introduction of the  $7\alpha$ -methoxy group may be attributed to the increased ability of the  $\beta$ -lactam ring to acylate RO<sup>-</sup> located on the  $\alpha$ -side.<sup>30</sup>

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  $(1/C_{\rm s})$  for antibacterial activity was observed. Hydrolysis rates (log k) and the  $\beta$ -lactam carbonyl frequencies remained almost constant.

Substitution of a methylene group for the sulfur atom in cephalosporins (compare 9 to 8) greatly diminished log  $(1/C_{\rm b})$  (-0.6), whereas log k significantly increased (0.56). The increase in the alkaline hydrolysis rate for  $7\alpha$ hydro-1-carbacephem at pH 10 and 35 °C was larger<sup>24</sup> 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  $7\alpha$ -hydro-1-carbacephem (24) against Gram-negative bacteria is of a similar level



to that for 22 and 23,<sup>22</sup> in which the side chain probably contributes to efficient complex formation with enzymes.

Introduction of the  $7\alpha$ -methyl group resulted in substantial decreases in log k and log  $(1/C_b)$  (-0.21 and -1.48, respectively). Steric hindrance against RO<sup>-</sup> caused by the bulky methyl group<sup>31</sup> and conformational changes in the side chain<sup>32</sup> might be the reason for the decreases, respectively. The indifferently high frequency of the  $\beta$ -lactam carbonyl probably indicates little contribution of the inductive effect of the  $7\alpha$ -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  $\beta$ -lactam ring. Second, introduction of the  $7\alpha$ -methoxy group results in some enhancement of the antibacterial activity mainly caused by the increased reactivity of the  $\beta$ -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  $7\beta$ -[[(4-hydroxyphenyl)malonyl]amino]-7 $\alpha$ -methoxycephalosporin lowers the antibacterial activity. Fourth, introduction of the  $7\alpha$ -methyl group greatly diminishes the antibacterial activity.

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**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), 86940-96-7; 4-hydroxyphenylacetic acid, 156-38-7; diphenylmethyl (4-hydroxyphenylacetate, 78984-21-1; diphenylmethyl [4-[(benzyloxycarbonyl)oxy]phenyl]acetate, 86862-92-2.

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

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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 2H-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

<sup>(30)</sup> 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.

<sup>(31)</sup> The inductive effect of the 6α-methyl group on the decrease in the hydrolysis rate of methyl 6β-[(phenylacetyl)amino]-6αpenicillinate 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.

<sup>(32)</sup> Virudachalam, R.; Rao, V. S. R. Int. J. Pept. Protein Res. 1977, 10, 51.

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 vaso-dilating properties,<sup>1</sup> 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<sup>2</sup> the regioselective formation of 7-substituted benzopyrans, while others describe<sup>3</sup> 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<sup>4</sup> 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,<sup>5</sup> 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<sup>1</sup> on compounds 13 and 28 have shown a direct vasodilator action. For example, compound 28,  $9.7 \times 10^{-6}$  M, inhibits spontaneous activity in rat isolated portal vein by  $32 \pm 1\%$ , and a higher concentration ( $1.5 \times 10^{-3}$  M) of hydralazine produces a comparable response ( $40 \pm 4\%$ ). In conscious hypertensive rats, compounds 13 and 28 possess antihypertensive ac-

<sup>(1)</sup> Hamilton, T. C.; Poyser, R. H., unpublished results.

Hlubucek, J.; Ritchie, E.; Taylor, W. C. Aust. J. Chem. 1971, 24, 2347, and references therein.

<sup>(3)</sup> Anderson, W. K.; LaVoie, E. J.; Whitkop, P. G. J. Org. Chem. 1974, 39, 881.

<sup>(4)</sup> Brancaccio, G.; Lettieri, G.; Viterbo, R. J. Heterocycl. Chem. 1973, 10, 623.

<sup>(5)</sup> 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.

<sup>(6)</sup> Miller, J. A.; Wood, H. C. S. British Patent 1 121 307, 1968.

