BULLETIN DE L'ACADÉMIE
POLONAISE DES SCIENCES
Série des sciences chimiques
Volume VIII, No. 10, 1960

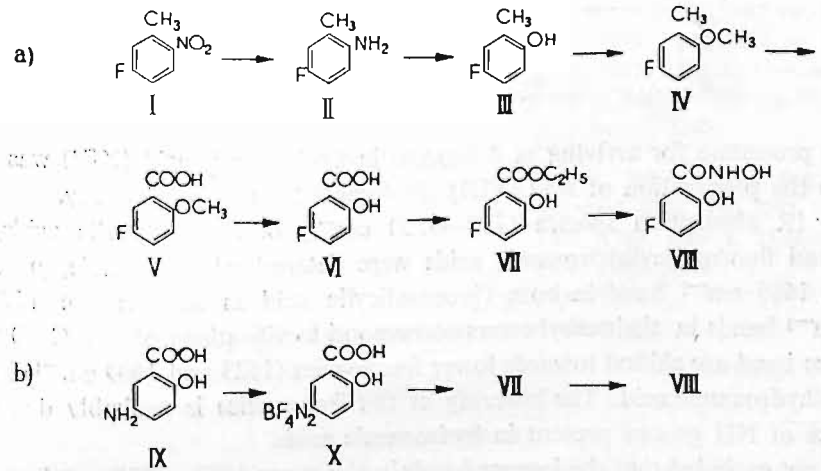
On Fluorosalicylhydroxamic Acids

by

A. OSTASZYŃSKI, Z. OLSZENKO-PIONTKOWA and T. URBAŃSKI

Presented by T. URBAŃSKI on August 24, 1960

Some derivatives of salicylhydroxamic acids have found application as drugs. Their use as antituberculous agents has been suggested by Urbański [1]. Among a series of tested compounds the preparation T40, i.e. 5-bromosalicylhydroxamic acid [2]—[5], proved to be the most active. In the light of the above facts it was interesting to establish what properties would be found in fluorine substituted derivatives, i.e. 5-fluorosalicylhydroxamic acid and 4-fluorosalicylhydroxamic acid, especially as Buu-Hoï and associates [6], [7] have worked out the synthesis of aromatic fluorine compounds (among these 5-fluorosalicylic acid hydrazide), anticipating their tuberculostatic properties.



5-fluorosalicylic acid has been prepared by Suter and Weston [8] from 2-ethoxy-5-fluorophenylmagnesium bromide while 4-fluorosalicylic acid was prepared by Hodgson and Nixon [9], from *m*-fluorophenol, *via* 4-fluorosalicylic aldehyde.

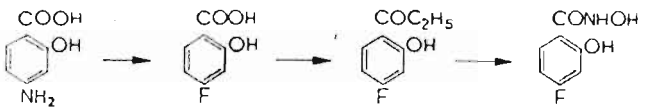
In our conditions it seemed easier to obtain 5-fluorosalicylhydroxamic acid starting from 5-aminosalicylic acid. Difficulties connected with fluorine introduction

by the Schiemann process imposed nevertheless the necessity of searching parallelly for another method. In this respect endeavours have also been made to prepare 5-fluorosalicylhydroxamic acid starting from *m*-fluorotoluene. The following formulations include the successive steps of both processes.

2-Nitro-5-fluorotoluene (I) was obtained from *m*-fluorotoluene. Compound (I) was reduced to 2-amino-5-fluorotoluene (II); the latter, *via* a diazonium compound, supplied 2-hydroxy-5-fluorotoluene (III), producing 2-methoxy-5-fluorotoluene (IV). Oxidation of compound (IV) yielded 2-methoxy-5-fluorobenzoic acid (V). From the acid (V) 5-fluorosalicylic acid (VI) was obtained, affording ethyl 5-fluorosalicylate (VII). Treatment of compound (VII) with free hydroxylamine led to 5-fluorosalicylhydroxamic acid as sodium salt.

