The Mannich Base of Troponoid and its Application. V. On the Mannich Base of 3-Isopropyltropolone (α-Thujaplicin)

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(Received December 2, 1960)

Seto and the present author applied the Mannich reaction to 3, 7-dibromotropolone and prepared various 5-substituted derivatives of tropolone[1-3]. In order to make further extension of the Mannich reaction to tropolones, examinations were made on the Mannich reaction of 3-isopropyltropolone. The present paper describes the syntheses of a few Mannich bases of 3-isopropyltropolone and some of their properties.

Treatment of 3-isopropyltropolone (I) with folmaldehyde solution and morpholine, in the presence of acetic acid, affords 3-isopropyl-5, 7-dimorpholinomethyltropolone (II) as colorless crystals,, m. p. 76°C. The use of piperidine in place of morpholine gives 3-isopropyl-5, 7-dipiperidinomethyltropolone (III) as yellow crystals, m. p. 79.5°C. The morpholinomethyl group in II and the piperidinomethyl group in III are easily substituted by cationoid reagents. Reaction of II and III with *p*-tolyldiazonium salt respectively gives 3-isopropyl-5-tolylazo-7-morpholinomethyl- (IV), m. p. 134°C, and 3-isopropyl-5-tolylazo-7-piperidinomethyltropolone (V), m. p. 192°C. Both II and III give the known 3-isopropyl-5, 7-dibromotropolone[4] (VI) by the action of two molar equivalents of bromine. Treatment of II with excess of piperidine and formaldehyde solution gives III. In this case, no reaction occurs if formaldehyde is not used so that the above reaction is not a simple amine exchange but the substitution of the morpholinomethyl group with piperidinomethyl group.

Addition of one molar equivalent of bromine to II and III affords the respective monobromo compounds of m. p. 93°C and of m. p. 137°C.

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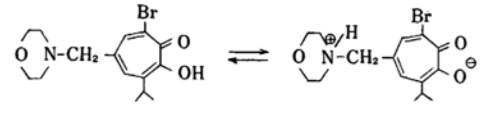
[1] S. Seto and K. Ogura, This Bulletin, 32, 493 (1959).
[2] S. Seto and K. Ogura, ibid., 32, 1118 (1959).
[3] S. Seto and K. Ogura, ibid., 33, 1084 (1960).

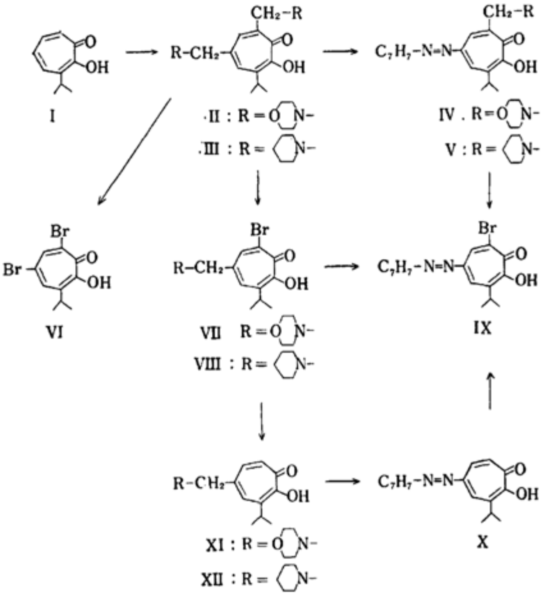
These were identified from experimental facts described below as 3-isopropyl-5-morpholinomethyl-7-bromotropolone (VII) and 3-isopropyl-5-piperidinomethyl-7-bromotropolone (VIII). Addition of formaldehyde solution and morpholine to 3-isopropyl-7-bromotropolone[4)] affords the same monobromo compounds as that derived from II. However, this fact alone is not sufficient to conclude that the structure of this substance is represented by VII since the bromine in the 7-position might have undergone rearrangement to 5-position during the Mannich reaction of 3-isopropyl-7-bromotropolone[*1].

The reaction of VII and VIII with *p*-tolyldiazonium salt results in the formation of 3-isopropyl-5-tolylazo-7-bromotropolone (IX), m. p. 145°C from both compounds and IX is also obtained by the application of bromine to IV, V or 3-isopropyl-5-tolylazotropolone[4)] (X). Hydrogenolysis of VII and VIII over palladium-carbon catalyst results in absorption of one molar equivalent of hydrogen and a monomorpholinomethyl- (m. p. 78°C) and a monopiperidinomethyl derivative (m. p. 113°C) are obtained respectively. Since these substances form 3-isopropyl-5-tolylazotropolone (X) by the reaction with *p*-tolyldiazonium salt, these are known to be 3-isopropyl-5-morpholinomethyl- (XI) and 3-isopropyl-5-piperidinomethyltropolone (XII). These facts prove that the above-mentioned monobromo compounds are VII and VIII.

