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Conversion of Bis(β-carbamoylethyl) Disulfides into Bis(β-carbamoylethyl) Trisulfides

Mitsuru Furukawa, Shooko Kato, and Seigoro Hayashi

Faculty of Pharmaceutical Sciences, Kumamoto University[1]

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The conversion of carbamoylmethylthiosulfates into the corresponding thio-oxamides has been extensively studied by Milligan[2] and by the authors.[3] We have also found that the same thio-oxamides were obtained by the reaction of bis-carbamoylmethyl disulfides with amines in the presence of sulfur. These have an obvious similarity to the Kindler reaction,[4] which developed as a variant of the Willgerodt reaction.[5] On the other hand, β-carbamoylethylthiousulfates, in which a second methylene group was introduced between the carbonyl and the thiosulfate radicals, reacted with amines to give β-carbamoylethylamines,[6] no trace of any thio-oxamide expected being isolated. Although, in the reaction of carbamoylmethylthiosulfates with amines, sulfur is made available from the thiosulfate radical by some peculiar process, Kindler reaction requires essentially sulfur added. Thus, in the present study, the reactions of bis(β-carbamoylethyl) disulfides and β-carbamoylethylthiosulfates with amines in the presence of sulfur were examined.

When bis(β-cyclohexylcarbamoylethyl) disulfide (Ia) was heated with an excess of amines in ethanol in the presence of an equimolar quantity of sulfur under reflux, bis(β-cyclohexylcarbamoylethyl) trisulfide (IIa) was unexpectedly obtained in 40—60% yields, no trace of any thio-oxamide and carbamoylethylamine expected being isolated. The use of hydrazine instead of amine gave also IIa in an almost equal yield. The structure of IIa was established by the identification with an authentic sample prepared by the treatment of β-cyclohexylcarbamoylthiosulfate with sodium sulfide. The yields of the trisulfide (IIa) in the use of a variety of amines were summarized in Table I.

As can be seen in Table I, the yield of IIa was quite similar and no relationship between the yield and the basicity of amines was observed. An exclusive low yield of IIa only in the case of benzylamine is presumed to be due to the facile formation of N-benzylthiobenzamide[7] by the reaction of benzylamine with sulfur. The other bis(β-carbamoylethyl) disulfides (I) also gave the corresponding trisulfides (II) under the similar conditions.

The formation of II is reasonably explained by assuming the intermediate β-carbamoylethyl hydrodisulfides, which would be formed through the initial nucleophilic attack of hydrogen sulfide to the positive sulfur atom of I with elimination of β-carbamoylethanethiols which convert into I by oxidation. The hydrogen sulfide is produced by dissolving sulfur

1) Location: *Oe-hon Machi, Kumamoto, 862, Japan.*
2) B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1959**, 2969; *idem, ibid.*, **1961**, 1194.
3) *a*) S. Hayashi, M. Furukawa, Y. Fujino, and K. Shiraishi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2247 (1971); *b*) M. Furukawa, K. Shiraishi, and S. Hayashi, *ibid.*, **20**, 1921 (1972).
4) *a*) K. Kindler, *Ann. Chem.*, **431**, 187 (1923); *idem, Arch. Pharm.*, **265**, 389 (1927); *b*) K. Kindler and T. Li, *Chem. Ber.*, **74B**, 321 (1941); *c*) K. Kindler and W. Peschke, *Arch. Pharm.*, **270**, 340 (1932).
5) M. Carmack and M.A. Spielman, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, 1946, p. 83.
6) M. Furukawa, T. Yuki, R. Kiyofuji, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 811 (1973).
7) F.H. McMillan, *J. Am. Chem. Soc.*, **70**, 868 (1948).

