Anal. Calcd. for $C_7H_{13}Br$: Br, 45.1; bromine no., 90.2 g. Br/100 g. Found: Br, 45.5, 45.7; bromine no., 82.2, 82.4 g. Br/100 g.

The infrared absorption spectrum indicated the presence of $R_2C{=}CH_2$ and $RCH{=}CR_2$ groupings but not the $RCH{=}CH_2$ grouping indicating that the product was a mixture of 6-bromo-2-methyl-1-(and 2)-hexene (XI).

2,5-Dimethyl-2-phenyltetrahydropyran.—A 19-g. sample of 2,5-dimethyl-2-phenyl-3,4-dihydro-2H-pyran was hydrogenated over Raney nickel at 25 p.s.i.g. and room temperature. Distillation gave 11.5 g. of 2,5-dimethyl-2-phenyltetrahydropyran boiling at 60–61° (1 mm.), $n^{20}D$ 1.5270, d^{20} 1.0083.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.07; H, 8.41. Found: C, 81.77, 81.69; H, 8.71, 8.71.

3-Methyl-5-hydroxy-5-phenylhexanal.—A mixture of 58 g. of 2,4-dimethyl-2-phenyl-3,4-dihydro-2H-pyran, 116 g. of 10% sulfuric acid and 200 ml. of dioxane was heated on the steam-cone for two hours and then allowed to stand at room temperature overnight. An oil layer was separated and the aqueous phase was extracted with petroleum ether. The combined oil and petroleum ether extract was dried and distilled to give 23.5 g. (36.8% yield) of 3-methyl-5-hydroxy-5-phenylhexanal boiling at 115–120° (0.3 mm.), $n^{20}D$ 1.4290.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 76.24, 76.11; H, 8.73, 8.80.

The infrared absorption spectrum showed bands at 2.95 μ (-OH), 5.83 μ (-CHO) and 6.23 μ ($-C_6H_5$).

EMERYVILLE, CALIF. RECEIVED MARCH 12, 1951

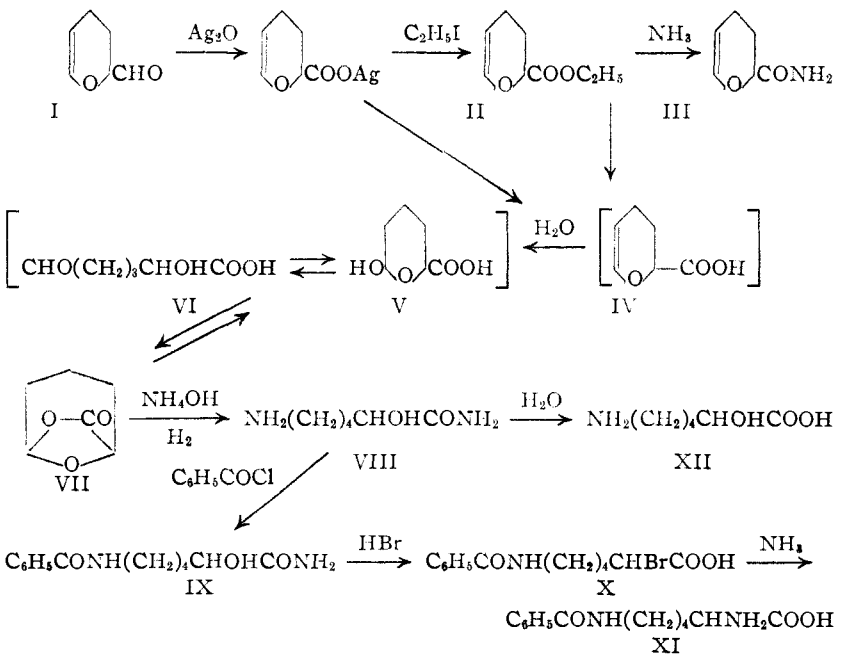
[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY]

Reactions of Acrolein and Related Compounds. IV. Preparation of a New Lactone, 7-Oxo-6,8-dioxabicyclo[3.2.1]octane from Acrolein Dimer, and Its Conversion to Lysine

BY RICHARD R. WHETSTONE AND SEAVER A. BALLARD

dl-N^{ϵ}-Benzoyllysine was prepared from acrolein dimer by a seven-step process. The preparation and properties of 7-oxo-6,8-dioxabicyclo[3.2.1]octane, a novel lactone of a carboxyhemiacetal, are described.