Recrystallization of VII from methanol produces yellow granular crystals (VIIa) of m. p. 93°C which, upon further recrystallization from petroleum ether, change into colorless rods (VIIb), m. p. 64°C. The mixed melting point of these substances gives an intermediate value and when VIIb is left in air, it gradually acquires a yellowish tint and changes into VIIa. From elemental analytical values and comparison of infrared absorption spectra in the solid state, the former VIIa was found to have one mole of water of crystallization and to take the zwitter-ion structure. The infrared spectrum of VIIa lacked the absorption band due to the OH stretching vibration of tropolone and exhibited an intense absorption of N$^+$H stretching mode at 2530 cm^{-1}. There were absorption bands at 3470 and 3400 cm^{-1} due to crystal water. On the other hand, the infrared spectrum of VIIb lacked the absorption corresponding to N$^+$H stretching mode but exhibited a strong absorption band of OH stretching mode at 3180 cm^{-1}. Similarly, examination of the infrared spectra showed that the yellow crystalline III, VIII and XII took the zwitter-ion structure and that the colorless crystalline II and XI did not take such a structure.



VIIb VIIa



Experimental[*2]

3-Isopropyl-5,7-dimorpholinomethyltropolone (II). — A mixture of 1 g. of 3-isopropyltropolone, 4 ml. of 37% formalin, 4 ml. of morpholine and 0.8 ml. of acetic acid was stirred mechanically at 60°C for 1 hr., 10 ml. of water was added, and wall of the vessel was scratched with a glass rod while being cooled with ice, by which crystals gradually precipitated. After allowing the mixture to stand overnight in an ice chamber, the crystals were collected by filtration, washed with water, and recrystallized from methanol to colorless needles (II), m. p. 74~76°C. Yield, 1.8 g.

Found: C, 66.22; H, 7.74; N, 7.83. Calcd. for $C_{20}H_{30}O_4N_2$: C, 66.27; H, 8.34; N, 7.73%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 246 (4.47), 326 (3.92), 370 (3.74).

3-Isopropyl-5,7-dipiperidinomethyltropolone (III). — A mixture of 0.6 g. of 3-isopropyltropolone, 2 ml. of 37% formalin, 2 ml. of piperidine, and 0.4 ml. of acetic acid was stirred mechanically at 60°C for 1 hr., 5 ml. of water was added, and wall of the vessel was scratched with a glass rod while being cooled in ice, by which yellow crystals gradually

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4) T. Nozoe, Y. Kitahara and T. Ikemi, *Proc. Japan Acad.*, 27, 193 (1951).

[*1] S. Seto and T. Sato found that application of the Mannich reaction to 4-isopropyl-7-bromotropolone afforded 3-bromo-4-isopropyl-7-morpholinomethyltropolone.

[*2] All melting points are uncorrected. The microanalyses were carried out by Mr. S. Oyama and Miss Y. Endo of this Institute, to whom the author is indebted.

precipitated out. After standing in an ice chamber overnight, the crystals were collected by filtration, washed with water, and recrystallized from methanol. M. p. 78~79.5°C. Yield, 0.9 g.

Found: C, 73.41; H, 9.22; N, 7.43. Calcd. for $C_{22}H_{34}O_2N_2$: C, 73.70; H, 9.56; N, 7.81%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 250 (4.36), 346 (3.88), 400 (3.58).

IR ν N^+-H 2220 and 2480 cm^{-1} (broad) (KBr disk).

3-Isopropyl-5-tolylazo-7-morpholinomethyltropolone (IV). — To a solution of 180 mg. of II in 1 ml. of pyridine, a diazonium salt prepared from *p*-toluidine, 40 mg. of sodium nitrite, and 0.2 ml. of concentrated hydrochloric acid was added under cooling with ice by which a red precipitate separated out immediately. The precipitate was collected and recrystallized from methanol to reddish orange crystals (IV), m. p. 133~134°C. Yield, 150 mg.

Found: C, 69.03; H, 7.02; N, 10.87. Calcd. for $C_{22}H_{27}O_3N_3$: C, 69.27; H, 7.13; N, 11.02%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 237 (4.26), 290 (4.07), 400 (4.36), 460 (4.08).