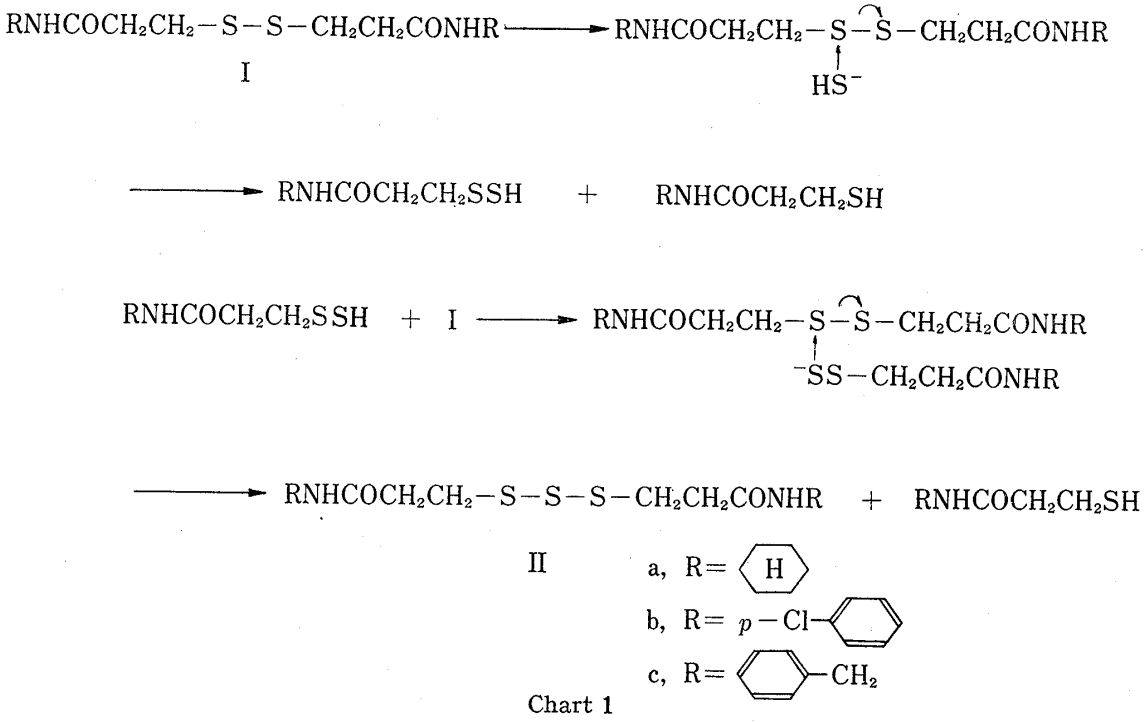

Chart 1

TABLE I. The Yields of Bis(β-cyclohexylcarbamoylethyl)Trisulfide (IIa) in the Use of a Variety of Amines

Amine	Yield (%)	Amine	Yield (%)
CH_3NH_2	44.3	$(C_2H_5)_3N$	44.1
H -NH_2	42.0	H NH	44.5
-NH_2	44.6	O H NH	59.4
-CH_2NH_2	2.5	$NH_2NH_2 \cdot H_2O$	54.2

into amines.[8] The intermediate hydrodisulfides react with amines to give II.[9] The trisulfides (II) may also be formed by the attack of the hydrodisulfides to the further I. In the reaction of I with some nucleophiles, the following three mechanistic pathways are possible: 1) direct disulfide cleavage by the attack of the nucleophiles on the positive sulfur atom of I. 2) initial formation of thiobenzaldehyde by elimination of an α-hydrogen atom adjacent to the sulfur atom. 3) olefin formation of β-elimination. If the reaction proceed through the pathway 2, Kindler reaction would occur to give the thio-oxamides. Pathway 3 would result in the formation of the addition product of the intermediate olefines with amines and in fact such a compound is obtained in the reaction of I with amines in the absence of sulfur. However, the result (pathway 1) that only II was yielded in the presence of sulfur should be noted. In order to examine the participation of hydrogen sulfide in the formation of II, Ia was allowed to react with hydrogen sulfide in ethanol in the presence of piperidine and actually IIa was obtained, though in the absence of piperidine the material (Ia) was quantitatively recovered unchanged. The reaction of Ia with thiols under the similar conditions was attempted and the corresponding unsymmetrical disulfides (III) were obtained in low yield, as expected.

8) R.E. Davis and H.F. Nakshbendi. *J, Am. Chem. Soc.*, **84**, 2085 (1962).
9) J. Tsurugi, Y. Abe, T. Nakabayashi, S. Kawamura, T. Kitao, and M. Niwa, *J. Org. Chem.*, **35**, 3263 (1970).

