NITROGEN-CONTAINING DERIVATIVES OF PYRONE-4-CARBOXYLIC ACID

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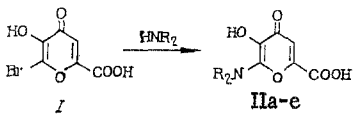
In a search for pharmacologically active pyrone-4-carboxylic acids, we have synthesized derivatives with nitrogen-containing functional groups: 6-dialkylaminocomenic acids and monoethyl esters of pyronedicarboxylic amides.

When 6-bromocomenic acid (I) [1] is heated in an organic solvent with an excess of a secondary amine, the bromine is replaced by an amino group, and the 6-**dialkylcomenic** acids (IIa-d) are formed in 20-50% yield.



I IIa-e

IIa: $R_2 = (CH_2)_5$; IIb: $R_2 = CH_2CH_2OCH_2CH_2$; IIc: $R = C_3H_7$;
IId: $R = C_4H_9$; IIe $R_2 = (CH_2)_2N(CH_3)(CH_2)_2 \cdot HCl$.

Compounds IIa-e give a blue color with iron chloride, in contrast to the acid I which gives a red color, and this enables the course of the reaction to be followed. Compounds IIa-e are amino acids and form salts with alkalis; the hydrochlorides are easily decomposed because the amino group is **weakly basic**: From dilute acid solutions of salts only the free bases can be obtained. An exception is the diaminocarboxylic acid betaine IIe which has a protonated nitrogen atom. In compounds IIa-e, the amino group is weakly basic because of conjugation between the amino group at C(6) and the carbonyl group of the pyrone ring.

The structures of the compounds were confirmed from UV, IR, and NMR spectra, and by mass spectrometry. The spectra of the amino acids IIa-c show a bathochromic shift of the absorption maxima (9-12 and 52-66 nm, respectively) compared with the starting acid I (λ_{max} 230 and 300 nm), and there is a new band at 278-284 nm. The COOH group in compounds IIa-d gives rise to bands at 1700-1725 cm^{-1}, confirming that the carboxyl group is not ionized, and therefore the compounds are not betaines. The structures of compounds IIa-e are consistent with their NMR spectra. The spectrum of IIa contain signals from the proton at C(3) (6.8 ppm), a broad singlet from the four aliphatic piperidine ring protons adjacent to the nitrogen atom (3.53 ppm), and a singlet due to the remaining 6 protons on the piperidine ring (1.6 ppm); the spectrum of IIb contains a singlet due to the proton at C(3) (7.0 ppm) and a broad signal from the 8 aliphatic protons of the morpholine group (4.0-3.43 ppm). In the mass spectra of compounds IIc and d there are peaks from the molecular ion M^+, corresponding to the calculated molecular weight. The spectra of compounds IIc and d contain peaks from ion fragments arising from the repeated splitting off of alkyl groups C_nH_{2n+1} (or C_nH_{2n}) from both the M^+ ion and from the resulting ion fragments: for IIc m/e is 240, 227, 226, 213, 212, 198, 197, 185, 184, 172, 171 (ion A); for IId, m/e is 268, 254, 241, 240, 227, 226, 211, 210, 198, 184, 183, 172, 171 (ion A). The length of the chain R is shown by the presence of ions with m/e 43 (IIc) and 57 (IId). The empirical formula of the ion A was confirmed by high-resolution mass spectroscopy: found, 171.0136; calculated for $C_6H_5NO_5$, 171.0168. The presence and location of the OH group in compounds IIa and b were confirmed by the specific elimination of this group from M^+ ions with m/e 238 and 266 (the ortho effect [2, 3]). The presence of the ion with m/e 116 is explained by the quinoid structure of the molecule resulting from the migration of the free hydrogen atoms when the ion-fragment A is destroyed. Similarly, ion A (by a type of "retrodiene" decay) gives rise to ions with m/e 70 and 69, confirming the presence of the carboxyl group in IIc and d.