Difficulties in obtaining the acid (VI) from 5-aminosalicylic acid (IX) consisted principally in obtaining and decomposing 3-carboxy-4-hydroxydiazonium fluoroborate (X). It was only possible to prepare (X) by employing critical reaction conditions. These consisted in using fluoroboric acid of ca. 50 per cent concentration, hot diazotizing and fluoroborate (X) decomposition by resultant acid (VI) sublimation. The latter (VI) differs from other compounds of this type, which are liquid at the decomposition temperature of fluoroborates. Further synthesis steps are identical with those described earlier.

Considering the smaller number of steps and the availability of the basic product, we resolved to obtain 4-fluorosalicylhydroxamic acid similarly as acid (VIII), as follows:



XI XII XIII XIV

The procedure for arriving at 4-fluorosalicylhydroxamic acid (XIV) was analogical to the preparation of acid (VIII). Biological tests are under way.

The IR absorption spectra (750—3750 cm^{-1}) of fluorosalicylic acids, their esters and fluorosalicylhydroxamic acids were determined. (see Table, p. 593)

The 1665 cm^{-1} band in both fluorosalicylic acid as well as the 1670 and 1676 cm^{-1} bands in their ethyl esters correspond to vibrations of the C=0 group.

These band are shifted towards lower frequencies (1623 and 1609 cm^{-1}) in fluorosalicylhydroxamic acid. The lowering of the frequencies is probably due to the influence of NH groups present in hydroxamic acids.

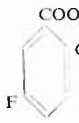
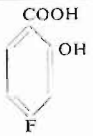
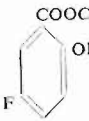
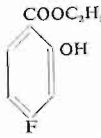
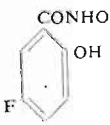
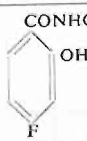
It is not excluded that the intense bands in the range 1207—1250 cm^{-1} occurring in these acids and their esters might also be ascribed to vibrations of the C=O group.

In fluorosalicylhydroxamic acis the bands 3280 and 3290 cm^{-1} occur, produced by the vibrations of the NH group linked with C=O.

The spectra were determined in paraffin oil mulls in a Hilger H-800 spectrophotometer with an NaCl prism (except the esters occurring in liquid form).

The examination in detail of the IR adsorption spectra of the halogen derivatives of salicylhydroxamic acid will constitute the subject of a further communication.

TABLE

No.	Compound	Structural formula	Bands
1	4-fluorosalicylic acid		760, 793, 820, 873, 934, 1066, 1123, 1217 vs, 1250, 1297, 1585, 1623, 1665 s, 1987 vw, 2644 w, 3071, 3250, 3424.
2	5-fluorosalicylic acid		778, 797 vw, 820 vw, 859, 887 w, 976, 1085 w, 1132, 1165 w, 1175, 1207, 1250 s, 1594, 1618, 1665 s, 2533, 3250.
3	ethyl ester of 4-fluorosalicylic acid		679, 698, 788, 830, 887 w, 943 w, 1016, 1208 vs, 1250, 1278, 1620, 1676 s, 3203 broad.
4	ethyl ester of 5-fluorosalicylic acid		774 s, 859, 976, 1016, 1090, 1132 s, 1156, 1227 s, 1259 vs, 1292, 1605, 1670 s, 3085 broad.
5	4-fluorosalicylhydroxamic acid		773, 821, 849, 877, 962 vw, 1052, 1085, 1094, 1142, 1184 vs, 1212, 1255, 1292, 1500 s, 1519 broad, 1585 vs, 1623 s, 1882 vw, 2321 w, 3113 broad, 3290.
6	5-fluorosalicylhydroxamic acid		736 w, 783 vw, 826, 849, 896, 986, 1012, 1099, 1156, 1212, 1264 s, 1307, 1580, 1609 s, 2330, 2552, 2651, 2693, 3280.

Legend: w — weak, vw — very weak, s — strong, vs — very strong

Experimental

2-nitro-5-fluorotoluene (I)

The compound (I) was obtained by nitration of *m*-fluorotoluene, as described in literature [11].

