3-(CARBOXYPOLYMETHYLENE)SYDNONES

I. S. Slyusarenko, N. G. Klushina,
L. E. Kholodov, and V. G. Yashunskii

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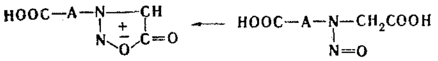
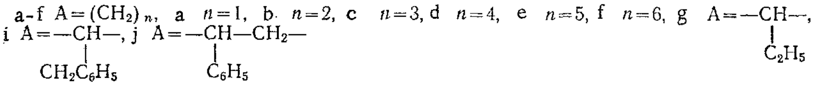
Spectral data and pK_a values found for a number of 3-(carboxypolymethylene)sydnones made it possible to establish the mutual effect of a heterocyclic ring and a carboxyl group in these compounds and to confirm the high electron-acceptor character of a 3-sydnonyl substituent.

A number of communications on sydnones and sydnonimines with a carboxyl function, which have attracted attention as substances that have antiphlogistic and analgesic activity [1] as well as antimicrobial action [2], have recently appeared. However, there is practically no information on the mutual effect of a carboxyl group and a heterocyclic ring in such compounds.

In a continuation of our research on the chemistry of carboxyalkyl derivatives of sydnones and sydnonimines [3-5], we have studied some physicochemical properties of a number of 3-(carboxyalkyl)sydnones (I).



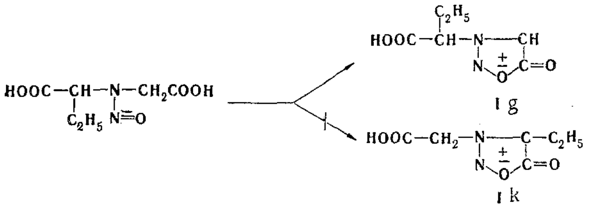
I a-j II a-j



a-f $A=(CH_2)_n$, a $n=1$, b $n=2$, c $n=3$, d $n=4$, e $n=5$, f $n=6$, g $A=-\underset{C_2H_5}{CH}-$, i $A=-\underset{CH_2C_6H_5}{CH}-$, j $A=-\underset{C_6H_5}{CH}-CH_2-$

We have previously described Ii, j [4]; the synthesis of acids Ia, b was reproduced in conformity with [6, 7], but Ib was obtained by a method that differed somewhat from that in [7].

Sydnones Ic,d,f,g were synthesized by cyanomethylation of the appropriate amino acids in alkaline media with subsequent saponification and nitrosation to N-nitroso-N-carboxyalkylglycines (II), which were cyclized to I in acetic or trifluoroacetic anhydride. Treatment of the nitroso acid (IId) with acetic anhydride gave a substance with a double melting point; treatment of this substance with water gave Id. Here, as in the preparation of Ib [8], the anhydride of Id apparently formed. As in the case of IIi [4], in the cyclization of nitroso acid IIg one might have expected the production of two isomeric sydnones Ig and Ik due to intramolecular cyclization of the nitroso group with one of the carboxyl groups of the molecule.



I g

I k

On the basis of the PMR spectrum, the cyclization product, which has a signal at δ 7.14 ppm (d_6-dimethyl sulfoxide), which is characteristic for 4-H of the sydnone ring [9], and a δ_{CH} signal at 5.27 ppm (triplet), a δ_{CH_2} signal at 2.20 ppm (multiplet), and a δ_{CH_3} signal at 0.87 ppm (triplet) with integral intensities of 1, 1, 2, and 3 proton units, respectively, the Ig structure can be assigned to the sydnone obtained.

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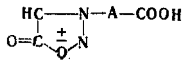
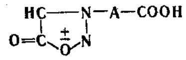
TABLE 1.



