anthracene hydrochloride was active at 160 mg/kg (the only level tested) against *P. gallinaceum* in chickens.

The increased antimalarial activity of these 10-halo-9-anthryl amino alcohols, along with the generally higher activity of the unsubstituted 9-anthryl amino alcohols over the unsubstituted 9-phenanthryl amino alcohols[6] indicates that substituents in other positions on the anthracene nucleus should lead to enhanced antimalarial activity. Further credence for such a conclusion lies again in the 9-phenanthryl amino alcohols, where the symmetrical (*i.e.*, 3,6-) dihalo or bis(trifluoromethyl) substituents markedly increase the antimalarial activity.[6] We plan the preparation of additional substituted anthracene amino alcohols.

Experimental Section#

Preparative methods and physical properties for the substituted 9-anthraldehydes prepared are given in Table I.

The target compounds listed in Table II were prepared by the method of Duncan, *et al.*,[5] using a 2-fold excess of ylid.

10-Chloro-9-anthronitrile. 10-Chloro-9-anthraldehyde was refluxed with $NH_2OH \cdot HCl$ and HCO_2Na in HCO_2H[29] for 3 hr. The resulting soln was cooled and filtered to give, in 96% yield, crude 10-chloro-9-anthronitrile, mp 238–241°. Six recrystns from HOAc gave mp 256–257°, lit.[30] 255°. *Anal.* ($C_{15}H_8ClN$) C, H, N.

10-Chloro-9-vinylanthracene. To a yellow suspension of 5.5 mmoles of triphenylphosphonium methylide (prepared[31] under N_2 from *tert*-BuOK–*tert*-BuOH in THF and methyl triphenylphosphonium iodide in Et_2O) was added 1.20 g (5 mmoles) of 10-chloro-9-anthraldehyde in 50 ml of THF (refluxed over and distd from NaH) dropwise over *ca.* 10 min. The resulting yellow mixture was stirred at 25° for 1 hr and concd on a rotary evaporator at 65° to give a yellow-green semisolid, which was extd 3 times with 50, 25, and 25 ml of hot petr ether. After cooling the combined extracts, the resulting yellow-orange crystals were filtered and discarded, as was the next crop, obtained after concg to 15 ml. The following two crops (0.76 g, 68% yield) of crude 10-chloro-9-vinylanthracene had mp 107–113°. Recrystn from EtOH and petr ether gave mp 113–114°. *Anal.* ($C_{16}H_{11}Cl$) C, H.

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#The chemicals employed in this investigation were used as obtained from chemical supply houses without purification unless otherwise noted. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and have not been corrected. Most reactions and purification procedures were followed by tlc on Gelman SG sheets; a convenient general purpose solvent system for these compounds on this medium is 5–15% Et_2O in petroleum ether (60–110°). Target hydrochlorides were separated on Mallinckrodt Chromar 1000 in a similar solvent system after over spotting with dilute Et_3N in THF. Visualization was accomplished with shortwave uv, 0.2% $KMnO_4$ in 1.0% aqueous Na_2CO_3, 0.4% Bromophenol Blue in MeOH (for bases; adjust to pH ≈ 8 for acids), or 0.04% 2,4-dinitrophenylhydrazine in 2 *N* HCl. Ir spectra were detd on a Beckman IR 5A prism instrument and nmr spectra were detd at 60 MHz by W. Simon Associates, Elgin, Ill. Elemental analyses were carried out with a Hewlitt Packard Model 185 CHN analyzer by the IMC Organic Analysis Group under the supervision of Mr. L. Ferrara. When analyses are indicated only by the symbols of the elements, the results were within ±0.4% of the theoretical values.

3-Chromanamine Hydrochlorides with Central Stimulant Activity

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The synthesis of a number of 3-chromanamine hydrochlorides that reduce the hyperirritability of rats that have been lesioned in the septal area of the brain and/or which suppress the killer instinct in rats has been carried out in these laboratories.[1] Many of these compounds caused some central excitation in rats as determined by the increase in locomotor activity determined with jiggle cages† using the procedure of Schulte, *et al.*[2] However, when some 3-chromanamine hydrochlorides with two alkyl groups in the aromatic ring were studied, it was found that many of them were potent stimulants when examined by this technique. This paper describes the preparation of such compounds and the examination of their stimulant activity.

