BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 1554—1556(1972)

An Attempted Synthesis of 3,6-Epidithio-2,5-piperazinedione by Cyclization of *N*,*N*′-dialkyl-2,2′-dithiodicinnamamide

Juji YOSHIMURA and Yuichi SUGIYAMA
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Meguro-ku, Tokyo

(Received September 21, 1971)

It has been known that several antibiotics such as gliotoxin[1] and sporidesmin[2] have a characteristic partial structure of 3,6-epidithio-2,5-piperazinedione skeleton (**1**), and the numbers of analogous antibiotics are yet increasing.[3,4] Recently, Trown,[5] and Poisel and Schmidt[6] have reported the synthesis of 1,4-dimethyl-3,6-epidithio-2,5-piperazinedione (**1a**; R=R″=H, R′=R‴=CH_3) by substitution of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione with sodium thioacetate followed by hydrolysis and oxidation, however, that of the corresponding alkyl derivatives (**1b**; R=methyl, hydroxymethyl) has not yet appeared in literatures.

On the other hand, it is known that an amide group can be added to unsaturated carbons such as olefins[7]

---

[1] M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 1001 (1958).

[2] S. Safe and A. Taylor, *J. Chem. Soc. C*, **1970**, 432.

[3] R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. Delong, M. M. Marsh, and N. Neuss, *J. Amer. Chem. Soc.*, **90**, 2980 (1968).

[4] D. Hauser, H. P. Weber, and H. P. Sigg, *Helv. Chim. Acta*, **53**, 1061 (1970).

[5] P. W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968).

[6] H. Poisel and U. Schmidt, *Angew. Chem.*, **83**, 114 (1971).

[7] Erf. A. S. Matlack, *Chem. Abstr.*, **49**, 3244 (1955).

and carbonyls,[8] and in fact, *N*-aryl-pyruvamide was dimerized to 1,4-diaryl-3,6-dihydroxy-3,6-dimethyl-2,5-piperazinedione[9] by treatment with aqueous ammonia. Therefore, it was considered that dimerization of 2-thiopyruvamide (or corresponding enthiol (**2**)) may offer the desired intermediate for the synthesis of **1b**.

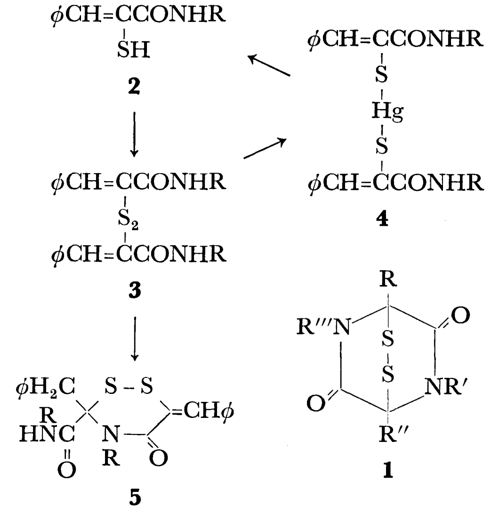
In this paper, the authors attempted to synthesize **1b** by dimeriaztion of *N*-alkyl-2-mercaptocinnamamide (**2**), or by intramolecular additive cyclization of *N,N′*-dialkyl-2,2′-dithiodicinnamamide (**3**).

Results and Discussion

As an analogous conversion of β-keto-acidamide to β-thio-analogue,[10] *N*-cyclohexyl-phenylglyoxylamide[11] was treated with hydrogen sulfide in ethanol saturated with dried hydrogen chloride at −90°C for 3 days, but only *N*-cyclohexyl-2,2-diethoxy-2-phenyl-acetamide (Found: C, 70.60; H, 9.29; N, 4.77%. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59%.) was obtained in 79% yield, and the same reaction at −10—+6°C for 10 hr gave white powder ($C_{28}H_{36}N_2O_2S_3$) in 68% yield, which could not be characterized. Moreover, attempted elimination of hydrogen sulfide from 2,2′-tetrathiodipropionanilide by thermal degradation or by treatment with heavy metals were unsuccessful.

On the other hand, 2,2′-dithiodicinnamyl chloride was synthesized by treatment of the free acid[12] in chloroform with phophorus pentachloride. Treatment of this unstable chloride with alkylamine gave no expected **3**, however, dropwise addition of the chloride in benzene to alkylamine hydrochloride in dimethylformamide under cooling gave **3** (R=methyl, ethyl, propyl, isopropyl, *n*-butyl) in 14—41% yield.