Compound	A	IR spectra			UV spectra		pK_a in 90% alcohol
		$\nu_{C=O}$ (COOH), cm^{-1}	$\nu_{C=O}$ (ring), cm^{-1}	$\nu_{C_{(4)}-H}$, cm^{-1}	λ_{max}, nm	lg ε	
I_a	$-(CH_2)-$	1715	1745	3185	298 203,5	3,84 3,59	3,89±0,02
I b	$-(CH_2)_2-$	1712	1735	3145	295 202,5	3,86 3,48	6,10±0,03
I c	$-(CH_2)_3-$	1715	1732	3145	295 202,5	3,80 3,48	6,72±0,03
I d	$-(CH_2)_4-$	1710	1732	3141	295 202,5	3,80 3,48	7,10±0,03
I e	$-(CH_2)_5-$	1710	1732	3138	292,5 203	3,83 3,71	7,27±0,01
I f	$-(CH_2)_6-$	1715	1725	3138	292,5 203	3,90 3,50	7,40±0,03
I g	$-\underset{C_2H_5}{\underset{\mid}{CH}}-$	1700	1735	3138	298 205	3,78 3,55	4,29±0,04
I i	$-\underset{CH_2C_6H_5}{\underset{\mid}{CH}}-$	1712	1730	3142	300 210	3,74 3,99	4,07±0,03
I j	$-CH_2-\underset{C_6H_5}{\underset{\mid}{CH}}-$	1694	1752	3145	270 204	3,55 3,88	5,92±0,02

TABLE 2



Compound	δ_{4-H}, ppm	δ, A, ppm					
Ia	6,98	$A=CH_2$ 5,27					
Ib	6,98	$A=CH_2$ 4,50	CH_2 2,98				
Ic	6,98	$A=CH_2$ 4,34	CH_2 2,08	CH_2 2,22			
Id	6,98	$A=CH_2$ 4,31	CH_2 1,86	CH_2 1,53	CH_2 2,16		
Ie	6,98	$A=CH_2$ 4,30	CH_2 1,84	CH_2 1,36	CH_2 1,36	CH_2 2,16	
If	6,98	$A=CH_2$ 4,30	CH_2 1,81	CH_2 1,31	CH_2 1,31	CH_2 1,31	CH_2 2,14
Ig	7,14	$A=CH$ 5,27	CH_2 2,20	CH_3 0,87			
Ii	7,14	$A=CH$ 5,64	CH_2 3,57	C_6H_5 7,20			
Ij	7,27	$A=CH$ 5,99 C_6H_5*	CH_2 2,43				

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*The δ-H(C_6H_5) value for Ij is 7.39 ppm.

The UV spectra of 3-carboxypolymethylenesydnones Ia-f are practically identical to one another and, as for 3-alkylsydnones [10], are characterized by two absorption maxima – a short-wave maximum at 203 nm and a long-wave maximum at 292.5-298 nm (Table 1). Small differences are observed in the spectra of sydnones that contain a phenyl substituent in the chain.

The short-wave maximum of Ia is shifted somewhat to the long-wave side, while the long-wave maximum of Ij, on the other hand, is shifted somewhat to the short-wave side.

The IR spectra of mineral oil suspensions of I (Table 1) have three intense absorption bands at 1725-1752, 1694-1715, and 3138-3185 cm^{-1}. The first two bands correspond to the stretching vibrations of the carbonyl groups in the ring and in the carboxyl group, while the last band corresponds to $\nu_{C_{(4)}-H}$ of the

