Chem. Pharm. Bull. 29(6)1606—1614(1981)

Reactions and Synthetic Applications of β-Keto Sulfoxides. X. Synthesis of Ellipticine Analogs modified at the 5-Position[1]

Yuji Oikawa, Masahide Tanaka, Hitoshi Hirasawa, and Osamu Yonemitsu*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

(Received December 19, 1980)

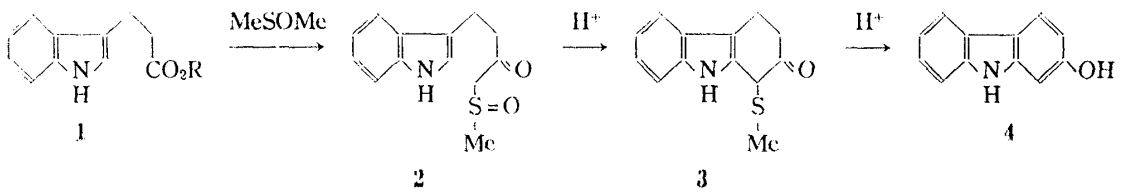
A β-keto sulfoxide (**12**) derived from ethyl indolebutyrate (**11**) and methyl methylthiomethyl sulfoxide (MMTS) was cyclized to 4-methyl-1,1-bismethylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (**13**) by treatment with *p*-toluenesulfonic acid (TsOH). Introduction of an acetic ester unit at the carbonyl group with *tert*-butyl lithioacetate gave a key intermediate (**14**) to all the 5-modified ellipticine analogs. An acid-catalyzed aromatization with acetic acid in xylene gave *tert*-butyl 4-methyl-1-methylthiocarbazole-2-acetate (**15**), which was readily converted to 5-methylthioellipticine (**7**) through a series of usual reactions. The overall yield of **7** from **11** was 25—27%. Desulfurization of **7** with Raney nickel in xylene gave 5-norellipticine (**8**). The bismethylthio group in **14** was easily hydrolyzed with TsOH in methanol to give a 1-keto compound (**21**), which was aromatized to a lactone (**22**), and then converted to 5-methoxyellipticine (**9**). Hydrolysis of **9** with 47% hydrobromic acid gave 5-hydroxyellipticine (**10**).

Keywords—cyclization of β-keto sulfoxide; 5-modified ellipticine analog; 6*H*-pyrido[4,3-*b*]carbazole; methyl methylthiomethyl sulfoxide; 1,2,3,4-tetrahydrocarbazol-2-one; carbazole-2-acetic ester

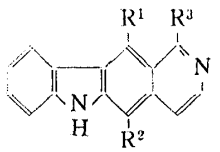
The discovery of the antineoplastic activity of ellipticine (**6**)[2] has stimulated many synthetic studies of analogous 6*H*-pyrido[4,3-*b*]carbazoles substituted at various positions, as well as of **6** itself, aimed at preparing more promising anti-cancer agents and at establishing more convenient syntheses.[3] Among many synthesized compounds, 9-hydroxyellipticine was proved to be one of the most active compounds on L 1210 mouse leukemia[4] and 1-substituted ellipticine analogs have still higher activity.[5] Synthesis of analogs functionalized at the 5-position, however, has not yet been achieved in spite of several attempts.[6]

We recently reported a new synthesis of condensed aromatics[7] and heteroaromatics based on the acid-catalyzed cyclization of β-keto sulfoxides, *e.g.*, the synthesis of carbazoles (**3**, **4**) from an indolepropionic ester (**1**) and dimethyl sulfoxide (DMSO) *via* **2**,[8] and this method was successfully applied to the synthesis of olivacine (**5**) and ellipticine (**6**).[9]

In analogy with DMSO, methyl methylthiomethyl sulfoxide (MMTS)[10] is known to react with esters to give β-keto sulfoxides of type **12**, which were expected to be potential inter-



1 2 3 4



5: $R^1=H$, $R^2=R^3=Me$
6: $R^1=R^2=Me$, $R^3=H$
7: $R^1=Me$, $R^2=SMe$, $R^3=H$
8: $R^1=Me$, $R^2=R^3=H$
9: $R^1=Me$, $R^2=OMe$, $R^3=H$
10: $R^1=Me$, $R^2=OH$, $R^3=H$

Chart 1

mediates to ellipticine analogs. We report here the first synthesis of ellipticine analogs (**7**—**10**) modified at the 5-position through the acid-catalyzed cyclization of **12**.

