Synthesis and Structure-Activity Relationships of 5*H*,11*H*-[2]Benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic Acids

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The synthesis and properties of the title compounds 1 are described. Many of these compounds are potent inhibitors of the passive cutaneous anaphylaxis reaction of rats against egg albumin challenge. Structural variations include substitutions in the 2, 3, 4, 5, 7, and 12 position of the nucleus 1. A novel rearrangement from a compound of the related [3,4-*f*] series to this group is reported.

The discovery that disodium cromoglycate[1] is useful in preventing allergic asthma attacks by the inhibition of mediator release marked the beginning of a new era in the design of antiallergic agents. This discovery stimulated widespread research not only because of the unique mode of action of this substance but also because of its limitations.[2] Disodium cromoglycate had utility only in a prophylactic sense and would not arrest an ongoing attack; it was inactive orally and had to be applied locally as a fine powdered aerosol. The resulting surge of papers in this field has described many new structural types. The reader is referred to the reviews presented in the more recent publications[3-5] and the references cited therein.

We have investigated the synthesis and antiallergic activity of a group of benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic acids[6] (1, Table I). The rat PCA reaction based on the method described by Mota[7] was used as a biological screen and to compare the relative potencies of the different compounds tested. Many of the compounds in this group were highly active in this test. Compound 1b (PR-D-92-Ea) has been studied pharmacologically in detail. It has been shown, using the mast cell degranulation test as described by Fügner,[8] to inhibit mediator release in a dose-dependent way and in this respect resembles disodium cromoglycate.[2] It has also been found to inhibit the increase in airway resistance following Ascaris challenge in sensitive Rhesus monkeys (*Macaca mulatta*) when administered by aerosol, intravenous injection,[9] and also when given by mouth.[10]

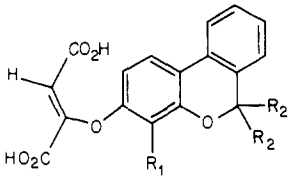
Unlike disodium cromoglycate, compound 1b has been shown to be a reversible antagonist of some of the mediators known to be released after antigen challenge such as SRS-A, serotonin, and the prostaglandins E_2 and F_{2a} and, to a lesser extent, bradykinin and histamine.[11]

Synthesis. The synthetic route which has been found to be most convenient for the preparation of 11-oxo-5*H*,11*H*-[2]benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic acids of the general formula 1 (Table I) involved the condensation of the corresponding 2-acetyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyrans[12] **2** (Table II) with diethyl oxalate, followed by ring closure and acid hydrolysis of the initial condensation product.[13]

An alternate but less efficient route to these substances was by the base-catalyzed reaction of 3-hydroxy-6*H*-dibenzo[*b*,*d*]pyrans[14] with dimethyl acetylenedicarboxylate followed by alkaline hydrolysis of the mixture of maleic and fumaric esters.[15] The fumaric acids **3** were conveniently isolated by selective extraction from an aqueous solution of the sodium salts at pH 4. Intramolecular condensation was readily effected with sulfuric acid at 80 °C.

Representatives having a nitro (**1m**) or sulfo grouping (**1n**) at C-3 were most conveniently prepared by direct nitration or sulfonation of the parent acid 1b. Reduction of **1m** provided the 3-amino representative **1o**.

Substituents at C-7 were readily introduced at the acetophenone stage, wherein chlorination (**2q**) and nitration (**2r**) occur selectively at this position. Reduction of **1r** provided the 7-amino representative **1u**.

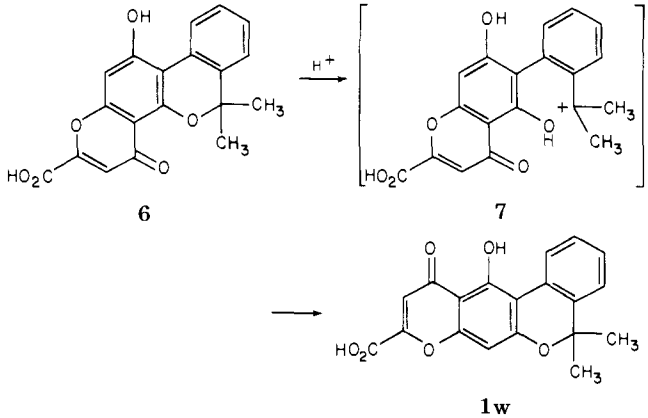


3a, R_1 = H; R_2 = CH_3
b, R_1 = OCH_3; $2R_2$ = -O-

The 3-hydroxy (**1g**) and 7-hydroxy (1t) representatives were obtained by demethylation of the corresponding methyl ethers **1h** and **1s**, respectively.