2-amino-5-fluorotoluene (II)

was obtained by 2-nitro-5-fluorotoluene reduction, as described in literature [11], [12].

2-hydroxy-5-fluorotoluene (III)

80 g of compound (II) were dissolved in diluted sulphuric acid (200 ml acid in 700 ml water). To the above solution 40 g sodium nitrite dissolved in 80 ml water were added dropwise. The diazonium solution was poured dropwise into a flask containing boiling water and provided with

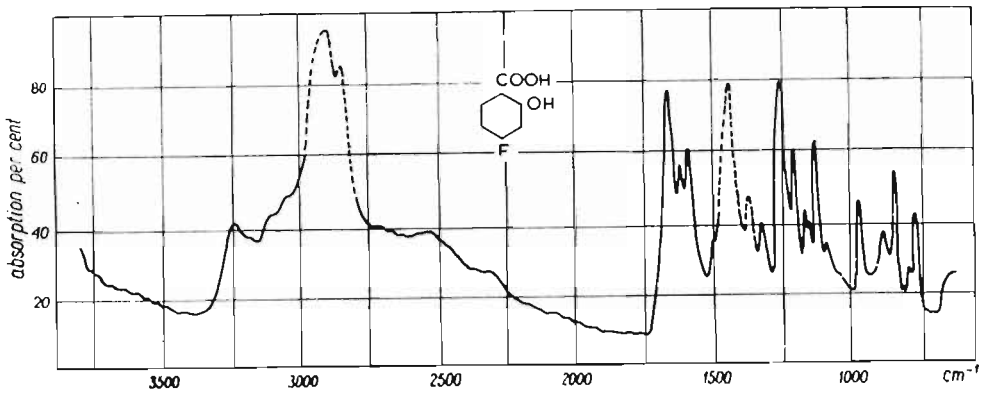


Fig. 1. Infrared absorption spectrum of 4-fluorosalicylic acid

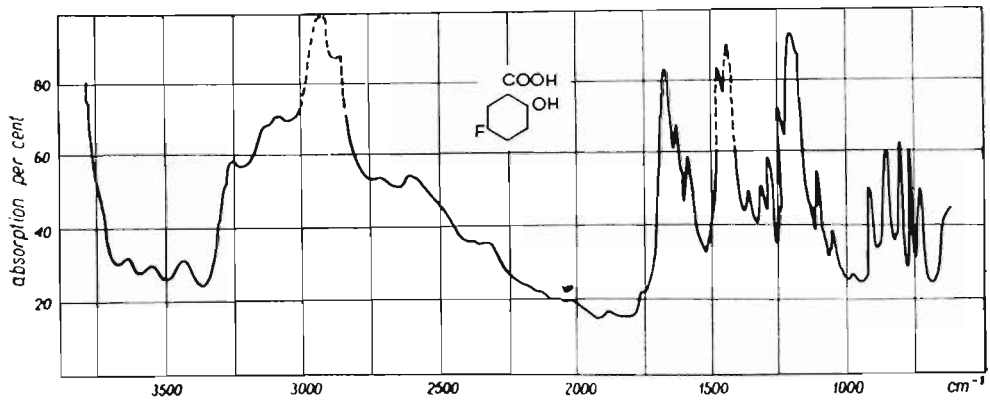


Fig. 2. Infrared absorption spectrum of 5-fluorosalicylic acid

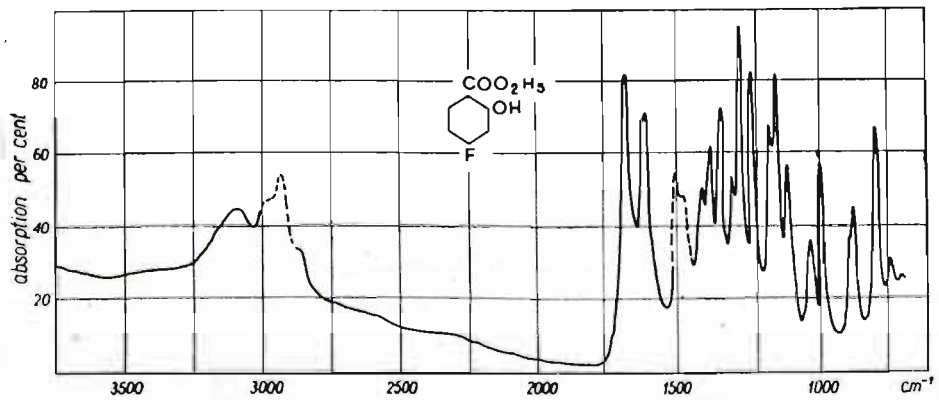


Fig. 3. Infrared absorption spectrum of ethyl 4-fluorosalicylate

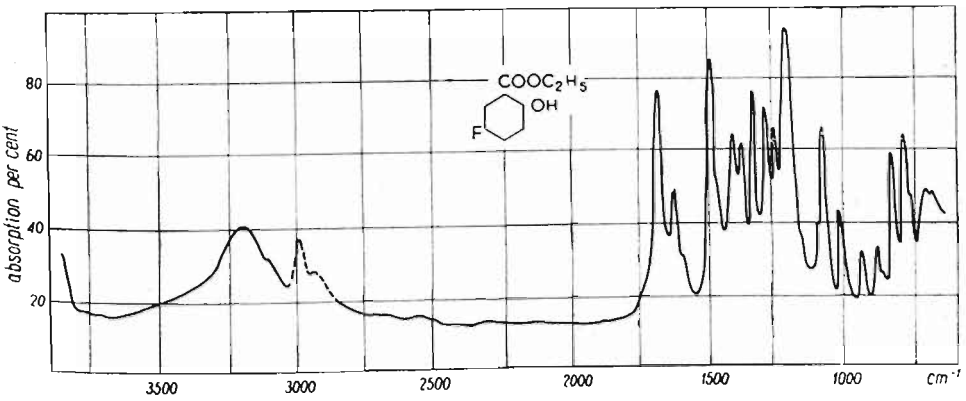


Fig. 4. Infrared absorption spectrum of ethyl 5-fluorosalicylate

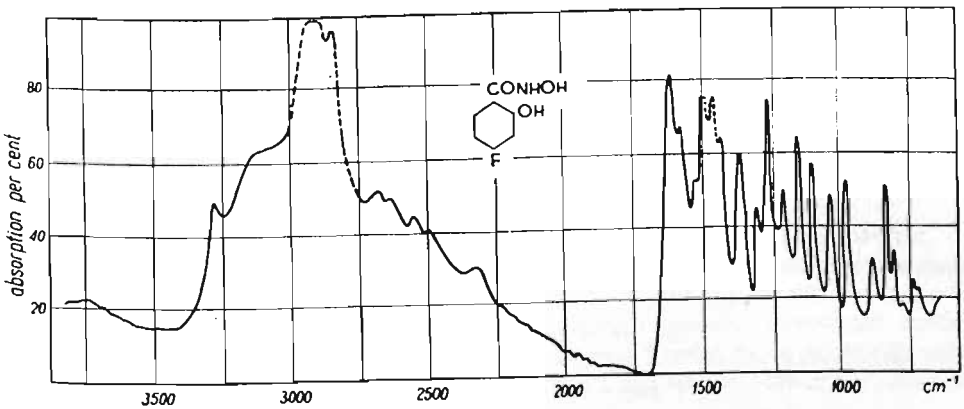


Fig. 5. Infrared absorption spectrum of 4-fluorosalicylhydroxamic acid

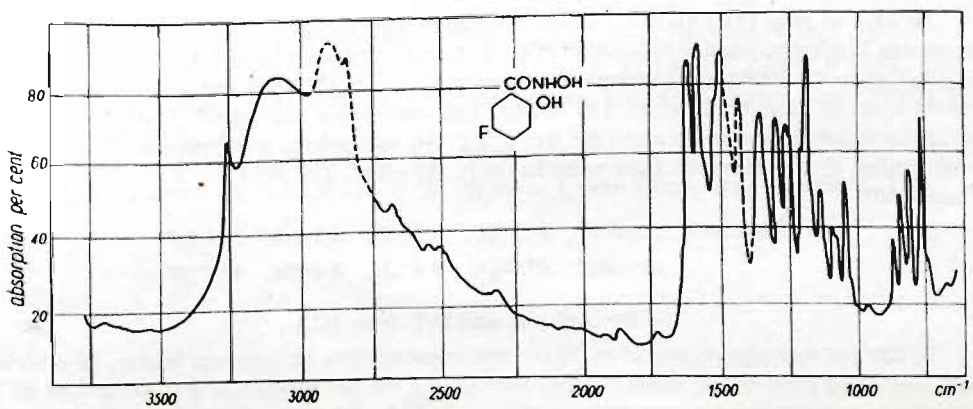


Fig. 6. Infrared absorption spectrum of 5-fluorosalicylhydroxamic acid

steam supply. Distillation was regularly accompanied by precipitation of tarry products. The distillate was salted out, extracted with ether, dried and distilled under reduced pressure. The yield was 23 g of compound (III) (26 per cent of theoretical), b. p. 90—93°,/17—19 mm Hg, m.p. 32—33°, melting point, as per literature data [13], [14].

