bon. The product was filtered and washed with 50% (vol.) methanol to give 33.1 g. (61%) of white crystals, m. p. 104.5–105.5°.

(C) **N-β-(3,4-Diethoxyphenethyl)-3,4-diethoxyphenylacetamide.**—A mixture of 35.5 g. of 3,4-diethoxyphenethylamine and 38 g. of 3,4-diethoxyphenylacetic acid suspended in 250 ml. of diphenyl ether was heated at 210° ± 5° for one-half hour. The crude amide was precipitated by adding Skellysolve B to the cooled reaction mixture. Two recrystallizations from dilute methanol yielded 49.5 g. (70%) of white crystals, m. p. 106.5–107°.

All the amides in Table I were treated substantially as in the following examples to obtain the isoquinolines as listed in Table II, and their salts, Table III.

6-Methoxy-7-ethoxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline.—A mixture of 45 g. of N-β-(3-methoxy-4-ethoxyphenethyl)-homoveratramide, 200 ml. of thiophene-1 free benzene, and 10 ml. of phosphorus oxychloride was refluxed two and one-half hours. The cooled solution was decomposed with excess dilute sodium hydroxide solution and washed with water. The operation from the time of addition of phosphorus oxychloride until beginning of dehydrogenation was carried out in an atmosphere of nitrogen. The washed benzene layer was distilled to remove the last of the water and most of the benzene, at which point 100 ml. of decalin was added. The distillation of solvent was continued under stirring until the flask contents reached 180°. One and one-half grams of 5% palladium on carbon suspended in 50 ml. of decalin was added. The dehydrogenation of the dihydroisoquinoline to isoquinoline was completed in five hours under total reflux. The reaction temperature varied from 184 to 196°. The hot solution was filtered to remove the catalyst and Skellysolve B was eventually added to complete the precipitation of the isoquinoline. The solid was filtered, washed well with Skellysolve B, and dried at 70° overnight to remove most of the residual decalin. The base was dissolved in hot 50% (vol.) ethanol, decolorized with carbon and allowed to cool. The solid was filtered, washed with dilute alcohol and dried. A second recrystallization gave 35.0 g. of a white solid, m. p. 129–130.5°.

6-Methoxy-7-ethoxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline Hydrochloride.—Thirty grams of the isoquinoline was dissolved in 100 ml. of absolute ethanol and 5 g. of dry hydrogen chloride was added. The salt was precipitated by the addition of ether. The white crystals were filtered and recrystallized from 95% ethanol, three volumes of ether being added to complete crystallization. Thirty-two grams (96%) of the hydrochloride was obtained, m. p. 200–204°.

Acknowledgments.—The authors are indebted to the following personnel of these laboratories for their invaluable aid: W. L. Brown, H. L. Hunter and W. J. Schenck for microanalyses; R. E. Shipley, K. K. Chen and R. C. Anderson for pharmacological evaluation; and Claudene K. Simmans for preparative assistance.

Summary

Fifteen ethoxy-methoxy homologs of papaverine have been prepared and their therapeutic value as coronary dilators has been determined. A minimum correlation of action and structure has been found.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Condensation of Acetoacetic Ester with Some Unsymmetrical Epoxides

BY ROY M. ADAMS[1] AND CALVIN A. VANDERWERF

No completely satisfactory explanation of the direction of ring-opening in S_N2 attack on unsymmetrical epoxides has yet been offered. It is becoming increasingly apparent,[2] however, that steric factors may be mainly responsible for the fact that attack by the nucleophilic agent has generally been found to occur preferentially at the unsubstituted or primary carbon of terminal epoxides. On the other hand, recent evidence[3] indicates that in the reaction of such epoxides as styrene oxide and 3,4-epoxy-1-butene with certain bases the effect of allylic resonance[3a] in lowering the energy of the transition state involved in nucleophilic attack at the secondary carbon atom may outweigh the steric factors which favor attack at the primary carbon.

In an attempt to shed further light on the relationship between steric and electronic factors and the direction of ring opening of unsymmetrical epoxides in S_N2 reactions, we have studied the base catalyzed condensation of acetoacetic ester with three representative epoxides, propylene oxide, styrene oxide and 3,4-epoxy-1-butene. Choice of acetoacetic ester was dictated by the facts that its reactions with epoxides should certainly be expected to proceed, like those of malonic ester,[4] by the S_N2 mechanism, but that steric requirements should be slightly less for acetoacetic than for malonic ester. In addition, the expected products of the condensation reactions themselves should be compounds of considerable chemical interest.