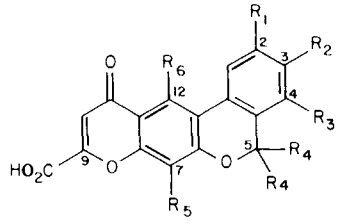
The 12-hydroxy acid **1w** was prepared by a rather indirect route. The acetophenone **4b**, which was the principle product from the acetylation of the phenol **4a**,[12] readily condensed with diethyl oxalate to provide the 4*H*,6*H*-[2]benzopyrano[3,4-*f*][1]benzopyran-2-carboxylic acid (**5**). While this novel series will be described in detail in a forthcoming paper, the demethylation product of this representative is of interest here. Treatment of **5** with hydriodic acid–acetic acid did not provide the hydroxy acid **6** but instead yielded an acid which gave an intense blue color reaction with ferric chloride solution, a behavior indicative of a hydroxyl grouping in the ortho position to a carbonyl function. The constitution (**1w**) was assigned on the basis of spectral information and was confirmed by the following degradation. Alkaline hydrolysis of the demethylated product yielded the corresponding acetophenone which was methylated to a dimethyl ether, identical in all respects with 1,3-dimethoxy-2-acetyl-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran[12] (**8**). The transformation (**5** → **1w**) undoubtably involved the initial formation of the hydroxy acid **6** which subsequently provided the carbonium ion **7** which rearranged and ring closed to the more favorable form (**1w**). The possibility that a Wessely–Moser rearrangement[16] also occurred was discounted by the nonidentity of the demethylation product

Scheme I



6 7 1w

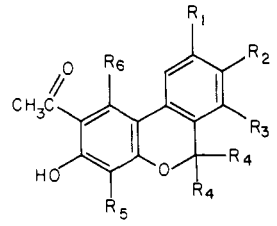
Table I. 11-Oxo-5*H*,11*H*-[2]benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic Acids (1)



