Anal. Calcd. for $C_{16}H_{22}O_2N_2Br$: C, 52.18; H, 6.02. Found: C, 51.94; H, 5.95.

8-Bromo-5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (X). A.—A solution of ketone VI (57 g.) in ether (100 ml.) was added dropwise to a cold solution of methylmagnesium iodide prepared from magnesium (6.1 g.), methyl iodide (40 g.) and dry ether (300 ml.). After standing overnight the reaction mixture was treated with ammonium chloride solution and the ether layer was separated, washed with water and concentrated. The crude alcohol VII (60 g.) was dissolved in benzene (40 ml.) and cyclized with sulfuric acid (600 ml.) and water (126 ml.) as in the preparation of VIII. The crude cyclized product crystallized when seeded and stirred with a small amount of absolute ethanol. The first crystals were obtained when a small sample purified by evaporative distillation was allowed to stand for six months. There was obtained 45 g. (78%) of X which melted at 85–89°. After recrystallization from ethyl acetate the pure product melted at 93–94°.

Anal. Calcd. for $C_{16}H_{21}OBr$: C, 62.14; H, 6.85; Br, 25.84. Found: C, 62.24; H, 6.93; Br, 25.82.

B.–A solution of 5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (IX) (230 mg.) in carbon tetrachloride (10 ml.) was treated with a solution of bromine (160 mg.) in carbon tetrachloride (3.2 ml.) at 0°. The reaction mixture was washed with water and the carbon tetrachloride evaporated. The residue crystallized on standing and was recrystallized from ethyl acetate. The melting points of this product and the mixture with the product from part A were 92–93.5°.

β-6-(5-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthroyl)-propionic Acid (XI).—A cold solution of aluminum chloride (6 g.) and succinic anhydride (2.2 g.) in nitrobenzene (80 ml.) was added to a solution of IX (4.5 g.) in nitrobenzene (70 ml.) and the mixture allowed to stand in the refrigerator for 72 hours. The reaction mixture was treated with dilute hydrochloric acid and ether. The ether layer was separated and the acidic products extracted with dilute potassium hydroxide solution. Acidification of the alkaline extract produced 5.6 g. (87%) of crude crystalline acid. The product (4.9 g.) melted at 151.5–153° after purification by recrystallization from methanol.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.90. Found: C, 72.53; H, 8.01.

β-8-(5-Methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthroyl)-propionic Acid (XII).—A solution of X (19.5 g.) and methyl iodide (8 g.) in dry ether (200 ml.) and dry benzene (70 ml.) was added dropwise to magnesium (5 g.). When the addition was complete the reaction mixture was refluxed for an hour to complete the formation of the Grignard reagent. The reaction flask was cooled in an ice-bath and dry cadmium chloride (15 g.) was added. The mixture was stirred and heated for 15 minutes and then 150 ml. of ether was distilled off and replaced by dry benzene. A solution of β-carbomethoxypropionyl chloride (14 g.) in dry benzene (20 ml.) was added quickly and the reaction mixture stirred and refluxed for an hour. After standing for a day at room temperature the contents of the flask was poured into a mixture of ice and hydrochloric acid and the product extracted with ether. The residue remaining after evaporation of the ether was boiled for 8 hours with a solution of potassium hydroxide (10 g.) in water (60 ml.) and ethanol (300 ml.). The ethanol was distilled off and water and ether were added to the residue. The ether layer was concentrated and after distillation 6.3 g. of IX and 1.9 g. of X were recovered. By acidification of the water layer there was obtained 8.8 g. (42%) of acid which solidified after seeding (first crystals were obtained after purification by chromatography on silicic acid). The product was recrystallized from ligroin, m.p. 120–121.5° (yield 6.2 g.). An additional amount (1.1 g.) of less pure material, m.p. 117–120°, was recovered from the mother liquors.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.90. Found: C, 72.94; H, 7.92.

Dehydrogenation of IX.—The bromine atom was removed from X (0.5 g.) by shaking with hydrogen and nickel in alkaline solution. The crude product was heated with palladium-on-charcoal (0.1 g.) for 6 hours at 270–300° and for one hour at 320°. Some crystalline product sublimed out of the reaction mixture. The crude dehydrogenated product was converted to the picrate which after recrystallization melted at 185–187° and was identical with an authentic sample of 4-methoxyphenanthrene picrate.[1] The trinitrobenzene adduct prepared as previously described[1] melted at 206–208°. Some cleavage of the methoxyl group occurred during this dehydrogenation since phenanthrene, m.p. 95–97°, was isolated by concentrating the filtrates after separating 4-methoxyphenanthrene picrate and treating the residual mixture of picric acid and phenanthrene picrate with ammonia and ether.

