added dropwise. The collected precipitate was recrystallized from absolute ethanol; m.p. 141–142°, yield 1.5 g. (75%).

Anal. Calcd. for $C_9H_7N_3OS$: N, 20.48. Found: N, 20.38.

Acknowledgments. The financial support of this investigation by the Research Corporation of New York through a Frederick Gardner Cottrell grant to the University of Nebraska is gratefully acknowledged. Infrared spectra were determined by C. W. Rook, Dr. W. C. Robison, E. M. Shelton, and E. Magnuson.

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[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

Chloroacetates and Dichloroacetates of Flavonol, 7-Hydroxyflavone, and Chrysin[1]

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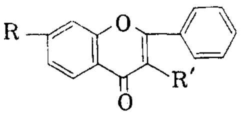
An improved synthesis of 7-chloroacetoxyflavone is reported. The procedure developed has been applied in the preparation of 7-dichloroacetoxyflavone, 3-chloroacetoxyflavone and 7-dichloroacetylchrysin. The attempted solubilization of 7-chloroacetoxyflavone by conversion to the pyridinium salt is reported.

A broad range of biological activity has been demonstrated by flavonoid materials. The present paper describes a series of chloroacetyl and dichloroacetyl derivatives of flavonol, 7-hydroxyflavone and chrysin, which were prepared for evaluation of possible biological activity. The possibility of solubilizing 7-hydroxyflavone as a pyridinium salt of the chloroacetate has been investigated.



I: R = OH; R′ = H
II: R = CH_2ClCOO; R′ = H
III: R = H; R′ = OH
IV: R = H; R′ = CH_2ClCOO
V: R = $CHCl_2COO$; R′ = H

7-Hydroxyflavone (I) was prepared by the method of Robinson and Venkataraman,[2] as well as by fusion of resacetophenone dibenzoate in the presence of benzoic acid and sodium benzoate. The latter procedure is somewhat similar to the modification introduced by Wheeler and coworkers,[3] but utilizes benzoic acid as the reaction medium instead of glycerol, which is quite hygroscopic. 7-Hydroxyflavone is described[2] as forming long colorless needles, m.p. 240°. The product obtained by the benzoic acid fusion method crystallized in long brilliant yellow needles (Form A), m.p. 244–244.5°. Upon hydrolysis of 7-chloroacetoxyflavone (sequel), colorless 7-hydroxyflavone was obtained. After recrystallization from ethanol, very pale yellow needles (Form B), m.p. 244–245° were obtained. Infrared absorption spectra of the two forms, A and B, showed them to be identical on a molecular basis to each other and to the flavone derivative prepared by the method of Robinson and Venkataraman.[2]

7-Chloroacetoxyflavone (II) has been prepared by Row and Seshadri[4] by heating 7-hydroxyflavone with an excess of chloroacetyl chloride. No yield for this reaction was reported, but it was noted that it was very difficult to remove a green color from the product. This procedure, upon being repeated by the authors, led to a greenish black tar, from which only a small amount of starting material proved isolable in pure form. Although an exhaustive study of the reaction mixture was not made, it appeared likely that recrystallization from methanol caused decomposition of any ester present to give 7-hydroxyflavone (sequel). Further experiments using xylene solutions showed the green color to be due to contact of the warm reactants with air. Accordingly, all succeeding reactions were carried out in xylene in an atmosphere of nitrogen with exclusion of air until all of the excess chloroacetyl chloride had been removed by distillation *in vacuo.* Under these conditions, the green color did not appear and colorless needles of 7-chloroacetoxyflavone were obtained in yields up to 77%.

Under anhydrous conditions, 7-chloroacetoxyflavone reacts with pyridine to give a solid product. Extraction of this product with ether removed unreacted starting material and left a light yellow residual solid with a wide melting range. The product, presumably the crude pyridinium salt, was tested for water solubility. Although the

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(1) Abstracted from the M.S. Thesis of Walter Wm. Hanneman, University of Nebraska, 1956.

(2) R. Robinson and K. Venkataraman, *J. Chem. Soc.*, 2344 (1926).

(3) A. T. M. Dunne, J. E. Gowan, J. Keane, B. M. O'Kelly, D. O'Sullivan, M. M. Roche, P. M. Ryan, and T. S. Wheeler, *J. Chem. Soc.*, 1252 (1950).

