INVESTIGATION ON PYRAN AND RELATED COMPOUNDS

XLII* THE SYNTHESIS OF 4-AMINOCOUMARINS AND THE MECHANISM OF THE REPLACEMENT OF THE HALOGEN IN 4-CHLOROCOUMARIN

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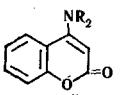
A convenient method for obtaining 4-aminocoumarins by the reaction of 4-chlorocoumarin with amines in dimethyl sulfoxide is proposed. The reactions of 4-chlorocoumarin with CD_3ONa in CD_3OD and with [N-D_1]piperidine, of [3-D_1]-4-chlorocoumarin with CH_3ONa in CH_3OH and with aniline and n-butylamine and of 4-methoxycoumarin with CD_3ONa in CD_3OD have been studied and the mechanism of nucleophilic and substitution in position 4 of the coumarin system is discussed.

It has been established previously [1,2] that nucleophilic reagents (alkali, alkoxides, amines) attack 4-chlorocoumarin both at position 4 and at the carbonyl group. In the first case the halogen is replaced – this reaction has been known for a long time for some amines and alkoxides [3]. The opening of the pyrone ring in 4-chlorocoumarin under the action of the reagents mentioned is in itself an interesting reaction, since it leads to a new type of compounds – o-hydroxyphenylpropiolic acid or its derivatives. However, this direction of the reaction may sometimes prove undesirable, e.g., in most cases where the synthesis of 4-aminocoumarins is desirable. In one of our papers we reported that in solution in dimethyl sulfoxide (DMSO) the formation of 4-aminocoumarins by the reaction of 4-chlorocoumarin with amines (with benzylamine and diethylamine as examples) takes place more smoothly than in alcoholic and benzene solutions or in solution in an excess of the amine.

TABLE 1. Preparation of 4-Aminocoumarins 

NR_2	Amount of starting materials, mole		mp, °C	Yield, %
	4-chlorocoumarin	amine		
Diethylamino	0,0083	0,033	58—59[1]	90
Piperidino	0,0055	0,022	105—107[1]	86
Morpholino	0,0055	0,022	140—141,5[6]	86
Pyrrolidino *	0,0055	0,02	129,5—130,5	92
Benzylamino	0,0055	0,033	240—242[1]	80
Anilino	0,006	0,018	267—268[1]	86†

*Found, %: C 72.6; H 6.1; N 6.6. Calculated for $C_{13}H_{13}NO_2$, %: C 72.57; H 6.04; N 6.50.

† The reaction was carried out at 60° C for 6 hr. The reaction product was washed additionally with hot benzene. When the reaction was carried out at 20°C for 24 hr, the yield of substance was 44% (46% of the initial chlorocoumarin was recovered.

*For Communication XLI, see [11].

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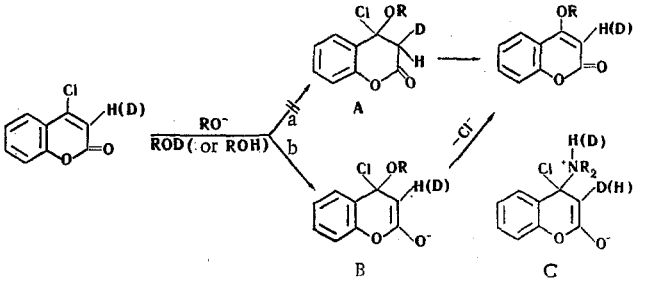
In the present work we have somewhat broadened the use of DMSO as solvent for this reaction and have convinced ourselves that 4-aminocoumarins are in fact obtained in high yields (Table 1). The reaction takes place extremely rapidly and practically no products of the opening of the coumarin ring are formed. An exception is the reaction of 4-chlorocoumarin with ammonia: instead of 4-aminocoumarin, o-hydroxyphenylpropiolamide [1] was obtained with a yield of 92%. It is possible that ammonia as the reagent exhibits specificity because of the comparatively strong solvation of its molecule by the solvent.

