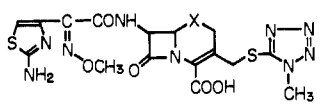
introduction of the 7α-methoxy group may be attributed to the increased ability of the β-lactam ring to acylate RO^- located on the α-side.[30]

The effects of introducing the carboxyl group to the side chain (compare **6** with **2**; **7** with **3**; **8** with **4**; and **1** with **5**) were not significant. Only a slight increase in the values of log $(1/C_a)$ for antibacterial activity was observed. Hydrolysis rates (log k) and the β-lactam carbonyl frequencies remained almost constant.

Substitution of a methylene group for the sulfur atom in cephalosporins (compare **9** to **8**) greatly diminished log $(1/C_b)$ (−0.6), whereas log k significantly increased (0.56). The increase in the alkaline hydrolysis rate for 7α-hydro-1-carbacephem at pH 10 and 35 °C was larger[24] than that caused by substitution of the oxygen atom. The increase was interpreted by a probable similarity in the geometry of 1-carbacephem to that of 1-oxacephems, which might force the lactam nitrogen atom into a more pyramidal structure. The diminished antibacterial activity might be ascribed to some disturbance in the complex formation to the target enzymes at the right position, probably caused by conformational changes in the amide side chain generated by the bulkier methylene group at the 1-position. Actually, antibacterial activity of 7α-hydro-1-carbacephem (**24**) against Gram-negative bacteria is of a similar level



22, X = S
23, X = O
24, X = CH_2

to that for **22** and **23**,[22] in which the side chain probably contributes to efficient complex formation with enzymes.

Introduction of the 7α-methyl group resulted in substantial decreases in log k and log $(1/C_b)$ (−0.21 and −1.48, respectively). Steric hindrance against RO^- caused by the bulky methyl group[31] and conformational changes in the side chain[32] might be the reason for the decreases, respectively. The indifferently high frequency of the β-lactam carbonyl probably indicates little contribution of the inductive effect of the 7α-methyl group.

We came to the following four conclusions. First, the enhancement of antibacterial activity, against sensitive Gram-negative bacteria, caused by substitution of an oxygen atom for the sulfur atom in cephalosporins can be interpreted as an increase in the chemical reactivity of the β-lactam ring. Second, introduction of the 7α-methoxy group results in some enhancement of the antibacterial activity mainly caused by the increased reactivity of the β-lactam ring which may be associated with the presumed transition state stabilized by a stronger hydrogen bond between the amide hydrogen and the charge-generating carbonyl oxygen atom. Third, substitution of a methylene group for the sulfur atom in 7β-[[(4-hydroxyphenyl)malonyl]amino]-7α-methoxycephalosporin lowers the antibacterial activity. Fourth, introduction of the 7α-methyl group greatly diminishes the antibacterial activity.

Acknowledgment. The authors are grateful to Drs. W. Nagata, M. Shiro, T. Kubota, Y. Matsui, and R. Konaka for their helpful discussions. The cooperation of Mrs. S. Sato and Messrs. N. Haga, F. Watanabe, K. Kuruma, and K. Motokawa is gratefully acknowledged.

Registry No. **1**, 76858-80-5; **2**, 77016-90-1; **3**, 77059-22-4; **4**, 77016-91-2; **5**, 77059-23-5; **6**, 86940-51-4; **7**, 86862-79-5; **8** (isomer 1), 74157-37-2; **8** (isomer 2), 86862-93-3; **9**, 86862-80-8; **10**, 86862-81-9; **11a**, 53090-86-1; **11b**, 66429-65-0; **11c**, 56610-72-1; **11d**, 66510-99-4; **11e**, 86862-82-0; **12**, 86862-83-1; **13**, 86862-84-2; **14a**, 86862-85-3; **14b**, 86862-86-4; **14c**, 86862-87-5; **14d**, 86862-88-6; **15a**, 81362-32-5; **15b**, 75007-69-1; **15c**, 86862-89-7; **15d**, 75007-70-4; **16**, 70371-42-5; **17**, 86862-90-0; **18**, 70175-90-5; **19**, 64952-86-9; **20a** (isomer 1), 86862-91-1; **20a** (isomer 2), 86862-94-4; **20c**, 66216-32-8; **20e**, 86884-68-6; **21a**, 86940-52-5; **21c** (isomer 1), 66216-37-3; **21c** (isomer 2), 86862-95-5; **21e** (isomer 1), 86940-95-6; **21e** (isomer 2), 86940-96-7; 4-hydroxyphenylacetic acid, 156-38-7; diphenylmethyl (4-hydroxyphenyl)acetate, 78984-21-1; diphenylmethyl [4-[(benzyloxycarbonyl)oxy]phenyl]acetate, 86862-92-2.

(30) The effects of the 7α-methoxy group in cephalosporins on the reactivity of the β-lactam ring and antibacterial activity have been discussed in a different way. See: (a) Ho, P. P. K.; Towner, R. D.; Indelicato, J. M.; Wilham, W. J.; Spitzer, W. A.; Koppel, G. A. *J. Antibiot.* **1973**, *26*, 313. (b) Indelicato, J. M.; Wilham, W. L. *J. Med. Chem.* **1974**, *5*, 528.

(31) The inductive effect of the 6α-methyl group on the decrease in the hydrolysis rate of methyl 6β-[(phenylacetyl)amino]-6α-penicillinate has been described. see: Bohme, H. W.; Applegate, H. E.; Ewing, J. B.; Funke, R.; Puar, M. S.; Dolfini, J. E. *J. Org. Chem.* **1973**, *38*, 231.

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Synthesis and Antihypertensive Activity of Substituted *trans*-4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols

John M. Evans, Charles S. Fake, Thomas C. Hamilton,* Robert H. Poyser, and Eric A. Watts

Beecham Pharmaceuticals, Research Division, Medicinal Research Centre, The Pinnacles, Harlow, Essex, CM19 5AD, England.
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A series of novel substituted *trans*-4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols was prepared and tested for antihypertensive activity in the conscious deoxycorticosterone acetate (DOCA)/saline treated hypertensive rat. Optimum blood pressure lowering activity requires 6-substitution by a strong electron-withdrawing group, together with a pyrrolidino or piperidino group at the 4 position. Exceptions to this were the 7-nitro-4-pyrrolidine analogue and the 6-nitro-3-chloropropylamine, which retained marked antihypertensive activity. All of these compounds were direct vasodilators and had comparable antihypertensive activity to hydralazine and to the calcium antagonist, nifedipine. The synthetic route to these compounds involves cyclization of propargyl ethers to 2*H*-1-benzopyrans, followed by conversion via bromohydrins to 3,4-epoxides, which were ring opened with the appropriate amines. Meta-substituted propargyl ethers gave both 5- and 7-substituted benzopyrans on thermal cyclization, the former predominating. A new route to 2,2-dimethyl-7-nitrobenzopyran is described.