The many published syntheses of lysine have invariably required lengthening of a chain of less than six carbon atoms, introduction of one or more functional groups into a six-carbon compound or a combination of the two. Acrolein dimer (3,4-dihydro-2H-pyran-2-carboxaldehyde) therefore appears to be unique as a starting material in that, through the facile opening of the dihydropyran ring, it contains three existing or potential functional groups in the requisite 1,2,6-positions of a six-carbon chain. The synthesis of lysine from acrolein dimer by the stepwise transformation of these functional groups has been accomplished as shown in the diagram.



The oxidation of acrolein dimer (I) with silver oxide in aqueous solution to the corresponding acid (IV) isolated in low yield as the sodium salt was described by Sherlin, *et al.*[1] This procedure has been greatly improved by the use of dry silver oxide in ether or benzene; by reaction of the resulting crude silver salt with ethyl iodide, ethyl 3,4-dihydro-2H-pyran-2-carboxylate (II) was obtained in 71.5% yield from the dimer. Oxidation of acrolein dimer may be accomplished also *via* the Tishchenko reaction using aluminum isopropoxide as catalyst[2]; this reaction will not be described in this paper.

Hydrolysis of the ethyl ester (II) of the dihydropyran-2-carboxylic acid was readily accomplished by aqueous sodium hydroxide at room temperature; the reactivity of the ester to bases was also shown by the easy conversion to the amide (III) by mild warming with aqueous ammonia. Preliminary experiments indicated the difficulty of isolating the free acid (IV) and consequently acidification of the ester hydrolysis product with aqueous hydrochloric acid was carried out under conditions favoring hydration or hydrolytic cleavage of the dihydropyran ring or both. Acid solutions prepared in this manner or by treatment of a suspension of the silver salt of the dihydropyran acid with hydrochloric acid responded to reagents for the carbonyl group indicating that hydration or

(1) S. M. Sherlin, A. Y. Berlin, T. A. Serebrennikova and F. E. Rabinovitch, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 22 (1938).

(2) Tishchenko, *J. Russ. Phys. Chem. Soc.*, **38**, 355, 482 (1906); *Chem. Zentr.*, **77**, II, 1309, 1552 (1906).

cleavage of the ring had occurred.[3] Ether extraction of the acidified hydrolysate yielded an unstable, viscous, water-soluble acid presumably 6-hydroxytetrahydropyran-2-carboxylic acid (V), δ-formyl-α-hydroxyvaleric acid (VI) or mixtures thereof, which gave glutaric acid on oxidation with hydrogen peroxide. The unstable acid mixture resinified on standing but if immediately distilled under vacuum was converted to the novel and interesting bicyclic lactone VII. Apparently the lactonization, which may proceed *via* 6-hydroxytetrahydropyran-2-carboxylic acid (V), does not require a strong acid as catalyst but it is possible that it was catalyzed by traces of hydrochloric acid still present. In an analogous reaction sequence from methacrolein dimer the related dimethyl substituted lactone [1,4-dimethyl-7-oxo-6,8-dioxabicyclo[3.2.1]octane] was prepared by lactonization through distillation of pure 2,5-dimethyl-3,4-dihydro-2H-pyran-2-carboxylic acid.[4] In this case the methyl groups hinder hydrolysis of the ring and the acid could be isolated as a solid and be purified by crystallization.

The structure of the lactone VII is considered to be established by its synthesis and its conversion to lysine. In addition, the infrared absorption spectrum indicated the absence of double bonds and of aldehyde, hydroxyl and carboxyl groups. The ester carbonyl band was at 5.57 μ or between the positions of the ester bands for conventional β-lactones, at 5.50 μ and for γ-lactones, at 5.65 μ. Probably either strain in the bicyclic system or the presence of a second oxygen in the five-membered ring caused the shift to a shorter wave length. A Fisher–Hirshfelder model of the molecule indicated that the two rings were approximately at right angles to each other giving a rigid system which was probably strained.

The lactone (VII), the ester of an inner hemiacetal, is stable in the absence of moisture, is insoluble in and only slowly hydrolyzed by water at room temperature but is rapidly dissolved by aqueous bases. Hydrogenation of a solution of the lactone in aqueous ammonia fortified with anhydrous ammonia converted it in about 90% yield to 6-amino-2-hydroxyhexanamide (VIII). The amide is hydrolyzed very easily by warm water or aqueous ethanol to the known 6-amino-2-hydroxyhexanoic acid (XII) and hydrogenated lactone-ammonia products therefore frequently contained both compounds. Reaction of the amide in cold sodium hydroxide solution with benzoyl chloride selectively benzoylates the amino group precipitating the water-insoluble 6-benzoylamino-2-hydroxyhexanamide (IX). The corresponding N-acetyl compound was similarly prepared by reaction of VIII with acetic anhydride in ether.

