SYDNONE IMINES FROM ε-AMINOCAPROIC ACID

I. S. Slyusarenko, V. V. Ogorodnikova,
V. I. Mamonov, and V. G. Yashunskii

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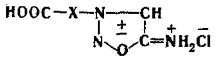
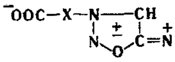
Sydnone imines and their acyl derivatives have been synthesized from ε-aminocaproic acid and its closest analogs. The possibility has been shown of the existence of internal salts in these sydnone imines and the impossibility of the formation of "betaine structures" in their acyl derivatives.

Continuing work on the search for biologically active substances among sydnonyl derivatives of amino acids [1, 2] we have synthesized sydnone imine derivatives from the closest analogs of ε-aminocaproic acid. The condensation of potassium δ-aminovalerate with the sodium bisulfite derivative of formaldehyde and potassium cyanide yielded (δ-carboxybutyl)aminoacetonitrile which, without isolation, was converted by treatment with sodium nitrite and hydrochloric acid into 3-(4-carboxybutyl)sydnone imine hydrochloride (Ia). Similarly, 3-(6-carboxyhexyl)sydnone imine hydrochloride (Ib) was synthesized from ω-aminoenanthic acid. In the preparation of 3-(4-carboxybenzyl)sydnone imine hydrochloride (Ic) from p-aminomethylbenzoic acid it was possible to isolate the intermediate N-(4-carboxybenzyl)-N-nitrosoaminoacetonitrile.



I a-c



II

a $X=(CH_2)_4$; b $X=(CH_2)_6$; c $X=p\text{-}C_6H_4CH_2$; d $X=(CH_2)_5$

In the UV spectra of the hydrochlorides (Ia) and (Ib), and also in the hydrochloride of 3-(5-carboxypentyl)sydnone imine (Id), described previously [1], in addition to the absorption in the 290-300-nm region characteristic for these heterocycles we observed a second strong absorption maximum at 200-205 nm. These bands are also present in the spectrum of the hydrochloride (Ic), in addition to a third band usually observed for sydnone imines containing aryl groups. The intense short-wave maximum is apparently generally characteristic for sydnone imines, as has been shown for a whole series of examples.*

In the 1500-1800-cm^{-1} region, the IR spectra of the compounds obtained have, in addition to the absorption bands characteristic for sydnone imines, a strong carbonyl band of a carboxy group (1710-1722 cm^{-1}).

By analogy with the internal salt (IId) described previously, the careful action of sodium bicarbonate on (Ia) and (Ic) yielded their internal salts (IIa) and (IIc). An attempt to isolate the analogous compound in the crystalline state for (Ib) was unsuccessful.

The IR spectra of the internal salts (IIa, c, d), in contrast to the spectra of the corresponding hydrochlorides, show a shift in the $\delta_{\overset{+}{N}H_2}$ absorption band in the short-wave direction by 40-50 cm^{-1} and the appearance in place of the high-frequency band of the carboxy group of an absorption band of the carbonyl of a carboxylate anion (1540-1550 cm^{-1}). The $\nu_{C=N}$ and ν_{C_4-H} absorption frequencies scarcely change.

The UV spectra of the "betaines" (IIa) and (IId) are practically identical with the spectra of the hydrochlorides, and only in the internal salt (IIc) is there a small bathochromic shift (18 nm) of the long-wave maximum (see Table 1). It may be concluded from this that, apparently, the nature of the anion has prac-

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*A detailed investigation of this question will be the subject of a special communication.

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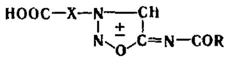
TABLE 1. Spectral Characteristics of Sydnone Imine Derivatives

