RESEARCH ON PYRANES, THEIR ANALOGS, AND RELATED COMPOUNDS

XXVII. 2-Acylamino-3-dialkylaminomethylchromones and 3,3'-Methylenebis-(2-acylaminochromone)s*

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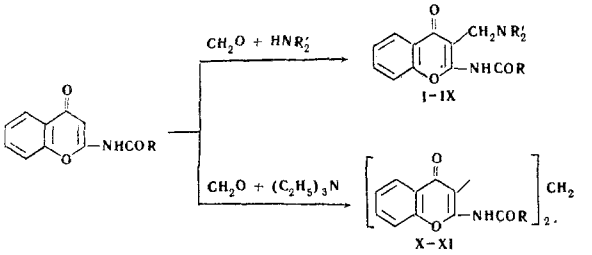
By the reaction of 2-acylaminochromones with formaldehyde and secondary amines, we have synthesized 2-acylamino-3-dialkylaminomethylchromones. On the basis of their chemical properties and their UV, IR, and NMR spectra, a hypothesis concerning the fine structure of these compounds has been put forward. When the reaction with formaldehyde is carried out in the presence of bases, 3,3'-methylenebis-(2-acylaminochromone)s can be obtained.

The 2-acylaminochromones (AC) that we have obtained previously [1] have at least two fairly active nucleophilic centers: in position 3 and on the nitrogen atom. The hydrogen atom of the amide group possesses fairly acidic properties: the AC are soluble in aqueous sodium carbonate.

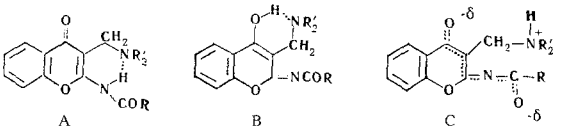
In order to study the capacity of the AC for electrophilic substitution, we have performed the condensation of AC with formaldehyde in the presence of secondary and tertiary amines. The reactions of the AC with formaldehyde and secondary amines in water or aqueous ethanol gave Mannich bases (MB)—2-acylamino-3-dialkylaminomethylchromones (I–IX)—in the form of crystalline bases of hydrochlorides.



I	$R=OC_2H_5$,	NR'_2 = piperidino	VII	R = piperidino	$R'=CH_3$
II	$R=OC_2H_5$,	NR'_2 = morpholino	VIII	R = piperidino, NR'_2 = piperidino	
III	$R=OC_2H_5$,	$R'=C_2H_5$	IX	R = piperidino, NR'_2 = morpholino	
IV	$R=OC_2H_5$,	$R'=n\text{-}C_3H_7$			
V	$R=CCl_3$,	NR'_2 = piperidino	X	$R=OC_2H_5$	
VI	$R=CCl_3$,	NR'_2 = morpholino	XI	R = piperidino	

These substances possess a mobile hydrogen atom and are soluble in alkalies (but give no coloration with stannic chloride). On acid hydrolysis in a solution of acetic and hydrochloric acids, substance I is converted into 3,3'-methylenebis(4-hydroxycoumarin) in a manner similar to the 3-dialkylaminomethyl-4-hydroxycoumarins [2]. By more careful hydrolysis it was possible to obtain an intermediate—(2-amino-3-chromonyl)(4-hydroxy-3-coumarinyl)methane (XII).

The fine structure of the MB is an interesting question. In addition to the chromone, i.e., amino ketone, form without an intramolecular hydrogen bond or with it (form A), they may have a form corresponding to a 4-hydroxycoumarin with an intramolecular bond (form B) or without it and a betaine-like form with a mesomeric anion of type C with an unsymmetrical charge distribution.



The IR spectrum of substance I (Fig. 1, curve 1) in chloroform solution has the vibrations of the carbonyl group of $COOC_2H_5$ at 1753 cm^{-1} and of a chromone carbonyl group with a frequency of 1626 cm^{-1}, which corresponds to the vibrations of these groups in the initial amino-2-ethoxycarbonylchromone (AC-1): 1758 and 1635 cm^{-1}, respectively [1]. However, in contrast to the latter compound, the spectrum of I (in chloroform, in oil, or in perfluorinated oil) does not exhibit the vibrations of free and bound NH groups (there is only a poorly identifiable band of low intensity in the 2500–2800 cm^{-1} region) and of the second amide band of the NHCO group. But in the NMR spectra (taken by E. I. Fedin, to whom the authors express their deep gratitude) in Fig. 2, curve 1 at δ 10.3 ppm, a broad singlet signal appears with an area of one proton unit which is undoubtedly due to an acidic proton forming an intramolecular hydrogen bond. There is no signal in this region in the spectrum of the initial AC-1 (Fig. 2, curve 2). Unfortunately, a comparison of the NMR spectra of I and AC-1 proves somewhat difficult because of the fact that in the spectrum of the latter compound it is difficult to determine the position of the signal of the amide proton. It is possibly located in the 7.4–7.8 ppm region. The results given are in agreement with form A to a greater extent than with B or C, while the structures without hydrogen bonds are completely excluded.

