Syntheses of Benzo[b]tropothiazine and its Derivatives

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The preparation of oxime and arylhydrazones of quinoxalotropone (I) by the condensation of 5-nitroso- or 5-arylazo-tropolones and *o*-phenylenediamine was reported earlier in this laboratory[1]. A parent compound II, named benzo[b]tropazine, was obtained also by condensation of 2-halo- or 2-methoxy-tropone, or 3-carboxy-tropolone and *o*-phenylenediamine[2]. In the present series of this work, several compounds having a new ring system IV containing sulfur and nitrogen atoms were synthesized and examinations were made on their properties.

A mixture of 2-halotropone (III) and *o*-aminothiophenol in methanol was allowed to stand at room temperature and red plates IV, m. p. 87°C, $C_{13}H_9NS$, were obtained. IV is stable to heating with alkali or hydrochloric acid, is easily soluble in various organic solvents and in dilute acid to form a deep red solution, and easily gives some molecular compounds such as picrate. The ultraviolet absorption spectrum of IV (Fig. 1) in hydrochloric acid solution shows a shift to a longer wavelength region compared with that in methanol.

Attempted catalytic hydrogenation of IV in

1) T. Nozoe, M. Sato and T. Matsuda, *Sci. Repts. Tohoku Univ., First Ser.*, 37, 407 (1953); T. Nozoe, S. Ito, S. Suzuki and K. Hiraga, *Proc. Japan Acad.*, 32, 344 (1956); S. Ito, *Sci. Repts. Tohoku Univ., First Ser.*, 42, 236 (1958).

2) T. Nozoe, Y. Kitahara, K. Takase and M. Sasaki, *Proc. Japan Acad.*, 32, 349 (1956).

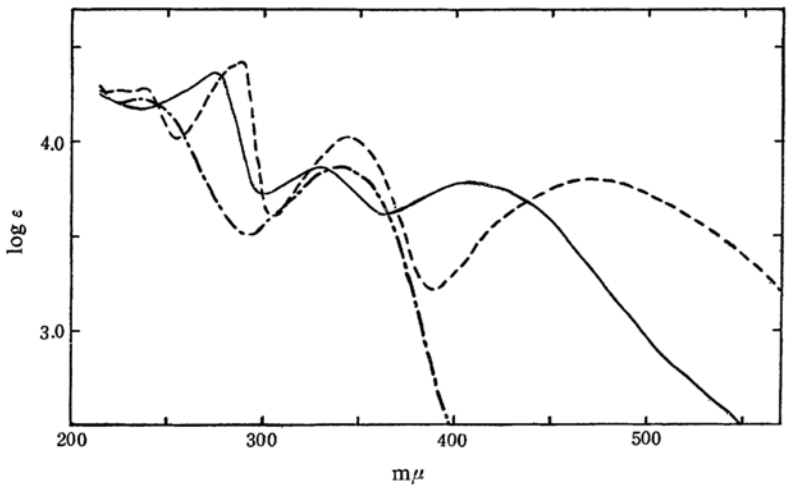
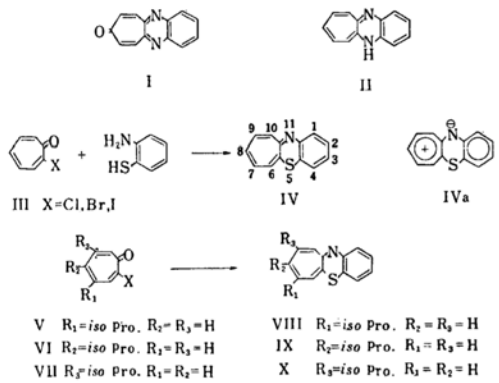


Fig. 1. Ultraviolet absorption spectra.
—·—· II (in methanol), —— IV (in methanol), ---- IV (in 0.1 N HCl).

the presence of palladium-carbon or Adams catalyst was unsuccessful with no hydrogen uptake and the complete recovery of the



original compound IV. The reaction of IV with methyl iodide did not give methiodide, but gave hydroiodide of IV. Hydrobromide of IV was also formed by treatment of IV with hydrobromic acid.

