SYNTHESIS OF 2,12-DITHIA[3](2,6)PYRIDINO[3](1,4)CYCL[3.2.2]AZINOPHANE AND IT'S BARRIER TO METHYLENE TWIST

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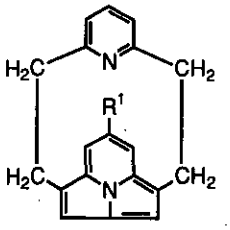
Abstract - A synthesis of the title compound (**11**) is completed starting from indolizine (**3**). Key intermediate, bis(mercaptomethyl)cycl[3.2.2]azine (**9**) has been synthesized by reduction of bis(acetylthiomethyl)cycl[3.2.2]azine (**8**) with $LiAlH_4$. 2,12-Dithia[3](2,6)pyridino[3](1,4)cycl[3.2.2]azinophanes (**11a,b**) have been synthesized by the reaction of **9** with 2,6-bis(bromomethyl)pyridine (**10**) in the presence of Cs_2CO_3 by the high dilution method. In the ^{1}H-nmr spectrum of **11a,b**, these exist in the *syn* conformation in their ^{1}H-nmr spectra. With regard to 2,12-dithia[3](2,6)pyridino[3](1,4)cycl[3.2.2]azinophane (**11a**), the coalescence temperature for the methylene twist yields an activation barrier, $\Delta G^{\ddagger}$, of 79.5 kJ mol^{-1} for variable temperature (VT) nmr method.

Cyclophanes have attracted much attention because of their unusual geometry and interesting proton nuclear magnetic resonance (^{1}H-nmr) spectra.[1] Recently syntheses of [2.2]cyclophanes containing heteroaromatic nuclei have been reported in the literature.[2] Among some of the common heteroaromatic nuclei which have been incorporated into the [2.2]cyclophane macrocycle are furan, thiophene, pyrrole, and pyridine.[2] However, except for our synthesis of [2.2.2.2](1,4)cycl[3.2.2]azine derivative,[3] the literature was devoid of [2.2]cyclophane containing cycl[3.2.2]azine nucleus[4] which was characterized as a nitrogen-bridged,

aromatic [10]annulene. As a part of our continuing work on the studies of cyclazines, we have reported the syntheses of 2,12-dithiacyclazinophanes (**11**) in the preliminary communication.[5] We now report a more detailed description of these earlier experiments and the examination of variable temperature (VT) nmr spectroscopy for dithiapyridinocyclazinophane (**11a**).



