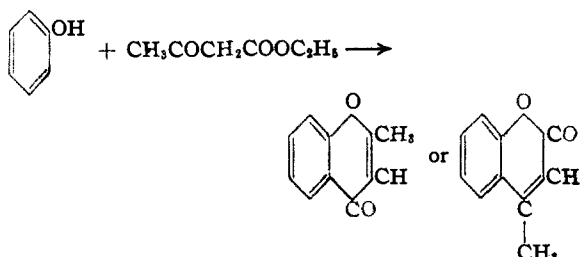


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Formation of a Chromone by the von Pechmann Condensation of Ethyl Acetoacetate with 4-Chloro-3,5-dimethylphenol

BY ROGER ADAMS AND J. W. MECORNEY

The condensation of ethyl acetoacetate or its substitution products with phenols proceeds under the influence of various reagents to give either chromones or coumarins.

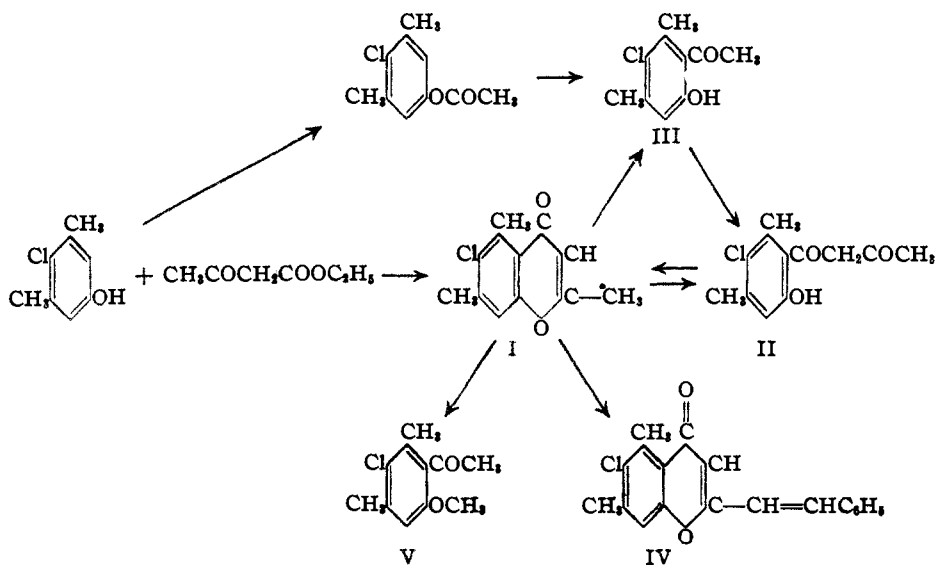


Experience has shown that the von Pechmann¹ reaction, namely, that which involves the use of concentrated sulfuric acid as a condensing agent, leads almost invariably to the coumarin. The report of Jacobson and Ghosh² that chromones had been synthesized by the von Pechmann procedure was shown to be incorrect by later investigators³ who demonstrated that coumarins actually had been obtained. Dey and Lakshminarayanan⁴ isolated merely the coumarin from the crude condensation product of ethyl acetoacetate and β -naphthol. From the same crude reaction product they were able by the action of benzal-

dehyde and sodium ethoxide to isolate a small yield of a styryl derivative of 1,4- β , α -naphthopyrone, indicating that some chromone was present. Chakravarti⁵ states that with this exception there is no other case in which the presence of a chromone has even been detected when sulfuric acid was used as a condensing agent.

The requirements in another research of a coumarin derived from 4-chloro-3,5-dimethylphenol led to experiments on the application of the von Pechmann reaction first to 3,5-dimethylphenol as a type compound and then to 4-chloro-3,5-dimethylphenol. The synthesis with 3,5-dimethylphenol proceeded smoothly to a coumarin as previously reported,⁶ but the chloro derivative yielded a pure product which was not a coumarin and was, therefore, assumed to be a chromone. Investigation has confirmed these facts. It does appear therefore that the von Pechmann condensation may lead to coumarins when the phenols are properly substituted.

