The Mannich Base of Troponoid and its Application. II.
On 5-Bromomethyltropolone Derivative

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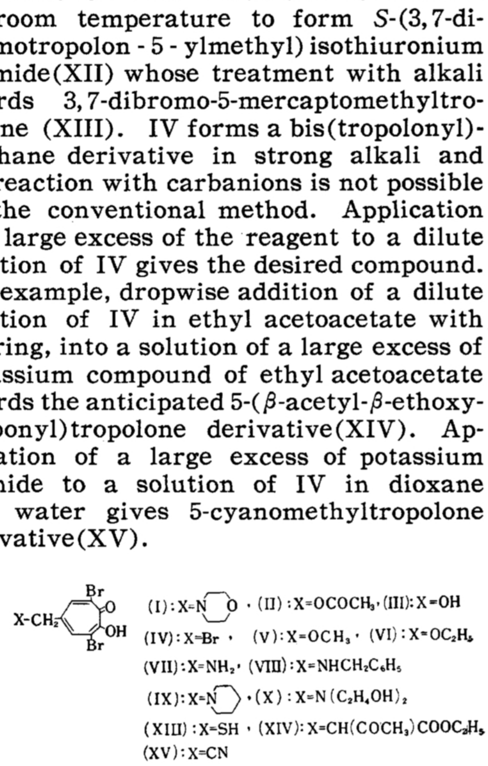
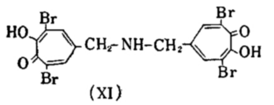
In the preceding paper[1], the authors reported on the derivation of 5-hydroxymethyl- and 5-formyltropolones from 3,7-dibromo-5-morpholinomethyltropolone, and on their reactions. In the present series of experiments, the 5-hydroxymethyl derivative was further led to 5-bromomethyl derivative and examination of this reaction showed some interesting results which are described herein.

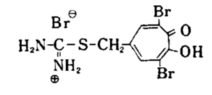
Warming of 3,7-dibromo-5-hydroxymethyltropolone(III), obtained from 3,7-dibromo-5-morpholinomethyltropolone (I), in hydrobromic acid affords 3,7-dibromo-5-bromomethyltropolone(IV) as colorless needless, m. p. 140°C, in a good yield. IV is very reactive and reacts with various anionoid reagents to undergo substitution of bromine in the bromomethyl group as *p*-bromomethylphenol does[2].

Under some conditions, for example, treatment with sodium hydroxide solution, it forms a bis(tropolonyl)methane derivative. When IV is heated in methanol or ethanol, 5-methoxymethyl-(V) or 5-ethoxymethyltropolone derivative(VI) is obtained. These substances are the same as the compounds obtained on refluxing 5-acetoxymethyltropolone derivative(II) in methanol or ethanol. Reaction of IV with sodium acetate afforded II. Reaction with amines occurs easily at room temperature to afford the corresponding aminoalkyltropolone derivatives. Treatment with liquid ammonia, benzylamine, morpholine, piperidine and diethanolamine, respectively, affords 5-aminomethyl-(VII), 5-benzylaminomethyl-(VIII), 5-morpholinomethyl-(I), 5-piperidinomethyl-(IX), and 5-bis (β-hydroxyethyl) aminomethyltropolone (X) derivatives. I and IX are also obtained by the Mannich reaction of 3,7-dibromotropolone, and VII is also obtained in some cases by treatment of II with liquid ammonia. Reaction of IV with concentrated ammonium hydroxide gives bis (3,7-dibromotropolon-5-ylmethyl) amine (XI). All these aminoalkyltropolone derivatives form a water-soluble green iron complex with ferric chloride. IV undergoes reaction with thiourea in *tert*-butanol at room temperature to form *S*-(3,7-dibromotropolon-5-ylmethyl) isothiuronium bromide(XII) whose treatment with alkali affords 3,7-dibromo-5-mercaptomethyltropolone (XIII). IV forms a bis(tropolonyl)-methane derivative in strong alkali and its reaction with carbanions is not possible by the conventional method. Application of a large excess of the reagent to a dilute solution of IV gives the desired compound. For example, dropwise addition of a dilute solution of IV in ethyl acetoacetate with stirring, into a solution of a large excess of potassium compound of ethyl acetoacetate affords the anticipated 5-(β-acetyl-β-ethoxycarbonyl)tropolone derivative(XIV). Application of a large excess of potassium cyanide to a solution of IV in dioxane and water gives 5-cyanomethyltropolone derivative(XV).





(XI)



(XII)

Experimental[3]

3,7-Dibromo-5-bromomethyltropolone (IV).— A mixture of 2 g. of 3,7-dibromo-5-hydroxymethyltropolone (III) and 40 ml. of hydrobromic acid (sp. g., 1.38) was warmed for 15 min. and the colorless needle crystals that separated out were recrystallized from a benzene-cyclohexane mixture: m. p. 139~140°C. Yield, 2 g.

