Oxidation of XIV.—XIV (6.8 g.) was oxidized by the procedure of Sherrill[23] to yield 3.8 g. (57%) of 3-heptanone (XVI) boiling at 56–58° at 25 mm.; $n^{25}D$ 1.4080; d^{25}_4 0.8162. Sherrill reported the values $n^{20}D$ 1.40917 and d^{20}_4 0.8183.

The semicarbazone melted at 102.5–103.1°, in agreement with the reported value 103°.[28]

Oxidation of XV.—XV (11.6 g.) was oxidized by the procedure of Powell, Huntress, and Hershberg[29] to yield 7.5 g. (58%) of 2-ethylpentanoic acid, XVII. The anilide melted at 93.4–93.8° in agreement with the reported value 94°.[30]

Acknowledgments.—The authors wish to thank the American Chemical Society for its financial support. We are also indebted to the Dow Chemical Company for the propylene oxide and styrene oxide used in this study.

Summary

1. Base-catalyzed attack of acetoacetic ester on both propylene oxide and styrene oxide has been found to occur exclusively at the primary carbon yielding as products α-aceto-γ-valerolactone and α-aceto-γ-phenyl-γ-butyrolactone, respectively. In the case of 3,4-epoxy-1-butene, however, the attack occurred at both the primary and secondary carbons to yield α-aceto-γ-vinyl-γ-butyrolactone and α-aceto-β-vinyl-γ-butyrolactone in approximately equal quantities. Necessary degradations for complete proof of structure of all of the products were accomplished.

2. The observed direction of ring opening in the S_N2 attack of the carbanion of acetoacetic ester on propylene oxide, styrene oxide and 3,4-epoxy-1-butene is interpreted from a consideration of both electronic and steric factors.

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[28] Michael, This Journal, **41**, 411 (1919).

[29] Powell, Huntress and Hershberg, "Organic Syntheses," Coll. Vol. I, p. 168.

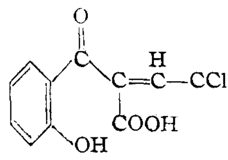
[30] Reichstein and Trivelli, *Helv. Chim. Acta*, **15**, 254 (1932).

[Contribution from the Department of Biochemistry, University of Wisconsin]

Studies on 4-Hydroxycoumarins. IX. The Condensation of Chloral with 4-Hydroxycoumarin and the Mechanism of Aldehyde Condensations with 4-Hydroxycoumarin[1]

By Miyoshi Ikawa[2] and Karl Paul Link

Grüssner[3] condensed chloral hydrate with 4-hydroxycoumarin and obtained an alkali-soluble product to which he assigned structure I. On the basis of the work here reported on this condensation product, structure II, 3-(α-hydroxy-β,β,β-trichloroethyl)-4-hydroxycoumarin, is proposed.



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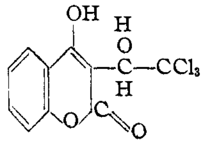

II

Structure II would not be unique for a derivative of chloral, since Pauly and Schanz[4] showed that chloral condenses with a number of phenols to yield the same type of compound, *i.e.*, an aldol condensation takes place at an active carbon atom without the subsequent loss of water as usually occurs following many aldol reactions.

The ultraviolet absorption spectrum (Fig. 1) of the compound very closely resembles that of 3-ethyl-4-hydroxycoumarin and of coumarin. That the absorption spectra of the 4-hydroxycoumarins resemble that of coumarin is also further evidence that these compounds exist mainly in the enol form. Huebner and Link[5] on the basis of the Kurt Meyer enol determination had concluded that 4-hydroxycoumarin was practically 100% enolized.

Titration of the chloral condensation product in 50% ethanol with sodium hydroxide, using the glass electrode, gave but a single inflection in the curve, showing that only one acidic function is present in the molecule. Only one inflection point would be expected from structure II whereas structure I should give two inflection points corresponding to the carboxyl group and the enolic group.

The product forms a diacetate and dibenzoate as would be expected from II. These derivatives are both insoluble in alkali. On treatment with an excess of ethereal diazomethane the condensation product forms an alkali-insoluble monomethyl derivative. In view of the fact that diazomethane readily methylates carboxyl and enolic groups but not ordinary hydroxyl groups, the formation of a monomethyl derivative favors structure II rather than I, which would be expected to yield a dimethyl derivative with diazomethane.

In the reaction of aldehydes (IV) in general with 4-hydroxycoumarin (III) the final product (VII) contains two molecules of the latter to one

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[2] Department of Chemistry, California Institute of Technology, Pasadena, California.

[3] Grüssner, "Jubilee Volume, F. Hoffmann-La Roche and Co., Ltd.," Basle, 1946, p. 238.

[4] Pauly and Schanz, *Ber.*, **56**, 979 (1923).

[5] Huebner and Link, This Journal, **67**, 99 (1945).

