

"soluble" 2-amino-4-arsenosphenol hydrochloride has been demonstrated and a mechanism for the conversion of arsonous acids to dichloroarsines suggested.

5. Structures for the various isomeric derivatives of 3-amino-4-hydroxybenzenearsonous acid have been postulated.

DETROIT, MICHIGAN

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

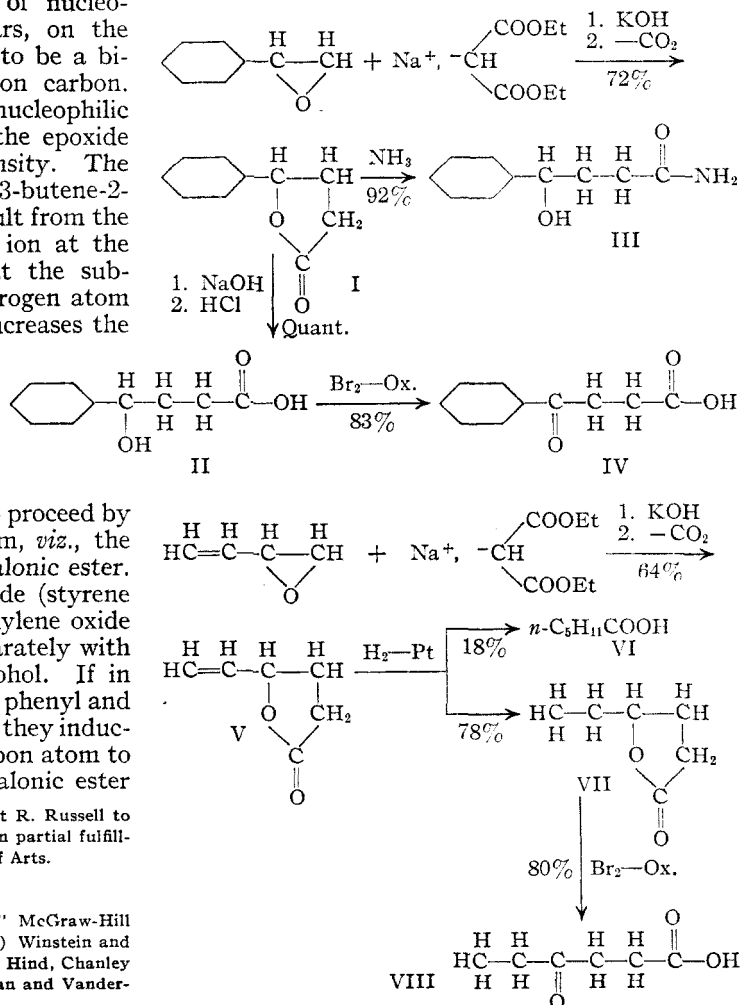
The Malonic Ester Synthesis with Styrene Oxide and with Butadiene Oxide¹

BY ROBERT R. RUSSELL AND CALVIN A. VANDERWERF

Although both the phenyl and vinyl groups are ordinarily considered by advocates of the electronic theory to be more electronegative than hydrogen,² nevertheless there is some indication that the vinyl group, when substituted for a hydrogen atom in ethylene oxide, serves to increase the electron density at the carbon to which it is attached. Kadesch³ has shown that the addition of methanol to butadiene oxide (3,4-epoxy-1-butene) in the presence of sodium produces predominantly 1-methoxy-3-butene-2-ol. The mechanism of this, and similar reactions of nucleophilic reagents with epoxides, appears, on the basis of the occurrence of inversion,⁴ to be a bimolecular nucleophilic displacement on carbon. Further, it is to be expected that the nucleophilic reagent would attack the carbon of the epoxide ring that has the lower electron density. The predominant formation of 1-methoxy-3-butene-2-ol in the reaction cited above must result from the preferential attack of the methoxide ion at the unsubstituted carbon, indicating that the substitution of the vinyl group for a hydrogen atom on a carbon atom in ethylene oxide increases the electron density at that carbon.

