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Halogenosalicylohydroxamic Acids. I. Dihalogenosalicylohydroxamic Acids

by

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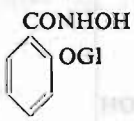
Presented by T. URBAŃSKI on March 8, 1965

Recent interest in salicylohydroxamic acid and its derivatives is due to their biological activity.

Salicylohydroxamic and 5-bromosalicylohydroxamic (BSH) acids have proved to be an effective fungicide [1] and an inhibitor of formation of strains resistant to isonicotinic acid hydrazide, [2] respectively. BSH inhibits also the action of coenzyme A, which is responsible for acetylation and thus deactivation *in vivo* of the hydrazide [3], [16]. Recently, BSH has been found to lower the cholesterol level in blood [4]. The phenol group-containing hydroxamic acids have been found [5] to undergo an *in vivo* detoxication owing to formation of glucuronides



(where Gl stands for the glucuronide residue).

Beside the BSH obtained by Urbański [6] and Eckstein [7], also other monohalogeno-substituted salicylohydroxamic acids, viz., 5-chloro- [8], 5- and 4-fluoro- [9] and 5-iodo- [10], are known. On the other hand, dihalogenosalicylohydroxamic acids are almost unknown (except for the 3,5-dichloro [8] and 3,5-dibromo-acids [11]). It was the purpose of the present paper to prepare the dihalogeno-acids and to investigate their biological activity.

The following dihalogeno-acids were obtained: 3-chloro-5-fluoro-, 3-bromo-5-fluoro-, 3-iodo-5-fluoro-, 4-fluoro-5-bromo-, 3-chloro-5-bromo, 3-bromo-5-chloro-, 3-iodo-5-chloro-, and 3-bromo-5-iodo- (Table I).

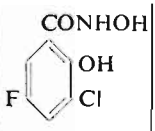
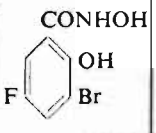
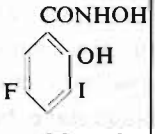
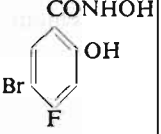
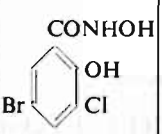
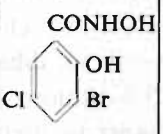
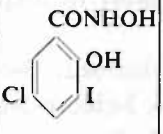
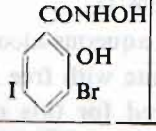
Hydroxamination was carried out in aqueous-alcoholic alkali solutions by treating a suitable methyl dihalogenosalicylate with free hydroxylamine.

The methyl dihalogenosalicylates required for this reaction were obtained by various methods depending on the halogen involved.

The 4- and 5-fluorine atoms were introduced by the Schiemann reaction of a suitable methyl aminosalicylate. The 5-iodine was introduced by decomposing a suitable diazonium salt with hydroiodic acid [12]. The second halogen was introduced into position 3 by treating methyl 5-halogenosalicylate with hydrogen halide in the presence of sodium chlorate as oxidant. Iodine was introduced into position 3 by boiling the suitable ester with iodine in methanol as solvent in the presence of freshly prepared silver oxide (AgO) [13].

TABLE I

Properties of the dihalogenosalicylohydroxamic acids

No.	Salicylohydroxamic acid	Formula	Yield, %	M.p., °C	Analysis, %			
					N		F	
					Calc.	Found	Calc.	Found
1	3-Chloro-5-fluoro-		87	158—9	6.81	6.80	9.24	9.95
2	3-Bromo-5-fluoro-		82	161—2	5.60	5.49	7.60	7.35
3	3-Iodo-5-fluoro-		61	143—4	4.71	4.94	6.40	6.43
4	4-Fluoro-5-bromo-		92	191—2	5.60	5.83	7.60	7.80
5	3-Chloro-5-bromo-		92.5	176—7	5.25	5.32	—	—
6	3-Bromo-5-chloro-		91.5	179	5.25	5.44	—	—
7	3-Iodo-5-chloro-		61	159—60	4.61	4.24	—	—
8	3-Bromo-5-iodo-		56	162—3	3.91	3.92	—	—

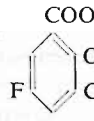
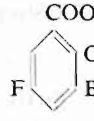
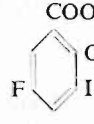
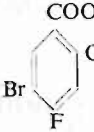
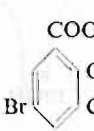
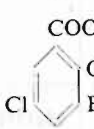
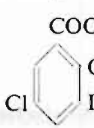
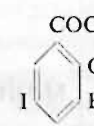
Except for Nos. 4 and 8 recrystallized from water — ethanol, all acids were recrystallized from water.

