Studies on the Derivatives of 3-Hydroxyflavanone (Dihydroflavonol). I. On the Action of Lead Tetraacetate on Flavanone and 4′-Methoxyflavanone.

By Taichiro OYAMADA.

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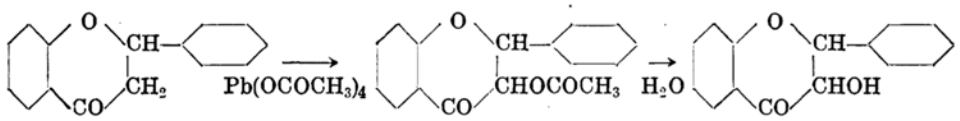
Several years ago, fustin[1], isolated from *Rhus succedanea* L., was confirmed by the present author to be a derivative of 3-hydroxyflavanone (dihydroflavonol), namely 3,7,3′,4′-tetrahydroxyflavanone. Since then two new derivatives of this group, alpinon[2] and ampeloptin[3], have been isolated from plants by Japanese workers. Consequently, it is possible that many other new derivatives of this series may occur in nature. It would, therefore, be of great interest to synthesise many compounds of this new class and to investigate the behaviour of these compounds.

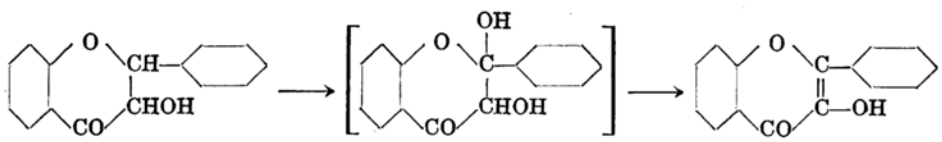
By the systematic studies of Criegee and others[4], it has been shown that lead tetraacetate is an important reagent for the oxidative fission of α-glycols. However, only a few researches[5] have been carried out as

(1) *J. Chem. Soc. Japan*, **55** (1935), 755–790; *Ann.*, **538** (1939), 44.
(2) Y. Kimura, *J. Pharm. Soc. Japan*, **57** (1937), 147.
(3) T. Kubota, *J. Chem. Soc. Japan*, **59** (1938), 1153.
(4) R. Criegee, *Ber.*, **64** (1931), 260; *Ann.*, **507** (1933), 159; *Ber.*, **68** (1935), 665 etc.
(5) R. C. Morris, W. E. Hanfold and R. Adams, *J. Am. Chem. Soc.*, **57** (1935), 951; W. Hückel and K. Hartmann, *Ber.*, **70** (1937), 961; O. Dimroth and R. Schweizer, *Ber.*, **56** (1923), 1375; T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22** (1939), 1212 etc.

to the use of this reagent in substitution. The present author attempted to synthesise the derivatives of 3-hydroxyflavanone, in replacing the active hydrogen (position 3) in flavanones with an acetoxy-group by lead tetra-acetate and the subsequent hydrolysis of the resulting esters, as shown in the following scheme:



The solution of flavanone (1 mol.) and lead tetraacetate (1 mol.) in glacial acetic acid was heated at 80–90°, until all unchanged tetraacetate disappeared, which was indicated by the absence of the formation of the brown colloidal lead peroxide on dilution of the solution with water. As the product thus obtained was viscous and difficult to purify, it was directly subjected to hydrolysis. The crude product was heated on the water-bath for a short time with alcohol containing concentrated hydrochloric acid and, on cooling, a colourless leaf-like crystalline compound, melting indefinitely at 140–175°, separated out. Even after several crystallisations from alcohol, the substance was still impure and melted indefinitely at 170–178°. However, it could be purified by converting it into the pure crystalline acetate by treatment with acetic anhydride and a drop of concentrated sulphuric acid, and then by hydrolysing it in an acidic medium in a current of carbon dioxide in order to prevent it from being oxidised. The compound thus purified melted at 183–184° and was very sensitive to oxygen, especially in the presence of alkali. It was partly soluble in hot alkali with the formation of a yellow solution. On acidifying the alkaline solution, a compound, melting at 170°, separated, which was proved to be flavonol by the method of the mixed melting point. For the explanation of the mechanism of this reaction, attention was directed to the fact that 7,3′,4′-trimethoxy-3-hydroxyflavanone (trimethylfustin) yielded 7,3′,4′-trimethoxy-3-hydroxyflavone (trimethylfisetin) when treated with alkali[6]. The formation of flavonol is obviously due to the oxidation of 3-hydroxyflavanone (dihydroflavonol), as probably indicated in the following scheme:



