BULLETIN DE L'ACADÉMIE
POLONAISE DES SCIENCES
Série des sciences chimiques
Volume XV, No. 6, 1967

ORGANIC CHEMISTRY

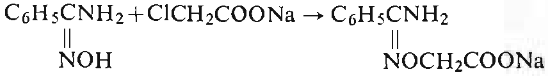
On Certain Derivatives of Halogenosalicylhydroxamic Acids

by

A. OSTASZYŃSKI, H. PLENKIEWICZ and T. URBAŃSKI

Presented by T. URBAŃSKI on April 17, 1967

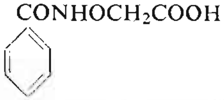
Koch [1] allowed benzamide oxime to react with chloroacetic acid in sodium ethoxide as solvent, namely



$$\begin{array}{c}C_6H_5CNH_2\\ \|\\ NOH\end{array} + ClCH_2COONa \rightarrow \begin{array}{c}C_6H_5CNH_2\\ \|\\ NOCH_2COONa\end{array}$$

and obtained upon acidification an acetic derivative of the oxime. Hantzsch and Wild [2] treated acetic and propionic acid oximes, as well as benzaldoxime, with chloroacetic acid and obtained acetic derivatives of the reactants, e.g. benzaldoximacetic acid $C_6H_5CH{=}NOCH_2COOH$.

While synthesizing canavanine, Kitagawa and Takani [3] allowed benzhydroxamic acid to react with ethyl bromoacetate to yield benzhydroxamacetic acid



A survey of the available literature disclosed no report on salicylhydroxamacetic acids.

In our earlier studies on salicylhydroxamic acids, and particularly on their halo-derivatives, intended to explore their biological activity, we allowed dihalogenosalicylhydroxamic acids [4] to react with chloroacetic acid and suggested the products to have structure (I).

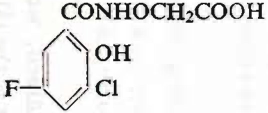
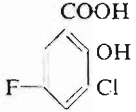
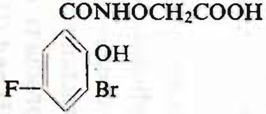
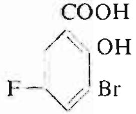
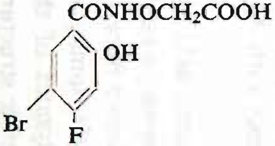
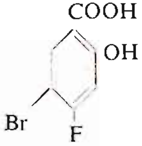
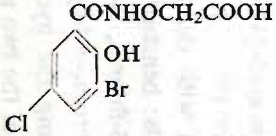
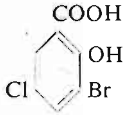
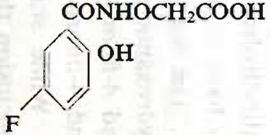
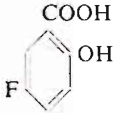
The reaction with chloroacetic acid was now investigated with the following hydroxamic acids: benzhydroxamic, *o*-methoxybenzhydroxamic, salicylhydroxamic, and 4-fluoro-, 5-fluoro-, 3-chloro-5-fluoro-, 3-bromo-5-fluoro-, 3-bromo-5-chloro-, and 4-fluoro-5-bromo-salicylhydroxamic, as reactants.

While studying the hydrolyzates of the products obtained, we came to the conclusion that of the two possible structures (I) and (II), it is the (I) that is correct, in agreement with our previous supposition.

Note. Part II on: Halogenosalicylhydroxamic Acids.

