Cycloheptathiazole Derivatives. III. The Synthesis of Cycloheptathiazol-8-one and Its Derivatives

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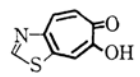
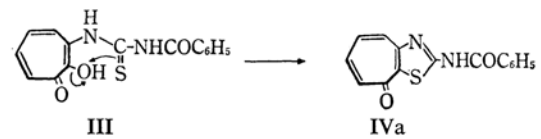
In the preceding papers of this series,[1,2] the syntheses of 7-hydroxycycloheptathiazol-6-one (I) and its 2-substituted derivatives were reported.



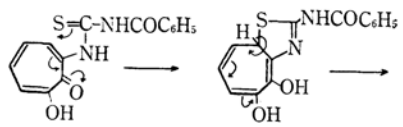
I

These series of compounds are interesting from the point of view of biological action and pharmacology, so the present authors have made a further investigation of the syntheses of another type of cycloheptathiazoles. This paper will describe the synthesis of cycloheptathiazol-8-one and its allied compounds.

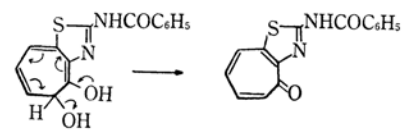
The reaction of 3-aminotropolone (II) with benzoylisothiocyanate gave *N*-tropolon-3-yl-*N'*-benzoylthiourea (III), which was easily dehydrated by the action of acid or alkali, or merely by heating, to afford a cyclization product (IV). The ultraviolet and infrared absorption spectra suggested that IV might be a tropone derivative with a fused ring. The fact that the oxidation of IV with potassium permanganate gave 2-benzamidothiazole-4, 5-dicarboxylic acid (V), which had been previously synthesized in an authentic route,[1] showed that IV should have a thiazole ring. Therefore, the product is likely to be 2-benzamidocycloheptathiazol-8-one (IVa). However, another type of cyclization product, cycloheptathiazol-4-one derivative (IVb) could not be excluded, since abnormalities have often been found in the cyclization reaction of troponoid compounds.[1,3]



III IVa



III



IVb

The following facts, however, exclude the structure IVb. 3-Aminotropolone (II) reacted smoothly with thiobenzoylthioacetic acid in the presence of alkali to give directly a cyclization product VI whose ultraviolet spectrum was similar to that of IV but quite different

1) S. Seto, Y. Nishiyama and K. Ogura, This Bulletin, **35**, 1998 (1962).

2) S. Seto, K. Ogura and Y. Nishiyama, ibid., **36**, 173 (1963).

3) T. Nozoe, S. Seto, S. Matsumura and T. Asano, *Proc. Japan Acad.*, **32**, 339 (1956); T. Nozoe et al., "Daiyukikagaku," Asakurashoten, Tokyo (1960), p. 182, etc.

from that of the 2-phenylcycloheptathiazol-4-one (VII) synthesized by Nozoe et al.[4] (Fig. 1). When VI was treated with alkali, 3-benzamidotropolone (VIII) was obtained. These facts show that VI must be 2-phenylcycloheptathiazol-8-one; consequently, IV probably has the structure IVa.

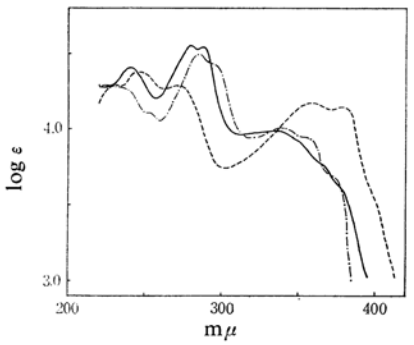
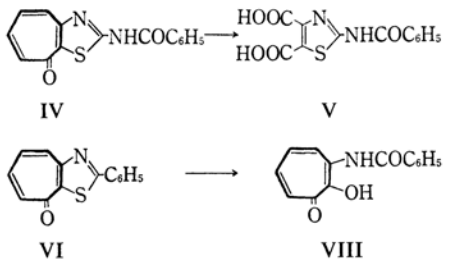


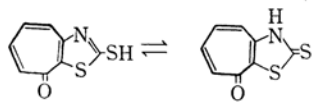
Fig. 1. Ultraviolet absorption spectra of IV (——), VI (·—·—·—·) and 2-phenylcycloheptathiazol-4-one[4] (------) in methanol.



