Cycloheptathiazole Derivatives. I. Synthesis of 7-Hydroxycyclohepta-[d]thiazol-6-one and its Derivatives

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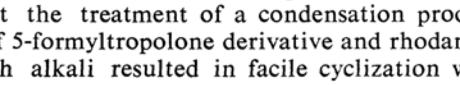
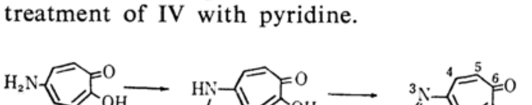
Tropolone derivatives with fused thiazole ring would be interesting compounds from the point of biology and pharmacology, but none has been reported to date. One of the authors (K. O.) found a noteworthy phenomenon during studies on 5-formyltropolone derivatives[1] that the treatment of a condensation product I of 5-formyltropolone derivative and rhodanine with alkali resulted in facile cyclization with liberation of bromide ion to form a thiophene derivative II.



I : R=Br or *i*-Pr II

It was thought that this type of reaction might be utilizable for the synthesis of tropolone derivatives with a fused thiazole ring. Therefore, thiourea derivatives obtained from 3-bromo-5-aminotropolone (III) were treated with a base and structure of the products was examined. It was thereby found that the reaction had proceeded as expected and tropolone derivatives with a fused thiazole ring could certainly be obtained. The cyclization was effected in one step by the reaction of III and carbon disulfide, and a tropolone derivative with a fused thiazole ring was obtained. This cyclization reaction and structural determination of its products will be described herein.

Treatment of III with benzoyl isothiocyanate and ethoxycarbonyl isothiocyanate in methanol respectively affords *N*-(3-bromotropolon-5-yl)-*N*'-benzoylthiourea (IV) and *N*-(3-bromotropolon-5-yl)-*N*'-ethoxycarbonylthiourea (V). By stirring IV in aqueous alkali solution at room temperature, the substance dissolves once to form an orange-yellow solution and yellow alkali salt begins to precipitate out after a few hours. The filtrate left after removal of this salt contains one atom equivalent of bromide ion. Treatment of this salt with an acid gives pale yellow crystals (VI), whose analytical values correspond to the formula of $C_{15}H_{10}O_3N_2S$. The ultraviolet spectrum of VI (Fig. 1) suggests the presence of a tropolone ring in VI. Compound VI is also obtained on treatment of IV with pyridine.



III IV : R=COC_6H_5 VI : R=COC_6H_5
V : R=$COOC_2H_5$ VII : R=$COOC_2H_5$
VIII : R=H

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[1] K. Ogura, This Bulletin, 35, 808 (1962).

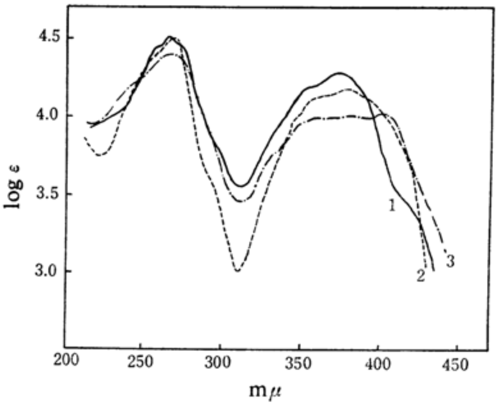
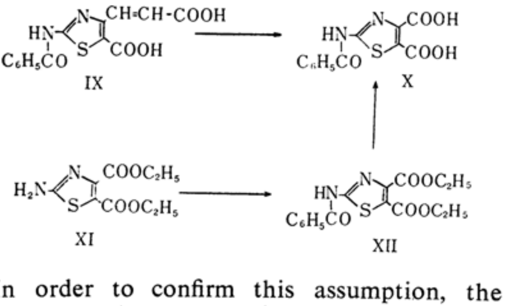


Fig. 1. The ultraviolet absorption spectra in methanol.
1 : VI 2 : VIII 3 : XIX

Thiourea derivative V undergoes similar reactions with alkali to form VII whose ultraviolet spectrum is similar to that of VI, indicating that VI and VII have a common skeleton. In fact, heating of VI and VII with concentrated sulfuric acid results in the formation of identical yellow crystals (VIII). While VI is stable to alkali and is recovered unchanged even when heated at 200°C, VII forms VIII on being heated with alkali.

