SYNTHESIS AND STUDY OF THE PROPERTIES OF 4-SUBSTITUTED 3-AMINOMETHYLCOUMARINS

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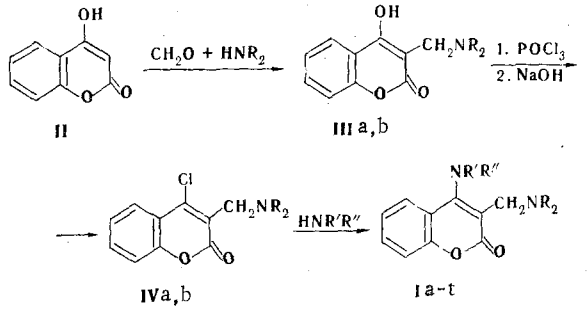
The aminomethylation of 4-hydroxycoumarin gave 3-pyrrolidinomethyl- and 3-piperidinomethyl-4-hydroxycoumarins, which were converted to 4-chloro derivatives by the action of phosphorus oxychloride. A number of 3-pyrrolidinomethyl- and 3-piperidinomethyl-4-aminocoumarins were synthesized by reaction of the 4-chloro derivatives with various amines, and some of their properties were studied.

While 2-amino-3-aminomethylchromones are accessible and have been studied quite adequately [1], their structural analogs — 4-amino-3-aminomethylcoumarins — have not been obtained up until now, whereas the study of heterocyclic compounds of this sort is fully justified within the framework of the search for pharmacologically active substances, since related compounds — 3-substituted 4-aminocoumarins — display analgesic, antiinflammatory, and neurotropic activity [2-6].

In the present research we developed a method for the synthesis of previously unknown 4-amino-3-aminomethylcoumarins (Ia-t) and studied some properties of these compounds.



II IIIa,b IVa,b Ia-t

Ia-j IIIa, IVa NR_2 = pyrrolidino; Ik-t, IIIb, IVb NR_2 = pyperidino; Ia,k R′=H, R″=CH_3; Ib,l R′=H, R″=n-C_4H_9; Ic,m R′=H, R″=$CH_2C_6H_5$; Id,n R′=H, R″=C_6H_5; Ie,o R′=R″=CH_3; If,o R′=R″=C_2H_5; Ig,f R′+R″=$(CH_2)_4$; Ih,r R′+R″=$(CH_2)_5$; Ii,s R′+R″=$CH_2CH_2OCH_2CH_2$; Ij,t R′+R″=$CH_2CH_2N(CH_3)CH_2CH_2$

Mannich bases IIIa,b were synthesized by the method described in [7, 8] from 4-hydroxycoumarin II. Compounds IVa,b, which are key substances for subsequent synthesis, were obtained by the action of phosphorus oxychloride on IIIa,b with subsequent treatment of the resulting adducts (with unestablished structures) with alkali. The chlorine atom in these substances is quite reactive and can be readily replaced by various amine residues by the action of primary and secondary amines to give Ia-t. Complex mixtures of products, from which 4-amino-3-aminomethylcoumarins could not be isolated, are obtained in the reaction of IVa,b with ammonia.

Attempts to obtain I by another method, viz., by aminomethylation of the corresponding 4-aminocoumarins, were unsuccessful (only the starting substances were isolated), although it is known that the isomeric (with respect to 4-aminocoumarins) 2-aminochromones readily undergo the Mannich reaction to give 3-aminomethyl derivatives [1, 9, 10].

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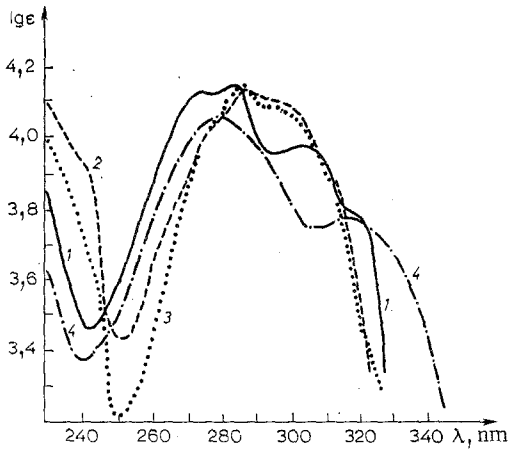

Fig. 1. UV spectra: 1) 4-hydroxy-3-pyrrolidinomethylcoumarin (IIIa) in 1 N hydrochloric acid; 2) IIIa in alcohol; 3) 4-hydroxycoumarin (II) in 1 N sodium hydroxide solution; 4) 3-pyrrolidinomethyl-4-chlorocoumarin (IVa) in alcohol.