Chemistry. The 3-chromanamine hydrochlorides have been prepared from 3-amino-4-chromanone hydrochlorides by conventional synthetic methods. Their physicochemical

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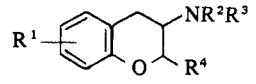
†D. A. McCarthy, unpublished observations.

Table I. 3-Chromanamine Hydrochlorides



Compd	R^1	R^2	R^3	R^4	Method	Mp, °C	Form	Crystd form	Yield, %	Formula[a]	Increase in motor activity[b]
1	5,7-Me_2	H	H	H	A	207.5	*c*	*g*	76	$C_{11}H_{16}ClNO$	6
2	5,7-Me_2	H	Me	H	B	194–195	*d*	*h*	35	$C_{12}H_{18}ClNO$	3
3	5,7-Me_2	H	Et	H	C	256–257	*d*	*h*	46	$C_{13}H_{20}ClNO$	100
4	5,7-Me_2	Me	Me	H	D	243–245	*d*	*h*	54	$C_{13}H_{20}ClNO$	N
5	5,7-Me_2	H	H	Me	A	243–245	*d*	*h*	24	$C_{12}H_{18}ClNO$	6
6	5,7-Me_2	Me	Me	Me	D	229–230	*d*	*h*	36	$C_{14}H_{22}ClNO$	13
7	5-Me, 8-*i*-Pr	H	H	H	A	267–269	*d*	*h*	59	$C_{13}H_{20}ClNO$	3
8	5-Me, 8-*i*-Pr	Me	Me	H	D	187–189	*d*	*h*	69	$C_{15}H_{24}ClNO$	25
9	6,7-Me_2	H	H	H	A	270–279[f]	*c*	*h*	65	$C_{11}H_{16}ClNO$	
10	6,7-Me_2	H	Me	H	B	234–235	*c*	*h*	52	$C_{12}H_{18}ClNO$	
11	6,8-Me_2	H	H	H	A	285–287	*d*	*h*	69	$C_{11}H_{16}ClNO \cdot 0.5H_2O$	N
12	6,8-Me_2	H	Me	H	B	219–220	*d*	*h*	63	$C_{12}H_{18}ClNO$	
13	7,8-Me_2	H	H	H	A	244–246	*e*	*h*	60	$C_{11}H_{16}ClNO$[i]	100
14	7,8-Me_2	H	H	Me	A	240–241	*d*	*h*	35	$C_{12}H_{18}ClNO$	N
15	7,8-Me_2	Me	Me	Me	D	207–209	*d*	*h*	61	$C_{14}H_{22}ClNO$	3
16	6-Cl, 5-Me, 8-*i*-Pr	H	H	H	E	223–224	*d*	*g*	56	$C_{13}H_{19}Cl_2NO \cdot 0.5H_2O$[j]	N

[a] All compounds were analyzed for C, H, N. [b] Lowest dose at which increase is comparable with effect of caffeine administered at 13 mg/kg sc. N indicates inactive at 100 mg/kg sc. [c] Rods. [d] Prisms. [e] Needles. [f] With sublimation and decomposition. [g] EtOH-Et_2O. [h] EtOH. [i] C: calcd, 61.8; found, 62.5. [j] C: calcd, 54.7; found, 54.2.

properties are collected in Table I and the following experimental details relate to that table.

Pharmacology. The central excitatory activity of the 3-chromanamine hydrochlorides was measured by the increase of motor activity in rats in jiggle cages of the type described by Schulte, *et al.*[2] The drugs were administered subcutaneously to groups of six male albino rats at each graded dose level.

The results are collected in the last column of Table I. The figure given indicates the lowest dose at which the compound caused an increase in motor activity comparable with that caused by caffeine administered at a dose of 13 mg/kg sc under the same conditions.

Experimental Section‡

4-Chromanones were prepared and converted to 3-amino-4-chromanone hydrochlorides by previously reported methods.[3] Subsequent reduction with $NaBH_4$ or $LiAlH_4$ afforded 3-amino-4-chromanols.

3-Chromanamine Hydrochlorides. Method A. The catalytic hydrogenation of 3-amino-4-chromanols in glacial HOAc–concd H_2SO_4 at atmospheric pressure in the presence of 10% Pd/C afforded the appropriate 3-chromanamine hydrochlorides.

