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Studies on Antitumor Substances. XIII.[1] Reaction of Sodium Ethoxycarbonylmethylthiosulfate and Sodium Phenacylthiosulfate with Amine

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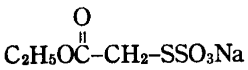
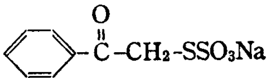
The reactions of sodium ethoxycarbonylmethylthiosulfate and sodium phenacylthiosulfate with amine was examined and found to proceed through the intermediate formation of bisethoxycarbonylmethyldisulfide and phenacyldisulfide at the first step to give the corresponding thiooxamides.

Chemical behaviors of Bunte salts (thiosulfates) are predictable to be similar to those of thiosulfonates, because of their structural similarity. In the preceding paper,[3] it was reported that sodium alkanethiosulfates (Bunte salts) reacted successfully with several active methylene compounds to give the alkylthio derivatives of the active methylene compounds. However, the reaction with amines failed to form the expected sulfenamides, which have been known to afford by the reaction of some thiosulfonates with amines.[4,5] Regarding the reaction of alkyl thiosulfonates with amines, Oae[6] has suggested that if the positive character of the sulfur atom in alkyl thiosulfonates is enhanced by introducing a stronger electronegative group into the alkyl group, the formation of sulfenamides would be promoted. Thus, the reaction between sodium ethoxycarbonylmethylthiosulfate (I) or sodium phenacylthiosulfate (II), in which the carbonyl group would enhance the positive character of the sulfur atom, and amines were attempted in this paper.



$C_2H_5O\overset{O}{\overset{\|}{C}}-CH_2-SSO_3Na$

I



II

It has been known by Milligan[7] that carbamoylmethylthiosulfates, when heated to boiling in amines, gave the corresponding thiooxamides. Under similar conditions, sodium ethoxycarbonylmethylthiosulfate (I) reacted with an excess of anhydrous cyclohexylamine to give 67% of N-cyclohexyl-N'-cyclohexyl(thiooxamide) (III), which was probably formed through the formation of the intermediate, ethoxycarbonyl-N-cyclohexylthiocarboxamide. N-Cyclohexyl-N'-cyclohexyl(thiooxamide) (III) was confirmed by the ready conversion to N,N'-dicyclohexyloxamide (IV) by oxidation with hydrogen peroxide in acetic acid. Heating of sodium ethoxycarbonylmethylthiosulfate (I) in aqueous cyclohexylamine under reflux was found to give cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (V) as a by-product in 17% yield. The yields of N-cyclohexyl-N'-cyclohexyl(thiooxamide) (III) and cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (V) at different reaction

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1) Part XII: S, Hayashi, M. Furukawa, Y. Fujino, M. Sugita, and T. Nakao, *Chem. Pharm. Bull.* (Tokyo), **19**, 2003 (1971).
2) Location: *Oe-moto-machi, Kumamoto.*
3) S. Hayashi, M. Furukawa, Y. Fujino, T. Nakao, and K. Inoue, *Chem. Pharm. Bull.* (Tokyo), **19**, 1557 (1971).
4) J.E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).
5) B.G. Boldyrev and S.A Kolesnikova, *Zh. Obshch. Khim.*, **35**, 198 (1965) [*C.A.*, **62**, 13076 (1965)].
6) S. Oae and T. Kurusu, *Chemistry* (*Japan*), **25**, 52 (1970).
7) B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1959**, 2969.

