INVESTIGATIONS ON PYRAN AND RELATED COMPOUNDS

XLI*. A FURTHER STUDY OF ELECTROPHILIC REACTIONS OF 2-AMINOCHROMONES AND 2-ACYLAMINOCHROMONES

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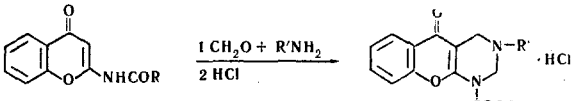
The reaction of 2-acylaminochromones with formaldehyde and primary amines leads to derivatives of 1,2,3,4-tetrahydrochromeno[2,3-d]pyrimidine, and with aromatic aldehydes in the presence of triethylamine, to arylidene-3,3'-bis(2-acylaminochromone)s. The chlorination of 2-acylaminochromones has yielded the corresponding 3-chloro derivatives. The aminomethylation of 2-aminochromone takes place in position 3.

We have previously [1-3] studied the action of a series of electrophilic reagents on 2-aminochromone and 2-acylaminochromones and have established that substitution may take place at the nitrogen atom, at the C_3 atom of the pyrone ring, or in position 6 of the benzene ring. Thus, for example, 2-acylaminochromones undergo aminomethylation with mixtures of formadehyde and secondary amines to form 2-acylamino-3-dialkylaminomethylchromones [1], while in the reaction with formaldehyde in the presence of tertiary amines methylene-3,3'-bis(2-acylaminochromone)s were obtained [1]. Bromination [3] nitration [2,3], and alkylation [3] reactions have also been studied.

In the present work we have made a study of electrophilic substitution reactions in derivatives of 2-aminochromone. If in the aminomethylation reaction of 2-ethoxycarbamoylchromone (Ia) and 2-benzyloxycarbonylaminochromone (Ib) a primary amine is used instead of a secondary amine, products of the closure of the pyrimidine ring – 1, 2, 3, 4-tetrahydro-5H-chromeno [2,3-d] pyrimidin-5-ones (IIa-e) – are formed in high yields (75-90%).



Ia, b IIa-e

Ia R = OC_2H_5; Ib R = $OCH_2C_6H_5$; a R = C_2H_5, R' = n-C_4H_9; b R = C_2H_5, R' = iso-C_3H_7; c R = C_2H_5, R' = $CH_2C_6H_5$; d R = C_2H_5, R' = CH_2CH_2OH; e R = R' = $CH_2C_6H_5$

It is appropriate to mention that condensed systems with conjugated heterocycles of the pyran of a chromene ring and pyrimidine have not been studied previously [4].

The substances obtained form monohydrochlorides and, in contrast to the initial Ia, are insoluble in alkalis and do not exhibit a mobile hydrogen atom. The IR spectrum (in chloroform, c 0.05 M) of the base IIc lacks the bands of the stretching vibrations of OH and NH groups. The NMR spectrum (60 MHz instrument, solvent $CDCl_3$, standard HMDS, δ scale) of the base IIc agrees with the structure given: 1.13 and 4.13 ppm (triplet and quartet from CH_3CH_2O), 3.60, 3.73, and 4.50 ppm (singlets, three isolated CH_2 groups).

*For Communication XL, see [5].

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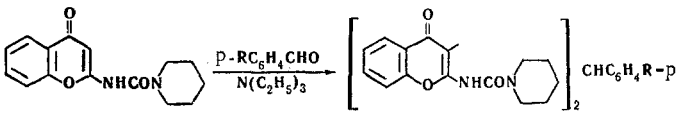
The reaction of 2-piperidinocarbonyl aminochromone (Ic) with aromatic aldehydes in the presence of triethylamine gave the corresponding arylidene-3,3'-bis(2-piperidinocarbonylaminochromone)s (IIIa-c).

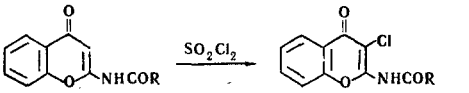


Ic IIIa-c

aR=H; bR=NO_2; cR=OCH_3

The introduction of an arylidene residue into position 3, and not at the nitrogen atom, proves the existence of mobile hydrogen: compound III dissolves in alkalis and is reprecipitated unchanged by acids from the alkaline solutions.

For the case of Ia and trichloroacetylaminochromone (Id), as examples, it has been shown that the reaction with sulfuryl chloride in chloroform leads exclusively to chlorination in position 3 of the chromone system.