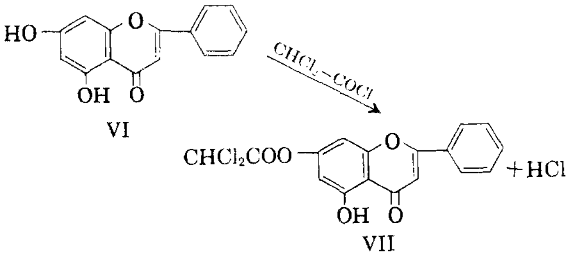
(4) R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 11A, 206 (1940).

salt dissolved instantly, almost immediately there appeared a colloidal precipitate which was shown to be pure 7-hydroxyflavone.

The water-labile nature of the crude pyridinium salt made it necessary to consider the possibility that 7-chloroacetoxyflavone itself was readily hydrolyzed. It was demonstrated that in boiling water hydrolysis began immediately, even though the starting ester was not water-soluble. The rate of hydrolysis depended apparently on the particle size. In boiling absolute methanol, decomposition was complete in less than 30 min. and upon standing overnight at room temperature in methanol, the conversion to 7-hydroxyflavone also was complete.

The procedure developed was extended to flavonol (III) to give 3-chloroacetoxyflavone (IV). Reaction of dichloroacetyl chloride with 7-hydroxyflavone according to the same general procedure led to 7-dichloroacetoxyflavone (V). Reaction mixtures containing dichloroacetyl chloride did not show as great a tendency to turn green as the monochloroacetylation mixtures. The method just outlined did not give a detectable reaction between flavonol and dichloroacetyl chloride. However, the addition of several drops of pyridine to the reaction mixture gave a 63% yield of colorless, crystalline product, m.p. 121–123°, presumably 3-dichloroacetoxyflavone. The latter product was unstable in moist air, undergoing rather rapid conversion to flavonol.

A readily available dihydroxyflavone containing the 4-carbonyl-5-hydroxy system is chrysin (VI), which was prepared by the method of Mentzer and Pillon.[5] The possibility of hydrogen-bonding involving the 5-hydroxyl made it reasonable to expect that substitution at the 7-position could be effected preferentially. By heating chrysin with an excess of dichloroacetyl chloride in xylene under reflux, a 70% yield of the pale yellow 7-dichloroacetylchrysin (VII) was obtained. In contrast to the dichloroacetate of flavonol, the dichloroacetate of chrysin is reasonably stable in a stoppered bottle.



The infrared spectra of both chrysin and 7-hydroxyflavone show a very broad zone of absorption in the region 3200–2100 cm.$^{-1}$ Although the strong C—H band of Nujol obscures the region near 3000 cm.$^{-1}$, definite peaks of moderate intensity occur between 2670–2580 cm.$^{-1}$ The strong bands at 1780 and 1772 cm.$^{-1}$ in the spectra of V and VII, respectively, are attributed to the ester carbonyl groups. In dichloroacetic esters, the shift toward frequencies higher than those of most ester carbonyl bands has been attributed to the inductive effect of the chlorine atoms.[6] The flavone carbonyl bands were present as follows: I, 1625 cm.$^{-1}$; V, 1640 cm.$^{-1}$; VI, 1647 cm.$^{-1}$; VII, 1658 cm.$^{-1}$.

EXPERIMENTAL[7]

All melting points are corrected. Infrared absorption spectra of Nujol mulls in sodium chloride cells were recorded with a Perkin-Elmer Model 21 spectrophotometer.

Resacetophenone. This compound was prepared by the procedure of Cooper.[8]

Resacetophenone dibenzoate. This substance was prepared by the method of Baker,[9] m.p. 80–81° (reported, 80–81°[9]).