Only a few isolated studies of the condensation of acetoacetic ester with specific epoxides have been reported.[5] In each case the product isolated was a substituted α-acetyl-γ-butyrolactone, presumably formed by inner transesterification of the expected β-hydroxyalkylacetoacetic ester.

Results

The sole product isolated in the base-catalyzed condensation of the saturated epoxide propylene

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[1] American Chemical Society Fellow 1946–1947. Geneva College, Beaver Falls, Pennsylvania.

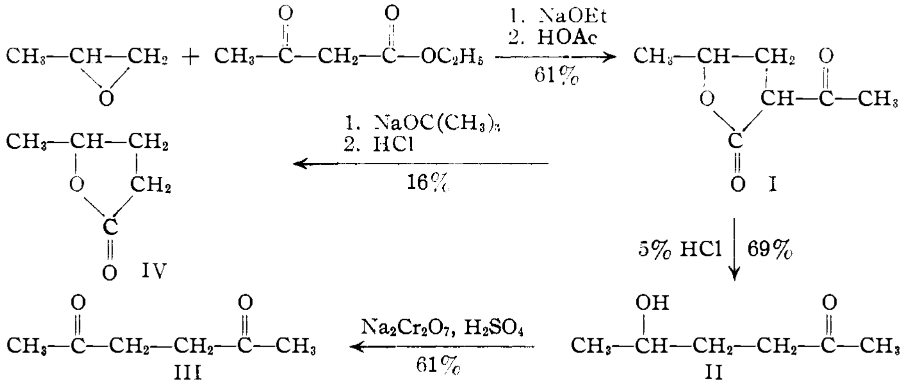
[2] See Brown and Eldred, THIS JOURNAL, **71**, 445 (1949).

[3] See (a) Bartlett and Ross, *ibid.*, **70**, 926 (1948); (b) Swern, Billen and Knight, *ibid.*, **71**, 1152 (1949); (c) Trevoy and Brown, *ibid.*, **71**, 1675 (1949); (d) Guss, *ibid.*, **71**, 3460 (1949).

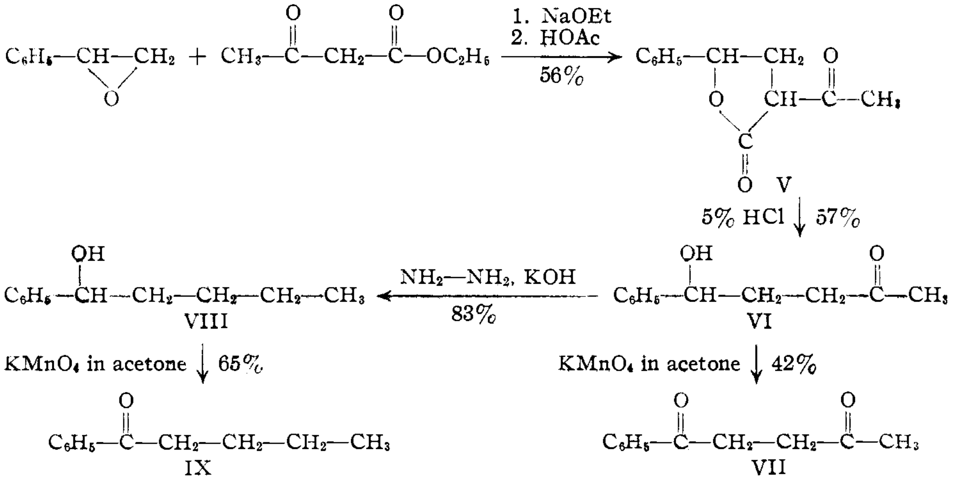
[4] Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2606 (1942).

[5] See Traube and Lehmann, *Ber.*, **34**, 1971 (1901); Knunyantz, Chilintzev and Osetrova, *Compt. rend. acad. sci. U. R. S. S.*, **1**, 315 (1934); Cheliutsev and Osetrova, *J. Gen. Chem. (U. S. S. R.)*, **7**, 2373 (1937).

oxide with acetoacetic ester was α-aceto-γ-valerolactone, I, indicating that the attack of the anion of acetoacetic ester on the epoxide occurred exclusively at the primary position. The structure of I was proved by decarboxylation to 5-hydroxy-2-hexanone (II), which was identified as the semicarbazone. The structure of II was further confirmed by oxidation to acetonylacetone (III), which was identified as the dioxime and the 2,4-dinitrophenylhydrazone. I was also cleaved in poor yield to γ-valerolactone (IV).