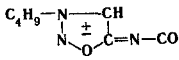
Compound	IR spectrum, ν, cm^{-1}						UV spectra								
							in ethanol						at pH 1		
	$C=N$	$C=O$ (CH_3CO)	$\overset{+}{N}H_2$ (δ)	CO(COOH)	C_4-H	COO^-	λ_{max}, nm			lg ε			λ_{max}, nm		
Ia	1680	—	1578	1722	—	—	300	—	205	3,87	—	3,91		—	
Ib	1690	—	1580	1710	3180	—	296	—	200	3,62	—	3,82		—	
Ic	1680	—	1589	1714	3170	—	285	225	199	3,85	4,04	4,48		—	
Id	1680	—	1590	1722	3130	—	296	—	200	3,91	—	3,91		—	
IIa	1698	—	1620	—	3150	1555	298	—	206	3,81	—	3,82		—	
IIb	1690	—	1640	—	3180	1550	303	225	204	3,80	4,10	4,61		—	
IIc	1695	—	1640	—	3110	1540	298	—	205	3,59	—	3,65		—	
IIIa	1570	1632	—	1718	3164	—	326	243	198	4,00	3,65	3,52		—	
IIIa*	1616	1739	1540	1710	3160	—	330	243	198	4,06	3,85	3,50	298^{sh}	210	204
IIIb	1577	1605	—	1728	3136	—	340	260	200	4,32	4,00	4,10		—	
IIIb*	1617	1742	1540	1720	3153	—	340	260	203	4,25	3,98	3,96	298	240	203
IIIc	1585	1645	—	1700	3170	—	330	235	198	3,78	3,87	3,34		—	
IIId	1595	1660	—	1695	3205	—	343	260	203	—	—	—	305	243	202
IIIe	1570	1640	—	1690	—	—	340	260	203	4,61	4,00	4,32	293	—	203
IIIe*	1615	1722	156°	1715	—	—	340	260	200	4,61	4,00	4,32	293	245	203
IIIf	1590	1622	—	1697	3140	—	346	262 225	203	3,95	4,15 3.95	4,28	310	240	203
IV	1559	1638	—	—	—	—	312	236	—	4,16	3.82	—	280	—	—
IV*	1627	1736	1574	—	—	—	—	—	—	—	—	—		—	

*Hydrochloride

tically no influence on the electronic state of the exocyclic bond and of the whole ring. The influence of the anion can be shown when a carboxy group is replaced by a carboxylate group apparently only if they are present in a substituent in position 3 in sufficient propinquity to the sydnone imine ring, i.e., when the electronic effect of this terminal group can be exerted to a considerable extent. In view of this, it becomes understandable why on passing from the hydrochloride to the internal salt of 3-(4-hydroxyphenyl)sydnone imine a considerable bathochromic shift (about 80 nm) of the absorption maxima in the UV spectrum is found [3].

From the hydrochlorides of the sydnone imines we synthesized their exocyclic N-derivatives (IIIa-f).


III a-f


IV

III a $X=(CH_2)_5$, $R=CH_3$; b $X=(CH_2)_5$, $R=C_6H_5$; c $X=(CH_2)_5$, $R=NH_2$;
d $X=(CH_2)_5$, $R=C_6H_5NH$; e $X=(CH_2)_6$, $R=C_6H_5$; f $X=p\text{-}C_6H_4CH_2$, $R=C_6H_5NH$

Although the basicity of the acyl derivatives of the sydnone imines is low [4], one cannot exclude a priori the possibility of the existence of a "betaine form" of a sydnone acylimine with a carboxy group in the substituent at position 3, i.e., an internal salt of type (II). To investigate the participation of the carboxyl group in internal-salt formation, we recorded the IR and UV spectra of all the exocyclic derivatives (III) obtained. 3-(5-Carboxypentyl)sydnone acetylimine (IIIa) was studied in greatest detail. If the sydnone imine (IIIa) existed in the form of an internal salt, then, with the exception of the absorption band of the carboxy group, its IR spectrum should be close to that of the hydrochloride or, for example, to the spectrum of the hydrochloride of 3-butylsydnone acetylimine (IV—base) [4]. However, in the 1500-1800-cm^{-1} region of the IR spectrum of (IIIa) there are three bands, two of which are close in frequency to the bands of the spectra of compound (IV), while the third represents $\nu_{C=O}$ of a nondissociated carboxy group. The spectrum of the hydrochloride of (IIIa) that we obtained differs substantially from the spectrum of the base (IIIa) and, with the exception of the additional $\nu_{C=O}$(COOH) band coincides almost completely with the spectrum of the hydrochloride of (IV), which contains three absorption bands.

For a clearer assignment of the absorption bands of the carbonyl groups, we recorded the IR spectrum of the sodium salt of (IIIa). While the absorption band in the 1632-cm^{-1} region remained unchanged, the band at 1718 cm^{-1} observed in (IIIa) was absent from the spectrum of the sodium salt, which enables this band to be assigned to $\nu_{C=O}$ of the carboxy group. In the IR spectra of all the compounds obtained, the ν_{C_4-H} absorption band was clearly observed in the 3110-3205-cm^{-1} range.