Compd no.	R_1	R_2	R_3	R_4	R_5	R_6	Mol formula[a]	Mp, °C	% yield[b]	Recrystn solvent[c]	Salt[d]	% inhibn of PCA at 1 mg/kg iv ± SEM	ED_{50}, mg/kg iv (95% confidence limits)
1a	H	H	H	H	H	H	$C_{17}H_{10}O_5$	309-311	56	A	Na	64.3 ± 7.2	0.32 (0.05 → 2.20)
1b	H	H	H	CH_3	H	H	$C_{19}H_{14}O_5$	279-282	89	A	EA	70.3 ± 3.7	0.50 (0.20 → 1.4)
1c	H	H	H	n-C_4H_9	H	H	$C_{25}H_{26}O_5$	230-232	35	A	EA	25.0 ± 25.0	
1d	Cl	H	H	CH_3	H	H	$C_{19}H_{13}O_5Cl$[e]	290-292	46	A	Na	25.0 ± 25.0	
1e	H	Cl	H	CH_3	H	H	$C_{19}H_{13}O_5Cl$[f]	304-306	54	A	Na	60.0 ± 0	
1f	H	F	H	CH_3	H	H	$C_{19}H_{13}O_5F$	297-300	39	M	EA	60.0 ± 12.3	0.87 (0.22 → 3.48)
1g	H	OH	H	CH_3	H	H	$C_{19}H_{14}O_6$	305-308	50[g]	A	Na	77.8 ± 6.7	0.30 (0.08 → 1.20)
1h	H	OCH_3	H	CH_3	H	H	$C_{20}H_{16}O_6$	230-274	48	M	Na	66.7 ± 9.6	
1i	H	$OCH_2CH_2CH_3$	H	CH_3	H	H	$C_{22}H_{20}O_6 \cdot 0.5AcOH$	251-264 dec	56[h]	G	EA	40.0 ± 20.0	
1j	H	$OCOCH_3$	H	CH_3	H	H	$C_{21}H_{16}O_7$	260 dec	65[i]	E	Na	73.4 ± 7.7	
1k	OCH_3	OCH_3	H	CH_3	H	H	$C_{21}H_{18}O_7$	294-295 dec	58	M	Na	67.7 ± 0	
1l	Br	OCH_3	H	CH_3	H	H	$C_{20}H_{15}O_6Br$	312-318	41	A	Na	0	
1m	H	NO_2	H	CH_3	H	H	$C_{19}H_{13}O_7N$	293-300	83[j]	G	E	50.0 ± 16.7	
1n	H	SO_3H	H	CH_3	H	H	$C_{19}H_{14}O_8S$[k]	290 dec	21[l]	W		0	
1o	H	NH_2	H	CH_3	H	H	$C_{19}H_{15}O_5N \cdot 2H_2O$	273-278 dec	54[m]	M	EA	77.8 ± 0	
1p	H	H	OCH_3	H	H	H	$C_{18}H_{12}O_6 \cdot Me_2SO$	287-289	48	A	EA	0	
1q	H	H	H	CH_3	Cl	H	$C_{19}H_{13}O_5Cl$	278-286 dec	59	G	EA	66.7 ± 6.7	
1r	H	H	H	CH_3	NO_2	H	$C_{19}H_{13}O_7N$	298-305	85	G	EA	20.0 ± 23.1	
1s	H	H	H	H	OCH_3	H	$C_{18}H_{12}O_6$	268-276 dec	69	M	EA	50.0 ± 16.7	
1t	H	H	H	H	OH	H	$C_{17}H_{10}O_6 \cdot MeOH$	292 dec	60[n]	M	EA	33.4 ± 19.3	
1u	H	H	H	CH_3	NH_2	H	$C_{19}H_5O_5N \cdot 2H_2O$	273-278 dec	34	M	EA	64.3 ± 7.2	
1v	H	H	H	CH_3	H	CH_3	$C_{20}H_{16}O_5$	281-285	65	M	Na	0	
1w	H	H	H	CH_3	H	OH	$C_{19}H_{14}O_6$	270-280 dec	57[o]	M	Na	0	
1x	H	H	H	-O-	OH	H	$C_{17}H_8O_7 \cdot Me_2SO$	250 dec	20[p]	MD	EA	55.6 ± 12.8	2.00 (0.50 → 7.50)
1y	H	OCH_2CH_2OH	H	CH_3	H	H	$C_{21}H_{18}O_7$	262-266	68[q]	M	EA	82.8 ± 3.1	0.11 (0.03 → 0.33)
Disodium cromoglycate												26.7 ± 14.1	2.88 (0.96 → 8.63)

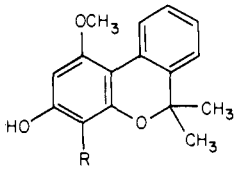
[a] All compounds were analyzed for C, H, N, S, and halogen as required. [b] Yields refer to the conversion 2 → 1 unless otherwise noted. [c] A, aqueous Me_2SO; E, EtOAc; G, glacial AcOH; M, MeOH; MD, MeOH-Me_2SO; W, H_2O. [d] EA, ethanolamine. [e] C: calcd, 63.96; found, 63.16. [f] C: calcd, 63.96; found, 63.20. [g] Demethylation of 1h. [h] Alkylation of ethyl ester of 1g with subsequent hydrolysis. [i] Acetylation of 1g. [j] Nitration of 1b. [k] C: calcd, 56.71; found, 56.29. [l] Sulfonation of 1b. [m] Reduction of 1m. [n] Demethylation of 1s. [o] See text. [p] Via 3b; see text. [q] Hydroxyalkylation of 1g.