In order to prove the presence of a thiazole ring in VI, its oxidative degradation was carried out. Oxidation of VI with alkaline hydrogen peroxide afforded a dicarboxylic acid (IX). If a cleavage had occurred in this case as in the oxidation of fused-ring tropolones with alkaline hydrogen peroxide[1,2], IX should be 2-benzamido-4-(β-carboxyvinyl)-5-carboxythiazole. Further oxidation of IX with alkaline potassium permanganate afforded a dicarboxylic acid (X), which was assumed to be 2-benzamido-4,5-dicarboxythiazole.

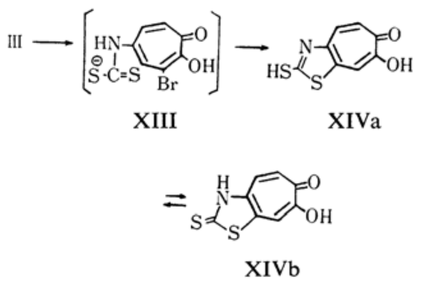


In order to confirm this assumption, the known 2-amino-4,5-bis(ethoxycarbonyl)thiazole[3] was benzoylated to XII which was hydrolyzed to form the structurally reliable 2-benzamido-4,5-dicarboxythiazole. The product (X) was found to be completely identical with this 2-benzamido-4,5-dicarboxythiazole through mixed melting point and by comparison of infrared and ultraviolet spectra.

The foregoing facts have shown that VI has a thiazole ring, as anticipated, and VI, VII and VIII were proved respectively as the 2-benzamido, 2-ethoxycarbamido, and 2-amino derivatives of 7-hydroxycyclohepta[d]thiazol-6-one.

Reaction of III and carbon disulfide, in the presence of a tertiary amine, will now be described. In this case, as in the reaction of amines in general and carbon disulfide, formation of a dithiocarbamate XIII may be expected.

However, as was witnessed in the case of IV and V, formation of a thiazole ring by the liberation of hydrogen bromide is very facile and there is a possibility that the reaction would proceed on to XIV without stopping at XIII.



Reaction of III and carbon disulfide in pyridine, evaporation of pyridine and excess carbon disulfide from the reaction mixture, and addition of dilute sulfuric acid to its residue precipitated yellow crystals (XIV). The filtrate left after removal of XIV contained one atom equivalent of bromide ion. The analytical values of XIV corresponded to the molecular formula of $C_8H_5O_2NS_2$. This fact supports the assumption that the reaction had progressed to cyclization and that XIV would be a 2-mercaptothiazole derivative. Ultraviolet spectrum of XIV is different from that of VI and exhibits absorption in a longer wavelength region. The ultraviolet spectrum of the *S*-methyl derivative XV, obtained by application of dimethyl sulfate to XIV in the presence of alkali, is similar to that of VI. Consequently, XIV may be assumed to have a thiazole ring. This assumption was found to be correct from following facts. Oxidation of XIV with hydrogen peroxide gives sparingly soluble substance (XVI) and easily soluble pale yellow crystals (XVII). Analytical values of XVII correspond to $C_8H_5O_2NS$ and the substance is assumed to be 7-hydroxycyclohepta[d]thiazol-6-one. It is known that application of hydroxylamine to

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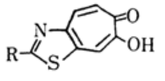
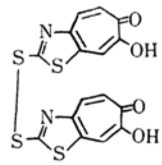
[2] H. Fernholz, E. Hartwig and J. C. Salfeld, *Ann.*, **576**, 131 (1952); J. W. Cook, A. R. M. Gibb, R. A. Raphael and A. R. Sommerville, *J. Chem. Soc.*, **1952**, 603.

[3] L. H. Conover and D. S. Tarbell, *J. Am. Chem. Soc.*, **72** 5222 (1950).

benzothiazole in the presence of alkali results in the formation of 2-aminobenzothiazole[4]. If XVII were a thiazole derivative as



XV : R=SCH_3
XVII : R=H
XVIII : R=SCH_2COOH



XVI

anticipated it should form a 2-aminothiazole derivative VIII by reaction with hydroxylamine, as in the case of benzothiazole. Experimental result showed that this assumption had been correct and the structure of XVII and XIV was therefore proved.

