A Series of Coumarin Derivatives with Central Stimulating Activity

P. Da Re, G. Bonola, and L. Verlicchi

Research Department, Recordati-Laboratorio Farmacologico S.p.A., Milan, Italy

Received May 17, 1963

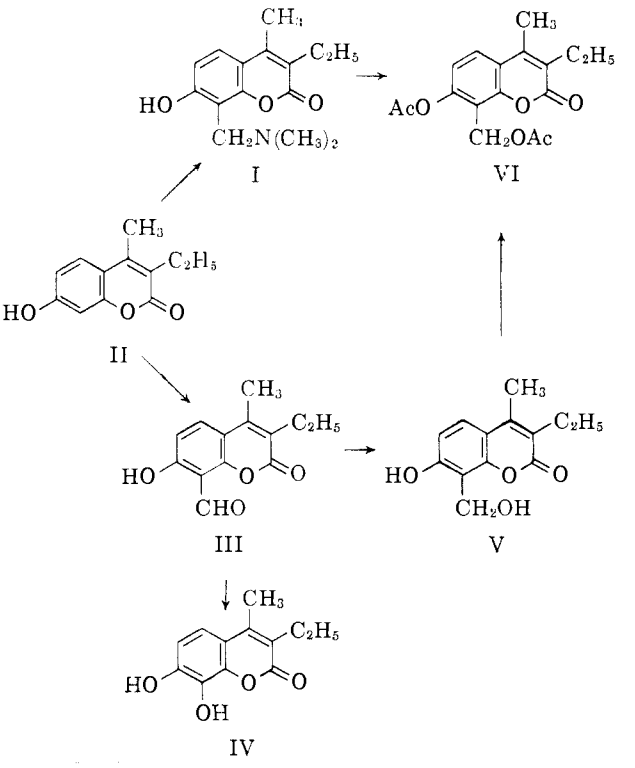
A series of N-disubstituted aminomethyl derivatives of methoxy- and hydroxycoumarins is described. These compounds possess central nervous system stimulatory activity but of a lower degree than the corresponding chromone and flavone derivatives.

Jongebreur's observation[1] on the pharmacological equivalence between coumarin and chromone derivatives as coronary dilators[2] prompted us to verify whether the centrally stimulating activity of a group of N-disubstituted 7-methoxy- and 7-hydroxy-8-aminomethylchromones and flavones[3] was retained in coumarin isomers. For this purpose we have synthesized a number of N-disubstituted aminomethyl derivatives of 7-methoxy- and 7-hydroxycoumarins, as well as 5-, 6-, and 8-methoxy- and hydroxycoumarins in order to ascertain suitable positions of the oxygen function (methoxyl or hydroxyl groups) and of the basic chain for best central activity.

N-Disubstituted aminomethyl derivatives of methoxycoumarins were prepared by chloromethylation[4] of the methoxycoumarins specified below. Since the formation of two isomers was possible, the structure of the resulting products had to be proved experimentally. Chloromethylation of 5-methoxy-4-methyl-3-phenylcoumarin gave a chlorine-free product, which analyzed for a methylenebis derivative but was not further investigated. 3,4-Dimethyl-, 3-phenyl- and 4-methyl-3-phenyl-6-methoxycoumarin furnished only the 7-chloromethyl derivatives. Their structure was proved in the case of 3,4-dimethyl-6-methoxycoumarin by reduction of its chloromethyl derivative to 6-methoxy-3,4,7-trimethylcoumarin identical with an authentic sample prepared by the Kostanecki–Robinson acylation of 2-hydroxy-4-methyl-5-methoxyacetophenone with propionic anhydride and sodium propionate. 3,4-Dimethyl-, 3-ethyl-4-methyl-, and 4-methyl-3-phenyl-7-methoxycoumarin yielded a mixture of 6- and 8-chloromethyl derivatives. The structure of each isomer was established by comparing its reduction derivative with the corresponding 6- or 8-methylcoumarin prepared by the Kostanecki–Robinson acylation of the methyl substituted 2-hydroxy-4-methoxyacetophenone. In the case of 4-ethyl-7-methoxy-3-phenylcoumarin, only the 8-chloromethyl derivative was obtained; its structure was recognized through the presence in the infrared spectrum of a strong band at 820 cm.$^{-1}$ attributable to the out of plane vibrations of two adjacent free hydrogen atoms at C_5 and C_6. This may be confirmed in the position of this band at 802–820 cm.$^{-1}$ in a group of 3,4,7,8-tetrasubstituted coumarins; by contrast, in several 3,4,6,7-tetrasubstituted coumarins the band attributable to the out of plane vibrations of the two isolated free hydrogen atoms at C_5 and C_8 falls at 832–860 cm.$^{-1}$.[5] Chloromethylation of 3-methyl- and 3-phenyl-8-methoxycoumarin gave only the 5-chloromethyl derivatives; the structure was proved in the case of 8-methoxy-3-phenylcoumarin by comparing the reduction product of its chloromethyl derivative with an actual sample of 5-methyl-8-methoxy-3-phenylcoumarin prepared by the Perkin reaction on 3-methoxy-6-methylsalicylaldehyde. Table I contains the chloromethyl derivatives together with their starting coumarins, reduction products, and comparable compounds. Table II shows the basic derivatives obtained by treating chlormethylcoumarins with secondary amines such as dimethyl- and diethylamine, morpholine, and piperidine.

