[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

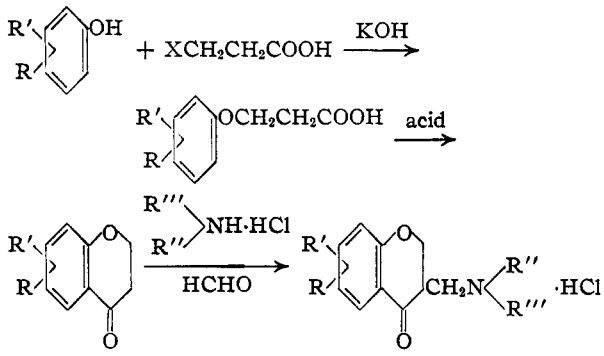
Amebacidal Chromanones

BY PAUL F. WILEY

A series of 3-alkyl- and 3-dialkylaminomethyl-4-chromanones has been synthesized, and the action of these compounds on *Endamoeba histolytica* and *Schistosoma mansoni* has been investigated.

In view of the close resemblance of chromanones to naturally occurring compounds such as flavanones, flavones, chromones and coumarins, and the common occurrence of basic side chains in therapeutically active compounds it was deemed worthwhile to incorporate basic groups into chromanones and study the action of such compounds on some lower organisms. Although Arndt and Källner[1] have reported the synthesis of one such compound, 3-(*p*-dimethylaminophenylamino)-4-chromanone, and Wittig[2] and Harradence and co-workers[3] have reported others, nothing is known of the biological activity of basic chromanones. Consequently a number of alkylaminomethyl-chromanones were synthesized and tested against *Endamoeba histolytica* and *Schistosoma mansoni*.

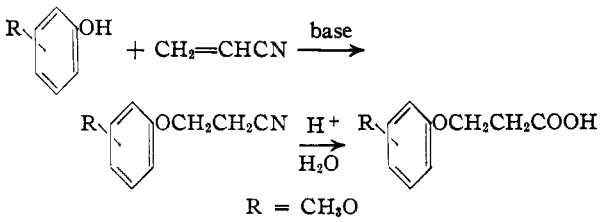
The general procedure followed for synthesis of the desired basic chromanones was



R and R′ = H, alkyl, alkoxy or halogen
R″ and R‴ = H or alkyl
X = Cl or Br

The first two steps in this series have been investigated thoroughly by Arndt and Källner,[1] Krollpfeiffer and Schultze,[4] Pfeiffer and co-workers[5,6,7] and Chichibabin and Nikitin[8] and their methods were followed. The final step was done by the method of Harradence, *et al.*[3]

All of the β-aryloxypropionic acids used for chromanone syntheses except β-(*p*-methoxyphenoxy)-propionic acid were synthesized by the reaction shown above. Although the yields were usually quite low (15–25%), the coupling failed completely in only three cases. The acid–phenol pairs from which no β-aryloxypropionic acids could be obtained were resorcinol:β-bromopropionic acid, hydroquinone:β-chlorobutyric acid, and *p*-methoxyphenol:β-bromobutyric acid. In order to obtain β-aryloxypropionic acids in better yields their synthesis *via* β-aryloxypropionitriles as shown in the following equations was attempted.



The first step occurred in about 50% yield using *p*-methoxyphenol and either sodium methoxide in the manner described by Cook and Reed[9] or trimethylbenzylammonium hydroxide according to Bachman and Levine.[10] The hydrolysis step gave yields of over 90%, making an over-all yield of over 45% as compared to about 20% using the older method. Syntheses of β-(*o*-methoxyphenoxy)-propionitrile and β-(*m*-methoxyphenoxy)-propionitrile with sodium methoxide as the basic catalyst were unsuccessful although Bachman and Levine[10] have reported syntheses of the latter nitrile using trimethylbenzylammonium hydroxide as catalyst. Application of this method to the preparation of β-(*p*-methoxyphenoxy)-butyronitrile using crotononitrile and *p*-methoxyphenol and either of the above catalysts was unsuccessful.