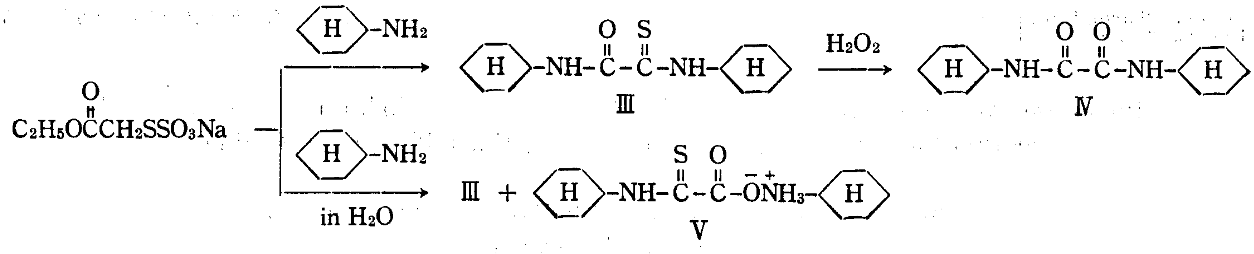
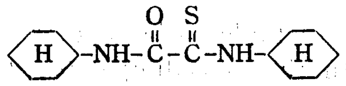
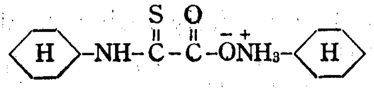


Chart 1

TABLE I. Yields of N-Cyclohexyl-N'-cyclohexyl (thiooxamide) and Cyclohexylammonium Cyclohexylaminothiocarbonylcarboxylate at Different Temperatures (Reaction Time, 15 min)

Compound	Temperature (°C)			
	5	20	50	100
	11%	13%	14%	20%
	—	—	6%	14%

temperatures were shown in Table I. The reaction was carried out most readily in the boiling condition.

It is noted that the reaction of sodium ethoxycarbonylmethylthiosulfate (I) with boiling piperidine and morpholine afforded ethoxycarbonyl-N-pentamethylenethiocarboxamide (VIIa) and ethoxycarbonyl-N-(3-oxapentamethylene)thiocarboxamide (VIIb), without any thiooxamide is isolated, in 61% and 72% yields, respectively. Similarly, heating of sodium phenacylthiosulfate (II) in anhydrous and aqueous cyclohexylamine solutions resulted in the

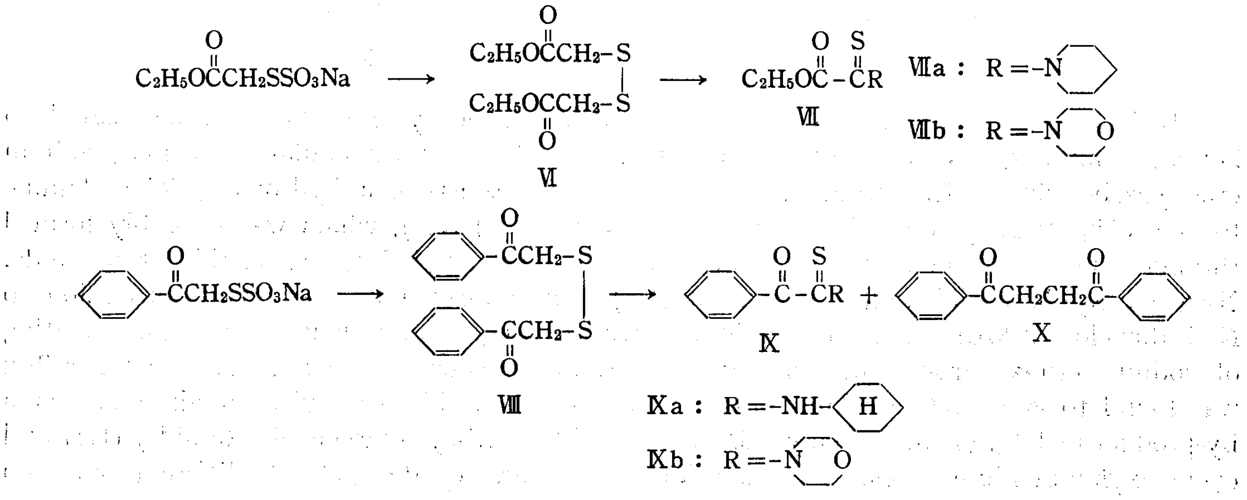


Chart 2

formation of benzoyl-N-cyclohexylthiocarboxamide (IX) in 43% and 40% yields, respectively. In both cases, it is noteworthy that 1,4-diphenyl-1,4-butanedione (X) was isolated in 5% and 16% yields, respectively, which was identified by analysis, infrared (IR) and nuclear magnetic resonance (NMR) spectra and comparison of the melting point with the recorded values.[8] He-

