The Mannich Base of Troponoid and its Application. IV. The Synthesis of Tropolon-5-ylalanine

By Shuichi SETO and Kyozo OGURA

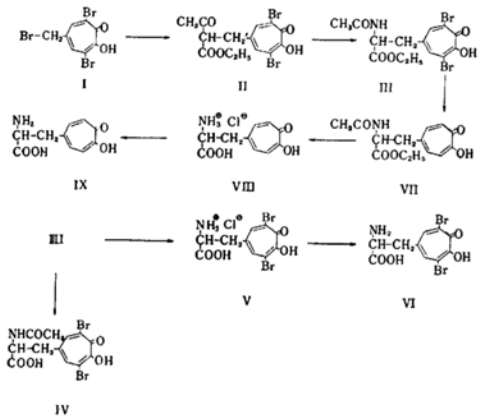
(Received February 13, 1960)

It was shown in previous reports[1,2] that 5-hydroxymethyl-, 5-formyl- and 5-bromomethyl-tropolone derivatives were derived from 3, 7-dibromo-5-morpholinomethyltropolone and that 3, 7-dibromo-5-formyltropolone and 3, 7-dibromo-5-bromomethyltropolone (I) were important starting materials for the synthesis of various tropolone derivatives possessing a substituent in the 5-position of the tropolone ring. The present paper describes the synthesis of tropolone derivative possessing an amino acid residue in the 5-position of tropolone ring, i. e. tropolon-5-ylalanine, and related compounds from I.

Application of a large excess of ethyl potassioacetoacetate to I affords 3, 7-dibromo-5-(β-acetyl-β-ethoxycarbonylethyl)tropolone (II)[2] whose Schmidt reaction gives 3, 7-dibromo-5-(β-acetamido-β-ethoxycarbonylethyl)tropolone (III), m. p. 198°C. Hydrolysis of III with dilute alkali produces 3, 7-dibromo-5-(β-acetamido-β-carboxyethyl)tropolone (IV), m. p. 217°C (decomp.), but the treatment of III with concentrated hydrochloric acid with boiling gives 3, 7-dibromotropolon-5-ylalanine hydrochloride (V), m. p. 223~230°C (decomp.). Neutralization of V liberates 3, 7-dibromotropolon-5-ylalanine (VI), m. p. 216°C (decomp.). Hydrogenolysis of III over palladium-carbon as a catalyst, in methanol affords 5-(β-acetamido-β-ethoxycarbonylethyl)tropolone (VII), m. p. 176°C. Treatment of VII with concentrated hydrochloric acid by boiling produces

1) S. Seto and K. Ogura, This Bulletin, 32, 493 (1959).
2) S. Seto and K. Ogura, ibid., 32. 1118 (1959).

tropolon-5-ylalanine hydrochloride (VIII), m. p. 215~220°C (decomp.), which liberates tropolon-5-ylalanine (IX), m. p. 240°C (decomp.), by neutralization. The amino acids so obtained, VI and IX, color reddish violet to ninhydrin and the aqueous layer turns green with ferric chloride. The infrared spectra of these compounds show absorption bands[3] originating in the zwitter ion structure characteristic of amino acid[4], by the presence of marked absorption at 3030, 1631 and 1575 cm^{-1} in VI and at 3020 and 1640 cm^{-1} in IX.



Experimental[5]

3, 7-Dibromo-5-(β-acetamido-β-ethoxycarbonylethyl) tropolone (III).— To a solution of 500 mg. of II dissolved in 25 ml. of benzene, 10 ml. of conc. sulfuric acid was added and the mixture was stirred under ice-cooling. To this mixture, 180 mg. of sodium azide was added and the stirring was continued for a further 1 hr. period, during which vigorous evolution of nitrogen gas occurred and the reaction product transited to the conc. sulfuric acid layer. The benzene layer was discarded, ca. 20 g. of cracked ice was added to the sulfuric acid layer, and the colorless precipitate thereby formed was collected by filtration. After washing the precipitate with water and drying, it was recrystallized from methanol and III was obtained as colorless needles, m. p. 197~198°C. Yield, 500 mg. The aqueous layer colored green to ferric chloride.

Found: C, 38.46; H, 3.62; N, 3.41. Calcd. for $C_{14}H_{15}O_5NBr_2$: C, 38.44; H, 3.43; N, 3.20%.

U. V. λ_{max}^{MeOH} mμ (log ε): 268 (4.50), 345 (3.99), 430 (3.88).

3, 7-Dibromo-5-(β-acetamido-β-carboxyethyl)-tropolone (IV).— A solution of 50 mg. of III dissolved in 0.5 ml. of 10% sodium hydroxide solution was heated on a water bath for about 10 min. and cooled to room temperature when yellow crystals of the sodium salt separated out. The salt was neutralized with 6 N hydrochloric acid, the colorless crystals that formed were collected, and recrystallized from ethanol. Yield, 20 mg. of m. p. 216~217°C (decomp.).