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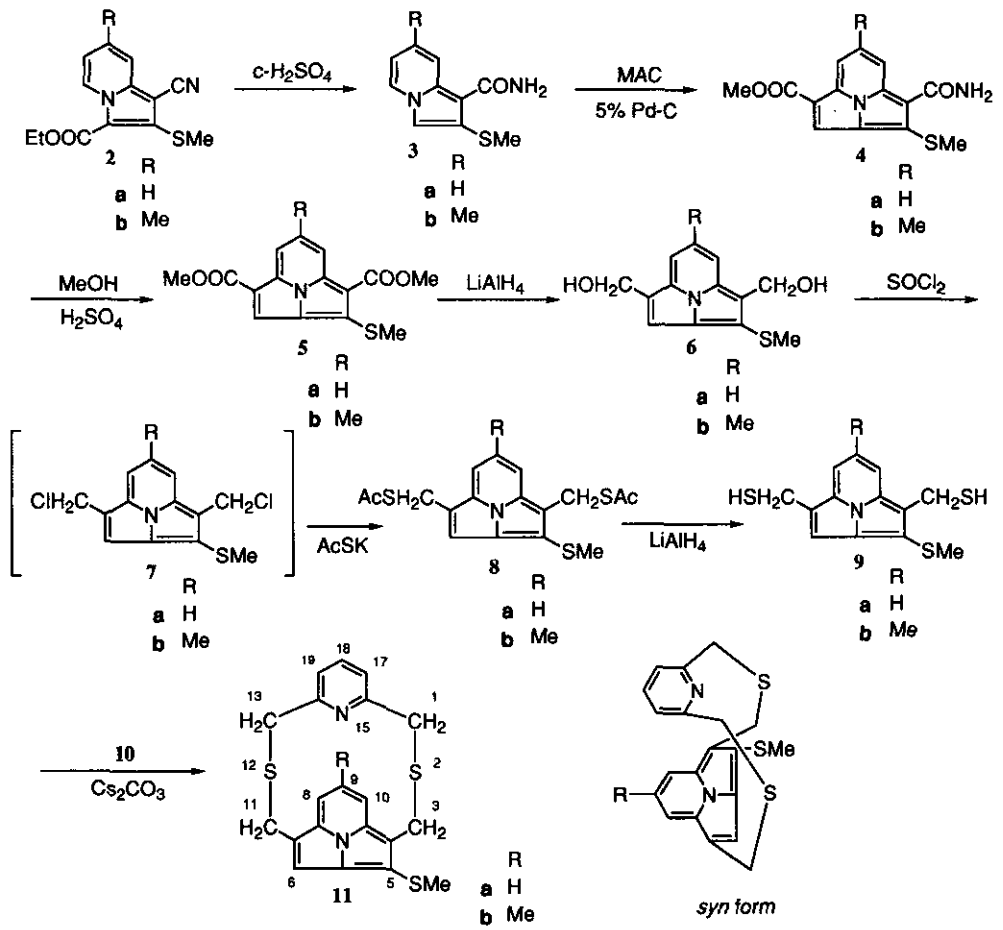
Generally, a procedure for the transformation of a sulfide linkage to a carbon-carbon single bond was demonstrated. This involved a Stevens rearrangement followed by the reduction with Raney Ni and has been utilized for syntheses of many cyclophanes.[2a] Hence, we have now tried to synthesize 2,12-dithia[3]-(2,6)pyridino[3](1,4)cycl[3.2.2]azinophane (**11**) which was the key intermediate for the synthesis of [2](2,6)pyridino[2](1,4)cycl[3.2.2]azinophane (**1**).

The starting indolizine derivatives (**3a,b**) used in the present work were prepared according to our previously reported method.[6] Compounds (**2a,b**) were treated with conc. H_2SO_4 at 100℃ for 5 h to give the carbamoyl derivatives (**3a,b**) with decarboxylation in 65% and 68% yields, respectively. Next, a synthesis of 1-carbamoylcycl[3.2.2]azines (**4a,b**) was achieved on employing the procedure of Boekelhide.[7] Thus, 1-carbamoylcyclazines (**4a,b**) were obtained by the reaction of **3a,b** with methyl acetylenecarboxylate (MAC) in the presence of 5% Pd-C in toluene under nitrogen atmosphere at 100℃ for 100 h in moderate yields. The diester derivatives (**5a,b**) were prepared by refluxing **4a,b** in MeOH with conc. H_2SO_4 for 70 h in good yields. Compounds (**5a,b**) were reduced by $LiAlH_4$ in THF to give 1,4-bis(hydroxymethyl)cyclazines (**6a,b**) in 78% and 72% yields, respectively. Attempts to separate in pure the desired bis(chloromethyl) compound (**7**) from the mixture obtained by the reaction of **6** with thionyl chloride were unsuccessful, because **7** was very unstable to heat. So the crude **7** was treated with potassium thioacetate in acetonitrile under nitrogen atmosphere at room temperature for 3 h to give the desired 1,4-bis(acethylthiomethyl)cyclazine (**8**). Key intermediates for the synthesis of cyclazinophanes, 1,4-bis(mercaptomethyl)cyclazines (**9a,b**) were obtained by the reduction of **8a,b** with $LiAlH_4$ in THF in good yields.