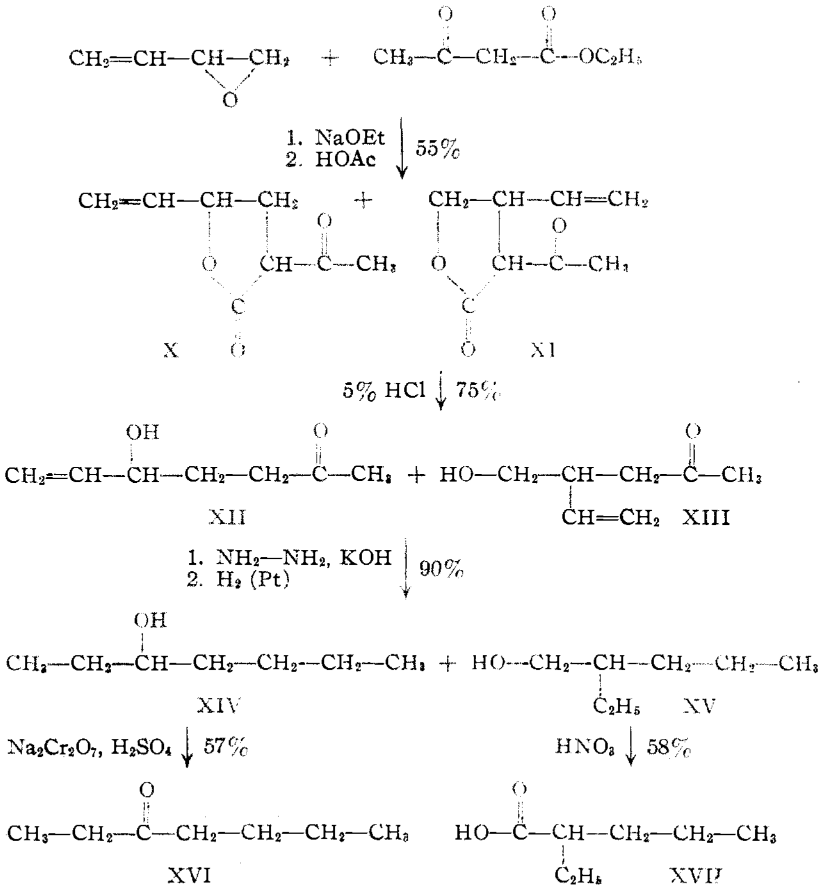
With styrene oxide the product was entirely α-aceto-γ-phenyl-γ-butyrolactone (V) formed by attack of the acetoacetic ester anion at the primary position of the epoxide. The structure of V was established by decarboxylation to 5-hydroxy-5-phenyl-2-pentanone (VI), which was oxidized to phenacylacetone (VII). The latter was identified by means of its derivatives with aniline and with *p*-phenylenediamine. The structure of VI was further confirmed by Wolff–Kishner reduction to 1-phenyl-1-pentanol (VIII) and oxidation of the latter to valerophenone (IX), which was identified as the semicarbazone.



In the condensation of acetoacetic ester with 3,4-epoxy-1-butene, the product resulting from attack at the primary carbon, α-aceto-γ-vinyl-γ-butyrolactone (X), and the isomeric product formed by attack at the secondary carbon, α-aceto-β-vinyl-γ-butyrolactone (XI), were obtained in what were apparently approximately equal quantities. All attempts to isolate the pure individual lactones by careful fractional distillation were unsuccessful. The mixture was decarboxylated directly to a mixture of the isomeric alcohols 5-hydroxy-6-hepten-2-one (XII) and 5-hydroxy-4-vinyl-2-pentanone (XIII). Because of the labile nature of these keto-alcohols, no attempt was made to separate them. Instead the mixture was reduced, first by a modification of the Wolff–Kishner reaction, and then by catalytic hydrogenation, to give a mixture from which the isomeric alcohols 3-heptanol (XIV) and 2-ethyl-1-pentanol (XV) were isolated in approximately equal quantities by fractional distillation. The structure of XIV was established by oxidation to 3-heptanone (XVI), which was identified as the semicarbazone. XV was identified by means of its 3-nitrophthalate, and its structure was confirmed by oxidation to 2-ethylpentanoic acid (XVII), which was identified as the anilide and the *p*-toluide.