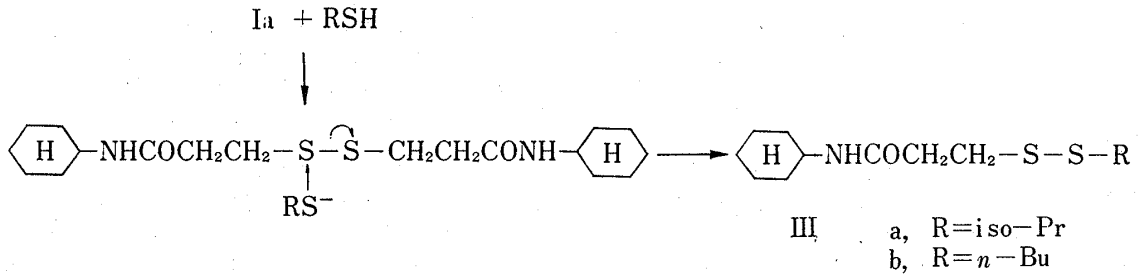

Chart 2

The reaction of sodium β-carbamoylethylthiosulfates (IV) with an amine in the presence of sulfur was also examined. When IV was heated with an excess of amine in the presence of an equimolar quantity of sulfur in water under the similar conditions, the corresponding trisulfides (II) were obtained in lower yields, together with the disulfides (I). Analogously in this case, thio-oxamides and β-carbamoylethylamines anticipated were not isolated at any rate.

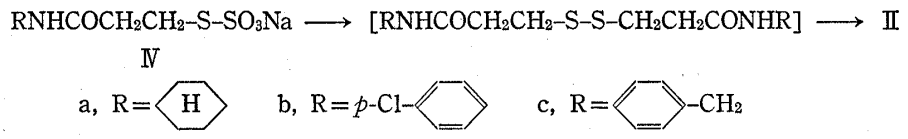

Chart 3

The sulfen sulfur atom of IV might possess stronger electrophilic property than the positive sulfur atom of I, because of the adjacent strong negative group. Therefore, the facile formation of II from IV rather than from I is anticipated. However the inverse result suggests that the reaction would proceed through the intermediate formation of I. It is well known that thiosulfates readily convert into disulfides.

Experimental

Reaction of Bis(β-carbamoylethyl) Disulfide (I) with Amines in the Presence of Sulfur——General Procedure: A mixture of bis(β-carbamoylethyl) disulfide (5 mmole), amine (10 mmole), sulfur (5 m atom) and EtOH (30 ml) was heated for 20 hr under reflux. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH. Detailed data in the case of using cyclohexylamine were summarized in Table II.

Table II. Bis(β-carbamoylethyl)Trisulfide (II)

No.	Yield (%)	mp (°C)	Formula	Analysis % Calcd. (Found) C	H	N
IIa	42	188—189	$C_{18}H_{32}O_2N_2S_3$	53.42 (53.03)	7.97 (7.94)	6.92 (6.84)
IIb	44	197—199	$C_{18}H_{18}O_2N_2S_3Cl_2$	46.85 (46.53)	3.90 (4.06)	6.07 (6.52)
IIc	67	144—145	$C_{20}H_{24}O_2N_2S_3$	57.13 (57.59)	5.75 (5.88)	6.66 (6.68)

Reaction of Bis(β-cyclohexylcarbamoylethyl) Disulfide (Ia) with Hydrogen Sulfide——Hydrogen sulfide gas was slowly passed through a solution of bis(β-cyclohexylcarbamoylethyl) disulfide (1.80 g, 5 mmole) and piperidine (0.85 g, 10 mmole) in EtOH (30 ml) for 20 hr under reflux. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH to give colorless prisms (0.35 g, 17%) of bis(β-cyclohexylcarbamoylethyl) trisulfide (IIa) melting at 188—189°. Under similar conditions but in the absence of piperidine, the material (Ia) was almost quantitatively recovered unchanged.

β-Cyclohexylcarbamoylethyl Isopropyl Disulfide (IIIa)——A solution of bis(β-cyclohexylcarbamoylethyl) disulfide (1.80 g, 5 mmole), cyclohexylamine (0.99 g, 10 mmole) and iso-propanethiol (0.38 g, 5 mmole) in

EtOH (30 ml) was heated for 20 hr under reflux. The solution was concentrated by partial evaporation and then chromatographed on silica gel. Development with benzene–AcOEt (1 : 1) gave colorless prisms (0.15 g, 12%) melting at 79—80° after recrystallization from dil. EtOH. IR ν_{max}^{KBr} cm^{-1}: 3250, 1640 (CONH). Mass Spectrum *m/e*: 261 (M^+). *Anal.* Calcd. for $C_{12}H_{23}ONS_2$: C, 55.17; H, 8.81; N, 5.36. Found: C, 55.41; H, 8.58; N, 5.04.