The proof of the structure of the chromone (I) from 4-chloro-3,5-dimethylphenol, ethyl acetoacetate and sulfuric acid was established by (1) hydrolysis to a 1,3-diketone (II) which was synthesized by the unequivocal method of condensation of 5-chloro-4,6-dimethyl-2-hydroxyacetophenone (III) with ethyl acetate and which by the action



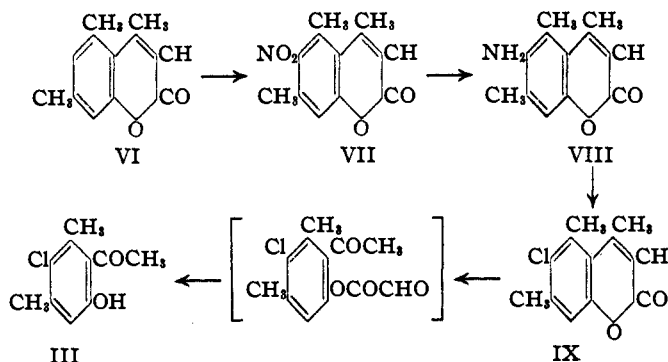
- (1) Von Pechmann, *Ber.*, **16**, 2119 (1883).
 (2) Jacobson and Ghosh, *J. Chem. Soc.*, **107**, 424, 959, 1051 (1915); Ghosh, *ibid.*, **109**, 105 (1916).
 (3) Baker and Robinson, *ibid.*, **127**, 1981 (1925); Baker, *ibid.*, **127**, 2349 (1925).
 (4) Dey and Lakshminarayanan, *J. Ind. Chem. Soc.*, **9**, 149 (1932).

of acid reverts to the chromone; (2) condensation with benzaldehyde to a styryl derivative (IV); (3) hydrolysis to a hydroxy ketone (III) or hy-

- (5) Chakravarti, *ibid.*, **12**, 536 (1935).
 (6) Clayton, *J. Chem. Soc.*, **93**, 2016 (1908).

drolisis followed by methylation to a methoxy ketone (V).

In order to obtain the desired chlorinated coumarin, the coumarin (VI) from 3,5-dimethylphenol and ethyl acetoacetate was nitrated to a mononitro compound (VII) which was reduced to the amine (VIII) and this was diazotized and treated with hydrochloric acid to replace the amino group with chlorine (IX).



The structure of the coumarin was confirmed by ozonization followed by treatment with alkali. 5-Chloro-4,6-dimethyl-2-hydroxyacetophenone was obtained, which serves to identify the original compound as a coumarin and at the same time to establish the position of the chlorine atom.

Experimental

6-Chloro-2,5,7-trimethylchromone (I).—To a mixture of 50 g. of 4-chloro-3,5-dimethylphenol (1 mol. equiv.) and 42 g. of freshly distilled ethyl acetoacetate (1 mol. equiv.), was added 300 cc. of concentrated sulfuric acid. The solution was warmed on a steam-bath for one-half hour and then allowed to stand at room temperature for one week. Fine needles separated from the reaction mixture on cooling and were redissolved by occasional warming. A large quantity of solid material was obtained by adding the solution to 3 kg. of crushed ice and allowing to warm to room temperature. The crude solid was removed by filtration, thoroughly washed with water, and after two crystallizations from aqueous ethanol, 25 g. (35%) of flat white rods 1–2 cm. long was obtained; m. p. 145–146° (cor.). The mother liquors contained considerable amounts of oily material which was not investigated further. Previous runs with a twenty-four hour reaction time gave lower yields (7–20%).

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.96 (64.97); H, 4.81; Cl, 15.80.

