3-Amino-4-chromanone Hydrochlorides

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The synthesis of some 3-amino-4-chromanone hydrochlorides as potential inhibitors of gastric secretion is described.

In spite of the extensive literature on 4-chromanones and flavanones, at the time this work was undertaken little attention had been paid to 3-amino-4-chromanone hydrochlorides. In fact, the claim[1] to have prepared 3-diethylamino-4-chromanone had been shown to be incorrect.[2,3] The synthesis of such compounds for biological evaluation was, therefore, undertaken.

3-Amino-4-chromanone hydrochloride was readily obtained from 4-chromanone O-(*p*-tolylsulfonyl)oxime by the Neber rearrangement. A similar reaction had been described with flavanones[4] and since this work was completed it has also been reported with 4-chromanones.[5]

Biological examination of 3-amino-4-chromanone hydrochloride showed that it was an active gastric secretory inhibitor. The series of related compounds described in this paper was therefore prepared but little activity was shown by other members of the series.

Chemistry.—The preparation of 4-chromanones, their conversion to O-(*p*-tolylsulfonyl)oximes, and the method used to effect the rearrangement of the latter to 3-amino-4-chromanone hydrochlorides are described in the Experimental Section.

Not unexpectedly, 3-amino-4-chromanone hydrochloride was unstable in base, an intermolecular Schiff's base being among the products of the reaction. The ether linkage of the chromanone ring, however, showed a high degree of stability to acid. Evidence for this, descriptions of the contrasting reactions of 3-amino-4-chromanone hydrochloride with potassium cyanate and potassium thiocyanate, and some observations of the formation of *cis* and *trans* isomers of 3-amino-2-methyl-4-chromanone hydrochloride are also given in the Experimental Section.

Pharmacology.—The gastric antisecretory properties of many of the aminochromanone hydrochlorides were studied by Dr. Paul Bass using a previously described technique.[6] The results are given in Table II.

Experimental Section[7]

Phenoxypropionitriles (from the reaction of phenols and acrylonitrile) and phenoxypropionic acids (either by hydrolysis of the appropriate nitrile or from the appropriate phenol and β-propiolactone) were prepared by standard methods. 3-(2,5-Dichlorophenoxy)propionic acid [white needles, mp 145–146° (from C_6H_6–petroleum ether) *Anal.* ($C_9H_8Cl_2O_3$) C, H] and 3-[(6-chloro-*m*-tolyl)oxy]propionic acid [white needles, mp 121–122° (from C_6H_6–petroleum ether) *Anal.* ($C_{10}H_{11}ClO_3$) C, H] do not appear to have been previously described. It has been noted both in the case of 3-(2,5-dichlorophenoxy)propionic acid and with 3-(*m*-nitrophenoxy)propionic acid that the partition coefficient of the acid in Et_2O–saturated $NaHCO_3$ favors the Et_2O phase and yields are improved considerably if extraction into $NaHCO_3$ is avoided.

4-Chromanones.—Cyclizations of phenoxypropionitriles or phenoxypropionic acids in the presence of a dehydrating agent or of phenoxypropionyl chlorides under Friedel–Craft conditions were used to prepare 4-chromanones unsubstituted in the 2 position.[1,8] The following is an illustration of the preparation (based on the method of Cavill, *et al.*[9]) of 2-methyl-4-chromanone using the Fries rearrangement. $AlCl_3$ (150 g, 1.1 moles) was added in portions to phenyl crotonate (162 g, 1 mole) in petroleum ether (bp 80–100°) (1100 ml). After allowing a 15-min induction period, the mixture was refluxed for 24 hr. (The mixture turned yellow after 1.5 hr, and set solid after 5–6 hr.) A mixture of ice (750 g) and 2 *N* HCl (500 ml) was added, the petroleum ether was separated, and the aqueous phase was extracted with C_6H_6. The organic phase was washed (H_2O) and dried (Na_2CO_3), and the solvent was removed to give a dark oil (85 g) which, on distillation, afforded a mixture of 2-methyl-4-chromanone, unchanged starting material, and some uncyclized intermediates (from both *ortho* and *para* migration). The latter were removed by washing with 2 *N* NaOH and the 2-methyl-4-chromanone was isolated by distillation or as its oxime (50 g).