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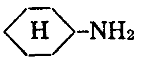
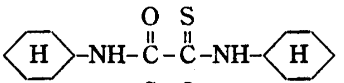
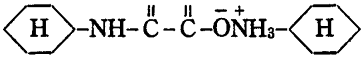
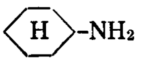
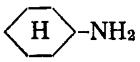
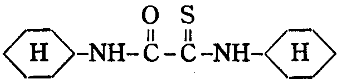
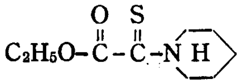
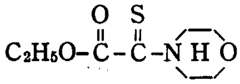
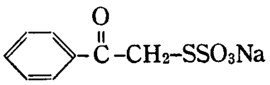
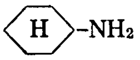
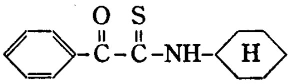
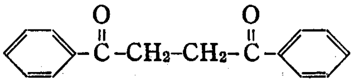
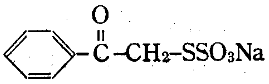
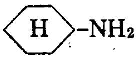
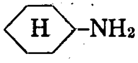
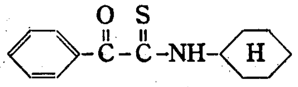
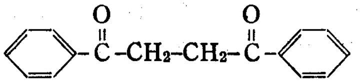
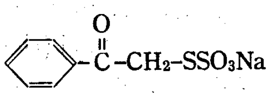
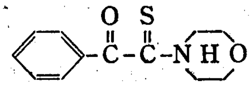
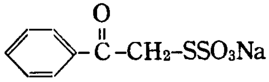
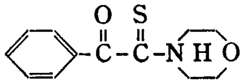
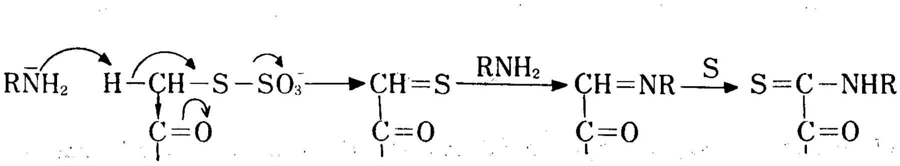
8) R.G. Hiskey, J.A. Kepler, and B.D. Thomas, *J. Org. Chem.*, **29**, 3686 (1964).

TABLE II

Thiosulfate	Amine	Solvent	Product	Yield
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-SSO_3Na$		H_2O	 	24 17
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-SSO_3Na$				67
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-SSO_3Na$				61
$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-SSO_3Na$				72
		H_2O	 	43 5
			 	40 16
		H_2O		47
				55

ating in anhydrous and aqueousmorpholine solutions gave analogously benzoyl-N-(3-oxapentamethylene)thiocarboxamide (IX) in 47% and 55% yields, respectively, though no 1,4-diphenyl-1,4-butanedione could be isolated. These results were summarized in Table II.

Regarding the reaction of carbamoylmethylthiosulfate with amine, Milligan⁷⁾ has proposed the following mechanism, which involved the elimination of α-hydrogen atom from sulfur atom of the SO_3 group at the first step to form the thioaldehyde. On the other hand, the reaction



of sodium ethoxycarbonylmethylthiosulfate (I) with cyclohexylamine was found to isolate a small amount of bisethoxycarbonylmethyldisulfide (VI), which disappeared in progress of the reaction. Bisethoxycarbonylmethyldisulfide (VI) isolated was confirmed to be identical with the authentic sample prepared by the alkaline decomposition of sodium ethoxycarbonylmethylthiosulfate⁹⁾. Analogously, the reaction of sodium phenacylthiosulfate (II) with cyclohexylamine also gave the intermediate (VIII), which showed the same melting point as the recorded value¹⁰⁾ of phenacyldisulfide and the IR absorption assignable to the carbonyl group