Synthesis of 5-Methylthioellipticine (7) and 5-Norellipticine (8)

Ethyl 3-(3-indolyl)butyrate (**11**)[11] was readily condensed with MMTS in the presence of sodium hydride at room temperature to give the β-keto sulfoxide (**12**) in 88% yield, essentially according to the published procedure.[12] The acid-catalyzed cyclization of β-keto sulfoxides usually proceeds with trifluoroacetic acid,[7,8] but **12** cyclized to **13** in only 38% yield with this acid. *p*-Toluenesulfonic acid (TsOH) monohydrate slightly improved the yield of **13**, though it was still unsatisfactory (51%). Dimethylmercaptal *S*-oxides (i) are known to readily undergo an acid-catalyzed hydrolysis to carbonyl compounds (iii) *via* hemimercaptal (ii).[12] The cyclization of **12**, however, obviously proceeded *via* the carbocation (iv), which was formed by the acid-catalyzed loss of water instead of the formation of ii by the substitution of the methylsulfinyl group with water.[13] The enhanced activity of the methine proton between the carbonyl and sulfoxide groups in **12** presumably facilitated the formation of iv. In order to avoid the undesirable side reaction to ii, anhydrous TsOH in benzene–tetrahydrofuran (1 : 4) was used to give **13** in 81% yield after silica gel chromatography.

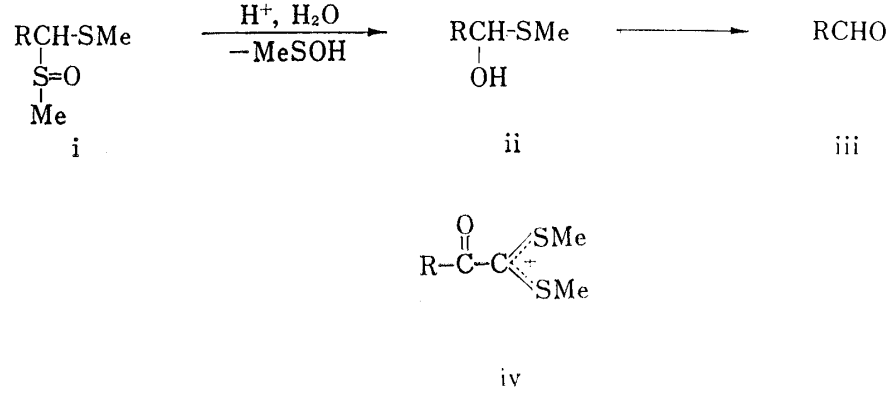


Chart 2

After many unsuccessful attempts to introduce an appropriate substituent at the carbonyl group of **13** by Reformatsky and Knoevenagel reactions, **13** was treated with *tert*-butyl lithioacetate (previously prepared from *tert*-butyl acetate and lithium diisopropylamide in toluene) to give **14**,[9,13] a key intermediate to all the 5-modified ellipticine analogs (**7**—**10**), as an oily diastereomeric mixture[14] in 97% yield after passage through a silica gel column. The acid-catalyzed aromatization of **14** was readily effected by heating with acetic acid in xylene to give the butyl ester (**15**) as colorless prisms in 57% overall yield from the starting ester (**11**). Chromatographic separation of synthetic intermediates is usually unfavorable, and hence **15** was practically obtained from **11** in 53% yield without any purification of intermediates (**12**—**14**).