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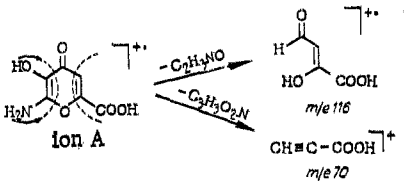


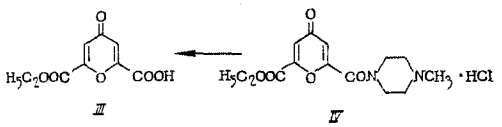
The formation of ion fragments in IIa is essentially the same. The cleavage of alkyl substituents during the first stage of the decomposition of M^+ occurs during the rearrangement of the piperidine ring [4, 5]. Compound IIa is characterized by the presence of peaks with m/e 238, 196, 183, and 171 (ion A). As in the preceding cases, ions with m/e 116, 70, and 69 are also recorded. The piperdine ring is identified from ion peaks with m/e 84, 68, 56, 55, and 41 [4, 5]. No cleavage of an OH group is observed for compound IIa. However, the presence of an ion with m/e 125 ($CH_2CH_2CH_2CH_2CH_2N$—C≡C—OH) confirms the relative positions of the hydroxy group and the nitrogen atom in IIa. The compsition of the ion with m/e 125 is determined by its mass (found 125.0814; calculated for $C_7H_{11}NO$, 125.0841).

The presence of the morpholine group in IIb is confirmed by the cleavage of the M^+ ion: CH_2O (for ion with m/e 211), CH_2CO (m/e 199), CH_2CH_2O (m/e 197), C_4H_6O (ion A), and by the presence of ion peaks from the morpholine group with m/e 86, 59, 58, and 56. The formation of A gives secondary peaks with m/e 116, 70, and 69. The ion with m/e 127 ($CH_2CH_2OCH_2CH_2N$—C≡C—OH) arises from cleavage of the pyrone ring [6].

The structures of compounds IIa-d are thus confirmed from their mass spectra. The course of the decomposition is seen from the spectra of the metastable ions.

Only one N-substituted amide of pyrone-4-caboxylic acid (6-phenylcomenic acid [7]) has previously been reported, and its biological activity was not examined.

Using the mixed-anhydride method, the monoethyl ester (III) [8] was converted to N-methylpiperazinamide monoethyl pyronedicarboxylate (IV), isolated as the hydrochloride salt.



III IV

EXPERIMENTAL CHEMISTRY

Infrared spectra were taken as follows: compounds IIa-e in mineral oil, and IV in a KBr pellet on a Perkin-Elmer spectrophotometer model 457 (Sweden). NMR spectra were obtained on a Varian T-60 (USA) instrument at 60 MHz, δ scale, internal standard tetramethylsilane. UV spectra were taken on a 402 Perkin-Elmer spectrophotometer (Sweden) using alcohol as solvent. Mass spectra were obtained on a Varian MAT-112 instrument at 70 eV and with a 200°C temperature source; the sample was introduced to the ion source directly. High-resolution spectra were recorded on a Varian MAT-311a. Chromatography of 2-dialkylaminocomenic acids was carried out on Leningrad 1B paper in butanol—water—acetic acid (2:2:1 for compounds IIa and b, and 5:1:1 for compounds IIc, d, and e). Spots were visualized in UV light. TLC of the amide IV was carried out on prepared Silufol UV-254 (USSR) plates in chloroform—methanol—triethylamine (10:2:0.05).

6-(N-Piperidyl)-comenic Acid (IIa). A mixture of 1.64 g of the acid I in 17 ml of dry dioxane and 2.1 ml of piperidine was heated for 30 min at 100°C. When cool, the precipitated material was filtered off and recrystallized. Compound IIb was obtained in the same way. Yields and physical data for these and other compounds prepared are presented in Table 1.

