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Studies on Fused Indoles. I. Novel Synthesis of 4-Aminomethyltetrahydrothiopyrano[2,3-*b*]indoles through a Thio-Claisen Rearrangement

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Two novel and simple methods for preparing 4-aminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles are described. Both involve thio-Claisen rearrangements of indol-2-yl propargyl sulfides as a key step which affords thiopyrano[2,3-*b*]indoles in good yields. Elaboration of these compounds led to fused tryptamine analogues which were found to have strong analgesic activity. The mechanism of this novel rearrangement is discussed.

Keywords——thiopyrano[2,3-*b*]indole; aryl propargyl sulfide; rigid tryptamine; thio-Claisen rearrangement; analgesic activity

A number of tryptamine derivatives (*e.g.*, serotonin, melatonin, *etc.*) are known to have physiological activity.[1] From a pharmacological point of view, it seemed interesting to prepare rigid analogues in which an extra ring system is introduced to limit the side-chain flexibility. Therefore, we tried to synthesize thiopyran-fused tryptamines by means of the thio-Claisen rearrangement,[2] which we have studied extensively.[3] This report describes the novel synthesis of 4-aminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles,[4] which were found to have analgesic activity. Structural modifications and the results of biological evaluation will be reported in the following paper.[5]

Synthesis

Chart 1 shows our routes for the preparation of 4-aminomethyltetrahydrothiopyranoindole derivatives (**5**, **8** and **9**). Indol-2-yl propargyl sulfide (**2**) was prepared from indoline-2-thione (**1**) and propargyl bromide in the presence of potassium carbonate in 98% yield. Thermolysis of **2** in refluxing ethanol afforded labile 2,9-dihydrothiopyrano[2,3-*b*]indole (**3**) in quantitative yield after careful work-up. This reaction is considered to involve the thio-Claisen rearrangement and subsequent ring-closure in a similar process to the thermolysis of **6**, which is described later. In practice, **3** prepared *in situ* was treated with aqueous potassium cyanide to give the nitrile **4** in 69% yield from **2**. Reduction of **4** with a mixture of $LiAlH_4$ and $AlCl_3$ afforded the desired tryptamine (**5**), in which analgesic activity was originally found, in 72% yield.

The analgesic potency could be enhanced by N^b-alkylation of **5**, and this finding led us to explore an improved synthetic method suitable for further modifications. We found that the aldehyde **7** could be readily obtained from the thione **1** in only two steps and could serve as a key synthetic intermediate. 4-Hydroxybutyn-2-yl indol-2-yl sulfide (**6**) was prepared quantitatively from **1** and 4-chloro-2-butyn-1-ol. Thermolysis of **6** in pyridine at 100 °C gave the aldehyde **7** in 79% yield. The mechanistic features of this unique transformation will be discussed later.

Treatment of **7** with methylamine in methanol followed by reduction with $NaBH_4$ in a one-pot procedure gave an *N*-methylaminomethylthiopyranoindole (**8**) in 90% yield. Alternatively, **7** was subjected to reductive amination with dimethylamine and formic acid in

benzene–*N*,*N*-dimethylformamide (DMF) (a modification of the Leuckart–Wallach reaction[6]) to afford an *N*,*N*-dimethylaminomethyl analogue **9** in 88% yield. These methods led to the synthesis of N^b-alkylated analogues in only three steps from the thione **1** and in excellent overall yields (*ca.* 70%). Their application for further modification will be described in the following paper.[5]