During the evaluation of a series of benzopyrans developed in these laboratories, we discovered that 3,4-dihydro-2,2-dimethyl-*trans*-4-(isopropylamino)-6-nitro-2*H*-1-benzopyran-3-ol (**1**) possessed antihypertensive activity

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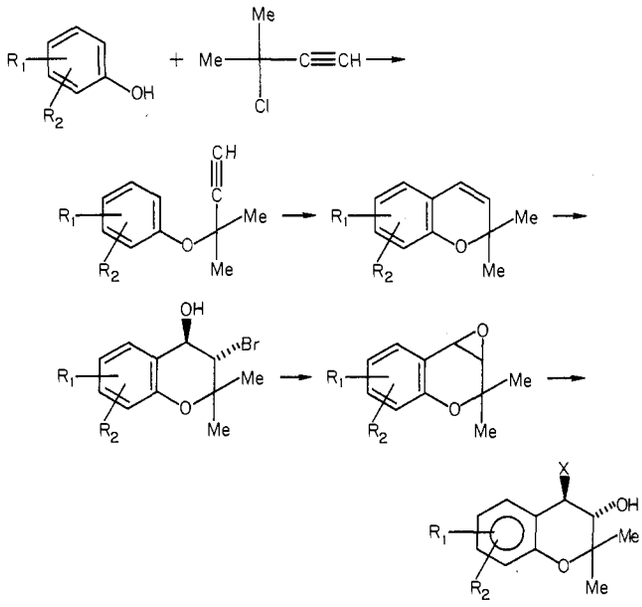
Scheme I



in conscious rats. This paper describes the synthesis and testing of a series of novel antihypertensive agents derived from compound 1. The antihypertensive activity of these compounds was found to be a consequence of their vasodilating properties,[1] and thus hydralazine and nifedipine, two standard vasodilator-type antihypertensive drugs, were included in the study for comparison.

Chemistry. The 4-aminobenzopyran-3-ols were prepared as shown in Scheme I. Heating the appropriate phenol and 3-chloro-3-methylbutyne in acetone with K_2CO_3 and KI (method A) or in toluene with NaH (method B) furnished the propargyl ethers. In certain cases, particularly for *p*-nitrophenol, yields were markedly increased by use of a phase-transfer catalytic method (method C). Cyclization of the ethers to the benzopyrans was accomplished in almost quantitative yield by heating in *o*-dichlorobenzene or *N,N*-diethylaniline. The ortho- and para-substituted ethers gave 8- and 6-substituted benzopyrans, respectively. For meta-substituted ethers, both 5- and 7-substituted benzopyrans are theoretically possible, and, in previous work, some authors report [2] the regioselective formation of 7-substituted benzopyrans, while others describe[3] the formation of both possible products. In this work, *m*-cyano and *m*-nitropropargyl ethers gave both isomers, with the 5-substituted benzopyran predominating. Since only partial separation of the isomers was achieved by laborious fractional distillations, an alternative route to the 7-nitrobenzopyran **55** was sought. Nitration of 6-(acetylamino)-3,4-dihydrobenzopyran is reported[4] to yield all three possible nitro products, which is not unexpected, since the competing orientation effects of *O*-alkyl and acetylamino might preclude any specificity. Surprisingly, nitration of 6-(acetylamino)-2,2-dimethylbenzopyran gave only the 7-nitro compound **60** which was converted to **55** by hydrolysis, diazotization, and reduction.

Treatment of the benzopyrans with moist *N*-bromosuccinimide yielded the 3-bromo-3,4-dihydrobenzopyran-4-ols, which were converted to the epoxides by reaction with KOH in ether or, in resistant cases, with NaOH in aqueous dioxane. Reaction of the epoxides with the appropriate amine gave the amino alcohols,[5] which were purified as the salts shown in Tables I and II. Compounds **39–42**, **47**, and **48** were prepared by standard reactions on the appropriate amino alcohol.

Results and Discussion

Compounds were evaluated for oral antihypertensive activity in deoxycorticosterone acetate (DOCA)/NaCl treated hypertensive rats. Systolic blood pressure, recorded indirectly from the tail, was determined before dosing and at various time intervals during the ensuing 6 h. Maximum falls in blood pressure obtained for all compounds are shown in Tables I and II.

Initially, a series of compounds was investigated in which the 6-nitro group was retained and the 4-amino moiety was varied (Table I). Change of the 4-substituent from isopropylamino, as in the lead compound **1**, to a cyclic amino function generally increased activity. The two most active of these compounds were the pyrrolidine and the piperidine analogues (**13** and **14**, respectively). Potency diminished if the ring was further increased in size (**15** and **16**). Similarly, substitution on the ring (as in **17–19**) and introduction of another heteroatom (as in **20** and **21**) caused a reduction in potency. Compounds (**2–12**) that possess amino, alkylamino, cycloalkylamino, and substituted alkylamino groups were also found to be less active than the pyrrolidine and piperidine analogues (**13** and **14**). The exception was the 3-chloropropylamine **11**, which was as active as **13** and **14**.

In the second series of compounds, the 4-substituent was fixed as pyrrolidine or piperidine, and the substitution pattern of the aromatic ring of the benzopyran structure was varied (Table II). These compounds were all less active than the 6-nitro compounds (**13** and **14**), apart from the 7-nitro-4-pyrrolidino analogue **25** and the 6-cyano analogues **27** and **28**, which were approximately as active as the corresponding 6-nitro compounds. The cyano and nitro groups are both powerful electron-withdrawing substituents, which cause only slight differences to the overall lipophilicity of the parent unsubstituted molecules. Compounds possessing substitutents with similar lipophilic properties but less powerful electron-withdrawing properties, such as 6-acetyl (as in **37** and **38**) and methoxycarbonyl (as in **36**), had approximately one-tenth the activity of the corresponding 6-nitro compounds.

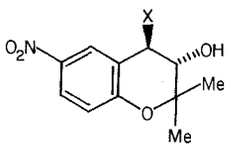
It was interesting to note that the 5- and 8-substituted compounds (**23**, **26**, and **30**) had less activity than the 6- and 7-substituted compounds.

