4- and 6-Isopropyl-2-mercaptotropones

By Kazuo MATSUI*

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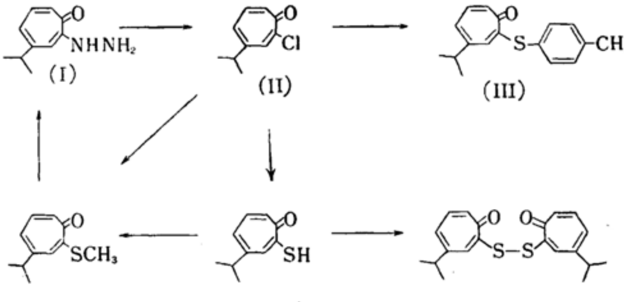
Detailed studies have been made by Nozoe and his co-workers on mercaptotropones[1-4] and mercapto derivatives of 2-phenyltropone has recently been studied by Muroi[5,6]. These studies still leave room for examination of the structure of the parent compound, 2-mercaptotropone, itself with reference to its tautomerism. As a preliminary study to this problem, homologous 4- and 6-isopropyl-2-mercaptotropones were synthesized and some reactions were carried out, which are described herein.

2-Hydrazino-4-isopropyltropone (I) and 2-hydrazino-6-isopropyltropone[7] (VII), obtained from hinokitiol (β-thujaplicin or 4-isopropyltropolone), were converted to 2-chloro-4-isopropyltropone (II) and 2-chloro-6-isopropyltropone[7] (VIII), respectively, and mercapto derivatives were prepared from them.



Scheme 1

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* On leave of absence from Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.

[1] T. Nozoe, M. Sato, and K. Matsui, *Sci. Repts. Tohoku Univ.*, Series I, **37**, 211 (1953).

[2] Idem., *Proc. Japan Acad.*, **28**, 408 (1952).

[3] Idem., ibid., **28**, 410 (1952).

[4] Idem., ibid., **29**, 21 (1953).

[5] T. Muroi, *J. Chem., Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 185 (1959).

[6] Idem., ibid., **80**, 303 (1959).

[7] S. Seto, *Sci. Repts. Tohoku Univ., Series* I, **37**, 286 (1953).

II easily reacted with potassium salt of *p*-thiocresol when heated in ethanol and formed 4-isopropyl-2-*p*-tolylthiotropone (III) as pale yellow plates, m. p. 110.5~112°C. Heating of II in methanol with four mol. of potassium hydrogensulfide produced 4-isopropyl-2-mercaptotropone (IV) as orange crystals, m. p. 63~65°C, in 80% yield. IV was stable in the air and the benzene layer colored dark red with ferric chloride. Methylation of IV with diazomethane in ether afforded 4-isopropyl-2-methylthiotropone (V) as a yellow oil. The identity of this compound was established by agreement of its ultraviolet spectrum with that of the product obtained by the reaction of II and potassium salt of methanethiol and admixture of their respective 2, 4-dinitrophenylhydrazone, purple needles, m. p. 183°C. Reaction of V with excess of hydrazine by refluxing in methanol for 5 hr. produced I which was identified by admixture of its benzylidene compound, yellow needles, m. p. 203°C, with that of the authentic sample.