	no. of rats	9	9 9	99	ອດຕ	<b>ლ დ</b> დ	ည္ကေရး	നന		നന പ	о ю и	0 U U	00 - J C	നനന	ით	ũ	co		0 W M
	max fall in BP, <sup>c</sup> mmHg <sup>c</sup> (mean ± SEM)	<b>36 ± 4</b>	$69 \pm 14$ $23 \pm 1$	45 ± 5 21 ± 8	$43 \pm 10$ $29 \pm 9$ $34 \pm 7$	$54 \pm 3$ $7 \pm 3$ $31 \pm 8$	$95 \pm 9$ 13 \pm 6 67 - 7	∠/ ± / 28 ± 2 3 ± 14	41 ± 11 85 ± 13	$81 \pm 12$ $23 \pm 6$ $52 \pm 7$	79 ± 3 08 ± 6	$28 \pm 10$ $23 \pm 13$ $73 \pm 13$	$105 \pm 15$ $17 \pm 2$	$egin{array}{c} 96 \pm 8 \\ 34 \pm 10 \\ 53 \pm 23 \end{array}$	$82 \pm 15$	20 ± 10	<b>26</b> ± 9	238 ± 4 238 ± 4 57 ± 4 7 ± 7	70 ± 6 10 ± 11
	dose, <sup>b</sup> mg/kg po	100	300 30	100 30	100 100 30	100 100 10	100	100 0.3	m ç	100	- s 1	ec	10 10	100 3 10	30	10	30	10 10 30	100
	anal. <sup>a</sup>	C, H, N, CI	C, H, N, CI	C, H, N, CI	C, H, N, CI C, H, N, CI	C, H, N C, H, N, S	C, H, N, CI C, H N, CI	C H N G C H N G		C, H, N, Cl C, H, N, S		C, H, N, S	C, H, N, CI	C, H, N		C, H, N, S	С, Н, N, СІ	C, H, N, Cl C, H, N, Cl	C, H, N, CI
O <sub>2</sub> N × Me	formula	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	$C_{11}H_{14}N_2O_4\cdot HCI$	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	C <sub>13</sub> H <sub>18</sub> N, O <sub>4</sub> ·HCl C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	C <sub>1s</sub> H <sub>22</sub> N <sub>2</sub> O4·MeSO <sub>3</sub> H C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O4·MeSO <sub>3</sub> H	C <sub>15</sub> H <sub>20</sub> N, O4 HCl C., H2 N, O. HCl	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> ·HCl C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>5</sub> ·HCl		C <sub>1</sub> ,H <sub>2</sub> ,N <sub>3</sub> O <sub>4</sub> ·2HCl C,,H <sub>3</sub> ,N,O <sub>4</sub> ·MeSO <sub>4</sub> H		C <sub>16</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> ·MeSO <sub>3</sub> H	C <sub>17</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	$C_{18}H_{26}N_2O_4\cdot HCl$		C <sub>19</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub> ·MeSO <sub>3</sub> H	C <sub>17</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	C <sub>17</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> ·HCl C <sub>15</sub> H <sub>26</sub> N <sub>2</sub> O <sub>5</sub> ·HCl	$C_{21}H_{25}N_{3}O_{4}\cdot HCI\cdot 0.5H_{2}O$
	mp, °C	244-247	287-290	296-299	260-261 198-204	229-233 209-211	256-259 264-267	264-267 243-247		179-182 214-215		226-228	215 - 220	214-220		223-226	214-219	226-230 250-252	210-213
	yield, %	84	13	83	30 63	39 56	23 89	68 10		49 36		83	67	46		18	15	68 43	12
	Х	NHCHMe <sub>2</sub>	NH2	NHMe	$NMe_2$ $NEt_2$	NHCMe <sub>3</sub> NH-c-Pr	NHCH,-e-Pr NH(CH,),OH	NH(CH <sub>2</sub> ) <sub>3</sub> OH NH(CH <sub>2</sub> ) <sub>3</sub> Cl		NH(CH2)2-c-NC4Hs c-NC4Hs		c-NC <sub>5</sub> H <sub>10</sub>	c-NC <sub>6</sub> H <sub>12</sub>	c-NC <sub>7</sub> H <sub>14</sub>			ž (	Me c-N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> CHMe c-N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O	c-N(CH <sub>2</sub> CH <sub>2</sub> ),N-Ph
	compd	1	2	က	4 Ю	9 9	<b>∞</b> ೧	10 11		12 13		14	15	16		17	18	19 20	21

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

## Substituted 2H-1-Benzopyran-3-ols

hydralazine	+- <b>1</b>	$32 \pm 8$	9	
	ŝ	$65 \pm 12$	9	
	10	$113 \pm 10$	5	
nifedipine	0.3	$20 \pm 6$	9	
	1	$33 \pm 2$	9	
	ŝ	$51 \pm 2$	9	
<sup><i>a</i></sup> Analyses for the elements indicated were within $\pm 0.4\%$ of the theoretical values. <sup><i>b</i></sup> Compounds were given	orally to DOCA/NaCl treated hype	ertensive rats; dos	ses are	1
tpressed as base. $^{c}$ Systolic blood pressure was measured indirectly at intervals from 1 to 6 h.		•		

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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<sub>2</sub>CO (500 mL) under N<sub>2</sub>. 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<sub>2</sub>, 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<sub>2</sub>O and 5 N NaOH, dried, and evaporated to give the crude ethers (30–85%).

Method C. The phenois (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-2H-1-benzopyrans during these reactions. The new ethers obtained without cyclized material have their properties recorded in Table III.

**2,2-Dimethyl-2H-1-benzopyrans.** The propargyl ethers were heated under N<sub>2</sub> 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 2H-1-benzopyrans (35–84%), which were purified as shown in Table IV for the new compounds. Compound 58: NMR (CDCl<sub>3</sub>)  $\delta$  1.40 [s, 6 H, C(Me)<sub>2</sub>], 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<sub>2</sub> 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<sub>3</sub>)  $\delta$  1.43 [s, 6 H, C(Me)<sub>2</sub>], 5.78 (d, 10, H-3), 6.75–7.51 (m, 3 aromatic and H-4). Compound 55: NMR (CDCl<sub>3</sub>)  $\delta$  1.45 [s, 6 H, C(Me)<sub>2</sub>], 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-2H-1-benzopyran** (55). To a stirred solution of 6-(acetylamino)-2,2-dimethyl-2H-1-benzopyran<sup>6</sup> (8.48 g, 0.04 mol) in glacial HOAc (40 mL) at 0 °C was added dropwise a solution of fuming HNO<sub>3</sub> (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<sub>2</sub>O, and 6.61 g (97%) of

