The Mannich Base of Troponoid and its Application. VII. The Synthesis of 5-Formyl Derivative of 3-Isopropyltropolone

By Kyozo OGURA

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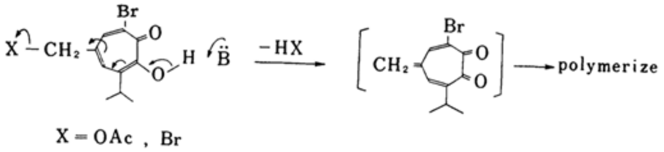
The present author has reported the synthesis of some Mannich bases of 3-isopropyltropolone (α-thujaplicin) and their properties[1]. The present paper describes the synthesis of 5-bromomethyl and 5-formyl derivatives of 3-isopropyltropolone from the Mannich base.

Treatment of 3-isopropyl-5-morpholinomethyl-7-bromotropolone (I) or 3-isopropyl-5-piperidinomethyl-7-bromotropolone (II) with acetic anhydride resulted in cleavage of the C–N bond to give 3-isopropyl-5-acetoxymethyl-7-bromotropolone (III). As in the case of 3, 7-dibromo-5-acetoxymethyltropolone[2], glacial acetic acid could also be used in place of acetic anhydride for the preparation of the acetoxymethyl derivative III, but the yield was lower. In the preparation of 3, 7-dibromo-5-acetoxymethyltropolone from 5-morpholinomethyl derivative, bis(3, 7-dibromotropolon-5-yl)methane was produced as a by-product[2], while the reaction of I or II with glacial acetic acid did not give such a by-product; instead the corresponding bis(3-isopropyl-7-bromotropolon-5-yl)methane (IV) was obtained by refluxing II in toluene in the presence of sodium hydroxide. The compound IV forms a ferric complex which is insoluble in both water and organic solvents.

Alcoholysis of III by methanol and ethanol gave 3-isopropyl-5-methoxymethyl-7-bromo- (V) and 3-isopropyl-5-ethoxymethyl-7-bromotropolone (VI) respectively. Treatment of III with morpholine and piperidine, respectively, gave I and II. When III was treated with diluted sodium hydroxide solution, a transitory red color appeared and a resinous substance was formed. When III was heated in hydrobromic acid, 3-isopropyl-5-bromomethyl-7-bromotropolone (VII) was obtained in a good yield. The bromomethyl derivative VII is also very unstable to alkali. The unstability of III and VII to alkali may be due to their tendency to form such a quinonoid structure as follows.



The bromine in the bromomethyl group of VII is very reactive, and it is easily replaced by various anionoid reagents, so that C–O, C–N, C–S and C–C bond can be formed at the end of the methylene in the 5-position of the tropolone ring. Treatment of VII with dimethysulfoxide afforded 3-isopropyl-5-hydroxymethyl-7-bromotropolone (VIII). Alcoholysis of VII gave 5-alkoxymethyl derivatives, V and VI, and aminolysis of VII by morpholine and piperidine gave I and II respectively. The reaction of VII with thiourea gave *S*-(3-isopropyl-7-bromotropolon-5-ylmethyl)isothiouronium bromide (IX), which was converted into 3-isopropyl-5-mercaptomethyl-7-bromotropolone (X) by alkaline hydrolysis. The reaction of VII and potassium cyanide afforded 3-isopropyl-5-cyanomethyl-7-bromotropolone (XI). The reaction of VII with pyridine also easily proceeded in dry benzene at room temperature forming (3-isopropyl-7-bromotropolon-5-ylmethyl)pyridinium bromide (XII) quantitatively, which was soluble in water and formed a water-soluble ferric complex; on the other hand, the reaction of VII with triethylamine resulted in dehydrobromination to give triethylamine hydrobromide and a deep greenish blue substance which was too unstable to be obtained as pure crystals. This substance was decolorized by the action of hydrochloric acid to give IV. The reaction of the pyridinium salt XII with piperidine gave II, and that with sodium acetate afforded III.

Kröhnke's method[3] was applied to XII in order to obtain the 5-formyl derivative. Reaction of XII with *p*-nitroso-*N*, *N*-dimethylaniline

