Cycloheptathiazole Derivatives. II. Synthesis of a Seven-membered Analog of Firefly Luciferin

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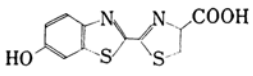
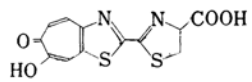
In the preceding paper of this series[1], syntheses of cyclohepta[d]thiazole derivatives from 3-bromo-5-aminotropolone were described. As a further investigation of this series, the synthesis of a seven-membered analog of firefly luciferin[2] was reported. Since tropolone is similar to phenol in their chemical properties, it would be interesting from the point of biological actions to synthesize such a compound as II which has a tropolone ring in place of the phenol ring in luciferin (I).



I

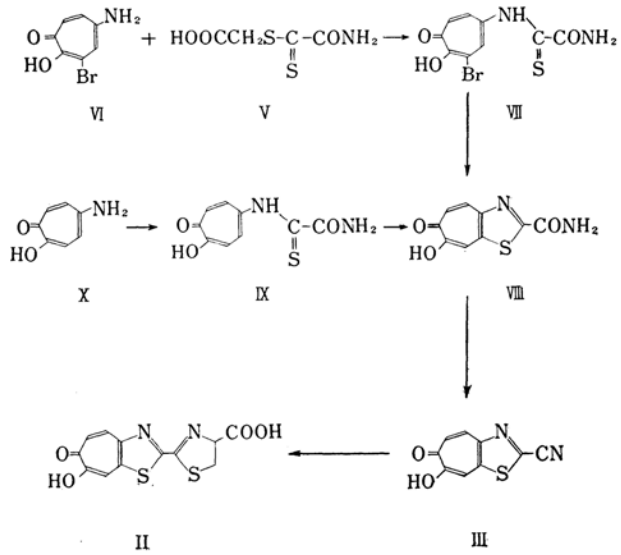


II

For this purpose the preparation of 2-cyano-7-hydroxycyclohepta[d]thiazol-6-one (III) is desirable, for it can be expected that III reacts with cysteine to afford II in the same manner described in the synthesis of I [2,3]. 2-Amino-7-hydroxycyclohepta[d]thiazol-6-one (IV) which has been easily obtained[1] seems apparently suitable for the starting material, but application of Sandmeyer reaction on IV was not successful. As the authors found a convenient method of carbamoylthiocarbonylation of aromatic amines by using carbamoylthiocarbonylthioacetic acid (V), this method was applied to 3-bromo-5-aminotropolone (VI). The reagent V reacted with VI in alkaline solution at room temperature, and *N*-(3-bromotropolon-5-ylthiocarbamoyl)carbamide (VII) was obtained. It shows absorption bands at 3390, 3240 and 1706 cm^{-1} due to its amide group.

Treatment of VII with pyridine resulted in intramolecular nucleophilic reaction[1] to give 2-carbamoyl-7-hydroxycyclohepta[d]thiazol-6-one (VIII). The structure of VIII was confirmed by comparison of its infrared and ultraviolet absorption spectra with those of

1) S. Seto, Y. Nishiyama and K. Ogura, This Bulletin, 35, 1998 (1962).
2) E. H. White, F. McCapra, G. F. Field and W. D. McElroy, *J. Am. Chem. Soc.*, 83, 2402 (1961).
3) S. Seto, K. Ogura and Y. Nishiyama, This Bulletin, in press.



cycloheptathiazole derivatives obtained previously[1]. The amide VIII could be also prepared by the action of bromine to a pyridine solution of *N*-(tropolon-5-ylthiocarbamoyl)carbamide (IX) which was obtained by the reaction of 5-aminotropolone (X) and the reagent V. Infrared spectrum of VIII exhibits absorption at 3370, 1690 and 1665 cm^{-1} for its amide residue, and other absorption bands correspond to those of the known cycloheptathiazole derivatives[1]. Reaction of VIII with phosphorus oxychloride gave 2-cyano-7-hydroxycyclohepta-[d]thiazol-6-one (III), which showed absorptions at 3190 and 2230 cm^{-1} due to a hydroxyl group on tropolone nucleus and a cyano group respectively. The reaction of III with D-cysteine proceeded smoothly in the same way as in the case of 2-cyano-6-hydroxybenzothiazole[2,3], and the analog II was obtained as pale yellow granular crystals. II shows absorption bands at 3200 cm^{-1} for a hydroxyl group in tropolone ring and at 2600 (broad) and 1734 cm^{-1} for a carboxyl group. Ultraviolet spectrum of II is similar to those of III, VIII and other cycloheptathiazoles obtained previously[1].

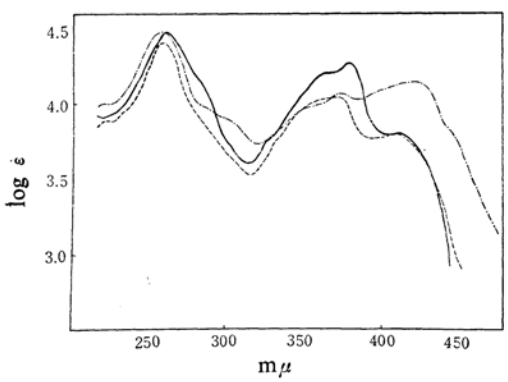


Fig. 1. Ultraviolet spectra of II(——), III(·-·-) and VIII(----) in methanol.