N-Disubstituted aminomethyl derivatives of hydroxycoumarins were prepared by means of the Mannich reaction.[6] 5- and 6-Hydroxycoumarins do not react satisfactorily, whereas 3- and 3,4-substituted-

Scheme I



(1) G. Jongebreur, *Arch. Intern. Pharmacodyn.*, **90**, 384 (1952).

(2) Unpublished results from this laboratory on the activity of ethyl 7-flavonoxyacetate (Recordil®) and of various ethyl 3,4-disubstituted 7-coumarinoxyacetates confirmed the above finding.

(3) P. Da Re, L. Verlicchi, I. Setnikar, W. Murmann, and M. J. Magistretti, *Nature*, **184**, 362 (1959).

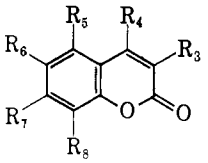
(4) S. S. Lele, G. N. Savant, and S. Setlur, *J. Org. Chem.*, **25**, 1713 (1960); *J. Indian Chem. Soc.*, **38**, 975 (1961), describe the chloromethylation of several 5-, 6-, and 7-hydroxy- (and methoxy) coumarins. The structure of the reaction products was established and the results are in agreement with our findings.

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., London, 1958, pp. 78–79.

(6) After completion of this work, two papers on the Mannich reaction applied to hydroxycoumarins having a hydroxyl group attached to the benzenoid ring were published by R. B. Desai, *J. Org. Chem.*, **26**, 5251 (1961), and by V. N. Gupta, B. R. Sharma, and R. B. Arora, *J. Sci. Ind. Res. (India)* **20B**, 300 (1961).

