General Method for the Preparation of the XVII-XIX (Table 1). A solution of 0.01 mole of bromine in 3 ml of carbon tetrachloride was added gradually at 20° to a solution of 0.01 mole of benzofuran in 7 ml of carbon tetrachloride, after which the mixture was stirred for 2 h. The solvent was then removed by vacuum distillation, and the residue was recrystallized.

General Method for the Preparation of VIII, X, XI, XIII, XX, and XXI (Table 2). A solution of 0.03 mole of nitric acid (sp. gr. 1.35) in 15 ml of acetic acid was added dropwise with stirring at 15° to a suspension of 0.01 mole of benzofuran in 65 ml of glacial acetic acid, after which the mixture was allowed to stand at this temperature for 1 h. It was then poured into water, and the resulting precipitate was separated and chromatographed on a column filled with silica gel (elution with chloroform). The eluate was evaporated, and the residue was recrystallized.

General Method for the Preparation of IX and XII (Table 2). A 6.5-ml sample of nitric acid (sp. gr. 1.42) was added to a solution of 5 mmole of the benzofuran in 34 ml of chloroform, after which the mixture was shaken at room temperature for 5 min and poured into 50 ml of water. The chloroform layer was separated, washed with water, and chromatographed on a column filled with silica gel (elution of the reaction product with chloroform). The eluate was evaporated, and the residue was recrystallized.

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3,4-DIAMINOCOUMARINS*

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A number of 3,4-diaminocoumarins was obtained by hydrogenation of 3-nitro-4-aminocoumarins. It was established that these compounds exist in the coumarin form, and monoacetylation of the 3-NH_2 group does not shift the tautomeric equilibrium.

Substances having various kinds of biological activity are found among 3- and 4-aminocoumarin derivatives [2-4]. The tautomerism and stereochemistry of these compounds have also been studied [5-7]. However, 3,4-diaminocoumarins, from which one might expect the manifestation of properties of both 3- and 4-aminocoumarins, as well as a novel combination of these properties, have not yet been investigated in this respect.

We have synthesized a number of 3,4-diaminocoumarins (Ia-j) by hydrogenation of the corresponding 3-nitro-aminocoumarin (IIa-j), the synthesis of which we previously described in [7], over $Pd/BaSO_4$.

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*See [1] for a previous communication.

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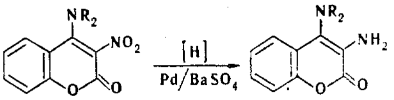

II a-j I a-j

I, II, a $NR_2=NH_2$, b $NR_2=CH_3NH$, c $NR_2=C_4H_9NH$, d $NR_2=C_6H_5CH_2NH$, e $NR_2=C_6H_5NH$,
f $NR_2=N(C_2H_5)_2$, g NR_2=piperidino, h NR_2= pyrrolidino, i NR_2=morpholino,
j NR_2=N-methylpiperazino

Most of the 3,4-diaminocoumarins obtained in this research melt over rather wide temperature ranges prior to recrystallization, although they are individual compounds according to thin-layer chromatography (TLC) and IR spectroscopy. In the case of Ic and Ii, we were able, by recrystallization from suitable solvents, to isolate samples with different melting points but with the same elementary composition, identical R_f values in the case of chromatography in a thin layer of Al_2O_3, and, respectively, identical UV and IR spectra (Table 2). The low-melting samples are converted to the higher-melting forms when they are heated above their melting points. Thus diaminocoumarins I have a tendency to form crystalline modifications.

The 3,4-diaminocoumarins obtained in this study are relatively weak bases: they give monohydrochlorides involving the 3-amino group (the amino group in the 4 position has amide character, as in β-aminovinyl ketones), which are relatively easily hydrolyzed by water to bases similar to 3-aminocoumarin (III) [8].

On brief treatment with acetic anhydride at 20°C Ia-c form 3-N-monoacetyl derivatives (IV-c). Under similar conditions aminocoumarins If, g remained virtually unchanged (according to TLC data only traces of the monoacetyl derivatives are formed), but they are converted to 3-N,N-diacetyl derivatives V and VI when they are refluxed in acetic anhydride.

