Summary

1. The viscosity of pectin sols as affected by the addition of various electrolytes has been determined.

2. Three separate effects are present with increasing electrolyte concentrations: (a) An increase in viscosity at low electrolyte concentration, when an alkaline substance is added. This is due to the formation of the more highly ionized pectin salt from the pectin acid. (b) A decrease in viscosity to a minimum, further increase in electrolyte concentration having no apparent effect on the pectin. The formation of practically uncharged, undissociated salts of pectin is suggested, causing dehydration, and thus decreased viscosity. (c) Increase in viscosity at high salt concentration, due to interaction of the added electrolyte and water; an increase greater than this being due, in part at least, to the increased concentration of pectin with respect to water alone.

3. Any increase in viscosity which could be ascribed to reversal of charge on addition of excess electrolyte is either absent or very small.

4. The viscosities of solutions of pectin and of truly soluble electrolytes change in similar manner with increasing electrolyte concentration.

HONOLULU, T. H. RECEIVED MARCH 20, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation of Acetyl-5-fluorosalicylic Acid

BY C. M. SUTER AND ARTHUR W. WESTON[1]

As a part of a program of preparing various aromatic fluorine compounds[2] for the purpose of determining their pharmacological properties, it has seemed of interest to synthesize 5-fluorosalicylic acid and its acetyl derivative (fluoroaspirin). 4-Fluorosalicylic acid (4-fluoro-2-hydroxybenzoic acid) was prepared some time ago by Hodgson and Nixon[3] but its physiological properties were not investigated.

5-Fluorosalicylic acid was prepared by carbonation of the Grignard reagent obtained from 2-bromo-4-fluorophenetole,[2] followed by deëthylation of the ethoxy acid by hydriodic acid. It was noted by Hodgson and Nixon[3] that while 4-methoxy-2-fluorobenzoic acid could not be demethylated, the 2-methoxy-4-fluoro isomer reacted readily with hydrogen iodide. It is evident from the behavior of 5-fluoro-2-ethoxybenzoic acid that the position of the fluorine has little effect upon the ease of dealkylation when the alkoxy group is ortho to carboxyl.

Preliminary data obtained in a comparison of the toxicity of the 5-fluorosalicylic acid and its acetyl derivative with the fluorine-free compounds[4] using white mice as test animals show that 5-fluorosalicylic acid is approximately twice as toxic as salicylic acid while the acetylfluoro acid is about 50% more toxic than aspirin. Although it has been reported[5] that 5-bromosalicylic acid is twice as effective against several types of bacteria as the chlorine compound, no experiments on animal toxicity have been carried out. 5-Chlorosalicylic acid has the same germicidal action as salicylic acid.

Experimental

2-Ethoxy-5-fluorobenzoic Acid.—A Grignard reagent was prepared using ethyl bromide as a starter from 35 g. (0.16 mole) of 2-bromo-4-fluorophenetole and 4 g. (0.17 mole) of magnesium and the ether solution dropped with stirring into a beaker containing 40 g. of crushed dry ice. After the excess carbon dioxide had evaporated, ice and dilute hydrochloric acid were added, the ether layer separated and the water again extracted with ether. The combined portions of ether were extracted several times with 10% sodium bicarbonate and the latter acidified. There resulted 19 g., a 64.5% yield, of a slightly yellow solid which after crystallization from dilute alcohol or a mixture of benzene and petroleum ether melted at 65.5–66.5°. The acid is soluble in benzene, alcohol, acetic acid and slightly soluble in carbon tetrachloride.

Anal. Calcd. for $C_9H_9O_3F$: neut. equiv., 184.1. Found: neut. equiv., 184.6.

5-Fluorosalicylic Acid.—The ethoxy compound was deëthylated by refluxing 17 g. with 150 ml. of hydriodic acid (d. 1.7) for ten hours. The white solid which separated as the reaction proceeded was filtered off on a sintered glass funnel. Dilution of the filtrate with water and extraction with ether gave only a little more product. 5-Fluoro-2-hydroxybenzoic acid crystallizes from water in fine white needles which melt at 178.5–179.5°. It is

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[1] Sharp and Dohme Post-doctorate Fellow, 1938–1939.

[2] Suter, Lawson and Smith, THIS JOURNAL, **61**, 161 (1939).

[3] Hodgson and Nixon, *J. Chem. Soc.*, 1632 (1929).

[4] We are indebted to Dr. Maurice L. Moore, Research Laboratories of Sharp and Dohme, for these results.

[5] Rochaix and Pinet, *Bull. sci. pharmacol.*, **34**, 486 (1927).

soluble in ether and alcohol. The yield was 12.5 g. or 87% of the theoretical amount. A purple-violet color was obtained with ferric chloride solution. The methyl ester has the "oil of wintergreen" odor.