NEW BRUNSWICK, NEW JERSEY

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY, AND THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Studies on the Mucohalic Acids. II. The Synthesis of Fused γ-Lactam-thiazolidines Related to Penicillin[1]

BY HARRY H. WASSERMAN, FRANK M. PRECOPIO AND TIEN-CHUAN LIU*

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Mucochloric, mucobromic and mucophenoxychloric acids were condensed with *dl*-penicillamine hydrochloride and its methyl ester to form fused γ-lactam-thiazolidines structurally related to the penicillins. The 2-thiazolidineacrylic acids pictured as intermediates appeared to cyclize to γ-lactams either spontaneously or after mild heating.

The condensation of cysteine and penicillamine with aldehydes and ketones to form thiazolidines takes place under a wide variety of conditons.[2–4] In the case of the reaction with aldehyde-acids, the initial thiazolidine formation may be followed by interaction of the carboxyl group with the cyclic imino group to produce a fused lactam-thiazolidine. Although β-lactam formation by this method, utilizing α-aldehydo-acids, has never been observed, γ-lactams have been prepared successfully by the use of β-aldehydo-acids. Thus, as reported in the recent monograph on the chemistry of penicillin,[5] derivatives of β-formylpropionic acid were condensed with the appropriate α-amino-β-mercapto acids to form thiazolidines which readily cyclized to fused-ring γ-lactams. Among

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(1) In part, from the doctoral dissertation of H. H. Wasserman, Harvard University, 1948.

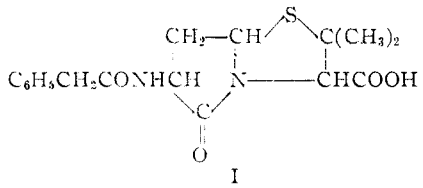
(2) H. T. Clarke, J. R. Johnson and R. Robinson, Editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 921.

(3) S. Lieberman, P. Brazeau and L. B. Hariton, THIS JOURNAL, **70**, 3094 (1948).

(4) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).

(5) Reference 2, p. 1004.

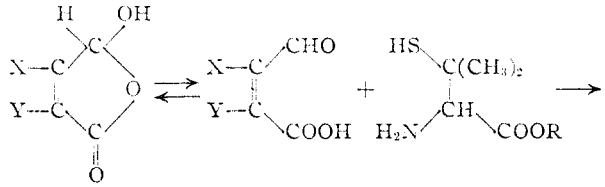
the compounds prepared by this procedure was the γ-lactam of benzylhomopenicilloic acid (I), a homolog of benzylpenicillin.



I

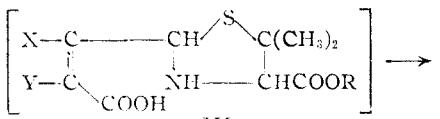
The present work describes the reactions of several β-formylacrylic acids in the mucohalic acid series with *dl*-penicillamine (II, R = H) and its methyl ester (II, R = CH_3) to form fused γ-lactam-thiazolidines (IV, V, VI and VII). These lactams are structurally related to the penicillins, and might provide, through suitable methods of ring contraction, a synthetic route toward the fused β-lactam-thiazolidine ring system present in the penicillins.

The condensations shown in the reaction scheme

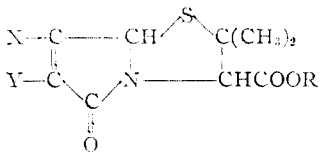


Ia, X = Y = Cl
Ib, X = Y = Br
Ic, X = Cl; Y = OC_6H_5

II



III



IV, R = H, X = Cl, Y = Cl
V, R = CH_3, X = Cl, Y = Cl
VI, R = CH_3, X = Br, Y = Br
VII, R = CH_3, X = Cl, Y = OC_6H_5

took place in cold aqueous ethanolic solution buffered with an equivalent of sodium acetate to form the lactams in yields of 50–80%. In three of the four cases cited, lactam formation appeared to take place spontaneously, and no intermediate thiazolidineacrylic acid was isolated. Thus, the reaction between mucochloric acid (Ia), and *dl*-penicillamine hydrochloride readily yielded a monocarboxylic acid $C_9H_9O_3NSCl_2$ which showed none of the characteristic tests for a free sulfhydryl group. Treatment with diazomethane converted the acid to a methyl ester which was identical with the product derived from the direct condensation of mucochloric acid with the methyl ester of *dl*-penicillamine hydrochloride. On the basis of these facts the above condensation products were assigned the fused γ-lactam-thiazolidine structures IV and V. A similar reaction took place with mucobromic acid (Ib), yielding the γ-lactam-thiazolidine (VI).

When mucophenoxychloric acid (Ic), was allowed to react with the methyl ester of *dl*-penicillamine hydrochloride under the same conditions, it was possible to isolate an acidic intermediate as well as the neutral lactam. The acid III (R = CH_3, X = Cl, Y = OC_6H_5) was characterized by its ready cyclization, through gentle warming, to the γ-lactam (VII).