The usual procedure for preparing the chromanone intermediates unsubstituted in the 3-position was cyclization of β-aryloxypropionic acids with an acid catalyst. In most cases the acid chloride was prepared first using phosphorus pentachloride, and the acid chloride was cyclized with aluminum chloride. However, it was found necessary to use only phosphorus pentoxide directly on the acid as described by Birch and co-workers[11] in the cases of dimethoxyaryloxypropionic acids and β-(*m*-methoxyphenoxy)-propionic acid. What was believed to be 8-methoxy-4-chromanone was synthesized but was never obtained in a pure state. Consequently a very crude product was converted directly to the aminochromanone.

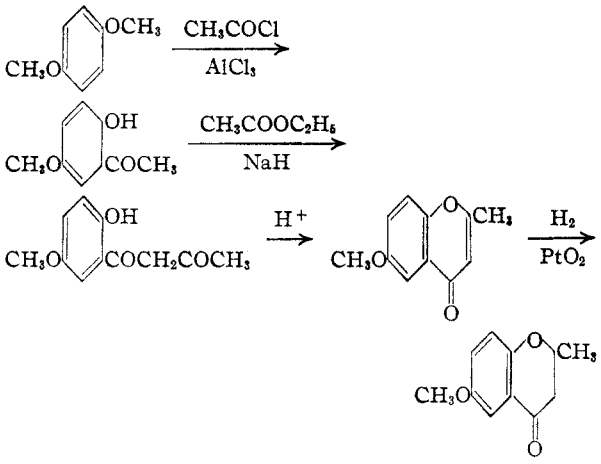
The preparation of 2-methyl-6-methoxy-4-chromanone was a special case since β-(*p*-methoxyphenoxy)-butyric acid, required for its synthesis by the above procedure, was not obtained. Instead the chromanone was prepared by the steps

(1) F. Arndt and G. Källner, *Ber.*, **57**, 202 (1924).
(2) G. Wittig, *ibid.*, **58**, 19 (1925).
(3) R. H. Harradence, G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 273 (1939).
(4) F. Krollpfeiffer and H. Schultze, *Ber.*, **57**, 206 (1924).
(5) P. Pfeiffer and J. Oberlin, *ibid.*, **57**, 208 (1924).
(6) P. Pfeiffer, H. Oberlin and E. Konermann, *ibid.*, **58**, 1947 (1925).
(7) P. Pfeiffer, E. Haack and J. Willems, *ibid.*, **61**, 249 (1928).
(8) A. E. Chichibabin and I. V. Nikitin, *J. Russ. Phys. Chem. Soc.*, **44**, 1135 (1912); [*C. A.*, **6**, 598 (1912)].
(9) A. H. Cook and K. J. Reed, *J. Chem. Soc.*, 920 (1945).
(10) G. B. Bachman and H. A. Levine, THIS JOURNAL, **70**, 599 (1948).
(11) A. F. Birch, A. Robertson and T. J. Subramaniam, *J. Chem. Soc.*, 1832 (1936).

TABLE I

PROPERTIES OF NON-BASIC CHROMANONES

No.	Substituents	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found
I	6-Ethoxy	27	63–65	$C_{11}H_{12}O_3$	68.75	68.70	6.25	6.48		
II	6-Bromo	80	76–79	$C_9H_7BrO_2$					35.24	35.08
III	7-Chloro	66	67–69	$C_9H_7ClO_2$	59.18	58.90	3.84	3.81	18.94	19.08
IV	5,8-Dimethoxy	32	113–115	$C_{11}H_{12}O_4$	63.46	63.47	5.77	6.01		
V	2-Methyl-6-methoxy	38	68–70	$C_{11}H_{12}O_3$	68.75	69.03	6.24	6.61		
VI	3-Bromo-6-methoxy	71	92–94	$C_{10}H_9BrO_3$					31.16	31.63
VII	3-Bromo-5,8-dimethoxy	4.6	131–133	$C_{11}H_{11}BrO_4$					27.84	27.72



Most of these reactions occurred in rather poor yield but could be run fairly easily. The conversion from 2-hydroxy-5-methoxyacetophenone to the chromone was made without isolation of the intermediate diketone. An acid solution was necessary for the reduction step, probably to maintain the hetero ring in the chromone form by oxonium salt formation rather than allowing it to exist as a resonance hybrid having a structure very nearly that of a phenolate ion.

The two 3-bromochromanones were prepared by direct bromination of 6-methoxy- and 5,8-dimethoxy-4-chromanone. 3-Bromo-6-methoxy-4-chromanone was easily dehydrohalogenated using aqueous dimethylamine to 6-methoxychromone. New chromanones are listed in Table I.