Conversion of the hydroxyl group of IX to an amino group proved unexpectedly difficult. However, reaction with 40% hydrogen bromide in glacial acetic acid at 110° gave 6-benzoylamino-2-bromohexanoic acid (X), an intermediate in the von Braun[5] lysine synthesis, which with ammonia gave N$^{\epsilon}$-benzoyllysine (XI). The over-all yield of benzoyllysine from acrolein dimer was 12%.

(3) Freshly prepared solutions of acrolein dimer in distilled water show the presence of only one equivalent of carbonyl by titration with hydroxylamine hydrochloride under mild conditions. Heating or addition of acid to these solutions increases the titer through the cleavage of the dihydropyran ring.

(4) Unpublished results from these laboratories. For preparation of the acid and lactone see R. R. Whetstone, U. S. Patents 2,479,283 and 2,511,890; G. G. Stoner and J. S. McNulty, THIS JOURNAL, **72**, 1531 (1950).

Experimental[6]

Ethyl-3,4-dihydro-2H-pyran-2-carboxylate (II).—Acrolein dimer (140 g., 1.25 moles) was added in 45 minutes to a stirred suspension of 415 g. (1.79 moles) of silver oxide in 1100 ml. of boiling benzene and the mixture was heated for an additional two hours. The solid mixture of silver salt and silver was filtered, washed with benzene, stirred again with 700 ml. of boiling benzene and 234 g. (1.50 moles) of ethyl iodide added in 15 minutes. After an additional two hours of heating, the product was filtered; the solid was washed well with hot benzene, and the combined filtrates were distilled giving 133 g. (71.5% yield based on silver oxide) of ethyl 3,4-dihydro-2H-pyran-2-carboxylate, b.p. 84–84.2° (10 mm.), $n^{20}D$ 1.4555.

Anal. Calcd. for $C_8H_{12}O_3$: sapn. equiv., 156.2; bromine no., 102.6 g. Br/100 g. Found: sapn. equiv., 156.3, 156.2; bromine no., 104.4, 104.9 g. Br/100 g.

The above ester (31 g., 0.20 mole) and 125 ml. of concentrated ammonium hydroxide were warmed with shaking until the mixture was homogeneous (30 minutes). On cooling in ice, 25 g. (100%) of 3,4-dihydro-2H-pyran-2-carboxamide, m.p. 112–112.5°, crystallized.

Anal. Calcd. for $C_6H_9O_2N$: C, 56.7; H, 7.1; N, 11.0. Found: C, 56.8, 57.0; H, 7.2, 7.3; N, 11.0, 11.1.

Hydrogenation of 156 g. (1.00 mole) of the unsaturated ester (II) at 1000 p.s.i. hydrogen and room temperature with commercial Raney nickel as catalyst was complete in 30 minutes giving 145 g. (94%) of ethyl tetrahydropyran-2-carboxylate, b.p. 89.8–89.4° (10–9 mm.), $n^{20}D$ 1.4439. Sherlin, *et al.*,[1] reported a boiling point of 101.3° (19–20 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.73; H, 8.92. Found: C, 60.75, 60.73; H, 9.03, 9.02.

Tetrahydropyran-2-carboxylic acid obtained by saponification of the ester was a viscous, water-soluble liquid, b.p. 110.5° (5 mm.), $n^{20}D$ 1.4665.

Anal. Calcd. neut. equiv., 130.1. Found: neut. equiv., 131.0.

7-Oxo-6,8-dioxabicyclo[3.2.1]octane (VII).—Ethyl 3,4-dihydro-2H-pyran-2-carboxylate 75 g. (0.48 mole) was stirred with 200 ml. of 2.5 *N* sodium hydroxide. The mixture warmed spontaneously and was homogeneous within 30 minutes. After evaporation of the water under vacuum, the solid sodium salt was acidified with cold 1:1 hydrochloric acid, rapidly extracted ten times with a total of 1500 ml. of ether and the combined ether solutions were well washed with small portions of saturated salt solution to remove traces of hydrochloric acid. Evaporation of a portion of the dried ether extract, equivalent to 0.18 mole of starting material, left a viscous, water-soluble liquid which on distillation through a column gave 18 g. (79%) of mobile, water-insoluble lactone, b.p. 62–64° (3 mm.) or 91–92° (14 mm.), $n^{20}D$ 1.4587. The compound crystallized in the ice-box and remelted at 18–20°; it did not decolorize a solution of bromine in carbon tetrachloride.