The question of the mechanism of the replacement of the halogen in 4-chlorocoumarin by the action of nucleophilic agents is of independent interest. At the present time, it is generally considered [4,5] that the nucleophilic replacement of activated halogen at an unsaturated carbon atom, e.g., in halogeno-2-4-dinitrobenzenes or β-chlorovinyl carbonyl compounds, takes place by a two-stage bimolecular mechanism via an intermediate charged compound – a complex in which the atom attached to the halogen and to the entering substituent undergoes sp^3 hybridization. Synchronous bimolecular substitution (S_N2) is regarded as very unlikely, and a mechanism of the "complete addition – splitting out" type is assumed only in those cases where the possibility of the additional delocalization of the negative charge in the anion mentioned through reaction with neighboring electron-accepting groups is absent. On the basis of these ideas, we have put forward the hypothesis that the reaction of amines with 4-chlorocoumarin takes place by the first of the mechanisms mentioned [1]. Here we shall give experimental proofs of the fact that the replacement of the halogen in 4-chlorocoumarin does not include a stage of the complete addition of the elements of the nucleophilic reagent at the position of the C_3-C_4 double bond of the coumarin system.

We studied the reactions of 4-chlorocoumarin with N-[D_1]-piperidine (90% deuterium enrichment) in the same amine and with CD_3ONa in CD_3OD* solution (containing 98% of deuterium). In addition, we performed the reactions of [3-D_1]-4-chlorocoumarin with aniline and n-butylamine in DMSO and also with CH_3ONa in CH_3OH solution. All the nondeuterized 4-substituted coumarins formed as a result of these reactions have been described in the literature. The synthesis of [3-D_1]-4-chlorocoumarin and [3-D_1]-4-anilinocoumarin has been reported recently. [7]. If the reactions are carried out under the mildest possible conditions, no isotopic change takes place at the C_3 atom of the coumarin heterocycle (checked by the PMR spectra, the error of the determination being ±10-15 %) which enables route a via adduct A (mechanism of reactions with nucleophiles in the manner of alkoxy ions) to be rejected:



The absence of isotopic exchange in position 3 during the reaction of [3-D_1]-4-chlorocoumarin with piperidine has also been reported by other workers [7]. In accordance with the mechanism proposed for the reaction of the ethanethiyl ion with ethyl β-chlorocrotonates [4,5], the mechanism of the replacement of the halogen in 4-chlorocoumarin by an alkoxy ion or an amino group most probably includes the formation of intermediate complexes (route b) of type B or C.

During the investigation it was also found that when a reaction mixture of 4-chlorocoumarin with piperidine or with an excess of methoxide in methanol was allowed to stand for a sufficiently long time, isotopic exchange took place at the C_3 atom, which is probably due to the continuous presence in the reaction mixture of a certain concentration of complexes of type B containing two amino groups or two alkoxy groups, respectively, in position 4. The possibility of the replacement of the amino group in 4-aminocoumarin by another amino group has been established previously [8], and we have now found that an alkoxy substituent in position 4 of coumarin is readily replaced by a similar group under the action of an alkoxide. It proved convenient experimentally to replace an alkoxy group by one of the same type but containing a deuterium label. Thus, on brief heating with a solution of CD_3ONa in CD_3OD, 4-methoxycoumarin acquired more than 90% of CD_3O groups in position 4. Under these conditions only 15% deuterization takes place

*In this case, the deuterium label in the methyl group is unnecessary.

in position 3. Consequently, the replacement of an alkoxy group by the action of a strong nucleophile takes place by the same mechanism as the replacement of the chlorine atom in 4-chlorocoumarin. However, the more prolonged heating of the reactants (25 min instead of 2-3 min) in the presence of an excess of alkoxide leads to considerable (50%) isotopic exchange at the C_3 atom. 4-Methoxycoumarin reacts considerably more slowly with neutral CD_3OD.