The UV spectra of I in chloroform and heptane are similar to the spectrum of AC-1 in ethanol (Fig. 4, curve 1; Table 1). However, the UV spectra of these compounds in ethanol differ markedly; for I a bathochromic shift of the long-wave maximum is found (Fig. 3, curve 1). This shift may be caused by the presence in ethanolic solution of a form of type B or C. In the spectrum of the hydrochloride of the base I (Fig. 3, curve 2), the long-wave absorption maximum is already located in the same region as in the spectrum of substance AC-1. The inflection on the curve of the spectrum of the hydrochloride in the long-wave region (~330 nm) shows the partial dissociation of the hydrochloride in ethanolic solution to give the free base. The addition of hydrogen chloride to the solution

*For part XXVI, see [3].

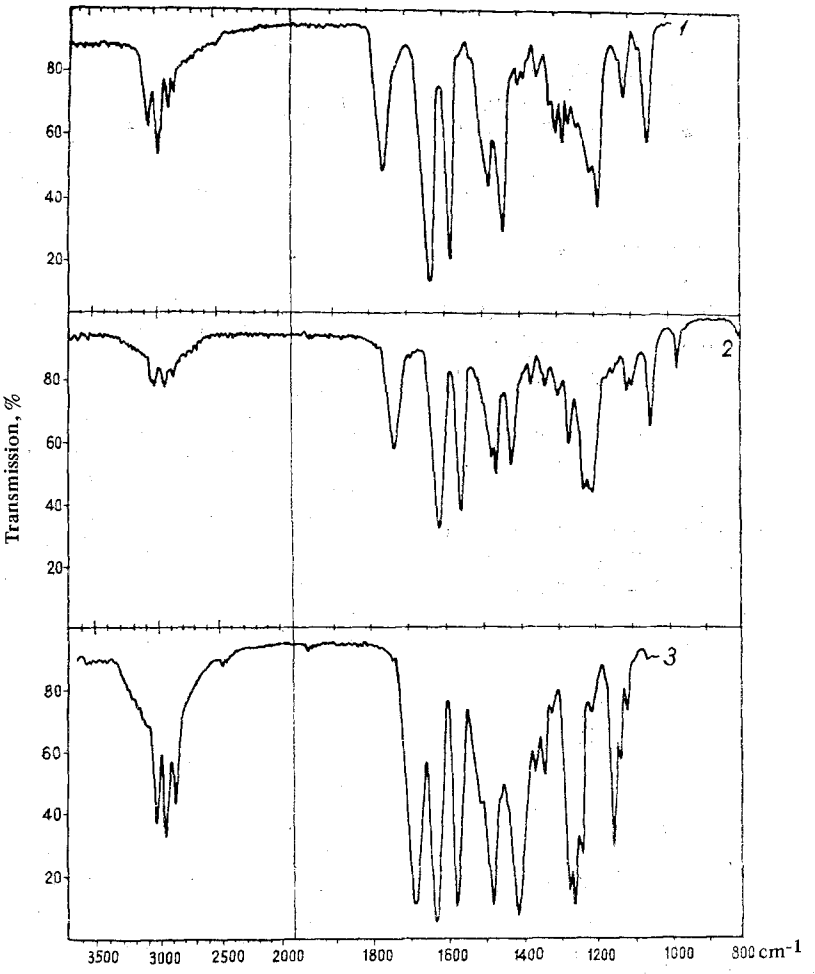


Fig. 1. IR spectra (in $CHCl_3$): 1) 2-ethoxycarbonylamino-3-piperidinomethylchromone **(I)** (c 0.020 M, d 0.4 mm); 2) 3,3'-methylenebis(2-ethoxycarbonylaminochromone) **(X)** (c 0.025 M, d 0.1 mm); 3) 3,3'-methylenebis(2-piperidinocarbonylaminochromone **(XI)** (c 0.05 M, d 0.15 mm).