IV V

VI VIII

The 2-benzamido derivative IV is stable to alkali, and the fission of the thiazole ring does not occur, even when it is heated in an alkaline solution, but a stable salt is formed. The warming of IV in concentrated sulfuric acid gave 2-aminocycloheptathiazol-8-one (IX). When 3-aminotropolone (II) was treated with carbon disulfide in the presence of alkali, yellow crystals of $C_8H_5ONS_2$(X), were obtained in a good yield. This substance is sparingly soluble in organic solvents and is fairly acidic. The infrared absorption spectrum exhibits multiplet absorption bands in the 2700~3100 cm^{-1} region due to its associated NH group, and the strongest absorption band corresponding to the carbonyl group shifted to a longer wave length region (1540 cm^{-1}) compared with those of IV and VI. The ultraviolet absorption spectrum of X is also markedly different from those of IV and VI. These facts indicate that X is probably 2-mercaptocycloheptathiazol-8-one, which exists as the thiazoline form Xb predominantly. This situation



Xa Xb

is quite similar to that of 2-mercaptobenzothiazole, which was tentatively investigated by Bellamy and Rogasch.[5] The ultraviolet absorption curve of X in methanol seems to correspond mainly to a stable anion formed by dissociation in the diluted solution, since the addition of acid causes a large hypsochromic shift, while the addition of alkali changes the spectrum only a few millimicrons.

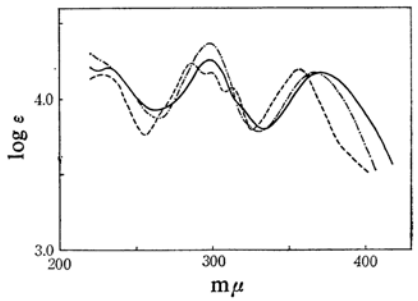
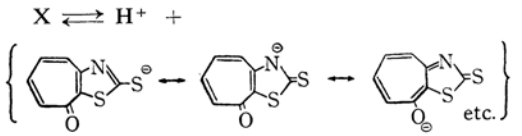


Fig. 2. Ultraviolet absorption spectra of X in methanol (——), in 0.1 N NaOH (·—·—·) and in 0.24 N HCl-MeOH (------).



The reaction of X with methyl iodide, benzyl chloride and monochloroacetic acid in the presence of alkali afforded *S*-methyl (XI), *S*-benzyl (XII) and *S*-carboxymethyl (XIII) derivatives respectively. All these compounds show ultraviolet absorptions of the same type as in the case of IV and VI. The treatment of X with thionyl chloride gave 2-chlorocycloheptathiazol-8-one (XIV), which was converted to 2-amino derivative (IX) by reaction with liquid ammonia. By this fact the relation between these compounds was established as is summarized in scheme 1. Finally, cycloheptathiazol-8-one (XV) was obtained by the treatment of X with hydrogen peroxide in *t*-butanol. The infrared absorption spectrum is shown in Fig. 4. Bis(cycloheptathiazol-8-on-2-yl)-disulfide (XVI) was also obtained by the reaction of X with hydrogen peroxide under rather mild conditions.

It is interesting to note that the ultraviolet absorption spectra of both XIV and XV are

4) T. Nozoe, T. Aso and K. Takahashi, This Bulletin, 35, 2003 (1962).

5) L. J. Bellamy and P. E. Rogasch, *Proc. Roy. Soc.*, 254, 103 (1960).