Mass Spectrum m/e IIa: 41 (82.8), 42 (31.9), 43 (9.0), 54 (13.6), 55 (21.6), 56 (14.8), 68 (12.3), 69 (92.9), 70 (15.2), 71 (7.6), 82 (7.6), 84 (27.9), 88 (6.0), 116 (21.5), 124 (20.0), 125 (24.3), 171 (56.0), 183 (15.0), 196 (7.0), 238 (9.7), 239 (100.0), 240 (12.7), W_M = 14.3. Mass spectrum m/e IIb: 41 (48.2), 42 (40.0), 43 (68.2), 56 (10.3), 58 (6.3), 59 (6.8), 69 (37.9), 70 (24.0), 71 (6.0), 85 (5.4), 86 (17.3), 116 (13.2), 127 (17.5), 171 (18.3), 197 (34.5), 199 (15.3), 211 (30.6), 241 (100.0), 242 (12.3), W_M = 12.6.

TABLE 1. Nitrogen-Containing Derivatives of Pyrone-4-carboxylic Acids

Compound	Yield, %*	mp, °C	R_f	Found, %			Empirical formula	Calculated, %			UV spectra λ_{max}, nm (log ε)	IR spectra ν, cm^{-1}				
				C	H	N		C	H	N		Ar—OH	OH в COOH	COOH	C=O ring	C=C
IIa	50	214—4	0,64	55,49	5,50	6,12	$C_{11}H_{13}NO_5$	55,23	5,43	5,85	242 (4,18); 283 (3,85); 362 (3,82)	3210	2300—2700	1700	1639	1606
IIb	43	227—8	0,82	49,80	4,52	5,92	$C_{10}H_{11}NO_6$	49,81	4,56	5,81	239—240 (4,24); 279 (3,78); 352 (3,80)	3170	2350—2700	1705	1625	1603
IIc	25	158—9	0,90	56,53	6,43	5,32	$C_{12}H_{17}NO_5$	56,46	6,71	5,48	242 (4,21); 284 (3,88); 366 (3,81)	3300	2300—2700	1721	1643	1605
IId	20	143—5	0,94	59,08	7,44	4,94	$C_{14}H_{21}NO_5$	59,35	7,47	4,94	—	3300	2300—2700	1720	1643	1603
IIe†	50	240—2	0,58	45,56	5,38	9,39	$C_{11}H_{14}N_2O_5 \cdot HCl$	45,42	5,16	9,63	—	3250	2100—2750	1725	1638	1610
V‡	55	202—3	0,65	50,75	5,79	8,53	$C_{14}H_{18}N_2O_5 \cdot HCl$	50,84	5,78	8,47	—	1730 ($COOC_2H_5$), 1653, 1620 (C=O ring + NH + C=C)				

*Compound IIa was recrystallized from 50% alcohol, IIb from water, IIc from toluene, IId from a petroleum ether-toluene mixture, IIc from alcohol acidified with HCl, and V from methylethylketone.

†Found, %: Cl 12.00 Calculated, %: Cl 12.30.

‡Found, %: Cl 10.44. Calculated, %: Cl 10.72.

6-Dipropylaminocomenic Acid (IIc). A mixture of 1.7 g of the acid I and 2.16 ml of dipropylamine in 10 ml of anhydrous alcohol was refluxed for 30 min, cooled, and acidified with HCl to pH 1.0, the solvent evaporated, 10 ml of water added, and the mixture extracted with dichloroethane. The extract was dried, the solvent evaporated, and the residue recrystallized.

Mass Spectrum, m/e, IIc: 41 (51.5), 42(20.7), 43 (100.0), 54 (6.8), 55 (6.5), 57 (5.0), 68 (11.2), 69 (27.9), 70 (67.4), 71 (6.8), 88 (6.5), 116 (7.8), 171 (18.8), 172 (5.7), 184 (41.6), 185 (6.5), 197 (5.8), 198 (10.0), 212 (97.3), 213 (23.8), 226 (44.8), 227 (5.6), 238 (19.0), 240 (5.0), 255 (52.8), 256 (7.4) W_M = 7.1.

