[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF "RECORDATI S.P.A."]

Mannich Reaction on 7-Hydroxychromones and Flavones. Synthesis of Powerful Central Nervous System Stimulants

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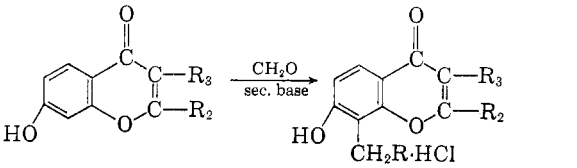
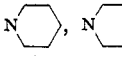
The application of the Mannich reaction to 7-hydroxychromones and flavones, which gives rise to the corresponding 8-aminomethyl derivatives, is described. Experimental proof of the position taken by the aminomethyl group is given. These derivatives act as powerful central nervous system stimulants, especially on the brain stem, and have a cardiokinetic and hypertensive action. The central nervous system stimulating activity of many of these compounds proved to be considerably greater than that of pentamethylentetrazol, which was taken as the standard.

Previous research[1,2] on the chromone and flavone groups led to the discovery of a new class of powerful central nervous system stimulants: the *N*-substituted 7-methoxy-8-aminomethyl derivatives. Pursuing this line of research, we prepared some Mannich bases starting from 7-hydroxychromones and flavones, substituted in the 2 and 3 positions, in order to extend the pharmacological investigation to derivatives with a free phenolic hydroxy group and to compounds not attainable by the procedure hitherto used.[2,3]

The application of the Mannich reaction to phenolic compounds is well known.[4,5] Wiley[6] tried it on the benz-substituted (including 7-methoxy) but 2,3-unsubstituted chromones; however, as far as we know, it has not been applied to 7-hydroxychromones and flavones. The conventional procedure was used, *i.e.*, condensation of the phenolic derivatives with formaldehyde and a secondary base such as dimethyl- or diethylamine, piperidine, or morpholine, in ethanol:



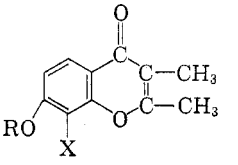
R_2 = CH_3, C_2H_5, C_6H_5
R_3 = H, CH_3, C_2H_5
R = $N(CH_3)_2$, $N(C_2H_5)_2$



The products were isolated as hydrochloride salts.

The position of the introduced aminomethyl group can be predicted on the basis of Rangaswami and Seshadri's work.[7] These authors, using the Claisen rearrangement on 7-allyloxyflavones, found that there was a peculiar distribution of aromatic double bonds in 7-hydroxyflavones, similar in every respect to that of β-hydroxynaphthalene, and such as to render the 8- position more reactive, as shown by the fact that they obtained 8-allyl derivatives.

Indeed, the Mannich reaction led to the 8-aminomethyl derivatives, as shown by the following series of reactions, limited to 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone (I). The same behavior was exhibited by the analogous flavone derivative (see Experimental).



I. R = H, X = $CH_2N(CH_3)_2$
II. R = H, X = CHO
III. R = H, X = H
IV. R = H, X = OH
V. R = CH_3CO, X = CH_2OOCCH_3
VI. R = H; X = CH_2OH
VII. R = H; X = CH_2N ⟨⟩ ; CH_2N ⟨O⟩
VIII. R = CH_3, X = CHO
IX. R = CH_3, X = CH_2OH
X. R = CH_3, X = CH_2OOCCH_3

Compound I, by boiling with acetic acid in the presence of hexamine, was converted into the 8-aldehydo-derivative (II), also obtainable by the Duff reaction from 7-hydroxy-2,3-dimethylchromone (III). The oxidation of II, following the Dakin modification of the Bayer-Williger procedure,[8] led to the corresponding 7,8-dihydroxy compound (IV), already described by Robertson *et al.*[9]

By boiling I with acetic anhydride using the Tiffeneau procedure[10] for *tert*-benzylamines, the dimethylamino group could be replaced by the ace-