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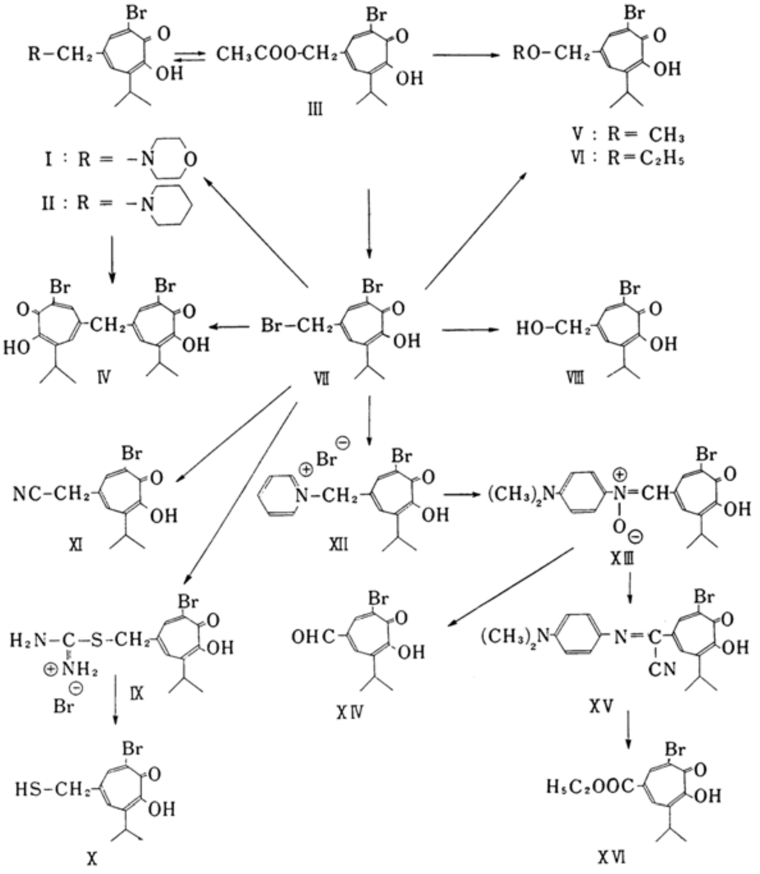
[1] K. Ogura, This Bulletin, **34**, 839 (1961).

[2] S. Seto and K. Ogura, ibid., **32**, 493 (1959).

[3] F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).



in the presence of sodium hydroxide gave brilliant red crystals of (3-isopropyl-7-bromotropolon-5-yl)-*N*-(*p*-dimethylaminophenyl)nitrone (XIII), which when hydrolyzed with hydrochloric acid afforded 3-isopropyl-5-formyl-7-bromotropolone (XIV). The aldehyde XIV reacts with ordinary ketonic reagents, and its infrared spectrum shows an absorption maxima at 1680 and 2880 cm^{-1} due to its formyl group. When nitrone XIII was treated with potassium cyanide, (3-isopropyl-7-bromotropolon-5-yl)-*N*-(*p*-dimethylaminophenyl)cyanoanile (XV) was obtained as deep wine red prisms, and treating this with alcoholic hydrochloric aicd gave 3-isopropyl-5-ethoxycarbonyl-7-bromotropolone (XVI).

The reaction of the aldehyde will be reported in the near future.

Experimental*

3-Isopropyl-5-acetoxymethyl-7-bromotropolone (III).—a) When II (1 g.) was warmed in acetic anhydride (10 ml.) at 95°C with occasional stirring, the solution turned black in a few minutes, and it was decolorized gradually. After being kept at the same temperature for 1 hr., the solution was filtered to remove a small amount of precipitate, and the filtrate was concentrated under reduced pressure. Colorless needles which separated on being cooled were collected and recrystallized from methanol, m. p. 124~125°C. Yield, 0.6 g.

Found: C, 49.86; H, 4.86. Calcd. for $C_{13}H_{15}O_4Br$: C, 49.52; H, 4.76%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε): 262(4.14), 344(3.82), 386(3.65).

b) The solution of I (300 mg.) in glacial acetic acid (3 ml.) was heated at 110~120°C for 3 hr., and colorless needles which separated on being cooled were collected. Evaporation of the filtrate under reduced pressure gave a syrup residue, from which the starting material (100 mg.) was recovered as its hydrochloride by addition of a few drops of 6 N hydrochloric acid.

Bis(3-isopropyl-7-bromotropolon-5-yl)methane (IV).—A suspension of II (150 mg.) and powdered sodium hydroxide (30 mg.) in toluene (1 ml.) was refluxed for 3 hr., and yellow crystals were collected and acidified by 6 N hydrochloric acid to yield colorless powder, which was recrystallized from methanol to afford colorless scales, m. p. 157~158°C. Yield, 50 mg.

Found: C, 50.50; H, 4.46. Calcd. for $C_{21}H_{22}O_4 \cdot Br_2$: C, 50.60; H, 4.42%.

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* All melting points are uncorrected. The microanalyses were carried out by Misses Yoko Endo and Yukiko Endo of this Institute, to whom the author is indebted.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 260(4.74), 340(4.24), 420(3.70).

3-Isopropyl-5-methoxymethyl-7-bromotropolone (V).—A solution of III (50 mg.) in methanol (0.5 ml.) was refluxed for 1 hr., and the removal of methanol left an oily residue, which solidified by addition of a few drops of water. The solid was collected and recrystallized from petroleum ether to give colorless needles, m. p. 60~61°C. Yield, 10 mg.