Anal. Calcd. for $C_6H_8O_3$: C, 56.26; H, 6.31; sapn. equiv., 129.1. Found: C, 56.29, 56.35; H, 6.60, 6.63; sapn. equiv., 116.2; acid, 0.001 eq./100 g.

The low saponification equivalent may have been due to base-catalyzed formation of acid from the potential aldehyde group of 6-hydroxytetrahydropyran-2-carboxylic acid resulting from hydrolysis of the lactone.

The water-soluble acid obtained by evaporation of a second portion of the ether extract slowly increased in viscosity and refractive index at room temperature and after several days at room temperature was a soft resinous solid. Titration of the acid with base and with hydroxylamine hydrochloride shortly after preparation showed 0.559 equiva-

(5) J. von Braun, *Ber.*, **42**, 839 (1909).

(6) All melting points and boiling points are uncorrected.

lent of acid and 0.327 equivalent of carbonyl per 100 g. of sample. Calculated values for δ-formyl-α-hydroxyvaleric acid (VI) are 0.779 equivalent of both acid and carbonyl per 100 g.; 6-hydroxytetrahydropyran-2-carboxylic acid would be expected to give the same values under the conditions used.

A third portion of the ether solution equivalent to 0.09 mole of starting material was added to 30 ml. of water and oxidized with hydrogen peroxide after removal of ether. Evaporation of the resulting solution left a solid residue which after crystallization from benzene and ether gave 7 g. (60%) of glutaric acid which melted at 96–98° alone or mixed with an authentic sample.

6-Amino-2-hydroxyhexanamide (VIII).—The lactone VII (30 g., 0.23 mole) was dissolved in 80 g. of cold concentrated ammonium hydroxide with stirring and cooling, and the resulting solution, after addition of 75 g. of anhydrous ammonia, was hydrogenated over Raney nickel at 80 to 118° and 1200 p.s.i. hydrogen pressure in three hours. During suction filtration of the product, the solution was cooled by evaporation of ammonia with precipitation of 19 g. (55% yield) of 6-amino-2-hydroxyhexanamide, which melted at 111–113° after washing with absolute ethanol and then ether. Evaporation of the filtrate under vacuum at a maximum temperature of 40° left an additional 14 g. (40%) of less pure amide, m.p. 100–105°.

Anal. Calcd. for $C_6H_{14}O_2N_2$: C, 49.28; H, 9.64. Found: C, 49.0, 48.9; H, 9.5, 9.4.

The amide (2.3 g.) was warmed with 70 ml. of absolute ethanol and water (10 ml.) was added until the solid dissolved; on cooling 1.1 g. of 6-amino-2-hydroxyhexanoic acid, melting at 205–210° with decomposition, was deposited. Fischer and Zemplén[7] reported that the acid melted at 220–225° with decomposition.

Anal. Calcd. for $C_6H_{13}O_3N$: C, 48.28; H, 8.90; N, 9.5. Found: C, 48.39, 48.43; H, 8.91, 9.00; N, 9.74.

Acetic anhydride (0.05 mole) in 5 ml. of ether was slowly added to a stirred suspension of 7.3 g. (0.05 mole) of the amide in 50 ml. of ether at room temperature. After 18 hours the solid was removed by filtration and recrystallized from 40 ml. of ethanol to give 7 g. (74%) of 6-acetylamino-2-hydroxyhexanamide, m.p. 155–156°.

Anal. Calcd. for $C_8H_{16}O_3N_2$: C, 51.05; H, 8.57; N, 14.88. Found: C, 50.85, 51.01; H, 8.55, 8.57; N, 14.7, 14.8.

A second sample of 15 g. (0.12 mole) of lactone was dissolved in ammonium hydroxide, hydrogenated as before and the product evaporated under vacuum at a maximum temperature of 60°. The residual solid was dissolved in 25 ml. of water, 50 g. of 20% sodium hydroxide was added, the solution was cooled in ice and 20 g. (0.14 mole) of benzoyl chloride was added slowly with precipitation of 18 g. (60% yield) of 6-benzoylamino-2-hydroxyhexanamide, m.p. 161.5–162.0°, after two crystallizations from ethanol. Addition of more benzoyl chloride caused no further precipitation.

