Baeyer-Villiger Oxidation of α-Substituted Ketones[1]

EDWARD E. SMISSMAN[2] AND JOHN V. BERGEN

Department of Pharmaceutical Chemistry, The University of Wisconsin, Madison, Wis.

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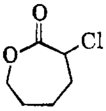
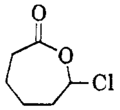
α-Chlorocyclohexanone, α-phthalimidocyclohexanone, 2-oximino-4-methylcyclopentanone, and 1-phenyl-1,2-propanedione-2-oxime were subjected to Baeyer-Villiger conditions. The products obtained from these rearrangements are discussed.

The peroxy acid rearrangement of ketones to esters (Baeyer-Villiger oxidation) has been known since 1899 when Baeyer and Villiger[3] reported the oxidation of camphor and other alicyclic ketones to lactones by treatment with permonosulfuric acid. This rearrangement has since been demonstrated to have wide applicability to aldehydes and ketones, employing various peroxy acids.[4,5] The usefulness of this reaction in the preparation of α-substituted lactones or esters has not been investigated thoroughly. Oxidation of an α-bromo ketone in the steroid series was reported by Wieland and Miescher[6] to afford a 20% yield of products containing an α,β-unsaturated lactone ring. This reaction involves Baeyer-Villiger migration of a primary alkyl group, as opposed to an α-bromoalkyl group, and subsequent loss of hydrogen bromide on treatment of the reaction mixture with pyridine. The material balance was not sufficient to enable any conclusions to be drawn relative to the migratory aptitudes. If, as might be anticipated from the example of Wieland and Miescher, the rearrangement of α-substituted ketones leads to α-substituted esters or lactones, then this reaction could be employed in a convenient synthesis of polyfunctional acids.

α-Chlorocyclohexanone was rearranged by treatment with peroxytrifluoroacetic acid to give a 62% yield of α-chloro-ε-caprolactone (I) and a small yield (approximately 6% of ε-chloro-ε-caprolactone (II). On hydrolysis in sodium carbonate solution the lactone I gave 2-chloro-6-hydroxyhexanoic acid and the lactone II yielded adipic semialdehyde. I was converted to a derivative of lysine *via* the formation of methyl 2,6-dichlorohexanoate, chlorination, and treatment with potassium phthalimide.

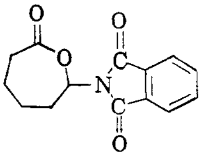


I



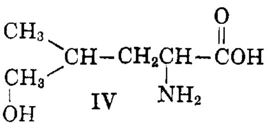
II

When α-phthalimidocyclohexanone was treated under Baeyer-Villiger conditions only one product could be isolated. α-Phthalimido-ε-caprolactone was prepared from α-chloro-ε-caprolactone for the purpose of comparison but was found to differ markedly from the product obtained. The isolated compound was shown to be ε-phthalimido-ε-caprolactone (III).



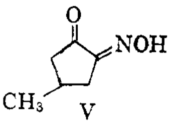
III

In 1944 σ-hydroxyleucine (2-amino-4-methyl-5-hydroxypentanoic acid) (IV) was reported to be present in casein.[7] This compound has not been prepared and the following synthetic scheme was devised: 2-Oximino-4-methylcyclopentanone (V) would undergo an oxidative rearrangement to give γ-methyl-α-nitrovalerolactone, which in turn would be reduced and hydrolyzed to yield δ-hydroxyleucine, IV.



$CH_3(CH_3OH)CH-CH_2CH(NH_2)-COOH$

IV



V

Oximination of ethyl 4-methylcyclopentanone-2-carboxylate with sodium nitrite afforded the oximino ketone V. The treatment of this ketone with peroxytrifluoroacetic acid produced β-methylglutaric acid as the major product and traces of a nitro compound and a trifluoroacetate of an oxime. The latter compounds were detected by infrared analysis. A possible explanation of these results is that Baeyer-Villiger oxidation of the ketone is slow compared to the oxidation of the oxime to a nitro group. The resulting α-nitro ketone is rapidly rearranged to β-methyl-α-nitrovalerolactone which is hydrolyzed to the observed dicarboxylic acid. The rearrangement of a more readily available oximino ketone, 1-phenyl-1,2-propane-

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[2] To whom inquiries should be addressed: Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kan.

[3] A. von Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899).

[4] C. H. Hassall, *Org. Reactions*, **9**, 73 (1957).

[5] W. D. Emmons and G. D. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

[6] P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949).