In the present investigation a study was made of the effect of the phenyl and vinyl groups in determining the direction of epoxide ring opening in a reaction which has been shown,^{3c,d} almost beyond any doubt, to proceed by a nucleophilic displacement mechanism, *viz.*, the condensation reaction with sodium malonic ester. The phenyl derivative of ethylene oxide (styrene oxide) and the vinyl derivative of ethylene oxide (butadiene oxide) were condensed separately with sodium malonic ester in absolute alcohol. If in these derivatives of ethylene oxide, the phenyl and vinyl groups exhibit a $-I_s$ effect, *i.e.*, if they inductively withdraw electrons from the carbon atom to which they are attached, then the malonic ester

anion would be expected to attack at that carbon. Successive protolysis, hydrolysis and decarboxylation starting with the products thus formed would be expected to yield β -phenyl- γ -butyrolactone and β -vinyl- γ -butyrolactone, respectively. If, on the other hand, the effect of the phenyl and vinyl groups is $+I_s$, the malonic ester anion would be expected to attack at the terminal carbon atom and the predicted final products are, respectively, γ -phenyl- γ -butyrolactone, I, and γ -vinyl- γ -butyrolactone, V.



(1) Abstracted from a thesis presented by Robert R. Russell to the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the Degree of Master of Arts.

(2) See Ingold, *Chem. Revs.*, **15**, 225 (1934).

(3) Kadesch, *This Journal*, **68**, 41 (1946).

(4) a) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 301-303; (b) Winstein and Lucas, *This Journal*, **61**, 1576 (1939); (c) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2606 (1942); (d) Newman and VanderWurf, *ibid.*, **67**, 233 (1945).

Substitution of the electron-releasing⁵ methyl group for a hydrogen atom in ethylene oxide does, indeed, direct the attack of the malonic ester anion to the terminal carbon atom, as indicated by the isolation⁶ of γ -valerolactone by successive hydrolysis and decarboxylation of the product obtained in the condensation of sodium malonic ester with propylene oxide.

It is significant that any electron release which may be indicated for the phenyl or vinyl group in the reaction of the substituted ethylene oxides with sodium malonic ester cannot be of the inductomeric time-variable or I_d type. According to the principles of the electronic theory,⁷ such an effect can be called into play only upon the demand of the attacking reagent. The demand of the malonic ester anion is for an electron deficient center, hence, that ion cannot evoke a temporary displacement of electrons toward the point of its attack.

Results

Condensation of styrene oxide with malonic ester in the presence of sodium ethoxide, followed by successive hydrolysis and decarboxylation of the resulting product, yielded only the single lactone I, indicating a $+I_s$ effect for the phenyl group. The product, I, was characterized by oxidation with bromine in a buffered solution to β -benzoylpropionic acid, IV, and by the preparation of the amide, III, of γ -hydroxy- γ -phenylbutyric acid.

Successive hydrolysis and decarboxylation of the product formed by the condensation of butadiene oxide with malonic ester in the presence of sodium ethoxide, gave only the single lactone V, indicating a $+I_s$ effect for the vinyl group. The product, V, was characterized by catalytic hydrogenation to a mixture, in varying proportions depending on the experimental conditions, of *n*-caproic acid, VI, and γ -caprolactone, VII. The former compound, VI, was identified by the melting point of its amide, and the latter, VII, by oxidation to homolevulinic acid, VIII, the semicarbazone of which gave no depression with the semicarbazone of an authentic sample prepared by the reaction of succinic anhydride with diethylcadmium.⁸

Incidental to the characterization of the major products obtained in this investigation, higher melting points than the corresponding values previously reported in the literature were obtained for several compounds, notably γ -phenyl- γ -butyrolactone, I, γ -hydroxy- γ -phenylbutyric acid, II, and the phenylhydrazone of homolevulinic acid, VIII.

(5) See Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 79.

(6) McRae, Charlesworth, Archibald and Alexander, *Can. J. Research*, **21B**, 186 (1943).

(7) See ref. 5, p. 62.

(8) General method of de Benneville. *J. Org. Chem.*, **6**, 462 (1941).