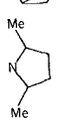
It can be concluded that for maximum oral antihypertensive activity in DOCA/NaCl treated hypertensive rats, a suitable electron-withdrawing substituent (preferably nitro or cyano) is required in the 6-position (or in the 7-position for nitro), with the amino moiety being a pyrrolidine or piperidine ring.

Detailed pharmacological studies[1] on compounds **13** and **28** have shown a direct vasodilator action. For example, compound **28**, 9.7×10^{-6} M, inhibits spontaneous activity in rat isolated portal vein by 32 ± 1%, and a higher concentration (1.5×10^{-3} M) of hydralazine produces a comparable response (40 ± 4%). In conscious hypertensive rats, compounds **13** and **28** possess antihypertensive ac-

(1) Hamilton, T. C.; Poyser, R. H., unpublished results.
(2) Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1971**, *24*, 2347, and references therein.
(3) Anderson, W. K.; LaVoie, E. J.; Whitkop, P. G. *J. Org. Chem.* **1974**, *39*, 881.
(4) Brancaccio, G.; Lettieri, G.; Viterbo, R. *J. Heterocycl. Chem.* **1973**, *10*, 623.
(5) The regioselective ring opening of the epoxides is shown by the chemical shifts and coupling constants of the protons located at C(3) and C(4) of the amino alcohol salts and confirmed by the retro-Diels-Alder cleavage [loss of C(2) to C(3) of 72 mass units) in the mass spectrum of, for example, compound **28**.
(6) Miller, J. A.; Wood, H. C. S. British Patent 1 121 307, 1968.

Table I. *trans*-4-Amino-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran-3-ol Salts



compd	X	yield, %	mp, °C	formula	anal.[a]	dose,[b] mg/kg po	max fall in BP,[c] mmHg[c] (mean ± SEM)	no. of rats
1	$NHCHMe_2$	84	244–247	$C_{14}H_{20}N_2O_4 \cdot HCl$	C, H, N, Cl	100	36 ± 4	6
						300	69 ± 14	6
2	NH_2	13	287–290	$C_{11}H_{14}N_2O_4 \cdot HCl$	C, H, N, Cl	30	23 ± 1	6
						100	45 ± 5	6
3	NHMe	83	296–299	$C_{12}H_{16}N_2O_4 \cdot HCl$	C, H, N, Cl	30	21 ± 8	6
						100	43 ± 10	6
4	NMe_2	30	260–261	$C_{13}H_{18}N_2O_4 \cdot HCl$	C, H, N, Cl	100	29 ± 9	5
5	NEt_2	63	198–204	$C_{15}H_{22}N_2O_4 \cdot HCl$	C, H, N, Cl	30	34 ± 7	3
						100	54 ± 3	3
6	$NHCMe_3$	39	229–233	$C_{15}H_{22}N_2O_4 \cdot MeSO_3H$	C, H, N	100	7 ± 3	6
7	NH-c-Pr	56	209–211	$C_{14}H_{18}N_2O_4 \cdot MeSO_3H$	C, H, N, S	10	31 ± 8	6
						100	95 ± 9	5
8	$NHCH_2$-c-Pr	23	256–259	$C_{15}H_{20}N_2O_4 \cdot HCl$	C, H, N, Cl	100	13 ± 6	3
9	$NH(CH_2)_2OH$	89	264–267	$C_{13}H_{18}N_2O_5 \cdot HCl$	C, H, N, Cl	100	27 ± 7	3
10	$NH(CH_2)_3OH$	68	264–267	$C_{14}H_{20}N_2O_5 \cdot HCl$	C, H, N, Cl	100	28 ± 2	3
11	$NH(CH_2)_3Cl$	10	243–247	$C_{14}H_{19}ClN_2O_4 \cdot HCl$	C, H, N, Cl	0.3	3 ± 14	3
						1	41 ± 11	3
						3	85 ± 13	3
						10	81 ± 12	3
12	$NH(CH_2)_2$-c-NC_4H_8	49	179–182	$C_{17}H_{25}N_3O_4 \cdot 2HCl$	C, H, N, Cl	100	23 ± 6	3
13	c-NC_4H_8	36	214–215	$C_{15}H_{20}N_2O_4 \cdot MeSO_3H$	C, H, N, S	1	52 ± 7	6
						3	79 ± 3	6
						10	98 ± 6	5
14	c-NC_5H_{10}	83	226–228	$C_{16}H_{22}N_2O_4 \cdot MeSO_3H$	C, H, N, S	1	28 ± 10	6
						3	73 ± 13	5
						10	105 ± 15	7
15	c-NC_6H_{12}	67	215–220	$C_{17}H_{24}N_2O_4 \cdot HCl$	C, H, N, Cl	10	17 ± 2	3
						100	96 ± 8	3
16	c-NC_7H_{14}	46	214–220	$C_{18}H_{26}N_2O_4 \cdot HCl$	C, H, N	3	34 ± 10	3
						10	53 ± 23	3
						30	82 ± 15	3
17		18	223–226	$C_{19}H_{26}N_2O_4 \cdot MeSO_3H$	C, H, N, S	10	20 ± 10	5
18		15	214–219	$C_{17}H_{24}N_2O_4 \cdot HCl$	C, H, N, Cl	30	26 ± 9	3
19	c-$N(CH_2CH_2)_2CHMe$	68	226–230	$C_{17}H_{24}N_2O_4 \cdot HCl$	C, H, N, Cl	10	28 ± 8	3
20	c-$N(CH_2CH_2)_2O$	43	250–252	$C_{15}H_{20}N_2O_5 \cdot HCl$	C, H, N, Cl	10	23 ± 4	6
						30	55 ± 7	6
						100	70 ± 6	6
21	c-$N(CH_2CH_2)_2$N-Ph	12	210–213	$C_{21}H_{25}N_3O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	10	10 ± 11	3

hydralazine	1	32 ± 8	6
	3	65 ± 12	6
	10	113 ± 10	5
nifedipine	0.3	20 ± 6	6
	1	33 ± 2	6
	3	51 ± 2	6

[a] Analyses for the elements indicated were within ±0.4% of the theoretical values. [b] Compounds were given orally to DOCA/NaCl treated hypertensive rats; doses are expressed as base. [c] Systolic blood pressure was measured indirectly at intervals from 1 to 6 h.

tivity comparable to that of hydralazine and nifedipine (see Table I), and compound **28** is currently being examined in the clinic.