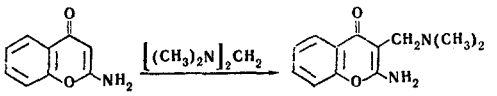


Ia, Id (R=CCl_3) IVa-b

aR=OC_2H_5; bR=CCl_3

Compound IVa hydrolyzes in an acid medium to the known 3-chloro-4-hydroxycoumarin. Substances IVa,b dissolve in alkali. The IR spectra of IVa in the crystalline state (mull in paraffin oil) and in chloroform solution show bands of the stretching vibrations of the NH group in the 3170 and 3410 cm^{-1} regions respectively.

2-Aminochromone (V) readily aminomethylates to 2-amino-3-dimethylaminomethylchromone (VI).



V VI

As in the case of 2-ethoxycarbonylamino-3-piperidinomethylchromone [1] the acid hydrolysis of VI leads to methylene-3,3'-bis(4-hydroxycoumarin). NMR spectrum of VI [in $(CD_3)_2SO$ solution, standard HMDS], ppm: 2.10 (singlet signal of the protons of two equivalent CH_3 groups), 3.33 (singlet signal of an isolated CH_2-N group), 7-8 (four protons of a benzene ring). There is no signal of a vinyl proton at C_3 in the 5-6 ppm region. The NH_2 group and the water in the solvent are not revealed, obviously, because of the existence of a slow exchange of protons. The addition to a solution of VIc in $(CD_3)_2SO$ of ~1 mole of trifluoroacetic acid leads to the formation of a salt of the aliphatic amino group, which is shown by a downfield shift of the signals of the protons of the $N(CH_3)_2$ and CH_2-N groups (2.4 and 3.7 ppm respectively). In the presence of an excess of this acid, further chemical shifts of the signals are found: 2.8 ppm for $N(CH_3)_2$ and 4.2 ppm for CH_2-N, which can be explained by an equilibrium between the form protonated at the aliphatic amino group and the nonprotonated form VI or, more probably, by a transition (possibly partial) of the monoprotonated form into the diprotonated form.

The acetylation of 2-amino-3-bromochromone (VII) takes place somewhat anomalously. While, as we have shown previously [3], in the case of the acetylation of V a monoacetyl derivative (namely 2-acetylaminochromone) is formed, in the case of VII a diacetyl derivative is formed to which we ascribe the structure of 2-(diacetylamino)chromone (VIII).

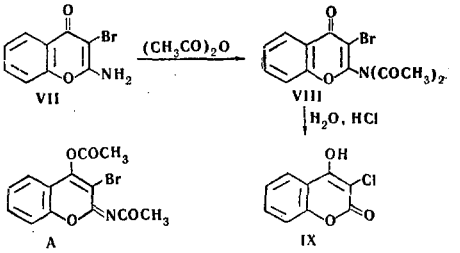


TABLE 1. Hydrochlorides of Derivatives of 1,2,3,4-Tetrahydro-5H-chromeno [2,3-d] pyrimidin-5-one.

Compound	mp, °C (from EtOH)	Empirical formula	Found %				Calculated %				Yield
			C	H	Cl	N	C	H	Cl	N	
IIa	139—140	$C_{18}H_{22}N_2O_4 \cdot HCl \cdot 0{,}5H_2O$	57,53	6,41	9,32	7,56	57,51	6,44	9,44	7,45	90
IIb	224—225	$C_{17}H_{20}N_2O_4 \cdot HCl$			10,08	7,90			10,05	7,94	91
IIc*	192—193	$C_{21}H_{20}N_2O_4 \cdot HCl$	63,16	5,28	8,89	6,83	62,90	5,28	8,85	6,99	75,5
IId	168—168,5	$C_{16}H_{18}N_2O_4 \cdot HCl$	54,19	5,45	9,94	7,94	54,16	5,40	9,99	7,90	76,2
IIe†	140—141	$C_{26}H_{22}N_2O_4$	73,48	5,12		6,54	73,25	5,20		6,57	84,5

*Base, mp 100-101°C (from ethanol), found %: C 69.46; H 5.67; N 7.87. Calculated for $C_{21}H_{20}N_2O_4$, %: C 69.20; H 5.53; N 7.69.

† The base separated out when the reaction mixture was cooled.

