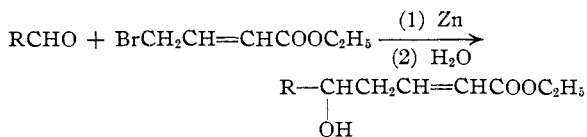


[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Synthesis of Some 5-Substituted-5-hydroxy-2-pentenoic Acids¹BY JAMES ENGLISH, JR., AND J. DELAFIELD GREGORY²

An approach to the synthesis of compounds related to the structure proposed by Kögl³ for auxin *a* is being investigated by the use of the Reformatsky reaction of ethyl 4-bromocrotonate with various cyclic aldehydes.^{4,5} The resulting 5-substituted-5-hydroxy-2-pentenoic esters differ from the auxin *a* structure in that they contain an α,β -double bond instead of the two α,β -hydroxyl groups of the natural product and have simpler substituents in the 5-position.



Ethyl 4-bromocrotonate was prepared by the reaction of N-bromosuccinimide⁶ on ethyl crotonate in the presence of dibenzoyl peroxide,⁷ and unsaturated hydroxy esters were obtained according to the equation above, although in relatively low yield. Much of the product apparently underwent dehydration to give substituted 2,4-pentadienoic esters. Fuson, Arnold and Cooke⁸ observed this dehydration in their work on the Reformatsky reaction between benzaldehyde and 4-bromocrotonic ester; they reported only the isolation of cinnamylidene acetic acid after saponification of the reaction product. In the present work the hydroxy esters were isolated by fractional distillation at low pressures.

Saponification of the 5-substituted-5-hydroxy-2-pentenoic esters with aqueous or alcoholic alkali yielded the corresponding acids except in those cases where the substituent was furyl or 1-cyclopentenyl. These two esters formed dark colored tarry materials from which no pure acids could be isolated.

In view of the physiological activity associated with a number of unsaturated lactones⁸ attempts were made to convert the free acids into the corresponding lactones by treatment with mineral acids. Lactone formation, however, did not take place under any of the conditions tried. It is felt that this is due to a *trans*-configuration of the double bond in the hydroxypentenoic acids which would be expected to prevent lactonization.

The addition of two hydroxyl groups to the double bond⁹ of the 5-substituted-5-hydroxy-2-pentenoic esters and acids is now being studied.

Experimental¹⁰

Cyclic Aldehydes.—Cyclohexylformaldehyde was prepared by the reaction of cyclohexylmagnesium chloride with ethyl orthoformate¹¹ and the acetal hydrolyzed with sulfuric acid. The aldehyde was distilled, b. p. 73–77° (39 mm.), *n*_D²⁰ 1.4514.

Cyclopentylformaldehyde was made by the rearrangement of 2-aminocyclohexanol¹² with nitrous acid by the method of Godchot and Mousseron.¹³ The product was distilled, b. p. 35–40° (16 mm.).

1-Cyclopentenyl-1-formaldehyde resulted from the cyclization of adipic dialdehyde made by the hydrogenation of the ozonide of cyclohexene.¹⁴ The crude dialdehyde was boiled with 6 *N* sulfuric acid¹⁵ and the resulting oil distilled, b. p. 43–47° (11 mm.), *n*_D²⁰ 1.4275.

Reformatsky Reactions.—The three above aldehydes were used immediately after distillation. Benzaldehyde and furfural were also freshly distilled.

Equimolar amounts of the aldehyde and ethyl 4-bromocrotonate were mixed in an equal volume of solvent consisting of five parts of dry benzene to one of dry ether. This solution was added slowly with continuous stirring to 120% of the theoretical amount of activated zinc dust,⁵ allowing the heat of reaction to maintain a brisk reflux. The refluxing was continued in a water-bath for one and one-half hours after the addition.