Attempted reduction of **3** to **2** with acetic acid and zinc was unsuccessful. Considering that **3** and **2** might be unstable both in alkaline and acid condition, reductive insertion reaction was tried by use of cuprous oxide or mercuric dichloride in the presence of potassium metabisulfate. In the former case **3** was recovered, but in the latter, the corresponding mercaptide (**4**) was afforded quantitatively, by adding triethylamine dropwise. Treatment of **4** with hydrogen sulfide gave no desired product, however, only *N*-isopropyl-2-mercaptocinnamamide (**2a**) was obtained in 45% yield. **2a** was successfully oxidized to **3d** by air, but conversion of **2a** to **1b** was not tried, because of its unstability.



Scheme 1

Table 1. Physical constants and analytical data of new compounds

	R′	Mp (°C)	Yield (%)	Found (Calcd),%			
				C	H	N	S
2a	Isopropyl	78	45	64.59	6.60	6.38	13.81
				(65.14)	(6.83)	(6.33)	(14.47)
3a	Methy	138	14	63.52	5.89	7.38	16.10
				(62.49)	(5.24)	(7.29)	(16.15)
3b	Ethyl	158	41	64.13	6.00	6.89	15.72
				(64.06)	(5.87)	(6.79)	(15.52)
3c	Propyl	120	28	65.16	6.62	6.58	14.62
				(65.44)	(6.41)	(6.36)	(14.53)
3d	Isopropyl	153	31	65.71	6.34	6.51	14.66
				(65.44)	(6.41)	(6.36)	(14.53)
3e	*n*-Butyl	116	31	66.56	6.62	6.15	13.68
				(66.65)	(6.88)	(5.98)	(13.67)
4a	Methyl	197	100	41.31	3.66	4.89	—
				(41.05)	(3.45)	(4.79)	—
4b	Ethyl	171	100	42.94	3.92	4.65	—
				(43.11)	(3.95)	(4.56)	—
4c	Propyl	163	100	45.00	4.45	4.36	—
				(44.95)	(4.40)	(4.37)	—
4d	Isopropyl	194	100	44.97	4.21	4.28	—
				(44.95)	(4.40)	(4.37)	—
4e	*n*-Butyl	154	100	46.89	4.84	4.22	—
				(46.66)	(4.82)	(4.19)	—
5a	Ethyl	234	10	64.00	6.07	6.60	15.33
				(64.06)	(5.87)	(6.79)	(15.52)
5b	Isopropyl	240	1	65.72	6.37	6.38	14.26
				(65.44)	(6.41)	(6.36)	(14.53)

In order to cyclize intramolecularly, **3b** and **3d** were treated with triethylamine to give 4-alkyl-3-alkylaminocarbonyl-3-benzyl-6-benzylidene-5-oxo-3,4,5,6-tetrahydro-1,2,4-dithiazine (**5a**; R=ethyl, **5b**; R=isopropyl) in 10 and 1% yield, respectively, accompanied with intractable sirup which seems to be intermolecular reaction products or degradated products. The structure of **5** was deduced from elemental analysis and the following facts. The existence of two triplet signals (τ 8.95, 9.35) of C-methyl protons of **5a** in NMR spectrum indicates that the two nitrogen atoms are in the different circumstances. Moreover, the presence of peaks *m/e* 379 (5a−SH) and 407 (5b−SH), and 308 (5a−$CONHC_2H_5$−S) and 322 (5b−$CONHC_3H_7$−S) in mass spectra of **5a** and **5b** (Fig. 1) indicated the presence of another intramolecular bond, in addition to a disulfide bond.

From these facts, it will be concluded that only one intramolecular cyclization was occured, because of a steric hindrance.

---

[8] A. Kaneda and R. Sudo, This Bulletin, **43**, 2159 (1970).

[9] A. Wohl and C. Oesterlin, *Ber.*, **34**, 1147 (1901).

[10] J. Goerdeler and W. Mittler, *ibid.*, **96**, 944 (1963).

[11] I. Ugi and U. Fetzer, *ibid.*, **94**, 1116 (1961).

[12] P. L. Julian and B. M. Sturgis, *J. Amer. Chem. Soc.*, **57**, 1126 (1935).