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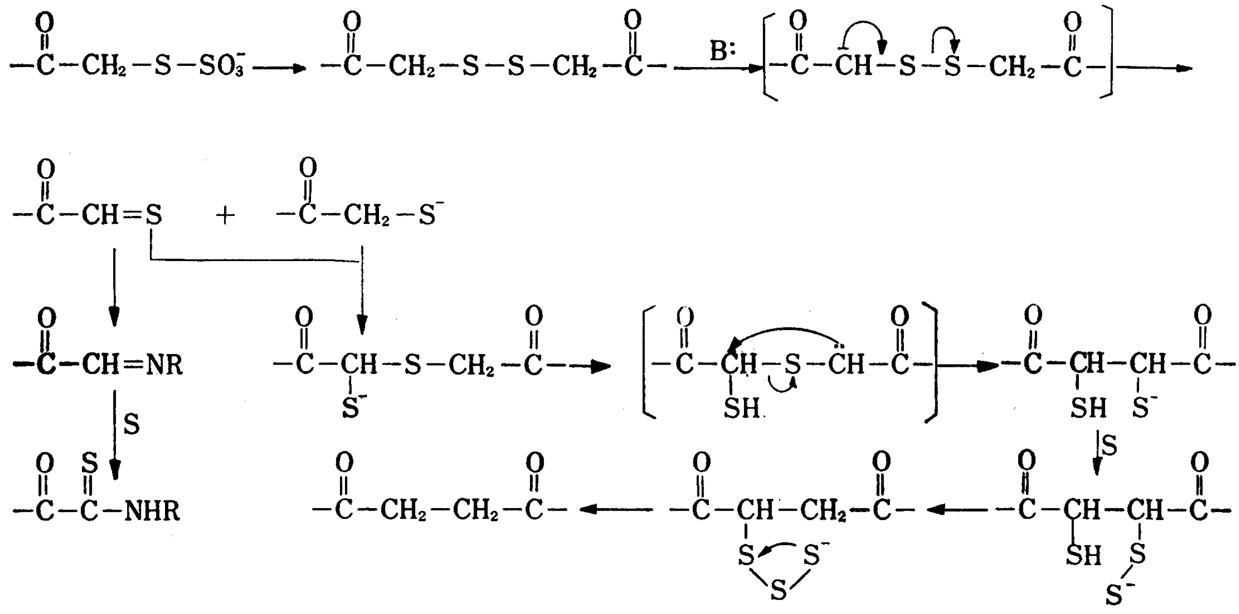
9) T.S. Price and D.F. Twiss, *J. Chem. Soc.*, **1908**, 1648.



at 1666 cm^{-1}. These results suggest that the initial formation of the disulfide occures prior the formation of the thioaldehyde. The fact that 1,4-diphenyl-1,4-butanedione (X) was yielded might also give a support to this mechanism through the initial formation of the disulfide, because phenacyldisulfide has been known to give readily 1,4-diphenyl-1,4-butanedione with base.[8] In order to reveal the mechanism, bisethoxycarbonylmethyldisulfide (VI) was attempted to react with cyclohexylamine. As expected, heating of bisethoxycarbonylmethyldisulfide (VI) with an excess of aqueous cyclohexylamine gave N-cyclohexyl-N'-cyclohexyl (thiooxamide) (III) and cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (V) in 8% and 30% yields, respectively.