(1) P. Da Re, L. Verlicchi, I. Setnikar, W. Murmann, and M. J. Magistretti, *Nature*, **184**, 362 (1959).
(2) P. Da Re, L. Verlicchi, and I. Setnikar, *Arzneimittel-Forsch.*, **10**, (1960), in press.
(3) P. Da Re, and L. Verlicchi, *Ann. Chim. (Rome)*, **46**, 904 (1956).
(4) F. F. Blicke, *Org. Reactions*, **1**, 314 (1942).
(5) Houben-Weyl, *Methoden der Organischen Chemie*, Vol. XI/1, George Thieme Verlag, Stuttgart, 1957, p. 755.
(6) P. F. Wiley, *J. Am. Chem. Soc.*, **74**, 4326 (1952).
(7) S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **9A**, 1, 7 (1939).
(8) C. H. Hassal, *Org. Reactions*, **9**, 73 (1957).
(9) F. W. Canter, A. R. Martin, and A. Robertson, *J. Chem. Soc.*, 1877 (1931).
(10) M. Tiffeneau and K. Fuhrer, *Bull. soc. chim. France*, **15**, 162 (1914).

toxy group, thereby yielding V, also obtainable by acetylating VI. The catalytic reduction of II (hydrogen on platinum at atmospheric pressure) led to the 8-hydroxymethyl derivative (VI) and the same course of the hydrogenolysis was observed with the 8-formyl-7-hydroxy-3-methylflavone (XI).

For an analogous compound, *i.e.*, the 8-formyl-7-hydroxy-3-methoxyflavone (XII), Rangaswami and Seshadri[7] obtained the 8-methyl derivative, as was to be expected if the reaction analogy between 7-hydroxyflavones and β-naphthol could be extended to the formyl derivatives: indeed, 1-formyl-2-hydroxynaphthalene is hydrogenolyzed to the 1-methyl-2-hydroxy derivative.[11]

The different behavior of II and XI as compared with XII could, perhaps, be attributed to the substituent in the 3-position, considering the influence exerted by a 2- or 3-substituent on the reactivity of the positions of the aromatic ring. Kelkar and Limaye[12] have shown that an acyl group in the 3-position of 7-benzoyloxy-2-methylchromone exerts an inhibitive influence on the Fries rearrangement, and one of us[13] has also noted that the nitration of some chromones takes a different course if an alkyl group is in the 2-position.

The reaction analogy, on the other hand, was observable between the products we have described and the β-naphthol Mannich bases: in both cases it was possible, with the amine exchange reaction, to substitute a secondary base such as piperidine or morpholine for the dimethylamino group (VII) using the Snyder and Brewster procedure.[14] The methylation of II gave the 7-methoxy derivative (VIII), the reduction of VIII yielded 8-hydroxymethyl-7-methoxy-2,3-dimethylchromone (IX), which was then acetylated to X. The mixture melting points of IX and X with authentic samples of the identical products obtained by another procedure as described earlier,[8] did not show depression.

As Rangaswami and Seshadri observed[7] in connection with the distribution of the aromatic double bonds in 7-hydroxyflavones, the 6-position also can become reactive. In fact, by carrying out the Mannich reaction on 7-hydroxy-2,3-dimethylchromone using two moles of piperidine and two moles of formaldehyde, the 6,8-dipiperidinomethyl derivative was obtained.

The compounds prepared and their pharmacological activity are summarized in Table I.

Pharmacological acknowledgment. The *N*-substituted 7-hydroxy-8-aminomethylchromones and flavones, like their 7-methoxy analogues, exert an intense stimulant action upon the central nervous system, probably at brain stem level. Administered in adequate doses by oral or parenteral route to mice, rats, rabbits, cats, or dogs, they cause clonic convulsions, followed by maximal tonic extension seizures. The general toxic picture is very similar to that induced by pentamethylentetrazol.