Discussion

Attack of the acetoacetic ester anion at the primary position of propylene oxide is consistent



with the findings of others[6,3b] in their studies of S_N2 attack on propylene oxide by other bases. The results of the condensation of acetoacetic ester with styrene oxide and with butadiene oxide, together with those recently reported for other S_N2 reactions involving these epoxides, seem to form a fairly consistent pattern if electronic and steric factors are considered together.

Actually the effect of allylic resonance in lowering the energy of the transition state involved in attack at the secondary carbon should be greater in the case of styrene oxide than in the case of 3,4-epoxy-1-butene. With such bulky bases as the anions of malonic ester[7] and acetoacetic ester, however, steric factors appear to preclude attack at the secondary carbon of styrene oxide. Study of space models suggests that this interpretation is entirely reasonable. Even in the case of the less hindered 3,4-epoxy-1-butene, steric factors still dictate the course of the reaction with malonic ester, but in the reaction with the smaller acetoacetic ester the lesser steric effects are apparently partially overcome by the allylic resonance effect. With a still smaller base such as the phenoxide ion,[3d] the steric effect in the case of styrene oxide is even more completely outweighed,[8] whereas with alloxide ion[3b] the steric effects are essentially entirely outweighed. Similarly in the case of 3,4-epoxy-1-butene, the resonance stabilization effect may largely or completely counterbalance the steric effects when relatively small bases such as methoxide ion[3a] or alloxide ion[3b] are the attacking agents. Unfortunately, the exact nature of the attacking base in the reduction of epoxides with lithium aluminum hydride[3c] is a matter of speculation. From the fact that the attack on styrene oxide is almost entirely, and on 3,4-epoxy-1-butene very largely, on the primary carbon, however, it would appear that the participating basic ions are comparable in size to the acetoacetic ester anion.

It should be emphasized that, although the steric hindrance explanation here offered seems reasonable and consistent, there is as yet no conclusive evidence for it.

Experimental[9]

Materials.—Propylene oxide, styrene oxide, and 3,4-epoxy-1-butene were the purest commercial products available. The last two were distilled through an efficient fractionating column just before use. Absolute ethanol was prepared from the commercial product by the method of Manske.[10]

α-Aceto-γ-valerolactone, I.—To 2 l. of absolute ethanol contained in a 5-l., 3-necked flask, cooled in a cold water-bath and equipped with a sealed mechanical stirrer and a reflux condenser fitted with a drying tube, 108 g. (4.7 g. atoms) of sodium was added in large pieces. The cooled mixture was stirred overnight while the sodium dissolved.

The flask was then packed in ice and equipped with a calibrated dropping funnel through which 635 ml. (650 g., 5.00 moles) of ethyl acetoacetate was added rapidly. Propylene oxide (350 ml., 290 g., 5.00 moles), previously chilled in a Dry Ice chest, was next added dropwise with stirring over a period of thirty minutes.

The mixture was stirred overnight while it was allowed to warm to room temperature. The alcohol was then taken off under reduced pressure (less than 100 mm.), the temperature never being permitted to rise above 50°. To the sirupy residue there was added 30 ml. (315 g., 5.25 moles) of glacial acetic acid and 300 g. of ice. The excess acetic acid was neutralized with sodium bicarbonate. The supernatant oily layer was separated, the residue extracted with ether, and the combined material was dried over anhydrous sodium sulfate. The ether was removed and the residue distilled from a modified Claisen flask

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[6] Chitwood and Freure, This Journal, **68**, 680 (1946); Reeve and Saddle, paper presented at the 113th meeting of the American Chemical Society held in Chicago, April, 1948.

[7] Russell and VanderWerf, *ibid.*, **69**, 11 (1947).

[8] The author's data suggest, however, that a small percentage of the primary alcohol resulting from attack at the secondary carbon of the epoxide was formed as a result of S_N1 reaction.

[9] Melting points corrected, boiling points uncorrected.

