Studies on Seven-Membered Heterocyclic Compounds Containing Nitrogen. VI. 7-Methyl-2,3,4,5-tetrahydro-1(H)-thiazolo[5,4-c]azepine

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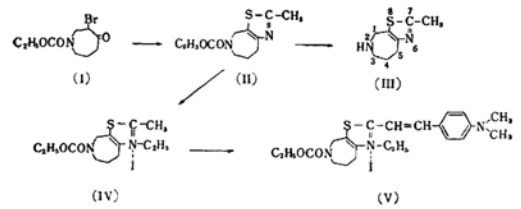
The present authors have synthesized 7-methyl-2,3,4,5-tetrahydro-1-(H)-thiazolo[5,4-c]-azepine (III). Spectral studies also supported the structure.



3-Bromo-1-ethoxycarbonyl-1-azacycloheptan-4-one (I)[1] yielded 2-ethoxycarbonyl-7-methyl-2, 3, 4, 5-tetrahydro-1(H)-thiazolo[5,4-c]azepine (II), b. p. 160~164°C/1 mmHg, by condensation with thioacetamide. II gave a chloroaurate of m. p. 180°C (decomp.). On deethoxycarbonylation of II by hydrogen bromide in glacial acetic acid, III was obtained as an oil of b. p. 101~102°C/4 mmHg, which gave a hydrochloride of m. p. 207~212°C (decomp.) and a chloroaurate of m. p. 179°C (decomp.) respectively. Ethiodide (IV) of II condensed with *p*-dimethylaminobenzaldehyde to afford 2-ethoxycarbonyl-7-(*p*-dimethylaminostyryl)-6-ethyl-2, 3, 4, 5-tetrahydro-1(H)-thiazolo[5,4-c]azepinium iodide (V), m. p. 203°C (decomp.). Dehydrogenation of III by heating with 10% palladium on carbon at elevated temperature evolved hydrogen, but led to decomposition of III.

It has already been reported[1] that bromine atom entered the 3-position by NBS bromination of 1-ethoxycarbonyl-1-azacycloheptan-4-one and that the indole compounds derived from the consequent bromoketone by the condensation with some arylamines might have angular structures. As shown in Fig. 1, III gave four bands at 1478, 1468, 1455 and 1430 cm^{-1} near the region due to the hydrogen bending vibration of methylene. These bands were assumed, as stated in the former paper[2], to be ascribed to 3-, 1-, 4- and 5-methylenes respectively. It was considered that the intensity of the band at 1455 cm^{-1} was too strong for the methyl group in the thiazole ring and therefore it

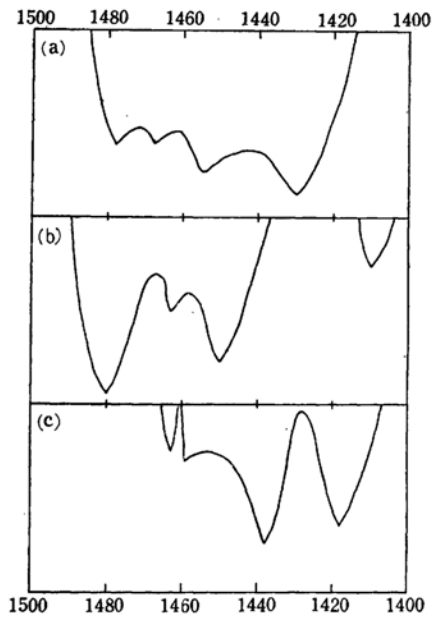


Fig. 1.

(a) III; (b) III hydrochloride; (c) III hydrobromide

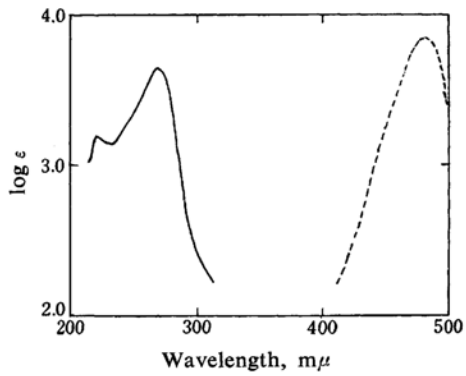


Fig. 2. (in methanol)

—— II, ---- V (concn. unknown)

appeared as an overlapping with 4-methylene. Both hydrochloride and hydrobromide of III gave also four bands, corresponding to the above absorptions. From these facts it may be reasonable to assume that III also had an angular

1) S. Morosawa, This Bulletin, 33, 1113 (1960).
2) S. Morosawa, ibid., 33, 1108 (1960).

form like the compounds reported before[1,2]. Ultraviolet absorption spectra of II and V are also given in Fig. 2.