6-Chloro-5,7-dimethyl-2- β -styrylchromone (IV).—This styryl derivative is readily formed by the condensation of the chromone with benzaldehyde in the presence of alcoholic sodium ethoxide following the general procedure of Heilbron, Barnes and Morton⁷; fluffy, flocculent crystals from absolute ethanol; m. p. 186–186.5° (cor.); yield, quantitative.

Anal. Calcd. for $C_{15}H_{15}ClO_2$: C, 73.43; H, 4.87; Cl, 11.41. Found: C, 73.61; H, 4.74; Cl, 11.56.

4-Chloro-3,5-dimethyl-6-acetylacetophenol (II).—A solution of 5 g. of 6-chloro-2,5,7-trimethylchromone and 5 g. of potassium hydroxide pellets in 50 cc. of absolute ethanol was refluxed with stirring for one-half hour. The solution which had turned a claret red, was added to crushed ice and gave a clear solution. Cold, dilute hydrochloric acid

was added dropwise and a yellow oil separated which solidified slowly. The crude solid was dissolved in 5% aqueous sodium hydroxide and warmed on the steam-bath for one minute. Norite (0.1 g.) was added and the solution was filtered. Upon careful addition of cold, dilute hydrochloric acid a solid was obtained which could be crystallized from toluene as fine, white needles, m. p. 148–150° (cor.), yield 2.5 g. (45%).

Anal. Calcd. for $C_{12}H_{11}ClO_3$: C, 59.88; H, 5.44; Cl, 14.73. Found: C, 60.06; H, 5.59; Cl, 14.70.

It is insoluble in 5% sodium bicarbonate solution, but readily soluble in 5% aqueous sodium hydroxide solution. Aqueous suspensions, as well as ethanolic and acetic solutions, gave no color with ferric chloride. A transient coloration could be obtained in the following way. Five cubic centimeters of glacial acetic acid is heated to boiling and a drop of 3% ferric chloride solution added. Upon addition of 50 mg. of the 1,3-diketone, an intense red color is obtained which disappears rapidly upon stirring.

The 1,3-diketone could be readily converted to the chromone by warming 0.2 g. in glacial acetic acid to which a drop of dilute hydrochloric acid had been added.⁸ Water is added to the reaction mixture and the crystals removed by filtration, m. p. 145–146° (cor.); yield, quantitative. A mixed m. p. with 6-chloro-2,5,7-trimethylchromone (I) prepared above showed no depression.

5-Chloro-4,6-dimethyl-2-hydroxyacetophenone (III).—A mixture of 2 g. of the chromone, 1.2 g. of sodium hydroxide and 13 cc. of water was refluxed vigorously for five hours. The reaction mixture was added to crushed ice and acidified with concentrated sulfuric acid. The solid was collected by filtration and crystallized from dilute aqueous methanol; long white needles, m. p. 89.5–90° (cor.).

Anal. Calcd. for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58. Found: C, 60.39; H, 5.76.

It is insoluble in 5% aqueous sodium bicarbonate but readily soluble in 5% aqueous sodium hydroxide.

5-Chloro-4,6-dimethyl-2-methoxyacetophenone (V).—A mixture of 10 g. of the chromone, 6 g. of sodium hydroxide and 65 cc. of water was refluxed with stirring for five hours, the chromone dissolving in about two hours. In the course of one hour, 26 cc. of dimethyl sulfate was added dropwise, the solution kept basic by portionwise addition of 20% aqueous sodium hydroxide. In all, 50 cc. of alkali was added. An insoluble oil soon separated from the reaction mixture. A further 50 cc. of 20% alkali was added and the heating and stirring continued for one hour. The solution was added to crushed ice and the oil which separated solidified readily. The solid was taken up in hot methanol and the solution was concentrated. Upon standing overnight at room temperature, large white rhombohedral crystals were obtained, m. p. 76–77° (cor.); yield, 5 g. (52%). von Auwers, Muerbe and Sauerwein⁹ report m. p. 76–77°. The melting point of a mixture with authentic material showed no depression.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 62.12; H, 6.16. Found: C, 62.53; H, 6.32.