TABLE I

CHLOROMETHYL DERIVATIVES OF 6-, 7-, AND 8-METHOXYCOUMARINS[a] AND RELATED PRODUCTS



Compd.	R_3	R_4	R_5	R_6	R_7	R_8	M.p., °C.	Formula	—% carbon— Calcd.	Found	—% hydrogen— Calcd.	Found	—% chlorine— Calcd.	Found
1	C_6H_5	H	H	OCH_3	H	H	159–160	$C_{16}H_{12}O_3$	76.18	76.34	4.79	4.90		
2	C_6H_5	H	H	OCH_3	CH_2Cl	H	194–196	$C_{17}H_{13}ClO_3$					11.79	11.62
3	CH_3	CH_3	H	OCH_3	CH_2Cl	H	201–203	$C_{13}H_{13}ClO_3$					14.03	13.85
4	CH_3	CH_3	H	OCH_3	CH_3	H	270–271	$C_{13}H_{14}O_3$	71.57	71.46	6.47	6.36		
5	C_6H_5	CH_3	H	OCH_3	CH_2Cl	H	201–204	$C_{18}H_{15}ClO_3$					11.26	11.18
6[b]	CH_3	CH_3	H	CH_2Cl	OCH_3	H	218–220	$C_{13}H_{13}ClO_3$					14.03	14.00
7	CH_3	CH_3	H	CH_2OH	OCH_3	H	189–190	$C_{13}H_{14}O_4$	66.65	66.70	6.03	6.10		
8[c]	C_2H_5	CH_3	H	CH_2Cl	OCH_3	H	185–187	$C_{14}H_{15}ClO_3$					13.29	13.11
9	C_2H_5	CH_3	H	CH_3	OCH_3	H	123–124	$C_{14}H_{16}O_3$	72.32	72.23	6.94	6.85		
10[b]	C_6H_5	CH_3	H	CH_2Cl	OCH_3	H	219–220	$C_{18}H_{15}ClO_3$					11.26	11.30
11[b]	CH_3	CH_3	H	H	OCH_3	CH_2Cl	200–202	$C_{13}H_{13}ClO_3$					14.03	14.22
12	CH_3	CH_3	H	H	OCH_3	CH_3	198–200	$C_{13}H_{14}O_3$	71.54	71.34	6.47	6.17		
13[c]	C_2H_5	CH_3	H	H	OCH_3	CH_2Cl	180–182	$C_{14}H_{15}ClO_3$					13.29	13.55
14	C_2H_5	CH_3	H	H	OCH_3	CH_3	198–200	$C_{14}H_{16}O_3$	72.32	72.11	6.94	6.69		
15[b]	C_6H_5	CH_3	H	H	OCH_3	CH_2Cl	210–212	$C_{18}H_{15}ClO_3$					11.26	11.58
16	C_6H_5	CH_3	H	H	OCH_3	CH_3	168–170	$C_{18}H_{16}O_3$	77.12	77.20	5.75	5.70		
17	C_6H_5	C_2H_5	H	H	OCH_3	CH_2Cl	209–211	$C_{19}H_{17}ClO_3$					10.78	10.58
18	C_6H_5	C_2H_5	H	H	OCH_3	CH_3	142–143	$C_{19}H_{18}O_3$	77.50	77.30	6.16	6.10		
19	CH_3	H	CH_2Cl	H	H	OCH_3	208–210	$C_{12}H_{11}ClO_3$					14.86	14.66
20	C_6H_5	H	CH_2Cl	H	H	OCH_3	157–160	$C_{17}H_{13}ClO_3$					11.79	11.76
21	C_6H_5	H	CH_3	H	H	OCH_3	149–151	$C_{17}H_{14}O_3$	76.67	76.39	5.30	5.55		

[a] Acetic acid 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 Experimental. Chloromethylation of 6-methoxycoumarins was accomplished in the presence of zinc chloride. [b] Separated from the accompanying isomer in the reaction mixture by fractional crystallization from benzene. [c] As in footnote *b*, by fractional crystallization from ethyl acetate.

7-hydroxycoumarins gave Mannich bases, the structure of which was proved by the series of reactions, shown in Scheme I, as applied to 8-dimethylaminomethyl-3-ethyl-7-hydroxy-4-methylcoumarin (I). 3-Ethyl-7-hydroxy-4-methylcoumarin (II) was converted by the Duff reaction into the formyl derivative (III), the structure of which was proved by Dakin oxidation to 7,8-dihydroxy-3-ethyl-4-methylcoumarin (IV).[7] The catalytic reduction of III led to the 8-hydroxymethyl derivative (V), the diacetate (VI) of which was found to be identical (infrared spectral comparion) with 7-acetoxy-8-acetoxymethyl-3-ethyl-4-methylcoumarin obtained by boiling I with acetic anhydride and sodium acetate. 8-Hydroxy-3-methylcoumarin gave a mixture of 5,7-dimorpholinomethyl and monomorpholinomethyl derivatives. The latter was proved to be the 7-substituted isomer as its methoxy derivative was quite different from 3-methyl-8-methoxy-5-morpholinomethylcoumarin, as described above (see Table II, 28). The Mannich bases are listed in Table III.