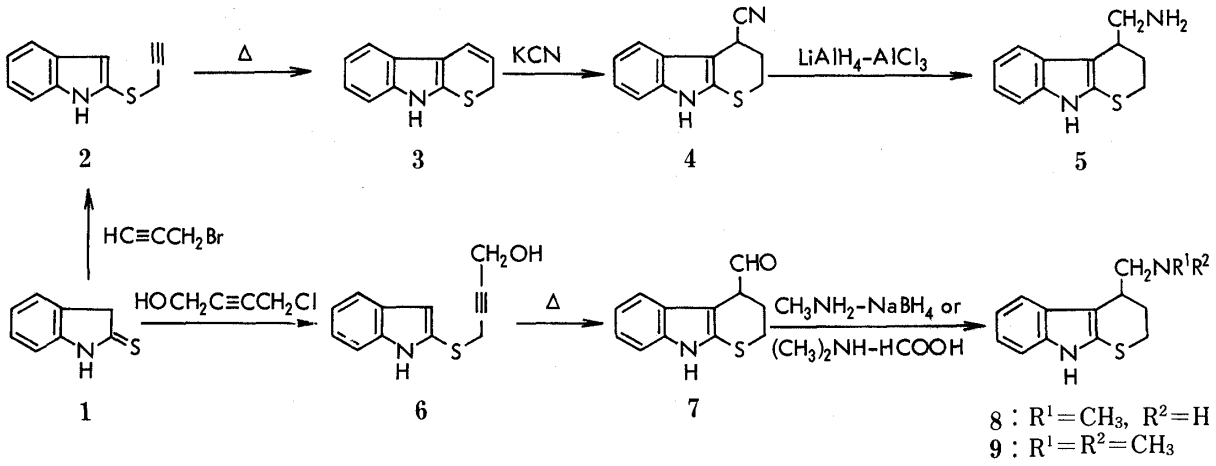

Chart 1

Mechanism of the Transformation of 6 into 7

Chart 2 shows a possible pathway for the transformation of **6** into **7**. The sequence for the conversion of **6** into the presumed intermediate **10** is probable, because a similar mechanism was established for the rearrangement of aryl propargyl ethers by Schmid.[7] However, further conversion of **10** into **7** is unusual in that its allylic alcohol moiety easily

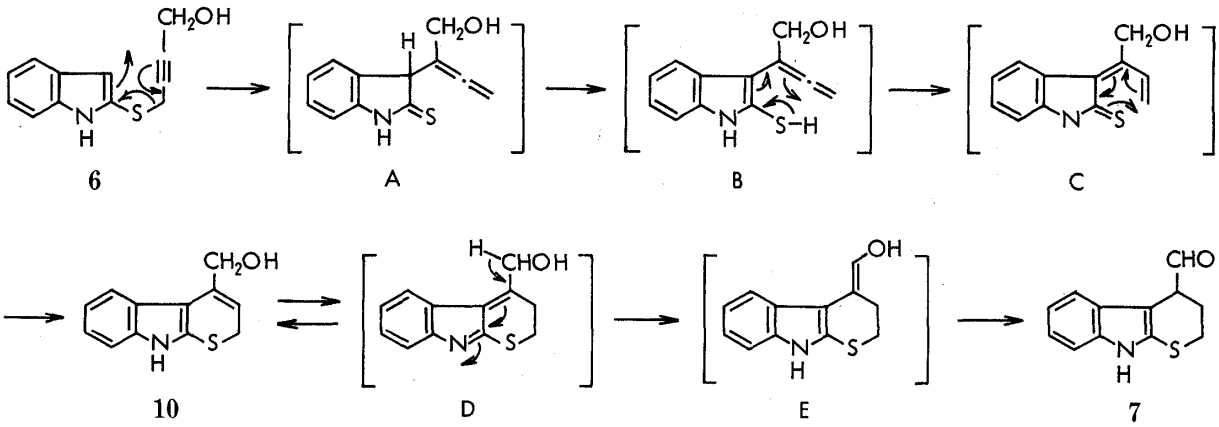

Chart 2

changes into an aldehyde group by thermal isomerization. Therefore, proof was needed that **10** was formed as an intermediate. Since attempted isolation of **10** from the thermal mixture failed, an alternative route was devised as shown in Chart 3. This route is based on the idea that introducing an electron-withdrawing group at the indole nitrogen of **10** may inhibit further thermal conversion.

Reaction of **6** with *tert*-butyldimethylchlorosilane followed by acetylation gave **12**, which was treated with hydrogen fluoride (HF) to afford **13** in good yield. Thermolysis of **13** in toluene–pyridine generated a cyclized product **14** in 88% yield. Careful hydrolysis with $NaOCH_3$ in methanol gave **10** as an unstable oil, which had a nuclear magnetic resonance