TABLE 1. IR and UV Spectral Data for 3,4-Diaminocoumarins (Ia-j)

Compound	IR spectra,[a] cm^{-1}				UV spectra	
	ν_{NH}	$\nu_{C=O}$	$\nu_{C=C}$	δ_{NH}	λ_{max}, nm	lg ε
Ia	3380, 3350 3280, 3230	1650	1620	1600[b]	227—229[b] 252 333—338	4,18 4,13 4,25
Ib	3450, 3400[b] 3380	1685	1625	1590[b]	236—242[b] 248—252 330—340	4,06 4,03 4,14
Ic	3455(3455)[c] 3400[b](3400)[b,c] 3365(3365)[c]	1685 (1710)[c]	1625 (1630)[c]	1595[b]	242[b] 250 339—343	4,15 4,11 4,12
Id	3455(3450)[c] 3400[b](3400)[b,c] 3360(3365)[c]	1690 (1710)[c]	1630 (1630)[c]	1600[b]	252—254 340—342	4,09 4,09
Ie	3510, 3440 3410	1708	1635	1590—1605 (doublet)	240—242 266—268 342—346	3,85 3,94 3,86
If	3495 3385	1700	1618	1595[d]	250 265[b] 329—331	3,91 3,88 4,18
Ig	3510(3505)[c] 3400(3395)[c]	1700 (1720)[c]	1620 (1623)[c]	1600[d]	258—264 328—336	3,97 4,08
Ih	3495 3395	1700	1620	1600[d]		
Ii	3500(3510)[c] 3395(3400)[c]	1705 (1722)[c]	1620 (1625)[c]	1595[d]		
Ij	3510 3400	1705	1623	1590[d]	250—256 324—330	3,94 4,16

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[a] The IR spectra were obtained under the following conditions: from a mineral oil suspension of Ia, from 0.01 M solutions of Ib-g in $CHCl_3$ at a layer thickness of 1 mm, and from 0.1 M solutions of Ih-j in $CHCl_3$ at a layer thickness of 0.16 mm.

[b] Inflection.

[c] These are the IR spectra of 0.01 M solutions of the compounds in CCl_4 at a layer thickness of 1 cm (for ν_{NH}) and 1 mm (for $\nu_{C=O}$).

[d] Weak.

TABLE 2. 3,4-Diaminocoumarins (Ia-j)

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
Ia·HCl	285—290[a]	$C_9H_8N_2O_2 \cdot HCl$	50,6	4,3	13,1	50,8	4,2	13,1	100
Ib	113,5—114,5[b]	$C_{10}H_{10}N_2O_2$	63,0	5,3	14,8	63,2	5,3	14,7	89
Ic	63,5—64,5[c] and 55—57[d])	$C_{13}H_{16}N_2O_2$	67,2	6,9	12,2	67,2	6,9	12,0	87
Id	93—94[c]	$C_{16}H_{14}N_2O_2$	72,0	5,3	10,5	72,2	5,3	10,5	73
Ie	199—203[e]	$C_{15}H_{12}N_2O_2$	71,7	4,9	11,1	71,4	4,9	11,1	92
Ie·HCl	223—231[a]	$C_{15}H_{12}N_2O_2 \cdot HCl$	62,3	4,4	9,7	62,4	4,4	9,7	98
If·HCl	162—164[a]	$C_{13}H_{16}N_2O_2 \cdot HCl$	58,0	6,3	10,4	58,1	6,4	10,4	91
Ih	119—120[f]	$C_{13}H_{14}N_2O_2$	67,9	6,1	12,4	67,8	6,1	12,2	81
Ii	148—149[g] (and 155[c,h])	$C_{13}H_{14}N_2O_3$	63,5	5,8	11,4	63,5	5,7	11,4	65
Ij	141—142	$C_{14}H_{17}N_3O_2$	64,9	6,8	16.3	64,8	6,6	16,2	65

[a] This compound melts with decomposition in sealed capillaries. Ia·HCl. Found: Cl 16.8%. Calculated: Cl 16.7%. Ie·HCl. Found: Cl 12.1%. Calculated: Cl 12.3%. If·HCl. Found: Cl 13.1%. Calculated: Cl 13.2%.

[b] From benzene.

[c] From benzene–hexane.

[d] From petroleum ether (bp 40-70°).

[e] With decomposition (from alcohol).

[f] From 50% methanol.

[g] From 70% alcohol.

[h] Shrinks at 146°.