The pharmacological properties of these new coumarin compounds, already summarized in a previous note,[8] have shown that the central nervous system stimulatory activity is retained but at a lower degree than in the corresponding chromone and flavone compounds. The most active coumarin derivative, 6-methoxy-7-dimethylaminomethyl-3-phenylcoumarin (erroneously formulated as 5-dimethylaminomethyl),[8] possesses about half the activity of the most active compound of the chromone series. This is not in agreement with the statement of Gupta and coworkers,[6] who claimed that the Mannich bases prepared from umbelliferone and 4-methylumbelliferone were more active than the corresponding chromone and flavone derivatives. There is no detectable difference between hydroxy and methoxy derivatives, although the latter seems to furnish the most active compounds. The optimum activity resulted with the methoxyl or hydroxyl group and the basic chain in the *ortho* position. The 6,5 position was found to be the best, while in the chromone series this was true for the 7,8 position.[9,10] Of the basic chains, dimethylaminomethyl gave the best results, as was also found in the corresponding chromone and flavone compounds.

Experimental[11]

The methods of synthesis of analogous compounds are similar and the particular derivatives described in detail are for illustrative purpose.

5-Chloromethyl-8-methoxy-3-phenylcoumarin.—A mixture of 11.8 g. of 8-methoxy-3-phenylcoumarin, 50 ml. of glacial acetic acid, 100 ml. of concentrated hydrochloric acid, and 4.2 ml. of 40% aqueous formaldehyde was stirred at 60° for 4 hr. while a stream of hydrogen chloride was introduced. The reaction mix-

(7) D. Chakravarti, *J. Indian Chem. Soc.*, **8**, 407 (1931).

(8) P. Da Re, G. Bonola, I. Setnikar, and M. J. Magistretti, *Experientia*, **18**, 387 (1962).

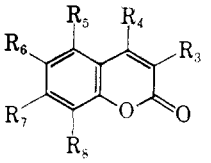
(9) I. Setnikar, W. Murmann, M. J. Magistretti, P. Da Re, and L. Verlicchi, *J. Med. Pharm. Chem.*, **3**, 471 (1961).

(10) P. Da Re and L. Cimatoribus, *Ann. Chim.* (Rome), **52**, 506 (1962).

(11) All melting points were measured on a Kofler block and are uncorrected. Infrared spectra were determined in Nujol mulls on a Perkin-Elmer Infracord spectrophotometer.

Table II

N-Substituted Aminomethyl Derivatives of 6-, 7-, and 8-Methoxycoumarins[a]



Compd.	R_3	R_4	R_5	R_6	R_7	R_8
1	CH_3	CH_3	H	$CH_2NC_5H_{10}$	OCH_3	H
2	CH_3	CH_3	H	$CH_2NC_4H_8O$	OCH_3	H
3	CH_3	CH_3	H	$CH_2N(C_2H_5)_2$	OCH_3	H
4	C_2H_5	CH_3	H	$CH_2NC_5H_{10}$	OCH_3	H
5	C_2H_5	CH_3	H	$CH_2NC_4H_8O$	OCH_3	H
6	C_2H_5	CH_3	H	H	OCH_3	$CH_2NC_5H_{10}$
7	C_2H_5	CH_3	H	H	OCH_3	$CH_2NC_4H_8O$
8	CH_3	CH_3	H	$CH_2N(CH_3)_2$	OCH_3	H
9	CH_3	CH_3	H	H	OCH_3	$CH_2N(C_2H_5)_2$
10	CH_3	CH_3	H	H	OCH_3	$CH_2NC_5H_{10}$
11	C_2H_5	CH_3	H	$CH_2N(C_2H_5)_2$	OCH_3	H
12	C_2H_5	CH_3	H	$CH_2N(CH_3)_2$	OCH_3	H
13	C_6H_5	CH_3	H	$CH_2N(C_2H_5)_2$	OCH_3	H
14	C_6H_5	CH_3	H	H	OCH_3	$CH_2N(C_2H_5)_2$
15	C_6H_5	CH_3	H	H	OCH_3	$CH_2NC_4H_8O$
16	C_6H_5	C_2H_5	H	H	OCH_3	$CH_2N(CH_3)_2$
17	C_6H_5	C_2H_5	H	H	OCH_3	$CH_2NC_5H_{10}$
18	C_6H_5	C_2H_5	H	H	OCH_3	$CH_2NC_4H_8O$
19	C_6H_5	C_2H_5	H	H	OCH_3	$CH_2N(C_2H_5)_2$
20	C_6H_5	H	$CH_2N(CH_3)_2$	H	H	OCH_3
21	C_6H_5	H	$CH_2N(C_2H_5)_2$	H	H	OCH_3
22	C_6H_5	H	$CH_2NC_4H_8O$	H	H	OCH_3
23	C_6H_5	H	$CH_2NC_5H_{10}$	H	H	OCH_3
24	C_6H_5	CH_3	$CH_2N(C_2H_5)_2$	OCH_3	H	H
25	C_6H_5	CH_3	$CH_2NC_4H_8O$	OCH_3	H	H
26	C_6H_5	CH_3	$CH_2NC_5H_{10}$	OCH_3	H	H
27	CH_3	H	$CH_2N(CH_3)_2$	H	H	OCH_3
28	CH_3	H	$CH_2NC_4H_8O$	H	H	OCH_3
29	CH_3	H	$CH_2NC_5H_{10}$	H	H	OCH_3
30	CH_3	H	$CH_2N(C_2H_5)_2$	H	H	OCH_3
31	C_6H_5	H	$CH_2NC_4H_8O$	OCH_3	H	H
32	C_6H_5	H	$CH_2NC_5H_{10}$	OCH_3	H	H
33	C_6H_5	H	$CH_2N(C_2H_5)_2$	OCH_3	H	H
34	C_6H_5	H	$CH_2N(CH_3)_2$	OCH_3	H	H
35	CH_3	CH_3	$CH_2NC_4H_8O$	OCH_3	H	H
36	CH_3	CH_3	$CH_2N(C_2H_5)_2$	OCH_3	H	H
37	CH_3	CH_3	$CH_2NC_5H_{10}$	OCH_3	H	H
38	C_6H_5	CH_3	$CH_2N(CH_3)_2$	OCH_3	H	H
39	CH_3	CH_3	$CH_2N(CH_3)_2$	OCH_3	H	H