[10] Manske, *ibid.*, **53**, 1106 (1931).

equipped with a 30-cm. Vigreux side arm. After a small forerun of unreacted acetoacetic ester, there was obtained 436 g. (61.4%) of the colorless lactone of 2-acetyl-4-hydroxypentanoic acid (α-aceto-γ-valerolactone, I) b. p. 88–90° at 2 mm. (118–119° at 8 mm.); n^{25}D 1.4489; d^{25}_4 1.1013.

Anal.[11] Calcd. for $C_7H_{10}O_3$: C, 59.1; H, 7.0. Found: C, 58.9; H, 7.0.

5-Hydroxy-2-hexanone, II.—In a 500-ml. flask equipped with a reflux condenser, a mixture of 100 g. (0.70 mole) of I, 50 ml. of 12 *N* hydrochloric acid and 250 ml. of distilled water was warmed to 70° on a steam-bath and immediately allowed to cool while carbon dioxide was evolved for the next three hours. The mixture was then neutralized and the solvent saturated with potassium carbonate. The supernatant oil was taken off, the aqueous residue extracted with ether, and the combined extracts dried over potassium carbonate. The solvent was removed, and upon distillation of the residue through a modified Claisen flask, there was obtained 56 g. (69.0%) of 5-hydroxy-2-hexanone, II, b. p. 79–82° at 16 mm.[12] A sample for analysis and physical properties was taken at 2 mm.[13]; b. p. 61° at 2 mm.; n^{25}D 1.4312; d^{25}_4 0.9626.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.1; H, 10.3. Found: C, 62.1; H, 10.3.

The semicarbazone melted at 151.0–151.5° in agreement with the reported[12] value 149–150°.

Anal. Calcd. for $C_7H_{15}O_2N_3$: N, 24.3. Found: N, 24.7.

Oxidation of II.—In a 500-ml. 3-necked flask packed in ice and equipped with reflux condenser, dropping funnel and mechanical stirrer, 40 g. (0.34 mole) of II, previously mixed with 50 g. of ice and 75 ml. of 12 *N* sulfuric acid, was added dropwise to 34 g. (0.11 mole) of sodium dichromate. After the initial strongly exothermic reaction had subsided, the mixture was warmed on a steam-bath for fifteen minutes, then allowed to stand overnight.

The mixture was then neutralized with sodium carbonate and distilled with steam until no more oil separated from saturated potassium carbonate solution. The entire distillate was saturated with potassium carbonate and extracted with ether. The combined extracts were dried over anhydrous sodium sulfate. The solvent was removed and the residue was distilled to give 24.0 g. (61.0%) of 2,5-hexanedione (acetonylacetone, III), b. p. 186–192°; n^{25}D 1.4227.[14]

Dioxime: m. p. 136.2–136.9°; reported[12] 137°.

Bis-2,4-dinitrophenylhydrazone: m. p. 255.8–257.0°; reported[15] 257°.

The residue from the initial steam distillation was acidified with sulfuric acid and then extracted with ether. The combined extracts were dried over anhydrous sodium sulfate. No high boiling residue remained after removal of the solvent.[16]

Acid Cleavage of I.—Sodium *t*-butoxide (9.6 g., 0.10 mole) and 28.4 g. (0.20 mole) of I were dissolved in 150 ml. of *t*-butyl alcohol freshly distilled from sodium. The mixture, protected from atmospheric moisture, was refluxed for twenty-four hours and was then made neutral to litmus with 12 *N* hydrochloric acid. The precipitated salt was removed by filtration and the filtrate distilled. After removal of the *t*-butyl alcohol and water from the filtrate by distillation at atmospheric pressure, the residue was distilled *in vacuo* to give 3.1 g. (16.0%) of the lactone of 4-hydroxypentanoic acid (γ-valerolactone, IV), b. p. 51–52° at 1 mm.; n^{25}D 1.4312. The physical constants agreed with those of an authentic sample of γ-valerolactone and the same derivative, the hydrazide of γ-hydroxy-*n*-valeric acid, m. p. 64.5–65.0°,[17] was obtained from both the product and the comparison sample. A small amount (2.0 g.) of I was also recovered in the distillation and considerable non-distillable gummy residue remained.

