The Mannich Base of Troponoid and its Application. I. Synthesis of 5-Hydroxymethyl and 5-Formyltropolone Derivatives

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Hartwig¹⁾ reported morpholinomethyl derivatives of tropolone, 3-bromotropolone and 5-bromotropolone, and Pauson²⁾ also gave a brief description on piperidino methyltropolone in his review. However, Mannich reaction of 3,7-dibromotropolone (I) has not been reported. The present authors applied Mannich reaction to I in order to introduce a carbon chain to the 5-position of the tropolone nucleus and obtained 3,7-dibromo-5-morpholinomethyltropolone (II) in a good yield, from which 5-hydroxymethyl and 5-formyl compounds were derived. This paper describes these results.

When I was treated with morpholine and formalin in acetic acid, II was obtained as yellow powder. II is sparingly soluble in water and usual organic solvents, produces a hydrochloride difficultly soluble in water when treated with hydrochloric acid and gives a green color to the water layer with ferric chloride. Catalytic hydrogenolysis of II in the presence of palladium-carbon gave 5-methyltropolone (III)³⁾. This indicates that the morpholinomethyl group of II has taken 5-position in the tropolone nucleus. 3,7-Dibromo-5-acetoxymethyltropolone (V) was obtained when II was heated with a large excess of acetic acid. If a small quantity of acetic acid is used, bis-(3,7-dibromotropololon-5-yl) methane (IV) is formed as a by-product. IV was also formed when II was treated with formalin and dimethylamine in acetic acid or V was heated in aqueous hydrobromic acid. V was easily hydrolyzed by alkali to give 3,7-dibromo-5-hydroxymethyltropolone (VI). The hydroxymethyl group of VI is readily displaced by other groups. For example, 5-nitro (VII)⁴⁾, 5-bromo (VIII)⁵⁾

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1) E. Hartwig, *Angew. Chem.*, **66**, 605 (1954).

2) P. L. Pauson, *Chem. Revs.*, **55**, 9 (1955).

3) T. Nozoe, T. Mukai and K. Matsui, *Proc. Japan Acad.*, **27**, 646 (1951).

4) K. Yamane, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **76**, 787 (1955); T. Nozoe, Y. Kitahara, K. Doi and T. Arai, *Bull. Chem. Research Inst. of Non-Aqueous Solutions, Tohoku Univ.*, **7**, 13 (1957).

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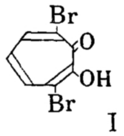
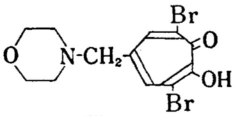

I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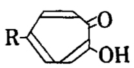
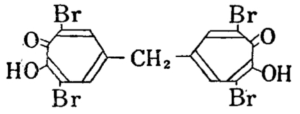
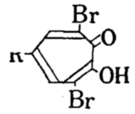
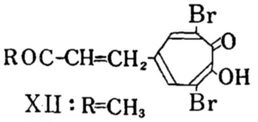
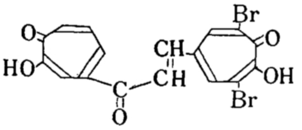

III: R=CH_3
X: R=CH_2OH


IV


V: R=CH_2OCOCH_3
VI: R=CH_2OH
VII: R=NO_2
VIII: R=Br
IX: R=$N_2C_6H_4CH_3$ (p)
XI: R=CHO


XII: R=CH_3
XIII: R=C_6H_5
XIV: R=C_6H_4OH (2')
XV: R=OH


XVI

and 5-azo (IX)⁶⁾ compounds were yielded by the reactions of VI with dinitrogen tetroxide, *N*-bromosuccinimide and diazonium salt respectively.

Sebe and Matsumoto⁷⁾ obtained the formyl derivative by oxidizing 3-hydroxymethyltropolone derivatives with activated manganese dioxide. The application of this method to VI gave 3,7-dibromo-5-formyltropolone (XI). Catalytic hydrogenolysis of VI afforded 5-hydroxymethyltropolone (X) which was an unstable substance. Oxidation of X with manganese dioxide gave 5-formyltropolone⁸⁾.