The synthesis of the various aminochromanones was relatively easy and straightforward in most cases although the yields were frequently low. In cases of low yields purification was more difficult. Complete failure of the Mannich reaction occurred with 6-nitro-4-chromanone. A compound containing no basic nitrogen was obtained. The product was believed to be 3,3′-methylenebis-[6-nitro-4-chromanone] resulting from the reaction of two molecules of the chromanone with one of formaldehyde. However, a good analysis for such a compound was never obtained so the structure is in doubt. It is interesting to compare the yields of compounds 2 and 3 with that of compound 20 (Table II). Introduction of a 2-methyl group decreased the yield of aminochromanone from 40–45% to 0.51%. This suggests steric hindrance in the Mannich reaction. All aminochromanones synthesized are listed in Table II.

Solutions of 3-aminomethyl-4-chromanones in water were unstable, depositing an oil on standing in solution. Investigation of the precipitate from compound 3, Table II, indicated that it was a polymer derived by polymerization of 3-methylene-6-methoxy-4-chromanone. This compound presumably arises from the basic chromanone by loss of dimethylamine hydrochloride. The solid salt was stable for a period of at least six months, no change in analysis or melting point being observed. 3-Dimethylaminomethyl-4-chromanone decomposed upon distillation although similar compounds[3] have been distilled successfully.

The *in vitro* amebacidal activities of the aminochromanones are shown in Table II. The tests were carried out by determining the maximum dilution at which the compound under test killed the organism and the maximum dilution of carbarsone oxide that would kill the same culture. The figures in the columns show dilutions in each case. The results indicate that compounds having dimethylaminomethyl in the 3-position are most active. Substitution in the benzene ring caused improvement in activity only in the case of 6-hydroxy and 6- or 7-alkoxy groups. Opening of the oxygen containing ring indicates considerable loss in activity as exemplified by the last compound in Table II. Several of the chromanones in Table I were tested for amebacidal activity but had none. Compound 3 was about as effective as Fuadin against *Schistosoma mansoni* when introduced intraperitoneally into infected mice.

Acknowledgment.—I wish to thank Mr. Max McCowen and his associates of our Parasitology Department for testing these compounds. Thanks are also due to Mr. W. L. Brown, Mr. H. L. Hunter and Mr. W. J. Schenck for microanalyses.

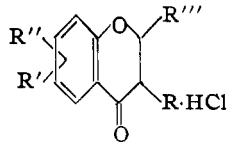
Experimental[12]

Phenols.—Most of the phenols used were commercial products. The only ones that were not were 2,5-dimethoxyphenol, prepared by the method of Gilman and Van Ess,[13] 3,4-dimethoxyphenol prepared according to Baker and Evans,[14] and *p*-methoxythiophenol synthesized by Suter's method.[15]

Aryloxypropionic Acids.—The aryloxypropionic acids used in this series of experiments were synthesized by the method of Gottesmann[16] with the exception of β-(*p*-methoxyphenoxy)-propionic acid. The known acids so prepared were β-(*p*-methoxyphenylmercapto)-propionic acid, β-phenoxypropionic acid and the following substituted β-phenoxypropionic acids: *p*-hydroxyphenoxy-, *o*-methoxyphenoxy-, *m*-methoxyphenoxy-, *p*-bromophenoxy-, 3,4-dimethoxyphenoxy-, *p*-nitrophenoxy-, *p*-tolyloxy-, and *m*-chlorophenoxy-. The acids shown in Table III are new.

(12) Melting points are uncorrected.
(13) H. Gilman and P. R. Van Ess, THIS JOURNAL, **61**, 1365 (1939).
(14) W. Baker and E. Evans, *J. Chem. Soc.*, 372 (1938).
(15) C. M. Suter and H. L. Hauser, THIS JOURNAL, **54**, 4100 (1932).
(16) E. Gottesmann, *Ber.*, **66**, 1168 (1933).