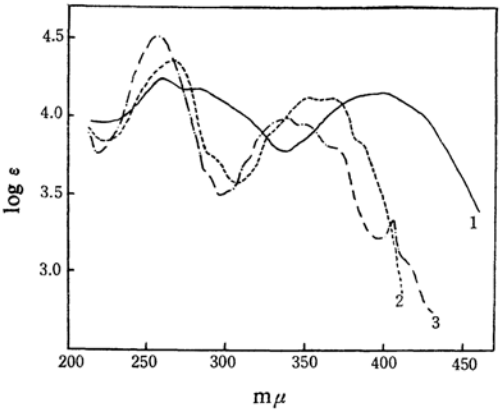
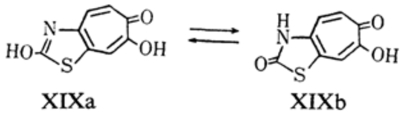


Fig. 2. The ultraviolet absorption spectra in methanol.
1 : XIV 2 : XV 3 : XVII

Compound XVI is assumed to be a disulfide derivative from its analytical values, and ultraviolet and infrared spectra.

Application of chloroacetic acid to XIV in the presence of sodium hydrogencarbonate gives a 2-carboxymethylthio derivative XVIII, which remains unchanged on treatment with liquid ammonia at room temperature but forms a 2-hydroxyderivative XIX on being heated with an acid.



XIXa XIXb

Experimental[5]

***N*-(3-Bromotropolon-5-yl)-*N′*-benzoylthiourea (IV).**—A solution of 1.2 g. of benzoyl isothiocyanate dissolved in 10 ml. of methanol was added dropwise into 1.2 g. of 3-bromo-5-aminotropolone (III) suspended in 50 ml. of methanol, maintained at 50°C, while stirring, during ca. 1 hr. The mixture was stirred for subsequent 3 hr., cooled to room temperature, and crystals that precipitated out were collected by filtration. The crystals were washed with a small amount of methanol and was obtained as pale yellow needles, m. p. 340°C (decomp.). Yield, 1.5 g.

Found : C, 47.75 ; H, 3.02 ; N, 6.60. Calcd. for $C_{15}H_{11}O_3N_2BrS$: C, 47.48 ; H, 2.92 ; N, 7.39%.

UV λ_{max}^{MeOH} mμ(log ε) : 258(4.54), 350(4.07).

***N′*-(3-Bromotropolon-5-yl)-*N*-ethoxycarbonylthiourea (V).**—To a suspension of 0.8 g. of III in 40 ml. of methanol, 1.5 g. of ethoxycarbonyl isothiocyanate was added dropwise during 30 min., while the suspension was stirred at 40°C, and the mixture was stirred at the same temperature for subsequent 1 hr. The mixture was cooled, precipitated crystals were collected, and washed a small amount of methanol to pale yellow scales (V), m. p. 280°C (decomp.). Yield, 1.1 g.

Found : C, 38.31 ; H, 3.23 ; N, 7.60. Calcd. for $C_{11}H_{11}O_4N_2BrS$: C, 38.03 ; H, 3.19 ; N, 8.07%.

UV λ_{max}^{MeOH} mμ (log ε) : 254 (4.51), 350 (4.05).

2-Benzamido-7-hydroxycyclohepta[d]thiazole-6-one (VI).—a) A mixture of 0.1 g. of IV and 4 ml. of 2 N sodium hydroxide was stirred, by which the mixture went into solution, coloring orange yellow. After about 10 min., orange-yellow crystals began to separate out. The mixture was stirred for 1 hr. at room temperature and the orange-yellow crystals were collected by filtration. The crystals were suspended in 4 ml. of water, the solution was adjusted to pH 3 with 6 N sulfuric acid, by which the solid became pale yellow, and the mixture was stirred for about 20 min. The solid was collected and washed with water to VI as pale yellow microcrystals, m. p. 340°C (decomp.). Yield, 75 mg.

Found: C, 60.36; H, 3.20; N, 9.27; S, 10.51. Calcd. for $C_{15}H_{10}O_3N_2S$: C, 60.37; H, 3.38; N, 9.40; S, 10.79%.

UV λ_{max}^{MeOH} mμ (log ε) : 264 (4.51), 375 (4.27).

b) A mixture of 0.1 g. of IV and 0.4 ml. of pyridine was warmed at 40°C for 2 hr., 3 ml. of water was added, and the solution was adjusted to pH 3 with 6 N sulfuric acid. The crystals of VI that separated out were collected and washed with water. Yield, 70 mg.

2-Ethoxycarbamido-7-hydroxycyclohepta [d] thiazol-6-one (VII).—A mixture of 0.8 g. of V in a solution of 1.2 g. of sodium hydroxide in 4 ml. of water was stirred for 1 hr. at room temperature and the orange yellow crystals sodium salt that separated out was collected by filtration. This sodium salt was suspended in 10 ml. of water, the solution was adjusted to pH 3 with 6 N sulfuric acid, and the mixture was stirred for 30 min. The solid that separated was collected by filtration and washed with water to give VII as pale yellow

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[4] S. Skraup, *Ann.*, **419**, 1 (1920).