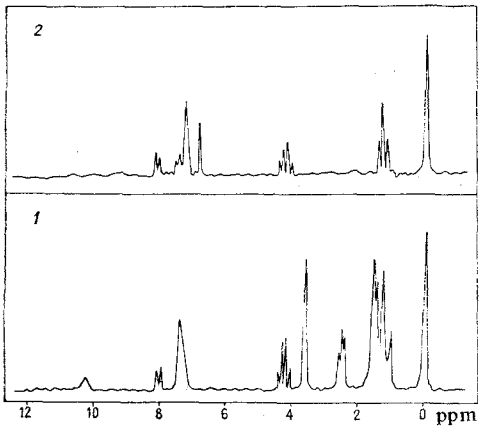


Fig. 2. NMR spectra (taken on a "Hitachi-H-60" instrument with a working frequency of 60 MHz in deuterochloroform on the δ-scale relative to hexamethyldisiloxane): 1) 2-ethoxycarbonylamino-3-piperidinomethylchromone (I); 2) 2-ethoxycarbonylaminochromone (AC-1).

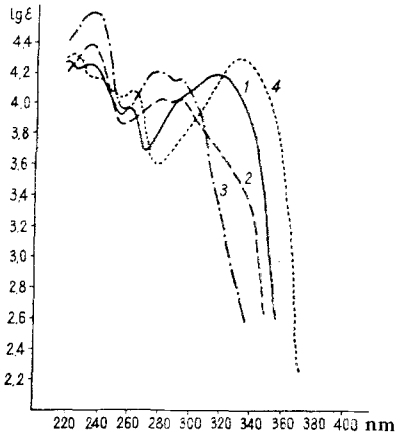


Fig. 3. UV spectra of 2-ethoxycarbonylamino-3-piperidinomethylchromone (I), c $1 \cdot 10^{-3}$: 1) in ethanol; 2) hydrochloride of I in ethanol; 3) hydrochloride of I in 0.1 N ethanolic HCl; 4) I in 0.1 N ethanolic NaOH.

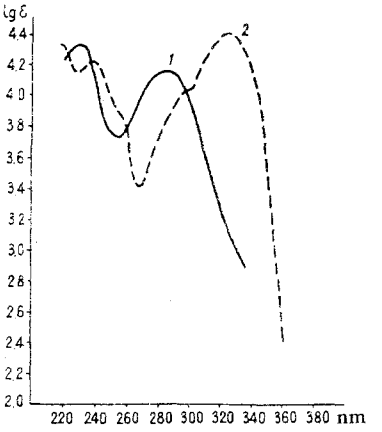


Fig. 4. UV spectra of 2-ethoxycarbonylaminochromone (AC-1); 1) in ethanol (c $1 \cdot 10^{-3}$); 2) in 0.01–0.1 N ethanolic NaOH (c $1 \cdot 10^{-4}$–$1 \cdot 10^{-3}$).

Table 1

UV Spectra

Compounds	Solvent (concentration)	λ_{max}, nm	lg ε
I	Chloroform ($2 \cdot 10^{-4}$—$1 \cdot 10^{-3}$)	237 290	4.38 4.18
II	Heptane ($2 \cdot 10^{-4}$)	231 290	4.19 4.23
AC-1	Chloroform ($1 \cdot 10^{-4}$)	273 284—286 (shoulder)	4.12 4.00
AC-1	Ethanol + 1.5 mole of piperidine ($1 \cdot 10^{-3}$—$1 \cdot 10^{-4}$)	231 284	4.32 4.10
AC-2	Ethanol ($1 \cdot 10^{-4}$)	228 293 336	4.35 4.26 3.52

Table 2

2-Acylamino-3-dialkylaminomethylchromones (I–IX)

Compound	Mp, °C (solvent)	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
I	112—112.5 (ethanol)	$C_{18}H_{22}N_2O_4$[a]	65.71 65.67	6.81 6.82	8.75 8.81	65.46	6.71	8.48	80
II	113—114 (ether)	$C_{17}H_{20}N_2O_5$[b]	61.73 61.67	6.01 6.12	8.70 8.55	61.44	6.07	8.43	100
III	147—148 (acetone)	$C_{17}H_{22}N_2O_4 \cdot HCl$[c]	57.59 57.72	6.70 6.81	8.11 8.00	57.51	6.53	7.90	71.8
IV	158—159 (ethanol)	$C_{19}H_{26}N_2O_4 \cdot HCl$[d]	59.61 59.93	7.09 7.10	7.51 7.35	59.60	7.11	7.32	70
V	190—191 (pyridine)	$C_{17}H_{17}Cl_3N_2O_3$[e]	50.73 50.75	4.36 4.33	—	50.57	4.24	—	98
VI	173—174 (dioxane)	$C_{16}H_{15}Cl_3N_2O_4$	47.18 47.46	3.80 3.79	—	47.36	3.73	—	93.5
VII	121—123 (decomp.)	$C_{18}H_{23}N_3O_3 \cdot H_2O$	62.41 62.45	7.28 7.32	12.54 12.52	62.24	7.25	12.10	61
VIII	90—91 (decomp.)	$C_{21}H_{27}N_3O_3 \cdot 2H_2O$	62.36 62.57	7.92 7.91	10.61 10.51	62.19	7.71	10.36	84
IX	115—116 (decomp.)	$C_{20}H_{25}N_3O_4 \cdot 0.75\ H_2O$	62.22 62.46	7.08 6.87	10.98 11.19	62.41	6.94	10.93	80.6