Table II. 2-Acetyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyrans (2)

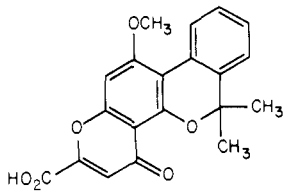


Compd no.	R_1	R_2	R_3	R_4	R_5	R_6
2a	H	H	H	H	H	H
2b	H	H	H	CH_3	H	H
2c	H	H	H	n-C_4H_9	H	H
2d	Cl	H	H	CH_3	H	H
2e	H	Cl	H	CH_3	H	H
2f	H	F	H	CH_3	H	H
2h	H	OCH_3	H	CH_3	H	H
2k	OCH_3	OCH_3	H	CH_3	H	H
2l	Br	OCH_3	H	CH_3	H	H
2p	H	H	OCH_3	H	H	H
2q	H	H	H	CH_3	Cl	H
2r	H	H	H	CH_3	NO_2	H
2s	H	H	H	H	OCH_3	H
2v	H	H	H	CH_3	H	CH_3

with **9a** which was derived from the corresponding methyl ether **9b**, the unambiguous synthesis of which has been previously reported.[12]



4a, R = H
b, R = $COCH_3$



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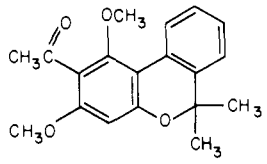

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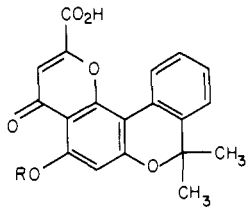

9a, R = H
b, R = CH_3

Compound **1i** was most conveniently prepared by the alkylation of the ethyl ester of **1g** with subsequent hydrolysis. Compound **1y** was readily obtained by hydroxyalkylation of **1g**.

Structure–Activity Relationships. The antiallergic activities of compounds of the general formula **1**, as observed in the PCA test, are presented in Table I.

Simple substitution as represented in the general formula **1** did not, with the exception of **1y**, significantly enhance activity over that of the basic molecule **1a**. A considerable reduction in activity was observed, however, with substitution at C-4 (R_3) and C-12 (R_6).

Significant reduction in activity by substitution at C-3 (R_2) was only observed when R_2 is SO_3H and is presumably a consequence of the disruption in the polarity of the molecule.

Experimental Section

Melting points were determined on a Reichert Kofler microheating stage and are uncorrected. UV spectra were recorded in ethanol solution on a Bausch and Lomb Spectronic 505 and IR spectra (KBr pellet) on a Perkin-Elmer 237B spectrophotometer. NMR spectra were taken on a Varian T-60 spectrometer. Tetramethylsilane was used as an internal standard. Elemental analyses were determined by Microanalyses Laboratories Ltd. (Toronto, Canada).

Biological Test Procedure. The rat passive cutaneous anaphylaxis (PCA) reaction was used as the screening test and was performed as follows. The "reaginic type" antibody was raised in adrenalectomized Sprague–Dawley rats immunized 4 days after adrenalectomy with 1 mg of ovalbumin and 1×10^9 killed *Bordetella pertussis* organisms were injected subcutaneously. The antisera were collected 12 days later by cardiac puncture and pooled. It was sterilized by passage through a millipore filter (0.45 μ pore size) and stored at −20 °C until used. The PCA test was done by injecting 0.1 ml of threefold dilutions of the antiserum intradermally on the shaved backs of unsensitized Sprague–Dawley rats weighing 150–170 g. Twenty-four hours later each rat was challenged intravenously with 5 mg of ovalbumin and 2.5 mg of Evans blue in a total volume of 0.5 ml of physiological saline. Thirty minutes later the rats were killed by CO_2 asphyxiation and the skin of the back was reflected so that the area of blueing could be determined on the inside surface. The PCA titer was taken as the reciprocal of the highest antiserum dilution that gave a blued area of 25 mm^2.

Control and test groups each containing four rats were set up. The test group received the compound to be tested intravenously along with the ovalbumin and Evans blue in a total volume of 0.5 ml of physiological saline. Four rats were used for each dosage point. The mean PCA titer was determined for each group and the figure for the control group was considered 100%. The results of the test groups were expressed as the percentage inhibition compared to that of the control values.

11-Oxo-5*H*,11*H*-[2]benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic Acids. General Procedure A (1a–f,h,k,l,p–s,v). A mixture of the appropriate 2-acetyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran[12] (0.1 mol) and diethyl oxalate (0.2 mol) in EtOH (200 ml) was added to a solution of sodium (1.0 mol) in EtOH (500 ml) under reflux. After 2 h the reaction mixture was cooled, acidified with 4 N HCl, and extracted with $CHCl_3$ (3×100 ml). The $CHCl_3$ extracts were combined, dried (Na_2SO_4), and evaporated. The residue was heated under reflux for 2 h in a mixture of AcOH (200 ml) and concentrated HCl (100 ml). The reaction mixture was cooled and the crude product isolated by filtration. Recrystallization provided the title compounds (see Table I).