The above conditions afforded 28.5% of the chromanone, 5.25% unchanged starting material, and 6.4% of uncyclized intermediates. Various other conditions were tried. Longer reflux times reduced the yield. Reduction of the time of reflux to 5 hr had little effect on the yield of 2-methyl-4-chromanone although there was a considerably higher amount of unchanged starting material. Increasing the proportion of $AlCl_3$ to 1.6 *M* gave a 26% yield of 2-methyl-4-chromanone and apparently no unchanged crotonate, but a further increase in the $AlCl_3$ to 2.2 *M* gave mainly uncyclized intermediates. Nitrobenzene and CCl_4 were also used as solvents but with no marked success.

Previously unreported chromanones are listed in Table I.

The following description illustrates an alternative procedure. *p*-Chlorophenol (11.25 g, 0.1 mole) and crotonic acid (17.2 g, 0.2 mole) were stirred vigorously with polyphosphoric acid (50–100 ml) at 120° for 8 hr. The slightly cooled mixture was poured onto crushed ice and 2 *N* NaOH (450 ml) and $CHCl_3$ (500 ml) were added and stirred until two homogeneous phases were obtained. The aqueous solution was extracted with $CHCl_3$ and the combined $CHCl_3$ solutions were washed with 2 *N* NaOH and H_2O. Evaporation of the dried $CHCl_3$ solution gave the chromanone as a gum (11 g) which could be purified by distillation or converted to the oxime directly.

(1) J. Colonge and A. Guyot, *Bull. Soc. Chim. France*, 329 (1958).

(2) P. W. Feit, *Acta Chem. Scand.*, **18**, 2401 (1964).

(3) I. M. Lockhart and E. M. Tanner, *J. Chem. Soc.*, 3610 (1965).

(4) C. O'Brien, E. M. Phillbin, S. Ushioda, and T. S. Wheeler, *Tetrahedron*, **19**, 373 (1963).

(5) N. V. Dudykina and V. A. Zagorevskii, *J. Org. Chem. USSR*, **2**, 2179 (1966).

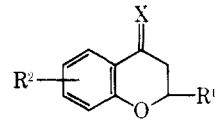
(6) R. F. Meyer, B. L. Cummings, P. Bass, and H. O. J. Collier, *J. Med. Chem.*, **8**, 515 (1965).

(7) Melting points are corrected and were determined in a capillary tube. Boiling points are uncorrected. Nmr spectra were determined in D_2O using TMS as standard. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Petroleum ether refers to the fraction of bp 60–80° unless otherwise stated.

(8) D. Huckle, I. M. Lockhart, and M. Wright, *J. Chem. Soc.*, 1137 (1965).

(9) G. W. K. Cavill, F. M. Dean, A. McGookin, B. M. Marshall, and A. Robertson, *ibid.*, 4573 (1954).

TABLE I
INTERMEDIATES



R¹	R²	X	Mp, °C	Form	Crystd from	Formula	Analyses
H	5,8-Cl_2	O	69–70	*a*	*c*	$C_9H_6Cl_2O_2$	C, H
H	5-Me, 8-Cl	O	42–43	*a*	*d*	$C_{10}H_9ClO_2$	C, H
H	7-NO_2	O	130–132	*a*	*e*	$C_9H_7NO_4$	C, H, N
H	5,8-Cl_2	NOH	167–169	*a*	*e*	$C_9H_7Cl_2NO_2$	C, H, N
H	5-Me, 8-Cl	NOH	130–131	*a*	*e*	$C_{10}H_{10}ClNO_2$	C, H, N
H	6,8-Cl_2	NOH	158–159.5	*a*	*e*	$C_9H_7Cl_2NO_2$	C, H, N
H	7-NO_2	NOH	185–186	*a*	*e*	$C_9H_8N_2O_4$	C, H, N
H	8-NO_2	NOH	186–187	*a*	*e*	$C_9H_8N_2O_4$	C, H, N
H	8-Cl	NOH	159.5–160.5	*a*	*e*	$C_9H_8ClNO_2$	C, H, N
H	5-Me, 8-Cl	NOTos[b]	128–130	*a*	*f*	$C_{17}H_{16}ClNO_4S$	C, H, N
H	6,8-Cl_2	NOTos	177–178	*a*	*f*	$C_{16}H_{13}Cl_2NO_4S$	C, H, N
H	7-NO_2	NOTos	166–168	*b*	*f*	$C_{16}H_{14}N_2O_6S$	C, H; N[g]
Me	6-Cl	NOTos	189–196	*b*	*f*	$C_{17}H_{16}ClNO_4S$	C, H, N
H	8-Cl	NOTos	120–121	*a*	*f*	$C_{16}H_{14}ClNO_4S$	C, H, N
H		NOTos	145–146	*b*	*f*	$C_{20}H_{17}NO_4S$	C, H, N