[7] H. D. Dakin, *J. Biol. Chem.*, **154**, 549 (1944).

dione-2-oxime, substantiated this postulation by giving a 70% yield of benzoic acid and 4% phenol.

The utilization of the Baeyer-Villiger rearrangement in the preparation of α,ω-disubstituted acids is dependent on the migratory aptitude of the substituted α-carbon. A further study of this rearrangement emphasizing migrational aptitudes is currently under investigation.

Experimental

Baeyer-Villiger Oxidation of α-Chlorocyclohexanone.—One hundred and two milliliters (0.72 mole) of trifluoroacetic anhydride at 0° was added over a 1-hr. period to a cooled, stirred suspension of 16.4 ml. (0.60 mole) of 90% hydrogen peroxide in 100 ml. of dry methylene chloride. Stirring was continued for an additional hour and the resulting solution was added in 1 hr. to a vigorously stirred suspension of 260 g. of anhydrous disodium hydrogen phosphate in 400 ml. of dry methylene chloride containing 52.2 g. (0.40 mole) of freshly distilled α-chlorocyclohexanone.[8]

The exothermic reaction maintained a gentle reflux during the course of addition. After addition, the mixture was refluxed an additional 2 hr. The reaction mixture was cooled and the insoluble salts removed by filtration. These salts were extracted with an additional 400 ml. of methylene chloride. The methylene chloride solutions were combined, washed with 10% sodium carbonate solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent (under reduced pressure) afforded a light yellow oil which was fractionally distilled to give 36.0 g. (62%) of α-chloro-ε-caprolactone (I), b.p. 85–87° (0.7 mm.), and 5.4 g. of a lower boiling fraction, b.p. 87–92° (2.0 mm.).

Anal. Calcd. for $C_6H_9O_2Cl$: C, 48.50; H, 6.11; Cl, 23.86. Found: C, 48.64; H, 6.51; Cl, 23.91.

A sample of the lower boiling fraction was treated with 2,4-dinitrophenylhydrazine. After standing overnight, the orange-red precipitate which formed was filtered. Cooling of the mother liquor caused precipitation of a yellow derivative. The orange-red derivative was passed through a column of neutral alumina using chloroform as an eluent in order to remove excess reagent. Evaporation of the eluate and three recrystallizations of the residue from chloroform–methanol gave orange-red crystals, m.p. 234–237°, postulated to be the 2,4-dinitrophenylhydrazone-2,4-dinitrophenylhydrazide of adipic semialdehyde.

Anal. Calcd. for $C_{18}H_{18}N_8O_9$: C, 44.18; H, 3.70; N, 22.85. Found: C, 44.87; H, 3.02; N, 22.00.

The yellow derivative was recrystallized four times from 95% ethyl alcohol to give yellow plates, m.p. 58.5–60.0°.

Anal. Calcd. for $C_{14}H_{18}H_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.15; H, 5.38; N, 16.10.

This compound was identical with the 2,4-dinitrophenylhydrazone of the ethyl ester of adipic semialdehyde.

Baeyer-Villiger Oxidation of α-Phthalimidocyclohexanone.—A solution of peroxytrifluoroacetic acid was prepared by adding 2.5 ml. (0.018 mole) of trifluoroacetic anhydride in one portion to a cooled, stirred suspension of 0.4 ml. (0.014 mole) of 90% hydrogen peroxide in 5 ml. of dry methylene chloride. Stirring was maintained for 1 hr. The resulting solution was added to a well stirred suspension of 16 g. of disodium hydrogen phosphate in 25 ml. of dry methylene chloride containing 2.43 g. (0.01 mole) of α-phthalimidocyclohexanone[9] (m.p. 176.5–178.5°). The reaction was cooled in ice during this addition which took 30 min. After the addition was complete, the mixture was allowed to warm to room temperature and stirring was continued an additional 3 hr. The methylene chloride layer was separated and combined with one 100-ml. and one 50-ml. methylene chloride digests of the insoluble material. The methylene chloride solution was washed with 10% sodium carbonate and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave 1.76 g. of a hard white solid which afforded 1.12 g. (43%) of white needles (m.p. 168–171°) after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.43; H, 5.09; N, 5.50.

When subjected to hydrolytic conditions the product gave a 58% yield of phthalimide. This proves the phthalimido group to be in the ε-position and not in the α-position.

Preparation of α-Phthalimido-ε-caprolactone.—The procedure of Sheehan and Bolhofer[10] was used to prepare this compound. A stirred mixture of 1.5 g. (0.01 mole) of α-chloro-ε-caprolactone and 1.85 g. (0.01 mole) of potassium phthalimide in 15 ml. of freshly distilled dimethyl sulfoxide was heated to 100–105° for 1 hr. The product was recrystallized from ethanol, m.p. 154–155.6°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.87; H, 4.95; N, 5.44.