α-Aceto-γ-phenyl-γ-butyrolactone, V.—This preparation was carried out by the same general method as was that of I. Styrene oxide (570 ml., 600 g., 5.00 moles) was used in place of propylene oxide. It was not necessary to pre-chill the styrene oxide, and the reaction flask was kept in a water-bath at room temperature. Benzene was used for extractions instead of ether. Distillation of the final product gave 572 g. (56%) of the colorless lactone of 2-acetyl-4-hydroxy-4-phenylbutanoic acid (α-aceto-γ-phenyl-γ-butyrolactone, V), b. p. 153–165° at 2 to 3.5 mm.; n^{25}D 1.5395; d^{25}_4 1.1772. In several runs there was always some pressure fluctuation during the distillation, indicating some decomposition. The refractive index of the product remained essentially constant throughout the distillation.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9. Found: C, 70.6; H, 5.8.

5-Hydroxy-5-phenyl-2-pentanone, VI.—A mixture of 100 g. (0.49 mole) of V dissolved in 200 ml. of absolute ethanol and 100 ml. of 6 *N* hydrochloric acid contained in a 500-ml. erlenmeyer flask was maintained at 40–50° on a steam-bath with stirring for twenty-four hours. At the end of this time evolution of carbon dioxide had subsided. The resulting solution was saturated with potassium carbonate, and the alcoholic layer was separated and dried over anhydrous sodium sulfate. After removal of the alcohol, there was obtained 50.0 g. (57%) of pale yellow 5-hydroxy-5-phenyl-2-pentanone, VI, b. p. 127–129° at 1 mm. Redistillation of this product for the preparation of an analytical sample left more than 30% of the material in the distillation flask as a clear yellow gum, perhaps the dimeric ether.[18] The analytical sample gave the physical constants n^{25}D 1.5311, d^{25}_4 1.1000.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.1; H, 7.5.

Phenacylacetone, VII.—To an ice-cooled solution of 19.7 g. (0.11 mole) of freshly prepared VI dissolved in 100 ml. of acetone there was added slowly with stirring a solution of 20 g. (0.13 mole) of potassium permanganate and 0.5 g. of sodium hydroxide in 100 ml. of acetone and 200 ml. of water. The solution was allowed to warm to room temperature overnight and was then acidified with 12 *N* sulfuric acid and decolorized by means of sulfur dioxide. The acetone was removed by distillation and the residual mixture extracted several times with benzene. The combined extracts were dried over anhydrous sodium sulfate and distilled to yield 8.1 g. (42%) of pale yellow 1-phenyl-1,4-pentanedione (phenacylacetone, VII), b. p. 109–112° at 0.35 mm.; n^{30}D 1.5250. Our product, although phenacylacetone is reported by Helberger[19] as a bright yellow solid melting at 29°, could not be induced to crystallize, nor could an authentic sample prepared by the Friedel–Crafts reaction of levulinyl chloride with benzene. Two derivatives, 2-methyl-1,5-diphenylpyrrole, m. p. 82.5–83.0°, and 2-methyl-5-phenyl-1-(4-aminophenyl)-pyrrole, m. p. 136.8–137.1°, prepared by the method of Helberger,[19] proved identical with the corresponding derivatives obtained from the authentic sample

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(11) Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(12) Lipp and Scheller, *Ber.*, **42**, 1960 (1909), reported the boiling point at 10 mm. as 80–81°.

(13) Samples taken at higher pressures and temperatures were all high in carbon and low in hydrogen. Lipp and Scheller[12] and Wohlgemuth, *Compt. rend.*, **159**, 80 (1914), both reported similar difficulties with γ-ketoalcohols, blaming loss of water through dihydrofuran formation. It is possible, however, that the ether formed between the two tautomeric modifications of the ketoalcohol may be involved [see Stevens and Stein, THIS JOURNAL, **62**, 1045 (1940)].

(14) Gray, *J. Chem. Soc.*, **79**, 681 (1901), reported n^{25}D 1.4232.

(15) Armstrong and Robinson, *ibid.*, 1650 (1934).

(16) If any α-aceto-β-methyl-γ-butyrolactone had been formed in the original condensation of acetoacetic ester with propylene oxide, some α-methyllevulinic acid, b. p. 153-156°, might be expected at this point.

(17) Darapsky, *et al.*, *J. prakt. Chem.*, [2] **147**, 145 (1936), reported the value 65°.

(18) See Stevens and Stein, THIS JOURNAL, **62**, 1045 (1940).

(19) Helberger, *Ann.*, **522**, 269 (1936).

of phenacylacetone, and the melting point values agree with those of Helberger.