[a] Needles. [b] Prisms. [c] C_6H_6–petroleum ether. [d] Distilled as a colorless oil, bp 184° (26 mm). [e] C_6H_6. [f] Washed with EtOH. [g] N: calcd, 7.7; found, 7.2. [h] Tos = *p*-$CH_3C_6H_4SO_2$.

Flavanone.—Flavanone was prepared according to the method of Reichel and Müller[10] except that the use of 0.1 *N* NaOH at 37° was replaced by an equivalent amount of 1 *N* NaOH at room temperature. This resulted in a considerable improvement in the yield, raising it to about 80%. The method was convenient and combined the advantages of the various methods reported by Reichel and his collaborators[10,11] without suffering the attendant disadvantages.

4-Chromanone O-(*p*-tolylsulfonyl)oximes.—4-Chromanones were converted to their oximes and the O-(*p*-tolylsulfonyl)oximes prepared as described by O'Brien, *et al.*[4] The tosylates were not normally purified but were washed with EtOH, dried, and used directly.

New 4-chromanone oximes and 4-chromanone O-(*p*-tolylsulfonyl)oximes which were obtained analytically pure are listed in Table I.

3-Amino-4-chromanone Hydrochlorides.—O-(*p*-Tolylsulfonyl)oximes were suspended in C_6H_6 and shaken or stirred with NaOEt at room temperature for 21 hr as previously described.[4] 3-Amino-4-chromanone hydrochlorides prepared by this method are listed in Table II. In the case of 5,7-dimethyl- and 2,5,7-trimethyl-4-chromanone O-(*p*-tolylsulfonyl)oximes it was found advantageous to heat the reaction mixture on a steam bath for up to 1 hr in addition to the period of stirring at room temperature. Such treatment increased the yield of the appropriate 3-amino-4-chromanone hydrochloride from 17 to 60% in the case of these sterically hindered O-(*p*-tolylsulfonyl)oximes.

In a variety of instances, it was shown that there was no essential difference in using KOEt or NaOEt in the Neber reaction with 4-chromanone O-(*p*-tolylsulfonyl)oximes unsubstituted in the 2 position. In the case of 2-methyl-4-chromanone O-(*p*-tolylsulfonyl)oxime, a comparison was made using NaOMe, NaOEt, NaO-*i*-Pr, and NaO-*t*-Bu; the yields of 3-amino-2-methyl-4-chromanone hydrochloride obtained were 50, 52, 60, and 23%, respectively. However, the products showed some variation in the proportions of the different stereoisomers present as determined by nmr spectra. [Each isomer gave a doublet for 2-CH_3, one centered at τ 8.51 (J = 6.5 cps), and the other centered at 8.22 (J = 5.5 cps).]

3-(Dimethylamino)-4-chromanone Hydrochloride.—3-Amino-4-chromanone hydrochloride was dimethylated by hydrogenation in the presence of formaldehyde using 10% Pd-C as catalyst.

Action of Triethylamine on 3-Amino-4-chromanone Hydrochloride.—3-Amino-4-chromanone hydrochloride (20 g), NEt_3 (20 ml), and H_2O (50 ml) were shaken at room temperature for 18 hr. The orange-red solid was filtered off, washed with H_2O, EtOH, and Et_2O, and dried. Recrystallization from EtOAc (550 ml) afforded orange needles (4.2 g), mp 252–254°. Ir and uv spectra indicated that the product was essentially 6,6a,13,13a-tetrahydrobis[1]benzopyrano[3,4-*b*:3′,4′-*e*]pyrazine. *Anal.* ($C_{18}H_{14}N_2O_2$) C, H, N.