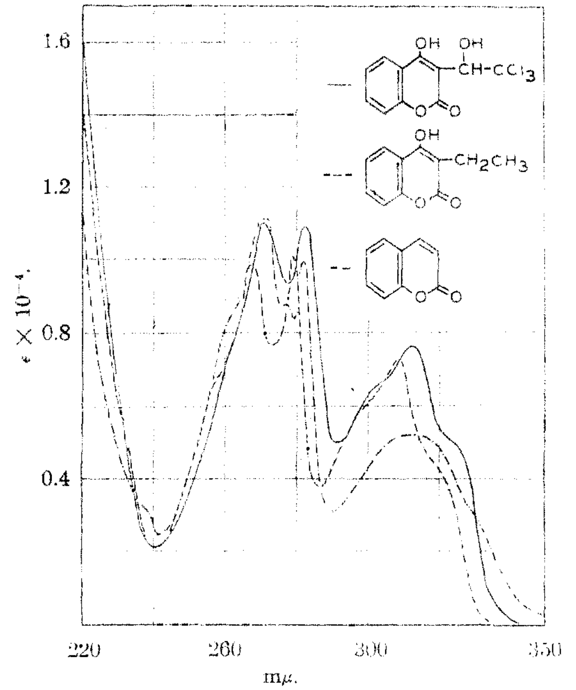
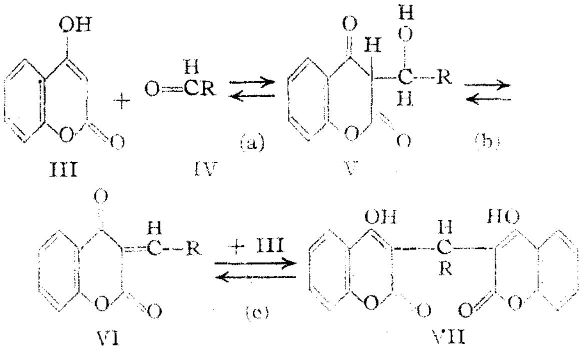


Fig. 1.—Ultraviolet absorption spectra in purified petroleum ether (b. p. range, 65–68°): — chloral condensation product; – – – – 3-ethyl-4-hydroxycoumarin; – · – coumarin.

of the aldehyde.[6] A mechanism has been proposed for this reaction[6] which may be generalized as: (step a) an aldol condensation between the aldehyde (IV) and 4-hydroxycoumarin (III) to yield the aldol (V); (step b) dehydration of the aldol to an α,β-unsaturated ketone (VI); and (step c) condensation of VI with another molecule of III by the Michael reaction to give the final product (VII).



When salicylaldehyde had been used, the intermediate product corresponding to VI was isolated and shown to react with a second molecule of 4-hydroxycoumarin to give a final *bis* type of structure.[6] That 4-hydroxycoumarin does enter into the Michael reaction has been shown by its reaction with a number of α,β-unsaturated ketones.[7] According to the above mechanism the product obtained from the condensation of chloral with 4-hydroxycoumarin represents the result of the first step, and thus completes the isolation of the various intermediates postulated by the mechanism.

Experimental

Condensation of Chloral with 4-Hydroxycoumarin.—The condensation was carried out according to Grüssner.[3] From 10 g. of 4-hydroxycoumarin and 12 g. of chloral hydrate were obtained 11.7 g. of the condensation product melting at 216–217° with decomposition. Grüssner reports 216°.

The **diacetate** was prepared by refluxing 1 g. of the material with 10 cc. of acetic anhydride for three hours. On pouring the reaction mixture into water the product separated out and was recrystallized from ethanol; melting point, 179–180.5°.

Anal. Calcd. for $C_{11}H_5O_4Cl_3(COOH_3)_2$: C, 45.77; H, 2.82; Cl, 27.0. Found: C, 46.09; H, 3.04; Cl, 26.5.

The **dibenzoate** was prepared by dissolving 1 g. of the material in 10 cc. of pyridine, adding 1.2 cc. of benzoyl chloride, and allowing the mixture to stand for three hours, with occasional warming to keep material from coming out of solution. On adding water and acidifying with hydrochloric acid an oil was obtained which partially crystallized. The crystals were washed with ethanol and recrystallized from *n*-propanol; melting point, 215–216°.

Anal. Calcd. for $C_{11}H_5O_4Cl_3(COC_6H_5)_2$: C, 57.99; H, 2.92; Cl, 20.5. Found: C, 57.98; H, 3.15; Cl, 20.56.

The **monomethyl ether** was prepared by distilling an excess of ethereal diazomethane into an ether suspension of the material and allowing the mixture to stand overnight. The excess diazomethane was destroyed by adding a few drops of glacial acetic acid, the ether distilled off, and the product recrystallized from methanol; melting point, 187–188°.

Anal. Calcd. for $C_{11}H_6O_3Cl_3(OCH_3)$: Cl, 32.9; OCH_3, 9.6. Found: Cl, 32.81; OCH_3, 9.7.

Ultraviolet Absorption.—The ultraviolet absorption spectra were determined with a Beckman spectrophotometer, using specially purified ligroin[8] of boiling point range 65–68°.

Acknowledgment.—We are indebted to Dr. Saul Roseman for carrying out the methylation with diazomethane.

Summary

1. The compound resulting from the condensation of chloral hydrate with 4-hydroxycoumarin is shown to be 3-(α-hydroxy-β,β,β-trichloroethyl)-4-hydroxycoumarin.

2. The mechanism of the condensation of aldehydes in general with 4-hydroxycoumarin is discussed.

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(6) Sullivan, Huebner, Stahmann and Link, THIS JOURNAL, **65**, 2288 (1943).

(7) Ikawa, Stahmann and Link, *ibid.*, **66**, 902 (1944).

(8) Weissberger, "Physical Methods of Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1946, p. 767.