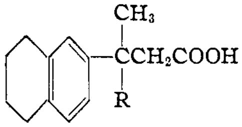
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Cyclization of β-(6-Tetralyl)-isovaleric Acid, and of 6-Senecioyltetralin

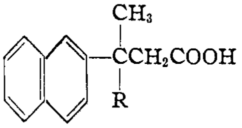
BY LEE IRVIN SMITH AND PHILIP N. GORDON[1]

β-(6-Tetralyl)-isovaleric acid (I) and 6-senecioyltetralin (VII)—the latter a new compound—have been prepared and cyclized by action of sulfuric acid. Cyclization of I produced two hydrindones, VIII and IX; cyclization of VII also produced two hydrindones, VIII and X. The structure of VIII follows from the fact that it was obtained from both I and VII and, knowing the structure of VIII, the structures of IX and X follow. Cyclization of I at room temperature gave a mixture containing largely IX, but containing a considerable amount of VIII; at lower temperatures, cyclization of I produced almost exclusively IX. Thus, the 5-position in the tetralin derivative I is more reactive in this reaction than position 7, and all the more so at lower temperatures. Cyclization of VII produced the two hydrindones VIII and X in approximately equal amounts; thus, in this reaction, the 5- and 7-positions of the tetralin derivative VII are about equally reactive.

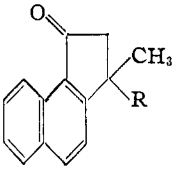
The previous paper[2] contained a report of the conversion of β-(6-tetralyl)-isovaleric acid (I) into β-(2-naphthyl)-isovaleric acid (II) and cyclization of the latter, by action of sulfuric acid, to a single product, the benzhydrindone III. Cauquil and Barrera[3] reported that action of sulfuric acid upon the tetralylbutyric acid IV led to a mixture of the two possible hydrindones V and VI.



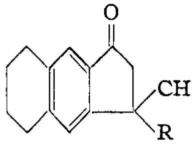
I, R = CH$_3$
IV, R = H



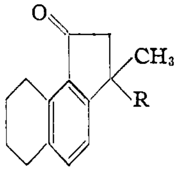
II, R = CH$_3$



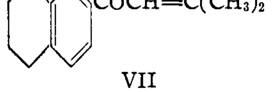
III, R = CH$_3$



V, R = H
VIII, R = CH$_3$



VI, R = H
IX, R = CH$_3$



VII

Schroeter[4] also obtained both the linear and angular tetralones when he subjected γ-(6-tetralyl)-butyryl chloride to the action of aluminum chloride, but Krollpfeiffer and Shafer[5] reported that action of sulfuric acid upon γ-(6-tetralyl)-butyric acid led to a single substance (75%), the linear tetralone.

In order to explore this reaction further, and to determine whether or not the direction of cyclization of 6-tetralyl acids to hydrindones might be controlled by changing somewhat the nature of the side chain, cyclization by action of sulfuric acid of β-(6-tetralyl)-isovaleric acid (I) and the α,β-unsaturated ketone 6-senecioyltetralin (VII) was investigated.

Action of sulfuric acid (95%) upon I at room temperature produced a mixture (90%) of the two possible hydrindones VIII and IX. This mixture, a liquid, could not be separated into its components directly, but a separation was achieved by conversion of the mixture to 2,4-dinitrophenylhydrazones and separation of the latter by a combination of fractional crystallization and chromatography. Hydrindone VIII gave a red DPH, whereas IX (present in larger amounts) gave an orange DPH. When sulfuric acid acted upon I at 1–3°, the product was a solid which consisted largely of the angular hydrindone IX. Thus, the direction of cyclization of I could be partially controlled by adjusting the temperature at which the reaction occurred.

Separation of the DPH's was a tedious and lengthy process; even when one was but slightly contaminated with the other, at least four recrystallizations were required. The DPH's were but slowly soluble in acetone and readily formed supersaturated solutions, hence it was necessary to allow a full day, and often longer, for each crystallization. The pure DPH's, prepared from the pure hydrindones, showed melting points (decomposition) appreciably higher than any of those obtained from the mixture.

