

STRUCTURE OF THE PRODUCTS OF THE CYCLIZATION
IN ACETIC ANHYDRIDE OF β -(2-CARBOXY-5-
CHLOROPHENYLAMINO)PROPIONIC ACID AND ITS
NITRILE

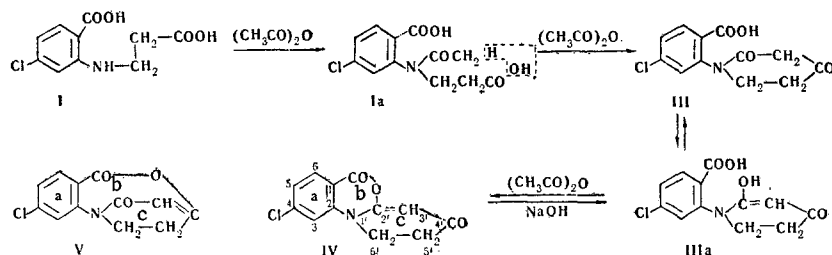
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β -(2-Carboxy-5-chlorophenylamino)propionic acid cyclizes in acetic anhydride to form 4-chloro-2-(2,4-dioxopiperidino)benzoic acid, which subsequently undergoes conversion into its lactone. Under the same conditions, β -[acetyl(2-carboxy-5-chlorophenyl)amino]-propionitrile forms 7-chloro-1- β -cyanoethyl-1,2,3,4-tetrahydroquinoline-2,4-dione. The structures of the compounds obtained were confirmed by their IR, UV, and PMR spectra. An evaluation of the stability of the ketonic and enolic forms of the compounds obtained on the basis of calculations by Hückel's method has been made.

One of us [1] has previously established that when β -(2-carboxy-5-chlorophenylamino)propionic acid (I) is heated with acetic anhydride and potassium acetate, 1-acetyl-7-chloro-1,2,3,4-tetrahydroquinolin-4-one (II) is obtained.

In the present work it has been shown that when I or its N-acetyl derivative (Ia) is heated with acetic anhydride in the absence of potassium acetate no carbon dioxide is evolved and a substance with mp 250-251°C (IV) is formed which, according to its elementary analysis and IR spectrum, is not, as might have been assumed, the internal anhydride of the acid Ia. When IV was heated with acetic anhydride and potassium acetate, it underwent no change, while treatment with aqueous alkali decomposed it with the formation of the acid III, differing from I and Ia. When III was heated with acetic anhydride and potassium acetate, it was converted not into II but into IV; when III was treated with hydrochloric acid, it underwent no hydrolytic or other change, which indicates that the acetyl group had become part of a ring system. These results, and also the absence from the IR spectrum of IV of the ν_{CO} bond at 1820 cm^{-1} characteristic for the CO-O-CO grouping, give grounds for ascribing to it the structure of the lactone IV (or V).*



The IR spectrum of IV in the form of crystals (Table 1) has a strong absorption band at 1765 cm^{-1} , which may be assigned to ν_{CO} of a δ lactone in ring b and a band at 1647 cm^{-1} representing ν_{CO} in ring c,

*The possible structure V appears less likely because of the pronounced steric strain at the fourth carbon atom of ring b.

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TABLE 1. Absorption Frequencies in the IR Spectra (cm^{-1})

Com- pound	Form of sam. *	ν_{OH}	$\nu_{\text{C}\equiv\text{N}}$	$\nu_{\text{C}=\text{O}}$	$\nu_{\text{C}=\text{C}}$
VII	A	2830 m 2630m. 2500m	2270 w	1714 s 1626 v.s	1594 s 1571m 1492
	B	2480 w 1900 m v. b. ‡	2255 w	1712s 1676 s	1590w.b 1495 w
	C	2475 1910 m. v.b.	2250 w	1704 1666s	1591 m 1565 w 1485 w
Ia	A	3100 m 2675 m 2600 m		1725 s 1710s	1624 m 1589v.s. 1566 w
IV	A			1765s 1647 m	1604 s 1584 v.s 1500 v.w
III	A	2620—2500 m		1725s 1633 v.s	1590 m 1569 m 1493 w
	B	2490 m b. 1940 w b.		1730s 1680s 1655 m	1590s 1480 w
	C	2600m 2500 m 1960 w b.		1710s 1672s 1647 s	1595m 1567w 1485 m
VIII	A	2580m 1900 w.b.	2265 m	1646 s† 1632s†	1595 s 1567 s 1537s
IX	A	3100m 2540 m 2350 m 1860 w.b.		1730 † 1700 s† 1645 † 1627†	1595 s 1567 s 1535s
	B	2545 v.b. 1900 w b.		1715m 1645s	1568w 1515 v.s

*A) Mull in paraffin oil; B) solution in pyridine; C) solution in DMSO.