4-Chloro-3,5-dimethylphenyl Acetate.—A mixture of 15 g. of 4-chloro-3,5-dimethylphenol, 16 cc. of acetic anhydride and two drops of concentrated sulfuric acid was warmed on the steam-bath for five hours, then poured onto crushed ice. The acetate separated as an oil which solidified on standing. The crude acetate is suitable for the Fries rearrangement without further purification. It can be crystallized from petroleum ether (b. p. 60–110°), m. p. 48° (cor.); yield 19 g. (93%).¹⁰

(8) Wittig, *Ber.*, **57**, 88 (1924).

(9) von Auwers, Muerbe and Sauerwein, *Fortschr. Chem. Physik physik, Chem.*, **18**, 33 (1924).

(10) Klarmann, Shternov and Gates, *THIS JOURNAL*, **55**, 2576 (1933).

(7) Heilbron, Barnes and Morton, *J. Chem. Soc.*, **123**, 2559 (1923).

5-Chloro-4,6-dimethyl-2-hydroxyacetophenone (III).—To a well-stirred melt of 4-chloro-3,5-dimethylphenyl acetate warmed to 50°, was added 12.5 g. of anhydrous aluminum chloride. The mixture became quite viscous and stirring had to be discontinued. The temperature of the bath was raised to and held at 155° for forty-five minutes. After cooling, the solids were decomposed and triturated with ice and dilute hydrochloric acid. The compound can be purified by steam distillation. The solids thus collected contained some unchanged acetate and were freed by washing with cold dilute alkali. Upon acidification, the solid was collected and crystallized from petroleum ether (b. p. 60–110°). It is a white, flaky substance, m. p. 106–110° (cor.), yield 7 g. (41%).^{9,10}

The substance was found to show the characteristics of dimorphs. von Auwers, Muerbe and Sauerwein,⁹ who prepared this compound by a different route, report m. p. 106–109° crystallizing from petroleum ether. Klarmann, Shternov and Gates¹⁰ report m. p. 89.7° but do not specify the solvent used for crystallization. The higher-melting form could be converted to the lower by two crystallizations from aqueous ethanol or methanol: long, white, well defined needles, m. p. 89–90° (cor.). It should be pointed out that although the lower modification melts quite sharply at 89–90° (cor.) the liquid does not remain clear until 110° (cor.). The lower-melting form could also be converted to the higher, by one crystallization from petroleum ether (b. p. 60–110°), m. p. 106–110° (cor.). That no unexpected migration of groups took place in the course of the Fries rearrangement was shown by conversion to the methyl ether with dimethyl sulfate, m. p. 76–77° (cor.).⁹ The possibility that the lower form might be a hydrate was excluded on the basis of the fact that its melting point remained 89–90° (cor.) both before and after drying for analysis.

4-Chloro-3,5-dimethyl-6-acetylacetophenol (II).—To 3 g. of 5-chloro-4,6-dimethyl-2-hydroxyacetophenone, m. p. 106–110° (cor.) in 16 g. of ethyl acetate, was added 1.2 g. of clean finely-chopped sodium.⁸ An immediate reaction took place with the liberation of hydrogen and the insoluble sodium phenolate precipitated. Upon gentle warming a lively reaction set in and the mixture was allowed to stand overnight. The reddish-brown solution was decanted from a small amount of tarry matter and added to water acidified with dilute acetic acid. An orange oil separated which solidified when scratched with a stirring rod. After two crystallizations from toluene, small white needles were obtained, m. p. 148–150° (cor.). A mixed m. p. with the 1,3-diketone isolated by the mild alcoholic hydrolysis of the chromone was not depressed; yield, 2 g. (56%).

6-Chloro-2,5,7-trimethylchromone (I).—The 1,3-diketone thus prepared could also be converted to the chromone by warming in glacial acetic acid to which a drop of dilute hydrochloric acid had been added, m. p. 145–146° (cor.). The mixed m. p. of this material with the chromone prepared by the von Pechmann reaction gave no depression.