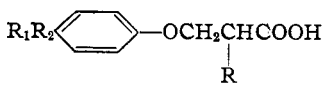
TABLE II



No.	Substituents	Yield, %	M.p., °C.	Formula	Analyses, % Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Testing results Carbarsone oxide	Testing results Chromanone
	Section A, R = $(CH_3)_2NCH_2$; R''' = H									
1		40	164–166	$C_{12}H_{16}ClNO_2$	14.70	14.71			64,000	64,000
2	6-Hydroxy	41	178–180	$C_{12}H_{16}ClNO_3$	13.76	13.37			50,000	100,000
3	6-Methoxy	45	157–159	$C_{13}H_{18}ClNO_3$	13.07	12.98	5.15	5.21	100,000	500,000
4	7-Methoxy	22	167–168	$C_{13}H_{18}ClNO_3$	13.07	13.23	5.15	5.11	128,000	1280,00
5	8-Methoxy	59	169–171	$C_{13}H_{18}ClNO_3$	13.07	13.02	5.15	4.98	200,000	200,000
6	6-Ethoxy	[a]	157–160	$C_{14}H_{20}ClNO_3$	12.41	12.31	4.88	4.93	50,000	50,000
7	6-Methyl	24	149–151	$C_{13}H_{18}ClNO_2$	13.65	13.89	5.62	5.48	100,000	50,000
8	6-Bromo	9.8	158–160	$C_{12}H_{15}BrClNO_2$	11.06	11.17	4.37	4.40	100,000	20,000
9	7-Chloro	9.9	154–156	$C_{12}H_{15}NCl_2O_2$	25.69	25.50			64,000	8,000
10	6,7-Dimethoxy	26	183–185	$C_{14}H_{20}ClNO_4$[b]			4.64	4.76	32,000	16,000
11	5,8-Dimethoxy		148–150	$C_{14}H_{20}ClNO_4$[c]					128,000	64,000
	Section B, R = various alkyl and dialkylaminomethyls; R' and R'' = H or CH_3O; R''' = H									
12	3-Diethylaminomethyl	6.1	121–124	$C_{14}H_{20}ClNO_2$			5.19	5.20	64,000	16,000
13	3-Piperidinomethyl		162–164	$C_{15}H_{20}ClNO_2$	12.61	12.68			64,000	32,000
14	3-Morpholinomethyl		169–171	$C_{14}H_{20}ClNO_4$			4.93	4.76	64,000	16,000
15	3-Piperidinomethyl-6-methoxy	65	216–218	$C_{16}H_{22}ClNO_3$	11.39	11.42	4.50	4.51	100,000	50,000
16	3-Diethylaminomethyl-6-methoxy	7	138–140	$C_{15}H_{22}ClNO_3$	11.82	11.52			200,000	200,000
17	3-Morpholinomethyl-6-methoxy		169–171	$C_{15}H_{20}ClNO_4$	11.32	11.17	4.48	4.35	128,000	16,000
18	3-(2-Dimethylaminoethyl)-aminomethyl-6-methoxy	40	202–209	$C_{16}H_{24}Cl_2N_2O_3$	20.23	20.23	7.98	7.88	50,000	20,000
19	3-Benzylaminomethyl-6-methoxy	44	174–176	$C_{18}H_{20}ClO_3N$	10.65	10.44	4.21	4.04	64,000	32,000
	Section C, miscellaneous compounds									
20	2-Methyl-3-dimethylaminomethyl-6-methoxy-4-chromanone hydrochloride		172–174	$C_{14}H_{20}ClNO_3$[d]	12.45	12.33			64,000	64,000
21	3-Dimethylaminomethyl-6-methoxythio-4-chromanone hydrochloride		157–159	$C_{13}H_{18}ClNO_2S$[e]			4.87	5.16	128,000	64,000
22	2,5-Dimethoxy-(β-dimethylamino) propiophenone hydrochloride[f]	13	145–147	$C_{13}H_{20}ClNO_3$	12.94	12.88	5.13	5.33	64,000	8,000

[a] In cases in which yields are not given the yields were less than 5%. [b] *Anal.* Calcd. for $C_{14}H_{20}ClNO_4$: C, 55.74; H, 6.63. Found: C, 55.64; H, 7.14. [c] *Anal.* Calcd. for $C_{14}H_{20}ClNO_4$: C, 55.74; H, 6.63. Found: C, 55.54; H, 6.40. [d] *Anal.* Calcd. for $C_{14}H_{20}ClNO_3$: C, 55.84; H, 7.02. Found: C, 58.83; H, 7.30. [e] *Anal.* Calcd. for $C_{13}H_{18}ClNO_2S$: S, 11.12. Found: S, 11.14. The sulfur atom of this compound replaces the ring oxygen of the preceding ones. [f] This compound is an open-chain analog of the aminomethylchromanones.