† Band split into two.

‡ v.b.) Very broad.

TABLE 2. Chemical Shifts of the Protons of Compounds III, IV, and IX

Com- pound	Solvent	δ , ppm						
III	TFA	CH(3)* 7,54	CH(5) 7,66	CH(6) 8,33	CH ₂ (5 ¹) 3,20	CH ₂ (6 ¹) 4,23	CH ₂ (3 ¹) 3,94	=CH(3 ¹) 5,58
	1 N NaOD	7,29	7,33	7,45	2,87 2,41	4,00 3,67	3,80	Deuterium exchange
IV	TFA	CH(3) 7,76	CH(5) 7,72	CH(6) 8,30	CH ₂ (5 ¹) 3,29	CH ₂ (6 ¹) 4,68		=CH(3 ¹) 5,93
IX	TFA	CH(8) 7,59	CH(6) 7,25	CH(5) 7,97	CH ₂ (2 ¹) 2,71	CH ₂ (1 ¹) 4,54		=CH(3) 6,48
	C ₅ H ₅ N				2,97	4,82		6,21

*The positions of the carbon atoms are shown in parentheses.

and also two very strong bands due to the stretching vibrations of C=C bonds. Similar bands are observed in the spectra of β -ketones with the —N—C=C—C=O grouping [2, 3].

The PMR spectrum of IV in trifluoroacetic acid (TFA) has a signal at 5.93 ppm with an intensity of one proton unit (p.u.) corresponding to the proton of the =CH group in ring c, and also two triplets corresponding to the protons of methylene groups (Table 2). Thus, the characteristics of the PMR also confirm the lactone structure IV.

In aqueous alkali, the ring of lactone IV opens with the formation of 4-chloro-2-(2',4'-dioxopiperidino)benzoic acid (III). The latter titrates with alkali as dibasic (carboxyl and hydroxy groups); with 2,4-dinitrophenylhydrazine it forms the corresponding hydrazone; and with FeCl₃ it gives a coloration. When III is heated with acetic anhydride with or without potassium acetate, it forms the lactone IV. The closure of the ring in IV is clearly shown by its UV spectra. In dioxane, the spectra of IV and III differ but in 0.1 N alkali they are identical (Fig. 1).

In the IR spectrum of III in the form of crystals there is a band at 1725 cm^{-1} (ν_{CO} of a carboxy group) and a very strong band at 1633 cm^{-1} (ν_{CO} of ring b), and also ν_{OH} absorption in the 2620–2500 cm^{-1} region. In the spectra of crystals of III the bands of the carbonyl of the amide group and $\nu_{\text{C}=\text{C}}$ of ring b of the enolic form are apparently superimposed to form a single strong band at 1633 cm^{-1} . In solution in dimethyl sulfoxide (DMSO) in addition to the ν_{CO} of the carboxyl and ν_{OH} bands at 1710 and 2600–2500 cm^{-1} , respectively, there are also absorption bands at 1672 and 1647 cm^{-1} (1680 and 1655 cm^{-1} in pyridine). The

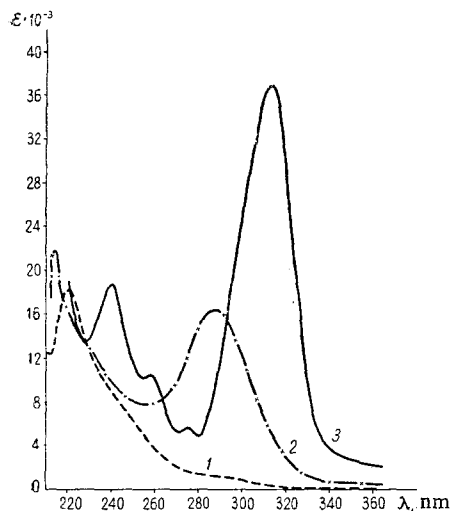
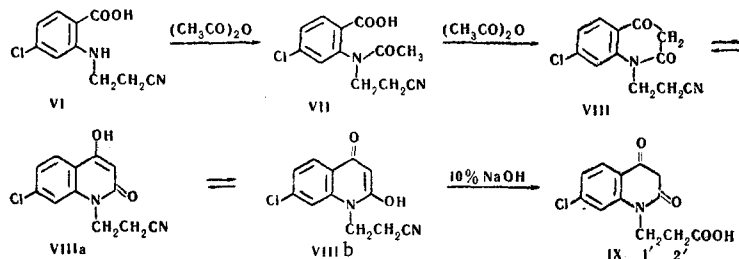