[5] All melting points are uncorrected. Microanalyses were carried out by Misses Yôko Endô and Yukiko Endô of this Institute, and microanalyses of sulfur were made in Takamine Research Laboratory of Sankyo Co., Ltd., to whom the present authors are indebted. Ultraviolet spectra were measured with a Hitachi EPU-2A type spectrophotometer.

microcrystals, m. p. 313°C (decomp.). Yield, 0.57 g.

Found: C, 49.89; H, 4.02; N, 10.32. Calcd. for $C_{11}H_{10}O_4N_2S$: C, 49.63; H, 3.79; N, 10.52%.

UV λ_{max}^{MeOH} mμ (log ε): 268 (4.45), 371 (4.11).

2-Amino-7-hydroxycyclohepta [d] thiazol-6-one (VIII).—a) A mixture of 40 mg. of VI in 0.2 g. of concentrated sulfuric acid was heated at 120°C for 5 hr. and 3 g. of ice was added to the mixture, by which the sulfate of VIII separated out as colorless crystals. Without collecting these crystals, the mixture was adjusted to pH 4 with ammonia water and cooled in ice. The yellow crystals that separated out were collected and washed with water to give VIII as yellow crystals, m. p. 280～285°C (decomp.). Yield, 20 mg.

Found: C, 49.65; H, 2.98; N, 13.85. Calcd. for $C_8H_5O_2N_2S$: C, 49.47; H, 3.12; N, 14.43%.

UV λ_{max}^{MeOH} mμ (log ε): 272 (4.52), 383 (4.17).

VIII colors brown with ferric chloride in methanol.

b) A mixture of 50 mg. of VII in 0.2 g. of concentrated sulfuric acid was heated at 110°C for 1 hr. and treated as in above method a), from which 30 mg. of VIII was obtained.

c) A mixture of 100 mg. of VII, 300 mg. of potassium hydroxide, and 1 ml. of water was heated at 130°C for 2 hr., diluted with 5 ml. of water, and adjusted to pH 4 with 6 N sulfuric acid. The crystals that separated out were collected and washed with water to 70 mg. of VIII.

d) A mixture of 20 mg. of XVII, 0.4 ml. of 2 N sodium hydroxide, 0.6 ml. of water, and 10 mg. of hydroxylamine hydrochloride was heated at 110°C for 1 hr., cooled, and yellow crystals (sodium salt of VIII) that separated out were collected by filtration. The crystals were suspended in water, the mixture was adjusted to pH 4 with acetic acid, and the free VIII that separated out were collected by filtration and washed with water. Yield, 18 mg.

This substance was found to be identical with VIII, obtained by the foregoing methods a), b) and c), through mixed melting point and by comparison of thier ultraviolet and infrared spectra.

Oxidation of VI with Hydrogen Peroxide.—A mixture of 100 mg. of VI, 200 mg. of potassium hydroxide, and 10 ml. of water, in which the potassium salt of VI is sparingly soluble in water and the majority remains as a solid in suspension, was stirred and 30% hydrogen peroxide was added in drops. One milliliter of hydrogen peroxide was added every 12 hr. until a total of 4 ml. was added, when the reaction mixture formed a pale yellow solution. 6 N Sulfuric acid was added to the mixture under ice-cooling to adjust the solution to pH 2 and 40 mg. of crystals, m. p. 220～223°C (decomp.), that separated out was collected. Recrystallization from methanol gave 2-benzamido-4-(β-carboxyvinyl)-5-carboxythiazole (IX) as colorless crystals, m. p. 229～230°C (decomp.) Yield, 20 mg.

Found: C, 50.48; H, 2.99; N, 8.53. Calcd. for $C_{14}H_{10}O_5N_2S$: C, 52.83; H, 3.17; N, 8.80%.

UV λ_{max}^{MeOH} mμ (log ε): 240 (4.23), 301 (4.24).