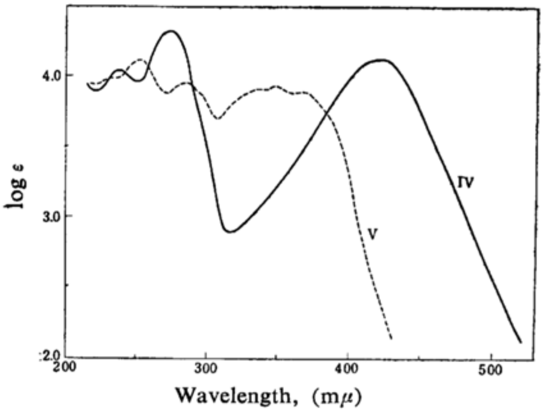
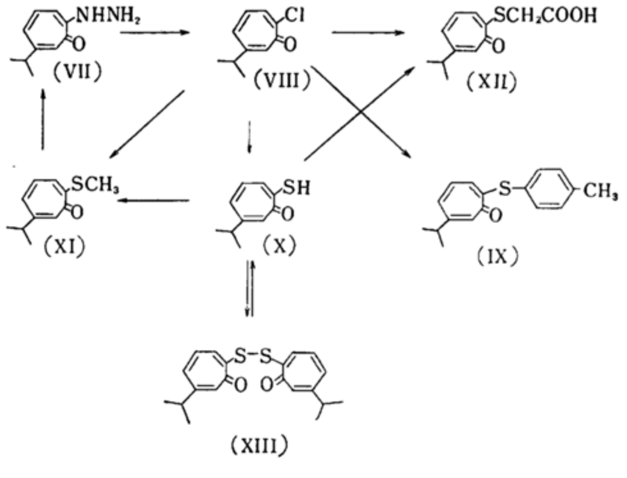


Fig. 1. Ultraviolet absorption spectra[8] of IV and V in methanol.

Application of 0.5 mol. of bromine to ethanolic solution of IV resulted in dehydrogenation from 2 mol. of IV to form 4, 4′-diisopropyl-2, 2′-ditroponyl disulfide (VI) as pale yellow cubic crystals, m. p. 155~156°C.

Heating of VIII with potassium salt of *p*-thiocresol in ethanol afforded 6-isopropyl-2-*p*-tolylthiotropone (IX) as pale yellow plates, m. p. 129~130.5°C. Similarly, application of 4 mol. of potassium hydrogensulfide gave 6-isopropyl-2-mercaptotropone (X) as dark red oil, b. p.$_2$ 125~130°C. X was stable in the air like IV and solely formed 6-isopropyl-2-methylthiotropone (XI) as yellow oil by the action of diazomethane. The identity of this compound was established by comparison of its ultraviolet spectrum with that of the product obtained by the reaction of VIII and potassium salt of methanethiol in ethanol and by admixture of respective 2, 4-dinitrophenylhydrazone, purple needles, m. p. 193~195°C.

Heating of XI with excess of hydrazine in methanol for 9 hr. produced VII, which was confirmed by admixture of the benzylidene compound of yellow prisms, m. p. 167°C. The formation of I from V and of VII from XI prove that in substitution reaction of halotropones with thiols, abnormal reaction seen in the case of substitution reaction with amines[9,10] does not take place.



Scheme 2

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[8] Measured by the Beckman Model DU spectrophotometer.

[9] T. Nozoe, S. Seto and T. Sato *Proc. Japan Acad.*, **30**, 473 (1954).

[10] T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1056 (1959).

The reaction of the sodium salt of X and sodium monochloroacetate produced 6-isopropyl-2-carboxymethylthiotropone (XII) as pale yellow prisms, m. p. 158~160°C. This compound agreed with the product obtained from the reaction of VIII and potassium thioglycolate through admixture.

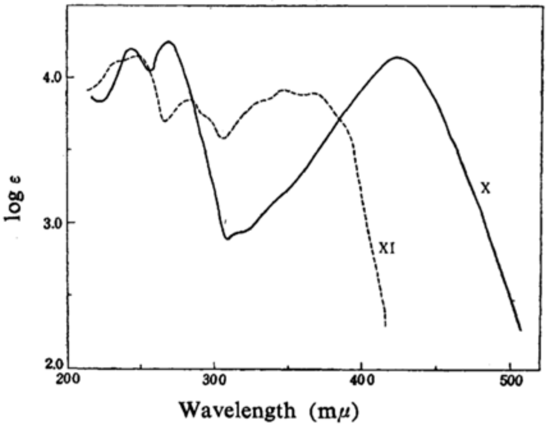

Fig. 2. Ultraviolet absorption spectra of X and XI in methanol.