TABLE 3. Acetyl Derivatives of 3,4-Diaminocoumarins (IVa-c, V and VI)

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IV a	264—265,5[a]	$C_{11}H_{10}N_2O_3$	60,7	4,6	13,1	60,6	4,6	12,8	73
IV b	214—215[b]	$C_{12}H_{12}N_2O_3$	62,0	5,2	12,0	62,1	5,2	12,1	94
IV c	186—187[c]	$C_{15}H_{18}N_2O_3$	66,0	6,6	10,2	65,7	6,6	10,2	92
V	130—131[c]	$C_{17}H_{20}N_2O_4$	64,7	6,5	8,9	64,5	6,4	8,9	74
VI	137,5—138,5[c]	$C_{18}H_{20}N_2O_4$	65,9	6,1	8,6	65,9	6,1	8,6	81

[a] From methanol.

[b] From water.

[c] From alcohol.

The spectral data provide evidence that Ia-e, for which several tautomeric forms are possible, exist in the coumarin form under the investigated conditions. Thus the PMR spectrum of Id in dimethyl sulfoxide (DMSO) contains a doublet of protons of the $-CH_2-N$ group at 4.6 ppm (J = 7 Hz, spin–spin coupling with the proton of the NH group), and the proton of the NH group resonates at 6.1 ppm (triplet, J = 7 Hz). The presence of spin–spin coupling of the vicinal protons of the $-CH_2-NH$ group was confirmed by double-resonance spectroscopy and deuteration with CD_3OD. The protons of the 3-NH_2 group give a narrow singlet at 4.5 ppm, and this constitutes evidence for rather rapid exchange of these two magnetically equivalent protons.

It is known [9] that the NH_2 and C=O groups in 3-amino-2-pyrones form an intramolecular hydrogen bond (IHB); this shows up in the lowering (by ~50 cm^{-1}) of the frequency of the stretching vibrations of the carbonyl group as compared with $\nu_{C=O}$ for unsubstituted 2-pyrone. According to our data, there is a smaller but, nevertheless, appreciable lowering of $\nu_{C=O}$ (1710 and 1720 cm^{-1}) as compared with coumarin (1740 cm^{-1} in $CHCl_3$ and 1750 cm^{-1} in CCl_4) or 3-piperidinocoumarin (1730 and 1740 cm^{-1}) [10] in the IR spectra of $CHCl_3$ and CCl_4 solutions of III.

A lowering of the frequency of the carbonyl group to 50 cm^{-1} for substances with a 4-sec-amino group and to 40 cm^{-1} for substances with a 4-tert-amino group as compared with unsubstituted coumarins is also observed in the IR spectra of diaminocoumarins I (Table 1). However, this shift of the carbonyl band to the longwave region in the case of I may be due not only to the possible formation of an IHB between the carbonyl group and the amino group in the 3 position but also to conjugation of the carbonyl group with the 4-amino group, inasmuch as a lowering of the $\nu_{C=O}$ band (1680-1700 cm^{-1} in $CHCl_3$ and 1720-1730 cm^{-1} in CCl_4) is also observed in the previously studied [6] 4-aminocoumarins. In the case of I it is therefore difficult to form a judgment regarding the presence of an IHB between the C = O and $3-NH_2$ groups only from the frequency of the carbonyl group. In this case the greater lowering of the $\nu_{C=O}$ band in the case of Ib-d than in the case of If-j can be explained by more efficient conjugation (because of lower steric hindrance) between the secondary amino group in the 4 position and the carbonyl group.

The stretching vibrations of the $3-NH_2$ groups in the IR spectra of If-j show up in the form of narrow bands at 3385-3400 (ν_s) and 3495-3510 cm^{-1} (ν_{as}). The IR spectrum of model compound III in $CHCl_3$ solution contains absorption bands of an NH_2 group at 3400 (ν_s) and 3500 cm^{-1} (ν_{as}). This indicates either that there is no IHB in aminocoumarins If-j or that it is extremely weak.

Two relatively intense bands at 3360-3380 and 3455-3465 cm^{-1}, which are related to the amino group in the 3 position, are observed in the IR spectra of Ib-e. The low-intensity band at 3400 cm^{-1} should be assigned to the 4-NH group, which has a weak IHB with the $3-NH_2$ group in analogy with 2-aminoacetanilides [11]. The ν_{NH} band is observed at 3470 cm^{-1} in the IR spectrum of the model compound 4-monobutylaminocoumarin [6].

From a comparison of the UV spectra of Ia-e and If-j it is apparent that there is a hypsochromic shift of the longwave absorption maximum in the spectra of compounds with a 4-tert-amino group (Table 1).