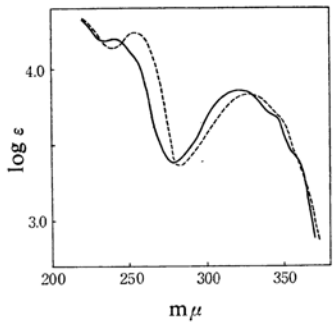
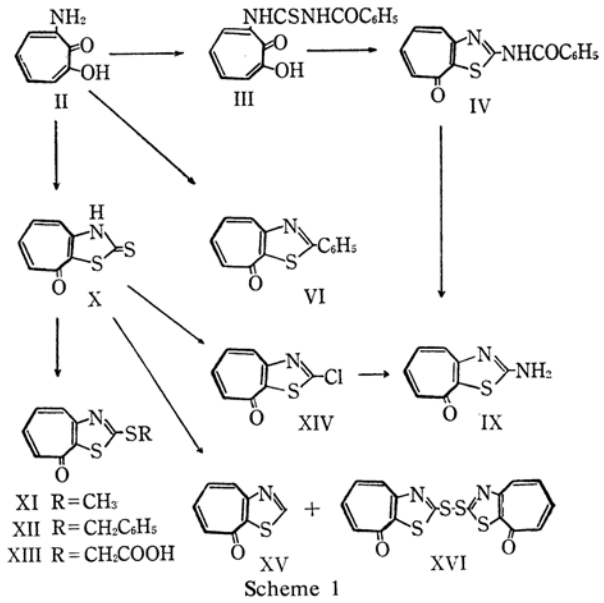


Fig. 3. Ultraviolet absorption spectra of XIV (------) and XV (——) in methanol.

of the tropone type and quite different from those of cycloheptathiazol-8-one derivatives replaced at the 2-position by an electron-releasing group. This seems to imply that the contribution of the conjugation between the



Scheme 1

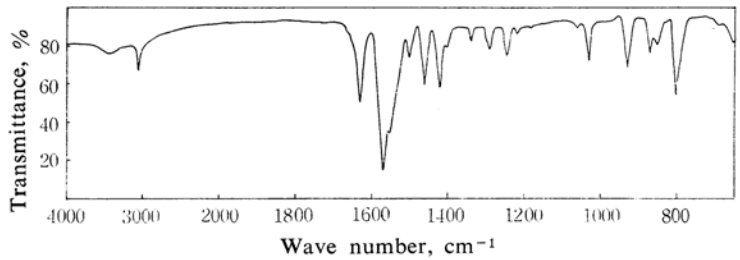
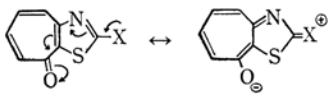
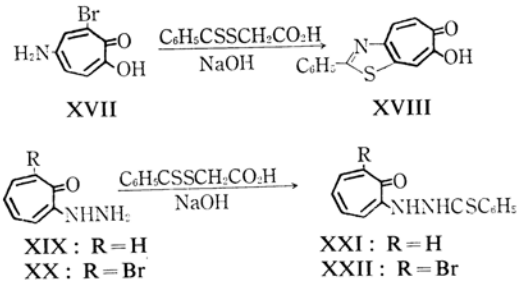


Fig. 4. Infrared absorption spectrum of XV in KBr disk.

electron-releasing group and the carbonyl group is very significant.



The reaction of thiobenzoylthioacetic acid with 3-bromo-5-aminotropolone (XVII) was also examined; it was found that the reaction proceeded easily in the presence of alkali at room temperature, furnishing 2-phenyl-7-hydroxycycloheptathiazol-6-one (XVIII) in the same manner as has been described in the preceding paper.[1] The elucidation of the structure was made by a comparison of its spectral data with those of the corresponding 7-hydroxycycloheptathiazol-6-one derivatives studied previously.[1] 2-Aminotropone did not react with thiobenzoylthioacetic acid, while 2-hydrazinotropone and its 7-bromo derivative reacted with the reagent to give *N*-thiobenzoyl derivatives, XXI and XXII respectively, which failed to be converted into any cyclization product.



Scheme 2

Experimental*

***N*-Tropolon-3-yl-*N'*-benzoylthiourea (III).**—A solution of II (100 mg.) and benzoylisothiocyanate (160 mg.) in ethanol (2 ml.) was stirred at 50~60°C for 1 hr. The yellow crystals that precipitated were collected and washed with methanol. This substance showed double melting point, 145~150°C and 260°C. Yield, 130 mg.

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

λ_{max}^{MeOH} mμ (log ε) : 268 (4.62), 380 (4.07).

Found : C, 60.30 ; H, 3.81 ; N, 9.08. Calcd. for $C_{15}H_{12}O_3N_2S$: C, 60.00 ; H, 4.03 ; N, 9.33%.

