 8.89 (2 br s, 2 H, NH's), 7.65 (s, 5 H, Ar H), 7.27 (br s, 4 H, NHArH's), 6.94 (2 d, 4 H, OArH's), 3.28 (d, 2 H, OCH_2-c-C_3H_5), 1.23 (d, 3 H, CH_3), 0.53, 0.18 (2 m, 4 H, cyclopropylmethylene).

6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone Methanesulfonate (4t, *n* = 2, R = CH_3, R^1 = 4-$CH_2CH_2OCH_2$-c-C_3H_5). A solution of **10** (*n* = 2, R = CH_3, R^1 = 4-$CH_2CH_2OCH_2$-c-C_3H_5) (0.85 g, 0.0014 mol) in EtOH (60 mL) was agitated for 6 h in a hydrogen atmosphere at 172 kPa (25 psi) in the presence of palladium hydroxide on

(19) The preparation of the epoxides **9** is outlined in the following references. R^1 = H, 2-CH_3, 2-CN: Kreighbaum, W. E.; Matier, W. L.; Dennis, R. D.; Minielli, J. L.; Deitchman, D.; Perhach, J. L.; Corner, W. T. *J. Med. Chem.* **1980**, *23*, 285–289. R^1 = 2-*c*-$N(CH_2)_2O(CH_2)_2$: Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; William, H. W. R.; Yates, C. H. *J. Med. Chem.* **1972**, *15*, 651–655. R^1 = (2)—CH=CHNH—(3): Tejani-Butt, S. M.; Brunswick, D. J. *J. Med. Chem.* **1986**, *29*, 1524–1527. R^1 = 2-OCH_3: Wasson, B. K.; Share, N. N. U.S. Patent 1 169 990, 1969. R^1 = (2)—CH=CHCH=CH—(3): Brooker, G.; Terasaki, W. L.; Linden, J. M. U.S. Patent 4 376 125, 1983. R^1 = 4-$CH_2CH_2OCH_3$: Brandstroem, A. E.; Carlsson, P. A. E.; Carlsson, S. A.; Corrodi, H. R.; Ek, L.; Ablad, B. A. H. U.S. Patent 3 928 601, 1975.

(20) Morselli, P. L.; Desantis, L.; Adamski, R. U.S. Patent 4 342 783, 1982.

carbon (0.2 g) as a catalyst. When hydrogen uptake ceased, the mixture was filtered and the solvent evaporated under reduced pressure to give a solid residue. Purification of the crude product was effected by elution from a silica gel column with $CHCl_3$/CH_3OH mixtures to give the product as the free base. This was dissolved in CH_2Cl_2, and a solution of methanesulphonic acid (0.1 g, 0.001 mol) in CH_2Cl_2 was added. The mixture was diluted with Et_2O, and the product as the salt precipitated out. This was collected by filtration, washed with Et_2O, and dried: yield, 0.50 g (58%); mp 176–178 °C; NMR (DMSO-d_6, 360 MHz) δ 10.82, 10.30 (2 s, 2 H, NH's), 7.75, 7.68 (2 m, 4 H, Ar H), 7.15, 6.88 (2 m, 4 H, Ar H), 4.21 (m, 1 H, C*H*OH), 3.99 (m, 2 H, CH_2O), 3.57 (t, 2 H, CH_2O), 3.5–3.1 (m, 5 H, C*H*CH_3, N*C*H_2, $COCH_2$), 3.25 (d, 2 H, OCH_2-c-C_3H_5), 2.88 (m, 2 H, CH_2N), 2.76 (m, 2 H, Ar CH_2), 2.70 (dd, 1 H, C$H_a$$H_b$CO), 2.38 (s, 3 H, CH_3S), 2.26 (m, 1 H, $CH_a$$H_b$CO) 1.09 (d, 3 H, CH_3), 0.98 (m, 1 H, cyclopropyl ring), 0.45, 0.14 (2 m, 4 H, cyclopropyl ring). Anal. ($C_{29}H_{38}N_4O_5$·1.05CH_4O_3S] C, H, N, S.

Preparation of 3c. 6-[4-[3-[(Benzyloxycarbonyl)amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (13). 3-[(Benzyloxycarbonyl)amino]propionic acid 4-nitrophenyl ester (9.45 g, 0.028 mol) and 6-(4-aminophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone[9a] (2.6 g, 0.0127 mol) in dry DMF (100 mL) were heated on a steam bath overnight. Evaporation of the solvent under reduced pressure gave an oil, which was treated with 1 M NH_4OH solution (100 mL), and the mixture was heated for 30 min on a steam bath. The resulting solid was collected, washed with water, and recrystallized from H_2O/EtOH to give **13**: yield, 3.8 g (73%); mp 137–138 °C.