Experimental⁹

Lactone of 4-Hydroxy-4-phenylbutanoic Acid (γ -Phenyl- γ -butyrolactone), I.—In a typical run, 266 g. (2.22 moles) of styrene oxide was run dropwise during the course of two hours into a 5-liter, three-necked flask, equipped with condenser, thermometer and mercury seal-stirrer and containing a boiling solution of sodiomalonic ester, prepared from 56 g. (2.44 moles) of sodium and 360 ml. (2.38 moles) of dry malonic ester, in 1800 ml. of absolute alcohol.¹⁰ Stirring was continued for three additional hours at the boiling point. The solution was next cooled to room temperature and a cold solution of 200 g. of potassium hydroxide in 800 ml. of water was added with stirring. The resulting solution was heated with stirring and the alcohol removed by means of a take-off condenser. The remaining mixture was cooled and acidified with a sulfuric acid solution obtained by the addition of 161 ml. of concentrated acid to 350 g. of ice. The product was isolated by ether extraction and decarboxylated by heating to 130–140° until evolution of carbon dioxide ceased. Distillation under reduced pressure gave 258 g. (72%) of γ -phenyl- γ -butyrolactone, I, b. p. 126–126.5° at 0.8 mm., 130–130.3° at 1.5 mm. The liquid distillate crystallized upon standing. Recrystallization from petroleum ether (b. p. 95–100°) yielded white translucent plates which melted at 45.5–46.0°.¹¹

4-Hydroxy-4-phenylbutanoic Acid (γ -Hydroxy- γ -phenylbutyric Acid), II.—Exactly 1.62 g. (0.01 mole) of I was added to a solution of 1.4 g. of sodium hydroxide in 10 ml. of water and refluxed until all of the lactone was dissolved. The solution was then cooled in an ice-bath and 7.0 ml. of 6 N hydrochloric acid was added. The solid which settled was recrystallized from boiling water to yield 1.75 g. (theoretical) of II, colorless plates, m. p. 111.0–112.0°.¹²

*Anal.*¹³ Calcd. for C₁₀H₁₂O₃: C, 66.7; H, 6.7. Found: C, 66.5, 66.7; H, 6.9, 6.7.

Ammonium Salt of 4-Hydroxy-4-phenylbutanoic Acid.—Dry ammonia gas was bubbled into a solution of 3.60 g. (0.02 mole) of II in 10 ml. of a mixture of benzene and ether. The ammonium salt, which precipitated, was obtained as a white powder, m. p. 150.4–152.0°, with decomposition at 155°.

Anal. Calcd. for C₁₀H₁₅O₃N: N, 7.1. Found: N, 7.1, 7.3.

4-Hydroxy-4-phenylbutanamide (γ -Hydroxy- γ -phenylbutyramide), III.—Exactly 3.25 g. (0.02 mole) of the lactone I with about 12 ml. of liquid ammonia was heated in a bomb for four hours. At the end of this time the bomb was cooled and the pressure was released gradually. The contents was transferred at once to a vacuum desiccator and the excess ammonia removed under reduced pressure. Recrystallization of the residue from benzene-petroleum ether gave 3.3 g. (92%) of III, a colorless solid, m. p. 85.5–86.5°.¹⁴

4-Keto-4-phenylbutanoic Acid (β -Benzoylpropionic Acid), IV.—Following the procedure of McRae, *et al.*,¹⁵ a hot solution of 174 g. of hydrated magnesium sulfate in 130 ml. of water was added to a hot solution of 60 g. of sodium hydroxide and 64.8 g. (0.4 mole) of I in 300 ml. of water. The solution was cooled below 10° and 22 ml. (0.4 mole) of bromine was added dropwise with stirring

(9) All melting points corrected.

(10) Manske, *This Journal*, **53**, 1106 (1931).

(11) Fittig and Jayne, *Ann.*, **216**, 97 (1883), reported a value of 37° for the product prepared by hydrolysis of the bromo compound obtained by addition of hydrogen bromide to styrylacetic acid.

(12) Fittig and Jayne reported 76° for the melting point of a sample of the acid prepared by hydrolysis of the lactone which they obtained as described above.¹¹

(13) Microanalysis by Carl Tiedcke Laboratories, New York, N. Y.

(14) In agreement with the value reported by Fittig, *Ann.*, **256**, 155 (1890).

(15) McRae, Charlesworth and Alexander, *Can. J. Research*, **21B**, 1 (1943).

over a two hour period. Upon addition of 130 ml. of 6 *M* sulfuric acid, a solid separated at the top and a thick yellow oil at the bottom of the water layer. The solid was removed by filtration and the oil extracted with ether and separated into neutral and acid fractions. Unreacted lactone, I,¹⁶ (18.5 g.) was recovered from the neutral fraction. The solid obtained upon acidification of the acid fraction with dilute hydrochloric acid was added to that obtained after the original acidification of the reaction mixture and the combined material recrystallized from hot water to yield 42 g. (83% based on lactone used) of IV, colorless plates, m. p. 115.0–115.5°. No depression was observed in a mixed melting point with an authentic sample of β -benzoylpropionic acid prepared by the reaction of succinic anhydride with benzene.