[a] Mobile hydrogen (determined in a mixture of dimethylformamide and ether by the action of sodium hydride): found 0.37%; calculated: 0.3%. Hydrochloride, mp 179° C (decomp., from ethanol). Found, %: Cl 9.76, 9.75; N 7.71, 7.61. Calculated for $C_{18}H_{22}N_2O_4 \cdot HCl$, %: Cl 9.66; N 7.64. [b] To isolate the II, the reaction mixture was evaporated in vacuum and the residue was treated with ether. Hydrochloride, mp 175° C (decomp., from ethanol). Found, %: Cl 9.38, 9.41; N 7.64, 7.89. Calculated for $C_{17}H_{20}N_2O_5 \cdot HCl$, %: Cl 9.61; N 7.60. [c] Obtained by evaporating the reaction mixture in vacuum, dissolving the residue in ether, and adding an ethereal solution of HCl. Found, %: Cl 9.99, 9.94. Calculated, %: Cl 9.99. [d] Obtained similarly to III. Found, %: Cl 9.19, 9.21. Calculated, %: Cl 9.26. [e] Found, %: Cl 26.11, 26.18. Calculated, %: Cl 26.35.

leads to the disappearance of this long-wave part of the curve (Fig. 3, curve 3). The general form of the curve of the UV spectrum of substance I in an alkaline medium (Fig. 3, curve 4) remains the same as when alkali is absent, but there is some (~10 nm) bathochromic shift and an increase in the intensity of the long-wave maximum. The curve of the UV spectrum of substance AC-1 taken in an alkaline solution (Fig. 4, curve 2) has roughly the same nature.

It is still impossible to state whether all MB are similar to MB I in respect to their fine structure. It can only be stated that the IR spectrum of substance II in the 1300–1800 cm^{-1} region is similar to that of substance I, while the spectrum of substance V (in oil and dioxane) differs markedly; the band at ~1750 cm^{-1} is absent and (in oil) bands are present at 1665, 1608, and 1530 cm^{-1}. We may note that in the initial 2-trichloroacetylaminochromone the frequency of the amide carbonyl (in oil) is fairly high (1742 cm^{-1}). It may be assumed that substance V exists in form B or C. When their solutions are heated in the presence of a base (sodium carbonate, amides), the MB can be converted with various degrees of ease into 3,3'-methylenebis-(2-acylaminochromone)s which, as has been shown with **X** and **XI** as examples, can be obtained more conveniently directly from the AC by reaction with formaldehyde in the presence of tertiary amines. These compounds probably have a structure of the aminovinyl ketone type, i.e., analogous to the initial AC, which is confirmed by their IR and UV spectra. For comparison, the UV and IR spectra of 2-piperidinocarbonylaminochromone (AC-2) (see Experimental and Table 1) were recorded. The study of the influence of structural and external factors on the fine structure of MB and compounds of type X and XI is proceeding.

EXPERIMENTAL*

2-Acylamino-3-dialkylaminomethylchromones (I–IX). Method A. To a solution of 2.33 g (0.01 mole) of 2-ethoxycarbonylaminochromone [1] in 15 ml of absolute ethanol were added 1.02 g (0.012 mole) of piperidine and 1.2 ml (0.012 mole) of a 32% aqueous solution of formaldehyde, and the mixture was heated to the boil and cooled. The precipitate was filtered off (1.75 g), the filtrate was evaporated, and the residue was washed with acetone to give another 0.9 g of substance. The total yield of 2-ethoxycarbonylamino-3-piperidinomethylchromone (I) was 2.65 g. Compounds II–IV were obtained similarly.