Acidification of the basic washings with 12 *N* sulfuric acid precipitated 2.0 g. of a colorless solid which melted sharply at 122° and gave no depression in a mixed melting point determination with benzoic acid. The material gave no indication of the phenylhydrazone formation characteristic of α-phenyllevulinic acid, which might be expected to appear at this point if any of the original lactone had been α-aceto-β-phenyl-γ-butyrolactone.

1-Phenyl-1-pentanol, VIII.—A solution of 46.9 g. (0.26 mole) of freshly distilled VI in 400 ml. of triethylene glycol was placed in a 1-l. 3-necked flask equipped with a thermometer, reflux condenser and take-off adapter. To the solution was added 35 ml. (36 g., 0.72 mole) of 100% hydrazine hydrate and 50 g. (0.89 mole) of potassium hydroxide, and the mixture was refluxed overnight. Aqueous distillate was then tapped off until the temperature reached 185°. Refluxing was continued for four hours. The solution was then cooled to 40° in an ice-bath and an equal volume of water was added. The solution was neutralized with 12 *N* hydrochloric acid, and the upper oily layer was separated. The residue was extracted repeatedly with ether, and the combined extracts were dried over anhydrous sodium sulfate. After removal of the solvent, the product was fractionated through a 20-cm. Vigreux column to yield 35.8 g. (83.0%) of 1-phenyl-1-pentanol, VIII (phenylbutylcarbinol), b. p. 140–142°[20] at 25 mm.; n^{25}D 1.4806; d^{25}_4 1.010.

Oxidation of VIII.—A solution of 21 g. (0.13 mole) of potassium permanganate in 400 ml. of water was added dropwise with stirring to a solution of 16.4 g. (0.10 mole) of VIII and 5 g. of potassium hydroxide in 50 ml. of acetone, contained in a 1-l. 3-necked flask placed in an ice-bath and equipped with a mechanical stirrer and a dropping funnel. The resulting solution was stirred overnight during which time it was allowed to come to room temperature. The precipitated manganese dioxide was removed by filtration, and the filtrate was acidified and extracted several times with benzene. The combined extracts were washed with 5% sodium carbonate solution, dried over sodium sulfate and distilled to yield 10.5 g. (65%) of valerophenone, IX (1-phenyl-1-pentanone), b. p. at 25 mm. 136–141°[21]; n^{25}D 1.5080.

The semicarbazone melted at 166.5–167.3°, in agreement with the reported value 166°.[22]

Acidification of the sodium carbonate washings yielded only benzoic acid (1.6 g.).

Condensation of Acetoacetic Ester with 3,4-Epoxy-1-butene.—This reaction was conducted just as was the preparation of I, except that 400 ml. (350 g., 5.00 moles) of 3,4-epoxy-1-butene was used in place of propylene oxide. After about four hours of stirring, the reaction mixture set to a heavy paste. The mixture was then allowed to stand overnight without stirring. The combined yield of the lactone of 2-acetyl-4-hydroxy-5-hexenoic acid (α-aceto-γ-vinyl-γ-butyrolactone, X) and the lactone of 2-acetyl-3-vinyl-4-hydroxybutanoic acid (α-aceto-β-vinyl-γ-butyrolactone, XI), b. p. 89–92° at 2 mm., was 425 g. (55.1%); n^{25}D 1.4714; d^{25}_4 1.1157.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.4; H, 6.5. Found: C, 62.4; H, 6.4.

All attempts to fractionate the mixture by means of efficient packed columns of various types were unsuccessful. The mixture distilled at constant temperature and the refractive index of the distillate remained essentially constant throughout the distillation. Attempts to separate the 2,4-dinitrophenylhydrazones of the two lactones by chromatographic methods failed.

Decarboxylation of X and XI.—A total of 88 g. (0.57 mole) of the mixture of lactones, X and XI, was stirred with 230 ml. of water and 50 ml. of 12 *N* hydrochloric acid at 40–50° for eight hours. At the end of this period the lactones had dissolved and evolution of carbon dioxide had ceased. The product was then isolated by the method used for II. There was obtained a total of 55 g. (75.0%) of a mixture of the isomeric ketoalcohols 5-hydroxy-6-hepten-2-one, XII, and 5-hydroxy-4-vinyl-2-pentanone, XIII, boiling at 76–87° at 5 mm.; n^{25}D 1.4546; d^{25}_4 0.9793. An analytical sample was prepared by taking a midcut of the third of three consecutive distillations. The analysis was made at once.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.9; H, 9.2.