TABLE III



Substituents	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
o-Hydroxy	<1	128–130	$C_9H_{10}O_4$	59.34	59.70	5.48	5.14
p-Ethoxy	24	108–110	$C_{11}H_{14}O_4$	62.78	62.96	6.68	7.12
5,8-Dimethoxy	21	112–114	$C_{11}H_{14}O_5$	58.40	58.64	6.19	6.48
α-Methyl-*p*-methoxy	4.5	99–101	$C_{11}H_{14}O_4$	62.85	63.01	6.67	6.93

β-(*p*-Methoxyphenoxy)-propionitrile.—This compound was synthesized by the reaction of acrylonitrile with *p*-methoxyphenol.[9,10] The yields of product melting at 60–63° were about 50% using either sodium methoxide or trimethylbenzylammonium hydroxide. Four recrystallizations of the nitrile from alcohol gave glistening white crystals, m.p. 63–64.5°.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.26; N, 7.91; mol. wt., 177. Found: C, 67.91; H, 6.68; N, 8.09; mol. wt., 160.

β-(*p*-Methoxyphenoxy)-propionic Acid.—A mixture of 115 g. (0.65 mole) of β-(*p*-methoxyphenoxy)-propionitrile and 290 ml. (3.4 moles) of concd. hydrochloric acid was stirred and refluxed for eight hours. As the mixture became hot the solid dissolved, but as hydrolysis proceeded a precipitate appeared. The reaction mixture was cooled in an ice-bath and filtered, and the filter cake was washed thoroughly with ice-cold water. The product was dissolved in a solution of 40 g. of sodium carbonate in 400 ml. of water. The resulting solution was filtered, and the filtrate was acidified slowly by adding concd. hydrochloric acid dropwise with vigorous stirring. The acidified mixture was cooled in an ice-bath and filtered. The filter cake was washed thoroughly with cold water and dried to constant weight in a vacuum

oven at 50°. The yield of β-(*p*-methoxyphenoxy)-propionic acid, m.p. 103–105° (lit.[6] 110°) was 116 g. (91%).

Chromanones.—All of the non-basic chromanones except 2-methyl-6-methoxy-4-chromanone and the 3-bromo-4-chromanones were prepared by the cyclization of appropriate β-aryloxypropionic acids. The following chromanones, in addition to 4-chromanone, were prepared by cyclization using phosphorus pentachloride and aluminum chloride: 6-methoxy-, 8-methoxy-, 6-bromo-, 6-ethoxy-, 6-methyl-, 6-nitro- and 7-chloro-4-chromanones. Cyclization with phosphorus pentoxide was used for 7-methoxy-, 5,8-dimethoxy- and 6,7-dimethoxy-4-chromanones and for 6-methoxythio-4-chromanone. Sulfuric acid and acetyl chloride were used to cyclize β-(*p*-hydroxyphenoxy)-propionic acid to 6-hydroxy-4-chromanone. Both 3-bromo-6-methoxy-4-chromanone and 3-bromo-5,8-dimethoxy-4-chromanone were prepared by direct bromination as described below. New chromanones are shown in Table I.

2-Hydroxy-5-methoxyacetophenone.—This was prepared according to the method of Buu-Hoï and Cagniant[17] for 2,5-dimethoxyacetophenone. The fact that one methyl group was removed in the present experiments is attributed to more active aluminum chloride.