Attempts to obtain **11** by the reaction of **9** and 2,6-bis(bromomethyl)pyridine (**10**) in the use of K_2CO_3-DMF or KOH-EtOH, etc., were fruitless. After much investigation, the synthesis of **11** was achieved on employing the procedure of Buter.[8] Reaction of **9a,b** with **10** in the presence of Cs_2CO_3 in DMF gave the desired cyclazinophanes (**11a,b**) in 7 % and 10 % yields, respectively. The assignment of structures of **11a,b** was confirmed by the spectroscopic properties.



Scheme 1

In the ^{1}H-nmr spectrum of **11a**, the proton of C_9-H shows an upfield shift due to the ring current of the opposite pyridine ring and appears as two triplets at δ 6.52-6.59 (C_6-H of **9a**: δ 7.62). In addition, the protons of 9-methyl group of **11b** are also shifted upfield to δ 1.67 (6-CH_3 of **9b**: δ 2.77). Thus, it is concluded that the conformer of **11** is the *syn* form (Scheme 1).

VT-Nmr has useful in the determination of energy barriers for meta-bridged ring flip in [2.2]-cyclophanes.[2a] However, relatively fewer investigations of energy barriers for methylene twist in [3.3]-cyclophanes with hetero atoms in bridge have been reported.[9] We now wish to describe the VT-nmr behavior of **11a** for methylene twist using standard VT-nmr method.

The ^{1}H-nmr spectrum of **11a** in $CDCl_3$ at 25℃ suggests that it exists in the conformational mixtures of **11a** because of the observation of the C_9-H proton signal as two triplet. When the temperature was raised stepwise to 80℃, the proton signal began to appear as single triplet at 70℃.

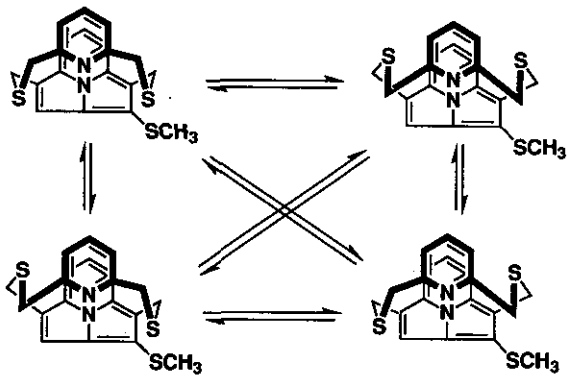
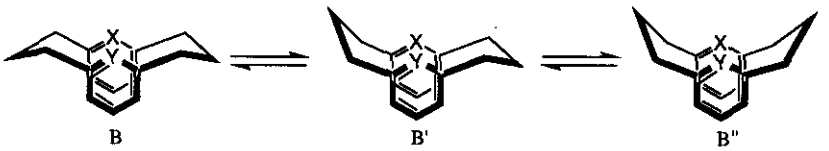


Figure 1

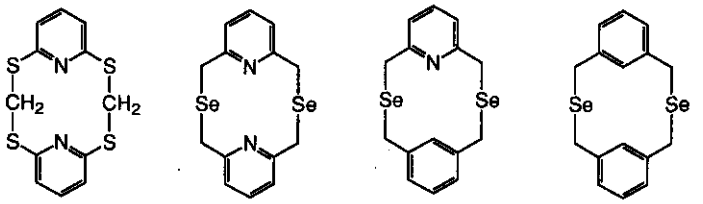
However, the aromatic proton signals of **11a** exhibited no change in the shape of the *syn* conformer and then the conformational change involving ring flip was not observed as in the present case. From the above, the transformation that is consistent with these VT-nmr studies is the rocking motion of the bridge as shown in Figure 1, originally suggested by Newkome.[9a]

The coalescence temperature (*Tc*) of 70℃ for the C_9-H proton signal along with the nmr line width (*kc*) of 1.44 Hz yields $\Delta G^{\ddagger}$ for the methylene twist of **11a** to be 79.5 kJ mol^{-1} (19.2 kcal mol^{-1}),[2a,10] which is higher than those of [3.3]metacyclophanes(**12**, **13**, **14**, **15**)[9] (Table 1).