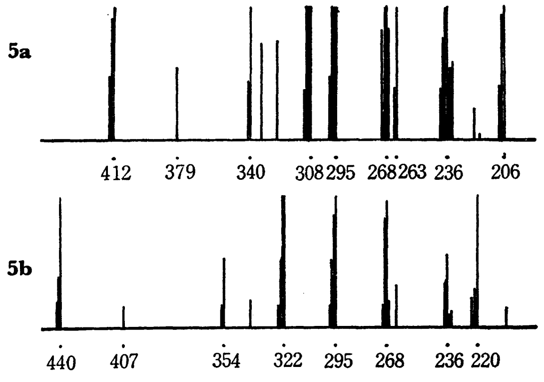


Fig. 1. Mass spectra of **5a** (R=ethyl, MW 412) and **5b** (R=Isopr., MW 440).

Experimental

All the melting points are uncorrected. The solutions were evaporated under reduced pressure at a bath temperature not exceeding 40°C. The infrared spectra were measured in KBr discs, and the NMR spectra were determined at 100 MHz with a JNM-100H spectrometer, using TMS as an internal reference. The mass spectra were obtained on a Hitachi RMU6E mass spectrometer, using a direct inlet and an ionization energy of 70 eV.

2,2′-Tetrathiodipropionanilide. Sulfur monochloride (0.34 g, 2.5 mmol) was added dropwise to 2-mercaptopropionanilide (0.9 g, 5 mmol)[13] in dried ether (100 m*l*) under cooling with ice-salt. This reaction mixture was allowed to stand for 1 day at room temperature, and white crystals deposited was filtered. Yield 0.9 g (73%); mp 134°C. Found: C, 50.92; H, 5.04; N, 6.68; S, 29.95%. Calcd for $C_{18}H_{20}N_2O_2S_4$: C, 50.94; H, 4.75; N, 6.60; S, 30.16%. IR (cm^{-1}): 3250 (N–H), 1650 (C=O).

General Synthesis of N,N′*-dialkyl-2,2′-dithiodicinnamamide (3).* A suspension of 2,2′-dithiodicinnamic acid (36 g, 0.1 mol) and excess amount of phosphorus pentachloride in chloroform mixed under cooling was stirred for 1 day at room temperature. After removal of phosphorus oxychloride, the resulted sirup was dissolved in water-free benzene, and then insoluble phosphorus pentachloride was filtered off. This filtrate was added dropwise into the dimethylformamide solution of alkylamine hydrochloride (0.2 mol) cooled with ice-salt. After standing for two hours at room temperature, this reaction mixture was neutralyzed with aqueous sodium bicarbonate and extracted with chloroform. The extract was washed with water, and concentrated to a viscous solution which gave white crystals. For example, *N*-ethyl derivative (**3b**) showed; IR (cm^{-1}): 3240 (N–H), 1620 (C=O). NMR (τ) in $CDCl_3$: 2.0 (s, 2H), 6.68 (m, 4H), 8.82 (t, 6H).

General Synthesis of Mercuric Biscinnamamide-2-thiolate (4). A suspended solution made by successive addition of water (100 m*l*) and potassium metabisulfate (2.0 g, 9 mmol) to a solution of **3** (4.5 mmol) and mercuric dichloride (2.0 g, 7.4 mmol) in methanol (500 m*l*), was stirred for 30 min. Further addition of a small amount of triethylamine gave white precipitates of **4**. After removal of methanol, precipitates were filtered and recrystallized from methanol to give white crystals.

N*-Isopropyl-2-mercaptocinnamamide (2a).* Hg thiolate (**4d**, 3.2 g, 4.9 mmol) and potassium sulfide (1 g, 9 mmol) were dissolved in water to give mercuric sulfide. After filtration, the filtrate was added into 5% solution of acetic acid in water (500 m*l*) to give **2a**, which was recrystallized from ethanol. IR (cm^{-1}): 3270 (N–H), 2550 (S–H).

4-Alkyl-3-alkylaminocarbonyl-3-benzyl-6-benzylidene-5-oxo-3,4,5,6-tetrahydro-1,2,4-dithiazine (5a and 5b). A solution of **3b** (1 g, 2.4 mmol) in chloroform was gradually added into the solution of triethylamine in chloroform for 30 min. After standing for 30 min at room temperature, the solution was concentrated, and the resulted powder was crystallized from chloroform–petroleum ether to give white crystals of **5a**. IR (cm^{-1}): 3300 (N–H), 1625 (C=O). NMR (τ) in DMSO (d_6): 8.95 (t, 3H), 9.35 (t, 3H). In the case of **5b**, it showed; IR (cm^{-1}): 3290 (N–H), 1620 (C=O).

The authors are indebted to Mr. K. Fukukawa for NMR measurements.

---

[13] H. Beckurts and G. Frerichs, *J. Prakt. Chem.*, **66**, 190 (1902).