Experimental Section

Melting points were determined with a Buchi capillary melting point apparatus. Both melting points and boiling points are uncorrected. IR, NMR, and mass spectra, which were in agreement with the structures cited, were recorded on a Pye-Unicam SP 200, a Perkin-Elmer R12A at 60 MHz, and an AEI MS9 at 70 eV, respectively, while GLC was performed with a Perkin-Elmer F11. Omissions from tables indicate that crude material, having the required spectral characteristics but showing signs of decomposition, was used directly for the next synthetic stage.

3-Methyl-3-phenoxybut-1-ynes. Method A. The phenols (0.20 mol), anhydrous K_2CO_3 (0.20 mol), and KI (0.02 mol) were stirred in dry Me_2CO (500 mL) under N_2. Addition of 3-chloro-3-methylbutyne (0.22 mol) was followed by refluxing for 18 h. Filtration and evaporation gave the crude ethers (24–72%).

Method B. NaH (0.20 mol) was added cautiously to a solution of the phenols (0.20 mol) in dry PhMe (500 mL) under N_2, followed by the addition of 3-chloro-3-methylbutyne (0.25 mol) in dry PhMe (100 mL) to the heated stirred solution. The solution was refluxed and stirred for 12–24 h, cooled, washed with H_2O and 5 N NaOH, dried, and evaporated to give the crude ethers (30–85%).

Method C. The phenols (0.165 mol) and NaOH (0.247 mol) were added to a stirred suspension of H_2O (150 mL) and CH_2Cl_2 (150 mL), followed by Me_3NCH_2PhOH (0.825 mol, 40% MeOH solution) and 3-chloro-3-methylbutyne (0.400 mol). After the solution was stirred for 4 days, the layers were separated and the aqueous layer was further extracted with $CHCl_3$. The combined organic extracts were evaporated, and the residue was taken up in Et_2O and washed with H_2O and 2 N NaOH, before drying and solvent removal gave the crude ethers (46–69%).

NMR analysis indicated that several of the ethers had undergone partial cyclization to 2,2-dimethyl-2*H*-1-benzopyrans during these reactions. The new ethers obtained without cyclized material have their properties recorded in Table III.

2,2-Dimethyl-2*H*-1-benzopyrans. The propargyl ethers were heated under N_2 at reflux temperature in *o*-dichlorobenzene (2 mL/g) or *N*,*N*-diethylaniline (5 mL/g) for 1–12 h. Removal of solvent left the crude 2*H*-1-benzopyrans (35–84%), which were purified as shown in Table IV for the new compounds. Compound **58**: NMR ($CDCl_3$) δ 1.40 [s, 6 H, $C(Me)_2$], 6.24 (d, 10, H-3), 5.61 (d, 10, H-4), 6.67 (d, 8, H-8), 6.93 (d, 3, H-5), 7.04 (q, 8, 3, H-7).

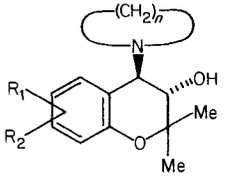
Thermal Cyclization of 3-Methyl-3-(3-nitrophenoxy)-but-1-yne (49) and 3-(3-Cyanophenoxy)-3-methylbut-1-yne (51). Compound **19** (13.20 g) was heated under N_2 in *N*,*N*-diethylaniline (65 mL) for 8 h. The resulting mixture (9.97 g) after solvent removal was shown to contain two components, the major one constituting 78% of the mixture by GLC examination. Repeated fractional distillation gave 2.60 g of compound **54** and, after an additional purification step on an alumina column, 0.71 g of compound **55**. The remaining fractions were mixutres of **54** and **55**. See Table IV. Compound **54**: NMR ($CDCl_3$) δ 1.43 [s, 6 H, $C(Me)_2$], 5.78 (d, 10, H-3), 6.75–7.51 (m, 3 aromatic and H-4). Compound **55**: NMR ($CDCl_3$) δ 1.45 [s, 6 H, $C(Me)_2$], 5.77 (d, 10, H-3), 6.36 (d, 10, H-4), 7.00 (d, 8, H-7), 7.48–8.81 (m, H-5 and H-6).

Similar treatment of **51** (25.70 g) gave 19.67 g of a two-component mixture, which was subjected to repeated fractional distillation, yielding 8.69 g of **56** and 1.34 g of substantially pure 7-cyano isomer, which was used directly for conversion to the bromohydrin **68**. The remaining fractions were mixtures of both isomers. See Table IV.

2,2-Dimethyl-7-nitro-2*H*-1-benzopyran (55). To a stirred solution of 6-(acetylamino)-2,2-dimethyl-2*H*-1-benzopyran[6] (8.48 g, 0.04 mol) in glacial HOAc (40 mL) at 0 °C was added dropwise a solution of fuming HNO_3 (4.8 mL, 0.05 mol) in glacial HOAc. After stirring for an additional 45 min without cooling, the solution was poured onto ice, and the precipitate was collected (8.40 g, 82%). Recrystallization of a small portion gave **60** as yellow needles (see Table IV).

The crude nitrated material (8.10 g, 0.03 mol) dissolved in EtOH (90 mL) and 5 N HCl (90 mL) was refluxed for 2.5 h. The red solution was cooled and poured into H_2O, and 6.61 g (97%) of

Table II. *trans*-3,4-Dihydro-2,2-dimethyl-4-(1-piperidinyl)-2*H*-1-benzopyran-3-ol and *trans*-3,4-Dihydro-2,2-dimethyl-4-(1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol Salts