Fig. 1. UV spectra: 1) 4-chloro-2-(2',4'-dioxopiperidino)benzoic acid (III) in dioxane; 2) III in 0.1 N NaOH; 3) lactone of the acid III (IV) in dioxane.

high-frequency band at 1672 cm^{-1} must be ascribed to ν_{CO} of the amide grouping of ring b; there is an analogous band at 1666 cm^{-1} (1672 cm^{-1} in pyridine, 1626 cm^{-1} in the crystals) in the spectra of the N-acetyl derivative of VI (VII). The band at 1647 cm^{-1} may be connected with ν_{CO} of the carbonyl group in position 4 or with $\nu_{\text{C}=\text{C}}$ of the enolic form IIIa; it is difficult to make an unambiguous assignment of this band because of the absence of suitable model compounds.

The PMR spectra in pyridine show the presence of two tautomeric forms of the acid, III and IIIa, with a considerable predominance of the diketo form III. At room temperature signals of CH_2 groups (3') at 3.80 ppm with an intensity of 1.6 p.u. and of $=\text{CH}$ (3') at 5.58 ppm with an intensity of 0.2 p.u. can be seen; the peaks of all the protons are appreciably broadened. With a rise in the temperature to 70°C , there is a further broadening of these signals, which shows an exchange of protons between these groups because of the equilibrium $\text{III} \rightleftharpoons \text{IIIa}$. The mean life (τ) of the tautomeric forms existing in the equilibrium is approximately $1/800$ sec at 60°C . * The PMR spectrum of III in TFA shows the presence of only the diketonic form - δCH_2 (3') 3.94 ppm (Table 2).

The lactone IV and the acid III can be formed only as a result of the splitting out of water in Ia during the interaction of the N-acetyl group with the aliphatic carboxyl, which has a lower acidity than the aromatic carboxy group. When it is treated with acetic anhydride in the absence of potassium acetate, β -(2-carboxy-5-chlorophenylamino)propionitrile (VI), which has no aliphatic carboxy group, forms 7-chloro-1- β -cyanoethyl-1,2,3,4-tetrahydroquinoline-2,4-dione (VIII).



Compound IX, in analogy with VIII, may have structure IXa or IXb. Both VIII and IX give a coloration with FeCl_3 , which is in harmony with their existence in the hydroxy form. Similar cyclization, leading to

TABLE 3. Energies of the π Electrons (E_π) and De-localization Energies (E_{deloc}) of the Tautomeric Forms of III and IX (in β units)

Structure	E_π	E_{deloc}	$\Delta E_{\text{deloc e-k}}$
IIIa	37,758	4,065	0,670
IIIb	37,655	4,012	0,617
III (without E_π C=O)	30,828	3,395	
IXa	27,946	3,903	0,790
IXb	27,928	3,845	0,732
IX	26,396	3,113	

*The calculation was carried out by means of the formula [4]: $\tau = \frac{\sqrt{2}}{2\pi\nu_0\delta_A - \delta_B}$, where ν_0 is the working frequency of the spectrometer, and δ_A and δ_B are the chemical shifts of the protons at C_3 in the ketonic and enolic forms, respectively.

the formation of the corresponding N-substituted 4-hydroxycarbostryls, is known for N-alkyl- and N-arylanthranilic acids [5, 6]. The nonidentity of the acids III and IX is a proof of the interaction of the acetyl group in I with the aliphatic, and not the aromatic, carboxyl, since otherwise the opening of the lactone IV would lead to IX.