TABLE I

Properties of derivatives of hydroxamacetic acid

No.	Hydroxamic acid	Yield, %	M.p., °C	Analysis, %N		Aqueous 10% HCl hydrolyzate
				calc.	found	
1		91	165—165.5	5.31	5.35	 + $HClNH_2OCH_2$—COOH
2		73	173—175	4.55	4.29	 + ,,
3		76	171—172	4.55	4.43	 + ,,
4		81	166—167	4.31	4.28	 + ,,
5		71	161—161.5	6.11	5.82	 + ,,

Continued Table I

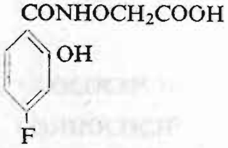
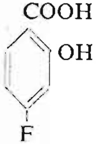
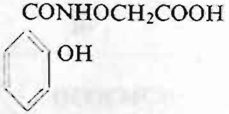
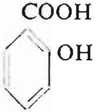
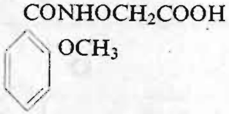
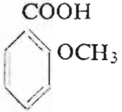
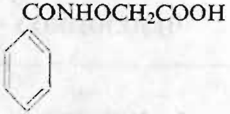
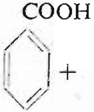
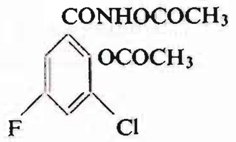
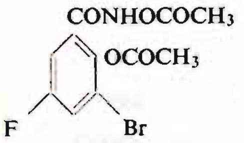
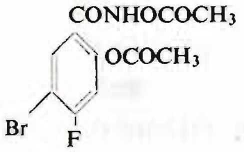
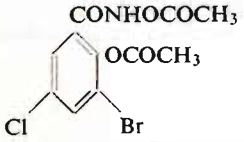
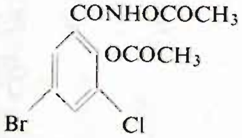
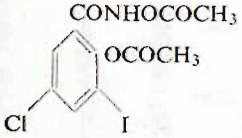
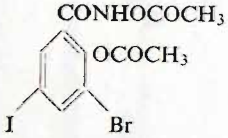
No.	Hydroxamic acid	Yield, %	M.p., °C	Analysis, %N		Aqueous 10% HCl hydrolyzate
				cal.	found	
6		80	159—160	6.11	5.72	 + ,,
7		82.5	180—181	6.64	6.58	 + ,,
8		66.7	105—106	622.	6.50	 + ,,
9		46	141—142	7.18	7.26	 + ,,

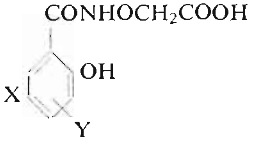
TABLE II

Diacetylated derivatives of salicylhydroxamic acid

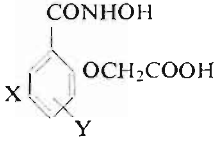
No.	Derivative	Yield, %	M.p., °C	Analysis, %							
				C		H		N		$COCH_3$	
				calc.	found	calc.	found	calc.	found	calc.	found
1		78	110.5—112	45.60	45.02	3.11	3.12	4.84	5.42	29.02	26.98
2		85.4	112 —113	39.52	39.05	2.67	2.63	4.19	4.56	25.75	24.34
3		75	148 —149	39.52	39.71	2.67	2.69	4.19	4.68	25.75	24.98
4		88	116 —117	37.66	37.88	2.57	2.75	3.99	3.95	24.54	26.26

Continued Table II

No.	Derivative	Yield, %	M.p., °C	Analysis, %							
				C		H		N		$COCH_3$	
				calc.	found	calc.	found	cal.	found	calc.	found
5		87	151	37.66	37.63	2.57	2.14	3.99	4.03	—	—
6		89	149	33.21	33.70	2.26	2.38	3.52	3.60	21.64	20.55
7		70	150.5—152	29.86	29.99	2.04	1.97	3.17	3.26	—	—



(I)



(II)

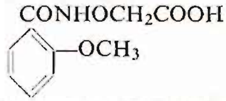
where X, Y=F, Cl, Br, I or H.

The hydrolysis was carried out with aqueous 10 per cent hydrochloric acid. The hydrolyzates were: salicylic acid or its halo-derivatives and O-hydroxylaminoacetic acid hydrochloride. If formula (II) were to be correct, the hydrolysis should afford hydroxylamine hydrochloride and a phenoxyacetic derivative of benzoic acid.