Anal. Found: C, 25.91; H, 1.89. Calcd. for $C_8H_5O_2Br_3$: C, 25.73; H, 1.34%. U. V. λ_{max}^{MeOH} mμ (log ε): 265(4.53), 350(4.21), 428(421).

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[1] S. Seto and K. Ogura, This Bulletin, **32**, 493 (1959).

[2] K. Auwers, *Ber.*, **34**, 4264 (1901).

[3] All melting points are not corrected.

3, 7-Dibromo-5-methoxymethyltropolone (V). — A solution of 10 mg. of IV in 1 ml. of methanol was heated on a water bath for about 10 minutes and the removal of methanol left colorless needles, m. p. 135°C, which showed no depression on admixture with the substance1) obtained by refluxing II in methanol.

Anal. Found: C, 33.98; H, 2.73. Calcd. for $C_9H_8O_3Br_2$: C, 33.33; H, 2.47%. U. V. λ_{max}^{MeOH} mμ (log ε): 267 (4.63), 346 (4.29), 428 (4.30).

3, 7-Dibromo-5-ethoxymethyltropolone (VI). — In exactly the same manner as in the cases of V and IV was heated in ethanol and colorless needles, m. p. 100°C, were obtained. These showed no depression on admixture with the substance1) obtained by the refluxing of II in ethanol.

Anal. Found: C, 35.62; H, 2.91. Calcd. for $C_{10}H_{10}O_3Br_2$: 35.54; H, 2.96%.

3, 7-Dibromo-5-aminomethyltropolone (VII).—(a) A solution of 100 mg. of IV dissolved in ca. 5 ml. of liquid ammonia was allowed to stand at room temperature for 4 days. The yellowish brown residue which was obtained by removal of liquid ammonia was extracted with 1.5 N hydrochloric acid. The extract was neutralized to pH 2.5 and the precipitate thereby formed was collected. Washing of this precipitate with water and methanol afforded yellow powder, m. p. 225°C (decomp.).

b) A solution of 100 mg. of II dissolved in ca. 100 ml. of liquid ammonia was allowed to stand for a week. VII was obtained by treating the residue in the same manner as in the case of a).

Anal. Found: C, 29.62; H, 3.27; N, 4.04. Calcd. for $C_8H_7O_2NBr_2 \cdot H_2O$: C, 29.35; H, 2.75; N, 4.28%. U. V. λ_{max}^{MeOH} mμ (log ε): 268 (4.44), 345 (3.95), 430 (3.98).

3,7-Dibromo-5-benzylaminomethyltropolone (VIII). —About 30 mg. of IV was dissolved in one drop of benzylamine and the solution was warmed at 50°C for a few minutes. By this process yellow crystals separated out. About 1 ml. of acetic acid-water was added to this mixture, the crystals were collected by filtration, and recrystallized from ethanol; m. p. 180°C. Yield, ca. 30 mg.

Anal. Found: C, 43.94; H, 3.57; N, 3.10. Calcd. for $C_{15}H_{13}O_2NBr_2 \cdot 2H_2O$: C, 43.17; H, 3.59; N, 3.35%. U. V. λ_{max}^{MeOH} mμ (log ε): 267 (4.32), 347 (3.95), 430 (3.87).

3, 7-Dibromo-5-piperidinomethyltropolone (IX).— a) The addition of 0.5 ml. of piperidine to 50 mg. of IV resulted in excessive generation of heat and a solution was effected. Addition of water to this solution produced a yellow precipitate. This mixture was adjusted to pH 5 with hydrochloric acid, the precipitate was collected, and washed with water and ethanol. m. p. 189~190°C (decomp.). Yield, ca. 20 mg.

b) A mixture of 400 mg. of 3,7-dibromotropolone (I) in 0.6 ml. of acetic acid and 0.4 ml. of piperidine was heated at 100°C and when in solution, 0.2 ml. of formaldehyde solution (37%) was added dropwise, with stirring. After about 10 min. of stirring and heating, the yellow precipitate that formed was collected and washed with water and ethanol, m. p. 190°C (decomp.). Yield, 490 mg. This substance showed no depression of melting point on admixture with the substance obtained by method a).

Anal. Found: C, 41.69; H, 3.95; N, 3.74. Calcd. for $C_{13}H_{15}O_2NBr_2$: C, 41.38; H, 3.98; N, 3.72%. U. V. λ_{max}^{MeOH} mμ (log ε): 268 (4.02), 350 (3.71), 425 (3.71).

3, 7-Dibromo-5-bis(β-hydroxyethyl)aminomethyltropolone (X). — A solution of 30 mg. of IV dissolved in 3 drops of diethanolamine was neutralized with 2 N hydrochloric acid and the yellow precipitate that formed was collected, washed with water and methanol; m. p. 160°C.