Distillation of the material after it had stood overnight yielded mainly a material boiling at 107–109° at 5 mm. The lower boiling mixture of ketoalcohols could be regenerated quantitatively by dissolving of this material in 5% hydrochloric acid followed by neutralization of the acid solution with potassium carbonate. It appears probable, therefore, that the high boiling material was a mixture of ethers formed between the two tautomeric modifications of each of the ketoalcohols.[18]

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.5; H, 9.2. Found: C, 69.9; H, 9.3.

Reduction and Hydrogenation of XII and XIII.—When the labile nature of XII and XIII was discovered, further degradations were carried past this stage without isolation of the mixture of ketoalcohols. Exactly 200 g. (1.30 moles) of the mixture of X and XI was stirred overnight with 510 ml. of distilled water and 90 ml. of concentrated hydrochloric acid. There was formed a clear, slightly darkened solution which was saturated with potassium carbonate. The supernatant layer was separated and added immediately to a 1-l. 2-necked flask equipped with a thermometer and a reflux condenser, and containing a mixture of 140 ml. (144 g., 2.50 moles) of 100% hydrazine hydrate and 140 g. (2.50 moles) of potassium hydroxide. A marked evolution of heat ensued. The flask was heated under reflux for two hours. The distillate was then tapped off while the temperature was allowed to rise slowly to 190°. Evolution of nitrogen began at 135°.

The upper layer of the distillate was separated and the aqueous residue extracted with ether. The combined product and extracts were dried over anhydrous sodium sulfate. Attempts to distill the product at reduced pressure resulted in excessive foaming. Finally the material was filtered through a column of 5 g. of Norite mixed with 5 g. of Hyflo Super-Cel. The column was washed with two 5-ml. portions of ether, and the total filtrate was hydrogenated directly over 0.2 g. of Adams catalyst in a Parr hydrogenator. When hydrogen absorption was complete, the catalyst was removed by filtration and washed with ether. The combined filtrates were dried over anhydrous sodium sulfate, the ether removed, and the residue distilled to yield 100.5 g. (66.7% based on the original lactones) of a mixture of 3-heptanol, XIV, and 2-ethyl-1-pentanol, XV, boiling at 155–169.5° at 741 mm.

Exactly 70.0 g. of the mixture was fractionated through a Todd column at a reflux ratio of 100:1. The first fraction consisted of 25.5 g. of XIV boiling at 155–157° at 736 mm.; n^{20}D 1.4228; n^{25}D 1.4208; d^{25}_4 0.8165. The physical constants reported for 3-heptanol are as follows: b. p. 155.9°[23] and 156.5–157°[24]; n^{20}D 1.4222[23]; d^{25}_4 0.8159.[25] An intermediate fraction of 21.5 g. boiling at 158–164° was obtained, followed by a third fraction consisting of 25.5 g. of XV boiling at 164–166°; n^{25}D 1.4251; d^{25}_4 0.8296. The physical constants reported for 2-ethyl-1-pentanol are: b. p. 164–166°[26]; n^{25}D 1.4250 (for the *d*-isomer)[27]; d^{25}_4 0.832.[26] The 3-nitrophthalate melted at 129.5–130.1° in agreement with the reported value 127–128°.[26]

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(20) Levene and Mikeska, *J. Biol. Chem.*, **70**, 355 (1926), reported a b. p. of 137° at 21 mm.

(21) Shriner and Turner, THIS JOURNAL, **52**, 1267 (1930), reported the value 135–140° at 25 mm.

(22) Layraud, *Bull. soc. chim.*, [3] **35**, 223 (1906).

(23) Sherrill, THIS JOURNAL, **52**, 1982 (1930).

(24) Blaise and Picard, *Compt. rend.*, **152**, 446 (1911).

(25) Dillon and Lucas, THIS JOURNAL, **50**, 1711 (1928).

(26) Morgan, Hardy and Proctor, *Chemistry and Industry*, **51T**, 7 (1932).

(27) Levene, *et al.*, *J. Biol. Chem.*, **115**, 401 (1936).

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]

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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.

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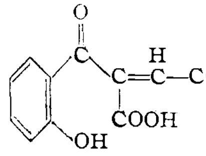
[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

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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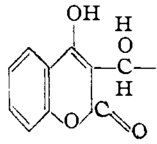

II

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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[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).