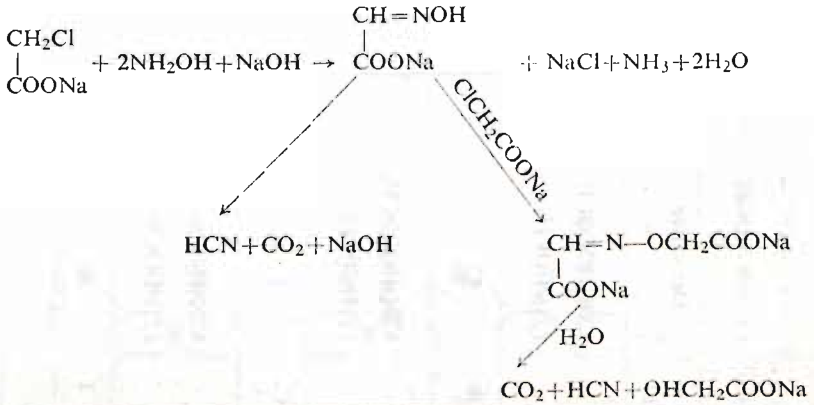
With *o*-methoxybenzhydroxamic acid as reactant, the product of the reaction could have the structure (I) only. The hydrolysis with dilute hydrochloric acid afforded *o*-methoxybenzoic acid and O-hydroxylaminoacetic acid hydrochloride. This fact is a further support for structure (I).

The salicylic acids obtained were identified by m.p. and equivalents, the latter being determined by titration with 0.1 N sodium hydroxide against phenolphthalein as indicator. O-hydroxylaminoacetic acid hydrochloride isolated upon hydrolysis had a m.p. of 156°C in agreement with the literature [5]. The properties of the hydroxamacetic acids obtained are listed in Table I.

Salicylhydroxamacetic acids give a colour reaction with ferric chloride. The colour is presumably produced by the phenolic group, because neither benzhydroxamacetic acid*) nor *o*-methoxybenzhydroxamacetic acid give the colour reaction with ferric chloride.



Carbon dioxide and hydrogen cyanide were found to evolve during the reaction of the hydroxamic acids with chloroacetic acid. The reaction is presumably accompanied by hydrolysis of the hydroxamic acids to corresponding carboxylic acids and hydroxylamine which, in turn, reacts with sodium chloroacetate to yield glyoxalic acid oxime; this, according to Hantzsch [2], undergoes decomposition in the presence of alkalis and yields carbon dioxide and hydrogen cyanide:



---

*) Kitagawa and Takani [3] claim their benzhydroxamacetic acid to give a colour reaction with ferric chloride. This is believed to be due to minute amounts of unreacted benzhydroxamic acid present in the product.

For verification of this hypothesis, hydroxylamine was made to react with sodium chloroacetate. Upon acidification of the mixture, carbon dioxide and hydrogen cyanide were found to evolve.

Of the various hydroxamic acids investigated, halogenosalicylhydroxamic acids were found to react most easily with chloroacetic acid. With unsubstituted salicylhydroxamic acids the reaction was slower and still more so with benzhydroxamic acid. Also the purity and uniformity of the reaction products decreases on passing from the dihalo-substituted derivatives to benzhydroxamic acid. This fact is presumably associated with the acid strength and related to the mobility of the hydroxamic group hydrogen. In this connection, *pK*-values of the hydroxamic acids were measured; they will be reported in a forthcoming communication.