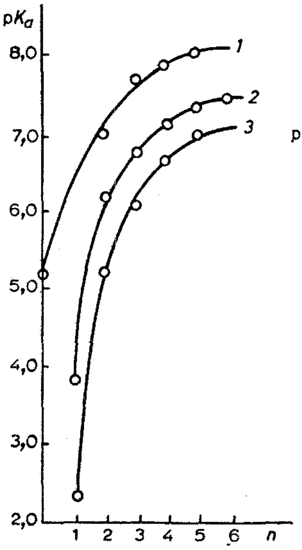


Fig. 1

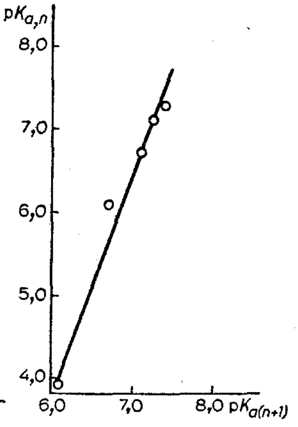


Fig. 2

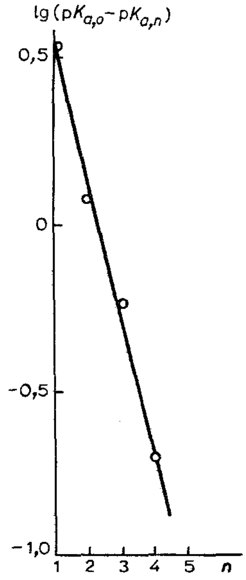


Fig. 3

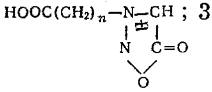
Fig. 1. Effect of the number of methylene groups (n) on the reactivity of: 1) $\overset{+}{N}H_3-(CH_2)_n-NH_2$ [16]; 2)  $HOOC(CH_2)_n-N\overset{\pm}{-}CH$; 3) $\overset{+}{N}H_3-(CH_2)_n-SO_3^-$ [16].

Fig. 2. Graph of the dependence of $pK_{a,n}$ on $pK_{a,n+1}$ for 3-(carboxypolymethylene)sydnones.

Fig. 3. Graph of the dependence of log $(pK_{a,o}-pK_{a,n})$ on the number of methylene groups (n) of 3-(carboxypolymethylene)sydnones.

heteroring. It was previously found [5] for sydnone-4-acetic acids that of the two carbonyl bands (1785-1825 and 1675-1695 cm^{-1}), the high-frequency band corresponds to ν_{CO} of the ring. In analogy with this, the shorter-wave band of I can also be assigned to the ring carbonyl group, especially since the second region of frequencies corresponds to ν_{CO} of alkyl and aralkyl carboxylic acids [11]. This is confirmed by a comparison of the spectra of Ie and the Na salt of Ie in chloroform solution, in which, as was shown in [12], the sydnone ν_{CO} is raised appreciably. In this case, bands are observed at 1718 and 1750 cm^{-1} in the spectrum of Ie and at 1753 and 1582 cm^{-1} ($\nu_{CO}[COO^-]$) in the spectrum of the Na salt.

The disappearance of the band at 1718 cm^{-1} and the retention of the higher-frequency band confirm that the latter pertains to ν_{CO} of the ring. Thus it was established that ν_{CO} of the ring carbonyl of sydnonecarboxylic acid is always higher than ν_{CO} of the carboxyl group, while this ν_{CO} is considerably lower in 3-carboxyalkylsydnones than in sydnone-4-carboxylic and sydnone-4-acetic acids.

It is seen from the data presented in Table 1 that the proximity of the mesoionic heteroring to the carboxyl group in I has practically no effect on ν_{CO} of the latter.

At the same time, the frequency of the stretching vibrations of the exocyclic group decreases somewhat as the chain length increases, since $\nu_{Ia}-\nu_{Ie}$ = 20 cm^{-1} (it is interesting that the sydnone ν_{CO} in the spectrum of Ia has the same magnitude as in the spectrum of 3-isopropylsydnone-4-acetic acid [5]). The decrease in the frequency of the stretching vibration of the $C_{(4)}-H$ bond of the ring with lengthening of the polymethylene chain is manifested even more clearly in this series, since $\nu_{Ia}-\nu_{Ie}$ here is ~ 50 cm^{-1}.