With ferric chloride, each hydroxamic acid turned intense cherry-red.

On hydrolysis with 1 per cent hydrochloric acid, the dihalogenosalicylohydroxamic acids yielded corresponding dihalogenosalicylic acids, hitherto unreported,

TABLE II

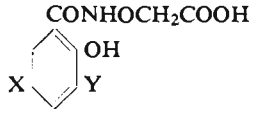
Properties of the dihalogenosalicylic acids

No.	Salicylic acid	Formula	M.p., °C	Recrystn. solvent	Mol. wt.		Analysis, F %	
					Cal.	Found	Calc.	Found
1	3-Chloro-5-fluoro-		220—1	H_2O	190.5	191.1	9.97	10.47
2	3-Bromo-5-fluoro-		233	H_2O	235	235.0	8.09	8.09
3	3-Iodo-5-fluoro-		233—4	H_2O	282	281.1	6.74	6.97
4	4-Fluoro-5-bromo-		206—7 [14] 208	dil. EtOH	235	235.5	8.09	7.97
5	3-Chloro-5-bromo-		220—1	dil. AcOH	251.5	251.1	—	—
6	3-Bromo-5-chloro-		231—2	dil. AcOH	251.5	250.7	—	—
7	3-Iodo-5-chloro-		223—4 [13]224	dil. AcOH	292	290.8	—	—
8	3-Bromo-5-iodo-		226—7	dil. AcOH	343	337.0	—	—

which with ferric chloride turned violet. Molecular weight of the salicylic acids was determined titrimetrically (0.1 N NaOH and phenolphthalein) (Table II).

Properties of the methyl esters used for preparing the corresponding salicylohydroxamic acids are given in Table III.

On treatment with sodium chloroacetate in alkaline solution, the dihalogenosalicylohydroxamic acids yielded derivatives of putative formula

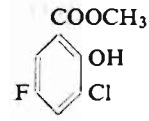
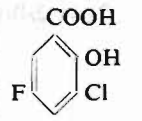
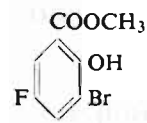
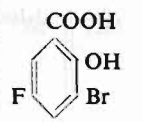
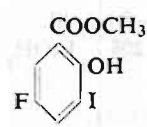
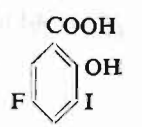
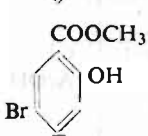
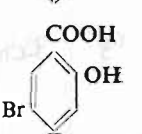
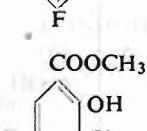
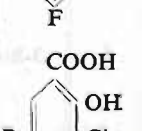
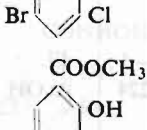
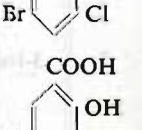
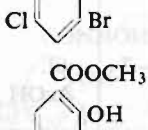
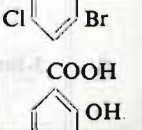
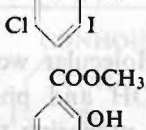
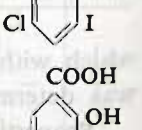


(X, Y — halogens).

Accurate determination of the structure of these acids and their properties will be reported in a separate paper.

TABLE III

Properties of the methyl dihalogenosalicylates

No.	Methyl salicylate	Formula	M.p., °C	Crystn. solvent	Analysis, F %		Hydrolyzate
					Calc.	Found	
1	3-Chloro-5-fluoro-		88—9	EtOH—H_2O	9.29	9.7	
2	3-Bromo-5-fluoro-		92	Acetone—H_2O	7.63	7.69	
3	3-Iodo-5-fluoro-		83—4	MeOH	6.42	6.35	
4	4-Fluoro-5-bromo-		69—70	EtOH	7.63	7.94	
5	3-Chloro-5-bromo-		151—3	MeOH	—	—	
6	3-Bromo-5-chloro-		140	MeOH	—	—	
7	3-Iodo-5-chloro-		131—2 [13] 129—30	MeOH	—	—	
8	3-Bromo-5-iodo-		141—2	Acetone—H_2O	—	—	

All the hydroxamic acids obtained and certain derivatives will be tested for biological activity at the Frank Horner Ltd. Research Centre, Canada.

