TAUTOMERISM OF 2-ACYLAMINO-3-DIALKYLAMINOMETHYLCHROMONES

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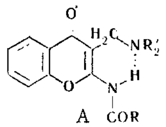
UDC 541.623 : 547.814.1 : 543.422.4.6 : 541.67

The determination of the ionization constants and UV, IR, and PMR spectroscopy established that 2-acylamino-3-dialkylaminomethylchromones can, depending on the character of the acyl group, the aggregate state, and the nature of the solvents, exist in the chromone form with an intramolecular hydrogen bond or as a zwitterion.

The possibility of the existence of Mannich bases — 2-acylamino-3-dialkylaminomethylchromones — as tautomeric forms A, B, and C was discussed in [1], but this problem was not solved definitively.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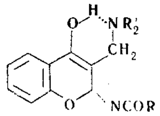
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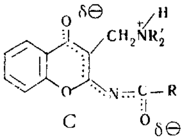
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In this paper, we have made a more detailed investigation of this sort of compound, particularly in the case of 2-carbethoxyamino- and 2-trichloroacetamido-3-piperidinomethylchromones (I and II) by determinining their ionization constants and by means of UV, IR, and PMR spectroscopy. (The spectral data were partially presented in a previous communication [1].) We immediately note that no special difficulties were encountered in setting up the line of demarcation between form A, on the one hand, and forms B and C on the other [1]. It was considerably more complex to assign the actually existing second form to form B or C. Nevertheless, this could be done comparatively simply for Mannich base II using ionization constants. Two values — pK_a^1 2.80 (addition of a proton) and pK_a^2 10.65 (detachment of a proton) — were obtained in a determination of the ionization constants of II. A model compound — 2-trichloroacetamidochromone (III) — which is a singly charged analog of II with one acid grouping, has pK_a 5.45. This value is much closer in magnitude to the value of the first constant of II than to the value of the second. This provides a basis [2] for assigning pK_a^1 2.8 to the dissociation of the acid group and pK_a^2 10.65 to dissociation of the basic group and to assign a zwitterion structure (form C) to compound II itself. An examination of the IR and UV spectra of II confirms this conclusion. In the IR spectra of II (in mineral oil [1] and in dioxane and alcohol solutions), the maximum high-frequency band in the region of the stretching vibrations of the double bonds is found, respectively, at 1665, 1635, and 1648 cm^{-1}. However, in the IR spectra of III (in mineral oil and in alcohol solution), the vibrations of the carbonyl group of the acyl group are characterized by frequencies of 1743 and 1742 cm^{-1}, respectively. There is a long-wave maximum at 328-330 nm in the UV spectrum of II (in alcohol), while 2-acylaminochromones without substituents in the 3 position, which exist in the chromone form [3], have a maximum at 290-300 nm.

On the other hand, in the case of I, one cannot with sufficient confidence establish whether I exists in the B or C form under the given conditions from only a determination of the ionization constants (pK_a^1 5.49, pK_a^2 11.45). The measurement of the ionization constants (pK_a 9.53) of a model compound — 2-carbethoxy-

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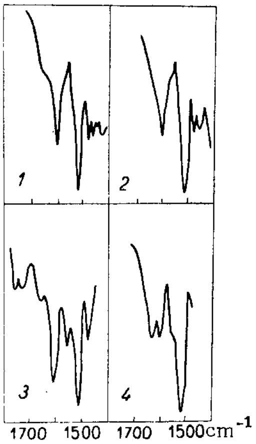

Fig. 1. IR spectra: 1) 2-carbethoxyamino-3-piperidinomethylchromone (I) in $C_2H_5OD + D_2O$ (1 : 1); 2) 2-carbethoxyamino-3-piperidinomethylchromone (I) in $C_2H_5OD + D_2O$ (1 : 1) + 1 one mole of NaOH; 3) 2-carbethoxyamino-3-piperidinomethylchromone (I) in C_2H_5OD; 4) 2-carbethoxyaminochromone (IV) in $C_2H_5OD + D_2O$ (1 : 1) + 1 mole of NaOH.