Table 1. *Tc* and $\Delta G^{\ddagger}$ data for [3.3]metacyclophanes B ⇌ B' ⇌ B" and **11a**



B B' B"



	12	**13**	**14**	**15**	**11a**
Tc (°C)	-50	-90	-105	-123	70
$\Delta G^{\ddagger}$ (kcal/mol)	12.2	9.0	8.2	7.3	19.2

Thus, compound (**11a**) is more rigid than these meta-cyclophanes because of the bulkiness of the large cyclazine skeleton and the large sulfur atom of the methylthio group. We suggested that these bulkiness should restrict the conformational change involving the ring flip. Our further attempts to synthesize [2.2]-cyclazinophane (**1**) by Stevens rearrangement *via* a bis(sulfonium) salt of **11**, were fruitless.

EXPERIMENTAL

Melting points were determined with a Mitamura Mel-Temp and are uncorrected. Ir spectra were recorded on a JASCO IRA-2 spectrophotometer. Uv spectra were recorded on a Hitachi 323 spectrophotometer. ^{1}H-Nmr spectra were obtained on a JNM-FX-90Q (90 MHz) spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in part per million (δ). Elementary analyses (C,H,N) of all compounds described here performed on a Yanagimoto MT-2 CHN recorder.

Synthesis of 1-Carbamoyl-2-methylthioindolizines (3a,b)

A solution of **2**[6] (100 mmol) in conc. H_2SO_4 (100 ml) was heated at 100℃ for 5 h. The reaction mixture was cooled at room temperature and poured into ice-cold water (2000 ml). The precipitate was filtered, washed with water, dried and recrystallized from $CHCl_3$-EtOH to give **3**.

3a: mp 140-141℃ (65 %) (*lit.*,[6c] mp 140℃).

3b: mp 176-177℃ (68 %); ir (KBr) 3400 (NH), 1620 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 224 (4.33)sh, 238 (4.38), 244 (4.37), 254 (4.22)sh, 272 (3.96)sh, 296 (3.84)sh, 308 (3.98), 338 (3.91) nm; ^{1}H-nmr ($CDCl_3$) 2.35 (3H, s, CH_3), 2.43 (3H, s, SCH_3), 6.52 (1H, d, *J*=7 Hz, C_6-H), 7.22 (1H, s, C_3-H), 7.77 (1H, d, *J*=7 Hz, C_5-H), 8.23 (1H, s, C_8-H). *Anal.* Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.14; H, 5.33; N, 12.61.

1-Carbamoyl-4-methoxycarbonyl-2-methylthiocycl[3.2.2]azines (4a,b)

A suspension of compound (**3**) (150 mmol) and methyl acetylenecarboxylate (MAC) (50.4 g, 600 mmol) in toluene (300 ml) containing 5% Pd-C (13 g) under nitrogen atmosphere was heated at 100℃ for 100 h. After being cooled, the precipitate was filtered and extracted with hot $CHCl_3$-MeOH (1:1), and the organic layer was then evaporated. The residue was recrystallized from $CHCl_3$-MeOH to give **4**.

4a: mp 222-225℃ (45 %); ir (KBr) 3150 (NH), 1680 (CO), 1660 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 226 (4.24), 252 (4.47), 272 (4.35)sh, 289 (4.25)sh, 298 (4.14)sh, 354 (4.15), 388 (4.17), 392 (4.23) nm; ^{1}H-nmr ($CDCl_3$) 3.04 (3H, s, SCH_3), 4.10 (3H, s, OCH_3), 8.00 (1H, t, *J*=8 Hz, C_6-H), 8.20-8.40 (3H, m, C3,5,7-H). *Anal.* Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.19; N, 9.72. Found: C, 58.06; H, 4.32; N, 9.74.