Although generally less active than their 7-methoxy analogues, some of the derivatives under examination were quite interesting. For example, the 3-methyl-7-hydroxy-8-dimethylaminomethylflavone (compound 21) is about nine times more active than pentamethylentetrazol, 2-ethyl-3-methyl-7-hydroxychromone (compound 9) about eight times more active, and the 2,3-dimethyl analogue (compound 1) is seven times more active than this well known bulbar stimulant. Furthermore, almost all these new derivatives, if administered intravenously in doses equivalent to a .1 to .05 of their intraperitoneal LD_{50}, exert pronounced and prolonged hypertensive and cardiokinetic effect. In addition, they have an intense respiratory stimulant action. This latter action together with the hypertensive and central nervous system stimulant actions should mean that these substances are indicated in cases of severe depression of the central nervous system, such as after barbiturate poisoning. In fact, mice intoxicated with lethal doses of pentobarbital survive if they are treated with these stimulants. A more detailed report on the pharmacology of these derivatives will be published elsewhere.[15]

EXPERIMENTAL

To exemplify the synthesis of the products of Table I, we shall describe the synthesis of 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone hydrochloride.

8-Dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone-hydrochloride (I). To nine grams of 7-hydroxy-2,3-dimethylchromone in 300 ml. of ethyl alcohol, 5.5 ml. of 40% dimethylamine, and 5 ml. of formalin were added and the mixture was refluxed for 5 or 6 hr. After cooling, the mixture was acidified with alcoholic hydrochloric acid, concentrated, and again cooled until a precipitate formed. The solid was filtered and purified on crystallization from alcohol. The white crystalline product, so obtained, weighed 6.3 g. and melted at 213–214°.

8-Formyl-7-hydroxy-2,3-dimethylchromone (II). Two grams of 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone and 2 g. of hexamine in 20 ml. of glacial acetic acid were refluxed for 1 hr. The reaction mixture was poured into ice water-hydrochloric acid mixture and left to stand overnight. The solid which separated was filtered, washed with water, and dried. The crude product on crystallizing from 40% acetic acid gave 0.3 g. of light yellow solid, m.p. 184–186°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.23; H, 4.77.

A mixture melting point with a sample of the same product, prepared by the Duff reaction on 7-hydroxy-2,3-dimethylchromone, was not depressed.

7,8-Dihydroxy-2,3-dimethylchromone (IV). 8-Formyl-7-hydroxy-2,3-dimethylchromone (II) (0.8 g.) and 40 ml. of 0.1*N* sodium hydroxide, were diluted with water to 100 ml. and 29.6 ml. of 4.9% hydrogen peroxide were added, while stirring, in the course of half an hour. The mixture, after

(11) A. Windaus and H. Schiele, *Ber.*, **56**, 846 (1923).

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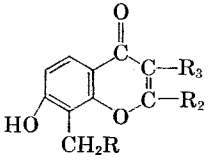
(13) P. Da Re, *Farmaco (Pavia) Ed. sci.*, **11**, 662 (1956).

(14) H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948).

(15) I. Setnikar, W. Murmann, M. J. Magistretti, and P. Da Re, *J. Pharmacol. exptl. Ther.*, **128**, 176 (1960).

TABLE I

N-SUBSTITUTED 7-HYDROXY-8-AMINOMETHYLCHROMONES AND FLAVONES[a]