Alkaline solutions of 2-cyano-6-hydroxybenzothiazole and luciferin exhibit greenish blue luminescence on exposure to ultraviolet light[3], while neither II nor III shows such property.

Experimental*

***N*-(3-Bromotropolon-5-ylthiocarbamoyl)carbamide (VII).**—To a solution of VI (500 mg.) in aqueous potassium hydroxide (potassium hydroxide, 130 mg.; water, 2 ml.), the reagent V prepared from 800 mg. of trichloroacetamide was added, and the mixed solution was allowed to stand at room temperature overnight. Orange crystals that formed was collected, and it was acidified with 6 N sulfuric acid to give yellow powder, which was collected, washed well with hot methanol, 200°C (darken). Yield, 270 mg. Evaporation of the methanol filtrate gave 130 mg. of the starting material VI. λ_{max}^{MeOH} mμ (log ε) : 253 (4.34), 420 (4.23).

Found: C, 35.52; H, 2.46; N, 8.56. Calcd. for $C_9H_7O_3N_2SBr$: C, 35.62; H, 2.31; N, 9.24%.

2-Carbamoyl-7-hydroxycyclohepta[d]thiazol-6-one (VIII).—a) When a solution of VII (270 mg.) in pyridine (4.2 ml.) was allowed to stand at room temperature for two days, yellow crystals deposited. The crystals were collected, washed with pyridine, water and hot methanol to afford pale yellow prisms, m. p. 317~325°C (decomp.). Yield, 100 mg. λ_{max}^{MeOH} mμ (log ε) : 258 (4.41), 370 (4.05), 410 (3.80).

Found: C, 48.19; H, 2.96; N, 12.13: Calcd. for $C_9H_6O_3N_2S$: C, 48.66; H, 2.72; N, 12.61%.

b) When a solution of bromine (30 mg.) in pyridine (0.5 ml.) was added to a suspension of IX (40 mg.) in pyridine (3 ml.), the whole was dissolved to form

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

a dark red solution. After the solution was allowed to stand at room temperature for 3 days, pale yellow crystals separated out. The crystals were collected, washed with pyridine, water and hot methanol. Yield, ca. 5 mg.

***N*-(Tropolon-5-ylthiocarbamoyl) carbamide (IX).**—To a solution of X (100 mg.) was added, and the mixed solution was allowed to stand at room temperature for two days. The crystals that formed were collected and acidified with 6 N hydrochloric acid to give yellow powder. Recrystallization from ethanol afforded yellow needles, m. p. 215~220°C (decomp.). λ_{max}^{MeOH} mμ (logε) : 228 (4.36), 305 (3.95), 380 (4.07). IR 3370, 3270, 1692 cm^{-1} (KBr).

Found : C, 48.88 ; H, 3.57 ; N, 12.24. Calcd. for $C_9H_8O_3N_2S$: C, 48.22 ; H, 3.60 ; N, 12.50%.

2-Cyano-7-hydroxycyclohepta[d]thiazol-6-one (III).—A mixture of VIII (50 mg.) in phosphorus oxychloride (2 ml.) was refluxed for 2 hr. During this time the mixture turned dark brown. After removal of an excess of phosphorus oxychloride under a reduced pressure, cracked ice was added to the residue and the precipitate was collected. It was sublimed in reduced pressure (4 mmHg) at 140°C and the sublimate was recrystallized from ethanol to afford pale yellow needles, m. p. 211~215°C (decomp.) Yield, 20 mg. λ_{max}^{MeOH} mμ (logε) : 255 (4.48), 375 (4.07), 420 (4.15).

Found : C, 52,98 ; H, 2.33 ; N, 13.90. Calcd for $C_9H_4O_2N_2S$: C, 52.92 ; H, 1.97 ; N, 13.72%.

2-(4'-Carboxy-2'-thiazolin-2'-yl)-7-hydroxycyclohepta[d]thiazol-6-one (II). — A mixture of III (40 mg.), potassium carbonate (30 mg.), D-cysteine hydrochloride (40 mg.) in 50% aqueous methanol (2 ml.) was stirred under nitrogen stream for 1.5 hr. After removal of methanol in a reduced pressure the mixture was filtered to remove a small amount of insoluble substance. The precipitate which was formed by neutralization with dilute hydrochloric acid was collected, washed with hot benzene and recrystallized from ethanol to afford pale yellow crystals, m. p. 198~201°C (decomp.). Yield, ca. 5 mg. λ_{max}^{MeOH} mμ (logε) : 260 (4.48), 370(4.20), 380 (4.27).

Found : C, 46.23 ; H, 3.08 ; N, 9.35. Calcd. for $C_{12}H_8O_4N_2S$: C, 46.76 ; H, 2.62 ; N, 9.09%.

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