a 2 N HCl solution. The acidic aqueous solution was cooled at 0 °C and then neutralized with a 2 N NaOH solution. The white precipitate was washed several times with water to give 5.4 g (59%) of **14**: NMR (Me_2SO-d_6) δ 3.60 (m, 4 H, $=NCH_2CH_2N=$), 5.60 (br s, =NH), 6.50–8.50 (m, 7 H, aromatic).

1-Phenyl-(4′-acetylamino)-1,2,3,4-tetrahydroquinolin-4-one (II, R_1 = NHCOCH$_3$; R_2 = H). 4-Acetylamino-*N*,*N*-diphenyl-β-alanine (14 g, 47 mmol) was added to 131 g of polyphosphoric acid and kept under vigorous stirring at 100 °C for 2 h. The mixture was cooled, diluted with ice water, and then extracted with EtOAc. The organic layer was first washed with 1 N NaOH and then with water, dried, concentrated in vacuo, and crystallized from EtOAc to give 9.8 g (74%) of yellow solid II (R_1 = $NHCOCH_3$; R_2 = H).

1-Phenyl-(4′-acetylamino)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (16). Sodium azide (10 g, 150 mmol) was added to 10 g (36 mmol) of 1-phenyl-(4′-acetylamino)-1,2,3,4-tetrahydroquinolin-4-one (II, R_1 = $NHCOCH_3$; R_2 = H) in $CHCl_3$. Concentrated H_2SO_4 (50 mL) was then added at 0 °C under vigorous stirring. The reaction mixture was allowed to stand at room temperature for 3 h and then neutralized with a Na_2CO_3 saturated solution; the precipitate was collected by filtration. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo; the small amount of the obtained compound was joined to the previously obtained precipitate. The combined residues were crystallized from acetone to give 7.8 g (74%) of **16**: NMR (Me_2SO-d_6) δ 2.05 (s, 3 H, $-CH_3$), 3.40 (m, 4 H, $=NCH_2CH_2N=$), 6.70–7.80 (m, 8 H, aromatic).

1-Phenyl-(4′-amino)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (15). 1-Phenyl-(4′-acetylamino)-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**16**, 1 g, 3.4 mmol) was refluxed in 100 mL of absolute EtOH and HCl(g) allowed to bubble in slowly for 4–5 h. The solvent was evaporated in vacuo, and amine hydrochloride thus obtained was washed several times with ethyl alcohol, then dissolved in a small amount of water, and alkalinized with 1 N NaOH to give 0.5 g (58%) of compound **15**: NMR (Me_2SO-d_6) δ 3.50 (m, 4 H, $=NCH_2CH_2N=$), 4.90 (br s, =NH), 6.70–7.60 (m, 8 H, aromatic).

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Antiallergic 9-Oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyrans

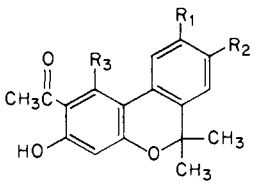
John P. Devlin,* Armin Bauen, Genus J. Possanza, and P. Brian Stewart

Pharma Research Canada Ltd., Pointe Claire, Quebec, H9R 1G8, Canada. *Received August 30, 1977*

The synthesis and properties of the title compounds **1** are described. Several of these compounds, in addition to being potent inhibitors of the passive cutaneous anaphylaxis reaction of rats against egg albumin challenge, significantly block the effects of several mediators of anaphylaxis in isolated smooth muscle preparations. An improved procedure for the isolation and partial purification of SRS-A from chopped guinea pig lung tissue is also described.

We have investigated the antiallergic activities of acidic representatives of polycyclic heterocyclic systems.[1] The 9-oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]-benzopyrans (**1**), a short series of which is herein described, are members of this group which have been found to possess significant activity both in the PCA assay and the inhibition of the effects of several mediators of anaphylaxis in isolated smooth muscle preparations.

Chemistry. The synthetic route which was generally employed for the preparation of **1** (see Table I) involved the condensation of 2-acetyl-3-hydroxy-6*H*-dibenzo-[*b*,*d*]pyrans[1,2] (**2**) with diethyl carbonate in the presence of sodium hydride.