Found: C, 50.34; H, 5.33. Calcd. for $C_{12}H_{15}O_3 \cdot Br$: C, 50.17; H, 5.22%.

3-Isopropyl-5-ethoxymethyl-7-bromotropolone (VI).—A solution of III (50 mg.) in ethanol (0.5 ml.) was refluxed for 1 hr., and colorless needles of VI were obtained in the same manner as in the case of V. The ethoxymethyl derivative VI was also obtained by refluxing 5-bromomethyl derivative VII in ethanol, m. p. 60~61°C. Yield ca. 10 mg.

Found: C, 51.89; H, 5.71. Calcd. for $C_{13}H_{17}O_3 \cdot Br$: C, 51.83; H, 5.65%.

3-Isopropyl-5-bromomethyl-7-bromotropolone (VII).—When III (1 g.) was heated in 4 ml. of hydrobromic acid (*d*, 1.4) at 95~100°C with occasional swirling for 40 min., yellow oil separated which was solidified on being cooled. The solid was collected, washed with water and dried well. Recrystallization from petroleum ether gave colorless prisms, m. p. 87~90°C. Yield, 0.95 g.

Found: C, 39.66; H, 3.55. Calcd. for $C_{11}H_{12}O_2 \cdot Br$: C, 39.29; H, 3.67%.

$\lambda_{\max}^{\text{isoöctane}}$ mμ(log ε) : 258(4.48), 330(3.94), 375(3.74).

3-Isopropyl-5-hydroxymethyl-7-bromotropolone (VIII).—After a solution of VII (50 mg.) in dimethylsulfoxide (0.2 ml.) was kept at room temperature for 14 hr., cracked ice (ca. 2 g.) was added to the solution. The solid, which was formed by scratching the wall of the vessel, was collected and recrystallized from benzene-petroleum ether, affording colorless needles, m. p. 84~87°C. Yield, 20 mg.

Found: C, 48.88; H, 5.13. Calcd. for $C_{11}H_{13}O_3 \cdot Br$: C, 48.35; H, 4.76%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 260(4.42), 338(3.73), 380(3.65).

***S*-(3-Isopropyl-7-bromotropolon-5-ylmethyl)isothiouronium Bromide (IX).**—When a solution of VII (100 mg.) and thiourea (40 mg.) was warmed in *tert*-butanol (0.7 ml.) on a water bath for 5 min., the colorless crystals separated, which were collected and washed with ethanol, m. p. 217°C (decomp.). Yield, 80 mg.

Found: C, 35.07; H, 3.88; N, 6.08. Calcd. for $C_{12}H_{16}O_2N_2SBr$: C, 35.05; H, 3.97; N, 6.45%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 259(4.52), 340(3.96), 395(3.70), 410(3.69).

3-Isopropyl-5-mercaptomethyl-7-bromotropolone (X).—After IX (80 mg.) was warmed in 45% sodium hydroxide (0.7 ml.) on a water bath for a few minutes, the solution was acidified with 6 N hydrochloric acid containing cracked ice (ca. 1 g.). The precipitate was collected, washed with water and recrystallized from methanol, affording 50 mg. of pale yellow needles, m. p. 80~81°C.

Found: C, 46.13; H, 4.73. Calcd. for $C_{11}H_{13}O_2 \cdot SBr$: C, 45.67; H, 4.50%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 258(4.49), 333(3.91), 375(3.73).

3-Isopropyl-5-cyanomethyl-7-bromotropolone (XI).—A solution of VII (100 mg.) in dioxane (2 ml.) was added dropwise into a solution of potassium cyanide (100 mg.) in dioxane (3 ml.) and water (0.5 ml.), while being stirred under ice cooling, the drop causing a transitory red color to appear. After completion of addition the mixture was stirred for 1 hr., and the solvent was removed under reduced pressure at room temperature, and the residue was acidified with diluted hydrochloric acid. The precipitate was collected and recrystallized from petroleum ether to colorless needles, m. p. 102~103°C. Yield, 20 mg.

Found: C, 51.27; H, 4.14; N, 5.03. Calcd. for $C_{12}H_{12}O_2NBr$: C, 51.06; H, 4.26; N, 4.97%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 260(4.56), 330(3.91), 375(3.79).

(3-Isopropyl-7-bromotropolon-5-ylmethyl)pyridinium Bromide (XII).—When pyridine (350 mg.) was added dropwise into a solution of VII (1.5 g,) dissolved in dry benzene (10 ml.), colorless precipitate appeared immediately. After being allowed to stand for 30 min. with occasional stirring, the precipitate was collected and washed with benzene, m. p. 214~215°C (decomp.). Yield, 1.8 g.