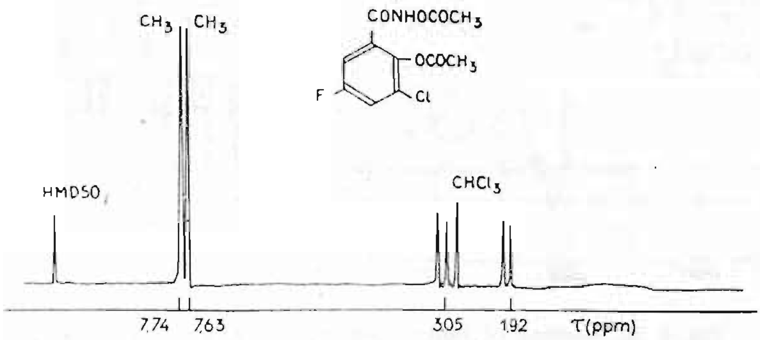


Fig. 1. NMR spectrum of diacetylated 3-chloro-5-fluorosalicylhydroxamic acid

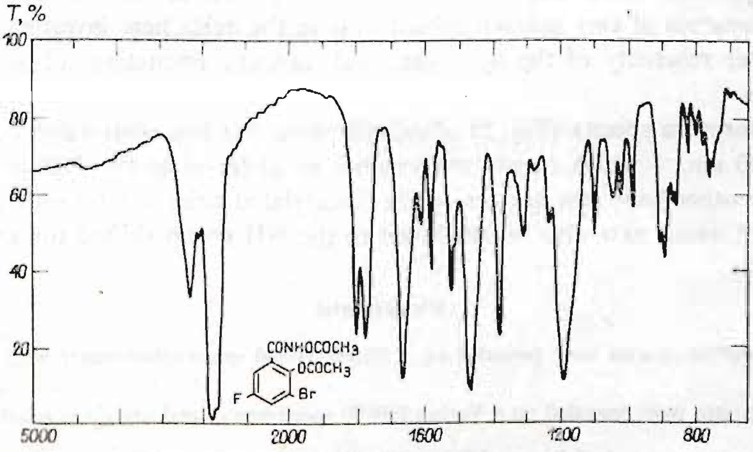


Fig. 2. IR spectrum of diacetylated 5-fluoro-3-bromosalicylhydroxamic acid

Attempted reactions of the hydroxamic acids with dichloro- and dibromoacetic acids were a failure. Nor was the acetylation of the salicylhydroxamacetic acids successful.

The dihalogenosalicylhydroxamic acids, viz., 3-chloro-5-fluoro-, 3-bromo-5-fluoro-, 4-fluoro-5-bromo-, 3-bromo-5-chloro-, 3-chloro-5-bromo-, 3-iodo-5-chloro-, and 3-bromo-5-iodo- were acetylated with acetic anhydride, and a number of diacetylated derivatives were obtained. Analytical and other data are listed in Table II. The structure of the diacetylated compounds was confirmed by NMR spectra. Two signals, $\tau = -7.74$ and -7.68 ppm, correspond to the double CH_3 group in the acetyl grouping. Then follows a signal characteristic of two protons of the benzene ring and a very diffuse signal $\tau = 1.5-0.5$ ppm attributable to the NH group proton (Fig. 1)

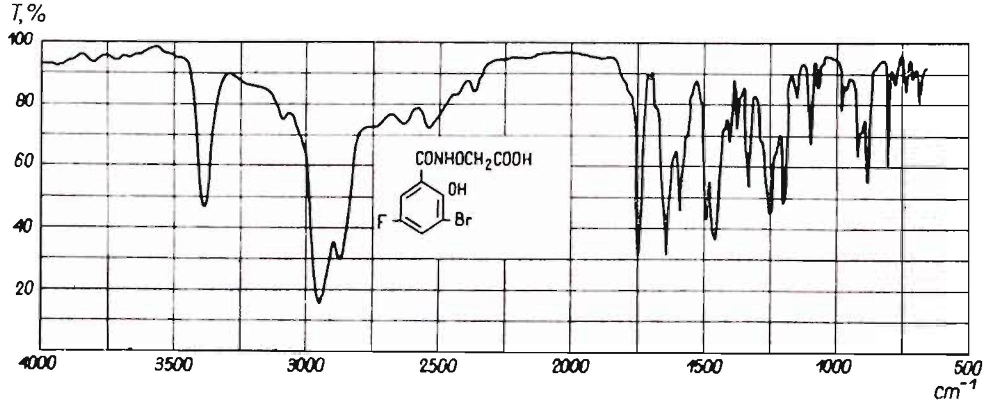


Fig. 3. IR spectrum of 3-bromo-5-fluorosalicylhydroxamacetic acid

Eckstein [6] acetylated salicylhydroxamic acid and bromomethyl-, and dibromo salicylhydroxamic acids and obtained monoacetylated derivatives. It is possible that the presence of two halogen substituents in the acids here investigated results in a greater reactivity of the hydrogen and favours formation of diacetylated derivatives.