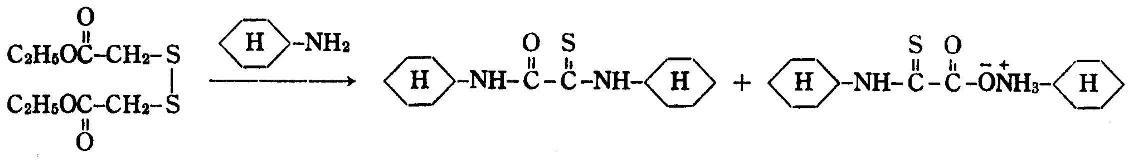


Chart 3

From these results, it is evident that the reaction of sodium α-ketomethylthiosulfate with amines proceeds through the initial formation of the corresponding disulfides.

Experimental

Reaction of Sodium Ethoxycarbonylmethylthiosulfate (I) with Cyclohexylamine——a) In Aqueous Solution: To a boiling solution of 5.7 g (0.025 mole) of sodium ethoxycarbonylmethylthiosulfate in 100 ml of H_2O was added 8.9 g (0.09 mole) of cyclohexylamine and the solution was heated for 15 min under reflux. The precipitates deposited on cooling were filtered and recrystallized from benzene to give 1.6 g (24%) of yellow plates of N-cyclohexyl-N'-cyclohexyl (thiooxamide) melting at 168°.[11] *Anal.* Calcd. for $C_{14}H_{24}ON_2S$: C, 62.66; H, 9.02; N, 10.44. Found: C, 62.65; H, 9.18; N, 10.15. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1665 (C=O), 1042 (C=S). The filtrate was evaporated and the precipitates deposited on cooling were recrystallized from EtOH to give 1.2 g (17%) of right yellow needles of cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate melting at 184—185°. *Anal.* Calcd. for $C_{14}H_{26}O_2N_2S$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.80; H, 8.85; N, 9.76. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1646 (C=O), 1032 (C=S).

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10) F. Asinger, M. Thiel, and W. Schäfer, *Ann.*, **637**, 146 (1960).

11) Ref. mp 165°. B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1961**, 1194.

b) In Anhydrous Solution: A mixture of 5.7 g (0.025 mole) of sodium ethoxycarbonylmethylthiosulfate and 50 ml of cyclohexylamine was heated for 15 min under reflux. The solution was cooled, acidified with dil. HCl and extracted with ether. The ethereal extract was evaporated to dryness and the residue was extracted with hot benzene. The precipitates deposited on cooling were recrystallized from benzene to give 4.5 g (67%) of yellow plates of N-cyclohexyl-N′-cyclohexyl(thiooxamide) melting at 168°.

Ethoxycarbonyl-N-pentamethylenethiocarboxamide (VIIa)——A solution of 19 g (0.09 mole) of sodium ethoxycarbonylmethylthiosulfate and 80 ml of piperidine was heated for 15 min udner reflux. After cooling, the solution was acidified with dil HCl and extracted with ether. The ethereal extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The oily residue was distilled under reduced pressure to give 10.5 g (61%) of yellow liquid boiling at 151—152°/3 mm. *Anal.* Calcd. for $C_9H_{15}O_2NS$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.43; H, 7.51; N, 7.26. IR ν_{max}^{film} cm^{-1}: 1730 ($CO_2C_2H_5$), 1048 (C=S).

Ethoxycarbonyl-N-(3-oxapentamethylene)thiocarboxamide (VIIb)——A mixture of 38 g (0.17 mole) of sodium ethoxycarbonylmethylthiosulfate and 100 ml of morpholine was treated as described above. Yellow liquid (24.8 g, 72%) boiling at 150—151°/3 mm was yielded. *Anal.* Calcd. for $C_8H_{13}O_3NS$: C, 47.27; H, 6.45; N, 6.89. Found: C, 46.79; H, 6.43; N, 6.81. IR ν_{max}^{film} cm^{-1}: 1735 ($CO_2C_2H_5$), 1064 (C=S).