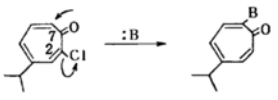
From these properties, the course of preparation, and the analytical values of IV and its several derivatives, the structure of IV could be proved to be cyclohepta[b]benzo-[e]-1,4-thiazine, for which the name of benzo[b]-tropothiazine is proposed.

It is interesting to compare compound IV with compound II. The latter compound II forms colorless prisms with poor solubility, and is unstable toward acids, reducible with palladium-carbon to 2,3-pentamethylene-quinoxaline. Also the ultraviolet spectrum of compound II is quite different from that of compound IV as shown in Fig. 1. These results would indicate that IV is stabilized by the resonance between IV and IVa.

Three kinds of isopropyl-2-halotropones (V, VI and VII)[3,4] were also reacted with *o*-aminothiophenol, easily affording 7-, 8- and 9-isopropylbenzo[b]tropothiazines (VIII, IX and X) as red oils. These isopropyl compounds have properties similar to those of the compound IV. In view of the fact that the abnormal nucleophilic substitution, which is frequently observed in troponoid chemistry*, does not occur in the reaction of 2-halotropone derivatives and methylmercaptane[5], it is considered that the same normal substitution occurs in the reaction of 2-halotropone derivatives and *o*-aminothiophenol; therefore it is assumed that the structure of VIII-X is correct.

2-Bromo-7-methoxytropone (XI)[6] gave a red oil XII, $C_{14}H_{11}ONS$, by the condensation with *o*-aminothiophenol. The compound XII, like IV, is soluble in dilute acid and gives molecular compounds such as picrate. Hydrolysis of XII with hydrochloric acid gave red needles XIII, m.p. 169°C, which were identical with a compound obtained by the reaction of 3-bromo-2-methoxytropone (XIV)[6]

3) S. Seto, *Sci. Repts. Tohoku Univ., First Ser.*, **37**, 286 (1953).
4) W. v. E. Docring and L. H. Knox, *J. Am. Chem. Soc.*, **75**, 297 (1953).
* It has been known that in the nucleophilic substitution reaction of 2-halotropones various reagents do not attack at the carbon-2 but at the carbon-7 in the majority of cases.



Cf. T. Nozoe, S. Seto and T. Sato, *Proc. Japan Acad.*, **30**, 473 (1954); T. Nozoe, "Non-Benzenoid Aromatic Compounds", Edited by D. Ginsburg, Interscience Publishers, Inc., New York (1959), p. 339.
5) K. Matsui, This Bulletin, **33**, 1448 (1960).
6) T. Nozoe, Y. Kitahara and S. Masamune, *Proc. Japan Acad.*, **27**, 649 (1951).

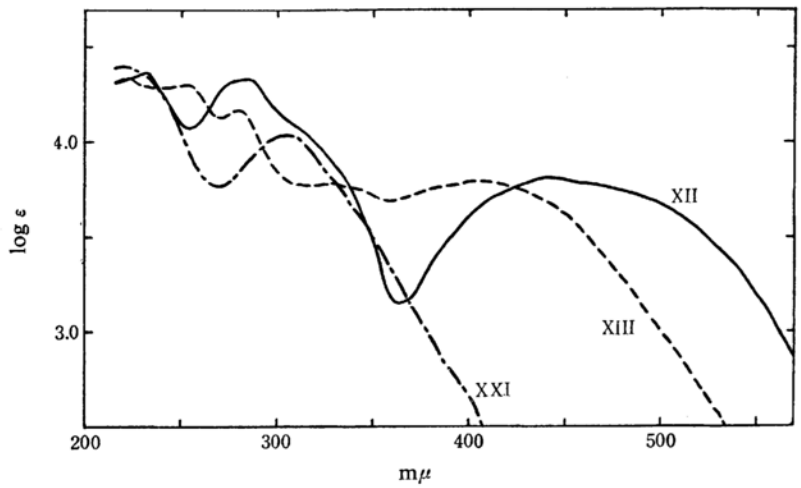
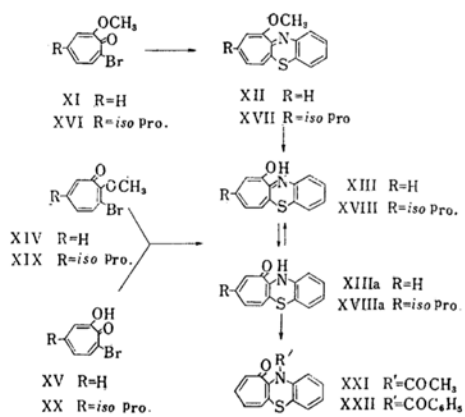