β-Cyclohexylcarbamoylethyl *n*-Butyl Disulfide (IIIb)——A solution of bis(β-cyclohexylcarbamoylethyl) disulfide (1.80 g, 5 mmole), cyclohexylamine (0.99 g, 10 mmole) and *n*-butanethiol (0.45 g, 5 mmole) in EtOH (30 ml) was heated for 20 hr under reflux. The solution was concentrated by partial evaporation and the residue was chromatographed on silica gel. Development with benzene–AcOEt (1 : 1) gave colorless prisms (0.11 g, 8%). IR ν_{max}^{KBr} cm^{-1}: 3250, 1630 (CONH). *Anal.* Calcd. for $C_{13}H_{25}ONS_2$: C, 56.70; H, 9.15; N, 5.09. Found: C, 56.51; H, 8.92; N, 5.14.

Bis(β-cyclohexylcarbamoylethyl) Trisulfide (IIa) from Sodium β-Cyclohexylcarbamoylethylthiosulfate (IVa)——Sulfur (0.16 g, 5 m atom) was suspended to a solution of sodium β-cyclohexylcarbamoylethylthiosulfate (1.45 g, 5 mmole) and morpholine (0.87 g, 10 mmole) in H_2O (30 ml), and the mixture was heated for 20 hr under reflux. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH to give colorless prisms (0.20 g, 20%) melting at 188—189°. *Anal.* Calcd. for $C_{18}H_{32}O_2N_2S_3$: C, 53.42; H, 7.97; N, 6.92. Found: C, 53.93; H, 8.01; N, 6.55. This compound was identified with an authentic sample prepared from bis(β-cyclohexylcarbamoylethyl) disulfide by mixed melting point determination and by comparison of the IR spectra.

Bis[β-(*p*-chlorophenylcarbamoyl)ethyl] Trisulfide (IIb) from Sodium β-(*p*-Chlorophenylcarbamoyl)ethylthiosulfate (IVb)——Sulfur (0.16 g, 5 m atom) was suspended to a solution of sodium β-(*p*-chlorophenylcarbamoyl)ethylthiosulfate (1.58 g, 5 mmole) and cyclohexylamine (0.99 g, 10 mmole) in H_2O (30 ml) and the mixture was heated for 20 hr under reflux. The precipitates deposited upon cooling were collected by filtration and recrystallized from EtOH to give colorless prisms (0.20 g, 19%) melting at 197—199°. This was identified with an authentic sample obtained from bis[β-(*p*-chlorophenylcarbamoyl)ethyl] disulfide by mixed melting point determination and by comparison of the IR spectra.

Bis(β-benzylcarbamoylethyl) Trisulfide (IIc) from Sodium β-Benzylcarbamoylethylthiosulfate (IVc)——Sulfur (0.16 g, 5 m atom) was suspended to a solution of sodium β-benzylcarbamoylethylthiosulfate (1.485 g, 5 mmole) and cyclohexylamine (0.99 g, 10 mmole) in H_2O (30 ml) and the mixture was heated for 20 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from EtOH to give colorless prisms (0.65 g, 67%) of bis(β-benzylcarbamoylethyl) disulfide melting at 168—169°. Isolation of bis(β-benzylcarbamoylethyl) trisulfide from the filtrate was unsuccessful, but it was confirmed by thin-layer chromatograph.

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Interaction between Iodine and Polyvinylpyrrolidone or α-Pyrrolidone

Nobuyoshi Kaneniwa and Akiko Ikekawa

School of Pharmaceutical Sciences, Showa University[1]

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Polyvinylpyrrolidone (PVP)-iodine-ethanol solutions keep germicidal action of iodine and have toxicity weaker than that of iodine.[2] Detailed mechanism of interaction of PVP with iodine has not been clarified yet. Therefore, in this work, interaction of PVP or α-pyrrolidone with iodine was investigated.

1) Location: *Hatanodai, 1-5-8, Shinagawa-ku, Tokyo.*
2) G. Oster and E.H. Immergut, *J. Am. Chem. Soc.*, **76**, 1393 (1954); S. Siggia, *J. Am. Pharm. Assoc.*, **46**, 201 (1957).