Compound	R_2	R_3	R	M.P., °[b,c]	Yield, %	Formula	Hydrochloride Salts: Analysis: Chlorine % Calcd.	Chlorine % Found	Nitrogen % Calcd.	Nitrogen % Found	C.N.S.[d] stimulating activity[e]	Free Bases: M.P. °[b,c]	Nitrogen % Calcd.	Nitrogen % Found
1	CH_3	CH_3	$N(CH_3)_2$	213–214	47	$C_{14}H_{18}ClNO_3$	12.50	12.38	4.94	4.93	7.1	178–179	5.66	5.60
2	CH_3	CH_3	$N(C_2H_5)_2$	196–198	55	$C_{16}H_{22}ClNO_3$	11.37	11.40	4.49	4.50	3.5	180–182	5.09	5.16
3	CH_3	CH_3	$N{=}C_5H_{10}$	246–247	26	$C_{17}H_{22}ClNO_3$	10.95	10.94	4.33	4.32	1.1	162–163	4.87	4.85
4	CH_3	CH_3	$N{=}C_4H_8O$	255–258	60	$C_{16}H_{20}ClNO_4$	10.88	10.87	4.30	4.28	1.3	209–210	4.84	4.89
5	CH_3	C_2H_5	$N(CH_3)_2$	226–228	41	$C_{15}H_{20}ClNO_3$	11.90	11.88	4.71	4.78	2.8	125–127	5.36	5.44
6	CH_3	C_2H_5	$N(C_2H_5)_2$	198–199	45	$C_{17}H_{24}ClNO_3$	10.88	10.83	4.30	4.32	0.7	119–120	4.84	4.76
7	CH_3	C_2H_5	$N{=}C_5H_{10}$	227–229	46	$C_{18}H_{24}ClNO_3$	10.50	10.47	4.15	4.17	0.9	147–148	4.64	4.57
8	CH_3	C_2H_5	$N{=}C_4H_8O$	225–226	53	$C_{17}H_{22}ClNO_4$	10.43	10.43	4.12	4.12	0.7	172–174	4.61	4.58
9	C_2H_5	CH_3	$N(CH_3)_2$	199–201	35	$C_{15}H_{20}ClNO_3$	11.90	11.88	4.81	4.83	7.9	139–141	5.36	5.46
10	C_2H_5	CH_3	$N(C_2H_5)_2$	188–190	42	$C_{17}H_{24}ClNO_3$	10.88	10.85	4.30	4.28	1.8	159–160	4.84	4.89
11	C_2H_5	CH_3	$N{=}C_5H_{10}$	246–247	75	$C_{18}H_{24}ClNO_3$	10.50	10.45	4.15	4.17	1.3	133–134	4.64	4.72
12	C_2H_5	CH_3	$N{=}C_4H_8O$	247–249	55	$C_{17}H_{22}ClNO_4$	10.43	10.44	4.12	4.12	1.4	177–178	4.61	4.64
13	C_2H_5	C_2H_5	$N(CH_3)_2$	219–220	38	$C_{16}H_{22}ClNO_3$	11.37	11.38	4.49	4.48	3.1	—[f]	5.09	5.11
14	C_2H_5	C_2H_5	$N(C_2H_5)_2$	182–183	44	$C_{18}H_{26}ClNO_3$	10.43	10.45	4.12	4.11	1.6	100–101.5	4.62	4.67
15	C_2H_5	C_2H_5	$N{=}C_5H_{10}$	210–212	48	$C_{19}H_{26}ClNO_3$	9.85	9.83	3.89	3.88	0.9	118–119	4.44	4.51
16	C_2H_5	C_2H_5	$N{=}C_4H_8O$	225–226	59	$C_{18}H_{24}ClNO_4$	10.02	10.00	3.96	3.93	0.3	145–146	4.41	4.47
17	C_6H_5	H	$N(CH_3)_2$	243–244	52	$C_{18}H_{18}ClNO_3$	10.68	10.65	4.22	4.23	5.4	169–170	4.74	4.74
18	C_6H_5	H	$N(C_2H_5)_2$	205–207	66	$C_{20}H_{22}ClNO_3$	9.85	9.85	3.89	3.90	7.1	112–113.5	4.33	4.28
19	C_6H_5	H	$N{=}C_5H_{10}$	202–205	62	$C_{21}H_{22}ClNO_3$	9.53	9.52	3.77	3.78	1.6	180–181	4.18	4.18
20	C_6H_5	H	$N{=}C_4H_8O$	256–259 dec.	88	$C_{20}H_{20}ClNO_4$	9.48	9.47	3.75	3.73	1.4	189–190.5	4.15	4.09
21	C_6H_5	CH_3	$N(CH_3)_2$	225–226	55	$C_{19}H_{20}ClNO_3$	10.25	10.21	4.05	4.00	8.9	168–169	4.53	4.35
22	C_6H_5	CH_3	$N(C_2H_5)_2$	205–207	40	$C_{21}H_{24}ClNO_3$	9.48	9.43	3.75	3.76	2.0	172–173	4.15	4.19
23	C_6H_5	CH_3	$N{=}C_5H_{10}$	229–231	87	$C_{22}H_{24}ClNO_3$	9.19	9.18	3.63	3.61	0.6	190–191	4.01	4.00
24	C_6H_5	CH_3	$N{=}C_4H_8O$	232–233	54	$C_{21}H_{22}ClNO_4$	9.14	9.17	3.61	3.59	—[g]	237–238	3.98	3.98
25	C_6H_5	C_2H_5	$N(CH_3)_2$	225–227	40	$C_{20}H_{22}ClNO_3$	9.85	9.81	3.89	3.88	2.0	180–181	4.33	4.41
26	C_6H_5	C_2H_5	$N(C_2H_5)_2$	207–209	51	$C_{22}H_{26}ClNO_3$	9.14	9.15	3.61	3.61	2.6	114.5–115.5	3.99	3.95
27	C_6H_5	C_2H_5	$N{=}C_5H_{10}$	236–237	55	$C_{23}H_{26}ClNO_3$	8.87	8.90	3.50	3.48	0.3	118–119	3.85	3.91
28	C_6H_5	C_2H_5	$N{=}C_4H_8O$	229–230	62	$C_{22}H_{24}ClNO_4$	8.82	8.80	3.48	3.50	0.03	199–200	3.83	3.74
Pentamethylenetetrazol			—	—	—	—	—	—	—	—	1	—	—	—