Found: C, 35.10; H, 2.61; N, 3.44. Calcd. for $C_{12}H_{11}O_5NBr_2$: C, 35.21; H, 2.69; N, 3.42%.

U. V. λ_{max}^{MeOH} mμ (log ε): 268 (4.48), 345 (4.00), 425 (3.80).

3, 7-Dibromotropolon-5-ylalanine Hydrochloride (V).— A mixture of 150 mg. of III and 5 ml. of conc. hydrochloric acid was heated on a water bath for 2 hr. when the crystals dissolved completely. The solution was evaporated to dryness and residual colorless prismatic crystals were collected after addition of ethanol. Yield, 100 mg. of m. p. 223~230°C (decomp.).

Found: C, 30.11; H, 2.59; N, 3.38. Calcd. for $C_{10}H_{10}O_4NBr_2Cl$: C, 29.78; H, 2.48; N, 3.46%.

U. V. λ_{max}^{MeOH} mμ (log ε): 267 (4.47), 340 (3.88), 425 (3.66).

3, 7-Dibromotropolon-5-ylalanine (VI).— Adjustment of 50 mg. of V to pH 6 by addition of diluted ammonia water produced a pale yellow precipitate which was collected, washed with water, and recrystallized from ethanol to colorless crystals, m. p. 215~216°C (decomp.). Yield, 30 mg.

Found: C, 32.70; H, 2.45; N, 3.82. Calcd. for $C_{10}H_9O_4NBr_2$: C, 32.91; H, 2.76; N, 3.25%.

U. V. λ_{max}^{MeOH} mμ (log ε): 270 (4.85), 348 (4.09), 435 (4.90).

5-(β-Acetamido-β-ethoxycarbonylethyl) tropolone (VII).—A suspension of 1.5 g. of III in a solution of 0.6 g. of potassium hydroxide in 200 ml. of ethanol was shaken in hydrogen atmosphere after the addition of palladium-carbon catalyst. After absorption of 2 molar equivalents of hydrogen, the catalyst was filtered off and ethanol was evaporated completely from the filtrate. The residual, yellow potassium salt was dissolved in a small quantity of water and neutralized with 6 N hydrochloric acid, by which a yellow precipitate was produced. The mother liquor left after removal of the precipitate also afforded a small quantity of VII, m. p. 171~173°C, by extraction with ethyl acetate. Yield, 0.6 g.

Found: C, 59.42; H, 5.90; N, 5.01. Calcd. for $C_{14}H_{17}O_5N$: C, 60.20; H, 6.14; N, 5.02%.

U. V. λ_{max}^{MeOH} mμ (log ε): 231 (4.37), 228 (4.05).

Tropolon-5-ylalanine Hydrochloride (VIII).—A solution of 100 mg. of VII dissolved in 0.5 ml. of conc. hydrochloric acid was heated on a water bath for 1 hr. and the solution was evaporated to dryness, leaving a syrupy residue. The addition of ethanol to this residue resulted in crystallization, the crystals were collected, and recrystallized from ethanol. Yield, 50 mg. of m. p. 220°C (decomp.).

Found: C, 48.76; H, 5.27; N, 5.45. Calcd. for $C_{10}H_{12}O_4NCl$: C, 48.40; H, 4.84; N, 5.70%.

U. V. λ_{max}^{MeOH} (log ε): 229 (4.37), 326 (4.01).

Tropolon-5-ylalanine (IX).— A solution of 100 mg. of VIII dissolved in a small quantity of water was adjusted to pH 6 by addition of dilute ammonia water, the precipitate formed was collected, and recrystallized from ethanol. Yield, 40 mg. of m. p. 240°C (decomp.).

Found: C, 52.20; H, 5.77; N, 5.83. Calcd. for $C_{10}H_{11}O_4N \cdot H_2O$: C, 52.86; H, 5.77; N, 6.17%.

U. V. λ_{max}^{MeOH} mμ (log ε): 230 (4.31), 330 (4.00).

3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen. London (1958), p. 234.

4) K. Ogura and Y. Ikegami, *Bull. Chem. Research Inst. Non-Aqueous Solutions, Tohoku Univ.*, **9**, 23 (1959).

5) All melting points are uncorrected. The microanalyses were carried out by Mr. S. Oyama and Miss Y. Endo of this Institute.

A part of the expense for the present research was defrayed by Sankyo Co., Ltd. The authors wish to express their sincere gratitude to Mr. S. Aono who carried out the measurement of infrared spectra.

The Chemical Research Institute of Non-Aqueous Solutions
Tohoku University
Katahira-cho, Sendai