As far as IR spectra are concerned, the monohalogeno- differ from the dihalogeno-acids in that the latter produce a 3400—3380 cm.$^{-1}$ band as illustrated by the spectra of 5-fluoro- and 5-fluoro-3-bromosalicylohydroxamic acids.

Comparison of the IR spectra of the substituted salicylohydroxamic acids will be the subject of another paper.

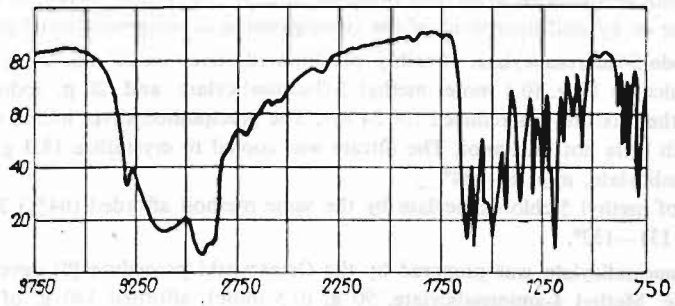


Fig. 1. IR absorption curve of 5-fluorosalicylohydroxamic acid

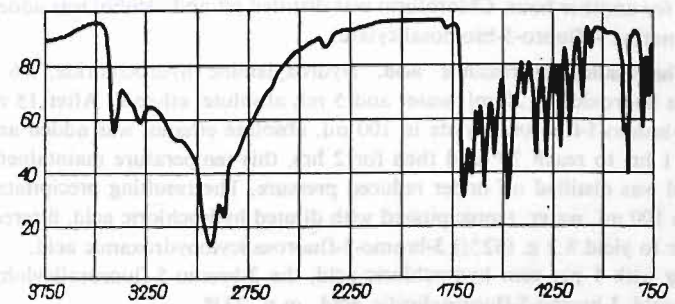


Fig. 2. IR absorption curve of 3-bromo-5-fluorosalicylohydroxamic acid

Experimental

Methyl 5-fluorosalicylate was prepared by the Schiemann method: 90 g. (0.54 mole methyl) 5-aminosalicylate gave 133 g. (92%) of the fluoborate complex, which was thermolyzed to yield 35 g. (38.2%) pure methyl 5-fluorosalicylate b. 133—135°/38 mm.

Methyl 3-chloro-5-fluorosalicylate. Methyl 5-fluorosalicylate, 34 g. (0.2 mole), was dissolved in 50 ml. acetic acid and 50 ml. aqueous 35 per cent hydrochloric acid was added. The mixture was heated to 60° and 7 g. aqueous sodium chlorate was added dropwise at 70°. The mixture was heated for 1 hr. at 70—75°, cooled and poured into water to yield 39 g. (85%) methyl 3-chloro-5-fluorosalicylate, m.p. 88—89°.

By the same method, methyl 5-chlorosalicylate (89%, m.p. 48°) [15] and methyl 3-chloro-5-bromosalicylate (94.5%, m.p. 151—153°) were obtained from methyl salicylate and methyl 5-bromosalicylate, respectively.

With hydrochloric acid replaced by 40 per cent hydrobromic acid, methyl 3-bromo-5-fluorosalicylate (98.5% m.p. 92°), methyl 3-bromo-5-chlorosalicylate (90%, m.p. 140°) and methyl 3-bromo-5-chlorosalicylate (92.5%, m.p. 141—142°) were prepared from methyl 5-fluoro-salicylate, methyl 5-chlorosalicylate and methyl 5-iodosalicylate, respectively.

Methyl 5-bromosalicylate and **methyl 5-iodosalicylate** were prepared by the Eckstein [7] and the Hübner procedures [12], respectively.

3-Chloro-5-fluorosalicylic acid was prepared by hydrolysis of methyl 3-chloro-5-fluorosalicylate with 10 per cent sodium hydroxide. The product was "salted-out" with diluted hydrochloric acid and recrystallized from water; m.p. 220—221°.

All other dihalogenosalicylic acids were prepared either by alkaline hydrolysis of the corresponding methyl esters or by acid hydrolysis of the corresponding dihalogenosalicylohydroxamic acids.