λ_{max}, nm (log ε): 232-234 (4.41); 298-300 (4.19).

The hydrolysis of VIII with hydrochloric acid gives 3-chloro-4-hydroxycoumarin (IX), like the analogous reaction of 3-bromo-2-ethoxycarbonylchromone [3]. The decision between structures VIII and A for the diacetyl derivative was made on the basis of the UV and IR spectra. IR spectrum of the substance (in oil), cm^{-1}: 1746 and 1705 (equal intensities C = O of amide groups), 1658 (apparently pyrone C = O), 1618, 1571. IR spectrum (in chloroform, c 0.1 M, d 0.16 mm), cm^{-1}: 1734 (one very strong band, two identical amide C = O groups), 1663 (apparently a pyrone C = O), 1620, 1557. UV spectrum of VIII (in ethanol, c 10^{-4}—10^{-5} M), nm (log ε): 238 (4.38), 306 (3.87).

EXPERIMENTAL

3-n-Butyl-1-ethoxycarbonyl-1,2,3,4-tetrahydro-5H-chromeno [2,3-d]pyrimidin-5-one (IIa). A mixture of 2.33 g (0.01 mole) of Ia, 0.88 g (0.012 mole) of n-butylamine, 1.44 g (0.048 mole) of a 32% aqueous solution of CH_2O, and 15 ml of absolute ethanol was boiled for a few minutes until it was completely homogeneous and was then left overnight. Then it was evaporated in vacuum, the residue was dissolved in anhydrous ether, and the solution was treated with ethereal hydrogen chloride solution. The precipitate that deposited was filtered off, giving 3.3 g (90%) of IIa. Substances IIb-e were obtained by the same method. Information on compounds IIa-e is given in Table 1.

Benzylidene-3,3'-bis(2-piperidinocarbonylaminochromone) (IIIa). A solution of 1.36 g (0.005 mole) of Ic, 0.53 g (0.005 mole) of benzaldehyde, and 0.5 g (0.005 mole) of triethylamine in 10 ml of absolute ethanol was boiled in the water bath for 3 hr. The precipitate that deposited was filtered off and washed with ether to give 0.85 g of IIIa. An additional 0.15 g of IIIa was isolated from the filtrate. The total yield of IIIa was 1 g (63.2%), mp 222-223°C (decomp, from ethanol). IR spectrum (in oil) cm^{-1}: 3000-3300 (broad band, bound NH groups), 1680 (amide C = O), 1620 (pyrone C = O). Found %: C 70.66; H 5.82; N 8.92. Calculated for $C_{37}H_{36}N_4O_6$, %: C 70.25; H 5.74; N 8.86.

4-Nitrobenzylidene-3,3'-bis(2-piperidinocarbonylaminochromone) (IIIb). A solution of 1.36 g (0.005 mole) of Ic, 0.75 g (0.005 mole) of 4-nitrobenzaldehyde, and 0.5 g (0.005 mole) of triethylamine in 10 ml of absolute ethanol was boiled for half an hour, and then the reaction mixture was left overnight and the precipitate was filtered off. Yield 1 g (59%), mp 216-217°C (decomp, ethanol). Found, %: C 65.23; H 5.22; N 10.32. Calculated for $C_{37}H_{35}N_5O_8$, %: C 65.57; H 5.20; N 1053.

4-Methoxybenzylidene-3,3'-bis(2-piperidinocarbonylaminochromone) (IIIc). A solution of 1.36 g (0.005 mole) of Ic, 0.68 g (0.005 mole) of 4-methoxybenzaldehyde, and 0.5 g of triethylamine in 10 ml of absolute ethanol was boiled for 2 hr. The reaction mixture was concentrated in vacuum, and the precipitate that deposited was filtered off and washed with ether to give the hydrate of IIIc, yield 1.2 g (70.6%), mp 208-209°C (ethanol). Found, %: C 67.42; H 5.94; N 8.22. Calculated for $C_{38}H_{38}N_4O_7 \cdot H_2O$, %: C 67.13; H 5.93; N 8.24.