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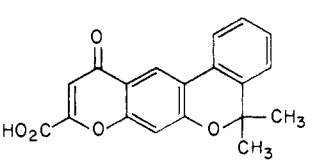

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Results and Discussion

The PCA reaction can be altered by the inhibition of mast cell degranulation so that no vasoactive mediators are released after antigen challenge. Disodium

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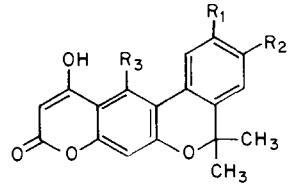
Table I. 9-Oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyrans and Their PCA Activities



Compd	R_1	R_2	R_3	Yield,[a] %	Recrystn solvent	Mp, °C	Mol formula[b]	Inhibn of the PCA reaction[c]: % at 10 mg/kg iv[d] (±SEM)	Inhibn of the PCA reaction[c]: ED_{50} (95% confidence limits), mg/kg iv	Inhibn of the PCA reaction[c]: No. of rats
1a	H	H	H	54	MeCN	245–270 dec	$C_{18}H_{14}O_4$[e]	67 (±11)		
1b	Br	OCH_3	H	18	Me_2SO	325–335 dec	$C_{19}H_{15}O_5Br$	33		
1c	H	Cl	H	48	MeCN	290–296 dec	$C_{18}H_{13}O_4Cl$	0		
1d	H	F	H	37	MeCN	286–294 dec	$C_{18}H_{13}O_4F$[f]	60 (±0)		
1e	H	OH	H	45[g]	AcOH	241–285 dec	$C_{18}H_{14}O_5$	61 (±11)		
1f	H	OCH_3	H	68	DMF–MeCN	260–294 dec	$C_{19}H_{16}O_5$	67 (±6.7)	9 (2.0–49.3)	20
1g	H	$OCH_2CH_2CH_3$	H	20	EtOH	243–255 dec	$C_{21}H_{20}O_5$	0		
1h	H	OCH_2CH_2OH	H	15[h]	EtOH	258–263 dec	$C_{20}H_{18}O_6 \cdot 0.5EtOH$	87[i] (±3.0)	0.30 (0.02–6.3)	20
1i	H	H	CH_3	38	DMF–MeCN	280–282	$C_{19}H_{16}O_4$	0		
3 (ethanolamine salt)								81 (±3.7)	0.50 (0.20–1.4)	36
Disodium cromoglycate								80[j] (±3.7)	2.9 (1.0–8.6)	12
Cyproheptadine								51[k]		

[a] Yields refer to the conversion 2 → 1 unless otherwise noted. [b] All compounds were analyzed for C, H, and halogen as required. [c] All compounds were assayed as their sodium salts unless otherwise noted. [d] Four rats were used unless otherwise noted. [e] C: calcd, 73.46; found, 73.04. [f] C: calcd, 69.22; found, 68.73. [g] Demethylation of 1f. [h] Hydroxyalkylation of 1e. [i] Eight rats were used. [j] Twelve rats were used. [k] 30% inhibition at 3 mg/kg iv; doses higher than 10 mg/kg iv were toxic.

Table II. Inhibition of Mediators of Anaphylaxis by 9-Oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyrans

Compd[a]	EC_{50}, μg/mL[b] (±SEM): Histamine[c] (0.25 μg/mL)	Serotonin[c] (0.05 μg/mL)	Bradykinin[c] (0.1 μg/mL)	PGE_2[d] (0.01 μg/mL)	$PGF_{2\alpha}$[d] (0.02 μg/mL)	SRS-A[c] (2 units/mL)[e]
1a	55 (±14)	10.2 (±3.5)	17 (±6.5)	56 (±9.0)	26 (±4.2)	
1b	39 (±21)	4.4 (±1.6)	51 (±33)	55 (±1.3)	14 (±2.2)	28 (±12)
1c	21 (±7.7)	10.2 (±3.2)	5.3 (±2.1)	45 (±18)		
1e	>200	15 (±6.0)	84 (±58)	40 (±18)	47 (±8)	
1f	13.2 (±3.9)	16 (±4.8)	9.2 (±2.6)	68 (±14)	23 (±6.5)	13 (±3.9)
1g	7.0 (±3.5)	4.7 (±2.0)	14.0 (±7.0)	70 (±7)		
1h	>200	11.0 (±8.0)	92 (±37)	62 (±19)	16 (±5)	
1i	14.5 (±4.5)	4.8 (±1.7)	17.5 (±6.1)			
3	150 (±28)	92 (±16)	145 (±70)	70 (±16)	47 (±9)	32 (±19)[f]
Disodium cromoglycate	>200	>200	>200	>200	>200	>200
Cyproheptadine	0.04 (±0.008)	0.04 (±0.03)	2.0 (±1)	~25[g]	~65[h]	<1[i]