2-Benzamido-4, 5-dicarboxythiazole (X).—a) To a solution of 15 mg. of IX dissolved in 0.08 ml. of 2 N sodium hydroxide, 0.6 ml. of 5% aqueous solution of potassium permanganate was added and the mixture was allowed to stand at room temperature. After 1 hr., manganese dioxide that separated out was filtered off, the filtrate was adjusted to pH 2 with dilute sulfuric acid, and the mixture was allowed to stand overnight in an ice box. The colorless crystals that separated out were collected by filtration, washed with water, and recrystallized from hydrous methanol to X as colorless crystals, m. p. 283～285°C (decomp.). Yield, 5 mg. This substance was identical with X obtained by the following method b), through mixed melting point and by comparison of ultraviolet and infrared spectra.

b) To a solution of 60 mg. of 2-amino-4, 5-bis-(ethoxycarbonyl)thiazole (XI) dissolved in 0.35 ml. of pyridine, 0.15 ml. of benzoyl chloride was added dropwise with stirring at room temperature, the mixture was stirred for further 15 min., and allowed to stand at room temperature. Pyridine was evaporated in a reduced pressure, 2 g. of ice was added to the residue, and colorless crystals that separated out were recrystallized from 50% methanol to 2-benzamido-4, 5-bis(ethoxycarbonyl)thiazole (XII) as colorless crystals, m. p. 151～153°C. Yield, 60 mg.

Found: C, 55.42; H, 4.51; N, 7.67. Calcd. for $C_{16}H_{16}O_5N_2S$: C, 55.17; H, 4.63; N, 8.04%.

UV λ_{max}^{MeOH} mμ (log ε): 232 (4.18), 301 (4.25).

A mixture of 50 mg. of XII, 3 ml. of ethanol, and 230 mg. of potassium hydroxide was allowed to stand overnight at room temperature, ethanol was evaporated in reduced pressure, and the residue was dissolved in 3 ml. of water. The solution was adjusted to pH 2 with dilute sulfuric acid, the crystals that separated out were collected by filtration, and washed with water. Recrystallization from hydrous methanol gave X as colorless crystals, m. p. 285°C (decomp.). Yield, 35 mg.

Found: C, 49.47; H, 2.86; N, 9.29. Calcd. for $C_{12}H_8O_5N_2S$: C, 49.32; H, 2.76; N, 9.59%.

UV λ_{max}^{MeOH} mμ (log ε): 235 (4.25), 301 (4.17).

2-Mercapto-7-hydroxycyclohepta[d]thiazol-6-one (XIV).—a) A mixture of 1 g. of 3-bromo-5-aminotropolone (III), 8 ml. of pyridine, and 1.2 ml. of carbon disulfide was stirred at room temperature for 1 hr., and then maintained at 45°C for 1 hr., and pyridine and excess carbon disulfide were evaporated in a reduced pressure. Water was added to the residue, the solution was adjusted to pH 2 with 6 N sulfuric acid, and the yellowish brown solid (XIV), m. p. 305～310°C (decomp.), was collected by filtration and washed with water. Yield, 0.95 g.

Found: C, 44.34; H, 2.59; N, 6.24. Calcd. for $C_8H_5O_2NS_2$: C, 45.51; H, 2.39; N, 6.63%.

UV λ_{max}^{MeOH} mμ (log ε): 258 (4.23), 280 (4.17), 390 (4.14), 400 (4.14).

b) A mixture of 30 mg. of III, 1 ml. of triethylamine, and 0.1 ml. of carbon disulfide was maintained at 50°C for 2 hr. and excess of the reagents was evaporated in a reduced pressure. The residue was added with 2 ml. of water, adjusted to pH 2 with 6 N sulfuric acid, and the yellowish brown solid (XIV) that separated out was collected. Yield, 26 mg.

2-Methylthio-7-hydroxycyclohepta[d]thiazol-6-one (XV).—To a solution of 200 mg. of XIV dissolved in a mixture of 6 ml. of 2 N sodium hydroxide and 4 ml. of water, 380 mg. of dimethyl sulfate was added with stirring under ice-cooling and yellowish orange crystals began to separate out after 1 hr. The mixture was stirred for 2 hr., diluted with 15 ml. of water to dissolved the crystals and treated with activated carbon. The filtrate was adjusted to pH 2 with 6 N sulfuric acid by which yellow precipitate formed. After standing the mixture in an ice box over night, the precipitate was collected and washed with water. This precipitate was sublimed at 140°C (bath temp.)/2 mmHg and the sublimate was redrystallized from ether to XV as pale yellow crystals, m. p. 191∼193°C. Yield, 190 mg.

Found: C, 47.76; H, 3.11; N, 6.35. Calcd. for $C_9H_7O_2NS_2$: C, 48.01; H, 3.13; N, 6.22%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 267 (4.35), 355 (4.10), 365 (4.11).