The analogous reaction between cysteine hydrochloride or its methyl ester with mucochloric acid did not take place smoothly. On mixing solutions of the reactants under the conditions described above, an immediate yellow coloration appeared, followed by gradual darkening of the solution. No crystalline product could be isolated from this reaction mixture.

The infrared absorption spectra of the γ-lactam-thiazolidines (V, VI and VII) (Fig. 1), are in accord with the assigned structures. Each of the products exhibits a broad band in the 5.8–5.85 μ region of the spectrum, corresponding to a superposition of ester and fused γ-lactam carbonyl groups. (It was not possible to resolve this band into the two carbonyl components.) Other fused γ-lactams have been reported to absorb in the 5.8 μ region of the infrared,[6] as in the case of the γ-lactam of benzylhomopenicilloic acid (I), the methyl ester of which has a band at 5.85 μ attributed to the carbonyl present in the fused γ-lactam ring.

Acknowledgment.—One of the authors (H.H.W.) acknowledges the very pleasant association with Professor R. B. Woodward at Harvard University during the course of which this work was begun.

Experimental[7]

Mucohalic Acids.—The mucochloric, mucobromic and mucophenoxychloric acids used in this investigation were prepared according to the methods of Hill and co-workers.[8,9]

Methyl Ester of *dl*-Penicillamine Hydrochloride.[10,11]—The methyl ester was prepared by bubbling dry HCl into a solution containing 19 g. of *dl*-penicillamine hydrochloride in 150 ml. of dry methanol in an ice-bath for three hours. After storage in the cold overnight, the solution was filtered, refluxed on the steam-bath for two hours, and then evaporated to dryness *in vacuo*. The residue was dissolved in *t*-butyl alcohol, decolorized with charcoal, and chilled. Clusters of needles gradually separated, m.p. 174–176°. After recrystallization from *t*-butyl alcohol, 6.2 g. (30%) of ester was obtained, melting 175–176°. The melting point previously reported[11] was 173–175°.

γ-Lactam of 4-Carboxy-5,5-dimethyl-2-thiazolidine-α,β-dichloroacrylic Acid (IV).—An aqueous solution (10 ml.) containing one gram of *dl*-penicillamine hydrochloride buffered with one equivalent of sodium acetate was mixed with 5 ml. of an ethanolic solution of mucochloric acid (0.91 g.), and enough ethanol was added to dissolve any solid precipitating. The solution was refrigerated overnight, whereupon a straw-colored oil separated. This oil was washed with 50% ethanol and the solid which separated was recrystallized from benzene. In this way, 0.8 g. (52%) of tiny prisms was obtained which melted 153–154° (dec.). On standing at room temperature the lactam slowly decomposed with the development of a green coloration. This acid showed none of the characteristic tests for a free sulfhydryl group (no transient blue coloration with ferric chloride, no deep red-violet coloration with alkaline sodium nitroprusside).

(6) Reference **2**, p. 391.
(7) All melting points are uncorrected.
(8) H. B. Hill, *Am. Chem. J.*, **3**, 165 (1881); *ibid.*, **3**, 33 (1881).
(9) H. E. Sawyer, *Proc. Am. Acad. Arts Sci.*, **29**, 242 (1894).
(10) Reference 2, p. 463.
(11) Reference 2, p. 470.

Anal. Calcd. for $C_9H_9O_3NSCl_2$: C, 38.22; H, 3.22; N, 4.96; S, 11.38; neut. equiv., 282. Found: C, 38.52; H, 3.28; N, 5.26; S, 11.54; neut. equiv., 279.

γ-Lactam of 4-Carbomethoxy-5,5-dimethyl-2-thiazolidine-α,β-dichloroacrylic Acid (V). (a).—One gram of the γ-lactam of 4-carboxy-5,5-dimethyl-2-thiazolidine-α,β-dichloroacrylic acid was dissolved in dry ether and ethereal diazomethane was added in slight excess till the yellow color persisted. The ether was allowed to evaporate slowly, whereupon large prisms (1 g.) were obtained, m.p. 99–100°.

Anal. Calcd. for $C_{10}H_{11}O_3NSCl_2$: C, 40.55; H, 3.74. Found: C, 40.63; H, 3.89.

(b).—A solution of 0.314 g. of mucochloric acid in 5 ml. of 95% ethanol was added to a solution containing 0.369 g. of penicillamine methyl ester hydrochloride and 0.309 g. of sodium acetate in 10 ml. of water. The oil which formed on cooling gradually solidified. Recrystallization from ethanol yielded 0.47 g. (85%) of white crystals m.p. 98–99°. This sample was shown, by mixed melting point and comparison of infrared spectra, to be identical with the methyl ester prepared by method (a).