	10. of rats	9	იიი იი	ოოდა	0000		994	о 10 0		നനം	იი იი	NON		က က ၊		• • • •	0 10 0 0 10 I	9
	max fall in BP, <sup>a</sup> mmHg r (mean ± SEM)	10 ± 6	46 ± 17 12 ± 9 18 ± 13	48 ± 8 79 ± 13 44 ± 9 00 ± 11	90 ± 11 99 ± 4 13 ± 4	33 ± 5 29 ± 6 27	35 ± 7 88 ± 8 107 ± 3	15 ± 4 43 ± 7	117 ± 2 7 ± 3	33 ± 10 5 ± 16	33 ± 16 7 ± 2 20	09 ± 5 34 ± 24 44 + 11	43 9 4 5 1 4 5 1 4 5 1 6 2 2 9 4 5 2 1 4 2 5 2 5 2 5 2 5 5 5 5 5 5 5 5 5 5 5 5	$17 \pm 10$ $16 \pm 3$	26±1 14±5 5×5	65 ± 6 65 ± 6 51 ± 7	$\begin{array}{c} 65 \pm 15 \\ 127 \pm 3 \\ 39 \pm 6 \\ 53 \pm 13 \\ 66 \pm 13 \\ 13 \\ 66 \pm 13 \\ 13 \end{array}$	$78 \pm 10$
	dose, <sup>a</sup> mg/kg po	30	100	$100\\100$	10 10	0.3 0.3	10 3 T	0.3	30 30	100	000000000000000000000000000000000000000	100 30	100 30 30	100	100 8 0	30 30 10 30	30 100 30 30 30	100
	anal. <sup>a</sup>	C, H, N, CI	C, H, N, Cl C, H, N	C, H, N, S	C, H, N	C, H, N, CI		C, H, N, CI	C, H, N, CI	C, H, N, CI	C, H, N	C, H, N, CI	C, H, N, Cl C, H, N, Cl	C, H, N, CI	C, H, N, S	C, H, N, CI	С, Н, N, СІ	
R <sub>2</sub> R <sub>2</sub> Me	formula	C <sub>15</sub> H <sub>21</sub> NO <sub>2</sub> ·HCl	C <sub>16</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> ·HCl C <sub>16</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	C <sub>1s</sub> H <sub>20</sub> N <sub>2</sub> O4·MeSO <sub>3</sub> H	$C_{17}H_{22}N_2O_2$ ·HCI	$C_{17}H_{22}N_2O_2\cdot HCI$		C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> ·HCl	$C_{17}H_{22}N_2O_2HCI$	$C_{17}H_{22}N_2O_3HCI$	C <sub>16</sub> H <sub>22</sub> CINO <sub>2</sub> ·HCI·0.5H <sub>2</sub> O	C17H25NO2.HCI-EtOH	C <sub>16</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl·H <sub>2</sub> O C <sub>16</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl	C <sub>16</sub> H <sub>22</sub> FNO <sub>2</sub> ·HCl	C <sub>17</sub> H <sub>23</sub> NO₄·MeSO₃H	C <sub>18</sub> H <sub>25</sub> NO <sub>3</sub> ·HCl	C <sub>17</sub> H <sub>23</sub> NO <sub>5</sub> HCI	
	mp, °C	195-197	188-194 187-192	208-209	206-208	253-257		201-203	224-229	242-245	229-331	201-219.5	163-164 210-211	214-216	138-140	234-236	209-212	
	yield, %	24	61 55	20	68	77		45	65	65	31	52	32 36	99	49	62	67	
	u	4	ດວ	4	л С	Ð		4	ß	5	ŋ	Ŋ	44	5	4	ъ	4	
	${f R}_2$	Н	н	Н	Η	Н		Η	Н	Н	Η	Н	Н	Н	Н	Н	Н	
	R	Н	5-NO <sub>2</sub> 7-NO <sub>2</sub>	7-NO2	5-CN	6-CN		6-CN	7-CN	8-CN	6-CI	6-Me	6-Me 6-OMe	6-F	6-COOMe	6-COMe	6-COMe	
	compd	22	23 24	25	26	27		58	29	30	31	32	33 34	35	36	37	38	

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

(CH<sub>2</sub>)