Bromination of X in ethanol afforded 6, 6′-diisopropyl-2, 2-ditroponyldisulfide (XIII) as pale yellow leaflets, m. p. 210~211°C. XIII is also obtained by tosylation of X in pyridine, while heating of XIII with alkaline aqueous solution of sodium sulfide results in its reduction to form X.

There are two possible tautomeric structures, A and B, for both IV and X but this problem will be discussed in a separate report, together with that of the parent 2-mercaptotropone.

Experimental[11]

4-Isopropyl-2-*p*-tolylthiotropone (III).—A solution of 80 mg. of *p*-thiocresol, 0.5 ml. of ethanol, and 0.1 ml. of 50% potassium hydroxide was added to a solution of 0.1 g. of 2-chloro-4-isopropyltropone (II) dissolved in 0.3 ml. of ethanol and the mixture was heated on a water bath for a short time. The mixture was diluted with water and the oil that separated out was taken up in benzene. The solid obtained therefrom was recrystallized from cyclohexane to 80 mg. of III as pale yellow plates, m. p. 110.5~112°C.

Found: C, 75.22; H, 6.46. Calcd. for $C_{17}H_{18}OS$: C, 75.51; H, 6.71%[12].

2, 4-Dinitrophenylhydrazone: Dark red prisms (from ethanol-benzene mixture), m. p. 206~207°C.

Found: C, 60.98; H, 4.73; N, 12.72. Calcd. for $C_{23}H_{22}O_4N_4S$: C, 61.32; H, 4.92; N, 12.44%.

4-Isopropyl-2-mercaptotropone (IV).—To a solution of 0.1 g. of II dissolved in 2 ml. of methanol, a solution of potassium hydrogensulfide, prepared by saturation of hydrogen sulfide in a solution of 0.26 ml. of 50% potassium hydroxide in 2 ml. of methanol, was added and the mixture was heated on a water bath for a short time. Methanol was evaporated under a reduced pressure, water was added to the residue, and the solution was treated with activated carbon. The filtrate thereby obtained was acidified with 6N sulfuric acid and the crystals that separated out were collected by filtration. Sublimation of this product under 5 mmHg pressure afforded IV as orange-red crystals m. p. 63~65°C. Yield, 80 mg.

Found: C, 66.39; H, 6.94. Calcd. for $C_{10}H_{12}OS$: C, 66.63; H, 6.71%.

Picryl derivative: Prepared from the potassium salt of IV and picryl chloride, and recrystallized from ethanol to yellow needles, m. p. 174°C.

Found: C, 49.24; H, 3.26; N, 10.88. Calcd. for $C_{16}H_{13}O_7N_3S$: C, 49.10; H, 3.35; N, 10.74%.

4-Isopropyl-2-methylthiotropone (V).—i) To a solution of 0.2 g. of II dissolved in 1 ml. of ethanol, 0.2 ml. of 50% potassium hydroxide saturated with methanethiol was added by which exothermic reaction took place. The mixture was diluted with water, extracted with benzene, and the extract was submitted to low pressure distillation, from which 0.2 g. of V was obtained as a yellow oil.

2, 4-Dinitrophenylhydrazone: Purple needles (from ethanol-benzene mixture), m. p. 183°C.

Found: C, 54.21; H, 4.62; N, 14.79. Calcd. for $C_{17}H_{18}O_4N_4S$: C, 54.53; H, 4.85: N, 14.97%.

ii) IV was methylated with diazomethane in ether by the usual process. The product thereby obtained showed good agreement with V obtained above, in ultraviolet absorption spectrum and 2, 4-dinitrophenylhydrazone.

Reaction of V and Hydrazine.—A mixture of 30 mg. of V, 0.5 ml. of methanol, and 1 drop of 80% hydrazine hydrate was refluxed for 5 hr., methanol was evaporated under a reduced pressure, and the residue was heated after addition of 2 drops of methanol and 3 drops of benzaldehyde. The crystals that separated out were collected and recrystallized from ethanol to give yellow needles, m. p. 202°C, identical with the bezylidene compound, m. p. 202°C, of 2-hydrazino-4-isopropyltropone (I).