In the PMR spectra of all of the investigated compounds (Table 2) the number of methylene groups that separate the carboxyl group and the heteroring in Ia-f has no effect on the chemical shifts of 4-H of the sydnone ring, which is 6.98 ppm (in C_2D_5OD 4-H for Ia is 6.83 ppm). This signal is shifted somewhat to weak field for Ig-j. The considerable deshielding of the protons of the methylene group in Ia (δ 5.27 ppm) is due to the effect of two electron-acceptor substituents – the sydnone ring and the carboxyl group. The signals of the α-CH_2 protons† in Ib are shifted to strong field by ~1 ppm as compared with Ia, while the chemical shift of the analogous protons in Ic is the same as for 3-alkylsydnones [9]. Further removal of the carboxyl group has practically no effect on the position of the signals of the α-CH_2 protons. A similar pattern is observed for the signal of the protons of a methylene group adjacent to the carboxyl group and for the signal of the protons of the β-methylene groups. To assign the signals of the two middle links in Id, we used the double-resonance method, owing to which we were able to unambiguously establish that the signals of the protons of the methylene groups in the β position relative to the sydnone ring are found at weaker field. The assignment of the signals of the CH_2 groups in Ie, f was made in analogy with Id. The PMR spectra once more confirmed that a 3-sydnonyl substituent is a strong electron acceptor.

To study the effect of the heterocyclic ring on the carboxyl group in I, we determined the dissociation constants of these acids. A pK_a of 1.7 is presented for Ia in [7], but the conditions and the method used to determine this constant are not indicated. We were unable to reproduce this value – a "trend" in the pK_a from 1.87 to 1.96 was observed in the potentiometric titration of Ia in water. A more convenient solvent for the potentiometric determination of the pK_a values of I was found to be 90% (by volume) aqueous ethanol (Table 1). The constants for the more water-soluble Ia and Ie were determined in 50% alcohol (pK_a for Ia was 2.97, while pK_a for Ie was 5.97).

Sydnone-3-acetic acid (Ia) proved to be stronger by 1.5 orders of magnitude than 3-alkylsydnone-4-acetic acid (pK_a 4.5 in 50% ethanol) [5]. This confirms the previously [13] drawn conclusion that the 3-sydnonyl substituent is a stronger electron acceptor than the 4-sydnonyl group.

The strength of acids Ia-f decreases rapidly as the number of methylene links increases. It can be seen (Fig. 1) that the character of transmission of the electronic effect of a 3-sydnonyl substituent through the polymethylene chain is qualitatively similar to the character of transmission for a number of other systems of the $Y(CH_2)_nX$ (III) type, where Y is the reaction center and X is a substituent (in the case of Ia-f, X = 3-sydnonyl and Y = COOH).

Quantitatively speaking, the attenuation of the inductive effect during transmission through the polymethylene chain can be described [14] by an equation of the Taft type:

$$pK_{a,n}-pK_{a,o}=\rho^*\sigma^*z^n, \tag{1}$$

where n is the number of CH_2 groups, $pK_{a,o}$ is the pK_a for CH_3Y, and z is the coefficient of attenuation of the inductive effect on transmission through one CH_2 group. The observance of Eq. (1) for sydnonecarboxylic acids Ia-f and the z value were verified as follows. Equation (1) has the following form for $X(CH_2)_{n+1}Y$:

$$pK_{a,\,n+1}-pK_{a,\,o}=\rho^*\sigma^*z^{n+1}. \tag{1a}$$

Dividing Eq. (1a) by (1) and transforming the result, we obtain

$$pK_{a,\,n+1}=(1-z)\,pK_{a,\,o}+zpK_{a,\,n}. \tag{2}$$

Since $(1-z)pK_{a,o}$ is a constant, a straight line should be observed in coordinates of $pK_{a,n+1}$ and $pK_{a,n}$; in fact, to a certain approximation, a straight line is observed (Fig. 2). From this graph, we find z = 0.36 from the slope of the line, while we determine $pK_{a,o}$ = 7.30 from the segment cut out on the $pK_{a,n+1}$ axis. These are completely reasonable values if one takes into account that for a number of systems of the III type [14] z = 0.375 ± 0.045, while pK_a = 7.24 for CH_3Y, i.e., CH_3COOH, in 90% ethanol.