3-Chloro-2-ethoxycarbonylaminochromone (IVa). A solution of 2.33 g (0.01 mole) of Ia in 50 ml of chloroform was treated with 1.5 g (0.011 mole) of SO_2Cl_2 and left for 48 hr, after which the chloroform was distilled off to give 2.4 g (90%) of the chloride IVa, mp 147-148°C (ethanol). IR spectrum (in chloroform, c 0.05 mole, d 0.16 mm), cm^{-1}: 3410 (νNH), 1760 (amide C = O), 1620 (pyrone C = O), 1570. Found, %: C 54.00; H 3.66; Cl 13.09. Calculated for $C_{12}H_{10}ClNO_4$, %: C 53.84; H 3.77; Cl 13.25.

Hydrolysis of IVa. A solution of 1 g of IVa and 10 ml of conc. HClin 10 ml of ethanol was boiled for 2 hr and left overnight. The precipitate that deposited was filtered off, giving 0.5 g (68.5 %) of 3-chloro-4-hydroxycoumarin mp 215-216°C (ethanol). A mixture with an authentic sample gave no depression of the melting point.

3-Chloro-2-trichloroacetylaminochromone (IVb) was obtained in a similar manner to IVa from 1.53 g (0.005 mole) of Id and 0.75 g (0.0055 mole) of SO_2Cl_2. Yield 1.7 g (100%), mp 170-171°C (ethanol). Found, %: C 39.08; H 1.62; Cl 41.31; N 4.34. Calculated for $C_{11}H_5Cl_4NO_4$, %: C 38.74; H 1.48; Cl 41.59; N 4.11.

2-Amino-3-dimethylaminomethylchromone (VI). A mixture of 0.8 g (0.005) of 2-aminochromone, 2 ml of $[(CH_3)_2N]_2CH_2$ and 60 ml of absolute ethanol were boiled for 1 hr. The ethanol was distilled off from the reaction mixture in vacuum. The resulting oil was triturated with a small amount of ether, giving VI with a yield of 0.9 g (82.5%), mp 159.5°C (decomp, ethanol). IR spectrum (in chloroform c 0.05 mole, d 0.4 mm), cm^{-1}: 3100-3480 (νNH_2), 1620 (pyrone C = O), 1568. Found, %: 65.96; H 6.40; N 12.71. Calculated for $C_{12}H_{14}N_2O_2$, %: C 66.05; H 6.47; N 12.84.

Dihydrochloride mp 205-206°C (decomp, ethanol). Found, %: C 49.56, H 5.54. Calculated for $C_{12}H_{16}Cl_2N_2O_2$, %: C 48.49; H 5.54.

Hydrolysis of VI. A mixture of 1.09 g of VI, 6 ml of conc. HCl and 20 ml of acetic acid was boiled for 6 hr. The reaction mixture was evaporated, and the residue was treated with an aqueous solution of $NaHCO_3$ and filtered, and the residue was dissolved in 10% NaOH solution. The alkaline solution was acidified with conc. HCl and the precipitate that deposited was filtered off and washed with water to give methylene-3,3'-bis(4-hydroxycoumarin), yield 0. 3 g (35.7%), mp 259-260°C. A mixture with an authentic sample gave no depression of the melting point. The two samples had the same mobility (R_f 0.4) in thin-layer chromatography on Al_2O_3 (activity grade II, benzene).

3-Bromo-2-diacetylaminochromone (VIII). A mixture of 0.2 g (0.8 mmole) of VII and 3 ml of acetic anhydride, together with a few milligrams of p-toluenesulfonic acid, was boiled for 4 hr and left overnight. Then it was poured into 50 ml of water, and the precipitate that deposited was filtered off and washed with water to give VIII, yield 0.23 g (84%), mp 141-142°C (ethanol). Found, %: C 48.14; H 3.16; N 4.45. Calculated for $C_{13}H_{10}BrNO_4$, %: C 48.19; H 3.11; N 4.32.

A mixture of 0.5 g of VIII, 4 ml of 10% HCl, and 10 ml of ethanol was boiled for 5 hr. The ethanol was distilled off from the reaction mixture and the precipitate was separated off to give 0.2 g (66.6%) of 3-chloro-4-hydroxycoumarin, mp 213-214°C (ethanol). A mixture with an authentic sample melted without depression.

2-Benzyloxycarbonylamino-3-nitrochromone was obtained in a similar manner to 2-ethoxycarbonylamino-3-nitrochromone [2], yield 20.6%, mp 124-125°C (ethanol). Found, %: C 59.78; H 3.74; N 8.25. Calculated for $C_{17}H_{12}N_2O_6$, %: C 59.99; H 3.55; N 8.23.

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