4, 4′-Diisopropyl-2, 2′-ditroponyl Disulfide (VI).—A solution of 50 mg. of bromine in 0.5 ml. of ethanol was added to 0.1 g. of IV dissolved in 2 ml. of ethanol, by which crystals began to separate out gradually. After about 30 min. the crystals were collected and recrystallized from ethanol to give 50 mg. of VI as pale yellow, cubic crystals, m. p. 155~156°C.

Found: C, 66.96; H, 5.89. Calcd. for $C_{20}H_{22}O_2S_2$: C, 67.00; H, 6.18%.

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[11] All melting points are not corrected.

[12] The microanalyses were carried out by Miss A. Iwanaga and Mr. S. Azumi to whom the author expresses his gratitude.

6-Isopropyl-2-*p*-tolylthiotropone (IX).—A solution of 80 mg. of *p*-thiocresol, 0.1 ml. of 50% potassium hydroxide, and 0.5 ml. of ethanol was added to 0.1 g. of 2-chloro-6-isopropyltropone (VIII) in 0.3 ml. of ethanol and the mixture was heated on a water bath for a short time. This was diluted with water, crystals that separated out were collected, and recrystallized from cyclohexane to give 90 mg. of (IX) as pale yellow plates, m. p. 129~130.5°C.

Found: C, 75.19; H, 6.41. Calcd. for $C_{17}H_{18}OS$: C, 75.51; H, 6.71%.

2, 4-dinitrophenylhydrazone: Purple prisms (from ethanol-benzene mixture), m. p. 227~228°C.

Found: C, 61.03; H, 4.76; N, 12.64. Calcd. for $C_{23}H_{22}O_4N_4S$: C, 61.32; H, 4.92; N, 12.44%.

6-Isopropyl-2-mercaptotropone (X).—A solution of potassium hydrogensulfide, prepared by saturating hydrogen sulfide in a mixture of 0.46 ml. of 50% potassium hydroxide and 1.5 ml. of methanol was added to the solution of 0.18 g. of VIII dissolved in 0.5 ml. of methanol and the mixture was heated on a water bath for a short time. Methanol was evaporated under a reduced pressure, the residue was dissolved in water, and acidified with 6N sulfuric acid. The oil that separated out was taken up in chloroform and the residue from the chloroform extract was distilled under a reduced pressure, affording 0.13 g. of X as a dark red oil, b. $p._2$ 125~130°C.

Found: C, 66.68; H, 6.48. Calcd. for $C_{10}H_{12}OS$: C, 66.63; H, 6.71%.

2, 4-dinitrophenyl derivative: Prepared from the potassium salt of X and 2, 4-dinitro-chlorobenzene and recrystallized from ethanol to give yellow prisms, m. p. 156~158°C.

Found: C, 55.17; H, 3.85; N, 8.46. Calcd. for $C_{16}H_{14}O_5N_2S$: C, 55.48; H, 4.07; 8.09%.

Picryl derivative: Prepared from the potassium salt of X and picryl chloride, and recrystallized from ethanol to give yellow needles, m. p. 145~147°C.

Found: C, 49.07; H, 3.29; N, 10.96. Calcd. for $C_{16}H_{13}O_7N_3S$: C, 49.10; H, 3.35; N, 10.74%.

6-Isopropyl-2-methylthiotropone (XI).—i) To a solution of 0.2 g. of VIII dissolved in 0.5 ml. of ethanol, 0.2 ml. of 50% potassium hydroxide saturated with methanethiol was added, by which an exothermic reaction occurred. The mixture was diluted with water, separated oil was extracted with benzene, and residue from the benzene extract was distilled under a reduced pressure, affording 0.17 g. of XI as a yellow oil.

2, 4-Dinitrophenylhydrazone: Purple needles (from ethanol), m. p. 193~195°C.