compd	R_1	R_2	n	yield, %	mp, °C	formula	anal.[a]	dose,[a] mg/kg po	max fall in BP,[a] mmHg (mean ± SEM)	no. of rats
22	H	H	4	24	195–197	$C_{15}H_{21}NO_2 \cdot HCl$	C, H, N, Cl	30	10 ± 6	6
								100	46 ± 17	3
23	5-NO_2	H	5	61	188–194	$C_{16}H_{22}N_2O_4 \cdot HCl$	C, H, N, Cl	100	12 ± 9	3
24	7-NO_2	H	5	55	187–192	$C_{16}H_{22}N_2O_4 \cdot HCl$	C, H, N	3	18 ± 13	3
								10	48 ± 8	3
								100	79 ± 13	3
25	7-NO_2	H	4	20	208–209	$C_{15}H_{20}N_2O_4 \cdot MeSO_3H$	C, H, N, S	1	44 ± 9	6
								3	90 ± 11	6
								10	99 ± 4	6
26	5-CN	H	5	68	206–208	$C_{17}H_{22}N_2O_2 \cdot HCl$	C, H, N	10	13 ± 4	6
								100	33 ± 5	3
27	6-CN	H	5	77	253–257	$C_{17}H_{22}N_2O_2 \cdot HCl$	C, H, N, Cl	0.3	29 ± 6	6
								1	35 ± 7	6
								3	88 ± 8	6
								10	107 ± 3	4
28	6-CN	H	4	45	201–203	$C_{16}H_{20}N_2O_2 \cdot HCl$	C, H, N, Cl	0.3	15 ± 4	6
								1	43 ± 7	5
								3	117 ± 2	6
29	7-CN	H	5	65	224–229	$C_{17}H_{22}N_2O_2 \cdot HCl$	C, H, N, Cl	30	7 ± 3	3
								100	33 ± 16	3
30	8-CN	H	5	65	242–245	$C_{17}H_{22}N_2O_2 \cdot HCl$	C, H, N, Cl	10	5 ± 16	3
								100	33 ± 16	3
31	6-Cl	H	5	31	229–331	$C_{16}H_{22}ClNO_2 \cdot HCl \cdot 0.5H_2O$	C, H, N	30	7 ± 2	3
								100	69 ± 5	2
32	6-Me	H	5	52	201–219.5	$C_{17}H_{25}NO_2 \cdot HCl \cdot EtOH$	C, H, N, Cl	10	34 ± 24	3
								30	44 ± 11	3
								100	43 ± 5	3
33	6-Me	H	4	32	163–164	$C_{16}H_{23}NO_2 \cdot HCl \cdot H_2O$	C, H, N, Cl	100	9 ± 5	3
34	6-OMe	H	4	36	210–211	$C_{16}H_{23}NO_3 \cdot HCl$	C, H, N, Cl	30	29 ± 6	3
								100	17 ± 10	3
35	6-F	H	5	66	214–216	$C_{16}H_{22}FNO_2 \cdot HCl$	C, H, N, Cl	10	16 ± 3	3
								100	26 ± 1	3
36	6-COOMe	H	4	49	138–140	$C_{17}H_{23}NO_4 \cdot MeSO_3H$	C, H, N, S	3	14 ± 5	6
								10	58 ± 5	6
								30	65 ± 6	6
37	6-COMe	H	5	79	234–236	$C_{18}H_{25}NO_3 \cdot HCl$	C, H, N, Cl	3	12 ± 8	6
								10	51 ± 7	6
								30	65 ± 15	6
								100	127 ± 3	5
38	6-COMe	H	4	67	209–212	$C_{17}H_{23}NO_3 \cdot HCl$	C, H, N, Cl	3	39 ± 6	6
								10	53 ± 13	6
								30	66 ± 13	5
								100	78 ± 10	6

39	6-CH(OH)Me	H	5	89	179–181	$C_{18}H_{27}NO_3 \cdot HCl$	C, H, N	10	20 ± 5	3
								30	115 ± 11	3
40	6-C(NOH)Me	H	5	32	208.5–210	$C_{18}H_{26}N_2O_3 \cdot MeSO_3H$	C, H, N, S	10	17 ± 4	3
								30	80 ± 19	3
								100	74 ± 5	3
41	6-$CONH_2$	H	5	46	229–230	$C_{17}H_{24}N_2O_3 \cdot MeSO_3H$	C, H, N	10	9 ± 4	6
								100	30 ± 6	6
42	6-$CONH_2$	H	4	45	168–170	$C_{16}H_{22}N_2O_3 \cdot MeSO_3H$	C, H, N, S	100	21 ± 8	6
43	6-NHCOMe	H	5	58	171–173	$C_{18}H_{26}N_2O_3 \cdot MeSO_3H \cdot 0.5H_2O$	C, H, N, S	10	6 ± 8	6
								100	14 ± 6	3
44	7-NO_2	8-Me	5	62	225–228	$C_{17}H_{24}N_2O_4 \cdot MeSO_3H$	C, H, N, S	100	39 ± 2	3
45		5,6-benzo	5	26	183–187	$C_{20}H_{25}NO_2 \cdot HCl$	C, H, N, Cl	100	4 ± 4	3
46		7,8-benzo	4	24	>340	$C_{19}H_{23}NO_2 \cdot C_4H_6O_6 \cdot 2H_2O$	C, N; H[b]	100	4 ± 5	3
47	6-COOH	H	4	13	228–232[c]	$C_{16}H_{21}NO_4 \cdot 3H_2O$	C, H, N	10	2 ± 5	6
48	6-NH_2	H	4	74	198–225	$C_{15}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$	C, H, Cl; N[d]	100	6 ± 8	6

[a] See footnotes a–c in Table I. [b] H: calcd, 6.9; found, 6.4. [c] Transition at 120–125 °C. [d] N: calcd, 7.9; found, 7.3.

Table III. Novel 3-Methyl-3-phenoxybut-1-ynes

compd	R_1 (R_2 = H)	bp, °C (mmHg)	formula	anal.[a]
49	*m*-NO_2	96–106 (0.2)	$C_{11}H_{11}NO_3$	C, H, N
50	*o*-CN	108–110 (0.1)	$C_{12}H_{11}NO$	H, N; C[b]
51	*m*-CN	97–98 (0.2)	$C_{12}H_{11}NO$	H, N; C[c]
52	*o*-OMe	80–110 (0.35–0.45)	$C_{12}H_{14}O_2$	C, H
53	*p*-Cl	50–53 (0.05)	$C_{11}H_{11}OCl$	C, H, Cl

[a] See footnote *a* in Table I. [b] C: calcd, 77.8; found, 78.4. [c] C: calcd, 77.8; found, 77.2.

red crystals was collected. Recrystallization of a small portion gave **61** as red needles (see Table IV).

The crude crystalline nitroamine **61** (3.68 g, 0.017 mol) was dissolved in concentrated H_2SO_4 (30 mL) and H_2O (75 mL) with warming, then cooled to O °C, and treated dropwise with stirring with a solution of $NaNO_2$ (1.27 g, 0.018 mol) and H_2O (5 mL). The solution was stirred for an additional 1 h, and then addition of 50% aqueous H_3PO_2 (85 mL) was followed by storage in a refrigerator for 5 days, by which time gas evolution had ceased. Extraction via EtOAc gave 2.95 g of a brown gum, which on recrystallization gave **55** as yellow needles (2.46 g, 72%), identical with the minor component obtained from the thermal cyclization of **49** (see Table IV).