The pure hydrindones, readily obtained from the DPH's by acid hydrolysis and steam distillation, were colorless solids with pleasant odors. One (IX) melted at 69–70°; the other (VIII) at 72–76°. A mixture of the two formed an oil from which the pure isomers could not be obtained by crystallization.

When senecioyl chloride and tetralin were subjected to the conditions of a Friedel–Crafts reaction, 6-senecioyltetralin (VII) (33%), an oil, was formed. Oxidation of VII converted it into the known 6-tetralylcarboxylic acid. The ketone VII was unsaturated toward bromine, and it formed a red 2,4-dinitrophenylhydrazone which could not be cyclized to a pyrazoline. Hydrolysis of this DPH by action of 60% sulfuric acid readily occurred, and when the reaction mixture was steam distilled immediately, the ketone VII was recovered. But when the reaction mixture was allowed to stand overnight before steam distillation, the chief product was a new hydrindone, X. When the ketone VII was subjected to the action of sulfuric acid at room temperature, the product was an uncrystallizable oil which was converted into a mixture of red DPH's and these

---

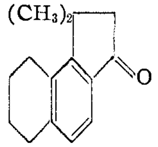
[1] Abstracted from a thesis by Philip N. Gordon, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the M.S. degree, February, 1950.

[2] L. I. Smith and C.-P. Lo, THIS JOURNAL, **70**, 2215 (1948).

[3] G. Cauquil and H. Barrera, *Compt. rend.*, **223**, 679 (1946).

[4] G. Schroeter, *Ber.*, **57**, 2003 (1924).

[5] F. Krollpfeiffer and W. Shafer, *ibid.*, **56**, 620 (1923).



X

then separated. One of the DPH's was identical with the red DPH obtained from VIII. The other differed from the DPH of IX and represented a derivative of a third hydrindone. These two substances were present in approximately equal amounts in the mixture. Hydrolysis of the DPH's regenerated the hydrindones: VIII, melting at 72–76°, and X, melting at 80–84°.

The fact that each of the compounds, I and VII, when cyclized, produced two hydrindones and that one of the hydrindones was produced from both I and VII, served to fix the structures of the hydrindones, for only VIII and IX may be derived from I, and only VIII and X may be derived from VII. If, then, VIII results from cyclization of both I and VII, it must have the structure assigned to it, and the structures of IX or X then follow.

6-Senecioyltetralin was also cyclized when subjected to the action of aluminum chloride and hydrochloric acid in carbon bisulfide. The product, an oil, was converted into a mixture of DPH's from which only one pure DPH—that derived from X—was isolated. No pure product could be obtained from the rest of the material.

The assignment of structures to the three hydrindones is based upon the assumption that the compounds are actually hydrindones, and are not tetralones or some other rearrangement products. Each of the hydrindones was subjected to the action of sulfuric acid at room temperature and, in each case, only the pure starting material was recovered.

Experimental Part[6]

Senecioic acid, m.p. 69–70° (13 g., 65%), was prepared using a modification of the procedure previously described,[7] from mesityl oxide (19.6 g.) and sodium hypochlorite.

β-(6-Tetralyl)-isovaleric acid (I) (21%, m.p. 87–88°) was prepared according to Smith and Lo.[2]

Cyclization of I.—A solution of I (10 g.) in sulfuric acid (110 cc., 95%) was allowed to stand at room temperature for one week. The deep yellow solution was poured over ice, and the mixture was extracted with ether. The extract was washed successively with water, aqueous sodium carbonate (10%) and water and was dried (sodium sulfate). Removal of the solvent left a light yellow oil (8.3 g., 90%), which could be separated by distillation into two fractions: (a) b.p., 165–175° (4 mm.), and (b) b.p., 180–210° (4 mm.). Neither fraction was pure, however. The crude mixture of hydrindones gave a mixture of oximes from which only one pure oxime could be separated. This melted at 144.5–146.5°, and was probably the oxime of IX, although this was not established with certainty.