[a] All compounds with the exception of cyproheptadine were assayed as their sodium salts. [b] μg/mL, final concentration. [c] Guinea pig ileum strips were used. [d] Rat stomach strips were used. [e] One unit of SRS-A is equivalent to the contraction produced by 0.005 μg of histamine. [f] Tested against SRS-A isolated from perfused monkey lung. [g] 54% inhibition at 25 μg/mL. [h] 33% inhibition at 25 μg/mL; 74% inhibition at 100 μg/mL. [i] 62% inhibition at 1 μg/mL.

cromoglycate[3] is an example of a drug with only this mechanism (Tables I and II). Inhibition of the PCA reaction may also be effected by substances which antagonize the mediators following degranulation of the mast cells (e.g., cyproheptadine,[4] Tables I and II). In this latter case an extrapolation of the in vitro concentrations, which are required for the antagonism of histamine and serotonin (Table II) to arrive at a dose level (iv) at which one would anticipate a significant inhibition of the PCA reaction, results in a value significantly lower than that found experimentally (Table I). This apparently anomalous behavior is presumably a consequence of the presence of mediator concentrations at the challenge site far greater than that employed in the in vitro assay, as well as the effect of mediators other than histamine and serotonin against which cyproheptadine is less active (Table II).

A substance which inhibits mast cell degranulation and also antagonizes the effects of the mediator of anaphylaxis would certainly be preferred. Such a substance would have therapeutic utility in prophylaxis as well as the ability to arrest an ongoing attack. The observation that PR.D.92[1,5] (**3**) was not only a potent inhibitor of mast cell degranulation but also exhibited weak but significant antagonism against the mediators of anaphylaxis (Table II) encouraged us to attempt to enhance this activity by structural modification. The series which is herein reported may be considered as poor isosteres of the benzopyranobenzopyrancarboxylic acids[1] (e.g., **3**). The mediator antagonism which has been observed with this group is more potent than that of **3** (Table II) while the PCA activity (Table I) was, with the exception of **1h**, much lower. That this PCA activity was a consequence of the inhibition of mast cell degranulation was established in one instance[6] (**1f**, ED_{50} = 14 ± 19 mg/kg iv). Compounds **1c**, **1g**, and **1i** were inactive in the PCA assay at 10 mg/kg (Table I) and yet were among the most potent representatives in antagonizing the activity of the mediators. Here again, however, we are faced with the inability to attain effective compound concentrations at the challenge site by systemic administration.

Experimental Section

Biological Test Procedures. The rat passive cutaneous anaphylaxis (PCA) reaction was used as the screening test and was performed as follows. The reaginic antibody was raised in adrenalectomized Sprague–Dawley rats immunized 4 days after adrenalectomy by subcutaneous injection with 1 mg of ovalbumin and 1×10^9 killed *Bordetella pertussis* organisms which were obtained from the Armana Frappier Institute (Montreal). The antisera, which were collected 12 days later by cardiac puncture, were pooled and sterilized by passage through a millipore filter (0.45-μ pore size). The antiserum was stored at −20 °C until used; it had a titer of 1/27 or 1/81 and its ability to produce a PCA reaction was abolished by heating at 56 °C for 4 h. 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, the skin of the back was reflected, and the area of bluing was measured 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.

Isolated organ assays were conducted in the manner described by Possanza et al.[5] Guinea pig ileum strips were used to test the effect of the compound against histamine, serotonin, bradykinin, and SRS-A. Rat stomach strips were employed to determine the effect against PGE_2 and $PGF_{2\alpha}$. Four strips were used per point.

The release of SRS-A from sensitized chopped lung tissue (guinea pig) was effected by the procedure described by Brocklehurst.[7] A partial purification of SRS-A was accomplished in the following manner.