Fig. 2. Ultraviolet absorption spectra of XII, XIII and XXI in methanol.

and *o*-aminothiophenol. XIII was also obtained from 2-bromotropolone (XV) in good yield. From these results, it is assumed that the structure of XII is 10-methoxybenzo [b] tropothiazine and of XIII is 10-hydroxybenzo [b] - tropothiazine.

Attempted substitution of methoxyl in XII with amino or substituted amino group was not successful. The original compound XII was recovered unchanged.

2-Bromo-5-isopropyl-7-methoxytropone (XVI)[7] gave 7-isopropyl-10-methoxybenzo [b] tropothiazine (XVII) by the reaction with *o*-aminothiophenol. Hydrolysis of XVII with hydrochloric acid afforded 7-isopropyl-10-hydroxybenzo [b] - tropothiazine (XVIII). This was also obtained by the reaction of 3-bromo-6-isopropyl-2-methoxytropone (XIX)[7] or 7-bromohinokitiol (3-bromo-6-isopropyltropolone) (XX) with *o*-aminothiophenol. XIII and XVIII do not dissolve in dilute acids. XIII does not give molecular compounds such as picrate, but XVIII gives them.



It is considered that compounds XIII and XVIII could exist in two tautomeric forms respectively, i. e. 10-hydroxy derivatives of benzo [b] tropothiazine (XIII and XVIII) and benzothiazinotropone derivatives (XIIIa and XVIIIa). Information on this problem comes from the following data: 1) The ultraviolet spectrum of XII is similar to IV rather than to XIII as shown in Fig. 2. 2) The infrared spectrum of XIII shows ν_{NH} at 3218 cm^{-1} and $\nu_{C=O}$ at 1607 cm^{-1} (small peak). 3) XIII did not react with diazomethane, but gave yellow acetate XXI with acetic anhydride and orange benzoate XXII with benzoyl chloride in poor yield. The hydrolysis of these acyl derivatives converts them into XIII. $\nu_{C=O}$ at 1673 cm^{-1} in infrared spectrum of XXI indicates that XXI is *N*-acetyl derivative. Remarkable shifts to a shorter wavelength region in the ultraviolet spectra of XXI and XXII (Fig. 2) seem to indicate that a conjugation of seven membered ring and benzene nucleus in XIII is broken by the introduction of the acyl group in the *N*-atom, as an additional reason for the decrease of the coplanarity of these nuclei is also considered.

From consideration of the above results, it seems reasonable to conclude that XIII would exist not as 10-hydroxybenzo [b] tropothiazine, but as its keto form, benzo-1, 4-thiazino [3,2-b] - tropone (XIIIa). XVIII would be named 8 - isopropylbenzo - 1, 4 - thiazino [3, 2-b] tropone (XVIIIa).

It is supposed that *N*-alkylation of the compound XII is possible as in the case of phenothiazine, but the attempted alkylations were not actually successful. Further experiments in this field will be reported in near future.

7) S. Seto, *Sci. Repts. Tohoku Univ., First Ser.*, 37, 298 (1953).