[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 Experimental. [b] Crystallization solvent was alcohol–ether for the hydrochloride salts and ligroin

ture was then poured into 300 ml. of water and the separated solid filtered and washed with water. After drying *in vacuo* the product weighed 125 g. and was pure enough for the subsequent amination. White crystals from ethyl acetate, m.p. 157–160°, formed.

Anal. Calcd. for $C_{17}H_{13}ClO_3$: Cl, 11.79. Found: Cl, 11.76.

8-Methoxy-5-methyl-3-phenylcoumarin.—A solution of 1 g. of 5-chloromethyl-8-methoxy-3-phenylcoumarin in 50 ml. of ethanol was hydrogenated over 5% palladized charcoal, under the usual conditions, until hydrogen uptake ceased. The solution was filtered from the catalyst and evaporated to dryness. The residue on crystallization from ethanol gave 0.7 g. of white solid, m.p. 149–151°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.39; H, 5.55.

8-Methoxy-3-phenyl-5-piperidinomethylcoumarin.—To a solution of 2.2 g. of 5-chloromethyl-8-methoxy-3-phenylcoumarin in 50 ml. of ethanol, 1 g. of piperidine was added and the mixture refluxed for 5–6 hr. After evaporation of the solvent the residue was suspended in water, filtered, washed with water, and dried *in vacuo*. On crystallization from ethanol 1.2 g. of white crystalline product, m.p. 170–171°, was obtained.

Anal. Calcd. for $C_{22}H_{23}NO_3$: N, 4.01. Found: N, 3.96. The hydrochloride salt was a white solid which melted at 208–210°.

Anal. Calcd. for $C_{22}H_{24}ClNO_3$: Cl, 9.19; N, 3.63. Found: Cl, 9.05; N, 3.75.

8-Dimethylaminomethyl-3-ethyl-4-methyl-7-hydroxycoumarin Hydrochloride (I).—To a solution of 4 g. of 3-ethyl-7-hydroxy-4-methylcoumarin in 150 ml. of absolute ethanol, 2.25 ml. of dimethylamine and 2 ml. of 40% aqueous formaldehyde were