Reaction of Sodium Phenacylthiosulfate (II) with Cyclohexylamine——a) In Aqueous Solution: To a boiling solution of 10.2 g (0.04 mole) of sodium phenacylthiosulfate in 30 ml of H_2O was added 11.9 g (0.12 mole) of cyclohexylamine and the solution was heated for 15 min under reflux. The solution was cooled and extracted with ether. The ethereal extract was acidified with dil. HCl and the yellow oil separated between ethereal layer and aqueous layer was isolated. The oil was added to EtOH and the precipitates deposited were recrystallized from EtOH to give 4.2 g (43%) of yellow needles of benzoyl-N-cyclohexylthiocarboxamide melting at 129.5—130°. *Anal.* Calcd. for $C_{14}H_{18}ONS$: C, 68.26; H, 6.55; N, 5.68. Found: C, 68.19; H, 6.93; N, 5.73. IR ν_{max}^{KBr} cm^{-1}: 1662 (C=O), 1066 (C=S). The ethereal layer was washed with H_2O, dried over Na_2SO_4 and evaporated. Benzene was added to the dark red residue and the precipitates deposited on cooling were recrystallized from a mixture of petrol ether and benzene to give 0.48 g (5%) of colorless needles of 1,4-diphenyl-1,4-butanedione melting at 145—145.5°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.62; H, 5.92. Found: C, 81.20; H, 6.05. IR γ_{max}^{KBr} cm^{-1}: 1678 (C=O).

b) In Anhydrous Solution: A mixture of 2.5 g (0.01 mole) of sodium phenacylthiosulfate and 30 ml of cyclohexylamine was heated for 15 min under reflux. The solution was treated as described above. Benzoyl-N-cyclohexylthiocarboxamide (0.9 g, 40%) and 1,4-diphenyl-1,4-butanedione (0.38 g, 16%) was yielded.

Benzoyl-N-(3-oxapentamethylene)thiocarboxamide (IXb)——A mixture of 5.1 g (0.02 mole) of sodium phenacylthiosulfate and 30 ml of morpholine was heated for 15 min under reflux. The solution was cooled, acidified with dil. HCl and extracted with a mixture of ether and ethyl acetate. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was extracted with ethyl acetate and the precipitates deposited on cooling were recrystallized from EtOH to give 2.4 g (55%) of yellow plates melting at 115.5—116.5°. *Anal.* Calcd. for $C_{12}H_{13}O_2NS$: C, 61.09; H, 5.55; N, 5.94. Found: C, 61.46; H, 5.58; N, 6.45. IR ν_{max}^{KBr} cm^{-1}: 1658 (C=O), 1029 (C=S).

Bisethoxycarbonylmethyldisulfide (VI)——A mixture of 61.3 g (0.5 mole) of ethyl chloroacetate and 124 g (0.5 mole) of sodium thiosulfate pentahydrate in dil. EtOH was heated with stirring for 1 hr under reflux. Continuing reflux, iodine was added little by little to the mixture until the color of iodine becomes to be not disappeared. After decolorized with $NaHSO_3$, the solution was evaporated under reduced pressure to remove EtOH and then extracted with ether. The extracts were washed with H_2O, dried over Na_2SO_4 and distilled under reduced pressure to give 63 g (53 %) of yellow liquid boiling at 150°/5 mm. IR ν_{max}^{film} cm^{-1}: 1732 ($CO_2C_2H_5$).

Reaction of Bisethoxycarbonylmethyldisulfide (VI) with Aqueous Cyclohexylamine——A suspension of 2.4 g (0.01 mole) of bisethoxycarbonylmethyldisulfide and 2.9 g (0.03 mole) of cyclohexylamine in 30 ml of H_2O was stirred for 15 min under reflux. The precipitates deposited on cooling were filtered and extracted with benzene. The insoluble precipitates were recrystallized from EtOH to give 0.8 g (30 %) of cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate melting at 184—185°. The benzene extracts were concentrated and the precipitates deposited on cooling were recrystallized from a mixture of EtOH and benzene to give 0.25 g (8%) of N-cyclohexyl-N′-cyclohexyl(thiooxamide) melting at 168°.

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