Experimental**

Benzo[b]tropothiazine (IV). — A solution of 2 g. of 2-chlorotropone and 2 g. of *o*-aminothiophenol in 20 ml. of methanol was allowed to stand at room temperature for 3 hr. The solvent was distilled off and 100 ml. of water added to the residue, and the insoluble portion was filtered off. The filtrate was extracted with two 10 ml. portions of benzene. The mother liquor left after benzene extraction was adjusted to make it slightly alkaline with sodium carbonate solution, then was extracted with five 10 ml. portions of benzene. The latter benzene extract was dried over sodium sulfate and the benzene was distilled off, affording 2.4 g. of deep red crystals. Recrystallization of the crude crystals from petroleum (b. p. 60～70°C) gave 2.2 g. of IV as red plates, m. p. 86～87°C.

The reaction of 2-bromo- or 2-iodo-tropone with *o*-aminothiophenol gave the same compound IV.

Found : C, 74.05 ; H, 4.20 ; N, 6.61. Calcd. for $C_{13}H_9NS$: C, 73.92 ; H, 4.30 ; N, 6.63%.

λ_{max}^{MeOH} mμ (log ε): 275 (4.37), 330 (3.86), 405 (3.79). $\lambda_{max}^{0.1N\ HCl}$ mμ (log ε): 224 (4.27), 238 (4.28), 289 (4.44), 343 (4.02), 470 (3.81).

Picrate ; dark brown needles, m. p. 188～189°C (decomp.).

Found : C, 51.75 ; H, 3.16; N, 12.73. Calcd. for $C_{19}H_{12}O_7N_4S$: C, 51.82 ; H, 2.75 ; N.12.72%.

Styphnate ; dark brown needles, m. p. 204～205°C (decomp.).

Found ; C, 50.09 ; H, 2.75 ; N, 12.10. Calcd. for $C_{19}H_{12}O_8N_4S$: C, 50.00 ; H, 2.65 ; N, 12.10%.

Hydriodide ; black violet needles, m. p. 194～195.5°C, 210～220°C (decomp.).

Found : C, 46.35 ; H, 3.42 ; N, 4.51. Calcd. for $C_{13}H_{10}NSI$: C, 46.00 ; H, 2.97 ; N, 4.13%.

Hydrobromide ; black violet needles, m. p. 207°C (decomp.).

Found : C, 51.95 ; H, 3.37 ; N, 4.28. Calcd. for $C_{13}H_{10}NSBr$: C, 53.42 ; H, 3.45 ; N, 4.79%.

7-Isopropylbenzo[b]tropothiazine (VIII). — Reaction of 150 mg. of 2-chloro-4-isopropyltropone (V) with 100 mg. of *o*-aminothiophenol in methanol afforded 150 mg. of VIII as red oil.

Picrate ; violet needles, m.p. 172～173°C(decomp.).

Found : C, 54.62 ; H, 3.68 ; N, 11.59. Calcd. for $C_{22}H_{18}O_7N_4S$: C, 54.77 ; H, 3.76 ; N, 11.62%.

Styphnate ; dark violet needles, m.p . 169～170°C (decomp.).

Found : C, 53.15 ; H, 3.53 ; N, 11.22. Calcd. for $C_{22}H_{18}O_8N_4S$: C, 53.01 ; H, 3.63 ; N, 11.24%.

8-Isopropylbenzo[b]tropothiazine (IX). — IX as red oil was obtained from 2-halo-5-isopropyltropone (VI) and *o*-aminothiophenol.

Picrate ; violet needles, m. p. 176～177°C.

Found : C, 54.74 ; H, 3.79 ; N, 11.52%.

Styphnate ; violet needles, m.p. 176.5～177.5°C.

Found : C, 52.74 ; H, 3.42 ; N, 11.23%.

9-Isopropylbenzo[b]tropothiazine (X). — X as red oil was obtained from 2-halo-6-isopropyltropone (VII) and *o*-aminothiophenol.

Picrate ; violet plates, m. p. 198～199°C (decomp.).

Found : C, 54.39 ; H, 3.27 ; N, 11.64%.

Styphnate ; violet prisms, m. p. 191～192°C (decomp.).

Found : C, 53.19 ; H, 3.77 ; N, 10.97%.