6-Dibutylaminocomenic Acid (IId). A mixture of 0.47 g of the acid I and 4.0 ml of dibutylamine in 5 ml of dry DMFA was heated for 20 min at 100°C, cooled, poured into 50 ml of water, acidified with HCl to pH 1.0, and extracted with dichloroethane, The extract was dried, filtered, evaporated in vacuum, and the residue recrystallized.

Mass Spectrum, m/e, IId: 41 (61.9), 42 (23.3), 43 (9.3), 54 (9.8), 55 (21.5), 56 (8.4), 57 (98.9), 69 (24. 3), 70 (12.8), 71 (5.9), 84 (34.2), 86 (16.0), 116 (8.0), 171 (20.5), 172 (9.2), 182 (13.0), 183 (6.1), 184 (54.0), 185 (9.8), 198 (37.1), 199 (6.0), 210 (6.3), 211 (5.8), 226 (100.0), 227 (25.1), 238 /15.2), 239 (5.3), 240 (56.8), 241 (10.2), 254 (11.5), 266 (49.8), 267 (7.8), 268 (5.0), 283 (60.4), 284 (10.3), W_M = 5.9.

6-(N-Methylpiperazino)-comenic Acid Hydrochloride (IIe). This was obtained by the same method as IIa from 1.88 g of the acid I in 25 ml of dry dioxane and 2.4 ml of N-methylpiperazine. After 12 h at 4°C, ether was added, the precipitated material filtered off, washed with ether, and recrystallized.

Hydrochloride of Ethyl N-methylpiperazine Amide Pyronedicarboxylate (IV). To 2.12 g of the ester III and 1.5 ml of triethylamine in 25 ml of dry dioxane at 10°C was added a cooled (5°C) solution of 1.37 g of isobutyl chlorocarbonate in 3 ml of dioxane. This was mixed for 30 min at 5-8°C, 1.2 ml of M-methylpiperazine added, and mixing continued for 30 min with cooling, followed by 30 min at room temperature. The reaction mixture was poured into 50 ml of water and extracted with chloroform. The extract was dried and evaporated in vacuum. The oily residue was dissolved in toluene and to this was added an excess of alcohol saturated with hydrogen chloride. The precipitated material was filtered off and washed with toluene.

EXPERIMENTAL PHARMACOLOGY

The 6-amino derivatives of the pyronedicarboxylic acids IIa-e and their amides IV have been tested as part of a study of drugs which act on the central nervous system and might be of use in the treatment of alcoholism.

Screening tests were carried out on compounds IIa-e and IV (potentiation of subnarcotic, and prolongation of narcotic effect of thiopental sodium, ethanol, and acetaldehyde); the acute toxicity was also determined. Tests were carried out on male mice. All the compounds, were injected intraperitoneally, with the exception of thiopental sodium which was administered intravenously in subnarcotic and narcotic doses (12 and 30 mg/kg, respectively). Subnarcotic and narcotic doses were 3.7 and 4.5 g/kg, respectively, for ethanol, and 320 and 450 mg/kg, respectively, for acetaldehyde. Ethanol was also injected intraperitoneally as a 25% solution.

The compounds showed little activity in these tests. Compounds IIa and b had an overall depressing action (ED_{50} toward the action of thiopental sodium, 75-200 mg/kg), but their activity toward ethanol was weak. Compounds IIc-e and IV in doses of up to 300 mg/kg were weakly active, the LD_{50} was from 500 to 750 mg/kg.