2-Methoxy-5-fluorotoluene (IV)

To 25.6 g of compound (IV) 24.5 g of dimethyl sulphate was added. Then 7.7 g sodium hydroxide dissolved in 30 ml water was poured in by small portions and the temperature was slowly raised to boiling point. Cooling was followed by ether extraction, drying and distillating under reduced pressure to yield 23 g of compound (IV) (86 per cent of theoretical), b.p. 69—70°/4 mm Hg as per literature data [14].

2-Methoxy-5-fluorobenzoic acid (V)

10 g of acid (IV) were oxidized with 35 g of potassium hypermanganate (saturated solution), slowly added, with constant stirring at water bath boiling temperature. The solution was heated for two hours, stirring constantly, and excess of permanganate was discoloured with formaldehyde. Precipitated manganese dioxide was filtered off and washed with boiling water. The acid (V), of m.p. 82—83°, was precipitated from the concentrated filtrate. The yield was 1.8 g (15 per cent of theoretical). The acid (V) crystallized from water melts at a temperature 4 degrees lower as compared with acid (V) crystallized from ligroin [15].

5-Fluorosalicylic acid (VI)

10 g of compound (V) was boiled for ten hours with 100 ml hydrogen iodide of d 1.7. The precipitate was filtered off. The water crystallized product melts at 179—180°. 8 g of acid (VI) was obtained (87 per cent of theoretical).