3,7-Dibromo-5-formyltropolone (XI) gives an acetal, reacts with various ketonic reagents and produces Schiff's base with aniline. Furthermore, the reactions of XI with acetone, acetophenone, 2-hydroxyacetophenone, malonic acid and 4-acetyltropolone⁹⁾ gave 3,7-dibromo-5-(γ-oxobutenyl)tropolone (XII), 3,7-dibromo-5-(γ-phenyl-γ-oxopropenyl)tropolone (XIII), 3,7 dibromo-5-[γ-(2'-hydroxyphenyl)-γ-oxopropenyl] tropolone (XIV), 3,7-dibromo-5-(β-carboxyethenyl)tropolone (XV), and 3,7-dibromo-5-[γ-(tropolone-4'-yl)-γ-oxopropenyl] tropolone (XVI) respectively.

Further experiments of 5-hydroxymethyl and 5-formyltropolone derivatives are in progress.

Experimental¹⁰⁾

3,7-Dibromo-5-morpholinomethyltropolone (II).—To a stirred mixture of 2 g. of 3,7-dibromotropolone (I), 3 ml. of acetic acid and 2 ml. of morpholine was added 1 ml. of formalin at 70°. The mixture became a clear orange solution and after a few min. a yellow precipitate began to deposit. Thereafter, stirring was continued at 80~90°C for 2 hr. Then 5 ml. of water was added to the cooled reaction mixture. The precipitate, 3,7-dibromo-5-morpholinomethyltropolone (II) was collected and washed with water. Yield, 2.6 g., m. p. 198~200°C.

Anal. Found: C, 38.40; H, 3.55; N, 3.82. Calcd. for $C_{12}H_{13}O_3NBr_2$: C, 38.00; H, 3.43; N, 3.70%. U. V. $\lambda_{\max}^{\text{MeOH}}$ (log ε): 268 mμ (4.32), 344 mμ (4.00), 427 mμ (3.92).

Hydrochloride of II; m. p. 225°C (decomp.).

Anal. Found: C, 34.65; H, 3.57; N, 3.35. Calcd. for $C_{12}H_{14}O_3NBr_2Cl$: C, 34.61; H, 3.61; N, 3.36%.

5-Methyltropolone (III).—When 500 mg. of II in aqueous sodium hydroxide was shaken with hydrogen at room temperature in the presence of palladium-carbon, 3 molar equivalents of hydrogen were absorbed. The catalyst was removed by filtration and the filtrate was acidified. A precipitate thereby formed was crystallized from benzene to give 5-methyltropolone (III) as colorless crystals, m. p. 109~110°C, undepressed by admixture with an authentic specimen.

Bis-(3,7-dibromotropolone-5-yl)methane (IV).—To a mixture of 500 mg. of I, 400 mg. of aqueous dimethylamine (40%) and 2 ml. of acetic acid was added 320 mg. of formalin (37%) at 90°C with stirring. After 40 min. the reaction mixture was cooled. Yellow crystals thereby formed

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6) S. Ito, unpublished work.

7) E. Sebe and S. Matsumoto, *Sci. Repts. Tohoku Univ., Ser.* I., **38**, 308 (1954).

8) J. W. Cook et al., *J. Chem. Soc.*, **1952**, 4416.

9) T. Nozoe, K. Takase and M. Ogata, *Chem. and Ind.*, **1957**, 1070.

10) Melting points are not corrected.

were collected and washed with a small quantity of methanol. Yield 450 mg., m. p. 225°C (decomp.).

Anal. Found: C, 31.37; H, 1.23. Calcd. for $C_{15}H_8O_4Br_4$: C, 31.48; H, 1.40%. U. V. λ_{max}^{MeOH} (log ε): 272 mμ (4.48), 345 mμ (4.16), 430 mμ (4.07).

When an aqueous solution of ferric chloride was added to a suspension of IV in benzene, a black solid formed at the interface of the benzene and aqueous layers.

Heating of 5-acetoxymethyl compound (V) in aqueous hydrobromic acid under reflux also gave IV.

3,7-Dibromo-5-acetoxymethyltropolone(V). —A suspension of 1 g. of II in 35 ml. of acetic acid was heated at 100°C for 1 hr. and then at 120° for 3 hr. with stirring. The mixture became a yellow solution. When it was cooled, pale yellow needles separated out. The crystals (0.5 g.) were collected. Concentration of the filtrate at 60°C under reduced pressure gave a further crop (0.2 g.). Recrystallization of the combined crystals from ethyl acetate afforded 3,7-dibromo-5-acetoxymethyltropolone (V), m. p. 184~185°C.