[a] Ethanol was used as solvent for the synthesis of the products reported. The reaction temperature and the reaction time are the same as in the example described in the Experimental. [b] Melting points are not corrected. [c] Crystallizing solvent was alcohol/ether for the hydrochloride salts and ligroin for the free bases. [d] Central nervous system. [e] Activity is expressed as the reciprocal of the intraperitoneal LD_{50} determined in mice with reference to the reciprocal LD_{50} of metrazol (LD_{50} = 71 mg/kg). [f] The product has no sharp melting point. [g] This compound was not assayed pharmacologically because in aqueous solution it decomposed.

stirring again for 1 hr., became dark and a solid separated. Acidification with dilute hydrochloric acid, completed the precipitation of the product, which was then filtered, washed with water, and dried. Crystallization of the crude product from 70% acetic acid afforded a white crystalline solid, m.p. 230–231°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.13; H, 4.89.

The *diacetate* was a white crystalline solid, m.p. 149–150°. A mixture melting point of (IV) with an authentic sample of 7,8-dihydroxy-2,3-dimethylchromone, prepared according to Robertson *et al.*,[9] was not depressed.

8-Acetoxymethyl-7-acetoxy-2,3-dimethylchromone (V). One gram of 8-dimethylaminomethyl-7-hydroxy-2,3-dimethylchromone (I) and 1 g. of anhydrous sodium acetate in 15 ml. of acetic anhydride were refluxed for 2 hr. The reaction mixture was poured into ice water and left to stand overnight. The solid which separated was collected on filtration, washed with water, and dried. On crystallizing from ligroin the yield was 0.8 g. of white product, m.p. 127–129°.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.31. Found: C, 63.15; H, 5.10.

8-Hydroxymethyl-7-hydroxy-2,3-dimethylchromone (VI). A solution of 1.1 g. of 8-formyl-7-hydroxy-2,3-dimethylchromone (II) in 150 ml. of absolute ethanol, with 0.15 g. of platinum oxide, was hydrogenated at atmospheric pressure until absorption ceased. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The crude product (1.1 g.) on crystallizing from ethanol gave a white crystalline solid with no sharp melting point.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.27; H, 5.66.

The *diacetate* was prepared from VI by boiling with acetic anhydride as a white crystalline solid, m.p. 127–129°. A mixture melting point of this diacetate with a sample of V was not depressed.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.31. Found: C, 63.16; H, 5.23.

8-Formyl-7-methoxy-2,3-dimethylchromone (VIII). A mixture of 2.18 g. of 8-formyl-7-hydroxy-2,3-dimethylchromone, 60 ml. of anhydrous acetone, 3 g. of anhydrous potassium carbonate, and 1.5 g. of methyl sulfate was boiled for 8 hr., cooled, filtered, and the solid washed with hot acetone. Removal of acetone left a residue which on crystallizing from ethanol, 95°, gave 0.8 g. of 7-methoxy derivative, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.21. Found: C, 67.45; H, 5.44.