In 4-butylaminocoumarin, deuteration in position 3 by means of deuteromethanol takes place considerably more readily than in 4-piperidinocoumarin. The isotopic exchange in position 3 of the heterocycle in the action of aniline on [3-D_1]-4-chlorocoumarin observed by other authors [7] is undoubtedly the result of a secondary reaction between the [3-D_1]-4-anilinocoumarin formed and an excess of aniline. As mentioned above, under sufficiently mild reaction conditions, this type of exchange does not take place either with secondary or with primary amines. The absence of isotopic exchange in position 3 in the reaction of 4-chlorocoumarin with amines is, at the same time, a direct proof of the fact that 4-aminocoumarins are not formed via o-hydroxyphenylpropiolamides under the conditions that we selected. The latter route is obviously independent and takes place only under comparatively severe conditions (obviously, when the reaction leads even partially to the formation of acetylene compounds) as reported in the previous paper [1].

In order to evaluate to some approximation the electrophilicity of positions 2 and 4 in the molecule of 4-chlorocoumarin we performed a calculation of π-electron densities on the atoms of the molecule of this compound by Hückel's MO LCAO method. For comparison, molecular diagrams* were also obtained for coumarin, 3-chloro- and 4-aminocoumarins, and 3,4-dichlorocoumarin – compounds, which, like 4-chlorocoumarin, undergo the attack of nucleophilic agents at position 2 or 4 (see [1,2,8-10]). The values of the electron densities on the atoms of the pyrone ring of the compounds are mentioned in Table 2.

Coulomb integral (αX): $h_{\ddot{O}}$ 2; $h_{\dot{O}}$ 1; h_C 0. Bond integral (β_{CX}): k_{CC} 1; $k_{C=O}$ 1.2; k_{C-O} 0.8. Auxiliary inductive parameter (δ); 0.1 h_X.

It can be seen from the table that in the molecules of 3- and 4-chlorocoumarins and also in 4-aminocoumarin, as in unsubstituted coumarin, the C_2 and C_4 atoms are electrophilic, which is in harmony with the experimental results. In 3-chlorocoumarin, the C_3 atom bears definite negative charge and therefore it can hardly be subjected to the direct attack of the nucleophilic reagent. (For the reaction of 3-halogenocoumarins with nucleophilic reagents see [8]).

In 4-methoxycoumarin, the grouping in position 4 is replaced under the reaction of nucleophilic reagents considerably more slowly than a chlorine atom which, in our opinion, is due primarily to the fact that the methoxy group has a greater electron-donating capacity than a chlorine atom and to the consequent decrease in the positive charge on C_4 atom. Thus, 4-methoxycoumarin scarcely reacts with an excess of diethylamine (20°C, 5 hr) or with benzylamine (20°C for 5 hr or 100°C for 10 min), while 4-chlorocoumarin is converted completely into 4-aminocoumarin under the same conditions.

EXPERIMENTAL

The PMR spectra were obtained on an instrument with a working frequency of 60 MHz on the δ scale relative to HMDS. The measurement of the intensities of the signals (±10-15%) was carried out either by means of an integrator or by the "area-weighing" method with an adequate development of the scale.

Preparation of 4-Aminocoumarins in DMSO. The appropriate amine was added to a solution of 4-chlorocoumarin in 4-5 ml of anhydrous DMSO. The reaction mixture was left at 20°C for 24 hr, after which it was diluted with five volumes of water. The precipitate that deposited was filtered off and washed with 10% HCl, water, 10% NaOH and water, and dried to give the desired product (Table 1).