Anal. Calcd. for $C_7H_5O_3F$: neut. equiv., 156. Found: neut. equiv., 157.4.

Acetyl-5-fluorosalicylic Acid.—Acetylation was effected by warming 4.5 g. of the hydroxy acid with 10 ml. of acetic anhydride and a few drops of sulfuric acid. After cooling the mixture, adding 100 ml. of water, and filtering there was obtained 3.2 g. (56% yield) of product which crystallized from benzene as fine needles melting at 130–131° which gave no ferric chloride color test. The compound is soluble in alcohol, ether, hot benzene and insoluble in ligroin.

Anal. Calcd. for $C_9H_7O_4F$: neut. equiv., 198.1. Found: neut. equiv., 198.4.

Summary

5-Fluorosalicyclic acid and its acetyl derivative have been prepared. These are more toxic than the unfluorinated compounds.

EVANSTON, ILL. RECEIVED APRIL 24, 1939

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

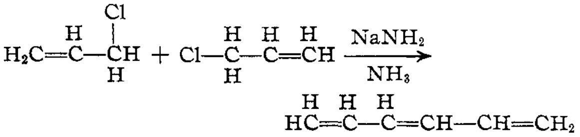
Syntheses of Polyenes. I. Hexatriene and its Polymers

BY M. S. KHARASCH AND E. STERNFELD[1]

Introduction

In the course of an investigation on highly unsaturated compounds containing conjugated systems, the need of a simple and efficient method of synthesis became apparent. The general method now in use (the reduction of unsaturated carbonyl compounds to pinacols, replacement of the hydroxyl groups by halogens, and elimination of the halogens by zinc) necessitates the use of large quantities of materials, involves difficult experimental procedures, and usually the over-all yield of the polyene is poor.

Preparation of Hexatriene and its Polymers.—Ordinarily, when organic halides are treated with bases, halogen acids are eliminated and ethylene derivatives are formed. In certain cases, however, two molecules of the halide condense in the course of the reaction to form an unsaturated dimer. Specifically, 9-fluorenyl bromide reacts with potassium hydroxide in acetone solution to yield bifluorenylidene.[2] In our laboratory sodamide in liquid ammonia has been used successfully as a condensing agent. The equation below represents the reaction of allyl chloride with sodamide in liquid ammonia.



$$H_2C{=}\overset{H}{C}{-}\underset{H}{\overset{\overset{Cl}{|}}{C}}H + Cl{-}\underset{H}{\overset{H}{C}}{-}\overset{H}{C}{=}CH \xrightarrow[NH_3]{NaNH_2} \overset{H}{HC}{=}\overset{H}{C}{-}\overset{H}{C}{=}CH{-}CH{=}CH_2$$

Our hypothesis which has now been verified in a number of cases is that halides of weakly electronegative radicals[3] will condense when treated with sodamide in liquid ammonia if there is a hydrogen atom on the carbon atom to which the halogen atom is attached.

Since the electronegativity of the allyl radical would be decreased by substituents on the α-carbon atom and only very little affected by substituents on the β-carbon atom, this general method applies to the preparation of many substituted hexatrienes.

Our method of preparing hexatrienes has many advantages over the methods of van Romburgh, namely, the decomposition of *s*-divinylglycol diformate,[4] or the dehydration of 1,5-hexadien-4-ol. The operations involved are simple and rapid. The sodamide used is produced preferably by the action of sodium on liquid ammonia in the presence of finely divided iron as a catalyst.[5] It is then added to a liquid ammonia solution of allyl chloride as rapidly as the violence of the reaction permits, and the products are isolated as described in the experimental part.

It was found that the yield of hexatriene was dependent upon the order of addition; thus sodamide added to allyl chloride gave 30% hexatriene, whereas when the allyl chloride was added to sodamide only a 10% yield of hexatriene was obtained along with a proportionately greater amount of a high boiling material. This is accounted for on the basis that a concentrated solu-

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[1] Eli Lilly Fellow. The authors wish to thank the Eli Lilly Company for generous support which made this work possible.

[2] Thiele and Wahnscheidt, *Ann.*, **376**, 278 (1910).

[3] Kharasch and Flenner, THIS JOURNAL, **54**, 674 (1932); Kharasch and Swarts, *J. Org. Chem.*, **3**, 405 (1938).

[4] Van Romburgh, *J. Chem. Soc.*, **90**, 130 (1906); *Proc. Roy. Acad. Amsterdam*, **15^2**, 1184 (1913).

[5] Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).