Anal. Found: C, 34.66; H, 2.64. Calcd. for $C_{10}H_8O_4Br_2$: C, 34.09; H, 2.27%. U. V. λ_{max}^{MeOH} (log ε): 265 mμ (4.64), 345 mμ (4.14), 425 mμ (4.06).

3, 7-Dibromo-5-alkoxymethyltropolone. — Heating of V in methanol under reflux gave 3,7-dibromo-5-methoxymethyltropolone as pale yellow crystals, m. p. 135°C.

Anal. Found: C, 34.08; H, 2.64. Calcd. for $C_9H_8O_3Br_2$: C, 33.33; H, 2.47%.

3,7-Dibromo-5-ethoxymethyltropolone, m. p. 100 °C, was similarly obtained.

Anal. Found: C, 35.19; H, 3.33. Calcd. for $C_{10}H_{10}O_3Br_2$: C, 35.54; H, 2.96%.

3, 7-Dibromo-5-hydroxymethyltropolone (VI).—A mixture of 1 g. of V, 5 ml. of 3 N sodium hydroxide and 0.5 ml. of ethanol was heated on a water bath for 5 min. with stirring. After being cooled, the reaction mixture was acidified with 6 N hydrochloric acid and a precipitate thereby formed was collected, washed with water and crystallized from methanol to give 3,7-dibromo-5-hydroxymethyltropolone (VI) as pale yellow needles, m. p. 164~165°C. Yield, 0.8 g.

Anal. Found: C, 31.35; H, 1.79. Calcd. for $C_8H_6O_3Br_2$: C, 30.97; H, 1.93%. U. V. λ_{max}^{MeOH} (log ε): 266 mμ (4.47), 345 mμ (4.12), 425 mμ (4.09).

Reaction of VI with Dinitrogen Tetroxide. —To a solution of 0.1 g. of VI in 40 ml. of chloroform was added 0.5 g. of dinitrogen tetroxide with ice-cooling. After being kept for 30 min. at room temperature, the solvent and excess reagent were removed under reduced pressure. Yellow crystals thereby formed failed to show any depression of m. p. on admixture with an authentic 3,7-dibromo-5-nitrotropolone (VII), m.p. 145~146°C.

Reaction of VI with *N*-Bromosuccinimide. —A mixture of 50 mg. of VI, 30 mg. of *N*-bromosuccinimide and 6 ml. of chloroform was boiled for 2 hr. After removal of succinimide by filtration, the filtrate was evaporated to give 50 mg. of colorless crystals, m. p. 124~125°C, undepressed by admixture with 3,5,7-tribromotropolone (VIII).

Reaction of VI with Diazonium Salt. — To a pyridine solution of 50 mg. of VI was added a solution of diazonium salt prepared from 30 mg. of *p*-toluidine. A red precipitate thereby formed was collected, washed with methanol and crystallized from methanol to give red prisms, m. p. 190~191°C, undepressed by admixture with 3,7-dibromo-(*p*-tolylazo)tropolone (IX).

5-Hydroxymethyltropolone (X). — A suspension of 350 mg. of VI in aqueous sodium hydroxide was shaken with hydrogen at room temperature in the presence of palladium carbon. After absorption of 2 molar equivalents of hydrogen and removal of the catalyst by filtration the filtrate was acidified. A small amount of yellowish brown precipitate thereby formed was removed by filtration and the filtrate was extracted with ethyl acetate. Evaporation of the solvent from the extract afforded 5-hydroxymethyltropolone (X) as colorless needles, m. p. 131~132°C. Yield, 100 mg.

Anal. Found: C, 62.82; H, 5.32: Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.27%. U. V. λ_{max}^{MeOH} (log ε): 233 mμ (4.40), 323 mμ (4.01).

5-Formyltropolone.—A mixture of 50 mg. of X, 5 ml. of acetone and 200 mg. of activated manganese dioxide was stirred for 2 days at room temperature. After removal of excessive manganese dioxide by filtration, the filtrate was concentrated to give a yellow manganese salt which was treated with 6 N hydrochloric acid and extracted with ethyl acetate. Evaporation of the extract left 20 mg. of 5-formyltropolone, m. p. 181°C.