7-Hydroxyflavone. In a 500 ml. round bottomed flask, fitted with a stirrer and thermometer, were placed 59 g. of resacetophenone dibenzoate, 48 g. of sodium benzoate, and 175 g. of benzoic acid. The resulting mixture was heated 4 hr. at 200°, cooled, and washed with 2 l. of 5% sodium bicarbonate, which was discarded. The residue was dissolved in 200 ml. of methanol, and a solution of 25 g. of sodium hydroxide in 50 ml. of water was added slowly. After heating under reflux 30 min., the base was neutralized with dilute hydrochloric acid and the alcohol removed by distillation. The residue was dissolved in 500 ml. of 5% sodium hydroxide and the solution saturated with carbon dioxide to precipitate the crude flavone; yield, 14 g. (36%). Recrystallization from ethanol gave long bright yellow needles (Form A), m.p. 244–244.5° (lit.[2] m.p. 240°). Both forms (A and B) showed infrared bands at 2580, 1625, 1609, 1575, 1553, 1512, 1386, 1358, 1286, 1260, 1191, 1173, 1140, 1097, 1047, 1030, 973, 960, 855, 845, 823, 777, 771, 688, and 674 cm.$^{-1}$

7-Chloroacetoxyflavone. A preliminary experiment demonstrated the deleterious effect of contact of the reaction mixture with air. In a 200 ml. round bottomed flask were placed 2 g. of 7-hydroxyflavone, 8 ml. of chloroacetyl chloride, and 50 ml. of xylene. The mixture was heated under reflux for 2 hr. As the reaction proceeded the heterogeneous reaction mixture was converted to a light brown solution. At the end of this time, most of the excess chloroacetyl chloride was removed by distillation, and the residual liquid was poured into a beaker to cool. On contact with air, the solution turned dark green and a tar resulted. Extraction of this tar with 500 ml. of ether and evaporation of the ether gave 400 mg. of crude 7-chloroacetoxyflavone, m.p. 132–138° (lit.[4] m.p. 138–139°).

In a 200 ml. round bottomed flask with a side arm were placed 3 g. of 7-hydroxyflavone, 12 ml. of chloroacetyl chloride, and 75 ml. of xylene. The reaction mixture was heated for 3 hr. in an atmosphere of nitrogen, which was introduced through the side arm. The resulting solution remained light yellow throughout the reflux period. At the end of this period, solvent and excess chloroacetyl chloride were removed by distillation *in vacuo*. Care was taken that all traces of the acid chloride were removed. On cooling,

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[5] C. Mentzer and D. Pillon, *Compt. rend.*, **234**, 444 (1952).

[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 156.

[7] Infrared spectra were determined by E. Magnuson. We are indebted to Myron J. Holm for assistance with chlorine analyses.

[8] S. R. Cooper, *Org. Syntheses*, **21**, 103 (1941).

[9] W. Baker, *J. Chem. Soc.*, 1381 (1933).

the product crystallized without a trace of green color. After extraction with ether, removal of solvent, and recrystallization of the residue from ethyl acetate–cyclohexane, 2.9 g. (77%) of 7-chloroacetoxyflavone was obtained as white needles, m.p. 136–137° (lit.[4] m.p. 138–139°).

Attempted solubilization of 7-chloroacetoxyflavone as the pyridinium salt. One g. of 7-chloroacetoxyflavone was dissolved in 10 ml. of dry pyridine and permitted to stand in a tightly stoppered flask at room temperature for 3 days. Then the reaction flask was opened, placed in a vacuum desiccator over paraffin, concentrated sulfuric acid and phosphorus pentoxide (in separate beakers), and permitted to stand *in vacuo* until excess pyridine was completely removed. The residual yellow powder was extracted with dry ether in a Soxhlet extraction apparatus for 24 hr. to remove unreacted 7-chloroacetoxyflavone. After additional drying *in vacuo* of the ether insoluble fraction, the product gave an indistinct melting point, *ca.* 150–180°. This fraction dissolved immediately upon addition to water, but almost instantly there appeared a water-insoluble substance which was collected by filtration and air dried; m.p. 238–240°. After recrystallization from ethanol, pale yellow needles, m.p. 244–245°, were obtained. Identity of the latter substance (Form B) with 7-hydroxyflavone[2] was shown by infrared absorption spectra and mixed melting point.

Decomposition of 7-chloroacetoxyflavone. A. In methanol: A 100 mg. quantity of 7-chloroacetoxyflavone in 25 ml. of absolute methanol was heated on a steam bath for 30 min. Additional methanol was added from time to time to replace that lost through boiling. The volume of methanol then was reduced to about 5 ml. and allowed to cool. Colorless crystals separated and were collected by filtration; m.p 238–240°. After recrystallization from methanol, the product was shown to be 7-hydroxyflavone by m.p. and mixed m.p. determination.