A series of subsequent reactions from **15** to 5-methylthioellipticine (**7**), except for the final dehydrogenation step, proceeded quite smoothyl in the usual way. When treated with TsOH in refluxing methanol, **15** was transesterified in 98% yield to the methyl ester (**16**), which was converted to the amide (**17**) in 97% yield by treatment with methanolic ammonia containing sodium methoxide at 60—65°, followed by dehydration with *p*-toluenesulfonyl chloride in refluxing pyridine to give the nitrile (**18**) in 94% yield. Reduction of **18** with aluminium hydride prepared from lithium aluminium hydride and aluminium chloride[15] at room temperature and subsequent formylation with refluxing ethyl formate gave the formamide (**19**) in 92% yield, and **19** was readily converted to 5-methylthiodihydroellipticine (**20**) in 92% yield by dehydrative cyclization with phosphorus oxychloride in refluxing toluene. Although catalytic

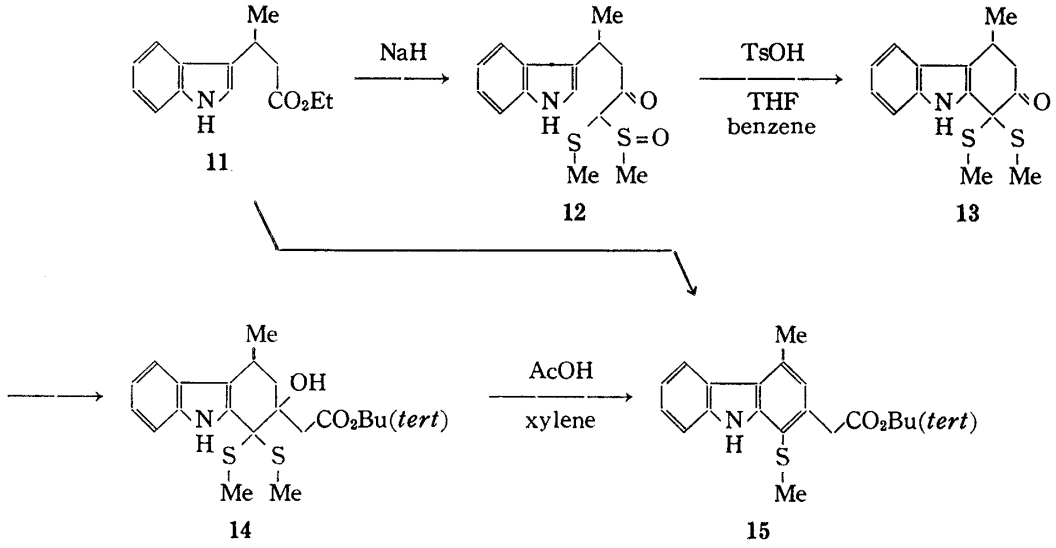


Chart 3

dehydrogenation of **20** with usual amounts of palladium on charcoal did not proceed efficiently, presumably because the methylthio group poisoned the catalyst, 5-methylthioellipticine (**7**) was obtained in 63% yield by treatment with rather large amounts of the catalyst in refluxing decalin.[16] The overall yield of **7** from the starting material (**11**) was 25—27%.

Desulfurization of **7** with Raney nickel in refluxing xylene readily gave 5-norellipticine (**8**)[19] in 61% yield.