2-Benzamidocycloheptathiazol-8-one (IV). — a) When III (450 mg.) was stirred in a 50% aqueous sodium hydroxide solution (10 ml.), an orange precipitate was formed immediately. When this precipitate was gradually dissolved while being stirred at room temperature, yellow crystals soon separated out. After it had been stirred for 1 hr., the mixture was acidified with diluted hydrochloric acid, and the crystals were collected and recrystallized from ethanol to afford colorless crystals, m. p. 285~287°C (decomp.). Yield, 400 mg.

λ_{max}^{MeOH} mμ (log ε) : 240 (4.41), 279 (4.55), 289 (4.54), 340 (3.99).

Found : C, 63.10 ; H, 3.37 ; N, 9.81. Calcd. for $C_{15}H_{10}O_2N_2S$: C, 63.83 ; H, 3.57 ; N, 9.93%.

b) A solution of III (40 mg.) in concentrated sulfuric acid (0.5 ml.) was allowed to stand at room temperature overnight. The colorless precipitate that separated upon the addition of cracked ice to the solution was collected and recrystallized from ethanol. Yield, 30 mg.

c) A suspension of III (40 mg.) in ethanol (10 ml.) was refluxed for 30 min. ; the yellow prisms that separated out when it was cooled to room temperature were collected. Yield, 20 mg.

The Oxidation of IV with Potassium Permanganate.—To a solution of IV (40 mg.) in a 10% aqueous sodium hydroxide solution (1 ml.), a potassium permanganate solution (potassium permanganate, 100 mg. ; water, 2 ml.) was added ; this mixture was stirred at room temperature for 3 hr. After the decomposition of the excess permanganate by the addition of formalin, manganese dioxide was removed by filtration. The acidification of the filtrate with diluted hydrochloric acid, adjusted to pH 1, caused the precipitation of colorless crystals, which were identified with an authentic specimen of 2-benzamidothiazole-4, 5-dicarboxylic acid by a comparison of their infrared and ultraviolet spectra.[6]

2-Phenylcycloheptathiazol-8-one (VI).—A solution of II (100 mg.) and thiobenzoylthioacetic acid (180 mg.) in a 10% aqueous sodium hydroxide solution (1 ml.) was allowed to stand overnight ; the colorless needles which separated were then collected and recrystallized from ethanol to give colorless prisms, m. p. 138~139°C. Yield, 25 mg.

λ_{max}^{MeOH} mμ (log ε) : 240 (4.25 sh.), 285 (4.50), 295 (4.43 sh.), 340 (4.00).

Found : C, 70.60 ; H, 3.45 ; N, 5.70. Calcd. for $C_{14}H_9ONS$: C, 70.29 ; H, 3.79 ; N, 5.86%.

The Reaction of VI with Alkali. — When a mixture of VI (20 mg.) in a 30% aqueous potassium hydroxide solution (1 ml.) was heated on a water bath for a few minutes, a yellow precipitate appeared. After it had been cooled, the mixture was acidified with diluted hydrochloric acid, and the precipitate was collected. Recrystallization from ethanol gave pale yellow needles of m. p. 142~144°C, undepressed on admixture with 3-benzamidotropolone.

2-Aminocycloheptathiazol-8-one (IX). — A solution of IV (400 mg.) in concentrated sulfuric acid (4 ml.) was heated at 110°C for 4 hr. The brownish-yellow solution thereby obtained was poured into cracked ice and neutralized with a saturated sodium bicarbonate solution, and the precipitate was collected. The acidification of the filtrate gave colorless crystals of benzoic acid. The precipitate collected was recrystallized from methanol to afford yellow prisms, m. p. 225~245°C (decomp.). Yield. 100 mg.

λ_{max}^{MeOH} mμ (log ε) : 244 (4.10), 280 (4.38), 290 (4.32 sh.), 322 (3.91), 335 (3.91).

Found : C, 53.56 ; H, 3.68 ; N, 14.53. Calcd. for $C_8H_6ON_2S$: C, 53.93 ; H, 3.40 ; N, 15.73%.

