Studies on Anti-cancer Agents. V. Desulfurization by Hydrazine Hydrate. II. The Reaction of Benzyl and Piperonyl Disulfide with Hydrazine*

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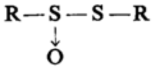
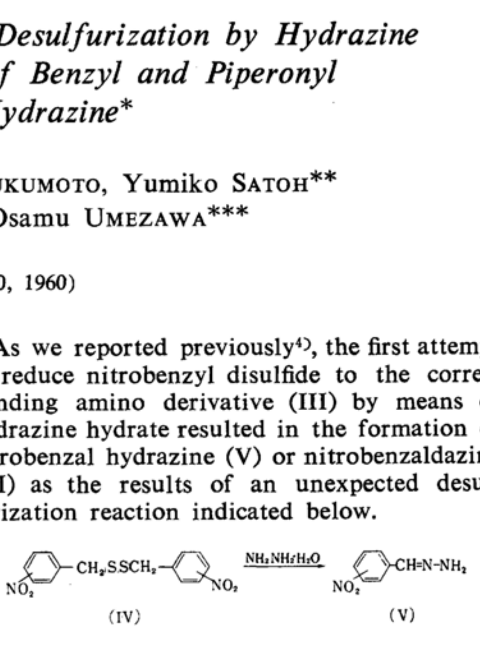
In the preceeding paper[1-3] Kametani and co-workers described the fact that three kinds of alkyl thiolsulfinates, namely, isobutyl, *tert*-butyl and *n*-amyl thiolsulfinates (I) were recognized to be effective against Ehrlich ascites tumor by their screening test among various thiolsulfinates synthesized by us, but almost all of these compounds are unstable for heat and irritative for the skin and eyes, so it is difficult to use them as anti-cancer agents. Among them, only dibenzyl thiolsulfinate (II) was found to form stable crystals, so we tried to synthesize various kinds of dibenzyl thiolsulfinate derivatives, bearing various functional groups in the phenyl nuclei, for instance, nitro, amino and so on.



$R-\underset{\overset{\downarrow}{O}}{S}-S-R$

I: R=isobutyl, *tert*-butyl-, *n*-amyl-
II: $R=C_6H_5$-
III: R=*p*-$NH_2C_5H_4$-

As we reported previously[4], the first attempt to reduce nitrobenzyl disulfide to the corresponding amino derivative (III) by means of hydrazine hydrate resulted in the formation of nitrobenzal hydrazine (V) or nitrobenzaldazine (VI) as the results of an unexpected desulfurization reaction indicated below.



In this paper desulfurization reaction was examined in the case of benzyl (XIIa) or piperonyl disulfide (XIIb), which has no electron-attractive radical, namely, the nitro group. The piperonyl disulfide (XIIb) was prepared according to the following reaction scheme. In this case, crossed-Cannizzaro reaction was applied the first time to obtain piperonyl alcohol, but the catalytic hydrogenation was found to be more excellent.

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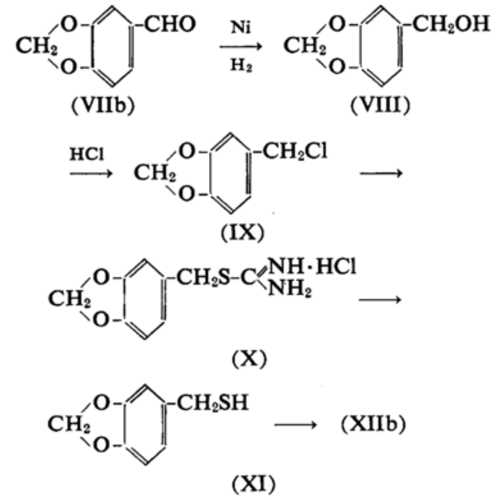
1) T. Kametani, K. Fukumo to and O. Umezawa, *Yakugaku Kenkyu*, **31**, 60 (1959).

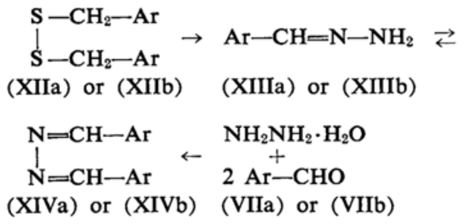
2) ibid., **31**, 125 (1959).

3) ibid., **31**, 132 (1959).

4) T. Kametani, K. Fukumoto, Y. Takayanagi, T. Teshigawara and O. Umezawa, *Chem. Pharm. Bull.*, in press.



When benzyl disulfide was heated with an excess of hydrazine hydrate, desulfurization occurred giving a small amount of yellowish crystals, which agreed with an authentic sample of m. p. 93°C[5] of benzaldazine (XIVa) by a mixed melting point test. As it was known that this compound XIVa turned to benzal hydrazine (XIII) by heating with hydrazine hydrate[6], the former substance was heated with an excess of hydrazine hydrate and it was observed that the color of the reaction mixture changed to colorless from yellow, indicating the formation of benzal hydrazine (XIIIa). This substance is known to be comparatively unstable against moisture in the air and easily decomposes to benzaldazine and hydrazine hydrate[7], therefore it seems possible that the benzal hydrazines initially formed from the disulfides give the corresponding benzaldazines by a prolonged period of reaction. Similarly, dipiperonyliden hydrazine (XIVb) was obtained from piperonyl disulfide and was proved to be identical with an authentic sample which was synthesized from piperonal and hydrazine hydrate[8].