On the other hand, the present author tried to purify the hydrolysed product by the chromatographic method, using magnesia as an adsorbent, and observed that most of the product was adsorbed by magnesia, which became yellow, and that the substance adsorbed was regenerated as flavonol on dissolving the adsorbent in hydrochloric acid. This phenomenon was also observed in the pure compound, melting at 183–184°, and, moreover, in 4′-methoxy-3-hydroxyflavanone (4′-methoxydihydroflavonol)

(6) *J. Chem. Soc. Japan*, **55** (1935), 763 and 786; *Ann.*, **538** (1939), 46 and 51.

and trimethylfustin (trimethyldihydrofisetin). It is noteworthy that the derivatives of 3-hydroxyflavanone showed an extreme facility in forming the corresponding flavonols when they were adsorbed by magnesia or a similar weak basic substance. Furthermore, the author conducted the chromatographic adsorption in a current of hydrogen in order to avoid oxidation, but he could not obtain a good result, owing to the difficulty of securing the complete exclusion of oxygen during the whole operation.

From the part unadsorbed by magnesia, a new compound, melting at 132–133°, was obtained in a small quantity. This compound was very stable and did not change on heating at a comparatively high temperature with mineral acid in a sealed tube. Further study of this compound is now in progress.

The similar treatment was applied to 4′-methoxyflavanone with a view to synthesise 4′-methoxy-3-hydroxyflavanone. After a number of experiments, the expected compound was obtained together with a small quantity of an unknown compound, melting at 118–119°, by the procedure described in the experimental part. As the author had previously prepared the same compound in another way[7], the compound obtained here was easily proved to be the expected one by direct comparison. The compound was also converted into the corresponding flavonol by adsorption with magnesia.

This investigation, both in the synthetic and the natural derivatives of flavanone, is now being extended at this laboratory.

Experimental. *Preparation of Lead Tetraacetate.* Lead tetraacetate was prepared according to the Dimroth method modified by Gattermann[8]. Red lead oxide (minium) (120 g.) was gradually added to glacial acetic acid (450 c.c.), containing acetic anhydride (12 c.c.), and thoroughly stirred while it was kept at 60–65°. Considerable amount of lead tetraacetate was deposited on cooling. On recrystallising from glacial acetic acid, it was obtained as colourless crystals. Although it is very unstable in the dry state, it can be kept for a long time by covering it with glacial acetic acid.

Action of Lead Tetraacetate on Flavanone. A solution of 24 g. of flavanone and 48 g. of lead tetraacetate in 400 c.c. of glacial acetic acid was heated in the water-bath at 80–90° for two hours. The completion of the reaction was proved by the absence of formation of brown colloidal lead peroxide on dilution of the solution with water. The solution was poured into water and extracted with ether. The ethereal extract was washed with water and then with sodium bicarbonate solution in order to remove acetic acid, dried over anhydrous sodium sulphate and evaporated. The residual oil was then distilled under a reduced pressure of 3 mm., and a viscous liquid, boiling at 198–200°, was obtained. The yield was 22 g. The viscous liquid was ascertained to be a mixture by further experiment.

Hydrolysis. The liquid thus obtained (13 g.) was heated with alcohol (150 c.c.) containing concentrated hydrochloric acid (30 c.c.) on the

(7) *J. Chem. Soc. Japan*, **56** (1936), 980.
(8) L. Gattermann, "Die Praxis des organischen Chemikers," (1936), 123.

water-bath for thirty minutes. On cooling, a leaf-like crystalline compound (6.2 g.), melting at 140–175°, was deposited. After several crystallisations from alcohol, it separated in crystals, sintering at 170° and melting completely at 178°. Although the purification by means of several recrystallisations from alcohol and other solvents was attempted, the substance remained impure and melted indefinitely. Therefore, the purification by recrystallisation was discarded and an adsorption method was then tried, but without success. Finally, it could be purified through its pure acetate in the way described in the following experiments.

Preparation of 3-Acetoxyflavanone. The acetylation of the hydrolysed product (4 g.), was effected by the action of acetic anhydride (20 g.) and a drop of concentrated sulphuric acid at room temperature. The acetylated product was poured into water, when an oil separated, and solidified on standing. After several crystallisations from alcohol, 3-acetoxyflavanone melted at 94–94.5°. The yield was 2.3 g. Found: C, 72.60; H, 5.21. Calc. for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96%.