2-Mercaptocycloheptathiazol-8-one (X).—A mixture of II (400 mg.), carbon disulfide (2 ml.) and ethanol (2.4 ml.) in a 10% aqueous sodium hydroxide solution (3 ml.) was stirred at room temperature for 2 hr. After the removal of the ethanol and the excess carbon disulfide under reduced pressure, the residual solution was acidified with diluted hydrochloric acid and adjusted to pH 3 ; the yellow precipitate thereby formed was collected and recrystallized from ethanol to give yellow scales, m. p. 255~300°C (decomp.). Yield, 550 mg.

λ_{max}^{MeOH} mμ (log ε) : 231 (4.21), 299 (4.25), 372 (4.16).

Found : C, 49.42 ; H, 3.17 ; N, 7.49. Calcd. for $C_8H_5ONS_2$: C, 49.24 ; H, 2.58 ; N, 7.18%.

2-Methylthiocycloheptathiazol-8-one (XI).—When a mixture of X (50 mg.), potassium carbonate (80 mg.) and methyl iodide (40 mg.) in water (1.5 ml.) was stirred at room temperature for 1.5 hr., a colorless precipitate appeared. This precipitate was collected and recrystallized from ethanol to give pale yellow prisms, m. p. 112~113°C. Yield, 40 mg.

λ_{max}^{MeOH} mμ (log ε) : 230 (4.20), 284 (4.36 sh.), 293 (4.38), 330 (3.96).

Found : C, 51.16 ; H, 3.15 ; N, 6.19. Calcd. for $C_9H_7ONS_2$: C, 51.68 ; H, 3.37 ; N, 6.76%.

2-Benzylthiocycloheptathiazol-8-one (XII).—A mixture of X (50 mg.), potassium carbonate (80 mg.) and benzyl chloride (40 mg.) in water (1.5 ml.) was stirred at 40°C for 2 hr. The precipitate thereby formed was collected and recrystallized from methanol to give pale yellow needles, m. p. 138~140°C. Yield, 40 mg.

λ_{max}^{MeOH} mμ (log ε) : 230 (4.26), 285 (4.33 sh.), 294 (4.37), 336 (4.00).

Found : C, 63.18 ; H, 3.88 ; N, 4.79. Calcd. for $C_{15}H_{11}ONS_2$: C, 63.16 ; H, 3.89 ; N, 4.91%.

2-Carboxymethylthiocycloheptathiazol-8-one (XIII).—A mixture of X (20 mg.), sodium carbonate (80 mg.) and monochloroacetic acid (30 mg.) in water (0.5 ml.) was stirred at room temperature for 1.5 hr. The solution thereby obtained was acidified with diluted hydrochloric acid and adjusted to pH ca. 2, and the precipitate was collected by filtration. Recrystallization from ethanol afforded pale yellow crystals, m. p. 233~235°C. Yield, 10 mg.

6) Y. Nishiyama and Y. Ikegami, *Bull. Chem. Res. Inst. Non-Aqu. Solns., Tohoku Univ.*, **12**, 43 (1963).

λ_{max}^{MeOH} mμ (log ε) : 235 (4.34), 285 (4.36 sh.), 295 (4.38), 338 (4.01).

Found : C, 47.93 ; H, 3.48 ; N, 5.73. Calcd. for $C_{10}H_7O_3NS_2$: C, 47.44 ; H, 2.79 ; N, 5.53%.

2-Chlorocycloheptathiazol-8-one (XIV). — To a solution of X (40 mg.) in dry benzene (0.5 ml.), thionyl chloride (0.3 ml.) was added, and the mixture was allowed to stand at room temperature for 1.5 hr. After the evaporation of benzene and the excess thionyl chloride, the residue was neutralized with an aqueous sodium bicarbonate solution and extracted with benzene. The combined benzene solution was evaporated and the residue was sublimed at 110°C under reduced pressure (3 mmHg). Recrystallization of the sublimate from benzene-petroleum ether gave colorless needles, m. p. 125~128°C. Yield, ca. 5 mg.

λ_{max}^{MeOH} mμ (log ε) : 255 (4.24), 332 (3.82).

Found : C, 48.58 ; H, 2.59 ; N, 7.19. Calcd. for C_8H_4ONSCl : C, 48.16 ; H, 2.02 ; N, 7.09%.