The mixture was filtered and shaken with 6 *N* sulfuric acid until a final washing with sodium bicarbonate solution gave no precipitate of zinc salt. Drying over sodium sulfate and evaporation of the solvents left an oil which was first rapidly distilled in a small Claisen flask at about 1 mm. The distillate was then fractionated, with a high reflux ratio, through either a 20-cm. column with a Podbielniak spiral packing or a 12-inch Stedman column. The yields and properties of the hydroxy esters are given in Table I.

The furyl analog could not be fractionated because of instability. It was therefore reduced under three atmospheres pressure of hydrogen with a platinum oxide catalyst. The resulting ethyl 5-[2-furyl]-5-hydroxyvalerate could be smoothly distilled, b. p. 87–95° (0.4 mm.), *n*_D²⁰ 1.4741.

Anal. Calcd. for C₁₁H₁₆O₄: C, 62.24; H, 7.60. Found; C, 61.90; H, 7.65.

5-Phenyl-5-hydroxy-2-pentenoic Acid.—Refluxing 4.0 g. of ethyl 5-phenyl-5-hydroxy-2-pentenoate for fifteen minutes with 20% aqueous sodium hydroxide, followed by acidification, gave a precipitate of 1.5 g. of cinnamylideneacetic acid,¹ which was recrystallized from dilute ethanol in large plates, m. p. 164–165.5°.

When the cinnamylideneacetic acid had been removed, the aqueous solution was extracted with ether, yielding 1.3 g. of solid. Repeated recrystallization from water gave colorless leaves of 5-phenyl-5-hydroxy-2-pentenoic acid, m. p. 115–116°.

Anal. Calcd. for C₁₁H₁₂O₃: C, 68.73; H, 6.30; neut. equiv., 192. Found: C, 68.88; H, 6.23; neut. equiv., 189.

(1) Taken from a dissertation submitted by J. Delafield Gregory to the Faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Kögl and Erxleben, *Z. physiol. Chem.*, **227**, 51 (1934).

(4) Ziegler, Schumann and Winkelmann, *Ann.*, **551**, 120 (1942).

(5) Fuson, Arnold and Cooke, *THIS JOURNAL*, **60**, 2272 (1938).

(6) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(7) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(8) Haynes and Jones, *J. Chem. Soc.*, 954 (1946).

(9) English and Gregory, *THIS JOURNAL*, **69**, 2120 (1947).

(10) All m. p. and b. p. are corrected.

(11) Kon, *J. Chem. Soc.*, 1797 (1926).

(12) Wilson and Read, *ibid.*, 1272 (1935).

(13) Godchot and Mousseron, *Compt. rend.*, **198**, 2000 (1934).

(14) Henne and Perilstein, *THIS JOURNAL*, **65**, 2183 (1943).

(15) Wohl and Schweitzer, *Ber.*, **39**, 895 (1906).

TABLE I
UNSATURATED HYDROXY ESTERS: $R-CHCH_2CH=CHCOOC_2H_5$
OH

R =	Yield, %	B. p., °C. (1 mm.)	n_D^{20}	Formula	% Composition			
					Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found	
Phenyl	21	143-145.5	1.5298	$C_{18}H_{16}O_3$	70.89	70.45	7.32	7.40
Cyclohexyl	14	125-127	1.4893	$C_{12}H_{22}O_3$	68.99	68.39	9.80	10.50
Cyclopentyl	23	116-117	1.4865	$C_{12}H_{20}O_3$	67.89	67.44	9.50	9.57
1-Cyclopentenyl	7.5	101-104	1.495	$C_{12}H_{18}O_3$	68.55	68.70	8.62	8.57
2-Furyl	35	101-107	1.4973	$C_{11}H_{14}O_4$

5-Phenyl-5-hydroxyvaleric Acid.—The above hydroxy acid was hydrogenated in absolute ethanol with Adams catalyst, and the product was crystallized from a mixture of chloroform and carbon tetrachloride; m. p. 65.5-66°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.06; H, 7.27; neut. equiv., 194. Found: C, 67.63; H, 7.26; neut. equiv., 193.