aminochromone (IV) – is of little help in this respect.* The necessary information for the establishment of the structure of I is provided by a study of the UV, IR, and PMR spectra of I and several related compounds. Thus, judging from the UV, IR, and PMR spectra, I in the crystalline state and in chloroform, heptane [1], or dioxane solutions has chromone form A with an intramolecular hydrogen bond (model compound IV was used for comparison). In addition to the earlier data [1] we point out the following: in the IR spectrum of IV (in chloroform), the bands of two carbonyl groups at 1760 and 1635 cm^{-1} were identified (in the case of the similarly constructed 2-carbobenzoxyaminochromone [4]) by means of O^{18} labeling, while the position (δ 7.47 ppm) of the signal of the proton of the NH group in the PMR spectrum (in $CDCl_3$) is determined by deuteration (by the action of CD_3OD). The signal of the amide proton in the PMR spectrum of I (in $CDCl_3$) is found at weaker field (10.3 ppm [1]), which is explained by the participation of the NH group in the formation of an intramolecular hydrogen bond. The addition of alkali to an alcohol solution of I has a substantial effect on the character of the curve of the UV spectrum, which has about the same shape as the curve of the spectrum of IV recorded in alkaline solutions [1]. Acidification of an alcohol solution of I with hydrochloric acid causes a hypsochromic shift of the long-wave absorption maximum from 336 nm to ~290 nm, i.e., to that value to which the absorption of I in a slightly polar solvent or of IV in alcohol corresponds [1]. In this connection, it is pertinent to mention that the IR and UV spectra of I in slightly polar solvents are similar to the spectra of the cyclic Mannich base – 1-carbethoxy-3-benzyl-5-oxo-1,2,3,4-tetrahydro-5H-chromeno[2,3-d]pyrimidine (V) – which is a fixed model.† The IR spectrum (in $CHCl_3$) of V contains bands at 1730, 1625, and 1573 cm^{-1}, while the UV spectrum (in alcohol) is characterized by λ_{max} 298-300 nm (log ε 4.19).

We also compared the IR spectra of a solution of I in a mixture of C_2H_5OD and D_2O (1 : 1 by volume) without alkali and when 1 mole of NaOH was present. In both cases, absorption of the urethane carbonyl group at ~1750 cm^{-1} is absent, and the maximum high-frequency (nonuniform) band in the region of an NaCl prism is situated at ~1600 cm^{-1} (Fig. 1, curves 1 and 2). A band with two peaks at 1735 and 1756 cm^{-1} of comparatively low intensity (Fig. 1, curve 3) appears in the spectra of solution in anhydrous deuteroalcohol or 95% alcohol (c 0.02 M), which attests to the presence of an appreciable amount of the A form in these solutions. The splitting of this band is probably caused by the presence of rotational isomers (with respect to the $NHCOOC_2H_5$ grouping). An unsymmetric, comparatively broad band of high intensity is observed in the spectra of mineral oil suspensions or chloroform solutions of I. The IR spectrum of an alcohol solution of model compounds IV has an unsymmetric intense band at 1750 cm^{-1}, which vanishes completely (Fig. 1, curve 4) when 1 mole of NaOH is added (a 1 : 1 solution in $C_2H_5OD + D_2O$ was used in the latter case). An appreciable decrease in the intensity of the band at 1745 cm^{-1} is observed in the IR spectrum of a solution of I in dimethyl sulfoxide (DMSO), and, as in the spectrum of the alcohol solution, the band at 1575 cm^{-1}, which is characteristic for the spectra of a mineral oil suspension or a chloroform solution of I and is absent in the spectra obtained for aqueous alcohol solutions, does not completely vanish.

In contrast to the spectrum of a solution of I in $CDCl_3$, the PMR spectrum of a DMSO solution of I does not display a signal for the acidic proton. This is undoubtedly due to proton exchange, despite the fact that proton exchange in solvents such as DMSO is usually more complicated than in chloroform.

All of the facts enumerated above compel us to conclude that I exists in the A or B forms as an equilibrium mixture, depending on the aggregate state of the substance and the nature of the solvent. The

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*We were unable to synthesize model compounds of the 2-(N-alkyl-N-acyl)amino-3-dialkylaminomethylchromone type and a betaine-like salt with a quaternary nitrogen atom in the 3 position.

†The ionization constant (pK_3 5.51) of V cannot be used for direct comparison with the pK_a of a Mannich base of the I type because of the considerable electron-acceptor action of the urethane grouping on the principle nitrogen atom through the methylene link.

selection between the B and C forms in strongly polar media in favor of zwitterion C is also facilitated by a comparison of the ionization constants of I and II: if $pK_a = 10.65$ for an amino group in the 3 position of II, it is hardly likely that a piperidine residue in I will have a lower basicity; in fact, $pK_a = 5.49$.