A solution of 69 g. (0.5 mole) of 1,4-dimethoxybenzene and 39.3 g. (0.5 mole) of acetyl chloride in 250 ml. of dry nitrobenzene was cooled to −5°. The solution was stirred and maintained at −10 to 0° while 133 g. (1.0 mole) of anhydrous aluminum chloride was added over a period of one hour. The reaction mixture was refrigerated for three days, then allowed to stand at room temperature for one day. This was followed by application of vacuum for one hour and decomposition of the aluminum chloride complex by cautious addition to a mixture of 1 kg. of ice and 100 ml. of concd. hydrochloric acid. After the ice had melted the mixture was filtered to remove a yellow solid that formed. The nitrobenzene layer was removed, and the aqueous layer was extracted with three 250-ml. portions of ether which were added to the nitrobenzene solution. The ether and nitrobenzene were distilled off, the latter under reduced pressure. The residue was distilled *in vacuo* retaining the fraction boiling at 78–86° at 0.1 mm. This fraction distilled as a yellow liquid but solidified on standing. It melted at 44–47° (lit. 52°). The yield was 37.5 g. (45%). The melting point of the product was raised to 52° by two recrystallizations from alcohol. A loss of about 25% was incurred in the purification.

2-Methyl-6-methoxychromanone.—A suspension of 9.6 g. (0.4 mole) of sodium hydride in 300 ml. of dry benzene was stirred vigorously while a solution of 33.2 g. (0.2 mole) of 2-hydroxy-5-methoxyacetophenone in 56.8 g. (0.6 mole) of dry ethyl acetate was added slowly. The reaction mixture was stirred at room temperature overnight and acidified with 40 ml. of concd. hydrochloric acid. Sufficient water was added to dissolve the salt formed. The benzene layer was removed, and the aqueous layer was extracted with two 150-ml. portions of benzene. The benzene solutions were combined, and the benzene was removed by evaporation under reduced pressure. The residue was dissolved in 400 ml. of ether, and the ether solution was washed successively with 160 ml. of saturated sodium bicarbonate solution and two 100-ml. portions of water. The ether solution was dried with magnesium sulfate, and the ether was evaporated off. The residue was refluxed for 15 minutes in 160 ml. of glacial acetic acid and 4 ml. of concd. hydrochloric acid. The cooled reaction mixture was poured into 500 ml. of water. The solution was neutralized with solid sodium bicarbonate. The solid which was deposited was filtered off and recrystallized twice from alcohol. The yield of white crystals was 10.7 g. (28%), m.p. 102–105°. Two more recrystallizations from the same solvent gave a sample melting at 105–107°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.48; H, 5.27. Found: C, 69.71; H, 5.15.

2-Methyl-6-methoxy-4-chromanone.—Nine and five-tenths grams (0.05 mole) of 2-methyl-6-methoxychromone was added to a solution of 5 ml. of concd. hydrochloric acid in 100 ml. of alcohol. This solution was shaken in the presence of 0.1 g. of platinum oxide under hydrogen at an initial pressure of 50 p.s.i. until the initial rapid reduction slowed down. Another 0.1 g. of platinum oxide was added and reduction continued until the rate of hydrogen uptake decreased sharply. This procedure was repeated until the theoretical amount of hydrogen was used. The mixture was filtered and the filtrate was evaporated to dryness. The residual solid was recrystallized six times from alcohol. The yield of white product melting at 68–70° was 0.6 g.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.24. Found: C, 69.03; H, 6.61.

3-Bromo-6-methoxy-4-chromanone.—A solution of 32 g. (0.2 mole) of bromine in 100 ml. of chloroform was added dropwise to a stirred solution of 35.6 g. (0.2 mole) of 6-methoxy-4-chromanone in 100 ml. of chloroform. Stirring was continued until hydrogen bromide evolution ceased. The chloroform solution was washed successively with 100 ml. of water, 100 ml. of 10% sodium hydroxide solution and 100 ml. of water. After the chloroform had been removed by evaporation the residue was triturated with petroleum ether (b.p. 60–70°). This mixture was filtered, and the solid so obtained was recrystallized from a mixture of equal volumes of benzene and petroleum ether (b.p. 60–70°). There was obtained 36.6 g. (71%) of 3-bromo-6-methoxy-4-chromanone, m.p. 83–91°. This compound was very irritating to sensitive skin areas.

Three more recrystallizations of a sample of the above compound from the same solvent gave material melting at 92–94°.

Anal. Calcd. for $C_{10}H_9BrO_3$: Br, 31.16. Found: Br, 31.63.

6-Methoxychromone.—A mixture of 10 g. (0.039 mole) of 3-bromo-6-methoxy-4-chromanone and 14 g. (0.078 mole) of 25% dimethylamine solution was stirred at room temperature for 24 hours. The aqueous layer was removed by decantation. The residue was mixed with 10% hydrochloric acid, and the solid that formed was filtered off and washed with cold water. Recrystallization from hot water (*ca.* 250 ml.) resulted in a white crystalline solid melting at 91–93°. The yield was 4.5 g. (65%).