***N*-Monomethyl-3-chromanamines. Method B.** Free amines were converted to their *N*-formyl derivatives by refluxing with 98% formic acid and Ac_2O for 5 hr. The crude formamido compound was reduced with $LiAlH_4$ in Et_2O to the *N*-monomethyl-3-chromanamine.

***N*-Ethyl-5,7-dimethyl-3-chromanamine Hydrochloride. Method C.** 3-Amino-5,7-dimethyl-4-chromanone hydrochloride was converted to the *N*-acetyl derivative by the method reported previously.[3] The acetamidochromanone was hydrogenated in EtOH in the presence of 10% Pd/C, and the resulting acetamidochromanol was converted to 3-amino-*N*-ethyl-5,7-dimethyl-4-chromanol using $LiAlH_4$ in Et_2O. A final hydrogenation in HOAc–H_2SO_4 in the presence of 10% Pd/C afforded the *N*-ethylchromanamine.

***N,N*-Dimethyl-3-chromanamine Hydrochlorides. Method D.** *N,N*-Dimethyl-3-chromanamines were prepared by refluxing the corresponding 3-chromanamines with 90% formic acid and 36% (w/v) HCHO for 7 hr.

6-Chloro-8-isopropyl-5-methyl-3-chromanamine Hydrochloride. Method E. 8-Isopropyl-5-methyl-3-chromanamine hydrochloride in $CHCl_3$ was chlorinated directly with Cl_2 in $CHCl_3$ at room temperature.

‡Melting points are corrected and were determined in a capillary tube. Boiling points are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

Discussion

An examination of the results reported in this paper showed that certain of the 3-chromanamine hydrochlorides produced a very strong stimulant effect in rats. Although only a limited number of compounds are reported here, many of those to be reported elsewhere[1b] have been tested in jiggle cages but none were as active as the more potent members of this series.† It seemed, therefore, that the substitution of two alkyl groups in the aromatic ring of a 3-chromanamine often had a profound effect on the stimulant properties.

However, it was difficult to elucidate possible structural requirements for potent stimulant activity. For example, with the 2,7,8-trimethyl-3-chromanamine, dimethylation of the amino group converted an inactive primary amine (**14**) to a very active tertiary amine (**15**). However, the reverse was true with the 5,7-dimethyl-3-chromanamine where a potent primary amine (**1**) on N-dimethylation was converted to an inactive tertiary amine (**4**). With the 2,5,7-trimethyl-3-chromanamines, both the primary amine (**5**) and the tertiary amine (**6**) showed strong stimulant properties.

The results reported here and elsewhere[1] illustrate some of the great variety of interests that 3-chromanamine hydrochlorides have to the medicinal chemist. The series also illustrates the very profound changes in biological activity that can occur as a result of relatively small changes in chemical structure.

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Benzopyrones. 7. Synthesis and Antiallergic Activity of Some 2-(5-Tetrazolyl)chromones[1]

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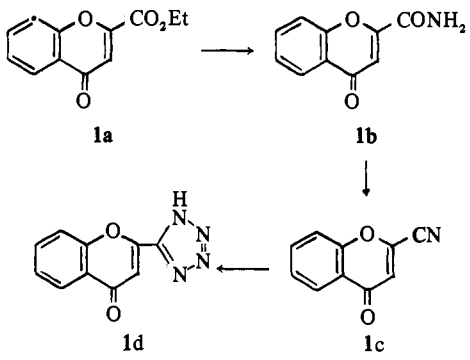
Antiallergic properties in the chromone series appear[2-4] to be largely confined to those compounds which contain a carboxyl group at C-2. Replacement of a carboxyl by a 5-tetrazolyl group in a biologically active carboxylic acid[5-8] has sometimes resulted in retention of activity but rarely in an improvement in potency. This paper reports the synthesis and antiallergic properties of a number of chromones,[9] such as **1d** and its substituted derivatives, which carry a 5-tetrazolyl group at C-2. The variations in structure are shown in Table I.

Chemistry. The title compounds which are listed in Table II were prepared by the route shown in Scheme I.