10-Methoxybenzo[b]tropothiazine (XII). — A solution of 215 mg. of 2-bromo-7-methoxytropone (XI) and 130 mg. of *o*-aminothiophenol in 3 ml. of methanol was warmed for twenty minutes. After allowing it to stand at room temperature for 10 min., the solvent was distilled off, and 20 ml. of water was added and extracted with two 5 ml. portions of benzene. The water layer left after the benzene extraction was adjusted to slightly alkaline with sodium carbonate and was extracted with benzene. The latter benzene extract was dried over sodium sulfate and the solvent was removed, affording 150 mg. of XII as red oil, and was purified by chromatogram, using an alumina.

λ_{max}^{MeOH} mμ (log ε): 222 (4.33), 253 (4.28), 280 (4.15), 328 (3.78), 408～410 (3.78).

Picrate ; dark brown needles, m. p. 184～185°C.

Found : C, 51.01 ; H, 2.83 ; N, 11.76. Calcd. for $C_{21}H_{14}O_8N_4S$: C, 51.07 ; H, 3.00 ; N, 11.91%.

Styphnate ; dark brown needles, m. p. 173～174°C.

Found : C, 49.55 ; H, 2.78 ; N, 11.25. Calcd. for $C_{21}H_{14}O_9N_4S$: C, 49.39 ; H, 2.90 ; N, 11.52%.

Benzo-1, 4-thiazino[3, 2-b]tropone (XIII). — a) A solution of 3 g. of 3-bromotropolone (XV) and 2 g. of *o*-aminothiophenol in 20 ml. of methanol was refluxed for 2 hr. The red needles which separated out by cooling thoroughly were collected by filtration and recrystallization from ethanol or acetic acid, giving 2.6 g. of XIII as red needles, m. p. 168～169°C.

Found : C, 68.84 ; H, 3.76 ; N, 6.11. Calcd. for $C_{13}H_9ONS$: C, 68.72 ; H, 3.99 ; N, 6.17%.

λ_{max}^{MeOH} mμ (log ε): 233 (4.36), 285 (4.33), 440 (3.82). $\lambda_{max}^{0.1N\ HCl}$ mμ (log ε): 230 (4.37), 285 (4.35), 450 (3.81).

b) After allowing a solution of 215 mg. of 3-bromo-2-methoxytropone (XIV) and 130 mg. of *o*-aminothiophenol in 2 ml. of a methanol to stand under cooling, 220 mg. of XIII was obtained.

c) A solution of 50 mg. of XII in 3 ml. of 2 N hydrochloric acid was refluxed for 5 hr., and the crystals which separated out were recrystallized from ethanol, affording 30 mg. of XIII.

10-Methoxy-8-isopropylbenzo[b]tropothiazine (XVII). — A solution of 520 mg. of 2-methoxy-4-isopropyl-7-bromotropone (XVI) and 250 mg. of *o*-aminothiophenol in 2 ml. of methanol was refluxed for thirty minutes. The solvent was distilled off and 7 ml. of water was added to the residue and the solution was extracted with benzene. The mother liquor left after the benzene extraction was adjusted to slightly alkaline with sodium carbonate and was extracted with benzene. The latter benzene extract was dried and the removal of the solvent left 270 mg. of red oil. The oil was crystallized with methanol and the recrystallization from methanol gave XVII as orange prisms, m. p. 123～124°C.

** All the melting points were uncorrected. The microanalyses were carried out by Mr. S. Azumi and Miss A. Iwanaga, and I. R. spectra were measured with Perkin-Elmer Model 112 by the member of Professor Kinumaki's laboratory, Research Institute, Chemistry of Non-Aqueous Solution, Tohoku Univ., to whom the authors' sincere acknowledgements are hereby extended.

Found: C, 71.70; H, 5.84; N, 4.93, Caled. for $C_{17}H_{17}ONS$: C, 72.06; H, 6.05; N, 4.94%.

λ_{max}^{MeOH} mμ (log ε): 225 (4.41), 255 (4.24 sh), 280 (4.14 sh), 333 (3.74), 408～410 (3.78).