IR absorption spectra (Fig. 3) of salicylhydroxamacetic acids exhibit a band at 3358—3340 cm.$^{-1}$ which should presumably be assigned to the NH group.

On the other hand, the spectra of the diacetylated acids exhibit only a band at 3150 cm.$^{-1}$ which may also be attributed to the NH group shifted towards longer wavelengths.

Experimental

IR absorption spectra were recorded on a Hilger H-800 spectrophotometer with a rock salt prism.

NMR spectra were recorded on a Varian HR-60 spectrometer and are given relative to TMS.

1. 3-Bromo-5-fluorosalicylhydroxamacetic acid

To a solution containing 2.5 g. (0.01 mole) 3-bromo-5-fluorosalicylhydroxamic acid and 0.8 g. (0.02 mole) sodium hydroxide in 50 ml. water, 1.9 g. chloroacetic acid dissolved in 50 ml. water containing 1 g. sodium hydroxide was added. The mixture was refluxed for 1 hr., cooled to room temperature, and acidified with diluted hydrochloric acid to precipitate 2.4 g. (73%) of 3-bromo-5-fluorosalicyl hydroxamacetic acid, m.p. 173—175°C upon recrystallization from water.

Other dihalogenosalicylhydroxamacetic acids were prepared in the same fashion.

2. Hydrolysis of 3-bromo-5-fluorohydroxamacetic acid

The acid was refluxed for about 2 hrs. with aqueous 10 per cent hydrochloric acid. The precipitate formed was filtered and identified as 3-bromo-5-fluorosalicylic acid, m.p. 232°—233°C. The filtrate was evaporated under reduced pressure to leave a crystalline O-hydroxylaminacetic acid hydrochloride m. about 115°C. After double recrystallization from water the hydrochloride melted at 147°—148°C (Analysis: N calc. 10.98; N found 11.12, 11.04%).

3. Reaction of chloroacetic acid with hydroxylamine

Hydroxylamine hydrochloride, 6.2 g., was refluxed 1 hr. with 9.5 g. chloroacetic acid in 100 ml. water containing 12 g. sodium hydroxide. Qualitative analyses confirmed the presence of carbon dioxide and hydrogen cyanide.

4. Acetylation of 3-bromo-5-chlorosalicylhydroxamic acid

The acid, 13.5 g. (0.05 mole), was dissolved in 15 ml. acetic anhydride and boiled for 5 min. on a glycerol bath. Then the mixture was cooled and a precipitate was formed; the mixture was shaken with 100 ml. distilled water to decompose unconverted acetic anhydride. The precipitate was filtered and washed thoroughly with distilled water to give 15.4 g. (88%) of the acetylated acid, m.p. 166.5°—167°C upon recrystallization from ethanol.

Other diacetylated hydroxamic acids were obtained in the same way.

INSTITUTE OF ORGANIC CHEMISTRY, POLISH ACADEMY OF SCIENCES
(INSTYTUT CHEMII ORGANICZNEJ, PAN)

REFERENCES

[1] M. Koch, Ber., **22** (1889), 3161.

[2] A. Hantzsch, H. Wild, Ann., **289** (1896), 285.

[3] M. Kitagawa, A. Takani, J. Agr. Chem. Soc. Japan No. 1077 (1935), 82; cf. Chem. Abstr., **30** (1936), 3409.

[4] H. Duda, A. Ostaszyński, T. Urbański, Bull. Acad. Polon., Sci., Sér. sci. chim., **13** (1965), 341.

[5] A. Werner, E. Sonnenfeld, Ber., **27** (1894), 3352.

[6] Z. Eckstein, Roczniki Chem., **28** (1954), 549.