Experimental

2-Ethoxycarbonyl-7-methyl-2, 3, 4, 5-tetrahydro-1 (H)-thiazolo[5, 4-c]azepine (II).—A solution of 5 g. of I and 2 g. of thioacetamide in 15 cc. of ethanol was boiled under reflux on a water bath for 5 hours. The ethanol was removed and the residue was heated in an oil bath kept at 160~165°C under reduced pressure (water pump) for 5 hours. After cooling, 10 cc. of 4 N hydrochloric acid was added and taken up three times in ether. The ether was washed twice with each 5 cc. portion of 4 N hydrochloric acid. Acidic solutions were united and made alkaline with anhydrous potassium carbonate, followed by adding 5 cc. of 5 N sodium hydroxide solution. The alkaline solution was shaken three times with each 20 cc. portion of ether. After drying over anhydrous potassium carbonate, the ethereal solution was concentrated and the residue was distilled in vacuo to give 1.6 g. of a light yellow viscous oil, b. p. 160~164°C/1 mmHg.

Found: C, 54.53; H, 6.74; N, 11.20. Calcd. for $C_{11}H_{16}O_2N_2S$: C, 54.99; H, 6.71; N, 11.65%.

The nitrogen content showed a slightly low value even after several repetitions, and the inclination was also observed in the following compounds of this series.

Ethanolic solution of the oil was mixed with an excessive chloroauric acid, heated for a while and allowed to cool. The **chloroaurate** formed was recrystallized twice from ethanol to yellow crystals, melting at 180°C with decomposition.

Found: C, 22.20; H, 3.33; Au, 32.50. Calcd. for $C_{11}H_{16}O_2N_2S \cdot HAuCl_4$: C, 22.60; H, 2.94; Au, 33.80%.

The oil and an excessive amount of ethyl iodide were allowed to stand for one day. The mixture was then refluxed for 8 hours to form an **ethiodide IV.** It was filtered and recrystallized from ethanol and ether to colorless crystals, m. p. 155~156.5°C.

Found: C, 39.05; H, 5.32; N, 6.39. Calcd. for $C_{11}H_{16}O_2N_2S \cdot C_2H_5I$: C, 39.40; H, 5.34; N, 7.07%.

7-Methyl-2,3,4,5-tetrahydro-1(H)-thiazolo[5,4-c]-azepine (III).—A solution of 0.8 g. of II in 20 cc. of glacial acetic acid was saturated with hydrogen bromide under ice-water cooling. After standing for 2 hours the solution was heated gradually in an oil bath and refluxed for 5 hours. The Hydrobromide which remained as a crystalline residue on evaporation of acetic acid was recrystallized from a mixture of ethanol and methanol to colorless crystals, m. p. 248~252°C (decomp.). These were dissolved in a small amount of water, made alkaline by adding concentrated sodium hydroxide solution and taken up in ether. After drying over anhydrous potassium carbonate, the ether was expelled and the residue was distilled in vacuo to yield 0.4 g. of a colorless, strongly hygroscopic oily substance, b. p. 101~102°C/4 mmHg.

Found: C, 56.60; H, 7.40; N, 16.29. Calcd. for $C_8H_{12}N_2S$: C, 57.14; H, 7.19; N, 16.65%.

The above oil was dissolved in concentrated hydrochloric acid and evaporated to dryness under reduced pressure to afford a **hydrochloride.** This was recrystallized twice from ethanol to extremely hygroscopic colorless plates, m. p. 207~212°C (decomp.).

Found: N, 11.16. Calcd. for $C_8H_{12}N_2S \cdot 2HCl$: N, 11.62%.

The **chloroaurate** which formed by mixing the oil with an excessive amount of chloroauric acid in ethanol containing one drop of concentrated hydrochloric acid was collected and washed with ethanol. This was dissolved in an ethanol-methanol mixed solvent with heating, the methanol was expelled and the solution was allowed to stand with one drop of concentrated hydrochloric acid to yield yellow crystals, which decomposed at about 179°C.

Found: N, 5.06. Calcd. for $C_8H_{12}N_2S \cdot HAuCl_4$: N, 5.50%.

2-Ethoxycarbonyl-7-(*p*-dimethylaminostyryl)-6-ethyl-2, 3, 4, 5-tetrahydro-1(H)-thiazolo[5, 4-c]azepinium Iodide (V).—A solution of 0.1 g. of IV and 0.1 g. of *p*-dimethylaminobenzaldehyde in 2 cc. of ethanol containing a small amount of piperidine was boiled under reflux for 10 hours. The ethanol was expelled and water was added to the residue to deposit crystals, which were collected and washed well with ether. The crystals were dissolved in a small volume of ethanol with heating and ether was added until the solution became turbid. The red crystals which formed were treated repeatedly like the above to give 40 mg. of V, m. p. 203°C (decomp.). The nitrogen content showed some deviation from the theoretical value even after several recrystallizations.

Found: N, 7.01. Calcd. for $C_{22}H_{30}O_2N_3SI$: N, 7.97%.

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