3-Isopropyl-5-tolylazo-7-piperidinomethyltropolone (V). — A diazonium salt, prepared from 30 mg. of *p*-toluidine, 20 mg. of sodium nitrite, and 0.1 ml. of concentrated hydrochloric acid, was added to pyridine solution (ca. 1 ml.) of 100 mg. of III and a red precipitate formed immediately. V was obtained as orange crystals of m. p. 191~192°C by the same procedure as for IV. Yield, 50 mg.

Found: C, 72.68; H, 7.48; N, 11.18. Calcd. for $C_{23}H_{29}O_2N_3$: C, 72.79; H, 7.70; N, 11.07%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 237 (4.05), 252 (4.16), 296 (4.04), 412 (4.35), 462 (4.37).

Reaction of II with Bromine. — A solution of 280 mg. of bromine in 0.5 ml. of methanol was added dropwise into a solution of II dissolved in 0.5 ml. of methanol, while being stirred under ice cooling. After completion of the addition, the solvent was evaporated under a reduced pressure and colorless needles, m. p. 75~77°C, precipitated out. This substance showed no depression of melting point on admixture with an authentic sample of 3-isopropyl-5, 7-dibromotropolone[4] and its analytical values and ultraviolet absorption spectra showed satisfactory agreement.

Reaction of II with Formaldehyde and Piperidine. — A mixture of 100 mg. of II, 0.5 ml. of 37% formalin, 0.5 ml. of piperidine, and 0.1 ml. of acetic acid was stirred mechanically at 70°C for 4 h., 1 ml. of water was added, and the wall of the vessel was scratched with a glass rod under ice-cooling by which III was obtained as yellow crystals.

3-Isopropyl-5-morpholinomethyl-7-bromotropolone (VII). — A solution of 1.76 g. of bromine dissolved in 12 ml. of methanol was added dropwise into 4 g. of II suspended in 30 ml. of methanol, while being stirred under ice cooling. The reaction mixture gradually aquired yellow tint as bromine was added. After completion of the addition, the solvent was evaporated to dryness under a reduced pressure and left a mixture of colorless crystals, m. p. 208~209°C (decomp.), and a yellow viscous residue. The crystals were the hydrobromide of VII.

Addition of hydrochloric acid to this residual mixture resulted in solidification of the viscous residue to colorless crystals, which were collected by filtration. Addition of 15 ml. of 2 N sodium acetate solution to these crystals, changed them to a yellow viscous substance which, when heated for ca. 10 min. at 60°C, formed a yellow solid. The precipitate so formed was collected, washed with water, and recrystallized from methanol to yellow granular crystals (VIIa), m. p. 91~93°C. Yield, 3.3 g.

Recrystallization of VIIa from petroleum ether produced colorless rods (VIIb), m. p. 64~65°C.

Found (for VIIa): C, 49.10; H, 5.65; N, 3.55. Calcd. for $C_{15}H_{20}O_3NBr \cdot H_2O$: C, 50.00; H, 6.11; N, 3.89%.

Found (for VIIb): C, 52.77; H, 5.79; N, 4.47. Calcd. for $C_{15}H_{20}O_3NBr$: C, 52.63; H, 5.85; N, 4.09%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 259 (4.44), 338 (3.78), 380 (3.67).

IR (VIIa): 3470 and 3400 cm^{-1} (water of crystallization), 2660 (sh.), 2530, and 2370 cm^{-1} (sh.) (ν N^+-H).

IR (VIIb): 3200 cm^{-1} (ν O-H).

3-Isopropyl-5-piperidinomethyl-7-bromotropolone (VIII). — A solution of 1.4 g. of bromine, dissolved in 12 ml. of methanol, was added dropwise into a suspension of 3.1 g. of III in 60 ml. of methanol, while being stirred under ice cooling, and the solvent was evaporated under a reduced pressure after completion of the addition. About 15 ml. of water was added to the residue and the yellow solid that formed was recrystallized from methanol. M. p. 135~137°C (decomp.). Yield, 2.6 g.

Found: C, 56.14; H, 6.41; N, 4.17. Calcd. for $C_{16}H_{22}O_2NBr$: C, 56.46; H, 6.46; N, 4.10%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 260 (4.47), 340 (3.91), 390 (3.59).