2-Carboxymethylthio-7-hydroxycyclohepta[d]thiazol-6-one (XVIII).—To a mixture of 200 mg. of XIV, 400 mg. of sodium hydrogen carbonate, and 5 ml. of water, 200 mg. of monochloroacetic acid was added with stirring, and the mixture was stirred for subsequent 3 hr. at room temperature. The reaction mixture remained a suspension at first but went completely into solution 2 hr. later. The solution was adjusted to pH 2 with 6 N sulfuric acid, by which a precipitate formed, and the mixture was allowed to stand in an ice box overnight. The precipitate was collected by filtration, washed with water, and XVIII was obtained as a pale yellow solid, m. p. 245∼250°C (decomp.). Yield, 250 mg.

Found: C, 43.67; H, 2.56; N, 5.01. Calcd. for $C_{10}H_7O_4NS_2$: C, 44.62; H, 2.62; N, 5.20%:

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 268 (4.44), 370 (4.22).

Reaction of XIV and Hydrogen Peroxide.—A mixture of 80 mg. of XIV, 3 ml. of *t*-butanol, and 0.4 ml. of 30% hydrogen peroxide was heated at 90°C for 15 hr. When cooled, 40 mg. of yellow insoluble matter (XVI), m. p. 230°C (decomp.), was collected by filtration.

Found: C, 44.88; H, 2.48; N, 6.55. Calcd. for $C_{16}H_8O_4N_2S_4$: C, 45.51; H, 2.28; N, 6.63%.

t-Butanol was evaporated in a reduced pressure from the filtrate left after removal of XVI, a small amount of water was added to the residue, and the solution was adjusted to pH 3 with sodium hydrogen carbonate. This was extracted with ethyl acetate, the solvent was evaporated from the extract, and the residue was sublimed at 120°C (bath temp.)/1 mmHg. The sublimate was recrystallized from methanol to 7-hydroxycyclohepta[d]thiazol-6-one (XVII) as pale yellow needles, m. p. 162∼163°C. Yield, 20 mg.

Found: C, 53.86; H, 2.76; N, 7.77; S, 17.68. Calcd. for $C_8H_5O_2NS$: C, 53.64; H, 2.81; N, 7.82; S, 17.90%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 258 (4.50), 340 (3.96).

The benzene solution of XVII colored brownish red in the organic layer with ferric chloride.

2,7-Dihydroxycyclohepta[d]thiazol-6-one (XIX).—a) A mixture of 30 mg. of XIV and 0.1 ml. of 85% phosphoric acid was heated at 160∼170°C for 11 hr., cooled and diluted with a small amount of water. The mixture was adjusted to pH 4 with ammonia water under ice-cooling, the black precipitate that formed was collected, and washed with water. The precipitate was sublimed at 200°C (bath temp.)/1 mmHg and the yellow sublimate was recrystallized from ethyl acetate. m. p. 275∼278°C (decomp). Yield, 10 mg.

Found: C, 49.20; H, 2.92; N, 7.12. Calcd. for $C_8H_5O_3NS$: C, 49.24; H, 2.58; N, 7.18%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 265.5 (4.43), 355 (3.99), 370 (3.99), 384 (4.00), 402 (4.01).

The ethyl acetate solution of XIX colors green in the aqueous layer by addition of aqueous solution of ferric chloride.

b) A mixture of 100 mg. of XVIII, 9 ml. of concentrated hydrochloric acid, and 3 ml. of water was heated at 120°C for 8 hr., cooled and insoluble matter was filtered off. The filtrate was evaporated to dryness in a reduced pressure, the residue was dissolved in water, and the solution was adjusted to pH 4 with ammonia water. The solid (A) that separated out was collected by filtration.

The filtrate left after removal of A was extracted with ethyl acetate and the solvent was evaporated from this extract. This residue was combined with A and sublimed at 200°C (bath temp.)/1 mmHg. The yellow crystalline sublimate was recrystallized from ethyl acetate. Yield, 40 mg.

Summary

It has been found that treatment of 3-bromotropolon-5-yl-thiourea derivatives with a base resulted in facile formation of 7-hydroxycyclohepta[d]thiazol-6-one derivatives, with liberation of hydrogen bromide. Out of such products, 2-benzamido derivative was submitted to oxidative degradation and its structure was confirmed.

Reaction of 3-bromo-5-aminotropolone and carbon disulfide, in the presence of a tertiary amine, was found to form a 2-mercapto derivative. Correlation of this product with the foregoing products proved the structure.

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