As already noted in [14], the following arises from Eq. (1): since $\rho^*_{X-Y} < 0$ for pK_a, the pK_a should not be greater than $pK_{a,o}$ at any n value for an electronegative substituent $X(\sigma^*_X > 0)$, but $pK_{a,n}$ for sydnonecarboxylic acids Ia-f becomes larger than $pK_{a,o}$ when n = 5; when n > 5, the electron-donor properties of the polymethylene chain shield the effect of the electronegative substituent. Equation (1) can therefore be observed only when $n \leq 4$. For the direct verification of this and for the determination of the parameters, Eq. (1) was converted to logarithmic form:

$$\lg(pK_{a,\,o}-pK_{a,\,n})=\lg(-\rho^*\sigma^*)+n\lg z. \tag{3}$$

The graph in coordinates of log $(pK_{a,o}-pK_{a,n})$ and n for $pK_{a,o}$ = 7.30 ± 0.05 and $n \leq 4$ has linear character (Fig. 3), and the slope of the line corresponds to log z = −0.41 ± 0.03, i.e., z = 0.39 ± 0.03; this is in

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†Here and subsequently, the methylene groups are reckoned from the sydnone ring.

TABLE 3. N-Nitro-Substituted Glycines

Compound	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
IIc	126—128 (acetone)	$C_6H_{10}N_2O_5$	37,9	5,3	14,6	37,9	5,3	14,7	18,8
IId	88—89	$C_7H_{12}N_2O_5$	41,0	5,8	14,0	41,2	5,9	13,7	24,1
IIe	81—83	$C_9H_{16}N_2O_5$	46,7	7,0	12,2	46,5	6,9	12,0	31,5

satisfactory agreement with the z value obtained above in the analysis of Eq. (2). Consequently, Eq. (1) for Ia-f when $n \leq 4$ has the form

$$pK_{a,n} = 7.30 - 8.5 \cdot 0.39^n.$$

Thus, judging from the z value of 0.36-0.39, the 3-sydnonyl substituent should be classified as "normal"; i.e., it should be classified with those substituents for which the coefficient of attenuation of the inductive effect through the polymethylene chain (z) is 0.375 ± 0.045 and the inductive constants (σ^*) have constant values.

The inductive Taft constant of the 3-sydnonyl substituent ($\sigma^*_{3\text{-Sy}}$) was calculated to be 4.8 for Ia [13] starting from a pK_a of 1.7. To more accurately determine this constant, we used our previously found correct dissociation constant of Ia in 50% ethanol ($pK_a = 2.97$). Substitution of this value into the Taft equation for XCOOH in 50% alcohol ($pK_a = 5.50 - 1.705\ \sigma^*$) [15] gives $\sigma^*_{\text{Sy-CH}_2} = 1.5$, and for $z = 0.36$ we obtain $\sigma^*_{3\text{-Sy}} = 1.5/z = 4.2$ for the 3-sydnonyl substituent.

EXPERIMENTAL

The UV spectra of ethanol solutions of the compounds were recorded with a "Shimadzu" MPS-50L spectrometer. The IR spectra were recorded with a UR-10 spectrophotometer, while the PMR spectra were recorded with a Varian HA-100 spectrometer with hexamethyldisiloxane as the internal standard. The potentiometric titration was made with an LPM-60m potentiometer (the concentration of the compounds was 10^{-3} mole, and the titrant was 0.1 N NaOH).