3, 7-Dibromo-5-formyltropolone (XI). — A mixture of 1 g. of X, 40 ml. of acetone and 4 g. of manganese dioxide was stirred for 20 hr. at room temperature. The mixture was then separated into a solid A and a filtrate B. Removal of the solvent from filtrate B under reduced pressure afforded a yellowish brown manganese salt. Treatment of the salt with 6 N sulfuric acid yielded a yellow precipitate which was crystallized from benzene to give 3,7-dibromo-5-formyltropolone (XI) as yellow prisms, m. p. 175~176°C. Extraction of solid A with acetone by means of a Soxhlet extractor gave a further crop of manganese salt which was also treated similarly to give XI. Yield, 0.95 g.

Anal. Found: C, 31.39; H, 1.43. Calcd. for $C_8H_4O_3Br_2$: C, 31.17; H, 1.30%. U. V. λ_{max}^{MeOH} (log ε): 260 mμ (4.21), 382 mμ (4.31), 410 mμ (4.33).

Heating of XI with methanol gave the acetal as colorless needles, m. p. 135°C.

Anal. Found: C, 33.58; H, 2.79. Calcd. for $C_{10}H_{10}O_4Br_2$: C, 33.90; H, 2.82%. U. V. λ_{max}^{MeOH} (log ε): 265 mμ (4.43), 350 mμ (4.02), 430 mμ (4.21).

Oxime of XI, yellow needles, m. p. 212~213°C.

Anal. Found: N, 4.21. Calcd. for $C_8H_5O_3NBr_2$: N, 4.35%. U. V. λ_{max}^{MeOH} (log ε): 270 mμ (4.42), 372 mμ (4.43), 433 mμ (4.10).

Semicarbazone of XI, yellow granular crystals, m. p. 249~250°C.

Anal. Found: C, 29.24; H, 2.18; N, 10.72. Calcd. for $C_9H_7O_3N_3Br_2$: C, 29.59; H, 1.92; N, 11.51%. U. V. λ_{max}^{MeOH} (log ε): 273 mμ (4.42), 378 mμ (4.55).

Thiosemicarbazone of XI, orange crystals, m.p. 280～288°C (decomp.).

Anal. Found: C, 28.79; H, 2.13. Calcd. for $C_9H_7O_2N_3SBr_2$: C, 28.35; H, 1.84%. U. V. λ_{max}^{MeOH} (log ε): 289 mμ (4.28), 395 mμ (4.47).

Phenylhydrazone of XI, red needles, m. p. 209～210°C.

Anal. Found: N, 6.97. Calcd. for $C_{14}H_{10}O_2N_2Br_2$: N, 7.04%. U. V. λ_{max}^{MeOH} (log ε): 265 mμ (4.42), 410 mμ (4.58).

2, 4-Dinitrophenylhydrazone of XI, red needles, m. p. 257～258°C.

Anal. Found: N, 11.78. Calcd. for $C_{14}H_8O_6N_4Br_2$: N, 11.48%. U. V. λ_{max}^{MeOH} (log ε): 260 mμ (4.41), 440 mμ (4.61).

Schiff's Base of XI. — A mixture of 100 mg. of XI, 1 ml. of aniline and 0.5 ml. of acetic acid was heated on a water bath for 10 min. Deep red crystals thereby formed were recrystallized from methanol. Yield 100 mg., m. p. 209～210°.

Anal. Found: C, 43.61; H, 2.55; N, 3.81. Calcd. for $C_{14}H_9O_2NBr_2$: C, 43.98; H, 2.36; N, 3.67%. U. V. λ_{max}^{MeOH} (log ε): 270 mμ (4.37), 390 mμ (4.40).

Condensation of XI with Acetone. — To a solution of 100 mg. of XI in 1 ml. of acetone was added 0.3 ml. of aqueous sodium hydroxide (10%) with stirring at room temperature. After 2 days, an orange precipitate was collected and acidified with 6 N hydrochloric acid to give a yellow precipitate. Its recrystallization from acetone afforded 100 mg. of 3, 7-dibromo-5-(γ-oxobutenyl) tropolone (XII), m. p. 195°C.