8-Hydroxymethyl-7-methoxy-2,3-dimethylchromone (IX). A solution of 1.16 g. of 8-formyl-7-methoxy-2,3-dimethylchromone (VIII) in 150 ml. of ethanol was hydrogenated, at atmospheric pressure, over 0.1 g. of platinum oxide catalyst until absorption ceased. After removal of the catalyst, the filtrate was concentrated to dryness and the crude product was crystallized from ethanol as a white crystalline powder, m.p. 188.5–189.5°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.64; H, 6.01. Found: C, 66.46; H, 5.80.

The *acetate* (X) was prepared from IX by boiling with acetic anhydride as white crystals from ligroin, m.p. 163–164°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 65.31; H, 5.57.

The mixture melting points of IX and X with the corresponding samples of the same products obtained by another procedure as described earlier,[3] were not depressed.

8-Acetoxymethyl-7-acetoxy-3-methylflavone. One gram of compound 21 (see Table I) with the same reactions as V, gave 0.8 g. (from ligroin) of diacetoxy derivative, m.p. 117–119°.

Anal. Calcd. for $C_{21}H_{18}O_6$: C, 68.83; H, 4.96. Found: C, 69.10; H, 5.24.

8-Hydroxymethyl-7-hydroxy-3-methylflavone (XII). A 1.4-g. sample of 7-hydroxy-8-formyl-3-methylflavone with the same reactions as VI, gave 1.1 g. (from ethanol) of XII, m.p. 183–185° dec.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.16; H, 5.31.

The *diacetate* was prepared as a white crystalline solid from ligroin, m.p. 118–119°. A mixture melting point with the same product obtained from compound 21 (see Table I) was not depressed.

8-Formyl-7-hydroxy-3-methylflavone (XI). Three grams of compound 21 (see Table I), with the same reactions as II, gave 1.5 g. (from dilute acetic acid) of the formyl derivative, m.p. 156–157°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.73; H, 4.39. Found: C, 72.49; H, 4.50.

A mixture melting point with a sample of the same product, prepared by the Duff reaction on 7-hydroxy-3-methylflavone, was not depressed.

8-Formyl-7-methoxy-3-methylflavone. Three grams of 8-formyl-7-hydroxy-3-methylflavone, methylated according to the procedure of VIII, gave 1.8 g. of the 7-methoxy derivative, m.p. 152–154°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.45; H, 4.80. Found: C, 73.23; H, 4.71.

8-Hydroxymethyl-7-methoxy-3-methylflavone. One gram of 8-formyl-7-methoxy-3-methylflavone hydrogenolyzed under the same conditions as IX gave 0.65 g. of the 8-hydroxymethyl derivative as a white crystalline solid with no sharp melting point.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.44. Found: C, 73.01; H, 5.34.

The *acetate* was prepared as a white solid from diluted ethanol, m.p. 168–169°.

Anal. Calcd. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.32. Found: C, 70.89; H, 5.20.

A mixture melting point with the same product obtained by another procedure,[3] was not depressed.

6,8-Dipiperidinomethyl-7-hydroxy-2,3-dimethylchromone-2-hydrochloride. To a solution of 1.9 g. of 7-hydroxy-2,3-dimethylchromone in 100 ml. of ethanol, 1.7 g. of piperidine, and 2 ml. of formalin were added, and then the mixture was refluxed for 8 hr. After cooling, alcoholic hydrochloric acid was added and the mixture was concentrated and again cooled until a precipitate formed. The crude product on crystallization from ethanol/ether gave 2.1 g. of white solid, m.p. 256–257°.

Anal. Calcd. for $C_{23}H_{34}Cl_2N_2O_3$: N, 6.12. Found: N, 6.04.

Amine exchange reaction of hydroxychromones Mannich bases. We employed the procedure of Snyder and Brewster[11] for β-naphthol Mannich bases. The product were identified by melting point and mixture melting point.

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