Method B. To a solution of 0.43 g (1.58 mM) of 2-piperidoncarbonylaminochromone [1] in 1 ml of water and 0.27 g (3.16 mM) of piperidine were added 0.32 ml (3.4 mM) of a 32% solution of formaldehyde, 0.27 g of piperidine, and 1 ml of water, and the reaction mixture was rapidly filtered and left to stand. After ~30 min, a precipitate of **VII** deposited, and it was separated off and washed with water and ethanol; yield 0.54 g (after 48 hr). Compounds **VIII** and **IX** were obtained similarly. Data on substances I–**IX** are given in Table 2.

Hydrolysis of 2-acylamino-3-dialkylaminochromones. a) A mixture of 1.25 g of substance **I**, 1.4 ml of concentrated HCl, and 30 ml of water was boiled for 5 hr. The precipitate that deposited was filtered off, washed with water, and dried in vacuum over P_2O_5. This yielded 0.55 g (87%) of (2-amino-3-chromonyl)-(4-hydroxy-3-coumarinyl)methane (**XIII**), mp 270.5–271.5° C (from ethanol). Found, %: C 68.14, 68.28; H 3.92, 3.88; N 4.18, 3.96. Calculated for $C_{19}H_{13}NO_5$, %: C 68.94; H 3.91; N 4.18. IR spectrum (in oil): 3330 (bound NH_2 and OH groups), 1690, 1670, and 1635 cm^{-1} (carbonyl groups and conjugated cyclic systems). UV spectrum (ethanol, c $1 \cdot 10^{-4}$–$1 \cdot 10^{-3}$ M): λ_{max} 230, 280, and 300 nm (log ε 4.38, 4.22, and 4.19).

b) A mixture of 1.83 g of the hydrochloride of I, 15 ml of concentrated HCl, and 20 ml of glacial acetic acid was boiled for 18 hr. The precipitate was separated off to give 0.4 g (47.5%) of 3,3'-methylenebis-(4-hydroxycoumarin), mp 278–280° C (reprecipitated from alkaline solution). A mixture with an authentic sample showed no depression of the melting point.

3-3'-Methylenebis(2-ethoxycarbonylaminochromone) (X). A solution of 1.17 g (0.005 mole) of substance AC-1 [1] in 5 ml of ethanol was treated with 0.6 ml (0.006 mole) of 32% formaldehyde solution and 0.52 g (0.005 mole) of triethylamine, and the mixture was boiled for 1 hr 30 min and left overnight. The precipitate that had deposited was filtered off and treated with 10% NaOH, and the alkaline solution was acidified with 10% HCl. The precipitate that deposited was filtered off and washed with water, ethanol, and ether to give 0.37 g (31%) of substance **X** mp 190–191° C (from ethanol). Found, %: C 63.02, 62.78; H 4.92, 4.81; N 6.07, 6.26. Calculated for $C_{25}H_{22}N_2O_8$, %: C 62.76; H 4.64; N 5.86.

3,3'-Methylenebis(2-piperidinocarbonylaminochromone) (XI). A mixture of 1.36 g (0.005 mole) of 2-piperidinocarbonylaminochromone [1], 1.01 g (0.01 mole) of triethylamine, and 0.6 ml (0.006 mole) of 32% formaldehyde was heated to the boil and cooled to ~20° C, After 2 hr it was evaporated in vacuum almost to dryness and the residue was treated with ether to give 1.22 g (88%) of substance **XI**, mp 242.5–243.5° C (from absolute ethanol). Found, %: C 66.66, 66.51; H 5.89, 5.77; N 10.02, 10.22. Calculated for $C_{31}H_{32}N_4O_6$, %: C 66.86; H 5.80; N 10.07. IR spectrum (in oil): 3100–3300, 1690, 1615, 1555 cm^{-1}. UV spectrum (ethanol, c $1 \cdot 10^{-4}$–$1 \cdot 10^{-3}$ M), λ_{max}: 239, 295 nm (log ε 4.79, 4.65). The IR spectrum of 2-piperidinocarbonylaminochromone taken (in oil) for comparison has the frequencies: 1688, 1615, 1570, 1535 cm^{-1}.

REFERENCES

1. V. A. Zagorevskii and Sh. M. Glozman, KhGS [Chemistry of Heterocyclic Compounds], **3**, 782, 1967.

2. D. H. Robertson and K. P. Zink, J. Amer. Chem Chem. Soc., **75**, 1883, 1953.

3. V. A. Zagorevskii and Z. D. Kirsanova, KhGS [Chemistry of Heterocyclic Compounds], **4**, 598, 1968.

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