Lactone of 4-Hydroxy-5-hexenoic Acid (γ -Vinyl- γ -butyrolactone), V.—This preparation was conducted exactly like that of γ -phenyl- γ -butyrolactone, I, excepting that 185 ml. (2.22 moles) of butadiene oxide was used in place of styrene oxide and that the condensation was carried out at 40–45° rather than at the boiling point and was continued until the mixture became sufficiently viscous to stop the stirrer (about four hours). Distillation of the final product under reduced pressure gave 160 g. (64%) of the colorless γ -vinyl- γ -butyrolactone, V, b. p. 75° at 2 mm.; n_D^{25} 1.4603; d_4^{25} 1.0659; MR_D calcd., 28.90; obsd., 28.83.

Anal. Calcd. for $C_6H_8O_2$: C, 64.3; H, 7.2. Found: C, 64.5, 64.4; H, 7.3, 7.5.

Catalytic Reduction of V.—Pressure reduction (40 lb.) of 93 g. (0.83 mole) of V dissolved in 150 ml. of alcohol in the presence of 0.7 g. of platinum catalyst was complete in one hour. The product was separated into acid and neutral fractions. Vacuum distillation of the former gave 17.4 g. (18%) of *n*-caproic acid, VI, identified by means of a mixed melting point of the amide with an authentic sample. The neutral fraction was distilled to yield 74.1 g. (78%)¹⁷ of γ -caprolactone, VII, b. p. 119° at 33 mm.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Found: C, 63.0, 63.2; H, 8.9, 9.0.

4-Ketohexanoic Acid (Homolevulinic Acid), VIII.—The keto-acid was prepared from VII by a procedure exactly analogous to that used in the preparation of IV from I,

(16) The hydroxy-acid, II, first formed when the sodium salt is acidified, is relactonized in the presence of excess sulfuric acid.

(17) It was found that the percentages of VI and VII obtained by the reduction of V could be varied within limits of from 10 to 33% of VI and from 85 to 65% of VII, depending upon the conditions of temperature and pressure and upon the catalyst used. In addition, a sample of VII was hydrogenated over platinum catalyst at 200° and a pressure of 1900 lb. per sq. in. to yield 13% of VI, and 84% of recovered lactone.

equal molar quantities of each reagent being employed. Distillation of the product gave 8 g. of recovered lactone, VII, and 32 g. (80% on the basis of lactone reacted) of a colorless liquid, b. p. 89.0° at 0.4 mm., 105° at 1.4 mm. Upon being cooled in an ice-salt bath, this distillate formed a solid mass which recrystallized from petroleum ether in colorless prisms of VIII, m. p. 39.1–40.0°. The semicarbazone, m. p. 174.8–176.0°,¹⁸ with decomposition at 181°, gave no depression with that of an authentic sample of homolevulinic acid prepared by the reaction of diethyl cadmium with succinic anhydride.⁸

Anal. Calcd. for $C_7H_{12}O_2N_2$: N, 22.4. Found: N, 22.2, 22.3.

The phenylhydrazone melted at 151.2–152.0°¹⁹ and did not depress the melting point of an authentic sample.

Anal. Calcd. for $C_{12}H_{16}O_2N_2$: N, 12.7. Found: N, 12.6, 12.6.

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Summary

1. The condensation of styrene oxide and of butadiene oxide with sodium malonic ester, followed in each case by hydrolysis and decarboxylation, has been found to yield γ -phenyl- γ -butyrolactone and γ -vinyl- γ -butyrolactone, respectively. The fact that no other lactone could be isolated in either case indicates that the attack of the nucleophilic anion of malonic ester occurs exclusively at the terminal (unsubstituted) carbon atom of the epoxide ring.

2. On the basis of the direction of epoxide ring opening in the reaction of styrene oxide and of butadiene oxide with sodium malonic ester, the generalization that the phenyl and vinyl groups always exhibit a $-I_s$ effect as compared with the hydrogen atom, appears unjustified.

LAWRENCE, KANSAS

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(18) Campbell and Thorpe, *J. Chem. Soc.*, **97**, 1299 (1910), reported that this product decomposes at 176°.

(19) Müller and Feld, *Monatsh.*, **58**, 22 (1931), reported the value 73°.