6-[4-(3-Aminopropionamido)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (3c). A solution of 6-[4-[3-[(benzyloxycarbonyl)amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (**13**) (3.8 g, 0.0093 mol) in DMF (100 mL) was hydrogenolyzed at atmospheric pressure and room temperature in the presence of 10% palladium on charcoal catalyst. Evaporation of the solvent followed by addition of H_2O to the residue gave the product as a solid: yield, 1.8 g (74%). The amine was characterized as its *p*-toluenesulfonic acid salt, which crystallized from H_2O as a partial hydrate: mp 257–258 °C; NMR (D_2O, 100 MHz), δ 7.70 (m, 6 H, Ar H), 7.36 (d, 2 H, Ar H), 3.45 (m, 1 H, C*H*CH_3), 3.42 (t, 2 H, CH_2N), 2.92 (t, 2 H, $COCH_2$), 2.60, 2.38 (2 m, 2 H, $COCH_2$), 1.17 (d, 3 H, CH_3). Anal. ($C_{14}H_{18}N_4O_2$·$C_7H_8O_3S$·0.254H_2O) C, H, N, S.

Preparation of Epoxides 9 (R^1 = 2-SO_2CH_3 and 2,3-$(CH_3)_2$). 1-[2-(Methylsulfonyl)phenoxy]-2,3-epoxypropane (9, R^1 = 2-SO_2CH_3). 2-Hydroxyphenyl methyl sulfone[21] (**8**) (R^1 = 2-SO_2CH_3) (6.8 g, 0.04 mol), epibromohydrin (11.6 g, 0.08 mol), and K_2CO_3 (5.6 g, 0.04 mol) were placed in a 250-mL flask, covered with 2-butanone (100 mL), and heated at reflux for 17 h. The mixture was cooled, filtered, and evaporated in vacuo to give crude product as an oil: yield, 9.0 g (98%). This crude material was used without further purification.

2,3-Dimethyl-1-(2,3-epoxypropoxy)benzene (9, R^1 = 2,3-$(CH_3)_2$). A mixture of 2,3-dimethylphenol (120 g, 1.0 mol), epibromohydrin (550 g, 4.01 mol), anhydrous potassium carbonate (500 g, 3.62 mol), and dry 2-butanone (1120 mL) was stirred and heated under reflux for 16 h. The hot reaction mixture was filtered, the inorganic residue was washed with 2-butanone, and the combined organic layers were evaporated to small volume under reduced pressure. Distillation of the residue gave the required epoxide **9** (R^1 = 2,3-$(CH_3)_2$) as a colorless oil: bp 110–112 °C (1.0 mmHg); yield, 148 g (83%); NMR ($CDCl_3$, 100 MHz) δ 2.17 and 2.25 (2 s, 6 H, 2 CH_3), 3.35 (m, 1 H, CH).

(21) Pederson, A. O.; Schroll, G.; Lawesson, S. O.; Laurie, W. A.; Reed, R. I. *Tetrahedron* **1970**, *26*, 4449–4471.

Acknowledgment. We thank Dr. J. C. Emmett for many helpful discussions, V. P. Shah and C. M. Whittaker for the preparation of some of the compounds, M. J. Graham for the microanalyses, and Dr. E. S. Pepper and his colleagues for the NMR spectra.