Anal. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.41. Found: C, 78.60; H, 8.36.

The crude product (0.5 g.), before any distillation, was converted into a mixture of 2,4-dinitrophenylhydrazones by reaction with 2,4-dinitrophenylhydrazine (1 g.) in ethanol (200 cc.). The mixture was refluxed until it was clear, then hydrochloric acid (1 cc.) was added, and the mixture was set aside overnight. The red solid (0.94 g., 100%) was removed and washed thoroughly with ethanol, when it melted at 210–225°. For separation into the pure components, the red solid was dissolved in acetone and the solution was quickly chilled, resulting in separation of the DPH's in very small crystals. The mixture was then quickly heated; the red 2,4-dinitrophenylhydrazone of VIII dissolved in a few minutes and the orange derivative of IX remained undissolved. The mixture was quickly filtered; several crystallizations of the orange solid produced short, orange needles which melted at 258–259° (dec.). The mother liquor, when concentrated, deposited the red derivative of VIII as needles which melted at 253–255° (dec.). A mixture of the two derivatives melted at 220–225° to a clear red liquid.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: C, 63.94; H, 5.62. Found (derivative of IX, orange, m.p. 258–259°): C, 63.77; H, 5.82. Found (derivative of VIII, red, m.p. 253–255°): C, 64.06; H, 5.78.

This process was quite wasteful of material, and much time was required, for after the preliminary separation, the successive crystallizations had to be carried out slowly in order to obtain the pure materials. The mixture of 2,4-dinitrophenylhydrazones could be separated also by chromatography from petroleum ether (b.p. 60–68°) onto alumina (Alcoa, 80–200 mesh, grade F-20), followed by development with carbon tetrachloride. The solid appeared on the column as a single band; after development, the column was extruded and sectioned arbitrarily and the sections were eluted with acetone. The orange derivative was found in the lower part of the column, and the red derivative at the upper part.

When the cyclization of I (3 g.) was conducted by action of sulfuric acid at 0° for two hours and the mixture was processed as described above, the oil remaining after removal of the solvent from the extract, solidified when cooled. It weighed 1.51 g. (52%) and melted at 55–69°. It formed a mixture of 2,4-dinitrophenylhydrazones, which after two crystallizations from acetone yielded the orange derivatives of IX melting at 252–257° (dec.). From the mother liquor a small amount of the red derivative of VIII was isolated. The product of cyclization of I at the lower temperature consisted of at least 90% IX.

Hydrolysis.—The pure derivative of VIII (0.5 g.) was refluxed for one hour with sulfuric acid (60%, 500 cc.) and the mixture was steam distilled for six hours. The distillate was extracted with ether, the extract was dried (sodium sulfate), the solvent was removed, and the residue was crystallized from petroleum ether (b.p. 30–60°). The material melted at 70–72°, and was yellow; the yellow impurity was removed by chromatography from petroleum ether onto alumina; development was with the same solvent and under ultraviolet light (violet fluorescence). The final white product melted at 72–76° and formed the red 2,4-dinitrophenylhydrazone melting at 256–259° (dec.).

3,3-Dimethyl-(5,6)-tetrahydrobenzhydrindone-1 (VIII): *Anal.* Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.15; H, 8.68. A solution of VIII (0.05 g.) in sulfuric acid (15 cc., 95%) was allowed to stand at room temperature overnight. The solution was poured over ice and the white solid was removed, washed with water, and dried. It melted at 76–78°, alone or when mixed with VIII.

The pure 2,4-dinitrophenylhydrazone of IX was hydrolyzed as described above. This derivative underwent hydrolysis with some difficulty, and the mixture was refluxed for 12 hours, and then processed as above. The purified hydrindone IX melted at 69–70°; a mixture of VIII and IX melted at 40–55° and the oil could not be crystallized. The 2,4-dinitrophenylhydrazone, prepared from pure IX, crystallized from ethanol in long orange needles melting at 255–258° (dec.).