$$\begin{array}{l}\text{S}-\text{CH}_2-\text{Ar}\\ |\\ \text{S}-\text{CH}_2-\text{Ar}\end{array} \rightarrow \text{Ar}-\text{CH}{=}\text{N}-\text{NH}_2 \rightleftarrows$$

(XIIa) or (XIIb) (XIIIa) or (XIIIb)

$$\begin{array}{l}\text{N}{=}\text{CH}-\text{Ar}\\ |\\ \text{N}{=}\text{CH}-\text{Ar}\end{array} \leftarrow \begin{array}{c}\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}\\ +\\ 2\ \text{Ar}-\text{CHO}\end{array}$$

(XIVa) or (XIVb) (VIIa) or (VIIb)

XIIa, XIIIa, XIVa, VIIa : Ar=C_6H_5-

XIIb, XIIIb, XIVb, VIIb : Ar=$CH_2O_2C_6H_3$-

Experimental

The Reaction of Dibenzyl Disulfide with Hydrazine Hydrate. — The mixture of dibenzyl disulfide (1 g.) and 80% $NH_2NH_2 \cdot H_2O$ (2 ml.) was refluxed. After 30 min., an evolution of a gas containing sulfur and the deposition of a small amount of grayish-white substance on the inner tube of the condenser was observed. After 13 hr. of reflux, the reaction mixture was treated with hydrochloric acid and then extracted with ether. Then an ethereal extract was washed with water, dried on sodium sulfate and evaporated, resulting in a yellow viscous substance. This was recrystallized from dilute acetone giving yellow needles of m. p. 91~92°C in poor yield. This was found to be identical with the authentic sample described below.

Benzaldazine (XIVa).—To benzaldehyde (2 g.), 1.1 g. of 80% $NH_2NH_2 \cdot H_2O$ was gradually added at room temperature and considerable heat generation which accompanied the separation of yellow needles was observed. After recrystallization from ethanol, 1.3 g. (68.4%) of yellow, long needles (m. p. 93°C)[5] were obtained***.

Piperonyl Thiuronium Chloride (X).—Piperonyl chloride (5 g.) was added to thiourea (2.2 g.) in 99% ethanol (33 ml.) and the mixture was heated for 1.5 hr. The solvent was removed by distillation and a small quantity of ether was added to induce crystallization. The solid was collected by filtration. Colorless prisms (m. p. 201°C) were obtained by recrystallization from ethanol. Yield, 5.3 g., 73.6% of theoretical.

Found: C, 43.17; H, 4.00. Calcd. for $C_9H_{11}O_2 \cdot NSCl$: C, 43.81; H, 4.49%.

Piperonyl Mercaptan (XI). — Thiuronium salt (5 g.) was admixed with 10% sodium hydroxide (34 ml.) and refluxed for 1.5 hr. on an oil bath. In this case an evolution of ammonia gas was observed. After cooling, the mixture was acidified with hydrochloric acid and extracted with ether. After being treated as usual, a fraction of 116~118°C/5 mmHg. (1.5 g., 44.1% of theoretical) was obtained by distillation in vacuo.

Piperonyl Disulfide (XIIb).—Iodine (1.2 g.) was gradually added to the stirred mixture of pyridine (1 g.) and piperonyl mercaptan (1.5 g.) at 15°C. After 1.5 hr., the reaction mixture was poured into water (50 ml.) and extracted with benzene, the extract was washed with saturated sodium thiosulfate, hydrochloric acid and water, successively and then evaporated. The residue was recrystallized from ethanol forming yellowish-white crystals (0.5 g., 35.8% of theoretical) of m. p. 68°C[9].

The Reaction of Piperonyl Disulfide with Hydrazine Hydrate.—The mixture of piperonyl disulfide (1 g.) and 80% $NH_2NH_2 \cdot H_2O$ (1.5 g.) was heated for 26 hr. and extracted with ether. The ethereal extract was evaporated after drying on sodium sulfate and the residue was recrystallized from acetone giving yellow needles (0.2 g., 22% of theoretical), m. p. 201°C. This was proved to be identical with an authentic sample prepared by the following method.

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[5] Th. Curtius and R. Jay, *J. prakt. Chem.*, [2] **39**, 44 (1889).

[6] Th. Curtius and H. Franzen, *Ber.*, **35**, 3236 (1902).

[7] Th. Curtius and L. Pflug, *J. prakt. Chem.*, [2] **44**, 537 (1891).

[8] D. Vorländer, *Ber.*, **39**, 807 (1906).

**** According to Ref. 5, this reaction was carried out in the presence of alkali.

[9] W. Manchot and Chr. Zahn, *Ann.*, **345**, 326 (1905).

Dipiperonyliden Hydrazine (Piperonal Azine) (XVb).—Hydrazine hydrate (0.1 g.) was added to the mixture of piperonal (0.4 g.) and ethanol (1 ml.). After a few minutes a small amount of water was added, a white crystal separating from it. This was recrystallized from dilute acetic acid giving yellow crystals (0.2 g., 50.1% of theoretical), m. p. 202~203°C.

Summary

The desulfurization reaction which was reported in the previous paper in case of the reaction of *p*-nitrobenzyl disulfide and hydrazine hydrate was also observed in the similar reaction of benzyl and piperonyl disulfide. The reaction product was found to be benzaldazine derivative instead of the derivative of benzal hydrazine.

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