#### Substituted 2H-1-Benzopyran-3-ols

იი თ	<b>ന</b> (	თ	9	9	9	9	ო	ო	ო	ო	9	9	
115 ± 11 17 ± 4	80:± 19	$74 \pm 5$	$9 \pm 4$	$30 \pm 6$	$21 \pm 8$	6 ± 8	$14 \pm 6$	$39 \pm 2$	$4 \pm 4$	$4 \pm 5$	$2 \pm 5$	<b>6</b> ± 8	
10	30	100	10	100	100	10	100	100	100	100	10	100	
C, H, N, S			C, H, N		C, H, N, S	C, H, N, S	•	C, H, N, S	C, H, N, CI	$C, N, H^b$	C, H, N	C, H, CI; N <sup>d</sup>	ő.
C,,,H <sub>3</sub> ,N <sub>2</sub> O <sub>3</sub> .MeSO <sub>3</sub> H	2 2 2		C,,H,,N,O,·MeSO,H		C, H, N, O, MeSO, H	CHN.O.MeSO.H.0.5H,O	2 2 2 2	C,,H,,N,O,-MeSO,H	C.H.NO.HCI	CHNOC.H.O.2H.O	ĊĹĤĨNOĴ3Ĥ,Ŏ	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> ·2HCI·H <sub>2</sub> O	-125 °C. <sup>d</sup> N: calcd, 7.9; found, 7.5
208.5-210			229-230		168-170	171-173		225-228	183-187	> 340	228-232°	198-225	<sup>c</sup> Transition at 120-
32			46		45	58		62	26	24	13	74	ıd, 6.4.
ъ			5 S		4	ы		л,	ъ	4	4	4	6.9; four
Н			Н		Н	Н		8-Me			Н	Н	<sup>b</sup> H: calcd,
6-C(NOH)Me			6-CONH <sub>3</sub>	1	6-CONH <sub>2</sub>	6-NHCOMe		7-NO,	5.6-benze	7,8-benzo	6-COOH	6-NH <sub>2</sub>	tes a-c in Table I.
40			41		42	43		44	45	46	47	48	<sup>a</sup> See footno
	40 6-C(NOH)Me H 5 32 208.5-210 $C_{1,H_{x}}N_{1}O_{3}$ ·MeSO <sub>3</sub> H C, H, N, S 10 17 $\pm 4$ 3	40 6-C(NOH)Me H 5 32 208.5-210 C <sub>16</sub> H <sub>36</sub> N <sub>2</sub> O <sub>3</sub> ·MeSO <sub>3</sub> H C, H, N, S 10 17 ± 4 3 30 80± 19 3	40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{36}N_2O_3$ ·MeSO_3H C, H, N, S 10 $17 \pm 4$ 3 30 $80 \pm 19$ 3 30 $80 \pm 19$ 3 10 $74 \pm 5$ 3 10 $100$ $74 \pm 5$ 10 $100$ $7$ $10$ $10$ $10$ $10$ $10$ $10$ $10$ $10$	40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{26}N_2O_3\cdot MeSO_3H$ C, H, N, S 30 117 ± 4 3   40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{26}N_2O_3\cdot MeSO_3H$ C, H, N, S 10 177 ± 4 3   41 6-CONH <sub>3</sub> H 5 46 229-230 C, H, N, O, MeSO_3H C, H, N 100 74 ± 5 3	40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{26}N_{2}O_{3}\cdot MeSO_{3}H$ C, H, N, S 30 117 ± 4 3   41 6-CONH <sub>2</sub> H 5 46 229-230 $C_{17}H_{26}N_{2}O_{3}\cdot MeSO_{3}H$ C, H, N, S 10 171 ± 4 3   41 6-CONH <sub>2</sub> H 5 46 229-230 $C_{17}H_{26}N_{2}O_{3}\cdot MeSO_{3}H$ C, H, N 10 9 ± 4 6   00 30 ± 6 6 6 6 6 6 6 6	40 6-C(NOH)Me H 5 32 208.5-210 $C_{18}H_{26}N_{2}O_{3}$ .MeSO_{3}H C, H, N, S 10 117 ± 4 3   41 6-CONH_{2} H 5 46 229-230 $C_{17}H_{26}N_{2}O_{3}$ .MeSO_{3}H C, H, N, S 10 $177 \pm 4$ 3   41 6-CONH_{2} H 5 46 229-230 $C_{17}H_{26}N_{2}O_{3}$ .MeSO_{3}H C, H, N 100 $9 \pm 4$ 6   42 6-CONH_{2} H 4 45 168-170 C, H, N, O, MeSO_{4}H C, H, N, S 100 21 \pm 8 6	40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{36}N_{1}O_{3}\cdotMeSO_{3}H$ C, H, N, S 10 117 ± 4 3   41 6-CONH <sub>3</sub> H 5 46 229-230 $C_{17}H_{38}N_{2}O_{3}\cdotMeSO_{3}H$ C, H, N, S 10 17 ± 4 3   41 6-CONH <sub>3</sub> H 5 46 229-230 $C_{17}H_{38}N_{2}O_{3}\cdotMeSO_{3}H$ C, H, N 100 $74 \pm 5$ 3   42 6-CONH <sub>3</sub> H 4 45 168-170 $C_{6}H_{28}N_{3}O_{3}\cdotMeSO_{3}H$ C, H, N, S 100 30 \pm 6 6   43 6-NHCOMe H 5 58 171-173 $C_{6}H_{28}N_{3}O_{3}\cdotMeSO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{3}O_{5}\cdotM_{5}SO_{3}H_{5}O_{5}\cdotM_{5}SO_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}O_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{5}\cdotM_{$	40 $6-C(NOH)Me$ H 5 32 $208.5-210$ $C_{16}H_{36}N_2O_3 \cdot MeSO_3H$ $C, H, N, S$ $10^{0}$ $117 \pm 4$ $3^{0}$ $80 \pm 19$ $30^{0}$ $171 \pm 4$ $3^{0}$ $80 \pm 19$ $30^{0}$ $171 \pm 4$ $3^{0}$ $80 \pm 19$ $30^{0}$ $10^{0}$ $74 \pm 5$ $30^{0}$ $80 \pm 19$ $3^{0}$ $80 \pm 19$ $3^{0}$ $80^{0} \pm 19^{0}$ $3^{0}$ $80^{0} \pm 19^{0}$ $3^{0}$ $8^{0} \pm 19^{0}$ $3^{0}$ $8^{0} \pm 19^{0}$ $3^{0}$ $8^{0} \pm 19^{0}$ $3^{0}$ $8^{0} \pm 19^{0}$ $3^{0} \pm 6^{0}$ $4^{2}$ $6-CONH_{2}$ H $4^{4}$ $5^{5}$ $5^{8}$ $171-173$ $C_{16}H_{20}N_{2}O_{3}\cdot MeSO_{3}H \cdot 0.5H_{2}O$ $C, H, N, S$ $100^{0}$ $21 \pm 8^{0}$ $6^{0}$ $4^{2}$ $6-NNCOMe$ H $5^{0}$ $5^{6}$ $171-173$ $C_{16}H_{20}N_{2}O_{3}\cdot MeSO_{3}H \cdot 0.5H_{2}O$ $C, H, N, S$ $100^{0}$ $21 \pm 8^{0}$ $6^{0}$ $3^{0} \pm 6^{0}$ $3^{0} \pm 6^{0}$ $5^{0} + 10^{0} $	40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{36}N_{1}O_{3}\cdot\text{MeSO_{3}H}$ C, H, N, S 30 110 17±4 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±19 33 80±16 7 8 6 6 6 7 100 10 10 10 10 10 10 10 10 10 10 10 10	40 $6-C(NOH)Me$ H 5 32 $208.5-210$ $C_{16}H_{36}N_{1}O_{3}\cdot MeSO_{3}H$ $C, H, N, S$ $10^{3}$ $112^{3}\pm 11^{3}$ $30^{3}$ $80\pm 19^{3}$ $80\pm 19^{3}$ $80\pm 19^{3}$ $80\pm 19^{3}$ $80\pm 19^{3}$ $100^{3}$ $74\pm 5^{3}$ $10^{3}$ $74\pm 5^{3}$ $10^{3}$ $74\pm 5^{3}$ $10^{3}$ $74\pm 5^{3}$ $10^{3}$ $10^{3}$ $74\pm 5^{3}$ $10^{3}$ $10^{3}$ $74\pm 5^{3}$ $10^{3}$ $10^{3}$ $74\pm 5^{3}$ $10^{3}$ $1$	40 6-C(NOH)Me H 5 32 208.5-210 $C_{18}H_{38}N_{2}O_{3}\cdot\text{MeSO_{3}H}$ C, H, N, S 30 110 171±4 33   41 6-C0NH <sub>3</sub> H 5 46 229-230 $C_{17}H_{34}N_{3}O_{3}\cdot\text{MeSO_{3}H}$ C, H, N, S 100 74 ± 5 3   42 6-C0NH <sub>3</sub> H 5 46 229-230 $C_{17}H_{34}N_{3}O_{3}\cdot\text{MeSO_{3}H}$ C, H, N, S 100 9 ± 4 6   43 6-C0NH <sub>3</sub> H 5 58 171-173 $C_{16}H_{38}N_{3}O_{3}\cdot\text{MeSO_{3}H}$ C, H, N, S 100 21 ± 8 6   44 7-NO <sub>4</sub> B-Me 5 62 225-228 $C_{17}H_{38}N_{2}O_{4}\cdot\text{MeSO_{3}H}$ C, H, N, S 100 21 ± 8 6   45 7-NO <sub>4</sub> B-Me 5 62 225-228 $C_{17}H_{38}N_{2}O_{4}\cdot\text{MeSO_{3}H}$ C, H, N, S 100 21 ± 8 6   46 7.8^{1} 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.3 6.	