Ethyl-4-methylcyclopentanone-2-carboxylate.—A modification of the procedure reported by Dieckmann was used.[11] One hundred and eight grams (0.5 mole) of diethyl β-methyl adipate, b.p. 91–93° (1 mm.) was added in one portion to 23 g. (1.0 mole) of finely divided sodium. Six hundred and twenty-five milliliters of dry benzene and 15 drops of absolute ethanol were added and the flask cautiously heated on a steam bath. During this time the contents of the flask were stirred intermittently. As the reaction became exothermic the steam bath was replaced by an ice bath. Most of the yellow sodio derivative precipitated during this reaction period. The contents of the flask were stirred and gentle reflux was maintained for 6 hr. The flask was cooled and the reaction mixture was slowly poured into 600 ml. of cold 10% acetic acid. One additional liter of 10% acetic acid was added intermittently. Additional benzene was necessary to complete the transfer of the sodio derivative from the reaction flask. The benzene layer was separated and combined with a benzene extract of the aqueous phase. The combined benzene solutions were washed with water, 7% sodium carbonate solution, and again with water. After a preliminary drying the benzene was removed by distillation at atmospheric pressure and the residual yellow oil, still containing some benzene, was distilled under reduced pressure to give 51 g. (60%) of colorless fragrant oil, b.p. 77–79° (2 mm.).

2-Oximino-4-methylcyclopentanone (V).—The reaction conditions described are critical. Stability of the product is affected by heat, air, and light.[12] A solution of 3.0 g. (0.018 mole) of ethyl 4-methylcyclopentanone-2-carboxylate, 1.23 g. (0.018 mole) of sodium nitrite, and 0.72 g. (0.018 mole) of sodium hydroxide in 100 ml. of water was placed in a glass stoppered bottle. A stream of nitrogen was passed through the solution for several minutes and the bottle quickly sealed and placed in the dark for 48 hr. The remainder of the procedure was performed as rapidly as possible immediately after opening the bottle. Small portions of 20% sulfuric acid were added, with shaking to expel carbon dioxide, until the Congo red end point had been reached. Four 50-ml. ether extracts of the acid solution were combined and washed with 5% sodium bicarbonate solution and then water. After drying over magnesium sulfate for 30 min., the ether was carefully removed *in vacuo* to give 1.57 g. of a light yellow solid. Purification was effected by dissolving in a small volume of anhydrous ether, adding twice the volume of petroleum ether, and removing

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[8] M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syntheses*, Coll. Vol. III, 188 (1955).

[9] D. Y. Curtin and S. Schmukler, *J. Am. Chem. Soc.*, **77**, 1105 (1955).

[10] J. C. Sheehan and W. A. Bolhofer, *ibid.*, **72**, 2786 (1950).

[11] W. Dieckmann, *Ann.*, **317**, 27 (1901).

[12] Facile decomposition has been noted with other cyclic α-oximinoketones. See T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).

the ether under a stream of nitrogen until crystallization was complete. This procedure gave 0.72 g. (32%) of a tan solid, m.p. 95–100°. Several recrystallizations from ether-cyclohexane raised the melting point to 104.5–105°.

Anal. Calcd. for $C_6H_9O_2N$: C, 56.91; H, 6.98; N, 11.36. Found: C, 56.68; H, 7.14; N, 11.02.

Baeyer-Villiger Oxidation of 1-Phenyl-1,2-propanedione-2-oxime.—A 50.8-ml. sample (0.36 mole) of trifluoroacetic anhydride at 0° was added to a cooled suspension of 8.2 ml. (0.3 mole) of 90% hydrogen peroxide in 50 ml. of dry methylene chloride. This addition took 30 min. and the solution was stirred for an additional 30 min. after which it was added over a 45-min. period to a stirred, cold suspension of 16.3 g. (0.1 mole) of 1-phenyl-1,2-propanedione-2-oxime, 2 g. of dry urea, and 150 g. of dry disodium hydrogen phosphate in 250 ml. of dry methylene chloride. After addition, stirring was continued for 1 hr. at 25° during which an additional 150 ml. of methylene chloride was added to maintain a fluid state. The insoluble buffer was removed by filtration and the filtrate combined with a 200 ml. of methylene chloride digest of the insoluble material. The methylene chloride was removed *in vacuo* and the residue placed on a silicic acid–chloroform chromatographic column to give a 41% yield of benzoic acid (4.9 g.) and 7.7 g. (40%) of a light yellow oil, b.p. 115–120° (1.0 mm.), identified as a nitro ester mixture of 1-nitroethyl benzoate and phenyl 2-nitropropionate.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 6.74.