N-Nitroso-N-(2'-carboxyethyl)glycine (IIb). A mixture of 8.91 g (0.1 mole) of β-alanine, 5.6 g (0.1 mole) of potassium hydroxide, 13.4 g (0.1 mole) of the sodium bisulfite derivative of formaldehyde, and 50 ml of water was treated in the course of 30 min with stirring with a solution of 6.5 g (0.1 mole) of potassium cyanide in 20 ml of water. After 3 h, a solution of 8 g of potassium hydroxide in 25 ml of water was added, and the mixture was refluxed for 3 h and heated in vacuo for a few min at 40°. It was then cooled, and 10 ml of concentrated hydrochloric acid was added. This mixture was then cooled to 2-0° and treated with a solution of 7.6 g of sodium nitrite in 30 ml of water, after which it was again acidified to pH 3.0 with concentrated hydrochloric acid. The mixture was then stirred for 3 h and extracted with ethyl acetate. The extract was dried, the solvent was removed by distillation, and the residue was recrystallized from ethyl acetate—petroleum ether to give 3 g (17.08%) of IIb with mp 114.5-116.5°.† Found: C 34.16; H 4.69; N 15.50%. $C_5H_8N_2O_5$. Calculated: C 34.10; H 4.57; N 15.89%.

N-Nitro-substituted glycines IIc-e, the physical constants and yields of which are presented in Table 3, were similarly obtained.

3-(3'-Carboxypropyl)sydnone (Ic). A mixture of 0.3 g of IIc and 5 ml of acetic anhydride was allowed to stand for 3 days at room temperature, after which the acetic anhydride and methanol were removed by distillation at 25°, and the resulting oil was treated with ether. The solid was crystallized from ethyl acetate—petroleum ether to give 0.21 g (77.2%) of Ic with mp 90-90.5°. Found: C 42.1; H 4.7; N 16.0%. $C_6H_8N_2O_4$. Calculated: C 42.0; H 4.7; N 16.2%.

3-(4'-Carboxybutyl)sydnone (Id). A mixture of 0.5 g of IId and 10 ml of acetic anhydride was allowed to stand for 24 h at room temperature, after which the acetic anhydride and methanol were removed by distillation at room temperature, and the oil was treated with ether. The solid was removed by filtration and crystallized from ethyl acetate—petroleum ether to give a substance with a double melting point (mp 94-96° and 109-110°). It was heated in water at 70° for 10 min, after which the water was removed by dis-

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†According to [7], this compound has mp 85.5-86.5° and 124.5-125.5° (water).

tillation and the residue was dried over P_2O_5 to give 0.38 g (84.4%) of Id with mp 117-118°. Found: C 45.3; H 5.4; N 15.1%. $C_7H_{10}N_2O_4$. Calculated: C 45.2; H 5.4; N 15.0%.

3-(6'-Carboxyhexyl)sydnone (If). This compound, with mp 103-104° (ethyl acetate–petroleum ether), was obtained in 24.0% yield from 2.8 g of IIf and 5 ml of trifluoroacetic anhydride by the method used to prepare Ic. Found: C 50.4; H 6.6; N 12.7%. $C_9H_{14}N_2O_4$. Calculated: C 50.5; H 6.6; N 13.1%.

3-(1'-Carboxypropyl)sydnone (Ig). A mixture of 2.57 g of α-aminobutyric acid, 1.40 g of potassium hydroxide, 3.35 g of the bisulfite derivative of formaldehyde, and 35 ml of water was treated with a solution of 1.62 g of potassium cyanide in 10 ml of water in the course of 30 min with stirring. After 3 h, a solution of 2.5 g of potassium hydroxide in 8 ml of water was added, and the mixture was refluxed for 3 h and heated in vacuo at 40° for a few min. It was then cooled and acidified to pH 6.0 with concentrated hydrochloric acid. The acidic mixture was then treated with a solution of 2.25 g of sodium nitrite in 20 ml of water, and the mixture was then again acidified to pH 3.0 with concentrated hydrochloric acid. It was then stirred for 3 h and extracted with ether. The extract was dried over $MgSO_4$, and the ether was removed by distillation. The residual oil was treated with 8 ml of acetic anhydride, and the mixture was allowed to stand in the dark for 3 days. Water was then added to it, and the mixture was evaporated to dryness. The residue was crystallized from ethyl acetate–petroleum ether to give 0.94 g (21.9%) of Ig with mp 139-141°. Found: C 41.9; H 4.7; N 16.1%. $C_6H_8N_2O_4$. Calculated: C 41.9; H 4.7; N 16.3%.

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