3-Acetamido-4-chromanones.—3-Amino-2-methyl-4-chromanone hydrochloride (6 g), H_2O (30 ml), EtOAc (100 ml), Ac_2O (15 ml), and NaOAc (12.3 g) were stirred for 4 hr. The acetamidochromanone was isolated from the EtOAc in 91% yield as needles of mp 148–150° (from C_6H_6). In acetylations of 3-amino-2-methyl-4-chromanone hydrochloride, it was found that the product was always the same, single isomer, regardless of the isomeric compositions of the starting chromanone, as determined by the nmr spectrum [doublet for the 2-methyl group centered at τ 8.48 (J = 6.0 cps)].

Hydrolysis of 3-Acetamido-4-chromanones.—Hydrolysis of 3-acetamido-4-chromanones to the corresponding 3-amino-4-chromanone hydrochlorides was achieved by refluxing with 2 *N* HCl. When examined by nmr spectroscopy, samples of 3-amino-2-methyl-4-chromanone hydrochloride obtained by such hydrolysis were always a single isomer [doublet for the 2-methyl group centered at τ 8.22 (J = 5.5 cps)] whatever the stereoisomeric composition of the 3-amino-2-methyl-4-chromanone hydrochloride was prior to acetylation.

3-Amino-6-hydroxy-4-chromanone Hydrobromide.—3-Amino-6-methoxy-4-chromanone hydrochloride (1.8 g) was refluxed in HBr (20 ml, 48% w/w) for 2 hr. The solid which separated on cooling was charcoaled in boiling EtOH. Addition of Et_2O to the EtOH solution afforded the 6-hydroxy compound as a pale yellow microcrystalline solid (1.2 g) (see Table II).

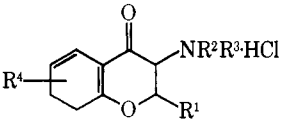
4-Oxo-3-chromanylurea.—3-Amino-4-chromanone hydrochloride (5.0 g) in H_2O (40 ml) and KCNO (2.2 g) were heated on a steam bath for 1 hr. The mixture was cooled and filtered, and the residue was washed with H_2O until the washings showed pH 4. The solid was recrystallized from EtOAc (200 ml) to give 1.5 g of cream rods, mp 200–225° dec. *Anal.* ($C_{10}H_{10}N_2O_3$) C, H, N.

3,4-Dihydro[1]benzopyrano[3,4-*d*]imidazole-2(1H)-thione.—3-Amino-4-chromanone hydrochloride (20 g) and KCNS (10.8 g) in H_2O (160 ml) were refluxed for 3 hr. The pale yellow solid

(10) L. Reichel and K. Müller, *Chem. Ber.*, **74B**, 1741 (1941).
(11) L. Reichel and W. Burkart, *ibid.*, **74B**, 1802 (1941).