B. In water: The same general procedure was employed as in Part A, but the heterogeneous nature of the reaction mixture resulted in a slow reaction and only partial conversion to the flavone. The 7-hydroxyflavone was separated mechanically and identified by melting point and mixed melting point determination.

7-(Dichloroacetoxy)flavone. Into a 200 ml. round bottomed three necked flask, fitted with reflux condenser, dropping funnel, and capillary tube for maintaining an atmosphere of nitrogen were placed 75 ml. of xylene and 2 g. of 7-hydroxyflavone. A 10-ml. volume of dichloroacetyl chloride in 50 ml. of xylene was added slowly over a 30-min. period through the dropping funnel. The pale yellow solution was heated under reflux an additional 3 hr. and allowed to stand overnight. Solvent and excess acid chloride were removed by distillation *in vacuo*, and the light yellow residual solid washed with ether. The crude product gave m.p. 130–150°, and was returned to the reaction flask and heated with the previously removed solvent and dichloroacetyl chloride under reflux for an additional 4 hr. Again solvent and excess acid chloride were removed by distillation *in vacuo*. There resulted as residue 1.5 g. (54%) of crude product, m.p. 156–160°. Recrystallization from xylene-cyclohexane gave colorless needles of 7-(dichloroacetoxy)flavone, m.p. 161–162°.

Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: Cl, 20.3. Found: Cl, 20.5.

3-Chloroacetoxyflavone. In a 200 ml. round bottomed flask with side arm (through which a nitrogen atmosphere was maintained) were placed 1.0 g. of flavonol, 0.57 g. of chloroacetyl chloride, and 50 ml. of xylene. The reaction mixture was heated under reflux for 30 min., and then excess acid chloride and solvent were removed by distillation *in vacuo*. The melting point of the residual crude product was 155–160°. Recrystallization from xylene gave 0.94 g. of 3-chloroacetoxyflavone as colorless needles, m.p. 159.5–160.3°.

Anal. Calcd. for $C_{17}H_{11}ClO_4$: Cl, 11.3. Found: Cl, 12.1.

7-Dichloroacetylchrysin. Into a 200 ml. round bottomed flask with side arm (through which a nitrogen atmosphere was maintained) 0.50 g. of chrysin, 0.3 g. of dichloroacetyl chloride, and 75 ml. of xylene were placed and allowed to stand at room temperature for 28 hr. At the end of this time no change was apparent, and the chrysin was recovered upon solvent removal by distillation *in vacuo*.

The recovered chrysin was returned to the reaction flask, and 70 ml. of xylene and 3.60 g. of dichloroacetyl chloride were added. Nitrogen was passed through the flask and the reaction mixture was heated to reflux temperature. After 4 to 5 min., white fumes were evolved for about 1 min. At this point the reaction mixture was homogeneous. Solvent and excess acid chloride were removed under reduced pressure. Upon cooling in Dry Ice, the residual yellowish brown oil formed crystals which were dissolved in 15 ml. of boiling xylene; charcoal was added, and the crystals were removed by filtration. Addition of isooctane to the cooled filtrate gave a brown gum, together with yellow crystals. Upon slow addition of xylene to the heated solution, the yellow crystals dissolved. The brown residue (20 mg.) was removed by filtration and discarded. The clear yellow filtrate produced upon cooling 510 mg. (70%) of yellow needles, m.p. 144–148°. Recrystallization from anhydrous ether (50 ml.) gave the pale yellow 7-dichloroacetylchrysin, m.p. 151–151.5°, which in acetone solution gave a rather pale reddish violet color with alcoholic ferric chloride.[10] In acetone solution, 7-hydroxyflavone gives a negative test with alcoholic ferric chloride.[10]

Anal. Calcd. for $C_{17}H_{10}Cl_2O_5$: Cl, 19.4. Found: Cl, 19.9.

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[10] That production of a color with ferric chloride solution is a property of 3-, 5- or 8-hydroxyflavones, but not of 6-, 7-, or 4′-hydroxyflavones has been reported L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3137 (1951) [additional references are cited by these authors].