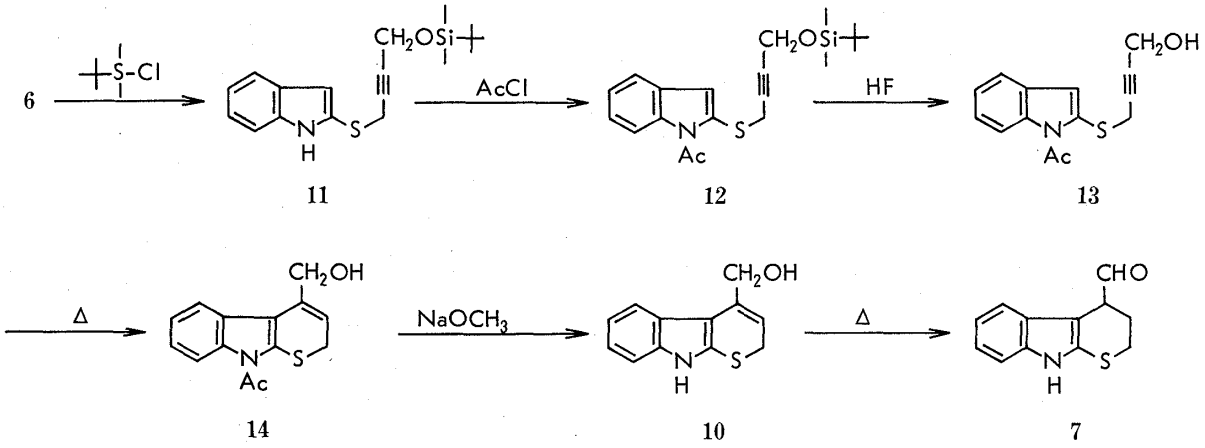

Chart 3

(NMR) spectrum consistent with its expected structure. As anticipated, heating of **10** in pyridine quantitatively yielded the aldehyde **7**. Alternatively, when highly purified[8] **6** was heated in pyridine-d_5 (Py-d_5) and quenched at 50% conversion, transitory formation of **10** was detected in the NMR spectrum of the solution (*ca.* 30% yield based on the signal ratios). These findings indicated the presence of **10** as a real intermediate in the transformation of **6** into **7**.

The conversion of **10** into **7** may be rationalized as follows. Compared to the tautomerism between **10** and D, conversion of D into E seems to be less favorable due to the need for deprotonation from the carbon carrying the hydroxyl group. However, even slight formation of E in the tautomerism should lead to complete production of **7** because the final step is essentially irreversible.

Conclusion

The present studies provide two novel and efficient methods for preparing 4-aminomethyltetrahydrothiopyrano[2,3-*b*]indoles and demonstrate the utility of the thio-Claisen rearrangement of aryl propargyl sulfides in the synthesis of fused heterocycles.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrophotometer. NMR spectra were recorded on a Varian T-60 instrument with tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Hitachi RMU-8GN mass spectrometer.

Unless otherwise noted, reactions were conducted under a nitrogen atmosphere and organic extracts were washed with water and dried over $MgSO_4$.

Indol-2-yl Propargyl Sulfide (2)——A solution of indoline-2-thione (**1**)[9] (14.9 g, 0.1 mol) in acetone (300 ml) was treated with K_2CO_3 (16.5 g, 0.12 mol) and propargyl bromide (14.3 g, 0.12 mol) at room temperature. The mixture was stirred at room temperature for 3 h, then filtered and the filtrate was concentrated. The residue was taken up in H_2O and extracted with Et_2O. The extract was washed, dried and concentrated, and the residual oil was chromatographed on silica gel [100 g, benzene–hexane (1 : 1)], giving **2** as a colorless oil (18.3 g, 98%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3300. NMR ($CDCl_3$) δ: 2.28 (1H, t, J=2.5 Hz), 3.43 (2H, d, J=2.5 Hz), 6.73 (1H, d, J=2 Hz), 6.9—7.7 (4H, m), 8.25 (1H, br, NH). *Anal.* Calcd for $C_{11}H_9NS$: C, 70.55; H, 4.84; N, 7.48; S, 17.12. Found: C, 70.28; H, 4.89; N, 7.66; S, 17.00.

2,9-Dihydrothiopyrano[2,3-*b*]indole (3)——A solution of the sulfide **2** (50 mg) and Et_3N (1 drop) in EtOH (5 ml) was refluxed for 1.5 h. Evaporation of the solution gave **3** as a pale green solid (*ca.* 50 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450. NMR ($CDCl_3$) δ: 3.60 (2H, dd, J=5, 1.5 Hz), 5.40 (1H, dt, J=10, 5 Hz), 6.78 (1H, td, J=1.5, 10 Hz), 7.0—8.0 (4H, m), 8.35 (1H, br).