TABLE II

3-AMINO-4-CHROMANONE HYDROCHLORIDES AND RELATED COMPOUNDS



Compd	R¹	R²	R³	R⁴	Mp, °C dec	Form	Crystd from	Yield, %	Formula	Analyses	Gastric antisecretory ED_{50} (rat), mg/kg sc[p]
1	H	H	H	H	192–193	*a*	*g*	77	$C_9H_{10}ClNO_2$	C, H, N	3.8
2	H	Me	Me	H	171–172	*a*	*g*	63	$C_{11}H_{14}ClNO_2$	C, H, N	21
3	H	H	COMe	H	106–108[o]	*b*	*h*	60	$C_{11}H_{11}NO_3$	C, H, N	2.6
4	H	H	COPh	H	167–168[o]	*a*	*g*	58	$C_{16}H_{13}NO_3$	C, H, N	N
5	Me	H	H	H	227–228	*a*	*g*	62	$C_{10}H_{12}ClNO_2$	C, H, N	N
6	Me	Me	Me	H	194–195	*b*	*g*	78	$C_{12}H_{16}ClNO_2 \cdot 0.25H_2O$	C, H, N	N
7	Ph	H	H	H	202–204	*b*	*i*	19	$C_{15}H_{14}ClNO_2$	C, H, N	N
8	Ph	H	COMe	H	192–193[o]	*b*	*j*	58	$C_{17}H_{15}NO_3$	C, H, N	N
9	H	H	H	6-Me	238–239	*b*	*g*	55	$C_{10}H_{12}ClNO_2$	C, H, N	50
10	H	H	H	7-Me	195–197	*b*	*k*	58	$C_{10}H_{12}ClNO_2$	C, H, N	58
11	H	H	H	8-Me	223–225	*a*	*g*	79	$C_{10}H_{12}ClNO_2 \cdot 0.25H_2O$	C, H, N	30
12	Me	H	H	6-Me	214–216	*a*	*g*	79	$C_{11}H_{14}ClNO_2$	C, H, N	N
13	H	H	H	6-MeO	228–229	*c*	*g*	53	$C_{10}H_{12}ClNO_3$	C, H, N	>20
14	H	H	H	7-MeO	236–237	*d*	*g*	40	$C_{10}H_{12}ClNO_3$	C, H, N	>25
15	H	H	H	8-MeO	220	*d*	*g*	33	$C_{10}H_{12}ClNO_3$	H, N; C[n]	N
16	Me	H	H	6-MeO	220–221	*a*	*g*	46	$C_{11}H_{14}ClNO_3 \cdot 0.5H_2O$	C, H, N	
17	H	H	H	6-OH	249–250	*e*	*k*	53	$C_9H_{10}BrNO_3$	C, H, N	N
18	H	H	H	6-Cl	235–236	*a*	*k*	38	$C_9H_9Cl_2NO_2$	C, H, N	>25
19	H	H	H	8-Cl	233–234	*a*	*l*	60	$C_9H_9Cl_2NO_2 \cdot 0.5H_2O$	C, H, N	
20	Me	H	H	6-Cl	215–220	*a*	*g*	42	$C_{10}H_{11}Cl_2NO_2$	C, H, N	
21	H	H	H	5-Me, 8-Cl	225–226	*a*	*l*	40	$C_{10}H_{11}Cl_2NO_2$	C, H, N	
22	H	H	H	5,8-Cl_2	227–228	*b*	*l*	74	$C_9H_8Cl_3NO_2$	C, H, N	
23	H	H	H	6,8-Cl_2	219–221	*a*	*l*	23	$C_9H_8Cl_3NO_2$	C, H, N	
24	H	H	H	5,7-Me_2	219–220	*f*	*g*	60	$C_{11}H_{14}ClNO_2$	C, H, N	
25	Me	H	H	5,7-Me_2	225–231	*a*	*g*	42	$C_{12}H_{16}ClNO_2$	C, H, N	
26	H	H	H	6-NO_2	234–236	*a*	*l*	44	$C_9H_9ClN_2O_4$	C, H, N	
27	H	H	H	7-NO_2	236–238	*a*	*l*	43	$C_9H_9ClN_2O_4 \cdot 0.5H_2O$	C, H, N	
28	H	H	H	8-NO_2	298	*a*	*l*	32	$C_9H_9ClN_2O_4$	C, H, N	
29	H	H	H		242	*d*	*g*	23	$C_{13}H_{12}ClNO_2 \cdot 0.25H_2O$	C, H, N	
30	H	H	H		248–250	*d*	*m*	48	$C_{13}H_{12}ClNO_2 \cdot 0.25H_2O$	C, H, N	

[a] Needles. [b] Prisms. [c] Plates. [d] Microcrystalline. [e] Yellow microcrystalline monohydrobromide. [f] Rods. [g] EtOH. [h] C_6H_6–petroleum ether. [i] 0.5 *N* HCl. [j] C_6H_6. [k] EtOH–Et_2O. [l] 2 *N* HCl. [m] MeOH. [n] C: calcd, 52.3; found, 51.8. [o] Melts with no decomposition. [p] N = compound inactive at 25 mg/kg.

which separated on cooling was filtered off, washed (H_2O), and dried. The solid was boiled with EtOH (300 ml), cooled, and filtered to give the crude thione as a yellow solid (14 g) which on analysis contained some inorganic residue. A sample of the crude thione (6.6 g) was stirred with H_2O (100 ml) for 1 hr. The solid was filtered off, washed (H_2O, EtOH, Et_2O), and dried to give the thione as a pale yellow microcrystalline solid (5.7 g) which decomposed with an indeterminate mp >270°. *Anal.* ($C_{10}H_8N_2OS$) C, H, N.

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