General Procedure B (1b and 1x). A mixture of the appropriate 3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran[14] (0.01 mol) and dimethyl acetylenedicarboxylate (1.4 g, 0.01 mol) at 90 °C was treated with benzyltrimethylammonium hydroxide (4 drops). The reaction mixture was heated at 90 °C for 1 h. A solution of NaOH (1.1 g, 0.027 mol) in H_2O (6 ml) and MeOH (3 ml) was then added. The resulting mixture was heated at 80 °C for 40 min and then diluted with H_2O (100 ml). The pH was adjusted to 7.5 with 2 N H_3PO_4 and the solution extracted with Et_2O (2×50 ml). The aqueous phase was then acidified to pH 4 and again extracted with Et_2O (4×50 ml). Evaporation of the ether extract provided the crude fumaric acid (**3a** or **3b**) which was dissolved in H_2SO_4 (20 ml) and kept at 80 °C 2 h. The reaction mixture was poured into ice water (50 ml) and the crude product was collected by filtration. Recrystallization provided the title compounds (**1b**, 10%;[17] **1x**, 20%[18]) (see Table I).

3-Hydroxy-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic Acid (1g). A suspension of **1h** (2.0 g, 5.7 mmol) in a mixture of AcOH (20 ml) and HI (57%, 20 ml) was heated under reflux for 90 min. The reaction mixture was cooled and diluted with water (10 ml). The insoluble crude product was collected and washed with H_2O. Recrystallization provided **1g** (see Table I).

The ethyl ester was prepared by heating **1g** (10 g, 0.03 mol) for 2 h under reflux in ethanol (500 ml) containing H_2SO_4 (5 ml). The reaction mixture was evaporated to 100 ml and diluted with water (500 ml). The crude product was extracted with $CHCl_3$ (3×200 ml). The extracts were evaporated and the residue was recrystallized from Me_2SO to provide yellow needles, mp 288–293 °C. Anal. ($C_{21}H_{18}O_6$) C, H.

3-Propoxy-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano-[4,3-*g*][1]benzopyran-9-carboxylic Acid (1i). A solution of 1-bromopropane (1.23 g, 10 mmol) and the ethyl ester of **1g** (3.0 g, 8.2 mmol) in DMF (70 ml) was treated with finely powdered anhydrous K_2CO_3 (1.38 g, 10 mmol) and the resulting mixture stirred at room temperature for 24 h. The reaction mixture was diluted with ice water (400 ml) and extracted with ethyl acetate (3 × 200 ml). The extracts were dried over Na_2SO_4, filtered, and evaporated.

The residue was dissolved in MeOH (100 ml) and the solution brought to pH 9 by the addition of aqueous 1 N NaOH. The resulting solution was then stirred at room temperature for 1 h. The pH was monitored throughout this period and adjusted to 9 by the addition of 1 N NaOH. The reaction mixture was then acidified and the crude product collected as the insoluble yellow precipitate. Recrystallization provided **1i** (see Table I).

3-Acetoxy-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano-[4,3-*g*][1]benzopyran-9-carboxylic Acid (1j). A mixture of **1g** (0.5 g, 1.5 mmol) and Ac_2O (1 g, 10 mmol) containing 5% H_2SO_4 was heated for 10 min at 100 °C. The reaction mixture was then cooled and diluted with Et_2O (10 ml). The crude product was collected by filtration, washed with H_2O, and recrystallized to yield **1j** (see Table I).

3-Nitro-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano-[4,3-*g*][1]benzopyran-9-carboxylic Acid (1m). Fuming HNO_3 (35 ml, sp gr 1.57) was added over 5 min to a solution of **1b** (24 g, 0.075 mol) in trifluoroacetic acid (300 ml) at 20 °C. The reaction mixture was kept at 20 °C for 30 min and then poured into ice water. The crude product was collected by filtration and on recrystallization provided **1m** as yellow needles (see Table I).