The tissue supernatant (705 mL from 30 animals) was poured into ethanol (2650 mL) at 10 °C. The resulting suspension was centrifuged (850g) for 10 min at 5 °C. The supernatant was evaporated (30 mm of pressure/40 °C bath temperature) to 350 mL. Saturated aqueous NaCl (150 mL) and 4 N HCl (1.5 mL) were then added, and the resulting solution was extracted with Et_2O (3 × 200 mL). The Et_2O extract was evaporated (30 mm of pressure/30 °C bath temperature). The aqueous residue (2 mL) was diluted with H_2O (10 mL), neutralized with 0.1 N NaOH to pH 7.5, and filtered through a glass wool plug. The plug was washed with H_2O and the washings were combined with the filtrate. The resulting translucent pale-green SRS-A concentrate (30 mL) assayed at 40 units of SRS-A/mL.

The EC_{50} values were calculated by the method of Miller and Tainter[8] and refer to that concentration of the compound which inhibited the contraction caused by the agonist by 50%.

Chemistry. Melting points were determined on a Reichert Kofler microheating stage and are uncorrected. Elemental analyses were determined by Microanalyses Laboratories Ltd. (Toronto, Canada). NMR, IR, and UV spectra were recorded for all compounds and are consistent with the assigned structures.

9-Oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyrans. General Procedure. A suspension of the appropriate 2-acetyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran[1,2] (0.1 mol) in diethyl carbonate (120 g, 1.0 mol) was heated to reflux temperature (124 °C). The heat source was removed and the interior of the flask flushed with nitrogen. Sodium hydride (20 g of a 55% suspension in oil, 0.45 mol) was added with vigorous stirring over 1 min. The reaction mixture was stirred without heating for 15 min and then cooled to 20 °C. MeOH (100 mL) was added cautiously while maintaining the temperature below 40 °C with external cooling. H_2O (300 mL) was then added and the mixture was extracted with Et_2O (2 × 250 mL). The aqueous phase was removed and acidified with 6 N HCl. The crude product was collected as the precipitated solid and recrystallized (see Table I).

3-Hydroxy-5,5-dimethyl-9-oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyran (1e). A mixture of **1f** (5.8 g, 0.018 mol), hydriodic acid (57%, 25 mL), and AcOH (25 mL) was heated under reflux for 90 min. The reaction mixture was poured into cold 20% $NaHSO_3$ solution (100 mL) with vigorous stirring. The precipitate was collected, washed with H_2O and with EtOAc, and recrystallized from methyl ethyl ketone to yield **1e** as colorless plates (see Table I).

3-(2-Hydroxyethoxy)-5,5-dimethyl-9-oxo-11-hydroxy-5*H*,9*H*-[2]benzopyrano[4,3-*g*][1]benzopyran (1h). An intimate mixture of **1e** (3.6 g, 0.012 mol), powdered K_2CO_3 (2.5 g, 0.018 mol), and ethylene carbonate (11 g, 0.12 mol) was heated at 110 °C for 1 h. The reaction mixture was cooled, diluted with H_2O (100 mL), and extracted with EtOAc (2 × 80 mL). The aqueous phase was acidified and extracted with Et_2O–MeOH (4:1, 2 × 100 mL). The latter extracts were combined and evaporated. The residue was crystallized from EtOH to provide **1h** (see Table I).

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Synthesis and Antibacterial Activity of Isomeric 6- and 7-Acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-Dioxides

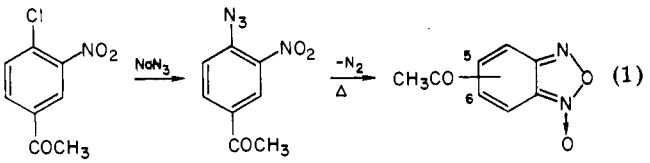
John P. Dirlam* and Joseph E. Presslitz

Pfizer Central Research, Groton, Connecticut 06340. *Received November 23, 1977*

The synthesis, separation, and structure determination of 6- and 7-acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-dioxides are reported together with a comparison of their antibacterial activity. The structural assignment of these 6- and 7-acetyl isomers was based on NMR analysis of related mono-*N*-oxide derivatives, which were obtained by treatment of the quinoxaline 1,4-dioxides with acetic anhydride–acetic acid or trimethyl phosphite. The compounds were screened for in vitro and in vivo activity against *Escherichia coli*, *Salmonella choleraesuis*, *Pasteurella multocida*, and *Streptococcus pyogenes*. Although the isomers were found to possess similar activity, the 7-acetyl isomer was more active therapeutically in mice than the 6-acetyl isomer when administered parenterally.