5-Cyclohexyl-5-hydroxy-2-pentenoic Acid.—Ethyl 5-cyclohexyl-5-hydroxy-2-pentenoate was saponified with aqueous-alcoholic potassium hydroxide on the steam-bath for one hour. After removal of most of the alcohol and acidification, an oil appeared which crystallized slowly. Several recrystallizations from a mixture of benzene and ligroin gave small needles of hydroxy acid, m. p. 91.5-92°.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; neut. equiv., 198. Found: C, 66.90; H, 9.44; neut. equiv., 198.

5-Cyclohexyl-5-valerolactone.—A sample of the above acid, reduced in absolute ethanol with Adams catalyst, absorbed 0.97 mole of hydrogen per mole of acid. Evaporation of the solvent left a solid, which was recrystallized in an ice-bath from low-boiling petroleum ether containing a little ethyl acetate, as bunches of needles, constant m. p. 59.5-60°. The analysis and properties indicated that the product had lactonized to 5-cyclohexyl-5-valerolactone.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.29; H, 9.54.

The complete hydrogenation of ethyl 5-phenyl-5-hydroxy-2-pentenoate with a particularly active sample

of Adams catalyst, followed by saponification, gave a product with the same properties as the above lactone. A mixed melting point showed no depression.

5-Cyclopentyl-5-hydroxy-2-pentenoic Acid.—Ethyl 5-cyclopentyl-5-hydroxy-2-pentenoate was saponified in the same manner as the cyclohexyl analog. The solid hydroxy acid was crystallized from a mixture of benzene and ligroin in tiny needles to constant m. p. 84.5-85°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76; neut. equiv., 184. Found: C, 64.93; H, 8.79; neut. equiv., 184.

This hydroxy acid, on reduction in absolute ethanol with Adams catalyst, absorbed 1.00 mole of hydrogen per mole of acid, but no crystalline product could be isolated.

Summary

The Reformatsky reaction has been employed in the synthesis of some 5-substituted-5-hydroxy-2-pentenoic esters of the general form $RCHOH-CH_2CH=CH-COOC_2H_5$. R represents phenyl, cyclohexyl, cyclopentyl, 1-cyclopentenyl, and furyl group.

The corresponding acids have been prepared from the phenyl, cyclohexyl and cyclopentenyl analogs.

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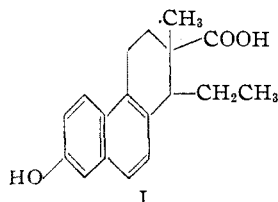
RECEIVED APRIL 25, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Synthesis of Certain Hydroxyacids with Possible Estrogenic Activity

BY JAMES H. HUNTER AND JEROME KORMAN

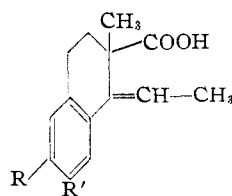
In a series of recent articles Miescher and co-workers reported the synthesis of bisdehydrodoisynolic acid (I) and certain homologs and analogs.¹



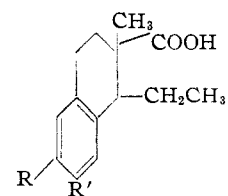
In connection with a more general investigation of synthetic sex hormones in progress in this Laboratory, the present communication describes the synthesis of analogs of I containing the tetrahy-

dronaphthalene nucleus in which the position of the hydroxyl group has been varied.²

In our work both the 7- and 6-hydroxy compounds were prepared by the same series of reaction. Following the procedure of Bachmann and



IIa R = OCH₃, R' = H
IIb R = H, R' = OCH₃



IIIa R = OH, R' = H
IIIb R = H, R' = OH

(1) (a) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); (b) Heer, Billeter and Miescher, *ibid.*, **28**, 1342 (1945); (c) Heer and Miescher, *ibid.*, **28**, 1506 (1945); (d) Anner and Miescher, *ibid.*, **29**, 586 (1946).

(2) While this work was in progress the synthesis of IIa and IIIa was reported.^{1d,3}

(3) Horeau, *Compt. rend.*, **222**, 961 (1946).