Hydrochloride salts						Free bases		
		% chlorine		% nitrogen			% nitrogen	
M.p., °C.[b]	Formula	Calcd.	Found	Calcd.	Found	M.p., °C.[b]	Calcd.	Found
245 (dec.)	$C_{18}H_{24}ClNO_3$	10.49	10.72	4.14	4.30	129–131	4.64	4.72
260 (dec.)	$C_{17}H_{22}ClNO_4$	10.43	10.46	4.12	4.24	138–140	4.62	4.50
215–218	$C_{17}H_{24}ClNO_3$	10.88	10.65	4.30	4.43	78–80	4.85	4.97
228–230	$C_{19}H_{26}ClNO_3$	10.08	10.09	3.98	3.80	108–110	4.43	4.52
230–232	$C_{18}H_{24}ClNO_4$	10.02	9.84	3.96	3.71	94–96	4.41	4.15
236–238	$C_{19}H_{26}ClNO_3$	10.08	10.33	3.98	3.93	162–164	4.43	4.37
163–165	$C_{18}H_{24}ClNO_4$	10.02	9.81	3.96	3.94	153–155	4.41	4.41
230–232	$C_{15}H_{20}ClNO_3$	11.91	11.91	4.70	4.72	127–129	5.36	5.15
206–209	$C_{17}H_{24}ClNO_3$	10.88	10.77	4.30	4.32	104–106	4.85	4.98
222–224	$C_{18}H_{24}ClNO_3$	10.49	10.71	4.14	4.35	173–175	4.63	4.50
204–206	$C_{18}H_{26}ClNO_3$	10.43	10.64	4.14	4.15			
330–332	$C_{16}H_{22}ClNO_3$	11.37	11.43	4.49	4.44	86–88	5.07	5.15
140–142	$C_{22}H_{26}ClNO_3$	9.14	8.85	3.61	3.48	103–105	3.99	3.85
194–196	$C_{22}H_{26}ClNO_3$	9.14	9.10	3.61	3.77	160–161	3.99	4.06
	$C_{22}H_{23}NO_4$					171–172	3.83	3.89
	$C_{21}H_{23}NO_3$					141–142	4.15	4.14
215–216	$C_{24}H_{28}ClNO_3$	8.56	8.63	3.38	3.53	218–220	3.71	3.72
228–230	$C_{23}H_{26}ClNO_4$	8.53	8.42	3.37	3.30	211–212	3.68	3.72
205–207	$C_{23}H_{28}ClNO_3$	8.82	8.79	3.49	3.41	131–133	3.83	3.61
257–258	$C_{19}H_{20}ClNO_3$	10.25	9.99	4.05	3.84	158–160	4.53	4.30
215–216	$C_{21}H_{24}ClNO_3$	9.48	9.50	3.74	3.53	129–132	4.15	3.99
257–258	$C_{21}H_{22}ClNO_4$	9.14	9.41	3.61	3.39	181–183	3.99	3.82
208–210	$C_{22}H_{24}ClNO_3$	9.19	9.05	3.63	3.75	170–171	4.01	3.96
244–245	$C_{22}H_{26}ClNO_3$	9.14	8.96	3.61	3.48	121–122	3.99	3.84
238–239	$C_{22}H_{24}ClNO_4$	8.82	8.67	3.48	3.68	144–146	3.83	3.94
275–276	$C_{23}H_{26}ClNO_3$	8.86	8.82	3.50	3.50	138–140	3.85	4.04
247–248	$C_{14}H_{18}ClNO_3$	12.50	12.46	4.94	4.97	118–119	5.67	5.61
255–259 dec.	$C_{16}H_{20}ClNO_4$	10.88	10.77	4.30	4.18	159–161	4.84	4.82
259–260	$C_{17}H_{22}ClNO_3$	10.95	10.93	4.32	4.32	134–136	4.88	4.68
258–260	$C_{16}H_{22}ClNO_3$	11.37	11.27	4.49	4.55	105–106	5.09	5.08
228–231	$C_{21}H_{22}ClNO_4$	9.14	9.07	3.61	3.42	185–187	3.99	4.01
243–246	$C_{22}H_{24}ClNO_3$	9.19	8.89	3.63	3.68	153–155	4.01	4.13
195–198	$C_{21}H_{24}ClNO_3$	9.48	9.49	3.74	3.58	115–117	4.15	3.97
248–250	$C_{19}H_{20}ClNO_3$	10.25	10.00	4.05	4.17	164–166	4.53	4.61
245–258 dec.	$C_{17}H_{22}ClNO_4$	10.43	10.23	4.12	3.94	171–173	4.62	4.56
222–227 dec.	$C_{17}H_{24}ClNO_3$	10.88	10.97	4.30	4.24	105–107	4.85	5.08
240–241	$C_{18}H_{24}ClNO_3$	10.49	10.29	4.14	3.95	131–135	4.64	4.72
250–253	$C_{20}H_{22}ClNO_3$	9.85	9.78	3.89	3.84	142–144	4.33	4.27
244-245	$C_{15}H_{20}ClNO_3$	11.91	11.74	4.70	4.63	124–125	5.36	5.46

for the free bases.