Anal. Calcd. for $C_{13}H_{18}O_3N_2$: C, 62.50; H, 7.27; N, 11.22. Found: C, 62.35, 62.52; H, 7.25, 7.18; N, 10.6, 10.9.

6-Benzoylamino-2-bromohexanoic Acid (X).—6-Benzoylamino-2-hydroxyhexanamide (4.03 g., 0.016 mole) and a solution of 10.6 g. of anhydrous hydrogen bromide in 16 g. of glacial acetic acid, sealed in a Carius tube, were heated at 110° for five hours. The product was stripped of acetic and hydrobromic acids at the water pump and the residue added to water. The oil (3.7 g., 61% yield) soon solidified and after crystallization from ethanol melted at 156–160° and contained 22.9% bromine compared with 25.4% calculated for $C_{13}H_{16}O_3NBr$. Eck and Marvel[8] reported a melting point of 166° for 6-benzoylamino-2-bromohexanoic acid.

Reaction of the crude bromoacid (3.7 g.) with aqueous ammonia following Eck and Marvel[8] gave 1.7 g. (58% yield) of *dl*-N$^{\epsilon}$-benzoyllysine (XI). The melting point varied between 225° and 265° depending on the rate of heating; a reported value[8] is 265°.

Anal. Calcd. for $C_{13}H_{18}O_3N_2$: C, 62.4; H, 7.2; N, 11.2. Found: C, 62.7, 62.9; H, 7.3, 7.3; N, 11.1, 11.1.

The dibenzoate prepared by addition of benzoyl chloride to a solution of the above material in 10% sodium hydroxide melted at 141–143° alone and at 142–144° when mixed with *dl*-benzoyllysine (m.p. 144–145°) prepared from authentic *dl*-lysine hydrochloride.

Acknowledgment.—We are indebted to G. H. Magruder and to G. G. Ecke for portions of the experimental work.

(7) E. Fischer and G. Zemplén, *Ber.*, **42**, 4878 (1909).

(8) J. C. Eck and C. S. Marvel, *J. Biol. Chem.*, **106**, 387 (1934).

EMERYVILLE, CALIFORNIA RECEIVED MARCH 12, 1951

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

Reactions of Acrolein and Related Compounds. V. Isomerization of 3,3-Diacyloxypropenes

BY CURTIS W. SMITH, DOUGLAS G. NORTON AND SEAVER A. BALLARD

Novel 1,3-diacyloxypropenes have been obtained by allylic rearrangement of 3,3-diacyloxypropenes. Addition of acetic acid to 3,3-diacetoxypropene has given 1,1,3-triacetoxypropane. Reactions of 1,3-diacetoxypropene and 3,3-diacetoxypropene with potassium cyanide have given a compound which may be α-acetoxyglutaronitrile.

Introduction

During an investigation of the properties of the known 3,3-diacetoxypropene (allylidene diacetate) from acrolein and acetic anhydride, it has been found that it can be isomerized in high yields to the previously unreported 1,3-diacetoxypropene. A study of equilibrium conditions for this isomerization was carried out and conversions to isomer as high as 31% were observed. This isomerization has also been carried out with 3,3-dibutyroxypropene (from acrolein and butyric anhydride), 3,3-diacetoxy-2-methylpropene[1] (from methacrolein and acetic anhydride) and 3,3-dipropionoxy-2-neopentylpropene (from α-neopentylacrolein and propionic anhydride).

As an extension of the above study it was found that acetic acid could be added to 3,3-diacetoxypropene to give the novel 1,1,3-triacetoxypropane. Other reactions of 1,3- and 3,3-diacetoxypropene have been carried out. During the course of this work certain improvements in the preparation of 3,3-diacetoxypropene were realized.

Discussion

Preparation of 3,3-Diacetoxypropene.—Previous preparations of 3,3-diacetoxypropene from acrolein and acetic anhydride with acidic catalysts have involved low reaction temperatures (<10°) and long reaction times[1,2] (5–10 hr.) or low yields (64%).[3] We have found that by adding

(1) J. H. Brant and F. R. Conklin (Eastman Kodak Co.), U. S. Patent 2,393,740 (1946).

(2) A. Kirrmann, *Bull. soc. chim.*, [5] **4**, 502 (1937).

(3) A. Wohl and R. Maag, *Ber.*, **43**, 3293 (1910).