4-Cyano-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (4)——A solution of the sulfide **2** (13.2 g, 0.07 mmol) and Et_3N (1 ml) in EtOH (300 ml) was refluxed for 1 h, a solution of KCN (25 g, 0.38 mmol) in EtOH (170 ml)–H_2O (80 ml) was added, and the mixture was refluxed for 2 h, then concentrated, diluted with H_2O and extracted with Et_2O. After the extract had been washed, dried and evaporated, the residual oil was chromatographed on silica gel (450 g, benzene) to give **4** as crystals (10.4 g, 69%), mp 125—126 °C (from EtOH–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 2230. NMR ($CDCl_3$) δ: *ca.* 2.5 (2H, m), *ca.* 3.3 (2H, m), 4.15 (1H, t, J=5 Hz), 7.0—7.7 (4H, m), 7.9 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07; S, 14.96. Found: C, 66.97; H, 4.61; N, 12.82; S, 15.07.

4-Aminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (5)——A solution of **4** (12 g, 0.056 mol) in anhydrous Et_2O (300 ml) was added dropwise to a mixture of $AlCl_3$ (18.7 g, 0.14 mol) and $LiAlH_4$ (5.4 g, 0.14 mol) in anhydrous Et_2O (200 ml) over 45 min at room temperature. The mixture was stirred at room temperature for 2 h, then 20% aq. NaOH (65 ml) was added at ice-bath temperature. The mixture was extracted with Et_2O and the extract was washed, dried and concentrated. The residual oil was treated with ethanolic oxalic acid to give an oxalate [15 g, mp *ca.* 238 °C (dec.)]. An aqueous suspension of this salt was basified with aq. NaOH and extracted again with Et_2O. The extract was washed, dried and evaporated, giving an oil (9.4 g), which when crystallized from EtOH–hexane–Et_2O, afforded **5** (8.8 g, 72%), mp 122—125 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450. NMR ($CDCl_3$) δ: *ca.* 1.3 (2H, br, NH_2), *ca.* 2.2 (2H, m), *ca.* 3.1 (5H, m), 6.9—7.6 (4H, m), *ca.* 8.5 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 66.24; H, 6.51; N, 12.72; S, 14.51.

4-Hydroxybut-2-ynyl Indol-2-yl Sulfide (6)——A mixture of indoline-2-thione (**1**) (7.45 g, 0.05 mol), K_2CO_3 (7.60 g, 1.1 eq) and 4-chloro-2-butyn-1-ol[10] (5.48 g, 1.05 eq) in acetone (75 ml) was stirred at room temperature for 5 h. The mixture was filtered and the filtrate was evaporated completely. The residue was treated with Et_2NH (10 ml) to decompose the unreacted reagent (room temperature, 1 h). The diethylamine was evaporated off and the residue was dissolved in Et_2O. The solution was washed (2 N HCl, H_2O) and dried. Removal of the solvent left **6** as an oil (12 g), which was used without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450. NMR ($CDCl_3$) δ: 2.01 (1H, s, OH), 3.57 (2H, t, J=2 Hz), 4.27 (2H, t, J=2 Hz), 6.80 (1H, d, J=2 Hz), 7.0—7.8 (4H, m); (Py-d_5) δ: 3.92 (2H, t, J=2 Hz), 4.50 (2H, t, J=2 Hz), *ca.* 4.6 (1H, br, OH), 6.62 (1H, s). 7.0—7.9 (4H, m). If pure **6** was required, the above oil was chromatographed on silica gel with benzene–ethyl acetate (10 : 1).

4-Formyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (7)——A solution of **6** (12 g) in pryidine (120 ml) was stirred at 100 °C for 2 h. After removal of the solvent, the residue was dissolved in Et_2O. The solution was washed (2 N HCl, H_2O) and dried, then evaporation provided an oil (11 g), which was chromatographed on silica gel (55 g, benzene) to give **7** as a colorless oil (8.14 g, 75% from **1**), which solidified on standing in a refrigerator (mp 60—65 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1720. NMR ($CDCl_3$) δ: 1.8—3.2 (4H, m), 3.85 (1H, m), 7.0—7.6 (4H, m), *ca.* 8.1 (1H, br), 9.83 (1H, d, J=2 Hz); (Py-d_5) δ: 1.8—3.6 (4H, m), 4.0 (1H, m), 6.4 (1H, br), 7.1—7.9 (4H, m), 10.02 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45; S, 14.76. Found: C, 66.16; H, 5.15; N, 6.20; S, 14.64.