LITERATURE CITED

1. G. A. Garkusha and G. A. Khutornenko, Khim. Geterotsikl. Soedin., No. 3, 341-344 (1966).
2. H. Schwarz, Top. Curr. Chem., 73, 231-235 (1978).
3. H. Borbalk, M. Knollmuller, and C. Weikowitsch, M. Chem., 109, 443-448 (1978).
4. A. M. Duffield, H. Budzikiewicz, D. Willimas, et al., J. Am. Chem. Soc., 87, 810-816 (1965).
5. N. A. Klyuev, R. A. Khmel'nitskii, S. B. Nikitina, et al., Zh. Org. Khim. No. 7, 391-394 (1971).
6. C. Mericier, Bull. Soc. Chim. Fr., 145-147 (1969).
7. F. Eiden, M. Beuttenmuller, and H. Schaumberg, Arch. Pharm. (Weinheim), 308, 489-498 (1975).

8. G. A. Garkusha and G. A. Khutornenko, Inventor's Certificate 170052 (USSR), Biol. Izobret., No. 8 (1965).

COMPLEXES OF COPPER(II) WITH CORDIAMIN

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The determination of microquantities of drugs is an important problem in analytical chemistry today [1, 2]. There is no reliable method of determining small quantities of cordiamin, and we have therefore examined the possibility of determining cordiamin using a method based on the formation of a complex of cordiamin with divalent copper ions and thiocyanate ions. A blue color is obtained when a solution of cordiamin is added to a solution containing copper(II) ions; addition of potassium thiocyanate to this solution gives a bright green precipitate [3]. This reaction is still used for the qualitative detection of the amide group [4]. We have developed a method for the determination of cordiamin based on the formation of complexes of cordiamin with divalent copper, and complexes of cordiamin with divalent copper ions and thiocyanate ions.

EXPERIMENTAL

The following solutions were used: $5.8 \cdot 10^{-3}$ M $Cu(NO_3)_2$ in 1 M HNO_3, obtained by dilution of a stock solution (copper content was determined gravimetrically): 25% solution of cordiamin in ampuls (for injection); 5 M aqueous solution of potassium thiocyanate. Optical densities were measured on an SF-16 spectrophotometer using a 0.5 cm cuvette.

Copper (II)—Cordiamin Complex. The addition of cordiamin to a solution of a copper salt gives a blue color which is stable for several days. Figure 1 shows the spectrum of the complex, which has an absorption maximum at 655 nm. Figure 2 illustrates the dependence of the optical density of a solution of the complex (A) on pH and on the concentration of the cordiamin solution; optimum conditions for the formation of the complex are pH 6.0, and initial concentration of cordiamin and copper 0.3 M and $5.8 \cdot 10^{-3}$ M, respectively.

The data, presented in Fig. 3, treated by the equilibrium shift method, show that the ratio of components in the complex is 1:1. These results agree with data obtained mathematically by the least-squares method on a Nairi computer using APL. The molar coefficient of light absorption is about 100. Beer's law is observed in the concentration range 0.014-0.28 M cordiamin. Table 1 gives the results of the determination of the stability constant for the complex (K_H, data treated statistically).

$$K_H = K^{aV}_{Cu \cdot cordiamin} = \frac{[Cu^{2+}] \cdot [cordiamin]}{[Cu \cdot cordiamin]} = (3.7 \pm 0.25) \cdot 10^{-1}. \quad (1)$$

The equilibrium constant for copper $[Cu^{2+}]$ was determined from the difference $[Cu^{2+}] = [Cu] - [Cu \cdot cordiamin]$, where the magnitude of $[Cu \cdot cordiamin]$ is equal to $A/\varepsilon l$. The concentration of I was determined as the difference $[cordiamin] = [cordiamin]_{init} - [Cu \cdot cordiamin]$.

Copper(II)—Cordiamin—SCN ion. The addition of a solution of potassium thiocyanate to a solution of the copper II—cordiamin complex gives a green precipitate. The latter is readily extracted with organic solvents, for example, chloroform. Moreover, the binary complex is not extracted by organic solvents, indicating that a complex containing all three components is formed.

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