4b: mp 274-275℃ (48 %); ir (KBr) 3160 (NH), 1720 (CO), 1640 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 228 (4.17)sh, 250 (4.41)sh, 256 (4.44), 274 (4.40)sh, 290 (4.26)sh, 300 (4.06)sh, 356 (4.14), 400

(4.15), 412 (4.17)sh, 430 (3.27)sh nm; ^{1}H-nmr ($CDCl_3$) 2.80 (3H, s, CH_3), 2.95 (3H, s, SCH_3), 4.02 (3H, s, OCH_3), 6.21 (2H, s, NH_2), 8.00-8.20 (3H, m, $C_{3,5,7}$-H). *Anal.* Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.38; H, 4.64; N, 9.10.

1,4-Bis(methoxycarbonyl)-2-methylthiocycl[3.2.2]azines (5a,b)

A solution of compound (**5**) (40 mmol) and conc. H_2SO_4 (25 ml) in MeOH (500 ml) was refluxed for 70 h. The reaction mixture was evaporated under reduced pressure. The residue was poured into ice-cold water (1000 ml), and extracted with $CHCl_3$ (3x50 ml). The extract was washed with water (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give **5**.

5a: mp 169-171℃ (90 %); ir (KBr) 1700 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 226 (4.64), 246 (4.83), 252 (4.83)sh, 278 (4.79), 288 (4.70)sh, 298 (4.61), 354 (4.60), 392 (4.65)sh, 400 (4.75); ^{1}H-nmr ($CDCl_3$) 2.95 (3H, s, SCH_3), 4.02 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.91 (1H, t, *J*=8 Hz, C_6-H), 8.15 (1H, s, C_3-H), 8.16 (1H, d, *J*=8 Hz, C_5-H or C_7-H), 8.25 (1H, d, *J*=8 Hz, C_5-H or C_7-H). *Anal.* Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62. Found: C, 59.10; H, 4.26; N, 4.90.

5b: mp 219-221℃ (11.68 g, 92 %); ir (KBr) 1690 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 227 (4.20), 250 (4.43)sh, 255 (4.44), 277 (4.47), 292 (4.40)sh, 300 (4.17), 356 (4.22), 398 (4.27), 408 (4.47) nm; ^{1}H-nmr ($CDCl_3$) 2.79 (3H, s, CH_3), 2.92 (3H, s, SCH_3), 4.03 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 7.91 (1H, s, C_5-H or C_7-H), 8.02 (1H, s, C_5-H or C_7-H), 8.05 (1H, s, C_3-H). *Anal.* Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.32; H, 4.76; N, 4.45.

1,4-Bis(hydroxymethyl)cycl[3.2.2]azines (6a,b)

A solution of compound (**5**) (10 mmol) in THF (300 ml) under nitrogen atmosphere was added in portion over 6 h at 0℃ to a stirred suspension of THF (200 ml) containing $LiAlH_4$ (3.80 g, 100 mmol). After stirring for 24 h at room temperature, ethyl acetate (20 ml) and a saturated solution of NH_4Cl in water (1000 ml) were added sequentially. After stirring for 24 h at room temperature, the reaction mixture was extracted with CH_2Cl_2 (5x100 ml). The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was recrystallized from CH_2Cl_2 to give **6**.

6a: mp 118-120℃ (78 %); ir (KBr) 3350 (OH) cm^{-1}; uv (EtOH) λmax (log ε) 214 (4.33), 226 (4.30)sh, 251 (4.45), 272 (4.17)sh, 331 (4.09), 416 (3.79) nm; ^{1}H-nmr (DMSO-d_6) 2.84(3H, s, SCH_3), 5.00-5.10 (4H, m, 2xCH_2), 7.57 (1H, s, C_3-H), 7.61 (1H, t, *J*=9 Hz, C_6-H), 7.94 (1H, d, *J*=9 Hz, C_5-H or C_7-H),

7.97 (1H, d, *J*=9 Hz, C_5-H or C_7-H). *Anal.* Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 62.93; H, 5.23; N, 5.64.