We have also observed for the first time a strong short-wave maximum in the UV spectra of (IIIa) and other acylimine derivatives, just as in the case of the sydnone imine hydrochlorides. The other two maxima have positions close to those in the spectrum of compound (IV). If a "betaine" structure were realized in compound (IIIa), by analogy with the internal salt (IId) its IR spectrum should be identical with the spectrum of the hydrochloride (IIIa). However, it is known that in ethanol the UV spectra of the acylimine derivatives and their hydrochlorides coincide because of the ready solvolysis of the latter [4]. In actual fact, the UV spectra of (IIIa) and its hydrochloride, taken in ethanol, proved to be identical, and only in 0.1 N HCl did the spectra of (IIIa) and of the other compounds (III) differ from the spectra of the corresponding bases. Here, also, characteristic short-wave maxima were observed (see Table 1). In order to exclude the influence of the solvents, the spectra of (IIIa) and its hydrochloride were taken in tablets of KCl and in paraffin oil – they differed from one another and corresponded to the spectra of (IIIa) in ethanol and in 0.1 N HCl.

Thus, it has been shown that acyl derivatives of 3-(carboxyalkyl)sydnone imines are incapable of forming "internal salts."

EXPERIMENTAL

The IR spectra were taken in a thin layer of paraffin oil on a UR-10 instrument and the UV spectra on an MRS-50L instrument with a layer thickness of 1 cm at a concentration of 10^{-4} M.

3-(4-Carboxybutyl)sydnone Imine Hydrochloride (Ia). To a mixture of 3 g (0.02 mole) of the hydrochloride of δ-aminovaleric acid, 2.2 g (0.04 mole) of caustic potash, and 2.65 g (0.02 mole) of the sodium bisulfite derivative of formaldehyde in 65 ml of water a solution of 1.28 g (0.02 mole) of potassium cyanide in 10 ml of water was added over 30 min. The temperature was raised to 40°C, and the reaction mixture was stirred for 3 h and was then cooled to 5°C and acidified with hydrochloric acid (pH 5). The resulting solution was treated with a solution of 2 g (0.03 mole) of sodium nitrite in 20 ml of water and was acidified further to pH 2. After extraction with ether, the extract was dried with sodium sulfate and, at 3°C, 20 ml of a 6 N ethereal solution of hydrogen chloride was added to it. The precipitate that deposited was filtered off and was reprecipitated from methanol with ether. This gave 1.6 g (37%) of the hydrochloride (Ia) with mp 146-147°C. Found: C 38.2; H 5.5; N 19.0; Cl 16.0%. $C_7H_{11}N_3O_3 \cdot HCl$. Calculated: C 37.9; H 5.5; N 19.0; Cl 16.0%. Internal salt (IIa). A solution of 0.5 g of the hydrochloride (Ia) in 1.5 ml of water was treated with 0.185 g of sodium bicarbonate, which gave 0.15 g (36%) of the salt (IIa) with decomp. pt. 122-123.5°C. Found: C 43.4; H 6.0; N 21.6%. $C_7H_{11}N_3O_3 \cdot 0.5H_2O$. Calculated: C 43.3; H 6.2; N 21.6%.

The Hydrochloride of 3-(6-Carboxyhexyl)sydnone Imine (Ib) was synthesized in a similar manner to (Ia) starting from ω-aminoenanthic acid; yield 62%, decomp. pt. 113-115°C. Found: C 43.2; H 6.6; N 16.5; Cl 14.0%. $C_9H_{15}N_3O_3 \cdot HCl$. Calculated: C 43.3; H 6.4; N 16.8; Cl 14.2%.

Hydrochloride of 3-(4-Carboxybenzyl)sydnone Imine (Ic). A solution of 3.96 g (0.06 mole) of potassium cyanide in 20 ml of water was added over 30 min to a mixture of 9.0 g (0.06 mole) of p-aminomethylbenzoic acid, 3.36 g (0.06 mole) of caustic potash, and 8.04 g (0.06 mole) of the sodium bisulfite derivative of formaldehyde in 125 ml of water. After 3 h, the reaction mixture was acidified at 3-5°C with 15 ml of concentrated hydrochloric acid to pH 3. After an hour, the precipitate that had deposited was filtered off, washed with water, and recrystallized from isopropanol. Yield 7.6 g (59%).