4,5,7-Trimethylcoumarin (VI).—Following the procedure described by Clayton,⁶ 50 g. of 3,5-dimethylphenol and 55 g. of freshly distilled ethyl acetoacetate were condensed in the presence of 300 cc. of concentrated sulfuric acid; yield, 25 g. (32%) of 4,5,7-trimethylcoumarin, m. p. 181° (cor.). Clayton⁶ reports m. p. 175–176°.

6-Nitro-4,5,7-trimethylcoumarin (VII).—This substance was prepared by the method of Jordan and Thorpe.¹¹ To 30 g. of 4,5,7-trimethylcoumarin dissolved in 300 cc. of concentrated sulfuric acid cooled to –10° by means of a salt-ice-bath, was added with stirring 46 cc. of a nitrating mixture comprised of three parts by volume of sulfuric acid to one part of nitric acid (sp. gr. 1.42) in the course of nine hours. If at any time the temperature reached –5° the addition was interrupted and the reaction mixture was cooled. After an additional hour the solution was allowed to warm to room temperature in the course of forty-five minutes, and added to crushed ice. The solid was collected, washed with water and crystallized from glacial

acetic acid. The first crop of fine, white needles weighed 21 g. The mother liquor can be worked up by further crystallization to yield additional material. In all 26 g. (80%) of nitrocoumarin, m. p. 209–211° (cor.) was obtained. Jordan and Thorpe¹¹ report m. p. 208°. If the rate of addition is increased materially or the temperature allowed to exceed 0°, the yield is much lower.

6-Amino-4,5,7-trimethylcoumarin (VIII).—To 7.5 g. of 6-nitro-4,5,7-trimethylcoumarin was added 8 g. of tin, 7.5 g. of stannous chloride, 75 cc. of concentrated hydrochloric acid and 20 cc. of ethanol. After standing overnight the contents were shaken mechanically for six hours at room temperature, when all the tin had dissolved. The solids were removed by filtration and dissolved in hot water. A slight amount of dark material was removed with the aid of Norite (0.1 g.) followed by filtration. The solution was cooled, a drop of iso-amyl alcohol added to prevent frothing and the solution rendered basic by the portionwise addition of solid sodium bicarbonate with stirring. The yellow solids thus obtained contain inorganic material. The amine is readily extracted by boiling ethanol. On standing overnight the extract deposited 3 g. of beautiful lemon-yellow needles several cm. long. Concentration of the mother liquor yielded a second crop. In all 4.1 g. (64%) of 6-amino-4,5,7-trimethylcoumarin was obtained, m. p. 199–200° (cor.).

Anal. Calcd. for C₁₂H₁₂NO₂: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.84; H, 6.57; N, 6.99.

The amine may also be obtained by reduction in 75% acetic acid with iron powder. The method is somewhat more laborious and the yield unreliable (25–70%).

6-Chloro-4,5,7-trimethylcoumarin (IX).—To 300 cc. of water and 35 cc. of concentrated hydrochloric acid heated to boiling was added 9.5 g. of 6-amino-4,5,7-trimethylcoumarin. The clear solution was then cooled rapidly to 0° with vigorous stirring, whereupon the amine hydrochloride separated as a light lavender solid in a finely divided state. In the course of one hour and fifteen minutes, 3.52 g. of reagent quality sodium nitrite dissolved in 45 cc. of water was added from a dropping funnel until the diazotized solution gave an immediate blue color with starch iodide paper. The clear, cold diazonium solution was then added to 15 g. of freshly prepared cuprous chloride dissolved in 60 cc. of concentrated hydrochloric acid cooled to 5° with vigorous stirring. Immediate evolution of nitrogen took place and a white solid separated. After one hour the stirring was discontinued and the contents were allowed to stand overnight. Crystallization from ethanol gave 8.7 g. (83%) of the chlorocoumarin. The material thus obtained has a light orange hue. Repeated crystallization from ethanol gave a colorless product, m. p. 194–195.5° (cor.).