Hydrolysis of 200 mg. of the oil in 5 ml. of refluxing 20% sodium hydroxide for 2 hr. gave 90 mg. (72%) of benzoic acid and 10 mg. of phenol (13%).

Baeyer-Villiger Oxidation of 2-Oximino-4-methylcyclopentanone.—Eleven and four tenth grams (0.1 mole) of trifluoroacetic anhydride in 30 ml. of acetonitrile was added to a solution of 2.3 ml. (0.084 mole) of 90% hydrogen peroxide in 20 ml. of acetonitrile which was maintained at 0°. The resulting solution was added dropwise over a period of 30 min. to a stirred suspension of 3.1 g. (0.024 mole) of 2-oximino-4-methylcyclopentanone, 1.0 g. of urea, 34 g. of disodium hydrogen phosphate, and 40 ml. of acetonitrile. The mixture was allowed to warm to room temperature and then stirred for 1.5 hr. After cooling, the insoluble salts were removed by filtration. The acetonitrile was removed *in vacuo* and 50 ml. of water was added to the residue. The aqueous mixture was extracted with four 50-ml. portions of methylene dried over anhydrous magnesium sulfate. The methylene chloride was removed *in vacuo* and a yellow oily residue remained.

The residue was chromatographed on a silicic acid–chloroform column to give three distinct fractions. By infrared analysis the fractions were designated as starting material, small amount of nitro ester, and a major amount of β-methylglutaric acid. The latter was compared with authentic acid and was found to be identical.

Methyl 2-Chloro-6-hydroxyhexanoate.—In a dry flask equipped with stirrer and gas inlet tube were placed 10.0 g. (0.67 mole) freshly distilled α-chloro-ϵ-caprolactone (I) and 100 ml. absolute methanol. Reflux was maintained for 50 min. while a slow, steady stream of anhydrous hydrogen chloride was passed through the reaction. Removal of the solvent under reduced pressure and distillation of the residue under nitrogen gave 9.7 g. (80%) of colorless oil, b.p. 110–118° (1 mm.). A second distillation gave 8.1 g. of product boiling at 100–102° (0.15 mm.).

Anal. Calcd. for $C_7H_{13}O_3Cl$: C, 46.54; H, 7.25; Cl, 19.63. Found: C, 46.64; H, 7.78; Cl, 19.61.

Methyl 2,6-Dichlorohexanoate.—This ester, b.p. 89–92° (1.5 mm.), was prepared in 47% yield by treatment of methyl 2-chloro-7-hydroxyhexanoate with thionyl chloride and pyridine.[13]

Anal. Calcd. for $C_{17}H_{12}O_2Cl_2$: C, 42.23; H, 6.08; Cl, 35. Found: C, 41.49; H, 6.25; Cl, 35.85.

Methyl *dl*-Diphthaloyllysine.—A mixture of 0.5 g. (2.5 mmoles) of methyl 2,6-dichlorohexanoate, 1.1 g. (6 mmoles) of potassium phthalimide, and 10 ml. of freshly distilled dimethyl sulfoxide was heated at 90°, with vigorous stirring for 45 min. The mixture was cooled, added to 60 ml. of water and then extracted several times with chloroform. The chloroform extract was washed with 5% sodium hydroxide solution and then with a saturated sodium chloride solution. The resulting solution was dried over magnesium sulfate, the solvent evaporated under reduced pressure, and the residue recrystallized from ethanol to give 0.85 g. (81%) of a white solid, m.p. 96–97.5°.

Anal. Calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.80; N, 6.66. Found: C, 65.73; 65.50; H, 4.73; 4.44; N, 6.38.

An authentic sample of this product was prepared from *dl*-lysine monohydrochloride by fusion with phthalic anhydride and treatment of an ether solution of the product with an ether solution of diazomethane. After evaporation of the solvent, the resulting tar was recrystallized from ethanol and decolorized with Norit to give a product, m.p. 93.5–97°. The melting point was not depressed by admixture with a sample prepared from methyl 2,6-dichlorohexanoate. The infrared spectra of the two samples were superimposable.

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(13) F. C. Whitmore, F. A. Karnatz, and A. H. Popkin, *J. Am. Chem. Soc.*, **60**, 2540 (1938).