6b: mp 131-132℃ (72 %); ir (KBr) 3350(OH) cm^{-1}; uv (EtOH) λmax (log ε) 217 (4.25), 230 (4.23)sh, 252 (4.39), 257 (4.36)sh, 275 (4.16)sh, 333 (4.03), 418 (3.81); ^{1}H-nmr (DMSO-d_6) 2.73 (3H, s, CH_3), 2.82 (1H, s, SCH_3), 4.80-5.00 (4H, m, 2xCH_2), 7.61 (1H, s, C_3-H), 7.82 (1H, s, C_5-H or C_7-H), 7.85 (1H, s, C_5-H or C_7-H). *Anal.* Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.60; H, 5.57; N, 5.57.

1,4-Bis(acetylthiomethyl)cycl[3.2.2]azines (8a,b)

A solution of $SOCl_2$ (2.86 g, 24 mmol) in THF (10 ml) was added in portion to a stirred solution of compound (**6**) (10 mmol) in THF (10 ml) under nitrogen atmosphere at 0℃. After stirring for 3 h at room temperature, the reaction mixture was evaporated under reduced pressure below 30℃. The residue and potassium thioacetate (24 mmol) were suspended in acetonitrile (200 ml) under nitrogen atmosphere and the suspension was stirred for 3 h at room temperature. The reaction mixture was evaporated under reduced pressure below 50℃ and the residue was submitted to column chromatography on silica gel. From a benzene fraction, compound (**8**) was obtained.

8a: mp 98-100℃ (40 %); ir (KBr) 1680 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 234 (4.43)sh, 252 (4.47), 280 (4.14)sh, 326 (4.04)sh, 338 (4.06), 420 (3.86) nm; ^{1}H-nmr ($CDCl_3$) 2.34 (3H, s, $COCH_3$), 2.35 (3H, s, $COCH_3$), 2.82 (3H, s, SCH_3), 4.63 (4H, s, 2xSCH_2), 7.47 (1H, s, C_3-H), 7.62 (1H, t, *J*=8 Hz, C_6-H), 7.90 (1H, d, *J*=8 Hz, C_5-H or C_7-H), 7.94 (1H, d, *J*=8 Hz, C_5-H or C_7-H). *Anal.* Calcd for $C_{17}H_{17}NO_2S_3$: C, 56.17; H, 4.71; N, 3.85. Found: C, 56.26; H, 4.68; N, 3.92.

8b: mp 128-129℃ (43 %); ir (KBr) 1690 (CO) cm^{-1}; uv (EtOH) λmax (log ε) 217 (4.33)sh, 253 (4.46), 262 (4.39)sh, 280 (4.17)sh, 330 (4.09), 340 (4.01), 430 (3.90); ^{1}H-nmr ($CDCl_3$) 2.34 (3H, s, $COCH_3$), 2.35 (3H, s, $COCH_3$), 2.76 (3H, s, CH_3), 2.80 (3H, s, SCH_3), 4.59 (4H, s, 2xSCH_2), 7.41 (1H, s, C_3-H), 7.68 (1H, s, C_5-H or C_7-H), 7.72 (1H, s, C_5-H or C_7-H). *Anal.* Calcd for $C_{18}H_{19}NO_2S_3$: C, 57.26; H, 5.07; N, 3.71. Found: C, 56.99; H, 5.02; N, 3.83.

1,4-Bis(mercaptomethyl)cycl[3.2.2]azines (9a,b)

A solution of compound (**8**) (4 mmol) in THF (100 ml) under nitrogen atmosphere was added in portion over 1 h at 0℃ to a stirred suspension of THF (100 ml) containing $LiAlH_4$ (0.76 g, 20 mmol). After

stirring for 3 h at room temperature, ethyl acetate (4 ml) and a saturated solution of NH_4Cl in water (100 ml) were added sequentially. After stirring for 1 h at room temperature, the reaction mixture was extracted with CH_2Cl_2 (5x100 ml). The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was recrystallized from CH_2Cl_2 to give **9**.