3,3-Dimethyl-(6,7)-tetrahydrobenzhydrindone-1 (IX): *Anal.* Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.76; H, 8.58. When kept in solution in sulfuric acid overnight, the hydrindone IX was recovered unchanged; it then melted at 69–72°, alone or when mixed with IX.

6-Senecioyltetralin (VII).—Aluminum chloride (54.5 g.) was slowly (80 minutes) added to a cooled (−5°) and stirred solution of dry tetralin (51.5 g.) and senecioyl chloride (46.2 g.) in carbon bisulfide (200 cc.). The temperature was maintained below 0° for three hours and then slowly raised to 40° and held there for one hour. The solvent was removed, the residue was poured over ice, and the mixture was extracted with ether. The ketone (7.4 g., 9%) formed a colorless oil boiling at 140.7–141° (2 mm.), and had n^{25}_D 1.5370.

---

(6) Microanalyses by J. Buckley, Wm. Cummings, H. Turner and R. Kelly.

(7) L. I. Smith, W. W. Prichard and L. J. Spillane, *Org. Syntheses*, **23**, 27 (1943).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.79; H, 8.76.

The 2,4-dinitrophenylhydrazone, crystallized from acetone, was red and melted at 273–275° (dec.).

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: C, 63.94; H, 5.62. Found: C, 64.09; H, 5.81.

This derivative was unaffected when heated in ethanol or in acetic acid for 24 hours; nor was there any change when a solution of the derivative in ethanol was made basic by addition of potassium hydroxide and then heated on the steam-bath for two hours. No pyrazoline was formed under any of these conditions.

Hydrolysis of the 2,4-Dinitrophenylhydrazone of VII.—The derivative (0.2 g.) was refluxed with sulfuric acid (60%, 500 cc.) for a few minutes to complete the rapid hydrolysis. The mixture was steam distilled at once until the distillate contained several drops of oil. This oil decolorized permanganate in acetone, reacted by addition with bromine in carbon tetrachloride, and gave the red 2,4-dinitrophenylhydrazone of VII melting at 270–275°. The residue from the steam distillation was allowed to stand overnight and was steam distilled again; the distillate contained a light yellow solid which melted at 76–85° and was the hydrindone X (mixed m.p., 79–85°; see below).

6-Tetralylcarboxylic Acid.—Powdered potassium permanganate (1.5 g.) was added in small portions and with shaking to a solution of the ketone VII (1.07 g.) in acetone (30 cc.) at room temperature and the acid was recovered after removal of the sludge of manganese dioxide. After crystallization from ethanol, it weighed 0.3 g., and melted at 151–153°, in agreement with the value in the literature.[8]

Cyclization of VII. A.—Aluminum chloride (1.5 g.) was added to a solution of VII (1 g.) in carbon bisulfide (5 cc.) and the mixture was saturated with hydrogen chloride. The flask was stoppered (care) and shaken for 30 minutes, then the solvent was removed and the residue was poured over iced hydrochloric acid. The viscous oil was removed and converted into a mixture of 2,4-dinitrophenylhydrazones, which was separated by crystallization from acetone into a red solid melting at 263–265° (dec.) and a mixture of red and orange crystals melting at 243–250°. The red solid (m.p. 263–265°), when chromatographed from petroleum ether as described above and then recrystallized from acetone, gave red crystals melting at 268–271° (dec.). This was the derivative of hydrindone X, but it was still not pure. The mixture (m.p. 243–250°) of derivatives was hydrolyzed (slow, seven hours), and then steam distilled, as described above. The light yellow solid (m.p. 71–76°) in the distillate was removed and chromatographed from petroleum ether (b.p., 45–70°) onto alumina. The section of the column fluorescing under ultraviolet light was removed and extracted with acetone; the white solid (X), recrystallized from petroleum ether (b.p. 30–60°), melted at 80–84°. When mixed with VIII, it melted at 45–63°; when mixed with IX, it melted at 45–65°.