Anal. Calcd. for C₁₂H₁₁ClO₂: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.81; H, 5.15; Cl, 15.73.

Ozonization of 6-Chloro-4,5,7-trimethylcoumarin (IX). A solution of 0.5 g. of 6-chloro-4,5,7-trimethylcoumarin in 75 cc. of ethyl acetate-methanol mixture 1:1, was subjected to a stream of ozone, 2.5% by volume, at the rate of 100 cc. per minute for three hours. The ozonide was decomposed with 20 cc. of water and the solvent removed on the steam-bath with an air blast. The intermediate glyoxalate was not isolated. The resulting oil was taken up in aqueous methanol, 0.5 g. of sodium hydroxide added and the solution refluxed for two hours. Upon acidification a dark oil separated and was removed by extraction with ether. The ethereal solution was extracted with dilute aqueous sodium hydroxide, acidified and reextracted with ether. Upon removal of the ether with an air blast, an oil resulted that was extracted twice with 10 cc. of petroleum ether (b. p. 60–110°). The extract was concentrated and upon standing overnight at 0° deposited about 50 mg. of 5-chloro-4,6-dimethyl-2-hydroxyacetophenone. The higher melting modification, m. p. 106–110°, was obtained.

Summary

1. It has been demonstrated that the von

(11) Jordan and Thorpe, *J. Chem. Soc.*, 107, 387 (1915).

Pechmann condensation of ethyl acetoacetate and phenols does not always yield coumarins as previously reported.

2. Although sulfuric acid causes the condensation of 3,5-dimethylphenol and ethyl acetoacetate to a coumarin, this same reagent results in the formation of a chromone from 4-chloro-3,5-dimethylphenol and ethyl acetoacetate.

3. The structure of the chromone was established by various hydrolytic reactions and by

condensation with benzaldehyde.

4. The coumarin expected in the initial condensation was synthesized by nitration of 4,5,7-trimethylcoumarin, followed by reduction and replacement of the amino group by chlorine. The proof that the product was a coumarin and that the chlorine was in the 6-position was determined by ozonolysis to 5-chloro-4,6-dimethyl-2-hydroxyacetophenone.

URBANA, ILLINOIS

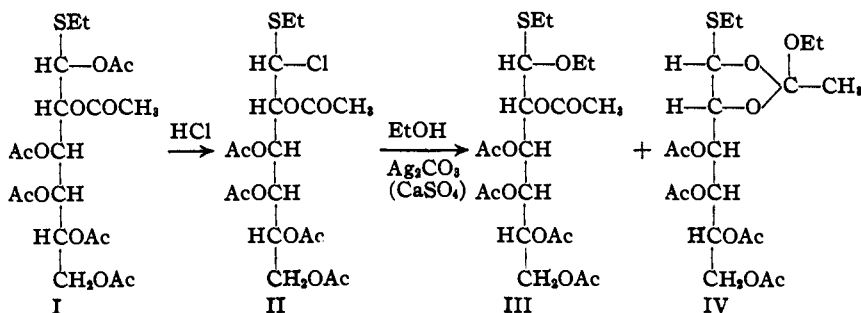
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

An Acyclic Sugar Orthoacetate

By M. L. WOLFROM AND D. I. WEISBLAT

1-Chloro-1-thioethoxy-*aldehydo*-D-galactose pentaacetate (II) has been prepared by the action of a dry ethereal solution of hydrogen chloride upon 1-thioethoxy-*aldehydo*-D-galactose hexaacetate (I).¹ On repeating this procedure in larger quantities, a crude preparation of II was treated with ethanol and silver carbonate. The main reaction product was III, designated D-galactose diethyl monothioacetal pentaacetate and previously synthesized² in a similar manner from pure II, prepared by the action of a mixture of acetyl chloride and phosphorus oxychloride upon D-galactose diethyl mercaptal pentaacetate. In addition there was obtained in low yield a product IV, to which is assigned an orthoacetate structure.