Anal. Found: C, 38.19; H, 2.61. Calcd. for $C_{11}H_8O_3Br_2$: C, 37.93; H, 2.30%. U. V. λ_{max}^{MeOH} (log ε): 280 mμ (4.38), 405 mμ (4.56).

Condensation of XI with Acetophenone.— A mixture of 100 mg. of XI, 0.3 ml. of acetophenone and 0.3 ml. of aqueous sodium hydroxide (10%) was stirred for 2 hr. at room temperature. A deep red precipitate thereby formed was collected and acidified with 6 N hydrochloric acid to give a yellow precipitate. Its crystallization from methanol yielded 120 mg. of 3, 7-dibromo-5-(γ-phenyl-γ-oxopropenyl) tropolone (XIII), m. p. 200 °C.

Anal. Found: C, 46.16; H, 2.40. Calcd. for $C_{16}H_{10}O_3Br_2$: C, 46.83; H, 2.44%. U. V. λ_{max}^{MeOH} (log ε): 260 mμ (4.14), 288 mμ (4.16), 418 mμ (4.38).

Condensation of XI with 2-Hydroxyacetophenone. — A mixture of 100 mg. of XI, 80 mg. of 2-hydroxyacetophenone, 1 ml. of ethanol, and 0.5 ml. of 6 N sodium hydroxide was stirred on a water bath for 30 min. The mixture became dark red and formed a small quantity of precipitate C. Precipitate C was removed by filtration. Acidification of the filtrate with 6 N hydrochloric acid gave a brown solid. Recrystallization of the solid from methanol afforded 50 mg. of 3, 7-dibromo-5-[γ-(2'-hydroxyphenyl)-γ-oxopropenyl] tropolone (XIV), m. p. 215°C (decomp.).

Anal. Found: C, 45.02; H, 2.60. Calcd. for $C_{16}H_{10}O_4Br_2$: C, 45.11; H, 2.35%. U. V. λ_{max}^{MeOH} (log ε): 260 mμ (4.20), 295 mμ (4.20), 440 mμ (4.54).

Acidification of precipitate C gave XI recovered.

Reaction of XI with Malonic Acid.—A mixture of 100 mg. of XI, 100 mg. of malonic acid, 1 ml. of pyridine and 3 drops of piperidine was heated for 1 hr. at 90°C, for 2 hr. at 100°C and finally for 2 hr. at 120°C. During this time, evolution of carbon dioxide was observed and the mixture turned brown in color. Then the mixture was poured into a mixture of 0.5 g. of ice and 1 ml. of concentrated hydrochloric acid. A brown precipitate thereby formed was crystallized from methanol after decolorization with carbon to give 50 mg. of 3, 7-dibromo-5-(β-carboxyethenyl) tropolone (XV), m. p. 195°C.

Anal. Found: C, 34.92; H, 2.01. Calcd. for $C_{10}H_6O_4Br_2$: C, 34.29; H, 1.71%. U. V. λ_{max}^{MeOH} (log ε): 268 mμ (4.39), 380 mμ (4.40).

Condensation of XI with 4-Acetyltropolone.—A mixture of 50 mg. of XI, 40 mg. of 4-acetyltropolone, 0.5 ml. of methanol and 0.5 ml. of aqueous sodium hydroxide (10%) was stirred for 30 min. at room temperature. The mixture turned red in color and deposited a deep red precipitate. The precipitate was collected, acidified with 6 N hydrochloric acid and recrystallized from methanol to give 50 mg. of 3, 7-dibromo-5-[γ-(tropolone-4'-yl)-γ-oxopropenyl] tropolone (XVI), m. p. 220°C (decomp.).

Anal. Found: C, 42.93; H, 2.23. Calcd. for $C_{17}H_{10}O_5Br_2 \cdot H_2O$: C, 43.01; H, 2.54%. U. V. λ_{max}^{MeOH} (log ε): 255 mμ (4.24), 430 mμ (4.25).

Summary

Application of the Mannich reaction to 3, 7-dibromotropolone gave 3, 7-dibromo-5-morpholinomethyltropolone, from which 5-hydroxymethyl and 5-formyl derivatives were derived. It was found that the hydroxymethyl group of 3, 7-dibromo-5-hydroxymethyltropolone can be easily displaced, and that 3, 7-dibromo-5-formyltropolone has the characteristics of an ordinary aldehyde and reacts with ketones and malonic acid.

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