4-(*N*-Methylaminomethyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (8)——A 30% methanolic solution of CH_3NH_2 (2.2 ml, *ca.* 1.5 eq) was added to a stirred solution of **7** (2.17 g, 10 mmol) in MeOH (20 ml) at room temperature. After 1 h, $NaBH_4$ (380 mg, 10 mmol) was added to the mixture at ice-bath temperature and stirring was continued at room temperature for 2 h. The mixture was concentrated and acidified with 2 N HCl, then extracted with $CHCl_3$ to remove the neutral material (*ca.* 100 mg). The aqueous layer was alkalized again (aq. NaOH) and extracted with $CHCl_3$. After the extract had been washed, dried and concentrated, the residue was treated with benzene to give almost pure **8** as a benzene adduct (mp 70—75 °C, 2.21 g, 90%). Recrystallization from benzene gave an analytical sample, mp 78—81 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450. NMR ($CDCl_3$) δ: *ca.* 2.3 (2H, m), 2.50 (3H, s), 2.7—3.5 (5H, m), 7.0—7.7 (5H, m). *Anal.* Calcd for $C_{13}H_{16}N_2S$ $(C_6H_6)_{1/6}$: C, 68.53; H, 6.98; N, 11.42; S, 13.07. Found: C, 68.36; H, 6.97; N, 11.38; S, 13.03. This was converted into a hydrochloride by treatment with HCl–Et_2O, mp 245—250 °C (dec.). *Anal.* Calcd for $C_{13}H_{17}ClN_2S$: C, 58.09; H, 6.37; N, 10.42; S, 11.93. Found: C, 58.27; H, 6.39; N, 10.50; S, 11.90.

4-(*N*,*N*-Dimethylaminomethyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (9)——A 20% methanolic solution of Me_2NH (5.77 ml, 20 mmol) was mixed with 98% HCOOH (940 mg, 20 mmol) at room temperature. The methanol was removed by distillation at atmospheric pressure and the residue was diluted with benzene (5 ml). To this, a solution of **7** (2.17 g, 10 mmol) in benzene (10 ml) was added dropwise at 60—70 °C, and the mixture was refluxed until evolution of CO_2 gas ceased (within 1 h). During this period DMF (*ca.* 4 ml) was added to dissolve the separating solid (presumably enamine salts). The mixture was taken up in 5% NaOH and extracted with Et_2O. The extract was washed, dried and concentrated, giving a solid which, when recrystallized from MeOH, afforded pure **9** (2.18 g, 88%), mp 122—124 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460. NMR ($CDCl_3$) δ: 2.33 (6H, s), 1.8—3.6 (7H, m), 6.9—7.6 (4H, m), *ca.* 8.0 (1H, br). *Anal.* Calcd for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37; S, 13.01. Found: C, 68.30; H, 7.43; N, 11.29; S, 13.12.

4-*tert*-Butyldimethylsilyloxybut-2-ynyl Indol-2-yl Sulfide (11)——Et_3N (2.27 g, 1.5 eq), 4-dimethylaminopyridine (183 mg, 0.1 eq), and *tert*-butyldimethylchlorosilane (2.49 g, 1.1 eq) were added to **6** (3.26 g, 15 mmol) in CH_2Cl_2 (60 ml) at room temperature. After being stirred for 1 h, the mixture was taken up in ice water and extracted with $CHCl_3$. The extract was washed (H_2O, cold 2 N HCl, H_2O, aq. $NaHCO_3$, H_2O) and dried. Removal of the solvent gave an oil (5 g) which, when chromatographed [silica gel 300 g, petroleum ether–EtOAc (20 : 1)], gave pure **11** as an oil (3.90 g, 78%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450. NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.92 (9H, s), 3.53 (2H, t, J=2 Hz), 4.23 (2H, t,

J=2 Hz), 6.70 (1H, d, J=2 Hz), 7.0—7.7 (4H, m). MS m/z (%): 331 (13, M^+), 199 (71), 148 (58), 75 (100), 73 (62). High resolution MS m/z: M^+ Calcd for $C_{18}H_{25}NOSSi$: 331.1426. Found: 331.1439.