The Reaction of XIV with Liquid Ammonia.—A solution of XIV (10 mg.) in liquid ammonia (15 ml.) was allowed to stand at room temperature for 2 days. After the evaporation of the liquid ammonia, water (2 ml.) was added to the residue and the precipitate was collected and recrystallized from methanol to give yellow prisms, which were identified with 2-aminocycloheptathiazol-8-one (IX) by a comparison of their infrared absorption spectra.

Cycloheptathiazol-8-one (XV).—A mixture of X (50 mg.) and 30% hydrogen peroxide (0.2 ml.) in *t*-butanol (2 ml.) was heated at 90°C for 2 hr. Then the color of the precipitate gradually faded, and finally all the precipitate was dissolved. After the evaporation of the solvent under reduced pressure, the residue was neutralized with sodium carbonate and extracted with ether. The combined ether solution, after being dried over sodium sulfate, was passed through a column of alumina. The evaporation of the eluate left colorless needles, which were collected and recrystallized from benzene-petroleum ether to give colorless needles, m. p. 134~138°C. Yield, 10 mg.

λ_{max}^{MeOH} mμ (log ε) : 240 (4.20), 320 (3.85).

Found : C, 58.26 ; H, 3.29 ; N, 8.18. Calcd. for C_8H_5ONS : C, 58.90 ; H, 3.09 ; N, 8.59%.

Bis(cycloheptathiazol-8-on-2-yl)disulfide (XVI).—A mixture of X (50 mg.) and 30% hydrogen peroxide (0.2 ml.) in *t*-butanol (2 ml.) was warmed while being stirred at 80°C for 10 min. The colorless crystals thereby formed were collected and washed with hot methanol, m. p. 200~203°C. Yield, 20 mg.

Found : C, 49.22 ; H, 2.40 ; N, 7.10. Calcd. for $C_{16}H_8O_2N_2S_4$: C, 49.46 ; H, 2.08 ; N, 7.21%.

2-Phenyl-7-hydroxycycloheptathiazol-6-one (XVIII).—A solution of XVII (100 mg.) and thiobenzoylthioacetic acid (100 mg.) in a 2 N sodium hydroxide solution (0.8 ml.) and water (2 ml.) was allowed to stand at room temperature for 30 min. A yellow precipitate began to separate out after about 10 min. After the mixture had been neutralized with diluted sulfuric acid and adjusted to pH 2, the precipitate was collected and recrystallized from acetone-methanol to give pale yellow crystals, m. p. 220~222°C. Yield, 120 mg. The filtrate contained one atom equivalent of bromide ions.

λ_{max}^{MeOH} mμ (log ε) : 268 (4.54), 380 (4.35).

Found : C, 65.70 ; H, 3.34 ; N, 5.40. Calcd. for $C_{14}H_9O_2NS$: C, 65.88 ; H, 3.55 ; N, 5.49%.

***N*-(Tropon-2-yl)-*N'*-thiobenzoylhydrazide (XXI).**—When a mixture of 2-hydrazinotropone (50 mg.) and thiobenzoylthioacetic acid (50 mg.) in a 5% sodium hydroxide solution (2 ml.) was stirred for 1 hr., orange crystals appeared. After the neutralization of the mixture with diluted hydrochloric acid, the crystals were collected and recrystallized from ethanol to give yellow needles, m. p. 169~170°C. Yield, 50 mg.

λ_{max}^{MeOH} mμ (log ε) : 234 (4.46), 457 (4.38).

Found : C, 65.27 ; H, 4.73 ; N, 10.70. Calcd. for $C_{14}H_{12}ON_2S$: C, 65.62 ; H, 4.72 ; N, 10.93%.

***N*-(7-Bromotropon-2-yl)-*N'*-thiobenzoylhydrazide (XXII).**—When a mixture of 2-hydrazino-7-bromotropone (50 mg.) and thiobenzoylthioacetic acid (50 mg.) in a 5% sodium hydroxide solution (2 ml.) was stirred at room temperature for 1 hr., orange scales appeared. The crystals were collected and acidified with diluted hydrochloric acid to yield a yellow powder, which was collected by filtration and recrystallized from methanol to afford orange scales, m. p. 272~273°C. Yield, 50 mg.

Found : C, 50.06 ; H, 3.33 ; N, 7.85. Calcd. for $C_{14}H_{11}ON_2SBr$: C, 50,15 ; H, 3.31 ; N, 8.36%.

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