Ethyl 5-fluorosalicylate (VII)

A mixture of 10 g acid (VI), 60 g abs. alcohol and 4.9 g sulphuric acid was heated for eight hours under reflux. Then excess alcohol was distilled off under reduced pressure. The unreacted acid (VI) was filtered off and the filtrate washed with water and neutralized with saturated sodium bicarbonate solution. Carbon tetrachloride was added for better layer separation. After distillation under reduced pressure 5.1 g of compound (VII) was obtained (42 per cent of theoretical). b.p. 145—147°/60 mm Hg.

$C_9H_9FO_3$ required: 58.7%C, 4.9%H,
obtained: 58.3%C, 4.5%H

5-Fluorosalicylhydroxamic acid (VIII)

To 15 g of ester (VII) alcohol alkaline solution of free hydroxylamine was added (obtained by mixing 10 g hydroxylamine hydrochloride alcoholic saturated solution with 4.5 g metallic sodium in ethyl alcohol solution and filtering off the resultant sodium chloride) and the mixture was left for 48 hours at room temperature. The isolated hydroxamic acid sodium salt (VIII) was filtered off. After dissolving the salt in water the free acid (VIII) was isolated with hydrochloric acid. The acid purified by crystallization from water has m.p. 189—190°. The yield was 5 g (35 per cent of theoretical).