According to the spectral data, IIIa, like its analog IIIb [7], exists in a zwitterionic form. Thus the UV spectrum of IIIa in alcohol is similar to the spectrum of II in 1 N alkali solution and differs from the UV spectrum of chloro derivative IVa (see Fig. 1). The form of the spectrum of IIIa changes markedly on passing to a solution in 1 N hydrochloric acid and becomes similar to the curve of the spectrum of IVa.

The IR spectra of IIIa,b contain absorption bands at 1654 cm^{-1} (νC=O) and at 1604 and 1536 cm^{-1} (νC=C of the coumarin system). An increase in the frequencies of the vibrations corresponding to the first and third bands to 1720 and 1570 cm^{-1} occurs on passing to IVa,b (the position of the second band remains virtually unchanged) with a simultaneous decrease in the integral intensities of the two low-frequency bands (from 4-5 and 7-8 proton units to 1.5-1.8 and 0.6-0.7 proton units, respectively). Absorption bands of a carbonyl group are observed at 1666-1690 cm^{-1} in the IR spectra of Ia-t. The absence in the spectra of Ia-d, k-n, which have a secondary amino group, of the NH absorption bands at 3400 cm^{-1} that appear in the spectra of 4-amino- and 3,4-diaminocoumarins [11] can be explained by the formation of a strong intramolecular hydrogen bond with the basic nitrogen atom of the amine residue in the 3 position.

In the case of Ib, c, g, h, l, m, q, r it was shown that under the influence of 5% hydrochloric acid under relatively mild conditions the aminomethyl group is readily split out to give known 4-aminocoumarins [12]. 3,3'-Methylene-bis(4-hydroxycoumarin) (V) is produced when a solution of Ig or Ir is refluxed in 5% hydrochloric acid. The formation of V under these conditions can be explained by the fact that the initially obtained 4-aminocoumarins undergo further hydrolysis to II, which reacts with the formaldehyde liberated in a retro-Mannich reaction to give dicoumarol V. It was demonstrated by a separate experiment that 4-piperidinocoumarine (VI) is converted completely to II by refluxing briefly in 5% hydrochloric acid.

Tests of Ia-t and IVa,b for their psychotropic activity showed that they have a slight depressing effect on the central nervous system; IVa,b proved to be the most active compounds.

EXPERIMENTAL

The UV spectra were recorded with a Perkin-Elmer 403 spectrophotometer. The IR spectra of solutions of the compounds in chloroform (c 0.05 mole/liter, d 0.077 mm) were recorded with a Perkin-Elmer 580 spectrometer. The course of the reaction and the purity of the substances were monitored by means of thin-layer chromatography (TLC) on Alufol (E type) in a benzene–ether system (3:1).

3-Aminomethyl-4-hydroxycoumarins (IIIa,b). A warm solution of 16.2 g (0.1 mole) of 4-hydroxycoumarin (II) in 150 ml of absolute alcohol was added dropwise with stirring to a refluxing solution of 8.5 g (0.1 mole) of 34% formalin and 0.12 mole of pyrrolidine or piperidine in 50 ml of absolute alcohol, and the mixture was refluxed for 30 min. The hot solu-

tion was filtered and allowed to stand in a refrigerator for 24 h. The resulting precipitate was removed by filtration and washed with a small amount of alcohol. The filtrate was concentrated, and an additional amount of the reaction product was removed by filtration. The precipitates were combined and recrystallized from alcohol. This procedure gave 22.4 g (91.2%) of IIIa with mp 179-181°C (dec.). Found: C 68.5; H 6.2; N 5.9%. $C_{14}H_{15}NO_3$. Calculated: C 68.7; H 6.2; N 5.7%: Also obtained was 22.1 g (85.4%) of IIIb with mp 180-182°C (dec.) [mp 182°C (dec.) [7, 8]].