3-Sulfo-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano-[4,3-*g*][1]benzopyran-9-carboxylic Acid (1n). A solution of **1b** (3.2 g, 0.01 mol) in concentrated H_2SO_4 (50 ml) was kept at 80 °C for 6 h. The reaction mixture was cooled and poured into ice water (100 ml). The crude product was collected by filtration and on recrystallization provided **1n** (see Table I).

3-Amino-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano-[4,3-*g*][1]benzopyran-9-carboxylic Acid (1o). Finely powdered **1m** (22 g, 0.06 mol) was added over 20 min in a nitrogen atmosphere to a suspension of 10% Pd/C (1 g) in H_2O (1000 ml) containing sodium borohydride (22 g). The reaction mixture was stirred for an additional 25 min and then filtered. The aqueous phase was carefully acidified with 2 N HCl. The crude product was collected by filtration and recrystallized to provide **1o** (see Table I).

7-Hydroxy-11-oxo-5*H*,11*H*-[2]benzopyran[4,3-*g*][1]-benzopyran-9-carboxylic Acid (1t). A suspension of **1s** (140 mg, 0.43 mmol) in a mixture of AcOH (2 ml) and HI (57%, 2 ml) was heated under reflux for 75 min. The reaction mixture was cooled and the crude product collected as an insoluble solid. One recrystallization provided **1t** (see Table I) as yellow needles.

5,5-Dimethyl-7-amino-11-oxo-5*H*,11*H*-[2]benzopyrano-[4,3-*g*][1]benzopyran-2-carboxylic Acid (1u). A suspension of **1r** (6.5 g, 0.018 mol) and tin (29 g) in 2 N HCl (100 ml) was heated under reflux for 30 min. The hot reaction mixture was decanted from the undissolved tin and cooled. The precipitated solid was collected and recrystallized to provide **1u** as yellow needles (see Table I).

3-Hydroxyethoxy-5,5-dimethyl-11-oxo-5*H*,11*H*-[2]benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic Acid (1y). A suspension of **1g** (10 g, 0.03 mol) and finely powdered anhydrous K_2CO_3 (5.7 g, 0.042 mol) in ethylene carbonate (24.1 g, 0.27 mol) was heated at 110 °C for 2 h. The reaction mixture was then cooled, diluted with water (500 ml), and extracted with $CHCl_3$ (3 × 200 ml). The aqueous phase was acidified and the precipitated crude product was collected. Recrystallization provided **1y** as yellow needles (see Table I).

2-Acetyl-3-hydroxy-4-chloro-6,6-dimethyl-6*H*-dibenzo-[*b*,*d*]pyran (2q). A solution of **2b** (2.4 g, 9 mmol) in MeOH (50 ml) and 2 N NaOH (50 ml) was treated with NaOCl solution (5% Cl_2, 50 ml) at room temperature and then stirred at room temperature for 16 h. The reaction mixture was then diluted with H_2O (100 ml), acidified with 2 N HCl, and extracted with $CHCl_3$ (2 × 50 ml). The extracts were combined, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from hexane and again from EtOH to provide **2q** (1.7 g, 63%) as yellow plates: mp 140–143 °C; NMR ($CDCl_3$) δ 1.67 [s, 6 H, $(CH_3)_2$], 2.67 (s, 3 H, CH_3CO), 7.32 (m, 3 H, C-7–H + C-8–H + C-9–H), 7.64 (m, 1 H, C-10–H), 8.00 (s, 1 H, C-1–H), 13.30 (s, 1 H, OH; disappears + D_2O). Anal. ($C_{17}H_{15}ClO_3$) C, H, Cl.

2-Acetyl-3-hydroxy-4-nitro-6,6-dimethyl-6*H*-dibenzo-[*b*,*d*]pyran (2r). A solution of **2b** (10 g, 0.037 mol) in isobutyric acid (300 ml) was treated with fuming HNO_3 (sp gr 1.59, 5 ml) over 2 min while maintaining the temperature at 5 °C with external cooling. The reaction mixture was stirred at 5 °C for 45 min and then diluted with H_2O (500 ml) followed by MeOH (500 ml). The insoluble solid was collected and recrystallized from EtOH to yield **2r** (6.4 g, 54%) as yellow plates: mp 187–190 °C; NMR (CD_3SOCD_3) δ 1.65 [s, 6 H, $(CH_3)_2$], 2.80 (s, 3 H, CH_3CO), 7.50 (m, 3 H, C-7–H + C-8–H + C-9–H), 8.16 (m, 1 H, C-10–H), 8.60 (s, 1 H, C-1–H), 13.33 (br s, 1 H, OH; disappears + D_2O). Anal. ($C_{17}H_{15}NO_5$) C, H, N.