A portion of the product was recrystallized four times from water treating twice with charcoal during recrystallization. The final melting point was 92–94°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.54. Found: C, 68.23; H, 4.68.

Aminochromanones.—These were synthesized by the Mannich reaction according to the directions of Harradence, Hughes and Lions.[3] In many cases it was possible to crystallize the product directly from the reaction mixture without using the purification procedure of the above authors. These compounds are shown in Table II. All except compounds 12, 13 and 14 are new. The last compound in the table, 2,5-dimethoxy-(β-dimethylamino)-propiophenone hydrochloride, was also synthesized by a Mannich reaction by the same experimental procedure.

3-Dimethylaminomethyl-6-methoxy-4-chromanone.—Four grams (0.1 mole) of sodium hydroxide was added to a solution of 20 g. (0.074 mole) of 3-dimethylaminomethyl-6-methoxy-4-chromanone hydrochloride in 200 ml. of water. The solution was extracted with four 100-ml. portions of ether. Evaporation of the ether from the combined extracts under reduced pressure at room temperature left a clear, slightly yellow liquid weighing 17.1 g. Attempted distillation of the liquid under a pressure of 0.15 mm. resulted in decomposition. The base could not be induced to solidify by refrigeration at −10° for several days. A small sample was maintained under a pressure of 0.15 mm. at room temperature for eight hours. This sample had $n^{25}D$ 1.5495 and was analyzed:

Anal. Calcd. for $C_{13}H_{17}NO_3$: N, 5.96. Found: N, 6.23.

Decomposition of 3-Dimethylaminomethyl-6-methoxy-4-chromanone Hydrochloride.—Twenty grams of 3-dimethylaminomethyl-6-methoxy-4-chromanone hydrochloride was dissolved in 180 ml. of water. After 12 hours of standing at room temperature a yellow oil had precipitated. At the end of seven days standing the supernatant liquid was poured off and evaporated to dryness. The residue was recrystallized four times from alcohol. There was obtained 6.4 g. of starting material, m.p. and mixed m.p. 155–157.5°.

Anal. Calcd. for $C_{13}H_{18}ClNO_3$: Cl, 13.07. Found: Cl, 12.74.

The filtrates from purification of the above salt were combined and evaporated to dryness. Addition of 20% potassium hydroxide solution to the residue caused evolution of a basic gas which was probably dimethylamine.

(17) Ng. Ph. Buu-Hoï and P. Cagniant, *Rec. trav. chim.*, **64**, 214 (1945).

The water insoluble precipitate from the seven days standing was purified by solution in chloroform and precipitation by addition of alcohol. This was done three times to give a white solid melting at 200–235°.

Anal. Calcd. for $(C_{11}H_{10}O_3)_x$: C, 69.47; H, 5.26. Found: C, 68.83; H, 5.49; mol. wt., very high.

Decompostion of Other Aminochromanone Hydrochlorides.—Ten per cent. aqueous solutions of compounds 1, 5, 8 and 18 of Table II deposited insoluble oils after 20 hours of standing at room temperature.

INDIANAPOLIS, INDIANA RECEIVED MARCH 30, 1951

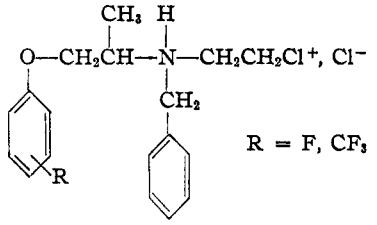
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Synthesis of Some Fluorine Substituted Adrenergic Blocking Agents

BY ALBERT F. LINDENSTRUTH[1] AND CALVIN A. VANDERWERF

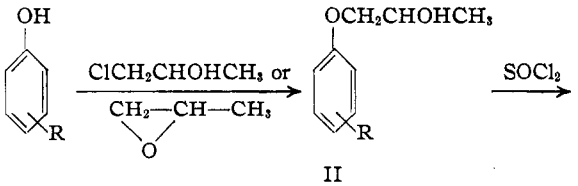
Synthesis and data on the adrenergic blocking activity of the hydrochlorides of N-benzyl-N-(2-chloroethyl)-1-(2-, 3- and 4-fluoro- and 2- and 3-trifluoromethyl-phenoxy)-isopropylamine are reported. The 4-fluorophenyl compound was the most active of the agents tested. Physical constants for these products and other new fluorine containing compounds prepared as intermediates are reported.