***trans*-3-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols.** Freshly recrystallized NBS (0.105 mol) was added in one portion to a vigorously stirred solution of the benzopyrans (0.1 mol) in Me_2SO (40 mL) and H_2O (0.1 mol). After the exothermic reaction, stirring was continued for an additional 0.5 h, followed by pouring into H_2O and extraction with EtOAc. The organic phase was washed with H_2O, dried, and evaporated, leaving the crude bromohydrins (72–98%). Methods of purification and properties of the new compounds are recorded in Table V. Compound **70**: NMR ($CDCl_3$) δ 1.31 [s, 3 H, $C(Me)_2$], 1.51 [s, 3 H, $C(Me)_2$], 2.23 (s, 3 H, Ph*Me*), 3.93 (d, 9, H-3), 4.68 (d, 9, H-4), 6.50 (d, 8, H-8), 6.93 (q, 8, 3, H-7), 7.11 (d, 3, H-5).

3,4-Epoxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans. The bromobenzopyranols (3.2–3.7 mmol) were stirred at room temperature with KOH pellets (0.018 mol) in Et_2O (50–100 mL/g of KOH) for 1–4 days. Filtration and evaporation gave the crude epoxides (72–98%). For bromohydrins **66–69** the compounds (5.4 mmol) were stirred with NaOH (0.025 mol) in dioxane (80 mL/g of NaOH) and H_2O (10 mL/g of NaOH) for 3 h. Dilution with H_2O and extraction via EtOAc gave the crude epoxides (75–95%). Purification and properties of the new epoxides are recorded in Table VI. Compound **82**: NMR ($CDCl_3$) δ 1.19 [s, 3 H, $C(Me)_2$], 1.49 [s, 3 H, $C(Me)_2$], 3.26 (d, 4, H-3), 3.66 (d, 4, H-4), 3.72 (s, 3 H, OMe), 6.56–6.82 (m, 3 H, aromatic).

***trans*-4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol Salts.** The epoxides (0.10 mol) and appropriate amines (0.11 mol) were refluxed in EtOH (250 mL) for 18–48 h. Cooling and evaporating the solvent gave the crude amino alcohols, which were purified by acid–base treatment. The salts were prepared by dissolving the bases in EtOH and dry Et_2O, followed by addition of an equivalent of the acid. The properties of the amino alcohol salts **1–38** and **43–46** and their yields based on the epoxide are presented in Tables I and II. Compound **28**: NMR ($CDCl_3$) δ 1.19 [s, 3 H, $C(Me)_2$], 1.73 [s, 3H, $C(Me)_2$], 2.22 (m, 4 H, NCH_2CH_2), 3.13 (m, 2 H, NCH_2), 3.97 (m, 2 H, NCH_2) 4.20 (d, 8, H-3), 4.86 (d, 8, H-4), 5.58 (m, exchangeable), 6.87 (d, 8, H-8), 7.47 (q, 8, 2, H-7), 8.72 (d, 2, H-5); mass spectrum, *m/z* 272 (M^+ – HCl, 2), 200 (100).

1-[*trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1-piperidinyl)-2*H*-1-benzopyran-6-yl]ethanol Hydrochloride (39). To a stirred solution of the free base of compound **37** (1.00 g, 3.3 mmol) in EtOH (10 mL) was added $NaBH_4$ (100 mg, 2.6 mmol) during 5 min. The solution was stirred for 1 h, H_2O (100 mL) was added, and extraction via Et_2O and treatment with anhydrous HCl in Et_2O gave **39** (1.00 g, see Table II).

1-[*trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1-piperidinyl)-2*H*-1-benzopyran-6-yl]ethanone Oxime Methanesulfonate (40). The free base of compound **37** (3.41 g, 0.011 mol), $HONH_2 \cdot HCl$ (780 mg, 0.011 mol), NaOH (450 mg, 0.011 mol), and MeOH (50 mL) were heated under reflux for 2 days.

Table IV. Novel 2,2-Dimethyl-2*H*-1-benzopyrans

compd	R_1, R_2	mp or bp, °C (mmHg)	formula	anal.[a]
54	5-NO_2	77–80 (0.5)	$C_{11}H_{11}NO_3$	C, H; N[b]
55	7-NO_2	83–85[c]	$C_{11}H_{11}NO_3$	C, H, N
56	5-CN	77–80 (0.5)	$C_{12}H_{11}NO$	C, H, N
57	8-CN	108–110 (0.6)	$C_{12}H_{11}NO$	C, H, N
58	6-Cl	49–50 (0.15)	$C_{11}H_{11}ClO$	H, Cl; C[d]
59	6-COOMe[e]	114–120 (0.15)	$C_{13}H_{14}O_3$	C, H
60	6-NHCOMe, 7-NO_2	127–128[f]	$C_{13}H_{14}N_2O_4$	C, H, N
61	6-NH_2, 7-NO_2	137–138[f]	$C_{11}H_{12}N_2O_3$	C, H, N
62	7-NO_2, 8-Me	75–78[c]	$C_{12}H_{13}NO_3$	C, H, N

[a] See footnote *a* in Table I. [b] N: calcd, 6.8; found, 7.4. [c] Recrystallized from 60–80 °C petroleum ether. [d] C: calcd, 67.8; found, 68.5. [e] NMR spectrum reported by Shima, K.; Hisada, S.; Inagaki, I. *Yakugaku Zasshi* 1971 *91*, 1124. [f] Recrystallized from EtOH.

Table V. Novel *trans*-3-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols

compd	R_1 (R_2 = H)	mp, °C	solvent of recrystn[a] or method of purifcn	formula	anal.[b]
63	5-NO_2	127–133	P	$C_{11}H_{12}NO_4Br$	C, H, N, Br
64	6-NO_2	114–116	P	$C_{11}H_{12}NO_4Br$	C, H, N
65	7-NO_2	105–106	PLC	$C_{11}H_{12}NO_4Br$	C, H, N, Br
66	5-CN	123–124	P'	$C_{12}H_{12}NO_2Br$	C, H, N, Br
67	6-CN	128–128.5	P	$C_{12}H_{12}NO_2Br$	C, H, N, Br
68	7-CN	131–132	P'	$C_{12}H_{12}NO_2Br$	C, H, N, Br
69	8-CN	glass	PLC	$C_{12}H_{12}NO_2Br$	C, H, N
70	6-Me	89–90	P	$C_{12}H_{15}O_2Br$	C, H, Br
71	6-OMe	83–84.5	P	$C_{12}H_{15}O_3Br$	C, H, Br
72	6-F	111–111.5	P	$C_{11}H_{12}O_2BrF$	C, H, Br
73	6-COOMe	84–85	P	$C_{13}H_{15}O_4Br$	*c*
74	6-COMe	109–113	P-Et	$C_{13}H_{15}O_3Br$	C, H, Br
75	6-NHCOMe	172	P-Et	$C_{13}H_{16}NO_3Br$	C, H, N, Br

[a] P = 60–80 °C petroleum ether; P' = 80–100 °C petroleum ether; Et = EtOAc. [b] See footnote *a* in Table I. [c] Consistent analyses could not be obtained. Exact mass at *m/e* 314.01. Calcd for $C_{13}H_{15}O_4{}^{79}Br$: 314.26.