Anal. Calcd. for $C_{10}H_{11}O_3NSCl_2$: C, 40.55; H, 3.74; N, 4.73. Found: C, 40.41; H, 3.78; N, 4.92.

γ-Lactam of 4-Carbomethoxy-5,5-dimethyl-2-thiazolidine-α,β-dibromoacrylic Acid (VI).—The condensation of mucobromic acid with *dl*-penicillamine methyl ester hydrochloride was carried out in the same manner as described for the mucochloric acid addition product above. The dibromolactam (VI) m.p. 96–98° was recrystallized from a mixture of ethanol and water, and then from ethanol alone. On standing the lactam slowly decomposed. The yield was 48%.

Anal. Calcd. for $C_{10}H_{11}O_3NSBr_2$: C, 31.19; H, 2.88; S, 8.32; N, 3.64. Found: C, 31.40; H, 3.03; S, 8.34; N, 3.70.

4-Carbomethoxy-5,5-dimethyl-2-thiazolidine-α-phenoxy-β-chloroacrylic Acid (III).—*dl*-Penicillamine hydrochloride methyl ester (0.304 g.) was dissolved in 10 ml. of water containing 0.131 g. of sodium acetate, and to the solution was added an equivalent amount (0.341 g.) of mucophenoxychloric acid in 5 ml. of 95% ethanol. Enough alcohol was added to dissolve the solid which separated. The solution was kept in the cold for 12 hours, whereupon a crystalline product separated. A second crop of crystals was obtained by adding water to the mother liquor and cooling. The solid product was washed with cold dilute sodium bicarbonate, the bicarbonate solution separated from neutral material, and then acidified. From the acid solution there was obtained 0.2 g. of acid, m.p. 95°. This product was characterized by conversion, through gentle warming, to the γ-lactam (VII).

Anal. Calcd. for $C_{16}H_{18}O_5NSCl$: C, 51.68; H, 4.84; N, 3.76; Cl, 9.53. Found: C, 51.68; H, 4.92; N, 3.86; Cl, 9.72.

γ-Lactam of 4-Carbomethoxy-5,5-dimethyl-2-thiazolidine-α-phenoxy,β-chloroacrylic Acid (VII).—The bicarbonate-insoluble product derived from the condensation of mucophenoxychloric acid with *dl*-penicillamine methyl ester hydrochloride was recrystallized from ethanol–water. Its melting point was 90.5–92°. The free acid (III) was converted to the same product (no depression of mixed melting point) by warming the bicarbonate solution of the acid on the steam-bath, whereupon the crystalline lactam m.p. 90.5–92° separated. The total yield of crude lactam was 0.48 g. (90%).

Anal. Calcd. for $C_{16}H_{16}O_4NSCl$: C, 54.31; H, 4.56; N, 3.96; S, 9.06. Found: C, 54.32; H, 4.95; N, 4.15; S, 10.27.

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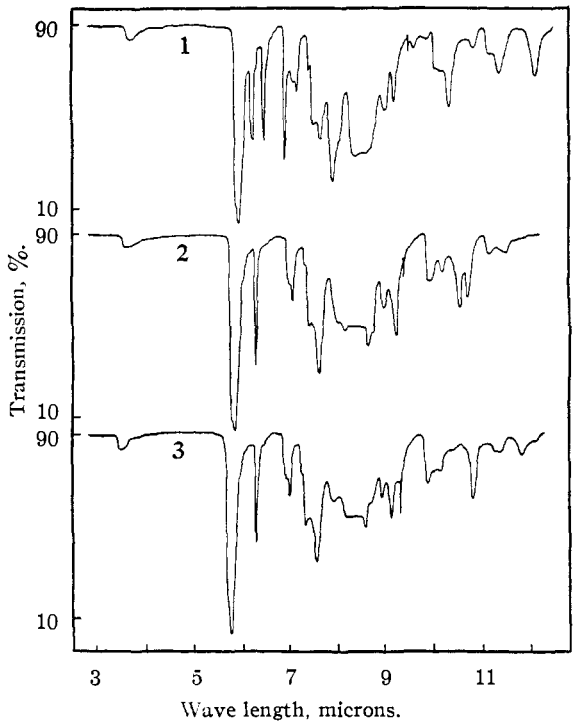

Fig. 1.—Infrared spectra: (1) γ-lactam of 4-carbomethoxy-5,5-dimethyl-2-thiazolidine-α-phenoxy-β-chloroacrylic acid (VII); (2) γ-lactam of 4-carbomethoxy-5,5-dimethyl-2-thiazolidine-α,β-dichloroarylic acid (V); (3) γ-lactam of 4-carbomethoxy-5,5-dimethyl-2-thiazolidine-α,β-dibromoacrylic acid (VI). All spectra were taken in chloroform solution (0.1-mm. cell), using a Perkin–Elmer, Model 21 instrument.