Reaction of [3-D_1]-4-chlorocoumarin with CH_3ONa in CH_3OH. A solution of 0.74 g (0.004 mole) of [3-D_1]-4-chlorocoumarin (containing more than 95% of deuterium as determined from the PMR spectrum in dioxane by comparing the intensity of the C_3H signal at 6.6 ppm with the intensity of the signals of the four protons of the benzene ring at 7-8 ppm) and CH_3ONa from 0.09 g (0.004 g-at.) of Na in 10 ml of absolute methanol was heated at 70°C for about 0.5 min, cooled, and diluted with 20 ml of water. The precipitate that deposited was filtered off, washed with water, and dried to give 0.7 g (97%) of [3-D_1]-4-methoxycoumarin, mp 124.5-125.5°C. PMR spectrum authentic nondeuterized 4-methoxycoumarin (in acetonitrile),

*The calculations of the molecular diagrams of the compounds of the coumarin series were carried out at our request by V. I. Minkin and V. G. Vinokurov, to whom the authors express their deep gratitude.

TABLE 2

Compound	-Electronic densities on the atoms					
	$O_{(1)}$	$C_{(2)}$	$O_{(CO)}$	$C_{(3)}$	$C_{(4)}$	others
Coumarin	1,819	0,819	1,527	1,032	0,857	—
3-Chlorocoumarin	1,802	0,799	1,612	1,094	0,801	3-Cl: 1,985
4-Chlorocoumarin	1,818	0,818	1,516	0,997	0,930	4-Cl: 1,978
3,4-Dichlorocoumarin	1,818	0,810	1,518	1,070	0,896	3-Cl: 1,983 4-Cl: 1,977
4-Aminocoumarin	1,826	0,833	1,552	1,090	0,872	4-N-: 1,873

ppm: 4.0 (singlet, 3H, CH_3O); 5.7 (singlet, 1H, C_3H); 7-8 (multiplet, 4H, benzene ring). PMR spectrum of [3-D_1]-4-methoxycoumarin (in a mixture of acetonitrile and DMSO), ppm: 4.0 (singlet, CH_3O); 7-8 (C_6H_4); the signal at 5.8 ppm had an intensity of less than 0.1H.

Reaction of 4-Chlorocoumarin with CD_3ONa in CD_3OD. A solution of 0.37 g (0.002 mole) of 4-chlorocoumarin and the CD_3ONa from 0.09 g (0.004 g-at.) of Na in 5 ml of CD_3OD (containing 98% of deuterium) was boiled at 70°C for 0.5 min, cooled and diluted with 10 ml of D_2O (99% enrichment). The precipitate that deposited was separated off, washed with a mixture of D_2O and CD_3OD and dried. The yield of 4-CD_3O-coumarin was 0.3 g (83%), mp 125-126°C. PMR spectrum (in acetonitrile), ppm: 5.7 (singlet, 0.9H, $C_{(3)}H$); 7-8 (C_6H_4); no signal of the protons of a CH_3O group at 4 ppm was detected ($\ll$0.1H). When solutions of this substance or of 4-methoxycoumarin were kept in acetonitrile or dioxane in the presence of D_2O or CD_3OD for 5-20 min, no appreciable replacement of hydrogen in position 3 by deuterium took place. When a solution of 4-methoxycoumarin was boiled with CD_3OD for 6 hr and was then allowed to stand at 20°C for 30 days, there was less than 15% exchange in positions 3 and 4. If the reaction is carried out by boiling a solution of 4-chlorocoumarin and CD_3ONa in CD_3OD for 25 min, isotopic exchange in position 3 of 4-CD_3O-coumarin takes place to the extent of 58%.