Anal. Found: C, 35.60; H, 3.89; N, 3.69. Calcd. for $C_{12}H_{15}O_4NBr_2$: C, 36.27; H, 3.78; N, 3.52%. U. V. λ_{max}^{MeOH} mμ (log ε): 267 (4.21), 350 (3.90), 430 (3.87).

Bis(3, 7-dibromotropolon-5-ylmethyl)amine (XI). —A mixture of ca. 30 mg. of IV in 0.5 ml. of concentrated ammonium hydroxide was stirred for a few minutes at room temperature. By this process yellow crystals precipitated out. This mixture was neutralized with 2 N hydrochloric acid, the yellow powder so formed was collected, and washed with water and methanol; m. p. 196°C.

Anal. Found: C, 31.31; H, 1.98; N, 2.59. Calcd. for $C_{16}H_{11}O_4NBr_4$: C, 31.94; H, 1.83; N, 2.31%. U. V. λ_{max}^{MeOH} mμ (log ε): 268 (4.40), 345 (4.06), 425 (4.00).

S-(3,7-Dibromotropolon-5-ylmethyl)isothiuronium Bromide (XII).—A solution of 40 mg. of IV and 20 mg. of thiourea dissolved in 3 ml. of *tert*-butanol was stirred at room temperature for a few minutes and the colorless crystals that separated out were collected, and washed with ethanol; m. p. 223~224°C (decomp.). Yield, 50 mg.

Anal. Found: C, 24.59; H, 2.42; N, 6.51. Calcd. for $C_9H_9O_2N_2SBr_3$: C, 24.05; H, 2.00; N, 6.24%. U. V. λ_{max}^{MeOH} mμ (log ε): 268 (4.59), 335 (3.88), 387 (3.71), 420 (3.58).

3, 7-Dibromo-5-mercaptomethyltropolone (XIII). —A mixture of 50 mg. of XII in 0.5 mol. of 45% sodium hydroxide solution was heated for a few minutes on a water bath and neutralized by pouring this mixture into 6 N hydrochloric acid containing cracked ice. The precipitate that formed was collected and recrystallized from ethanol to give pale yellow needles, m. p. 128°C. Yield, 20 mg.

Anal. Found: C, 30.10; H, 1.84. Calcd. for $C_8H_6O_2Br_2S$: C, 29.45; H, 1.82%. U. V. λ_{max}^{MeOH} mμ (log ε): 267 (4.46), 350 (4.01), 430 (3.86).

3, 7-Dibromo-5-(β-acetyl-β-ethoxycarbonylethyl)-tropolone (XIV). — A solution of 500 mg. of IV dissolved in 50 ml. of ethyl acetoacetate was added dropwise into a solution of 1 g. of potassium dissolved in 50 ml. of ethyl acetoacetate, with stirring at room temperature. The solution was further stirred for 2 hr. at room temperature, neutralized with 6 N sulfuric acid to pH 5, and the ethyl acetoacetate layer was separated. The acetate layer was washed with water and evaporated under reduced pressure to remove the acetate. The dark red, oily residue crystallized on addition of ether, the crystals were collected, washed with ether, and recrystallized from a mixture of benzene and petroleum ether; m. p. 114~115°C. Yield, 350 mg.

Anal. Found: C, 39.83; H, 3.74. Calcd. for $C_{14}H_{14}O_5Br_2$: C, 39.81; H, 3.32%. U. V. λ_{max}^{MeOH} mμ (log ε): 268(4.55), 345(4.07), 430(3.96).

3, 7-Dibromo-5-cyanomethyltropolone (XV). — A solution of 150 mg. of IV dissolved in 3 ml. of dioxane was added dropwise, with stirring, into a solution of 150 mg. of potassium cyanide dissolved in 6 ml. of dioxane and 1 ml. of water at room temperature, the drops causing a transitory red color to appear. After completion of addition, the mixture was stirred for 1 hr., the solvent was removed under reduced pressure at room temperature, and the residue was acidified with hydrochloric acid. The brown precipitate that formed was collected and recrystallized from benzene; m. p. 148~151°C. Yield, 100 mg. During recrystallization, bis(3, 7-dibromotropolon-5-yl)-methane formed as a benzene-insoluble by-product.

Anal. Found: C, 34.04; H, 1.80; N, 3.82. Calcd. for $C_9H_5O_2NBr_2$: C, 33.86; H, 1.57; N, 4.39%. U. V. λ_{max}^{MeOH} mμ (log ε): 267(4.50), 345(4.04), 430(3.98).

Summary

Reaction of 3,7-dibromo-5-hydroxymethyltropolone with hydrobromic acid affords 3, 7 - dibromo - 5 - bromomethyltropolone, which has a high reactivity and reacts with various anionoid reagents to undergo substitution of bromine in the bromomethyl group. In this manner it is possible to extend the substituent by forming C–O, C–N, C–S and C–C bonding at the tip of the methyl group in position 5 of the tropolone ring.

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