IR 2540 cm^{-1} (broad) (ν N^+-H)

3-Isopropyl-5-tolylazo-7-bromotropolone (IX). — a) To a solution of 100 mg. of VII or VIII dissolved in ca. 0.2 ml. of pyridine, diazonium salt solution prepared from 40 mg. of *p*-toluidine, 30 mg. of sodium nitrite, and 0.1 ml. of concentrated hydrochloric acid was added while being stirred under ice cooling and red crystals precipitated out immediately. The crystals were collected and recrystallized from methanol to orange crystals (IX), m. p. 142~145°C. Yield, 120 mg.

b) To a suspension of 50 mg. of IV or V in ca. 0.2 ml. of methanol, a solution of 20 mg. of bromine dissolved in 0.5 ml. of methanol was added with stirring and the crystals that formed were collected by filtration. Recrystallization from methanol gave a product, m. p. 143~145°C which showed no depression of the melting point on admixture with the product obtained by the method (a). Yield, 30 mg.

c) A solution of 20 mg. of bromine dissolved in ca. 0.5 ml. of methanol was added to 40 mg. of 3-isopropyl-5-tolylazotropolone suspended in ca. 0.2 ml. of methanol and the crystals formed were collected by filtration. Recrystallization from methanol afforded a product which showed no depression in the melting point on admixture with the products obtained by the methods (a) and (b). Yield, 50 mg.

Found: C, 56.58; H, 4.23; N, 7.85. Calcd. for $C_{17}H_{17}O_2N_2Br$: C, 56.52; H, 4.74; N, 7.85%.

UV λ_{max}^{MeOH} mμ (log ε): 256 (4.20), 299 (4.15), 415 (4.38), 477 (4.39).

3-Isopropyl-5-morpholinomethyltropolone (XI).— A solution of 1 g. of VII dissolved in ca. 20 ml. of ethanol and added with 220 mg. of sodium hydroxide and 200 mg. of palladium-carbon was shaken in a hydrogen stream. Absorption of hydrogen stopped after an equivalent mole was absorbed. The solvent was evaporated under a reduced pressure and addition of hydrochloric acid to the residue to neutralization precipitated crystals. The crystals were collected and recrystallized from petroleum ether to colorless prisms (XI), m. p. 77~78°C. Yield, 500 mg.

Found: C, 68.17; H, 7.64; N, 5.14. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32%.

UV λ_{max}^{MeOH} mμ (log ε): 242 (4.41), 326 (3.92).

Treatment of XI with 3 N hydrochloric acid afforded colorless crystals, m. p. 124~129°C, the hydrochloride of XI.

Found: C, 56.23; H, 7.05; N, 4.08. Calcd. for $C_{15}H_{22}O_3NCl \cdot H_2O$: C, 56.69; H, 7.61; N, 4.41%.

3-Isopropyl-5-piperidinomethyltropolone (XII). — A suspension of 0.9 g. of VIII in 20 ml. of ethanol with 0.3 g. of potassium hydroxide and 0.1 g. of palladium-carbon added was shaken in a hydrogen stream. After absorption of an equivalent mole of hydrogen the solvent was evaporated under a reduced pressure and addition of hydrochloric acid to the yellow viscous residue to neutralization precipitated slight yellow crystals. The crystals were collected and recrystallized from methanol or benzene. M. p. 110~113°C. Yield, 0.6 g.

Found: C, 72.91; H, 8.78; N, 5.11. Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36%.

UV λ_{max}^{MeOH} mμ (log ε): 242 (4.41), 326 (3.89).

IR ν N^+-H, 2500 cm^{-1} (broad) (KBr disk).

Reaction of XI with *p*-Tolyldiazonium Salt. — To a solution of 160 mg. of XI dissolved in ca. 0.2 ml. of pyridine, a diazonium salt prepared from 30 mg. of *p*-toluidine, 20 mg. of sodium nitrite, and ca. 0.1 ml. of concentrated hydrochloric acid was added while being stirred under ice cooling, by which orange crystals separated out. The crystals were collected and recrystallized from methanol to orange prisms, m. p. 129~130°C, undepressed on admixture with an authentic sample of 3-isopropyl-5-tolylazotropolone.

Summary

The Mannich reaction was applied to 3-isopropyltropolone and 3-isopropyl-5, 7-dimorpholinomethyl, and 3-isopropyl-5, 7-dipiperidinomethyltropolone were obtained. These substituents were easily substituted by diazonium salt or bromine. Some of the Mannich bases obtained were found to retain the zwitterion structure in the solid state.

The author expresses his deep gratitude to Professor Shuichi Seto for his kind guidance. He is indebted to Mr. S. Aono for infrared spectral measurements and to Mr. F. Sato for ultraviolet spectral measurements. A part of the expense for the present research was defrayed by Sankyo Co., Ltd., to whom the author wishes to express his sincere gratitude.

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