Registry No. **2**, 24912-35-4; **3a**, 21394-91-2; **3b**, 36725-27-6; **3c**, 88421-57-2; **3c**·TsOH, 111794-61-7; **4a**, 111793-97-6; **4a**·TsOH, 111793-98-7; **4b**, 88421-36-7; **4b**·TsOH, 111793-99-8; **4c**, 111794-00-4; **4c**·TsOH, 111794-01-5; **4d**, 111794-02-6; **4d**·TsOH, 111794-03-7; **4e**, 111794-04-8; **4e**·TsOH, 111794-05-9; **4f**, 111794-06-0; **4f**·XTsOH, 111794-07-1; **4g**, 111794-57-1; **4g**·HBr, 111794-08-2; **4h**, 111794-09-3; **4h**·TsOH, 111794-10-6; **4i**, 111794-11-7; **4i**·TsOH, 111794-12-8; **4j**, 111794-13-9; **4j**·TsOH, 111794-14-0; **4k**, 111794-15-1; **4k**·TsOH, 111794-16-2; **4l**, 111794-17-3; **4l**·XAcOH, 111794-18-4; **4m**, 111794-19-5; **4m**·TsOH, 111794-20-8; **4m**, 111794-58-2; **4m**·HCl, 111794-21-9; **4o**, 111794-22-0; **4o**·TsOH, 111794-23-1; **4p**, 111794-24-2; **4p**·TsOH, 111794-25-3; **4q**, 111794-59-3; **4q**·HCl, 111794-26-4; **4r**, 111794-27-5; **4r**·XTsOH, 111794-28-6; **4s**, 111794-29-7; **4s**·TsOH, 111794-30-0; **4t**, 101328-82-9; **4t**·$MeSO_3H$, 111794-31-1; **5**(R = H), 21282-90-6; **5** (R = Me), 36725-28-7; **6** (*n* = 1,R = H,X = Br), 88555-40-2; **6** (*n* = 1,R = MeX, = Br), 111794-32-2; **6** (*n* = 2,R = H,X = Br), 111794-33-3; **6** (*n* = 2,R = Me,X = Br), 111794-34-4; **7** (*n* = 1,R = H), 39754-17-1; **7** (*n* = 1,R = Me), 111794-35-5; **7** (*n* = 2,R = H), 111794-36-6; **7** (*n* = 2,R = Me)·HBr, 111794-37-7; **8** (R' = 2-Me), 95-48-7; **8** (R' = 2-OMe), 90-05-1; **8** (R' = 2-CN), 611-20-1; **8** (R' = 2-SO_2Me), 27489-33-4; **8** (R' = 2-C-$N(CH_2)_2O(CH_2)_2$), 41536-44-1; **8** (R' = 2-H), 108-95-2; **8** (R' = (2)-CH=CHCH=CH-(3)), 90-15-3; **8** (R' = (2)-CH=CHNH-(3)), 2380-94-1; **8** (R' = 2,3-Me_2), 526-75-0; **8** (R' = 4-$(CH_2)_2OMe$), 56718-71-9; **8** (R' = 4-$(CH_2)_2OCH_2$-c-C_3H_5), 63659-16-5; **9** (R' = 2-Me), 2210-79-9; **9** (R' = 2-OMe), 2210-74-4; **9** (R' = 2-CN), 38465-16-6; **9** (R' = 2-H), 122-60-1; **9** (R' = 2-SO_2Me), 58048-49-0; **9** (R' = 2-c-$N(CH_2)_2O(CH_2)_2$), 30301-29-2; **9** (R' = (2)-CH=CHCH=CH-(3)), 2461-42-9; **9** (R' = (2)-CH=CHNH-(3)), 35308-87-3; **9** (R' = 2,3-Me_2), 41457-31-2; **9** (R' = 4-$(CH_2)_2OMe$), 56718-70-8; **9** (R' = 4-$(CH_2)_2OCH_2$-c-C_3H_5), 63659-17-6; **10** (*n* = 1,R = Me, R' = 2-Me), 111794-39-9; **10** (*n* = 1,R = H,R' = 2-Me), 111794-38-8; **10** (*n* = 1,R = H, R' = 2-OMe), 111794-40-2; **10** (*n* = 1,R = Me,R' = 2-OMe), 111794-41-3; **10** (*n* = 1,R = H,R' = 2-CN), 111794-42-4; **10** (*n* = 1,R = Me,R' = 2-CN), 111794-43-5; **10** (*n* = 2,R = Me, R' = 2-H), 111794-44-6; **10** (*n* = 2,R = H,R' = 2-Me), 111794-45-7; **10** (*n* = 2,R = Me,R' = 2-Me), 111794-46-8; **10** (*n* = 2,R = H,R' = 2-OMe), 111794-47-9; **10** (*n*, 2,R = Me,R' = 2-OMe), 111794-48-0; **10** (*n* = 2,R = H,R' = 2-CN), 111794-49-1; **10** (*n* = 2, R = Me, R' = 2-CN), 111794-50-4; **10** (*n* = 2,R = Me,R' = 2-SO_2Me), 111822-66-3; **10** (*n* = 2,R = Me,R' = 2-c-$N(CH_2)_2O(CH_2)_2$), 111794-51-5; **10** (*n* = 1,R = H,R' = (2)-CH=CHCH=CH-(3)), 111794-52-6; **10** (*n* = 2,R = Me,R' = (2)-CH=CHNH-(3)), 111794-53-7; **10** (*n* = 2,R = Me,R' = 2,3-Me_2), 111794-54-8; **10** (*n* = 2,R = Me,R' = 4-$(CH_2)_2OMe$), 111794-55-9; **10** (*n* = 2,R = Me,R' = 4-$(CH_2)_2OCH_2$-c-C_3H_5), 111794-56-0; **13**, 111794-60-6; ClCO-$(CH_2)_2Br$, 15486-96-1; $ClCOCH_2Br$, 22118-09-8; $PhCH_2NH_2$, 100-46-9; *p*-$NO_2C_6H_4O_2C(CH_2)_2NHCO_2CH_2Ph$, 3642-91-9; epibromohydrin, 3132-64-7.