Reaction of 4-Chlorocoumarin with [N-D_1]-piperidine. To 0.9 g (0.005 mole) of 4-chlorocoumarin was added 4.2 g (0.05 mole) of [N-D_1]-piperidine (containing 90% of deuterium, determined by IR spectroscopy). After 1 hr (20°C) a large amount of hot absolute benzene was added and the precipitate of piperidine hydrochloride that deposited was filtered off and washed with hot absolute benzene. The combined solutions were evaporated in vacuum with protection from atmospheric moisture. The residue was washed with boiling absolute hexane, giving 0.016 g (14%) of the piperidine of o-hydroxyphenylpropiolic acid [1], mp 160-162°C. The solution was cooled, and the precipitate that deposited was filtered off to give 4-piperidinocoumarin, mp 106-106.5°C, yield 0.88 g (79%). PMR spectrum of an authentic nondeuterized sample (in $CDCl_3$), ppm: 1-2 (broadened signal, 6H, three CH_2 groups of the β,β'- and γ-positions of the piperidine ring); 2.5-3.5 (broadened signal, 4H, two CH_2 groups in the α- and α'-positions of the piperidine ring); 5.5 (singlet, 1H, C_3H); 7-7.7 (C_6H_4). In the 4-piperidinocoumarin obtained as described in this experiment, the intensity of the C_3H signal is 0.85H (for comparison, the intensities of the signals of the three CH_2 groups in the 1-2 ppm region were used). When the reaction was performed for 68 hr, 4-piperidinocoumarin (yield 70%), deuterized in position 3 to the extent of 50-60%, was obtained.

Reaction of [3-D_1]-4-chlorocoumarin with Aniline. A solution of 0.74 g (0.004 mole) of [3-D]-4-chlorocoumarin and 0.72 g (0.007 mole) of aniline in 4 ml of DMSO was left at 20°C for 17 hr and diluted with water and the precipitate was filtered off, well pressed out, and washed with boiling absolute benzene to give 0.14 g (14.4%) of [3-D_1]-4-anilinocoumarin, mp 267-268°C. PMR spectrum of the authentic nondeuterated substance (in a mixture of acetonitrile and DMSO), ppm: 5.3 (singlet, C_3H); 7-7.7 (sum of the C_6H_5, $C_{(6)}H$, $C_{(7)}H$, $C_{(8)}H$ signals); 8.2 (doublet $C_{(5)}H$ signal). In the PMR spectrum of the substance obtained in this experiment, the $C_{(3)}H$ signal at 5.3 ppm had an intensity of less than 0.1H.

Reaction of [3-D]-4-Chlorocoumarin with n-Butylamine. A solution of 0.74 g (0.004 mole) of [3-D]-4-chlorocoumarin and 0.56 g (0.007 mole) of n-butylamine in 4 ml of DMSO was kept at 20°C for 1 hr and was then diluted with 10 ml of water. The precipitate was separated off, washed with water, dried and washed with absolute benzene. This gave 0.5 g (56%) of [3-D]-4- n-butylaminocoumarin, mp 116-117°C (from absolute benzene). PMR spectrum of authentic nondeuterized 4-butylaminocoumarin (in a mixture of acetonitrile and DMSO), ppm: 5.2 (singlet $C_{(3)}H$); 7-7.7 (sum of the C_6H, C_7H, and C_8H); 8.1 (quartet $J_1 \approx 8$ Hz and $J_2 \approx 1.5$ Hz, C_5H). After the addition of CD_3OD to a solution of the nondeuterized sample in a mixture of acetonitrile and DMSO and standing for 30 min, the intensity of the C_3H signal had decreased by 35%.

The PMR spectrum of the substance obtained in this experiment (in DMSO) had the C_6H_4 signals in the 7-8.4 ppm region, and the C_3H signal at 5.5 ppm was practically absent (< 0.1H).

Reaction of 4-Methoxycoumarin with CD_3OD. A solution of 0.17 g (0.001 mole) of 4-methoxycoumarin and 0.023 g (0.001 mole) of CD_3ONa in 3 ml of CD_3OD was heated at 70°C for 2-3 min (the substance dissolved completely), cooled, and diluted with 3 ml of D_2O, and the 4-CD_3O-coumarin was filtered off. PMR spectrum (in acetonitrile), ppm: 5.7 (singlet 0.85H, C_3H); at 4 ppm, the CH_3O signal had an intensity corresponding to the presence of not more than 5% of this group. If the reaction mixture was boiled for 25 min, isotopic exchange in position 3 of the 4-CD_3O-coumarin took place to the extent of 51%.

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