40 6-C(NOH)Me H 5 32 208.5-210 $C_{16}H_{a}N_{2}O_{3}$ ·MeSO <sub>3</sub> H C, H, N, S $\frac{30}{100}$ $\frac{117 \pm 4}{17 \pm 4}$ 3 41 6-CONH <sub>3</sub> H 5 46 229-230 $C_{17}H_{a}N_{1}O_{3}$ ·MeSO <sub>3</sub> H C, H, N 100 $\frac{17}{10}$ $\frac{4}{10}$ $\frac{5}{10}$ 42 6-CONH <sub>3</sub> H $\frac{4}{10}$ $\frac{5}{10}$ $\frac{46}{171-173}$ $C_{16}H_{23}N_{2}O_{3}$ ·MeSO <sub>3</sub> H C, H, N S 100 $\frac{9}{14} \pm 6$ $\frac{6}{6}$ 43 6-NHCOMe H $\frac{4}{10}$ $\frac{4}{5}$ $\frac{5}{58}$ $\frac{171-173}{171-173}$ $C_{16}H_{23}N_{2}O_{3}$ ·MeSO <sub>3</sub> H $0.5H_{3}O$ C, H, N, S 100 $\frac{110}{10}$ $\frac{9}{14} \pm 6$ $\frac{6}{6}$ 44 $7$ -NO <sub>3</sub> $\frac{8}{10}$ ·MeSO <sub>3</sub> H $0.5H_{3}O$ C, H, N, S 100 $\frac{110}{10}$ $\frac{14}{2} \pm 6$ $\frac{14}{5}$ $\frac{5}{5}$ $\frac{6}{6}$ $\frac{123-228}{171-173}$ $C_{10}H_{23}N_{3}O_{3}$ ·MeSO <sub>3</sub> H $0.5H_{3}O$ C, H, N, S 100 $\frac{14}{2} \pm 6$ $\frac{14}{3}$ $\frac{7}{5}$ , $\frac{6}{6}$ ·MeSO <sub>3</sub> H $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{5}$ , $\frac{1}{6}$ ·MeSO <sub>3</sub> H $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{5}$ , $\frac{1}{6}$ ·MeSO <sub>3</sub> $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{7}$ , $\frac{1}{8}$ ·MeSO <sub>3</sub> $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{7}$ , $\frac{1}{8}$ ·MeSO <sub>3</sub> $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{7}$ , $\frac{1}{8}$ ·MeSO <sub>3</sub> $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{7}$ , $\frac{1}{8}$ ·MeSO <sub>3</sub> $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{10}$ $\frac{1}{14} \pm 6$ $\frac{3}{10}$ $\frac{1}{7}$ , $\frac{1}{8}$ ·MeSO <sub>3</sub> $\frac{1}{10}$ $\frac{1}$	40 6-C(NOH)Me H 5 32 208.5-210 $C_{18}H_{36}N_{1}O_{3}$ ·MeSO_{3}H C, H, N, S $\overset{30}{10}$ $\overset{1113 \pm 11}{110}$ $\overset{3}{3}$ 41 6-CONH <sub>4</sub> H 5 46 229-230 $C_{17}H_{36}N_{1}O_{3}$ ·MeSO_{3}H C, H, N 100 $\overset{30}{21} \pm \frac{4}{6}$ 6 42 6-CONH <sub>4</sub> H 4 45 168-170 $C_{16}H_{36}N_{1}O_{3}$ ·MeSO_{3}H 0.5H <sub>4</sub> O C, H, N, S 100 $\overset{9}{21} \pm \frac{6}{6}$ 6 43 6-NHCOMe H 5 68 171-173 $C_{16}H_{36}N_{1}O_{3}$ ·MeSO_{3}H 0.5H <sub>4</sub> O C, H, N, S 100 21 \pm 8 6 44 7-NO <sub>4</sub> $\overset{4}{5} = 5$ 62 225-228 $C_{17}H_{36}N_{1}O_{3}$ ·MeSO_{3}H 0.5H <sub>4</sub> O C, H, N, S 100 21 \pm 8 6 45 $\overset{4}{5} = \frac{7}{5}$ 62 225-228 $C_{17}H_{36}N_{1}O_{3}$ ·MeSO_{3}H 0.5H <sub>4</sub> O C, H, N, S 100 $\overset{114 \pm 6}{14} = \frac{3}{3}$ 46 $\overset{7}{7} (\overset{7}{3} \cdot 6 - COOH$ H 4 1 2 4 23 47 $\overset{7}{7} (\overset{7}{3} \cdot 10)$ $\overset{1100}{14} = \overset{3}{5} = 5$ 62 225-228 $C_{17}H_{36}N_{1}O_{3}$ ·MeSO_{3}H 0.5H <sub>4</sub> O C, H, N, S 100 $\overset{114 \pm 6}{14} = \frac{3}{3}$ 48 $\overset{6}{6} -COOH$ H 4 1 2 $\overset{7}{2} = 3240$ $\overset{7}{2} = 6$ $\overset{7}{6} = 3340$ $\overset{7}{6} = 6$ $\overset{7}{6} =$