The PMR spectrum of IVc in pyridine contains signals of the protons of a $COCH_3$ group (2.3 ppm, singlet) and of a $-CH_2-N$ group (3.7 ppm, quartet, J = 7 Hz; this signal is converted to a triplet on dilution of the solution with CF_3COOH). Two absorption bands of NH groups (3455 and 3400 cm^{-1}) and a very intense unsymmetrical band at 1700 cm^{-1} (amide and pyrone $\nu_{C=O}$) are observed in the IR spectrum of a solution of this compound in chloroform.

The signals of the protons of the two $COCH_3$ groups in V form a narrow singlet at 2.4 ppm (in $CHCl_3$). The IR spectrum of a solution of this compound in $CHCl_3$ does not contain ν_{NH} vibrations; the vibrations of three carbonyl groups appear in the form of an unsymmetrical broad intense band at 1720 cm^{-1}.

EXPERIMENTAL

The UV spectra* of alcohol solutions of the compounds ($2.5 \cdot 10^{-5}$ to $5 \cdot 10^{-5}$ M) were recorded with a Perkin-Elmer 402 spectrophotometer. The IR spectra† were obtained with UR-10 and Perkin-Elmer 457 spectrometers. The PMR spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The purity of the synthesized compounds was monitored by means of TLC on activities IV and V Al_2O_3 with benzene and chloroform as the solvents.

3-Aminocoumarin (III) was obtained by the method in [8] and had mp 133-134° (from aqueous alcohol).

3-Nitro-4-pyrrolidinocoumarin (IIh) and 3-Nitro-4-(N-methylpiperazino)-coumarin (IIj). These compounds were synthesized by the method in [7]. Compound IIh, with mp 188-190° (dec., from glacial acetic acid), was obtained in 85% yield. Found: C 60.0; H 4.6; N 10.7%. $C_{13}H_{12}N_2O_4$. Calculated: C 60.0; H 4.6; N 10.8%. Compound IIj, with mp 195-196° (from benzene), was obtained in 80% yield. Found: C 58.1; H 5.2; N 14.4%. $C_{14}H_{15}N_3O_4$. Calculated: C 58.1; H 5.2; N 14.5%. The hydrochloride had mp 246.5-247.5°. Found: Cl 10.9%. $C_{14}H_{15}N_3O_4 \cdot HCl$. Calculated: Cl 10.9%.

3,4-Diaminocoumarins (Ia-j, Table 2). A suspension of 0.01 mole of nitroaminocoumarin (II) in 100 ml of methanol was hydrogenated over 0.3-0.6 g of 10% $Pd/BaSO_4$ until 3 mole-eq of hydrogen had been absorbed, after which the catalyst was removed by filtration (in the case of Ia and Ie another 100 ml of methanol was added prior to this step in order to dissolve the precipitate) and washed with methanol. The filtrate was vacuum evaporated, and the residue was worked up in various ways. In the case of Ia, b, e, the residue was washed successively with 5% alkali solution, water, and a small amount of cold methanol or ether. In the preparation of Ic, f-i, the residue was dissolved in benzene, the solution was filtered, the filtrate was washed successively with 5% alkali solution and water, and the solvent was evaporated. The residue was then washed with hexane. In the isolation of Id, the residue was treated with a small amount of benzene, the insoluble Ia was removed by filtration, and the filtrate was then worked up as described above. In the case of Ij, the residue was dissolved in chloroform, and the solution was washed successively

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†The IR spectra were studied jointly with V. S. Troitskaya.

with 5% alkali solution and water and extracted with 5% HCl solution. The extract was then washed with benzene and neutralized with sodium bicarbonate solution, and the resulting precipitate was removed by filtration and washed with water. Oily If was dissolved in absolute ether, and the solution was treated with a saturated ether solution of hydrogen chloride to give the hydrochloride of If. The hydrochlorides of Ia and Ie were obtained by treatment of the bases in a solution of absolute dioxane with a saturated ether solution of hydrogen chloride. The results of analysis of bases Ia and Ig are presented in [1]. The yield of Ig was 86%.

3-Acetamido-4-aminocoumarins (IVa-c, Table 3). A suspension of 3 mmole of diamines Ia-c in 5 ml of acetic anhydride was stirred at 20° for 30 min, after which it was diluted with water, and the aqueous mixture was cooled for 30 min. The resulting precipitate was removed by filtration and washed with water.

3-Diacetamido-4-aminocoumarins (V and VI, Table 3). A solution of 3 mmole of If, g in 5 ml of acetic anhydride was refluxed for 1 h, after which it was cooled and worked up as described above.

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