N-(4-Carboxybenzyl)-N-nitrosoaminoacetonitrile, mp 164-165°C. Found: C 54.7; H 3.9; N 19.2%. $C_{10}H_9N_3O_9$. Calculated: C 54.8; H 4.1; N 19.2%. A suspension of 7.6 g of the nitroso nitrile in 50 ml of absolute ethanol at 0°C was treated with 20 ml of a 6 N solution of hydrogen chloride in absolute ether. The solid matter dissolved, and after some time crystals deposited. The reaction mixture was diluted with 200 ml of absolute ether and left at 5°C for a day. The precipitate was filtered off, washed with ether, and reprecipitated from methanol with ether. This gave 5.25 g (59%) of the hydrochloride (Ic), decomp. pt. 157-158°C. Found: C 46.7; H 3.8; N 16.4; Cl 13.8%. $C_{10}H_9N_3O_3 \cdot HCl$. Calculated: C 47.0; H 3.9; N 16.4; Cl 13.9%. The internal salt (IIc). The hydrochloride (Ic) (1.28 g) and sodium bicarbonate (0.42 g) gave 0.55 g (50%) of a salt with mp 128-129°C (from ethanol). Found: C 54.6; H 4.2; N 19.3%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1; N 19.2%.

3-(5-Carboxypentyl)sydnone Acetylimine (IIIa). A solution of 2.35 g of the hydrochloride (Id) in 20 ml of acetic anhydride was treated with 0.85 g of sodium bicarbonate at 3°C, giving 1.23 g (51%) of (IIIa) with mp 154-155°C (from ethanol). Found: C 49.5; H 6.2; N 17.0%. $C_{10}H_{15}N_3O_4$. Calculated: C 49.8; H 6.2; N 17.4%. Hydrochloride, decomp. pt. 128-130°C (from isopropanol). Found: Cl 12.8%. $C_{10}H_{15}N_3O_4 \cdot HCl$. Calculated: Cl 12.8%.

3-(5-Carboxypentyl)sydnone Benzoylimine (IIIb) was obtained from the hydrochloride (Id) and benzoyl chloride in the presence of sodium bicarbonate; yield 48%, mp 171-173°C (from isopropanol). Found: C 59.1; H 5.7; N 13.8%. $C_{15}H_{17}N_3O_4$. Calculated: C 59.4; H 5.6; N 13.8%. Hydrochloride, mp 142-143°C. Found: C 53.2; H 5.5; N 12.2; Cl 10.4%. $C_{15}H_{17}N_3O_4 \cdot HCl$. Calculated: C 53.0; H 5.3; N 12.4; Cl 10.4%.

3-(6-Carboxyhexyl)sydnone Benzoylimine (IIIe) was synthesized similarly; yield 47%, mp 82-83°C (from a mixture of ethyl acetate and hexane). Found: C 60.4; H 6.2; N 13.1%. $C_{16}H_{19}N_3O_4$. Calculated: C 10.6; H 6.0; N 13.2%. Hydrochloride, decomp. pt. 138-139.5°C (from acetone). Found: Cl 9.7%. $C_{16}H_{19}N_3O_4 \cdot HCl$. Calculated: Cl 10.0%.

3-(5-Carboxypentyl)sydnone Carbamoylimine (IIIc). A solution of 1.18 g (0.005 mole) of the hydrochloride (Id) and 0.39 g (0.0055 mole) of sodium cyanate in 30 ml of methanol was boiled for 3 h. After the mixture had cooled, the precipitate was filtered off, washed with water, and recrystallized from 3% aqueous methanol. Yield 0.47 g, decomp.pt. 164-166°C. Found: C 44.5; H 5.9; N 23.0%. $C_9H_{14}N_4O_4$. Calculated: C 44.6; H 5.8; N 23.1%.

3-(5-Carboxypentyl)sydnone Phenylcarbamoylimine (IIId). A mixture of 2 g (0.008 mole) of the hydrochloride (Id) and 1.7 g (0.02 mole) of sodium acetate was treated with 1.07 g (0.009 mole) of phenyl isocyanate at 0°C. After 2 h, the precipitate that had deposited was filtered off, washed with water, and recrystallized from ethanol. Yield 0.46 g, decomp. pt. 174.5-175°C. Found: C 56.5; H 5.7; N 17.5%. $C_{15}H_{18}N_4O_4$. Calculated: C 56.5; H 5.7; N 17.6%.

3-(4-Carboxybenzyl)sydnone Phenylcarbamoylimine (IIIf) was synthesized similarly; yield 45%, decomp. pt. 193-195°C (from ethanol). Found: C 60.1; H 4.1; N 16.1%. $C_{17}H_{14}N_4O_4$. Calculated: C 60.4; H 4.2; N 16.6%.

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