The discovery[2] that N-(2-chloroethyl)-dibenzylamine (Dibenamine)[3] hydrochloride blocks and reverses the excitatory effects of epinephrine has stimulated marked interest in N,N-disubstituted β-chloroethylamines as adrenergic blocking agents. An interesting series of compounds of this type which show noteworthy adrenergic blocking activity are the N-benzyl-N-(2-chloroethyl) hydrochlorides substituted in the phenoxy ring by alkyl groups, reported by Gump and Nikawitz.[4] As part of a study dealing with the effect of the substitution of fluorine into the molecule on the pharmacological behavior of medicinals, we have synthesized for pharmacological evaluation a series of closely related compounds, the N-benzyl-N-(2-chloroethyl)-1-(2-, 3- and 4-fluoro- and 2- and 3-trifluoromethyl-phenoxy)-isopropylamine hydrochlorides (I).

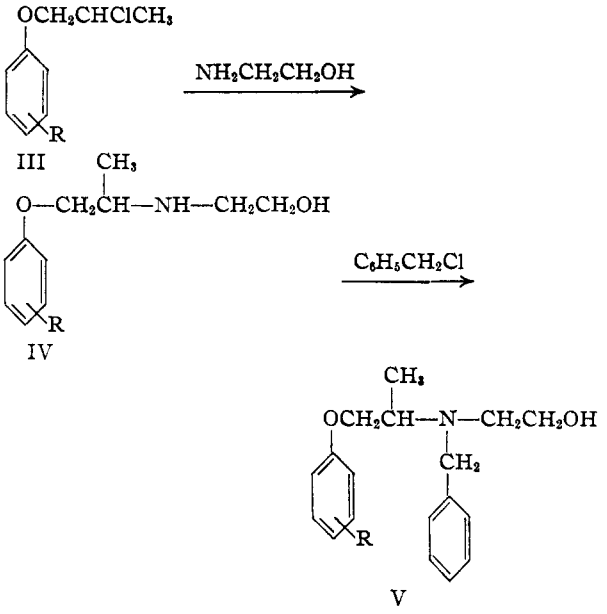


I

All of these compounds were prepared from the corresponding amino alcohols by treatment with thionyl chloride. The intermediate tertiary amino alcohols were synthesized from the appropriate fluoro- or trifluoromethyl-phenols according to the scheme



II



Because of the lability of *o*-trifluoromethylphenol in basic solution, its condensation with propylene chlorohydrin and with propylene oxide[5] to yield 1-(2-trifluoromethylphenoxy)-2-propanol presented experimental difficulties and the yield was poor.

In the condensation reactions of propylene chlorohydrin with the sodium salts of the various phenols, it was observed that an almost quantitative amount of sodium chloride was precipitated rapidly, before appreciable quantities of the desired ether could be isolated from the mixture. Immediate working up of the material at this stage led to recovery of most of the starting phenol. Obviously, the condensation reaction of propylene chlorohydrin with sodium phenoxides proceeds, at least in part, *via* the epoxide. It was also found that the epoxide and the chlorohydrin could be used interchangeably in the reactions. These facts suggest that proof of structure of an alcohol formed in a base-catalyzed condensation with a halohydrin, based on the assumption that the attacking base directly replaces the halogen atom, is not reliable. Assignment of structure in the present work follows from the fact that the

(1) E. I. du Pont de Nemours & Co., Waynesboro, Virginia.

(2) M. Nickerson and L. S. Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharmacol. Exptl. Therap.*, **89**, 167 (1947); M. Nickerson and W. S. Gump, *ibid.*, **97**, 25 (1949).

(3) Trademark of Smith, Kline and French Laboratories, Philadelphia, Pa.

(4) W. S. Gump and E. J. Nikawitz, THIS JOURNAL, **72**, 3846 (1950).

(5) A. R. Sexton and E. C. Britton, *ibid.*, **70**, 3606 (1948).