Found: C, 54.23; H, 4.48; N, 15.19. Calcd. for $C_{17}H_{18}O_4N_4S$: C, 54.53; H, 4.85; N, 14.97%.

ii) Methylation of X with diazomethane by the usual process afforded a product which was identical with the product obtained in (i) in ultraviolet absorption spectrum and 2, 4-dinitrophenylhydrazone.

Reaction of XI and Hydrazine.—A mixture of 0.1 g. of XI, 1 ml. of methanol, and 2 drops of 80% hydrazine hydrate was refluxed for 9 hr. Methanol and excess of hydrazine were removed by low pressure distillation and the residue was heated after addition of 0.5 ml. of ethanol and 5 drops of benzaldehyde. The crystals that separated out were recrystallized from ethanol to give 50 mg. of yellow prisms, m. p. 165~167°C, undepressed on admixture with the benzylidene compound, m. p. 167°C, of 2-hydrazino-6-isopropyltropone (VII).

2-Carboxymethylthio-6-isopropyltropone (XII).—(i) A solution of 60 mg. of monochloroacetic acid in 0.5 ml. of 2 N sodium hydroxide and 1 ml. of water was added to the mixture of 0.1 g. of X, 0.3 ml. of 2 N sodium hydroxide, and 1 ml. of water, and the mixture was heated on a water bath for 10 min. by which the solution changed its color from red to yellow. After treatment with activated carbon, the filtrate was acidified with 6N sulfuric acid and the crystals that separated out were collected by filtration. Recrystallization from hydrous ethanol afforded 50 mg. of XII as pale yellow prisms, m. p. 158~160°C.

Found: C, 60.88; H, 5.91. Calcd. for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92%.

ii) A solution of 50 mg. of thioglycolic acid, 0.3 ml. of 20% potassium hydroxide, and 3 ml. of ethanol was added to the solution of 90 mg. of VIII dissolved in 1 ml. of ethanol, and the mixture was heated on a water bath for 30 min. After evaporation of ethanol under a reduced pressure, water was added to the residue and the solution was treated with activated carbon. The filtrate was acidified with 6 N sulfuric acid and the crystals that precipitated out were recrystallized from hydrous ethanol to give 50 mg. of XII, m. p. 158~159°C, undepressed on admixture with the product obtained in (i).

6, 6′-Diisopropyl-2, 2′-ditroponyl Disulfide (XIII).—i) A solution of 50 mg. of bromine in 0.5 ml. of ethanol was added to the solution of 0.1g. of X dissolved in 1 ml. of ethanol, with stirring and ice-cooling. After an hour, the crystals that separated out were collected and recrystallized from benzene-ethanol mixture to give 60 mg. of XIII, as pale yellow leaflets, m. p. 210~211°C.

Found: C, 66.71; H, 6.05. Calcd. for $C_{20}H_{22}O_2S_2$: C, 67.00; 6.18%.

ii) A solution of 50 mg. of X dissolved in 0.3 ml. of pyridine was cooled with ice and 60 mg. of tosyl chloride was added to it, by which the reaction occurred with evolution of heat. The mixture was acidified with 2N hydrochloric acid and the crystals that separated out were recrystallized from a large amount of ethanol affording 30 mg. of XIII, m. p. 210~210.5°C, undepressed on admixture with the product obtained in (i).

Found: C, 67.25; H, 6.03%.

Reduction of (XIII).—A mixture of 50 mg. of XIII, 2 ml. of 2N sodium hydroxide, and 50 mg. of sodium sulfide was heated on a water bath for 10 min. by which XIII dissolved completely to form a red solution. After treatment with activated carbon, the filtrate was acidified with 6 N sulfuric acid and the oil that separated was extracted with chloroform. The residue from the chloroform extract was distilled under a reduced pressure to yield 30 mg. of X as a dark red oil, which was identified by ultraviolet absorption spectrum and the picryl derivative.

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Department of Chemistry
Faculty of Science,
Tohoku University
Katahira-cho, Sendai