added. The mixture was heated under reflux for 8 hr. and then evaporated. The residue was taken up in alcoholic hydrochloric acid and the resulting solution was evaporated to dryness. On crystallization of the crude product from ethanol–ether 2.8 g. of white solid, m.p. 196–198°, was obtained.

Anal. Calcd. for $C_{15}H_{20}ClNO_3$: Cl, 11.91; N, 4.70. Found: Cl, 11.83; N, 4.58.

3-Ethyl-8-formyl-7-hydroxy-4-methylcoumarin (III).—To a solution of 3.1 g. of 3-ethyl-7-hydroxy-4-methylcoumarin in 30 ml. of acetic acid 6.2 g. of hexamine was added and the mixture stirred at 100° for 6 hr. The solution was treated with 40 ml. of hot 10% aqueous hydrochloric acid, stirred for 15 min., and allowed to stand overnight. The separated solid was collected and washed with water. After drying *in vacuo* 0.5 g. of white crystalline product, m.p. 150–152°, was obtained.

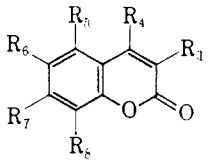
Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.10; H, 5.30.

7,8-Dihydroxy-3-ethyl-4-methylcoumarin (IV).—A solution of 1.1 g. of 3-ethyl-8-formyl-7-hydroxy-4-methylcoumarin (III) in 40 ml. of 10% sodium hydroxide was added dropwise to 10 ml. of 5% hydrogen peroxide. The mixture, after stirring for 1 hr., became dark and a solid separated. Acidification with dilute hydrochloride acid completed the precipitation of the product which was filtered, washed with water, and dried. On crystallization from ethanol a white crystalline solid, m.p. 222–224°, was obtained.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.50. Found: C, 65.41; H, 5.58. A mixture melting point of this product with an authentic sample of 7,8-dihydroxy-3-ethyl-4-methylcoumarin prepared according to Chakravarti[7] was not depressed.

Table III

N-Substituted Aminomethyl Derivatives of 7- and 8-Hydroxycoumarins[a]