Picrate; brown needles, m.p. 160～161°C.

Found: C, 53.99; H, 3.93; N, 10.85. Calcd. for $C_{23}H_{20}O_8N_4S$: C, 53.91; H, 3.93; N, 10.93%.

Styphnate; brown needles, m. p. 145～146°C.

Found: C, 52.74; H, 3.75; N, 10.60. Calcd. for $C_{23}H_{20}O_9N_4S$: C, 52.25; H, 3.81; N, 10.61%.

8-Isopropylbenzo-1, 4-thiazino[3, 2-b] tropone (XVIII). — a) A solution of 500 mg. of 7-bromohinokitiol (3-bromo-6-isopropyltropolone) (XX) and 250 mg. of *o*-aminothiophenol in 3 ml. of methanol was refluxed for an hour, the solvent was distilled off and 20 ml. of water was added to the residue, and then extracted six times with 3 ml. each of benzene. The benzene solution was dried over sodium sulfate, passed through an alumina column, and 440 mg. of oily substance was obtained after removal of the solvent from the effluent. The oil crystallized with cyclohexane and the recrystallization from cyclohexane afforded XVIII as red needles, m. p. 94～95°C.

Found: C, 71.01; H, 5.50; N, 5.27. Calcd. for $C_{16}H_{15}ONS$: C, 71.36; H, 5.61; N, 5.20%.

λ_{max}^{MeOH} mμ (log ε): 237 (4.31), 277 (4.23), 430 (3.65).

Picrate; brownish violet plates, m.p. 141～142°C.

Found: C, 53.70; H, 3.98; N, 11.19. Calcd. for $C_{22}H_{18}O_8N_4S$: C, 53.01; H, 3.64; N, 11.24%.

Styphnate; brownish violet plates, m. p. 170～171°C.

Found: C, 51.47; H, 3.47; N, 10.39. Calcd. for $C_{22}H_{18}O_9N_4S$: C, 51.36; H, 3.53; N, 10.89%.

b) A solution of 260 mg. of 2-methoxy-3-bromo-6-isopropyltropone (XIX) and 130 mg. of *o*-aminothiophenol in 3 ml. of methanol was allowed to stand for an hour. 300 mg. of red crystals was obtained after treatment using the same method as (a). These crystals showed no depression of melting point on admixture with a specimen obtained in (a).

c) After refluxing a solution of 50 mg. of XVII in 3 ml. of 2 N hydrochloric acid for 5 hr., the solution was extracted with benzene and the benzene extract was passed through an alumina column, affording 30 mg. of red needles, m. p. 92～93°C. The crystals showed no depression of melting point on admixture with XVIII.

Acetate (XXI) of XIII. — One hundred mg. of XIII were dissolved in 0.5 ml. of acetic anhydride, to which one drop of concentrated sulfuric acid was added, and then the mixture was allowed to stand at room temperature. After removing the acetic anhydride, the residue was dissolved in benzene and the benzene solution was passed through an alumina layer. The first elution gave unreacted XIII, but the second effluent afforded yellow prisms. Recrystallization of the latter crystals from methanol gave XXI as yellow prisms, m.p. 169.5～170.5°C.

Found: C, 66.62; H, 3.71; N, 5.36. Calcd. for $C_{15}H_{11}O_2NS$: C, 66.91; H, 4.12; N, 5.20%.

λ_{max}^{MeOH} mμ (log ε): 220 (4.39), 303 (4.04).

Benzoate (XXII) of XIII. — To a solution of 100 mg. of XIII in 1 ml. of pyridine, 0.2 ml. of benzoylchloride was added and heated for 20 min. The crystals separated out by adding water were dissolved into benzene and the insoluble portion was recrystallized from methanol, affording XXII as orange prisms, m. p. 193～194°C.

Found: C, 72.39; H, 3.71; N, 4.38. Calcd. for $C_{20}H_{13}O_2NS$: C, 72.50; H, 3.96; N, 4.23%.

λ_{max}^{MeOH} mμ (log ε): 220 (4.49), 308 (4.01).

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