A large number of quinoxaline 1,4-dioxides (QNO's) exhibit antibacterial activity.[1,2] Although the synthesis of some mixtures of 6- and 7-substituted QNO's has been reported,[3,4] only in a few cases has each isomer been isolated and characterized.[4] Furthermore, to our knowledge there are no studies reported where the antibacterial activity has been determined for both isomers of such a pair.[5] This paper describes the synthesis, separation, and structure determination of 6- and 7-acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-dioxides (**1** and **2**, respectively) and a comparison of their antibacterial activity.[6]

Synthesis. The starting material for the synthesis of compounds **1** and **2** was 5(6)-acetylbenzofurazan 1-oxide (**3**), prepared in an analogous manner to that reported for 5(6)-formylbenzofurazan 1-oxide by Ghosh and Whitehouse[7] (eq 1). The intermediate azide was synthesized by allowing 4-chloro-3-nitroacetophenone to react with sodium azide in dimethyl sulfoxide (Me_2SO) at room temperature. Thermal decomposition of the azide in refluxing toluene gave the desired benzofurazan 1-oxide (BFO) **3** in 74% overall yield.



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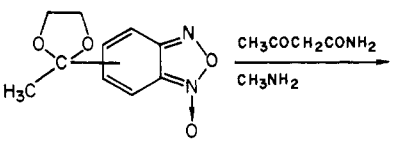
The 6- and 7-substituted QNO mixture **4**, containing a protected acetyl group, was isolated in 84% yield from the "Beirut reaction"[8] of 5(6)-acetylbenzofurazan 1-oxide ethylene ketal (**5**) and acetoacetamide (eq 2). The use of unprotected BFO **3** in this reaction led to low yields of **1** and tar formation apparently due to side reactions of the acetyl group.[9] Dilute acid hydrolysis of **4** gave a 1:1 mixture of the 6- and 7-acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-dioxides (**1** and **2**, respectively) that was readily separated by fractional crystallization.

In general, the structural assignment of 6- and 7-substituted QNO isomers is difficult since both isomers have very similar spectral properties. However, their conversion to mono-*N*-oxide derivatives allows structure determination by NMR;[10] in these, aromatic protons H-5 and H-8, unlike their counterparts in the parent compounds, are in a different chemical environment. For example, the 6-isomer **1** was converted to the 1- and 4-mono-*N*-oxides **6** and **7**, as shown in eq 3. The NMR spectrum of **1** possesses an H-5 doublet ($J_{H\text{-}5\text{–}H\text{-}7}$ = 2 Hz) at 0.38 ppm lower field than the multiplet for H-7 and H-8. After the loss of a neighboring *N*-oxide, i.e., in the formation of the 1-oxide **6** upon treatment of **1** with acetic anhydride–acetic acid,[11] H-5 moves upfield 0.25 ppm. The chemical shifts of protons H-7 and H-8 are unaffected. Reduction of **1** with trimethyl phosphite in refluxing 1-propranol[12] gave the 4-oxide **7**. The H-5 doublet is found at the same chemical shift as H-5 in the parent dioxide **1**.



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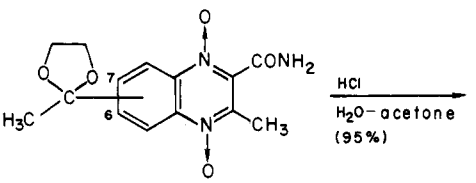

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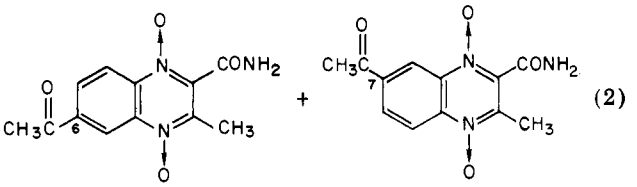

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In contrast with what was observed with the 6-isomer **1**, the low-field doublet in the NMR spectrum of the 7-isomer **2** (H-8, $J_{H\text{-}6\text{–}H\text{-}8}$ = 2 Hz) remains at the same chemical shift after acetic anhydride–acetic acid rearrangement to the 1-oxide **8** as illustrated in eq 4. A portion of the H-5–H-6 multiplet moves upfield slightly. Reduction of **2** with trimethyl phosphite gave the 4-oxide **9**. The H-8 doublet moves upfield by 0.38 ppm relative

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