Preparation of 3-Hydroxyflavanone. The above acetate (2 g.) was heated with alcohol (40 c.c.), containing concentrated hydrochloric acid (20 c.c.), on the water-bath for an hour in a current of carbon dioxide. On cooling, a leaf-like crystalline compound separated out. After recrystallisation from alcohol, in an atmosphere of carbon dioxide in order to avoid the contact with oxygen, 3-hydroxyflavanone separated in crystals, melting at 183–184° when heated rapidly in the bath which had been previously heated to about 175°. However, it began to melt at lower temperature when heated from low temperature. The yield was 0.8 g. It is insoluble in cold alkali, but soluble in hot alkali with the formation of a yellow solution. On acidifying this alkaline solution, flavonol, melting at 170°, separated out. The 3-hydroxyflavanone was adsorbed by magnesia, which became yellow, and, on dissolving the magnesia in hydrochloric acid, flavonol was recovered. Further study of the 3-hydroxyflavanone is now in progress. Murakami and Irie[9] had prepared the same compound by the action of hydrogen peroxide on 2′-hydroxychalkone in the presence of alkali and reported its melting point as 174–177°. Found: C, 75.28; H, 5.42. Calc. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00%.

Chromatographic Adsorption of the Hydrolysed Product. With the object of purifying the hydrolysed product, a chromatographic adsorption was tried, using magnesia as an adsorbent. When the colourless solution of the hydrolysed product (0.5 g.) in benzene (100 c.c.) was passed through the Tswett column, modified by Winterstein (22 cm. in height) and which was filled with magnesia (37 g.), the upper layer (3/4) of the magnesia became yellow, indicating an adsorption. On dissolving the yellow part of the magnesia in hydrochloric acid, a yellowish compound separated. It was collected and recrystallised from alcohol, when it separated in yellowish crystals, melting at 170°. No depression of the melting point was caused by admixture with an authentic specimen of flavonol. The yield was 0.3 g. The solution passed through magnesia was evaporated and a needle-like crystalline compound, melting at 132–133°, was obtained on recrystallising from alcohol. The yield was 0.08 g.

(9) M. Murakami and T. Irie, *Proc. Imp. Acad.* (Tokyo), **11** (1935), 229.

No change was observed on heating this substance with a 20% alcoholic solution of hydrochloric acid in a sealed tube. Further study of this compound is now being carried out.

Hydrolysis of the Product formed in the Action of Lead Tetraacetate on Flavanone by means of Methyl-alcoholic Soda. The reaction product (2 g.) was dissolved in a 2.5% methyl-alcoholic soda (50 c.c.) and the solution was allowed to stand at room temperature for five days, when a dark yellow crystalline compound was deposited. On recrystallising it from alcohol, containing a small quantity of hydrochloric acid, a yellow compound, melting at 170°, was obtained and identified as flavonol by the method of the mixed melting point. The yield was 0.8 g.

Action of Lead Tetraacetate on 4′-Methoxyflavanone. A solution of 4′-methoxyflavanone (4 g.) and lead tetraacetate (7 g.) in glacial acetic acid (100 c.c.) was heated in the water-bath at 80–90° for two hours. After the removal of lead compound by the saturation with hydrogen sulphide, most of the acetic acid was distilled off under the reduced pressure, and the residue was poured into water and extracted with ether. The ethereal extract was washed with water, dried over anhydrous sodium sulphate and evaporated. On standing, the residue partly crystallised. The crystals were collected and recrystallised from ether, from which they separated in colourless crystals, melting at 118–119°. The yield was 0.7 g. Further study of this compound is now in progress.

The viscous filtrate from the above-mentioned crystalline compound was subjected to hydrolysis. The viscous liquid (3 g.) was heated with alcohol (40 c.c.), containing concentrated hydrochloric acid (4 g.) and water (2 c.c.), on a water-bath for an hour and, on cooling, a crystalline compound, melting at 143–153°, separated. This compound was purified by several crystallisations from alcohol and then from benzene. The compound thus purified melted at 172–174°. The yield was 0.5 g. This compound was proved to be identical with the 4′-methoxy-3-hydroxyflavanone, which had been previously prepared in another way by the present author. It was also converted into 4′-methoxy-3-hydroxyflavone (4′-methoxyflavonol), melting at 230–231°, by adsorption with magnesia.

In conclusion, the author wishes to express his sincere thanks to Mr. Shigemi Oba, the Director of the Yonezawa Higher Technical School, and to Prof. Tosaziro Yoshida of this school for their encouragements throughout this work. He also expresses his hearty thanks to the Department of Education for the Scientific Research Expenditure which has defrayed most of the cost of this research.

Yonezawa Higher Technical School,
Yonezawa.