Table VI. Novel 3,4-Epoxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans

compd	R_1, R_2	mp, °C	solvent of recrystn[a] or method of purifcn	formula	anal.[b]
76	5-NO_2	glass	*c*	$C_{11}H_{11}NO_4$	C, H, N
77	6-NO_2	91–93	*c*	$C_{11}H_{11}NO_4$	C, H, N
78	7-NO_2	85–86	P	$C_{11}H_{11}NO_4$	C, H, N
79	5-CN	73–75	P'	$C_{12}H_{11}NO_2$	C, H, N
80	6-CN	glass	PLC	$C_{12}H_{11}NO_2$	C, H; N[d]
81	7-CN	131–132	P	$C_{12}H_{11}NO_2$	C, H, N
82	6-OMe	66–67.5	P	$C_{12}H_{14}O_3$	C, H
83	6-COOMe	51–52	P	$C_{13}H_{14}O_4$	C, H
84	6-COMe	75–76	P	$C_{13}H_{14}O_3$	C, H
85	6-NHCOMe	173–175	P-E	$C_{13}H_{15}NO_3$	C, H, N
86	7,8-benzo	121	P	$C_{15}H_{14}O_2$	H; C[e]

[a] See footnote *a* in Table V. [b] See footnote *a* in Table I. [c] No purification necessary. [d] N: calcd, 7.0; found, 6.5. [e] C: calcd, 79.6; found, 78.9.

Workup by addition of H_2O and extraction with Et_2O gave a crude solid. Column chromatography on silica gel with petroleum ether–EtOAc mixtures gave starting material (0.39 g) and the desired oxime (1.62 g), which was converted to **40** by treatment with $MeSO_3H$ in EtOH–anhydrous Et_2O. See Table II.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1-piperidinyl)-2*H*-1-benzopyran-6-carboxamide Methanesulfonate (41) and *trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1-pyrrolidinyl)-2*H*-1-benzopyran-6-carboxamide Methanesulfonate (42).** To a stirred solution of the free base of compound **27** (2.64 g, 0.009 mol) in *t*-BuOH (35 mL) was added powdered KOH (5 g, 0.09 mol), and the mixture was heated under reflux for 50 min. Cooling and diluting with NaCl solution (100 mL), extracting with EtOAc, and treating with $MeSO_3H$ in EtOH–anhydrous Et_2O gave **41** (1.70 g). Similar treatment of the free base of **28** yielded compound **42**. See Table II.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1-pyrrolidinyl)-2*H*-1-benzopyran-6-carboxylic Acid (47).** A solution of the free base of compound **36** (4.01 g, 0.013 mol) in concentrated NH_4OH (35 mL) and EtOH (25 mL) was warmed for 6 days. Dilution with H_2O and extraction with Et_2O gave a mixture of the free bases of **36** and **42** (2.12 g). Evaporation of the aqueous residue gave **47** (590 mg) as the trihydrate. See Table II.

***trans*-6-Amino-2,2-dimethyl-4-(1-pyrrolidinyl)-2*H*-1-benzopyran-3-ol Dihydrochloride (48).** To a stirred suspension of the free base of compound **13** (1.00 g, 3.4 mmol) in 5 N HCl (25 mL) was added electrolytic Fe (1.00 g, 0.18 mol) in portions. After 4 h, the clear solution was filtered, and extraction with EtOAc, after dilution with H_2O, gave a gum, which on treatment with anhydrous HCl in ether gave **48** (900 mg) as the monohydrate. See Table II.

Pharmacological Testing. DOCA/Saline Hypertensive Rats. Hypertension was induced by subcutaneous implantation of 50 mg of deoxycorticosterone acetate (DOCA) into male Sprague-Dawley rats weighing 60–80 g, together with unilateral

nephrectomy and replacement of the drinking water with 1% w/v, NaCl solution for the first 5 weeks after nephrectomy. The rats were left at least 2 months after the operative procedure, by which time their body weights were between 300 and 450 g and their blood pressure had usually attained a stable level. A minimum value of systolic blood pressure of 160 mmHg (1 mmHg ≈ 133 Pa) was taken for selection of animals as hypertensive. Systolic blood pressure was recorded by the tail-cuff method using a W + W B.P. recorder, Model No. 8002. For all measurements of blood pressure, the rats were held in restraining cages in a heated environment (33.5 ± 0.5 °C), and each determination was the mean of at least six recordings.

All compounds were administered orally (by an oral dosing needle placed in the esophagus) as a solution or suspension in 1%, w/v, methylcellulose solution. Doses are expressed as free base.

Rat Isolated Portal Vein. Male Sprague-Dawley rats (250–350 g) were killed by cervical dislocation. Portal veins were set up under 1-g tension in a 10-mL organ bath containing Krebs-Henseleit solution of the following composition (mM): NaCl, 118; $NaHCO_3$, 25; glucose, 5; KH_2PO_4, 1.18; KCl, 4.69; $MgSO_4$, 0.59; $CaCl_2 \cdot H_2O$, 1.87. The tissue was aerated with a 95% oxygen and 5% carbon dioxide mixture. Isometric tension was recorded with a Devices strain gauge and recorder. Each preparation was allowed 1 h to equilibrate before the addition of drug. The percentage inhibition (mean ± SEM; six tissues for each drug) of the amplitude of the spontaneous contractions in each tissue was determined after 15-min contact time with the drug.