The IR spectra of VIII and IX in the form of crystals show split ν_{CO} bands at 1646-1627 cm^{-1} * and two broad absorption bands of ν_{OH} (1900 and 2580 cm^{-1} and 1860 and 2540 cm^{-1} , respectively). The spectrum of III also has a sharp ν_{CN} band at 2265 cm^{-1} and that of IX a strong ν_{CO} band of a carboxyl at 1700 cm^{-1} (with a shoulder at 1730 cm^{-1}). The presence in the spectrum of VIII of the bands of ν_{OH} stretching vibrations and the absence of ν_{CO} absorption in the 1680-1700 cm^{-1} region [7] does not agree with the diketo structures VIII and IX. The existence of mixtures of the two oxo-hydroxy tautomeric forms has been postulated for analogous systems (2,4-dihydropyridine and 2,4-dihydroxyquinoline) in the crystalline state; in aqueous solutions, 2,4-dihydropyridine is ascribed the structure of 4-hydropyridin-2-one [7,8]. From a comparison of our results and literature data it may be concluded that the compounds studied have a similar oxo-hydroxy structure in the crystalline state (VIIIa-VIIIb, IXa-IXb) and in solutions (VIIIa, IXa). In the PMR spectra of IX in TFA and pyridine, the signal of a =CH proton is observed (Table 2) and peaks which could be ascribed to the protons of the CH_2 group in position 3 are absent. This result is in harmony with the hydroxy-oxo forms of the compounds - IXa and IXb (VIIIa and VIIIb).

It is interesting to compare the results obtained on the keto-enol tautomerism of III and IX with the energetic advantage of the tautomeric forms evaluated by semiempirical calculations (Table 3). It is obvious that the amount of the enolic form present in the equilibrium with the keto form is determined by the magnitude

$$\Delta E_{e-k} = \Delta E_{\text{loc } e-k} + \Delta E_{\text{deloc } e-k}, \quad (1)$$

where $\Delta E_{\text{loc } e-k}$ is the difference between the energies of the enolic and ketonic forms on the assumption that all the bonds are localized [9] and $\Delta E_{\text{deloc } e-k}$ is the difference in the delocalization energies of the electrons in each of the forms [10, 11]:

$$\Delta E_{\text{loc } e-k} = E_{\text{loc enol}} - E_{\text{loc ketone}} \quad (2)$$

$$\Delta E_{\text{deloc } e-k} = E_{\text{deloc enol}} - E_{\text{deloc ketone}} \quad (3)$$

The values of $\Delta E_{\text{deloc } e-k}$ will be approximately the same for III and IX, since they are determined only by the localized bonds:

$$\Delta E_{\text{loc IIIa(b)}} - \Delta E_{\text{loc IXa(b)}} - \text{IX} \quad (4)$$

Since the keto form is characterized by a high internal stability [12], $\Delta E_{\text{loc } e-k} < 0$ (in the symbols that we have adopted). Conversely, the values of $\Delta E_{\text{deloc } e-k}$ are positive (Table 3), and

$$\Delta E_{\text{deloc IXa(b)}} - \text{IX} > \Delta E_{\text{deloc IIIa(b)}} - \text{III} \quad (5)$$

On the basis of (1), (4), and (5) we obtain $\Delta E_{\text{IXa(b)}} - \text{IX} > \Delta E_{\text{IIIa(b)}} - \text{III}$, i.e., the enolic forms of IX are more favorable than the enolic forms of III:

$$\left(\frac{c_e}{c_k} \right)_{\text{IX}} > \left(\frac{c_e}{c_k} \right)_{\text{III}},$$

where c_e and c_k are the concentrations of enolic and ketonic forms. This result is in harmony with the facts obtained from a study of the spectra.

A similar consideration of the question of the greater stability of one of the two tautomeric enolic forms IIIa-IIIb and IXa-IXb has shown that the delocalization energies of structures IIIa and IXa are somewhat greater than those of IIIb and IXb. Thus, according to the calculation, the forms IIIa and IXa are more stable than IIIb and IXb ($\Delta E_{\text{loc}} = 0$). However, the differences in the delocalization energies of the a and b

*In the IR spectrum of IX in pyridine, there is a single strong unsplit band at 1645 cm^{-1} . Analogous information could not be obtained for VIII because of its poor solubility.

forms do not exceed 0.06β (~ 1 kcal/mole).* Consequently, a considerable role in the determination of the equilibrium constant will be played by other factors, as well, such as interaction with the solvent or hydrogen bonds.