Scheme I

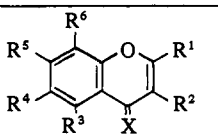


The carboxylic esters, prepared[14] from the appropriate 2-hydroxyacetophenone and diethyl oxalate, reacted with gaseous NH_3 at 0° to give high yields of the carboxamides. Although several carboxamides of this kind are known, their dehydration to the 4-oxo-4*H*-1-benzopyran-2-carbonitriles has not been reported. The unsubstituted carbonitrile **1c**, the only known member of this series, was synthesized[12] in five stages from 2-methylchromone *via* the 2-carboxaldehyde. A more convenient method is now described through the dehydration of the carboxamide by means of an arylsulfonyl chloride and pyridine in DMF. Other reagents,[19] such as $POCl_3$, PCl_5-$POCl_3$, $SOCl_2$, or P_2O_5, proved to be ineffective while benzenesulfonyl chloride in pyridine[20] gave a low yield. 3-Chloro-4-oxo-4*H*-1-benzopyran-2-carbonitrile (**17c**) was prepared by reacting the unsubstituted nitrile (**1c**) with sulfuryl chloride.

The carbonitriles were converted smoothly to the tetrazoles by reaction with sodium azide and ammonium chloride in DMF.[21] A recent study[22] showed that the pK_a of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid was 2.96. The low solubility of the corresponding tetrazole (**1d**) in water and ethanol caused difficulties in the accurate determination of its pK_a but, using a potentiometric method, a value (2.8) was obtained which showed that the acidity of both carboxylic acid and tetrazole are comparable.

†Science Research Council Postgraduate Student.

Table I. Substituted Chromones Synthesized



a, $R^1 = CO_2Et$
b, $R^1 = CONH_2$
c, $R^1 = CN$
d, R^1 = 5-tetrazolyl

Compd No.	R^2	R^3	R^4	R^5	R^6	X
1	H	H	H	H	H	O
2	Me	H	H	H	H	O
3	H	H	Me	H	H	O
4	H	H	H	Me	H	O
5	H	H	H	H	Me	O
6	H	Me	H	Me	H	O
7	H	H	Cl	H	H	O
8	H	H	Br	H	H	O
9	H	H	Br	H	Br	O
10	H	H	Me	H	Br	O
11	H	OMe	H	H	H	O
12	H	H	H	OMe	H	O
13	H	H	H	OCH_2Ph	H	O
14	H	H	NO_2	H	H	O
15	H	H	NO_2	H	Me	O
16	H	H	H	H	H	S
17	Cl	H	H	H	H	O

Biological Results. The tetrazoles were screened for antiallergic activity in rats by means of the passive cutaneous anaphylaxis test using an extract of *Nippostrongylus brasiliensis* as antigen[23] and disodium cromoglycate as standard. Those compounds which showed activity comparable with or better than disodium cromoglycate are listed in Table III. Although the nature of the test makes it difficult to quantify the results, **1d**, **3d**, **4d**, and **14d** are appreciably more potent than the standard drug. Substitution by alkyl or halogen at C-3 or C-8 lowers activity as does the replacement of the 4-oxo by 4-thioxo group. The activity level is very susceptible to comparatively small changes in the substituents at C-7 (*cf.* **4d**, **12d**, and **13d**). This study shows that a carboxyl group in chromone-2-carboxylic acids may be advantageously replaced by a tetrazolyl group which confers a comparable degree of acidity on the molecule.

Four compounds, **2b**, **2c**, **9d**, and **14b**, showed activity similar to aspirin in reducing writhing induced by phenylquinone[24] but were almost inactive in the hot plate test.[25] The oral LD_{50} values of all the compounds in mice were greater than 100 mg/kg.

Experimental Section

Melting points were determined on a Reichert hot stage apparatus using a calibrated thermometer. A low value for the N content of a few tetrazoles was obtained although the combustion time was increased as recommended by the manufacturers of the instrument (Hewlett Packard).

General Method of Synthesis. (a) Ethyl 4-Oxo-4*H*-1-benzopyran-2-carboxylates. The esters were prepared by the method of Zagorevskii, *et al.*[14] The following new substituted 4-oxo-4*H*-1-benzopyran-2-carboxylic acids (from EtOH) were obtained from the esters by hydrolysis with a mixture of HCl and AcOH (analyzed for C and H): 8-methyl-, mp 272–273° dec; 5,7-dimethyl-, mp 251–252° dec;