3,3-Dimethyl-(4,5)-tetrahydrobenzhydrindone (X): *Anal.* Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.21; H, 8.63. The 2,4-dinitrophenylhydrazone of X, crystallized several times from acetone, formed deep-red feathery crystals melting at 273–274° (dec.). A mixture of this with the corresponding derivative of VII (m.p. 267–268°) melted at 265–269°.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$: C, 63.94; H, 5.62. Found: C, 63.92; H, 5.65.

Hydrindone X (0.05 g.) was dissolved in sulfuric acid (95%, 15 cc.) at room temperature; the solution was allowed to stand overnight, and then poured over ice. The solid was removed and dried; it melted at 84–86° alone or when mixed with X.

B.—The ketone VII (3 cc.) was dissolved in sulfuric acid (95%, 30 cc.) and the deep red solution was allowed to stand at room temperature for 18 days. The solution was poured over ice and extracted with ether; the extract was washed with water, dried (sodium sulfate) and the ether was removed. The residual yellow oil was converted into a mixture of 2,4-dinitrophenylhydrazones which were separated by fractional crystallization from acetone. Two red derivatives were obtained: one identical with the derivative of hydrindone VIII, m.p. and mixed m.p. 253–255°. The second red derivative was identical with the derivative of hydrindone X, m.p. 273–274°. Hydrolysis of the latter (slow, six hours) by refluxing it with aqueous sulfuric acid (60%) gave the hydrindone X which, after crystallization from petroleum ether, melted at 82–84°, alone or when mixed with X as prepared in A above.

MINNEAPOLIS 14, MINN. RECEIVED FEBRUARY 23, 1951

---

[8] G. Stork, THIS JOURNAL, 69, 579 (1947).

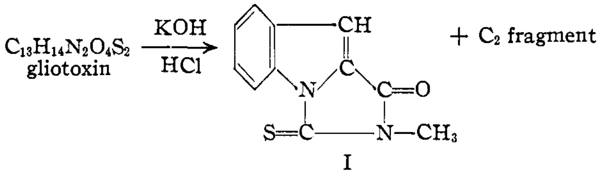
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin. IX. Synthesis of the $C_{11}H_8N_2OS$ Degradation Product[1]

BY JOHN R. JOHNSON AND JAMES B. BUCHANAN[2]

The crystalline sulfur-containing degradation product derived from gliotoxin by the action of alcoholic alkalies, $C_{11}H_8N_2OS$, has been synthesized by cyclization of the condensation product from 2-bromobenzaldehyde and 3-methyl-2-thiohydantoin. This mode of synthesis establishes definitely the position of the sulfur atom in the degradation product. The structure of this compound is consistent with the view that one of the sulfur atoms in gliotoxin is attached at the 4-position of the pyrazinoindole nucleus.

The action of methanolic potassium hydroxide on gliotoxin or its diaroyl derivatives, followed by acidification of the hydrolysate, gives rise to a yellow-orange, crystalline product, m.p. 188°, for which the molecular formula $C_{11}H_8N_2OS$ has been established.[3] On the basis of its chemical and physical properties, this sulfur-containing degradation product was assigned the structure (I) of a thiohydantoin related to 2-indolecarboxylic acid: 2-methyl-3-thioxoimidazo[3,4a]indol-1(2)-one. The nature of the C_2-fragment which is eliminated in the formation of the C_{11}-compound could not be established.



I

The carbon–nitrogen skeleton of the proposed thiohydantoin structure has been established by Dutcher and Kjaer[4] through oxidative desulfurization to the corresponding hydantoin, $C_{11}H_8N_2O_2$, which was shown by degradation and by synthesis to be the oxygen analog of the thiohydantoin I. This evidence does not fix the location of the sulfur atom of the thiohydantoin, since an isomer of structure I having the thioamide group attached at

---

[1] Previous paper, THIS JOURNAL, 72, 2862 (1950).

[2] The Wm. S. Merrell Company Fellow in Chemistry, 1948–1949.

[3] J. D. Dutcher, J. R. Johnson and W. F. Bruce, THIS JOURNAL, 67, 1736 (1945).

[4] J. D. Dutcher and A. Kjaer, *ibid.*, 73, in press (1951).