1-Acetylindol-2-yl 4-*tert*-Butyldimethylsilyloxybut-2-ynyl Sulfide (12)——(n-Bu)$_4$NHSO$_4$ (40 mg, 0.01 eq) and NaOH (1 g, powdered) were added to a solution of **11** (3.90 g, 11.78 mmol) in CH_2Cl_2 (30 ml) at ice-bath temperature, then a solution of AcCl (1.38 g, 1.5 eq) in CH_2Cl_2 (10 ml) was added. The mixture was stirred at the same temperature for 50 min, then filtered, and the filtrate was washed (H_2O, cold $NaHCO_3$, H_2O), dried and evaporated. The residue was chromatographed [silica gel, 150 g, petroleum ether–benzene–EtOAc (20 : 10 : 1) to provide **12** as an oil (3.87 g, 88%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.87 (9H, s), 2.84 (3H, s), 3.67 (2H, t, J=2 Hz), 4.31 (2H, t, J=2 Hz), 6.65 (1H, s), 7.1—8.0 (4H, m). MS m/z (%): 373 (28, M^+), 199 (53), 148 (62), 75 (86), 73 (100). High resolution MS m/z: M^+ Calcd for $C_{20}H_{27}NOSSi$: 373.1530. Found: 373.1537.

1-Acetylindol-2-yl 4-Hydroxybut-2-ynyl Sulfide (13)——A solution of **12** (1.492 g, 4 mmol) in CH_3CN (20 ml) was treated with 46% aq. HF (0.53 ml, 3 eq) at ice-bath temperature. After being stirred at the same temperature for 2 h, the mixture was diluted with Et_2O (150 ml) and washed (H_2O, cold aq. $NaHCO_3$, H_2O). The solution was dried and evaporated, giving a solid which, when washed with benzene, afforded **13**, (1.01 g, 97%), mp 110—112 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, *ca.* 3400, 1700. NMR ($CDCl_3$) δ: 1.87 (1H, br, OH), 2.83 (3H, s), 3.60 (2H, t, J=2 Hz), 4.20 (2H, t-like), 6.60 (1H, s), 7.0—8.0 (4H, m). *Anal.* Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.01; N, 5.40; O, 12.34. Found: C, 64.80; H, 4.99; N, 5.36; O, 12.05.

9-Acetyl-4-hydroxymethyl-2,9-dihydrothiopyrano[2,3-*b*]indole (14)——A solution of **13** (777 mg, 3 mmol) in toluene (20 ml)–pyridine (2 ml) was heated at 110 °C for 1 h. The solution was evaporated to give a solid, which was washed with benzene, affording **14** (680 mg, 87%), mp 120—122 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, *ca.* 3400, 1700. NMR ($CDCl_3$) δ: 1.78 (1H, s, OH), 2.78 (3H, s), 3.73 (2H, d, J=5.5 Hz), 4.60 (2H, br s), 5.64 (1H, tt, J=1.5 Hz, 5.5), 7.0—7.4 (2H, m), 7.6—8.0 (2H, m). *Anal.* Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.37. Found: C, 64.69; H, 5.20; N, 5.42; S, 12.42.

4-Hydroxymethyl-2,9-dihydrothiopyrano[2,3-*b*]indole (10)——CH_3ONa (81 mg, 1.5 eq) was added to a suspension of **14** (259 mg, 1 mmol) in MeOH (4 ml) at −15 °C and the mixture was stirred at −15 °C for 1 h, then diluted with Et_2O, washed (H_2O, sat. NaCl) and dried. These operations were carried out at <10 °C. Evaporation of the solution left **10** as an unstable oil (220 mg), which was dissolved in Py-d_5 and kept in a refrigerator. NMR (Py-d_5) δ: 3.60 (2H, d, J=6 Hz), 5.03 (2H, d, J=1.5 Hz), 5.78 (1H, tt, J=6, 1.5 Hz), 6.0 (1H, br, OH), 7.0—7.6 (3H, m), 8.1 (1H, m).

Thermal Transformation of 10 to 7——A solution of **10** (*ca.* 100 mg) in Py-d_5 (1 ml) was heated at 100 °C until complete decomposition of **10** was observed by NMR spectroscopy (*ca.* 4 h). The solution was evaporated to give almost pure **7**, which was identical with the product obtained above on the basis of comparisons of IR and NMR spectra as well as thin layer chromatography (TLC) behavior.

References and Notes

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8) When **6** was used without purification, the conversion of **6** into **7** (more precisely, **10** to **7**) was so facilitated that **10** was hardly detected. Similar rate enhancement was observed when isolated **10** was heated in pyridine containing a small amount of the thione **1**.
9) This was prepared from oxindole by thiation with P_2S_5. The procedure will be described in detail in the following paper.[5]
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