Registry No. 1, 58740-91-3; 1·HCl, 58740-62-8; 2, 86823-96-3; 2·HCl, 86823-97-4; 3, 86823-98-5; 3·HCl, 58740-63-9; 4, 86823-99-6; 4·HCl, 58740-64-0; 5, 86824-00-2; 5·HCl, 58740-65-1; 6, 86824-01-3; 6·$MeSO_3H$, 86834-45-9; 7, 86824-02-4; 7·$MeSO_3H$, 86824-03-5; 8, 86824-04-6; 8·HCl, 58740-67-3; 9, 86824-05-7; 9·HCl, 58740-66-2; 10, 86824-06-8; 10·HCl, 86824-07-9; 11, 66343-26-8; 11·HCl, 66343-25-7; 12, 86824-08-0; 12·2HCl, 86824-09-1; 13, 86824-10-4; 13·$MeSO_3H$, 86824-11-5; 14, 64169-71-7; 14·$MeSO_3H$, 86824-12-6; 15, 86824-13-7; 15·HCl, 58740-73-1; 16, 86824-14-8; 16·HCl, 58740-74-2; 17, 86824-15-9; 17·$MeSO_3H$, 86824-16-0; 18, 86824-17-1; 18·HCl, 58740-76-4; 19, 86824-18-2; 19·HCl, 58740-72-0; 20, 86824-19-3; 20·HCl, 58740-70-8; 21, 86824-20-6; 21·HCl, 86824-21-7; 22, 86824-22-8; 22·HCl, 86824-23-9; 23, 86824-24-0; 23·HCl, 86824-25-1; 24, 72592-00-8; 24·HCl, 86824-26-2; 25, 86824-27-3; 25·$MeSO_3H$, 86824-28-4; 26, 86824-29-5; 26·HCl, 86824-30-8; 27, 86824-31-9; 27·HCl, 65018-83-9; 28, 86824-32-0; 28·HCl, 86824-33-1; 29, 86824-34-2; 29·HCl, 86824-35-3; 30, 86824-36-4; 30·HCl, 86824-37-5; 31, 86824-38-6; 31·HCl, 86824-39-7; 32, 86824-40-0; 32·HCl, 86824-41-1; 33, 86824-42-2; 33·HCl, 86824-43-3; 34, 86824-44-4; 34·HCl, 86824-45-5; 35, 86824-46-6; 35·HCl, 86824-47-7; 36, 65018-79-3; 36·$MeSO_3H$, 65018-80-6; 37, 86824-48-8; 37·HCl, 65018-71-5; 38, 86824-49-9; 38·HCl, 86824-50-2; 39, 86824-51-3; 39·HCl, 65018-77-1; 40, 65018-73-7; 40·$MeSO_3H$, 65018-74-8; 41, 65018-84-0; 41·$MeSO_3H$, 65018-85-1; 42, 86824-52-4; 42·$MeSO_3H$, 86824-53-5; 43, 86824-54-6; 43·$MeSO_3H$, 86824-55-7; 44, 86824-56-8; 44·$MeSO_3H$, 86824-57-9; 45, 86824-58-0; 45·HCl, 86824-59-1; 46, 58747-00-5; 46·$C_4H_6O_6$, 58747-01-6; 47, 86824-60-4; 48, 86824-61-5; 48·2HCl, 86824-62-6; 49, 86824-63-7; 50, 86824-64-8; 51, 86824-65-9; 52, 86824-66-0; 53, 86824-67-1; 54, 82305-06-4; 55, 64169-76-2; 56, 86824-68-2; 57, 86824-69-3; 58, 80055-54-5; 59, 34818-57-0; 60, 64169-74-0; 61, 64169-75-1; 62, 86824-70-6; 63, 86824-71-7; 64, 58740-89-9; 65, 64169-77-3; 66, 86824-72-8; 67, 65018-89-5; 68, 86824-73-9; 69, 86824-74-0; 70, 86824-75-1; 71, 86824-76-2; 72, 86824-77-3; 73, 65018-81-7; 74, 65018-69-1; 75, 58740-92-4; 76, 86824-78-4; 77, 58740-90-2; 78, 64169-78-4; 79, 86824-79-5; 80, 65018-90-8; 81, 86824-80-8; 82, 13229-61-3; 83, 65018-82-8; 84, 65018-70-4; 85, 58740-93-5; 86, 58740-86-6; *m*-nitrophenol, 554-84-7; *o*-cyanophenol, 611-20-1; *m*-cyanophenol, 873-62-1; *o*-methoxyphenol, 90-05-1; *p*-chlorophenol, 106-48-9; 3-chloro-3-methylbutyne, 1111-97-3; 7-cyano-2,2-dimethyl-2*H*-1-benzopyran, 86824-81-9; 6-(acetylamino)-2,2-dimethyl-2*H*-1-benzopyran, 19849-34-4.

2-Benzazepines. 5.[1,2] Synthesis of Pyrimido[5,4-*d*][2]benzazepines and Their Evaluation as Anxiolytic Agents

Eugene J. Trybulski,*[†] Louis E. Benjamin, Sr.,[†] James V. Earley,[†] R. Ian Fryer,[†] Norman W. Gilman,[†] Earl Reeder,[†] Armin Walser,[†] Arnold B. Davidson,[‡] W. Dale Horst,[‡] Jerry Sepinwall,[‡] Robert A. O'Brien,[‡] and Wallace Dairman[§]

Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received February 17, 1983*

A series of 5*H*-pyrimido[5,4-*d*][2]benzazepines has been synthesized, starting from the corresponding 2-benzazepin-5-ones, and evaluated as potential anxiolytic agents. Selected compounds from this series show a pharmacological profile of action different than that of diazepam. They are more potent than diazepam in the anti-pentylenetetrazole test and in the [^{3}H]diazepam binding assay, yet show less activity in the inclined screen test. A pharmacological data profile is given for 9-chloro-7-(2-chlorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine (**7c**). The structure–activity relationships of these potential anxiolytic agents are discussed.

Since the discovery of chlordiazepoxide and diazepam,[3] the 1,4-benzodiazepines have been a fruitful source of research activity for both the medicinal chemist and the pharmacologist.[4] In the search for new anxiolytic agents, the 1,4-benzodiazepine structure has been modified in a variety of ways.[5] As part of a program directed toward the discovery of novel anxiolytic agents, the synthesis and pharmacological evaluation of 2-benzazepine derivatives were a logical extension of the work in the 1,4-benzodiazepine area. The preparation and pharmacological profile of thiazolo-[6] and triazolo-2-benzazepine[2] derivatives, in which the heteroaromatic ring was annulated to the corresponding 4,5-positions of the 2-benzazepine ring system, have recently been reported. This report describes the synthesis of pyrimido[5,4-*d*][2]benzazepines and the pharmacological evaluation of these compounds as anxiolytic agents.

Chemistry. The preparation of the pyrimido[5,4-*d*]-[2]benzazepine ring system I was readily accomplished

[†] Chemical Research Department.
[‡] Pharmacology Department.
[§] Toxicology Department.

(1) Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.
(2) For the previous paper in the series, see Trybulski, E. J.; Benjamin, L.; Vitone, S.; Walser, A.; Fryer, R. I. *J. Med. Chem.* **1983**, *26*, 367.
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