9a: mp 94-95℃ (98 %) (*lit.*,[5] mp 95℃).

9b: mp 133-135℃ (97 %) (*lit.*,[5] mp 135℃).

2,12-Dithia-5-methylthio[3](2,6)pyridino[3](1,4)cycl[3.2.2]azinophanes (11a,b)

Compound (**9**) (3.7 mmol) and 2,6-bis(bromomethyl)pyridine (**10**) (0.93 g, 3.7 mmol) were each dissolved separately in DMF (60 ml). They were added constantly into a suspension of DMF (500 ml) containing Cs_2CO_3 (5 g, 15.3 mmol) over 10 h at 60℃ under nitrogen atmosphere. After stirring for 48 h at room temperature, the reaction mixture was evaporated under reduced pressure below 60℃ and the residue was submitted to column chromatography on silica gel. From a benzene fraction, compound (**11**) was obtained.

11a: mp 167-170℃ (7 %) (*lit.*,[5] mp 170℃).

11b: mp 161-163℃ (10 %) (*lit.*,[5] mp 163℃).

REFERENCES

1. a) M. P. Keehn and S. M. Rosenfold, 'Cyclophanes', Academic Press, New York, Vols I and II, 1983. b) M. W. Haenel, B. Lintner, R. Benn, A. Rufinsha, G. Schroth, C. Kruger, S. Hirsch, H. Irngartinger, and D. Schweitzer, *Chem. Ber.*, 1985, **118**, 4884. c) R. A. Pascal, C. G. Winans, and D. V. Engen, *J. Am. Chem. Soc.*, 1989, **111**, 3007. d) S. Muralidharan, M. Hojjatie, M. Firestone, and H. Freiser, *J. Org. Chem.*, 1989, **54**, 393.
2. a) I. Gault, B. J. Price, and I. O. Sutherland, *J. Chem. Soc., Chem. Comm.*, **1967**, 540. b) H. Wynberg and R. Helder, *Tetrahedron Lett.*, **1971**, 4317. c) S. M. Rosenfold and P. M. Keehn, *ibid.*, **1973**, 4021. d) V. Boekelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Comm.*, **1973**, 406.
3. H. Gotou, K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles*, 1982, **17**, 325.
4. a) A. Taurin, *Chem. Heterocycl. Compd.*, 1977, **30**, 245. b) K. Matsumoto, T. Uchida, and S. Yamauchi, *J. Syn. Org. Chem. Japan*, 1977, **35**, 739. c) W. Flitsh and U. Kramer, *Adv. Heterocycl. Chem.*, 1979, **22**, 321. d) S. J. Lee and J. M. Cook, *Heterocycles*, 1983, **20**, 87. e) Y. Matsuda and H. Gotou, *ibid.*, 1989, **26**, 2757.
5. Y. Matsuda, H. Gotou, K. Katou, H. Matsumoto, M. Yamashita, K. Takahashi, and S. Ide, *Heterocycles*, 1990, **31**, 983.
6. a) C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1974, **94**, 839. b) S. Hidaki, Y. Tominaga, Y. Matsuda, G. Kobayashi, and K. Sakemi, *ibid.*, 1979, **99**, 1234. c) Y. Tominaga and Y. Matsuda, *J. Syn. Org. Chem. Japan*, 1985, **43**, 669.
7. V. Boekelheide and T. Small, *J. Am. Chem. Soc.*, 1961, **83**, 462.
8. J. Buter and R. M. Kellogg, *J. Org. Chem.*, 1981, **46**, 4481.
9. G. R. Newkome, S. Pappalardo, and F. R. Fronczek, *J. Am. Chem. Soc.*, 1983, **105**, 5152.
10. H. Gunter, 'NMR Spectroscopy', Wiley, New York, 1980, p. 240.

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