Methyl 3-iodo-5-fluorosalicylate. Freshly precipitated silver oxide (aq. 20 g. $AgNO_3$+5 g. NaOH) was added to 17 g. (0.1 mole) methyl 5-fluorosalicylate and 20 g. iodine in methanol as solvent and the mixture was refluxed for 24 hrs. The precipitated silver iodide was filtered hot and washed with little hot methanol. The filtrate was cooled to crystallize 18.3 g. (62%) methyl 3-iodo-5-fluorosalicylate, m.p. 83—84°.

Iodination of methyl 5-chlorosalicylate by the same method afforded (64%) 3-iodo-5-chlorosalicylate, m.p. 131—132°.

Methyl 4-fluorosalicylate was prepared by the Ostaszyński procedure [9] developed for ethyl 4-fluorosalicylate. Methyl 4-aminosalicylate, 90 g. (0.5 mole), afforded 140 g. of the fluoborate complex, which on thermolysis yielded 38 g. (44.7%) methyl 4-fluorosalicylate, b.p. 93°/10 mm.

Methyl 4-fluoro-5-bromosalicylate. Bromine, 16 g. in 5 ml. dry chloroform added dropwise to 17 g. (0.1 mole) methyl 4-fluorosalicylate in 20 ml. dry chloroform at 15—20°; the temperature was maintained for another hour. Chloroform was distilled off and alcohol was added to precipitate 19 g. (76.3%) methyl 4-fluoro-5-bromosalicylate.

3-Bromo-5-fluorosalicylohydroxamic acid. Hydroxylamine hydrochloride, 3.6 g., was added to 3.5 g. sodium hydroxide in 20 ml. water and 5 ml. absolute ethanol. After 15 min. 10 g. (0.04 mole) methyl 3-bromo-5-fluorosalicylate in 100 ml. absolute ethanol was added and the mixture was heated for 1 hr. to reach 70° and then for 2 hrs. this temperature maintained with constant stirring. Ethanol was distilled off under reduced pressure. The resulting precipitate was triturated thoroughly with 100 ml. water, reprecipitated with diluted hydrochloric acid, filtered and recrystallized from water to yield 8.2 g. (82%) 3-bromo-5-fluorosalicylohydroxamic acid.

On refluxing with 1 per cent hydrochloric acid, the 3-bromo-5-fluorosalicylohydroxamic acid hydrolyzed to yield 3-bromo-5-fluorosalicylic acid, m.p. 233°.

All dihalogenosalicylohydroxamic acids obtained in the present work were prepared according to the above-described procedure.

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REFERENCES

[1] T. Chęciński, R. Dąbkowski, Lancet, (1961) I, 1352.

[2] S. Hornung et al., Brit. J. Tuberc. Dis. Chest, (1958), 19.

[3] W. Johnson, E. Mankiewicz, R. Jasmin, G. Corte, Am. Rev. Respirat. Diseases, **84** (1961), 872.

[4] W. M. McIsaac, R. T. Williams, Biochem. J., **66** (1957), 369.

[5] A. Czyżyk, T. Urbański, Nature, **197** (1963), 381.

[6] T. Urbański, W. Lewenstein, Roczniki Chem., **26** (1952), 565.

[7] Z. Eckstein, Z. Dominiak, ibid., **28** (1954), 139.

[8] Ng. Ph. Buu-hoi, Ng. D. Xuong, Ng. H. Nam, Compt. rend. **236** (1953), 635.
[9] A. Ostaszyński, Z. Olszenko-Piontkowa, T. Urbański, Bull. Acad. Polon. Sci., Sér. sci. chim., **8** (1960), 591.
[10] A. Ostaszyński, T. Urbański, [in preparation].
[11] C. Musante, Gazz. chim. ital., **78** (1948), 536 (Chem. Abstr. **43** (1949), 2116).
[12] H. Hübner, Ber., **12** (1879), 1347.
[13] E. F. Smith, E. B. Knerr, Am. Chem. J., **8** (1886), 95.
[14] O. Danek, Collection, **29** (1964), 730.
[15] L. Varnholt, J. prakt. Chem., (2) **36** (1887), 21; Beilstein, 10, 103.
[16] S. Hornung et al., Acta Tuberc. Pneum. Scand., **42** (1962), 233.