EXPERIMENTAL

Lactone of 4-Chloro-2-(2',4'-dioxopiperidino)benzoic Acid (IV). A mixture of 4.5 g of I and 40 ml of acetic anhydride was boiled for 30 min. The precipitate that separated out on cooling was filtered off and washed with dioxane; yield 1.5 g (33%), mp 250–251°C (from dioxane). Light yellow crystalline powder soluble on heating in dioxane and acetic anhydride, moderately soluble in ethanol, and insoluble in water. When Ia was heated in acetic anhydride, the yield of IV was 54.7%. Found %: C 57.6; H 3.4; N 6.0; Cl 14.1. $C_{12}H_8ClNO_3$. Calculated %: C 57.7; H 3.2; N 5.6; Cl 14.2. The reaction of IV with 2,4-dinitrophenylhydrazine in aqueous alcohol led to the opening of the lactone ring with the formation of a 2,4-dinitrophenylhydrazone, mp 220–221°C (without depression in a mixture with the 2,4-dinitrophenylhydrazone of III).

4-Chloro-2-(2',4'-dioxopiperidino)benzoic Acid (III). With heating, 3 g of IV was dissolved in 10 ml of 5% NaOH, and then acidification with hydrochloric acid precipitated 2.9 g (93.5%) of III. Colorless crystals, mp 188–188.5°C (decomp., from water); III is soluble in hot water, warm ethanol, and cold acetone, and is insoluble in ether and benzene; an alcoholic solution of III gives a reddish brown coloration with a solution of $FeCl_3$. Found %: C 54.0; H 3.5; N 5.6; Cl 13.2; equiv. 263.8. $C_{12}H_{10}ClNO_4$. Calculated %: C 53.8; H 3.7; N 5.2; Cl 13.2; equiv. 267.6. When 0.5 g of III was boiled with 15 ml of acetic anhydride, 0.4 g (87%) of IV was obtained. 2,4-Dinitrophenylhydrazone of III: yellow crystalline powder with mp 220–221°C (decomp., from ethanol). Found %: N 15.5. $C_{18}H_{14}ClN_5O_7$. Calculated %: N 15.6.

1- β -(Cyanoethyl)-7-chloro-1,2,3,4-tetrahydroquinoline-2,4-dione (VIII). A mixture of 11.2 g of VI and 50 ml of acetic anhydride was heated at 120°C for 4 h. The acetyl derivative of VI (VII) that deposited after cooling was filtered off and washed with acetone; yield 8.6 g, mp 208–209°C. The filtrate was treated with water, the brown resinous precipitate that deposited was dissolved in sodium carbonate solution and the solution was filtered, and the filtrate was acidified to give 1.1 g (8.8%) of VIII. Under similar conditions, the yield of VIII from VII was 51.3%, mp 292–293°C (from acetic acid). Light-colored crystalline powder, soluble in ethanol, acetic acid, solutions of caustic alkalis and sodium carbonate, and insoluble in water; with $FeCl_3$, an ethanolic solution forms a reddish-brown coloration. Found %: N 11.2. $C_{12}H_9ClN_2O_2$. Calculated %: N 11.2.

β -(7-Chloro-2,4-dioxoquinolin-1-yl)propionic Acid (IX). 0.7 g of VIII was boiled with 7 ml of 10% NaOH until the evolution of ammonia ceased (14 h). After the usual working up, 0.95 g (98%) of IX was obtained in the form of small colorless crystals, mp 276–277°C (decomp., from aqueous ethanol). Compound IX is soluble in warm alcohol, dioxane, and glacial acetic acid, and is insoluble in water; with $FeCl_3$ solution an ethanolic solution of IX forms a reddish-brown coloration. Found %: C 53.8; H 3.7; N 5.5%. $C_{12}H_{10}ClNO_4$. Calculated %: C 53.8; H 3.8; N 5.2. The IR spectra of the compounds in the form of mulls in paraffin oil or of 4% solutions in pyridine and DMSO were obtained on a UR-10 infrared spectrophotometer. The UV spectra were obtained on a EPS-3 recording ultraviolet spectrophotometer. The PMR spectra were obtained in pyridine in TFA (with TMS as internal standard), and in deuterated alkali (with dioxane as internal standard, δ 3.70 ppm) on a JNM-4H-100 spectrometer.

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