4-Oxo-6,6-dimethyl-11-methoxy-4*H*,6*H*-[2]benzopyrano-[3,4-*f*][1]benzopyran-2-carboxylic Acid (5). Compound **4b** (7.1 g, 0.024 mol)[12] was condensed with diethyl oxalate (7.3 g, 0.05 mol) in the general manner described above for representatives of the general formula **1**. The intermediate product was similarly ring closed in AcOH–HCl. The crude product on recrystallization from 2-propanol provided **5** (6.9 g, 82%): mp 226–229 °C; NMR (CD_3SOCD_3) δ 1.60 [s, 6 H, $(CH_3)_2$], 4.05 (s, 3 H, OCH_3), 6.66 (s, 1 H, C-3–H), 6.93 (s, 1 H, C-12–H), 8.25 (m, 1 H, C-10–H). Anal. ($C_{20}H_{16}O_6$) C, H.

5,5-Dimethyl-11-oxo-12-hydroxy-5*H*,11*H*-[2]benzopyrano[4,3-*g*][1]benzopyran-9-carboxylic Acid (1w). A suspension of **5** (12.7 g, 0.036 mol) in a mixture of AcOH (80 ml) and HI (57%, 80 ml) was heated under reflux for 2 h. The reaction mixture was cooled and the precipitated solid collected and washed with acetic acid (5 ml) and then with water (4 × 20 ml). The crude product on recrystallization provided **1w** as yellow needles (see Table I).

1,3-Dimethoxy-2-acetyl-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (8). A solution of **1w** (100 mg) in 1 N NaOH (10 ml) was heated under reflux for 20 min. The reaction mixture was cooled, acidified with 2 N HCl, and extracted with Et_2O (2 × 15 ml). The ether extract was dried (Na_2SO_4) and evaporated. The crude product was purified by thick-layer chromatography (silica gel/$CHCl_3$–10% MeOH) and then treated with MeI (0.4 ml) in acetone (5 ml) in the presence of anhydrous K_2CO_3 (100 mg) at room temperature for 24 h. The reaction mixture was filtered and evaporated. The crude product was dissolved in toluene (2 ml) and filtered and the solution evaporated. Recrystallization from acetonitrile provided **8** (20 mg, 22%), mp 121–122 °C, identical (melting point, IR, and TLC) with an authentic sample.[12]

4-Oxo-5-hydroxy-8,8-dimethyl-4*H*,8*H*-[2]benzopyrano-[3,4-*h*][1]benzopyran-2-carboxylic Acid (9a). A suspension of **9b**[12] (0.3 g, 0.85 mmol) in a mixture of AcOH (2.5 ml) and HI (2.5 ml) was heated under reflux for 45 min. The reaction mixture was poured into 30% $NaHSO_3$ solution (25 ml) and the crude product collected by filtration. Recrystallization from EtOH provided **9a** (0.15 g, 52%) as yellow needles: mp 286–300 °C dec; NMR (CD_3SOCD_3) δ 1.63 [s, 6 H, $(CH_3)_2$], 6.48 (s, 1 H, C-3–H), 7.00 (s, 1 H, C-6–H), 7.43 (m, 3 H, C-9 + C-10 + C-11), 8.60 (m, 1 H, C-12–H), 12.43 (s, 1 H, OH; disappears + D_2O). Anal. ($C_{19}H_{14}O_6$) C, H.

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(17) A 20% yield of the sulfonic acid **1r** was also obtained.
(18) Demethylation of **3b** was a concurrent process.