3-Aminomethyl-4-chlorocoumarins (IVa,b). A) A solution of 0.05 mole of IIIa or IIIb in 100 ml of phosphorus oxychloride was refluxed for 6 h and allowed to stand overnight. It was then evaporated in vacuo, and the traces of phosphorus oxychloride were removed by distillation with toluene. The residue was dissolved in water, and the solution was filtered and made alkaline with 5% sodium hydroxide solution. The precipitate was removed by filtration, washed with water, and dried. This procedure gave 10 g (76%) of IVa with mp 74-75°C (purified by reprecipitation from 5% hydrochloric acid by the addition of alkali) and R_f 0.48. Found: C 63.5; H 5.3; Cl 13.3; N 5.2%. $C_{14}H_{14}ClNO_2$. Calculated: C 63.8; H 5.3; Cl 13.4; N 5.3%. Also obtained was 11.54 g (83%) of IVb with mp 120-121°C (from alcohol) and R_f 0.66. Found: C 64.9; H 5.9; Cl 12.8; N 5.1%. $C_{15}H_{16}ClNO_2$. Calculated: C 64.9; H 5.8; Cl 12.8; N 5.0%.

B) The reaction was carried out similarly, and the residue obtained after removal of the phosphorus oxychloride by distillation was shaken with benzene and 5% alkali solution. The organic layer was separated, washed with water, and evaporated. Compounds IVa and IVb were obtained in 93 and 98% yields, respectively.

3-Aminomethyl-4-aminocoumarins (Ia-t). A 0.03-mole sample of the corresponding amine was added dropwise with stirring to a solution or suspension of 0.01 mole of IVa or IVb in 30 ml of dry DMSO, and the mixture was stirred for 6-7 h and allowed to stand overnight at 20°C. It was then diluted with 70 ml of cold water and stirred for 1 h. The precipitate was removed by filtration, washed with water, dried, and recrystallized from a suitable solvent. This procedure was used to obtain Ia-p, r-t. In the case of the reaction of IVb with pyrrolidine the oily product that was liberated when the reaction mixture was diluted with water was extracted with benzene. The extract was washed with water and filtered through a layer of Al_2O_3. The filtrate was evaporated to give oily Iq. Data on Ia-t are presented in Table 1.

Action of Hydrochloric Acid on 3-Aminomethyl-4-hydroxycoumarins (IIIa,b). A solution of 1 mmole of IIIa or IIIb in 5 ml of 5% hydrochloric acid was refluxed for 3 h, after which it was cooled, and the precipitate was washed with water and dried. This procedure gave dicoumarol V in 77 and 83% yields, respectively; the product had mp 274-276°C (dec., from toluene). The substance was identical to the sample obtained by the usual method from 4-hydroxycoumarin II and formaldehyde.

Action of Hydrochloric Acid on 3-Aminomethyl-4-aminocoumarins (I). A) A mixture of 2.5 mmole of the corresponding I and 15 ml of 5% hydrochloric acid was stirred at 20°C for 3-5 h, after which the precipitate was removed by filtration, washed with water, and dried. 4-Butylaminocoumarin, with mp 116-117°C (from benzene–hexane), was obtained in 91 and 94% yields from Ib and Iℓ, respectively. 4-Pyrrolidonocoumarin, with mp 129-130°C (from benzene–hexane), was obtained in 73 and 76% yields, respectively. Compound VI, with mp 105-106°C (from hexane), was obtained in 78 and 76% yields, respectively.

B) A mixture of 0.85 g (2.5 mmole) of Ic in 15 ml of 5% hydrochloric acid was stirred for 6 h and allowed to stand overnight at 20°C. The precipitate was removed by filtration and washed with water and alcohol to give 0.16 g (44%) of 4-benzylaminocoumarin (VII) with mp 243-245°C (from alcohol). Alkalization of the acidic solution gave 0.46 g (55%) of starting Ic.