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

compd	$\begin{array}{c} R_{1} \\ (R_{2} = H) \end{array}$	bp, °C (mmHg)	formula	anal. <sup>a</sup>
49	m-NO <sub>2</sub>	96-106 (0.2)	C <sub>11</sub> H <sub>11</sub> NO <sub>3</sub>	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 <sup>c</sup>
52	o-OMe	80-110 (0.35-0.45)	$C_{12}H_{14}O_2$	С, Н
53	<i>p-</i> Cl	50-53 (0.05)	$C_{11}H_{11}OCl$	C, H, Cl

<sup>a</sup> See footnote a in Table I. <sup>b</sup> C: calcd, 77.8; found, 78.4. <sup>c</sup> 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<sub>2</sub> (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-2H-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<sub>2</sub>SO (40 mL) and H<sub>2</sub>O (0.1 mol). After the exothermic reaction, stirring was continued for an additional 0.5 h, followed by pouring into H<sub>2</sub>O and extraction with EtOAc. The organic phase was washed with H<sub>2</sub>O, 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<sub>3</sub>)  $\delta$  1.31 [s, 3 H, C(Me)<sub>2</sub>], 1.51 [s, 3 H, C(Me)<sub>2</sub>], 2.23 (s, 3 H, PhMe), 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-Époxy-3,4-dihydro-2,2-dimethyl-2H-1-benzopyrans. The bromobenzopyranols (3.2-3.7 mmol) were stirred at room temperature with KOH pellets (0.018 mol) in Et<sub>2</sub>O (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<sub>2</sub>O (10 mL/g of NaOH) for 3 h. Dilution with H<sub>2</sub>O 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<sub>3</sub>)  $\delta$  1.19 [s, 3 H, C(Me)<sub>2</sub>], 1.49 [s, 3 H, C(Me)<sub>2</sub>], 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-2H-1-ben zopyran-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<sub>2</sub>O, 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<sub>3</sub>)  $\delta$  1.19 [s, 3 H, C(Me)<sub>2</sub>], 1.73 [s, 3H, C(Me)<sub>2</sub>], 2.22 (m, 4 H, NCH<sub>2</sub>CH<sub>2</sub>), 3.13 (m, 2 H, NCH<sub>2</sub>), 3.97 (m, 2 H, NCH<sub>2</sub>) 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<sup>+</sup> - HCl, 2), 200 (100).

1-[trans -3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1piperidinyl)-2H-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<sub>4</sub> (100 mg, 2.6 mmol) during 5 min. The solution was stirred for 1 h, H<sub>2</sub>O (100 mL) was added, and extraction via Et<sub>2</sub>O and treatment with anhydrous HCl in Et<sub>2</sub>O gave 39 (1.00 g, see Table II).

1-[trans-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1piperidinyl)-2H-1-benzopyran-6-yl]ethanone Oxime Methanesulfonate (40). The free base of compound 37 (3.41 g, 0.011 mol), HONH<sub>2</sub>·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-2H-1-benzopyrans

compd	R <sub>1</sub> , R <sub>2</sub>	mp or bp, °C (mmHg)	formula	anal. <sup>a</sup>	
54	5-NO <sub>2</sub>	77-80 (0.5)	C., H., NO.	C. H: N <sup>b</sup>	
55	$7 \cdot NO_2$	83-85 c	C <sub>11</sub> H <sub>11</sub> NO <sub>3</sub>	C. H. N	
56	5-CN	77-80 (0.5)	C <sub>12</sub> H <sub>11</sub> 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 <sub>1</sub> H <sub>1</sub> ClO	$\mathbf{H}, \mathbf{C}; \mathbf{C}^{d}$	
59	6-COOMe <sup><i>e</i></sup>	114 - 120(0.15)	$C_{13}H_{14}O_{3}$	C, H	
60	6-NHCOMe, 7-NO <sub>2</sub>	127-128	$C_{13}H_{14}N_2O_4$	C, H, N	
61	$6-NH_2$ , $7-NO_2$	137–138 <sup>†</sup>	$C_{11}H_{12}N_{2}O_{3}$	C, H, N	
62	7-NO2, 8-Me	75-78°	$C_{12}H_{13}NO_3$	C, H, N	

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

Table `	V.	Novel	trans-3-Bromo-3	.4-dih	vdro-2.	2-dimeth	vl-2H-1	-benzopy	an-4-ols

compd	$\mathbf{R}_1 \ (\mathbf{R}_2 = \mathbf{H})$	mp, °C	solvent of recrystn <sup>a</sup> or method of purificn	formula	anal. <sup>b</sup>
63	5-NO2	127-133	P	C <sub>11</sub> H <sub>12</sub> NO <sub>4</sub> Br	C, H, N, Br
64	6-NO <sub>2</sub>	114-116	Р	C <sub>11</sub> H <sub>12</sub> NO <sub>4</sub> Br	C, H, N
65	$7 \cdot NO_2$	105-106	PLC	C <sub>11</sub> H <sub>12</sub> NO <sub>4</sub> Br	C, H, N, Br
66	5-CN	123 - 124	$\mathbf{P}'$	C <sub>12</sub> H <sub>12</sub> NO <sub>2</sub> Br	C, H, N, Br
67	6-CN	128 - 128.5	Р	$C_{12}H_{12}NO_2Br$	C, H, N, Br
68	7-CN	131-132	Ρ'	$C_{12}H_{12}NO_2Br$	C, H, N, Br
69	8-CN	glass	PLC	$C_{12}H_{12}NO_2Br$	C, H, N
70	6-Me	89-90	Р	$C_{12}H_{15}O_2Br$	C, H, Br
71	6-OMe	83-84.5	Р	$C_{12}H_{15}O_{3}Br$	C, H, Br
<b>72</b>	6-F	111-111.5	Р	$C_{11}H_{12}O_2BrF$	C, H, Br
73	6-COOMe	84-85	Р	$C_{13}H_{15}O_4Br$	c
74	6-COMe	109-113	P-Et	$C_{13}H_{15}O_{3}Br$	C, H, Br
75	6-NHCOMe	172	P-Et	C <sub>13</sub> H <sub>16</sub> NO <sub>3</sub> Br	C, H, N, Br