A comparison of the PMR spectra of Mannich base I, recorded in various solvents, is of definite interest. Thus, while the signals of the $C-CH_3$ protons of the ethyl group in the PMR spectrum of I in $CDCl_3$ and CD_3OD have about the same shifts (1.31 and 1.29 ppm, respectively, everywhere), δ CH_2O amounts to 4.30 and 4.20 ppm. On the other hand, the signals of the protons of a substituent in the 3 position have shifts at stronger field in $CDCl_3$ than in CD_3OD: 1.5 and 1.6 ppm (approximately determined from the center of the broaded but rather symmetrical overall signal of these six protons) for β,β',γ-$(CH_2)_3$ groups of the piperidine ring, 3.69 and 3.95 ppm for $C_{(3)}-CH_2N$, and 2.5 and 2.9 ppm (approximately determined from the center of the upper point of the broadened signal of four protons) for α,α'-$(CH_2)_2$ groups. To this it must be added that all of the indicated shifts have the same value in the PMR spectrum of solutions of I in d_6-DMSO as for a solution in CD_3OD. The shift in the signals to weak field for a solution of I in CD_3OD therefore should not be explained by the formation of intermolecular hydrogen bonds between the principal nitrogen atom and CD_3OD or by the water present in the DMSO (judging from the intensity of the signal at 4.8 ppm, the water concentration is no more than 2 moles per mole of substance). When trifluoroacetic acids is added to a solution of I in CD_3OD, the signals in the PMR spectrum are shifted to weaker field: CH_3 1.29, CH_2O 4.25, β,β',γ-$(CH_2)_3$ 1.7, $C_{(3)}-CH_2N$ 4.15, and α,α'-$(CH_2)_2$ 3.2 ppm. The addition of a large excess of trifluoroacetic acid causes a further shift in the indicated signals in the same direction, for example, 4.27 ppm for $C_{(3)}-CH_2N$. Dilution of a solution of I in CD_3OD with an equal volume of D_2O also promotes a shift in the indicated signals to weaker field, for example, 4.2 ppm for $C_{(3)}-CH_2N$. In this connection, it is important to point out that the shifts of the $O-CH_2$ group in $CDCl_3$ and CD_3OD are practically identical for model compound IV. The PMR spectral data presented are in better agreement with the concept that, in CD_3OD (or CH_3OH) and DMSO solutions, I is primarily in the zwitterion form. Since II exists only in the zwitterion form, a labile proton is not displayed in the PMR spectrum (in DMSO) (up to 16 ppm).

Like II, 2-dichloroacetamido-3-piperidinomethylchromone (VI) and 2-trichloroacetamido-3-(N'-methylpiperazinomethyl)chromone (VII) have the zwitterion form in the crystalline state. The maximum high-frequency band in the region of the stretching vibrations of double bonds is found at 1620 and 1682 cm^{-1} in the IR spectra of VI and VII (in mineral oil), respectively, while the acyl group carbonyl is characterized by bands at 1742 and 1743 cm^{-1}, respectively, in the starting 2-dichloroacetamidochromone (VIII) and 2-trichloroacetamidochromone (III).

EXPERIMENTAL

The UV spectra were recorded with an SF-4 spectrophotometer in quartz cuvettes. The IR spectra were recorded with a UR-10 spectrophotometer. The PMR spectra were obtained with a spectrometer with an operating frequency of 60 MHz with hexamethyldisiloxane as the standard. The ionization constants were determined potentiometrically in 70% (by volume) ethanol. The titration with 0.001 M solutions was carried out at 25° with an LPU-01 pH meter.

2-Carbethoxyaminochromone (IV) [3]. IR spectrum (in dioxane, c 0.2 M), cm^{-1}: 1753, 1630, 1575.

2-Trichloroacetamidochromone (III) [3]. IR spectrum, cm^{-1}: 1743, 1625, 1540 (in mineral oil); 1738, 1633, 1624 (in C_2H_5OD).

2-Carbethoxyamino-3-piperidinomethylchromone (I) [1]. IR spectrum (in dioxane, c 0.2 M), cm^{-1}: 1753, 1630, 1575.

2-Trichloroacetamido-3-piperidinomethylchromone (II) [1]. IR spectrum, cm^{-1}: 1648, 1605, 1538 (in alcohol, c 0.1 M); 1635, 1612 (in dioxane, c 0.01 M). UV spectrum (in alcohol, c $1 \cdot 10^{-4}$-10^{-3} M), λ_{max}, nm (log ε): 242 (4.00), 328-330 (4.01).

2-Dichloroacetamidochromone (VIII). This compound was obtained via the method in [3] and had mp 249-250° (dec., from dimethylformamide and then from alcohol). IR spectrum (in mineral oil), cm^{-1}: 1742, 1635, 1604, 1576, 1542. Found: C 48.7; H 2.5; Cl 26.0; N 5.3%. $C_{11}H_7Cl_2NO_3$. Calculated: C 48.6; H 2.6; Cl 26.1; N 5.2%.

2-Dichloroacetamido-3-piperidinomethylchromone (VI). This compound was obtained via the method in [1] and had mp 142-144° (dec., from alcohol). IR spectrum (in mineral oil), cm^{-1}: 1620, 1588, 1532. Found: C 55.3; H 5.1; N 7.5; Cl 19.0%. $C_{17}H_{18}Cl_2N_2O_3$. Calculated: C 55.3; H 4.9; N 7.6; Cl 19.2%.

2-Trichloroacetamido-3-(N'-methylpiperazinomethyl)chromone (VII). This compound was similarly obtained and had mp 178-179° (dec., from alcohol). IR spectrum (in mineral oil), cm^{-1}: 1662, 1603, 1528. Found: C 49.2; H 4.5; N 9.9; Cl 25.5%. $C_{17}H_{18}Cl_3N_3O_3$. Calculated: C 48.8; H 4.3; N 10.0; Cl 25.4%.

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