The orthoacetate structure of IV, designated 1-thioethoxy-*aldehydo*-D-galactose ethyl 1,2-orthoacetate tetraacetate, is based upon the fact that one acetyl group in the compound was resistant to alkaline hydrolysis but was removable by acid hydrolysis. This fact, among others, has been employed in establishing the orthoacetate structure³ in the cyclic sugar derivatives. In formula IV, the placement of the sulfur atom and the size of the ring are probable but arbitrary. To our knowledge, this is the first recorded occurrence of

an orthoacetate structure in an acyclic sugar derivative.

Experimental

1-Thioethoxy-*aldehydo*-D-galactose Ethyl 1,2-Orthoacetate Tetraacetate.—Crude unrecrystallized 1-chloro-1-thioethoxy-*aldehydo*-D-galactose pentaacetate (m. p. 95–98°, 45 g.), prepared from 1-thioethoxy-*aldehydo*-D-galactose hexaacetate as previously described¹ and thoroughly washed with an ether-petroleum ether (1:1) mixture, was added to a suspension of 25 g. of Drierite (anhydrous calcium sulfate) and 60 g. of silver carbonate in 250 cc. of absolute ethanol. The reaction was then allowed to run at room temperature, under mechanical stirring and protection from atmospheric moisture, for approximately sixteen hours. The inorganic salts were removed by filtration through a bed of Super-cel (Johns-Manville) and the clear filtrate was made just opalescent with water.

One crop of crystals was deposited on cooling to ice-box temperature; a second and third crop of crystals were obtained by treating the successive filtrates in a like manner. The first two crops (15–16 g.) were recrystallized from six parts of hot absolute ethanol; m. p. 103–105°, spec. rot. +50° (25°, c 4, abs. CHCl₃, D line). This product was therefore identified (mixed m. p. with an authentic sample unchanged) as D-galactose diethyl monothio-

acetal pentaacetate for which the following constants are recorded:² m. p. 104–105°, spec. rot. +50° (20°, c 3.5, abs. CHCl₃, D line). The third crop (6–8 g.) had a melting point of 85–95°. Pure material was obtained after five recrystallizations from four parts of hot methanol; yield 1.5–2.0 g., m. p. 125–126° (mixed m. p. with D-galactose diethyl monothioacetal pentaacetate of m. p. 104–105°, 93°), spec. rot. +54° (24°, c 4, abs. CHCl₃, D line).

The substance crystallized in transparent, elongated prisms and exhibited properties and solubilities similar to the isomeric D-galactose diethyl monothioacetal pentaacetate, except that it was more sensitive to acidity.

Anal. Calcd. for C₁₀H₁₇O₆S(CH₃CO)₄: C, 49.99; H, 6.71; S, 6.67; CH₃CO (4 equiv.), 8.33 cc. 0.1 N NaOH per 100 mg.; CH₃CO (5 equiv.), 10.41 cc. Found: C, 49.92; H, 6.73; S, 6.86; CH₃CO (alkaline hydrolysis, Kunz and Hudson⁴ method), 8.39 cc.; CH₃CO (acid

(1) M. L. Wolfrom, D. I. Weisblat and A. R. Hanze, *THIS JOURNAL*, **62**, 3246 (1940).

(2) M. L. Wolfrom and D. I. Weisblat, *ibid.*, **62**, 878 (1940).

(3) K. Freudenberg and E. Braun, *Naturwissenschaften*, **18**, 393 (1930); E. Braun, *Ber.*, **65B**, 1972 (1930); H. G. Bott, W. N. Haworth and R. L. Hirst, *J. Chem. Soc.* 1395 (1930).

(4) A. Kunz and C. S. Hudson, *THIS JOURNAL*, **48**, 1982 (1926).