Derivatives of Tetrahydro-1,4-benzodiazepines as Potential Antihypertensive Agents

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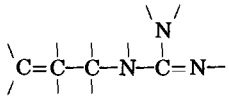
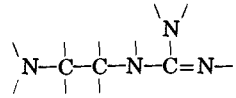
4-Amidino derivatives and quaternary salts of tetrahydro-1,4-benzodiazepines were synthesized and evaluated for antihypertensive activity in conscious rats by the oral route. Included in this study were derivatives of 1,2,4,5,-6,7-hexahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepine and 1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,5,4-*jk*]carbazole in which the 1 and 9 positions of tetrahydro-1,4-benzodiazepine are linked by an ethylene and a cyclohexenyl chain, respectively. Four compounds exhibited marked blood pressure lowering activity (>50 mmHg) at doses of 75 mg/kg. Further study indicated that these compounds are effective by impairing transmission in the sympathetic nervous system.

Many currently available clinically effective antihypertensive agents are derivatives of nitrogen heterocycles obtained as a result of careful selection among series of active compounds which were synthesized with systematic structural modification. In each active series, there seems to exist a common structural feature, the presence of which is essential for the activity.

Recently, Schier and Marxer postulated that for the aralkylguanidine type of antihypertensive agents, the partial structure I or II is a requisite feature for lowering blood pressure.[1,2]



I



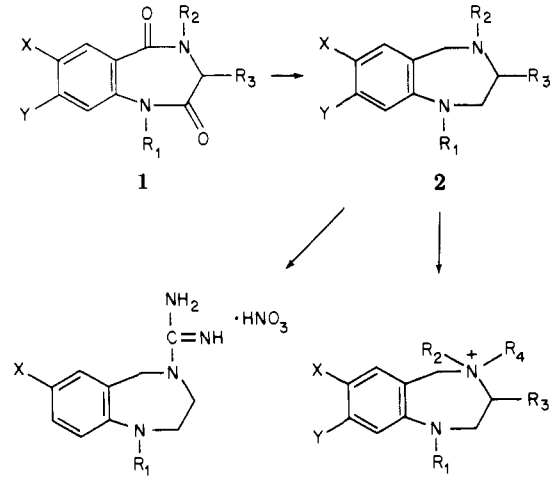
II

This proposition led us to examine amidino derivatives of tetrahydro-1,4-benzodiazepine as potential antihypertensive agents, for those compounds would satisfy simultaneously the above two essential structural requirements. Furthermore, since 1,4-benzodiazepines have a number of pharmacological actions on the central nervous system,[3] agents obtained from these basic structures are of interest as potential "centrally" acting antihypertensive agents.[4]

Also examined in this study were quaternary salts of the tetrahydro-1,4-benzodiazepines and related compounds. Many quaternary ammonium salts are known to possess hypotensive properties. Although most of them are known to be effective by blockade of ganglia, recently it has been shown that some quaternary salts lower blood pressure by other mechanisms, as demonstrated by bretylium.[5]

1,2,3,5-Tetrahydro-4*H*-1,4-benzodiazepine-4-acetamidoxime (**12**) was synthesized and evaluated for antihypertensive effects, since some amidoximes were reported to have blood pressure lowering activity when tested in hypertensive dogs.[6]

Scheme I



1,2a, R_1 = H; R_2 = H; R_3 = H; X = H; Y = H
1,2b, R_1 = Me; R_2 = H; R_3 = H; X = H; Y = H
1,2c, R_1 = H; R_2 = H; R_3 = Me; X = H; Y = H
1,2d, R_1 = H; R_2 = H; R_3 = H; X = Cl; Y = H
1,2e, R_1 = H; R_2 = H; R_3 = H; X = OMe; Y = OMe

Chemistry. Tetrahydro-1,4-benzodiazepines **2a–e** were obtained by a standard lithium aluminum hydride reduction of 1,4-benzodiazepine-2,4-diones **1a–d** which were prepared from appropriately substituted isatoic anhydrides and α-amino acids by a literature method.[7] In the case of **1e**, a synthetic route which is different from the above one was used and is shown in Scheme II. *N*-Amidino derivatives (see Table I) were prepared by fusion of the tetrahydro-1,4-benzodiazepines with 3,5-dimethylpyrazole-1-carboxamidine nitrate and were isolated as nitrate salts (Scheme I). Quaternary salts shown in Table II were obtained by the treatment of the cyclic amines **2a–e** with