<sup>a</sup> P = 60-80 °C petroleum ether; P' = 80-100 °C petroleum ether; Et = EtOAc. <sup>b</sup> See footnote *a* in Table I. <sup>c</sup> 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	3,4-Epoxy-3	3,4-dihydro-2,	2-dimethy	l-2 <i>H</i> -1-benzopyrans
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compd	R <sub>1</sub> , R <sub>2</sub>	mp, °C	solvent of recrystn <sup>a</sup> or method of purificn	formula	anal. <sup>b</sup>
76	5-NO,	glass	с	$C_{11}H_{11}NO_4$	C, H, N
77	6-NO,	91-93	с	$C_{11}H_{11}NO_{4}$	C, H, N
78	7-NO2	85-86	Р	$C_{11}H_{11}NO_4$	C, H, N
79	5-CN <sup>°</sup>	73-75	P'	$C_{12}H_{11}NO_{2}$	C, H, N
80	6-CN	glass	PLC	$C_{12}H_{11}NO_{2}$	$\mathbf{C}, \mathbf{H}; \mathbf{N}^{d}$
81	7-CN	131-132	Р	$C_{1}, H_{1}, NO_{2}$	C, H, N
82	6-OMe	66-67.5	Р	$C_{12}H_{14}O_{3}$	C, H
83	6-COOMe	51-52	Р	$C_{13}H_{14}O_{4}$	C, H
84	6-COMe	75-76	P	$C_{13}H_{14}O_{3}$	C, H
85	6-NHCOMe	173 - 175	P-E	C, H, NO,	C, H, N
86	7,8-benzo	121	Р	$C_{15}H_{14}O_{2}$	H; C <sup>e</sup>

<sup>a</sup> See footnote a in Table V. <sup>b</sup> See footnote a in Table I. <sup>c</sup> No purification necessary. <sup>d</sup> N: calcd, 7.0; found, 6.5. <sup>e</sup> C: calcd, 79.6; found, 78.9.

Workup by addition of  $H_2O$  and extraction with Et<sub>2</sub>O 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<sub>3</sub>H in EtOH-anhydrous Et<sub>2</sub>O. See Table II.

trans -3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1piperidinyl)-2H-1-benzopyran-6-carboxamide Methanesulfonate (41) and trans-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(1-pyrrolidinyl)-2H-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<sub>3</sub>H in EtOH-anhydrous Et<sub>2</sub>O 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-(1pyrrolidinyl)-2H-1-benzopyran-6-carboxylic Acid (47). A solution of the free base of compound 36 (4.01 g, 0.013 mol) in concentrated NH<sub>4</sub>OH (35 mL) and EtOH (25 mL) was warmed for 6 days. Dilution with H<sub>2</sub>O and extraction with Et<sub>2</sub>O 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)-2H-1benzopyran-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  $\approx$  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<sub>3</sub>, 25; glucose, 5; KH<sub>2</sub>PO<sub>4</sub>, 1.18; KCl, 4.69; MgSO<sub>4</sub>, 0.59; CaCl<sub>2</sub>·H<sub>2</sub>O, 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  $\pm$  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<sub>3</sub>H, 86834-45-9; 7, 86824-02-4; 7·MeSO<sub>3</sub>H, 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<sub>3</sub>H. 86824-11-5; 14, 64169-71-7; 14.MeSO<sub>3</sub>H, 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<sub>3</sub>H, 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<sub>3</sub>H, 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<sub>3</sub>H, 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.MeSO3H, 65018-74-8; 41, 65018-84-0; 41.MeSO<sub>3</sub>H, 65018-85-1; 42, 86824-52-4; 42.MeSO<sub>3</sub>H, 86824-53-5; 43, 86824-54-6; 43-MeSO<sub>2</sub>H, 86824-55-7; 44, 86824-56-8; 44.MeSO<sub>3</sub>H, 86824-57-9; 45, 86824-58-0; 45.HCl, 86824-59-1; 46,  $58747\text{-}00\text{-}5; \textbf{46}\text{-}\textbf{C}_{4}\textbf{H}_{6}\textbf{O}_{6}, 58747\text{-}01\text{-}6; \textbf{47}, 86824\text{-}60\text{-}4; \textbf{48}, 86824\text{-}61\text{-}5;$ 48-2HC1, 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-2H-1-benzopyran. 86824-81-9; 6-(acetylamino)-2,2-dimethyl-2H-1-benzopyran, 19849-34-4.

# 2-Benzazepines. 5.<sup>1,2</sup> Synthesis of Pyrimido [5,4-d] [2] benzazepines and Their Evaluation as Anxiolytic Agents

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A series of 5H-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 [<sup>3</sup>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)-5H-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,<sup>3</sup> the 1,4-benzodiazepines have been a fruitful source of research activity for both the medicinal chemist and the pharmacologist.<sup>4</sup> In the search for new anxiolytic agents, the 1,4-benzodiazepine structure has been modified in a variety of ways.<sup>5</sup> 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-<sup>6</sup> and triazolo-2-benzazepine<sup>2</sup> 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

- (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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- (5) For reviews, see (a) Sternbach, L. H. In ref 4, pp 1–25. (b) Gschwend, H. "Industrial Pharmacology"; Fielding, S.; Lal, H., Eds.; Futura: Mount Kisco, NY, 1979; Chapter 1.
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