C) A mixture of 1 mmole of Ic or Im in 5 ml of 5% hydrochloric acid was refluxed for 30 min, after which it was cooled, and the precipitate was removed by filtration and washed with water and alcohol. This procedure gave VII in 82 and 84% yields, respectively.

D) A mixture of 1 mmole of Ig or Ir in 5 ml of 5% hydrochloric acid was refluxed for 5 h, after which it was cooled, and the precipitate was removed by filtration, washed with water, and dissolved in 5% alkali solution. The solution was filtered and acidified. This procedure gave dicoumarol V in 41 and 75% yields, respectively.

Action of Hydrochloric Acid on 4-Piperidinocoumarin (VI). A suspension of 0.32 g (1 mmole) of VI in 5 ml of 5% hydrochloric acid was refluxed for 30 min, after which it was

TABLE 1. 3-Aminomethyl-4-aminocoumarins (Ia-t)

Compound	mp,* °C	R_f	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
Ia	137—139	0,10	69,4	7,0	10,8	$C_{15}H_{18}N_2O_2$	69,7	7,0	10,8	40
Ib	92—93	0,29	71,9	8,1	9,3	$C_{18}H_{24}N_2O_2$	71,9	8,4	9,3	64
Ic	123—125	0,22	75,7	6,6	8,6	$C_{21}H_{22}N_2O_2$	75,4	6,6	8,4	60
Id	138—140	0,49	75,0	6,3	8,7	$C_{20}H_{20}N_2O_2$	75,0	6,3	8,7	68
Ie	73—74	0,47	70,3	7,5	10,4	$C_{16}H_{20}N_2O_2$	70,6	7,4	10,3	81
If	102—103	0,45	71,8	8,1	9,5	$C_{18}H_{24}N_2O_2$	71,9	8,4	9,3	90
Ig	109—111	0,10	72,3	7,4	9,5	$C_{18}H_{22}N_2O_2$	72,4	7,4	9,4	88
Ih	159—160	0,47	73,1	7,7	9,1	$C_{19}H_{24}N_2O_2$	73,0	7,7	9,0	95
Ij	183—185	0,37	68,8	7,0	8,8	$C_{18}H_{22}N_2O_3$	68,8	7,1	8,9	95
Ij	141—143	0,10	69,7	7,6	12,7	$C_{19}H_{25}N_3O_2$	69,7	7,7	12,8	94
Ik	152—153	0,33	70,3	7,4	10,4	$C_{16}H_{20}N_2O_2$	70,6	7,4	10,3	55
Il	113—114	0,40	72,3	8,3	9,0	$C_{19}H_{26}N_2O_2$	72,6	8,3	8,9	70
Im	151—152	0,39	75,8	7,0	8,1	$C_{22}H_{24}N_2O_2$	75,8	6,9	8,0	67
In	169—171	0,70	75,6	6,6	8,5	$C_{21}H_{22}N_2O_2$	75,4	6,6	8,4	72
Io	121—122	0,66	71,2	8,0	9,8	$C_{17}H_{22}N_2O_2$	71,3	7,7	9,8	90
Ip	86—88	0,71	72,9	8,3	8,9	$C_{19}H_{26}N_2O_2$	72,6	8,3	8,9	95
Iq	Oil	0,31	73,3	7,7	8,9	$C_{19}H_{24}N_2O_2$	73,1	7,7	9,0	77
Ir	119—120	0,74	73,6	8,0	8,8	$C_{20}H_{26}N_2O_2$	73,6	8,0	8,6	97
Is	115—116	0,57	69,6	7,5	8,5	$C_{19}H_{24}N_2O_3$	69,5	7,4	8,5	90
It	151—152	0,31	70,5	8,0	12,4	$C_{20}H_{27}N_3O_2$	70,4	8,0	12,3	91

*The compounds were recrystallized: Ia,c,d,k,m,n from 70% ethanol, Ib,f,j,l,o,p,s from hexane, Ie,g from petroleum ether, and Ih,i,r,t from benzene—hexane.

worked up as in the preceding experiment to give 0.15 g (94%) of II with mp 201-203°C (dec.).

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