For $C_7H_6FNO_3$ required: 49.1%C, 3.5%H, 8.2%N, 11.1%F
obtained: 49.0%C, 3.4%H, 8.4%N, 10.9%F

5-Fluorosalicylic acid (VI) from (IX)

To 200 g of hydrofluoric acid of ca. 70 per cent concentration, in a copper beaker, 78 g boric acid was added portionwise, under constant stirring. To the hot solution 51 g of compound (IX) was added. After obtaining a homogeneous mixture, 23 g of solid sodium nitrite was added by small portions. The filtered off fluoroborate precipitate after washing with water and alcohol and air

drying, had a m.p. 160—162° (with decomposition). The thermal decomposition of dried fluoroborate was performed in small portions in a funnel-covered copper beaker. The acid (VI) collected from the funnel walls was crystallized from water. The yield was 5.6 g (11 per cent of theoretical), b.p. 179—180° corresponds to literature data. The melting point of the mixture with a sample of acid (VI) obtained from compound (V) shows no depression.

4-Fluorosalicylic acid (XII)

The acid (XII) was obtained from 4-aminosalicylic acid (XI) in an identical way as acid (VI) from compound (IX). The product, several times purified by crystallization from water, has a m.p. 192—193°, i.e. 5 degrees higher than that given in literature [9].

Ethyl 4-fluorosalicylate (XIII)

The ester of acid (XIII) was obtained as ester (VII); b.p. 145°/50 mm Hg.

For $C_9H_9FO_3$ required: 58.7%C, 4.9%H,
obtained: 58.3%C, 4.5%H,

4-Fluorosalicylhydroxamic acid (XIV)

Hydroxamation of ester (XIII) was carried out analogically to that of ester (VII), except that it lasted longer, i.e. seven days instead of two. The free acid (IV) has a m.p. is 186—187° with decomposition.

$C_7H_6NFO_3$ required: 49.1%C, 3.5%H, 8.2%N, 11.1%F,
obtained: 50.0%C, 3.4%H, 8.3%N, 10.9%F.

INSTITUTE OF ORGANIC SYNTHESIS, POLISH ACADEMY OF SCIENCES
(ZAKŁAD SYNTEZY ORGANICZNEJ, PAN)

REFERENCES

[1] T. Urbański, Nature, **166** (1950), 267; Gruźlica, **18** (1950), 206.
[2] T. Urbański, W. Lewenstein, Roczn. Chem., **26** (1952), 565.
[3] S. Hornung et al., British J. Tuberculosis, **52** (1958), 19.
[4] J. M. Robson, R. Knox, R. W. Ridell, E. M. Bavin, Lancet, (1958), 746.
[5] Z. Eckstein, Z. Dominiak, Roczn. Chem., **28** (1954), 139.
[6] Ng. Ph. Buu-Hoï, D. Levit, Ng. D. Xuong, J. Org. Chem., **19** (1954), 1617.
[7] Ng. Ph. Buu-Hoï, Ng. D. Xuong, D. Levit, J. Org. Chem., **18** (1953), 910.
[8] C. M. Suter, A. W. Weston, J. Am. Chem. Soc., **61** (1939), 2317.
[9] H. H. Hodgson, J. Nixon, J. Chem. Soc., (1929), 1932.
[10] G. C. Finger, F. H. Reed, J. Am. Chem. Soc., **66** (1944), 1972.
[11] A. Ostaszyński, Bull. Soc. Sci. et Lettres Łódź, Classe III, **3** (1952), No. 15.
[12] N. M. Löfgren, B. J. Lundqvist, S. Lindström, Acta Chem. Scand., **9** (1955), 1079.
[13] G. C. Finger, F. H. Reed, L. R. Tehon, Illinois State Geol. Survey, Circ., **199** (1955), 15; C.A., **50** (1956), 9312.
[14] S. Hunnig, W. Daum, Ann., **595** (1955), 131.
[15] H. Gilman, W. Langham, F. W. Moore, J. Am. Chem. Soc., **62** (1940), 2327.