Found: C, 46.70; H, 4.25; N, 3.70. Calcd. for $C_{16}H_{17}O_2NBr$: C, 46.51; H, 4.00; N.3.37%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 260(4.53), 340(3.93), 380(3.80).

(3-Isopropyl-7-bromotropolon-5-yl)-*N*-(*p*-dimethylaminophenyl)nitrone (XIII).—To a mixture of XII (1.5 g.), *p*-nitrosodimethylaniline (0.6 g.) and ethanol (14 ml.), 3.9 ml. of sodium hydroxide solution (3.8%) was added, while being stirred under ice cooling. After completion of addition the mixture was stirred at room temperature, and red crystals began to appear in a few minutes. After being stirred for 30 min., the mixture was diluted with water (5 ml.), and the crystals were collected, washed well with water and recrystallized from ethanol, affording brilliant red needles, m. p. 142~143°C (decomp.). Yield, 1.45 g.

Found: C, 55.79; H, 5.55; N, 6.61. Calcd. for $C_{19}H_{21}O_3N_2Br$: C, 55.30; H, 5.18; N, 6.92%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ(log ε) : 264(4.60), 355(4.17), 427(4.00).

3-Isopropyl-5-formyl-7-bromotropolone (XIV).—When 6 N hydrochloric acid was added to XIII (1 g.), the mixture turned yellow. After being warmed on a water bath for a few minutes, the mixture was allowed to stand at room temperature for 1 hr. with occasional stirring. The precipitate was collected, washed well with water and recrystallized from petroleum ether to give colorless scales, m. p. 102~103°C. Yield, 0.67 g.

Found: C, 48.85; H, 4.22: Calcd. for $C_{11}H_{11}O_3 \cdot Br$: C, 48.81; H, 4.06%.

$\lambda_{\max}^{\text{isooctane}}$ mμ (log ε) : 277(4.40), 345(4.02).

Oxime.—Yellow prisms, m. p. 143~144°C.

Found: C, 46.80; H, 4.25; N, 4.89. Calcd. for $C_{11}H_{12}O_3NBr$: C, 46.15; H, 3.85; N, 4.90%.

Phenylhydrazone.—Red needles, m. p. 186~191°C.

Found: C, 56.87; H, 4.71; N, 7.74. Calcd. for $C_{17}H_{17}O_2N_2Br$: C, 56.53; H, 4.74; N, 7.76%.

2,4-Dinitrophenylhydrazone.—Red prisms, m. p. 236~237°C.

Found: C, 44.80; H, 3.46; N, 11.99. Calcd. for $C_{17}H_{15}O_6N_4Br$: C, 45.25; H, 3.32; N, 12.41%.

Thiosemicarbazone.—Orange prisms, m. p. 210°C (decomp.).

Found: C, 42.39; H, 3.68; N, 11.12. Calcd. for $C_{12}H_{14}O_2N_3SBr$: C, 41.83; H, 4.07; N, 12.21%.

(3-Isopropyl-7-bromotropolon-5-yl)-*N*-(*p*-dimethylaminophenyl)cyanoanile (XV).—When a mixture of XIII (100 mg.), potassium cyanide (60 mg.) and ethanol (1 ml.) was stirred at room temperature, a yellow precipitate appeared. Addition of a few drops of water to the mixture effected a clear solution, and red crystals separated in a few minutes, which were collected, acidified with 6 N hydrochloric acid and recrystallized from petroleum ether to wine red prisms, m. p. 195~196°C. Yield, 20 mg.

Found: C, 57.22; H, 4.18; N, 9.41. Calcd. for $C_{20}H_{20}O_2N_3Br$: C, 57.97; H, 4.83; N, 10.14%.

$\lambda_{\max}^{\text{MeOH}}$ mμ(log ε): 265(4.24), 423(4.22), 500(4.35).

3-Isopropyl-5-ethoxycarbonyl-7-bromotropolone (XVI).—When XV (100 mg.) was heated in 6 N hydrochloric acid (1 ml.) and ethanol (1 ml.) on a water bath, yellow crystals separated, which were collected and recrystallized from petroleum ether to pale yellow needles, m. p. 123~128°C. Yield, 50 mg.

Found: C, 49.48; H, 4.55. Calcd. for $C_{13}H_{15}O_4 \cdot Br$: C, 49.52; H, 4.76%.

$\lambda_{\max}^{\text{MeOH}}$ mμ(log ε): 256(4.27), 271(4.21), 370(3.99), 386(4.20).

Summary

3-Isopropyl-5-bromomethyl-7-bromotropolone and 3-isopropyl-5-formyl-7-bromotropolone were synthesized from 3-isopropyl-5-piperidinomethyl-7-bromotropolone, and some 5-substituted 3-isopropyl-7-bromotropolones were derived from the bromomethyl derivative.

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