Compd.	R_3	R_4	R_5	R_6	R_7	R_8	M.p., °C.	Formula	% chlorine Calcd.	% chlorine Found	% nitrogen Calcd.	% nitrogen Found
1	H	CH_3	H	H	OH	$CH_2NC_5H_{10}$	246–248	$C_{16}H_{20}ClNO_3$	11.45	11.37	4.52	4.48
2	CH_3	CH_3	H	H	OH	$CH_2NC_5H_{10}$	274–275	$C_{17}H_{22}ClNO_3$	10.95	10.87	4.32	4.40
3	CH_3	CH_3	H	H	OH	$CH_2NC_4H_8O$	237–238.5	$C_{16}H_{20}ClNO_4$	10.88	10.95	4.30	4.25
4	CH_3	CH_3	H	H	OH	$CH_2N(CH_3)_2$	237–238	$C_{14}H_{18}ClNO_3$	12.50	12.38	4.94	4.90
5	CH_3	CH_3	H	H	OH	$CH_2N(C_2H_5)_2$	181–183	$C_{16}H_{22}ClNO_3$	11.37	11.45	4.49	4.51
6	C_6H_5	H	H	H	$CH_2N(CH_3)_2$	OH	233–234	$C_{18}H_{18}ClNO_3$	10.68	10.57	4.22	4.17
7	C_6H_5	H	H	H	$CH_2NC_5H_{10}$	OH	261–264	$C_{21}H_{22}ClNO_3$	9.54	9.39	3.77	3.48
8	C_6H_5	H	H	H	$CH_2NC_4H_8O$	OH	259–261	$C_{20}H_{20}ClNO_4$	9.49	9.41	3.75	3.81
9	H	CH_3	H	H	OH	$CH_2N(C_2H_5)_2$	204–206	$C_{15}H_{20}ClNO_3$	11.91	11.77	4.70	4.62
10	H	CH_3	H	H	OH	$CH_2N(CH_3)_2$	207–208	$C_{13}H_{16}ClNO_3$	13.17	13.29	5.20	5.13
11	H	CH_3	H	H	OH	$CH_2NC_4H_8O$	231–233	$C_{15}H_{18}ClNO_4$	11.37	11.25	4.49	4.45
12	C_2H_5	CH_3	H	H	OH	$CH_2NC_5H_{10}$	250–251	$C_{18}H_{24}ClNO_3$	10.49	10.53	4.14	4.01
13	C_2H_5	CH_3	H	H	OH	$CH_2NC_4H_8O$	225–226	$C_{17}H_{22}ClNO_4$	10.43	10.37	4.12	4.20
14	C_2H_5	CH_3	H	H	OH	$CH_2N(CH_3)_2$	196–198	$C_{15}H_{20}ClNO_3$	11.91	11.83	4.70	4.58
15	C_2H_5	CH_3	H	H	OH	$CH_2N(C_2H_5)_2$	170–172	$C_{17}H_{24}ClNO_3$	10.88	10.75	4.30	4.49
16	CH_3	H	H	H	$CH_2NC_4H_8O$	OH	230–232	$C_{15}H_{18}ClNO_4$	11.37	11.36	4.49	4.49
17[b]	CH_3	H	$CH_2NC_4H_8O$	H	$CH_2NC_4H_8O$	OH		$C_{20}H_{26}N_2O_5$				

[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 Experimental. Crystallizing solvent was alcohol–ether. [b] This product was isolated as a free base, m.p. 210–211° (from methanol). *Anal.* Calcd. for $C_{20}H_{26}N_2O_5$: N, 7.48. Found: N, 7.28.

3-Ethyl-7-hydroxy-8-hydroxymethyl-4-methylcoumarin (V).—An ethanolic solution of 0.5 g. of 3-ethyl-8-formyl-7-hydroxy-4-methylcoumarin (III) was hydrogenated over Raney nickel until 1 mole of hydrogen was absorbed. The solution, filtered from the catalyst, was evaporated to dryness and the residue was crystallized from ethanol; 0.3 g. of white solid, m.p. 170–172°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.03. Found: C, 66.46; H, 6.10.

The diacetate (VI) was a white crystalline solid (from ethanol), with no sharp melting point.

7-Acetoxy-8-acetoxymethyl-3-ethyl-4-methylcoumarin (VI).—8-Dimethylaminomethyl-3-ethyl-7-hydroxy-4-methylcoumarin (I) (1 g.) 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 the separated solid was filtered, washed, and dried *in vacuo*. On crystallization from ethanol 0.8 g. of white crystalline product, with no sharp melting point, was obtained.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.71. Found: C, 64.20; H, 5.80.

The infrared spectrum of this product and that of the diacetate obtained from 3-ethyl-7-hydroxy-8-hydroxymethyl-4-methylcoumarin (V) were identical.

8-Methoxy-3-methyl-7-morpholinemethylcoumarin.—A methanolic solution of 0.31 g. of 8-hydroxy-3-methyl-7-morpholinemethylcoumarin hydrochloride (Table III, **16**) was treated with 2 equivalents of methanolic KOH; the solvent was removed and the residue suspended in 15 ml. of anhydrous acetone. Dimethyl sulfate (0.16 g.) was added and the mixture was refluxed on a steam bath for 4 hr. The evaporation of the solvent left a residue which was taken up with water and extracted with benzene. The organic layer was washed successively with 2% NaOH and water. After removing the solvent, the residue was crystallized from benzene–petroleum ether, 0.1 g. of white crystals, m.p. 89–90°.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.83. Found: C, 66.51; H, 6.50; N, 4.77.

This compound was quite different from 8-methoxy-3-methyl-5-morpholinemethylcoumarin (derived from Table II, **28**), m.p. 159–161° (from methanol).

Anal. Calcd. for $C_{16}H_{19}NO_4$: N, 4.83. Found: N, 4.82.