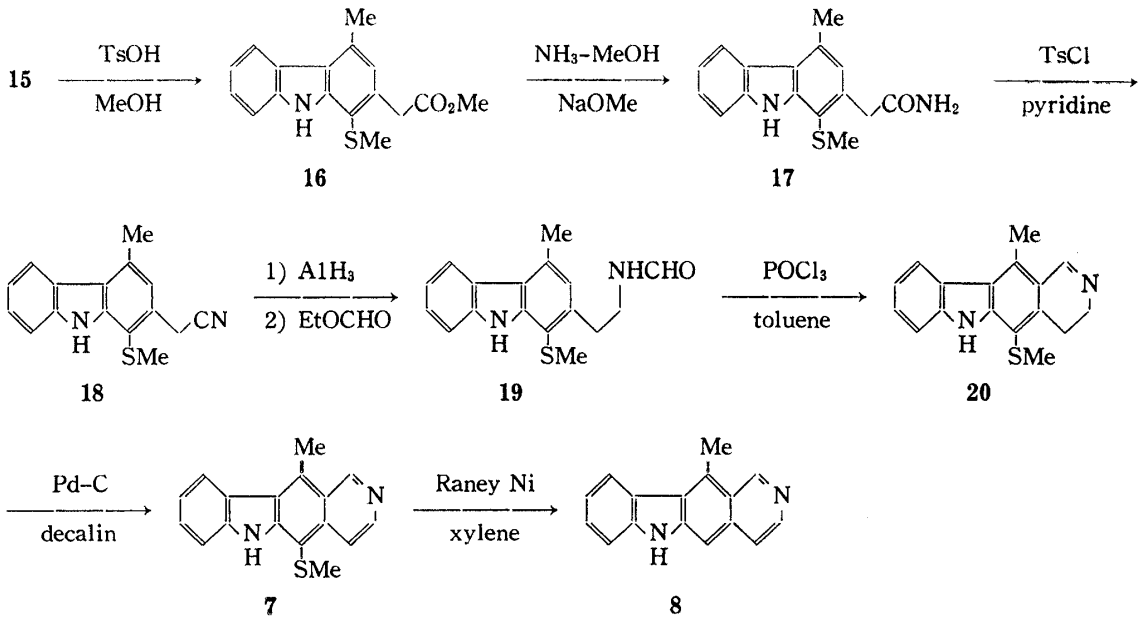


Chart 4

Synthesis of 5-Methoxyellipticine (9) and 5-Hydroxyellipticine (10)

When **11** was heated at 50° in methanol in the presence of TsOH monohydrate, a facile hydrolysis of the dithioacetal group and transesterification concurrently occurred to give the keto-ester (**21**) in 87% yield. Although an acid-catalyzed dehydrative aromatization was expected to occur readily, **21** was recovered unchanged on heating with TsOH or trifluoroacetic acid in benzene. In refluxing toluene, **21** aromatized to the lactone (**22**), though in only 22%

yield. When **21** was treated with TsOH in refluxing xylene, the yield of **22** was improved to 50% though this was still unsatisfactory. In spite of many attempts, no satisfactory direct or indirect aromatization method is so far available. At present the following indirect method *via* **23** and **24** is a little better than others. After acetylation of **21** with acetic anhydride, the acetate (**23**) (91%) was treated with sodium hydride in benzene at room temperature to give the olefin (**24**) as a mixture of *E*- and *Z*-isomers, which were readily separable by recrystallization and silica gel column chromatography. On heating with TsOH in toulene, **24** gave **22** in 81% yield. This indirect transformation from **21** to **22** (58%) is a slight improvement over the direct one, at least in terms of yield.

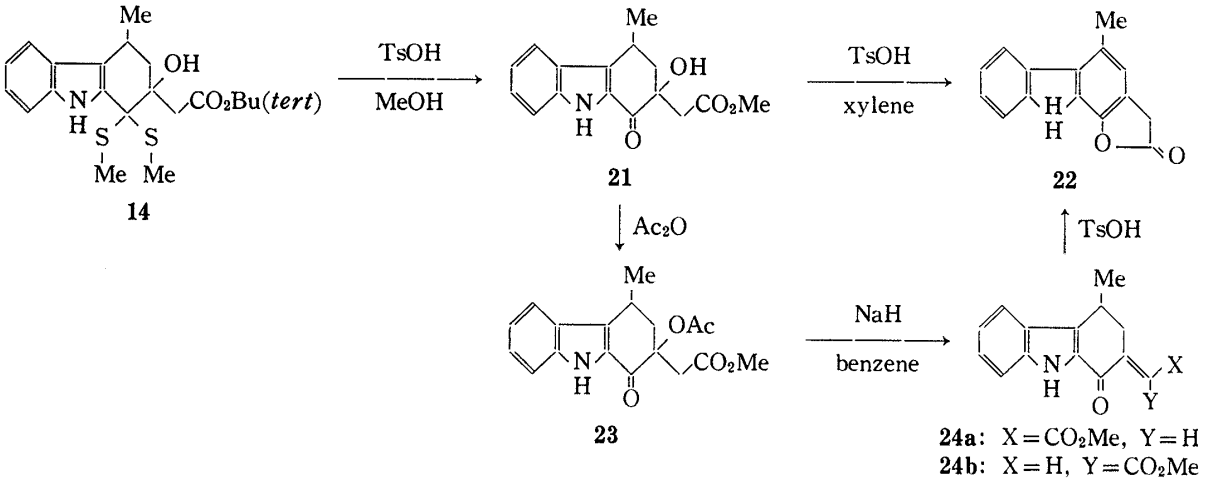


Chart 5

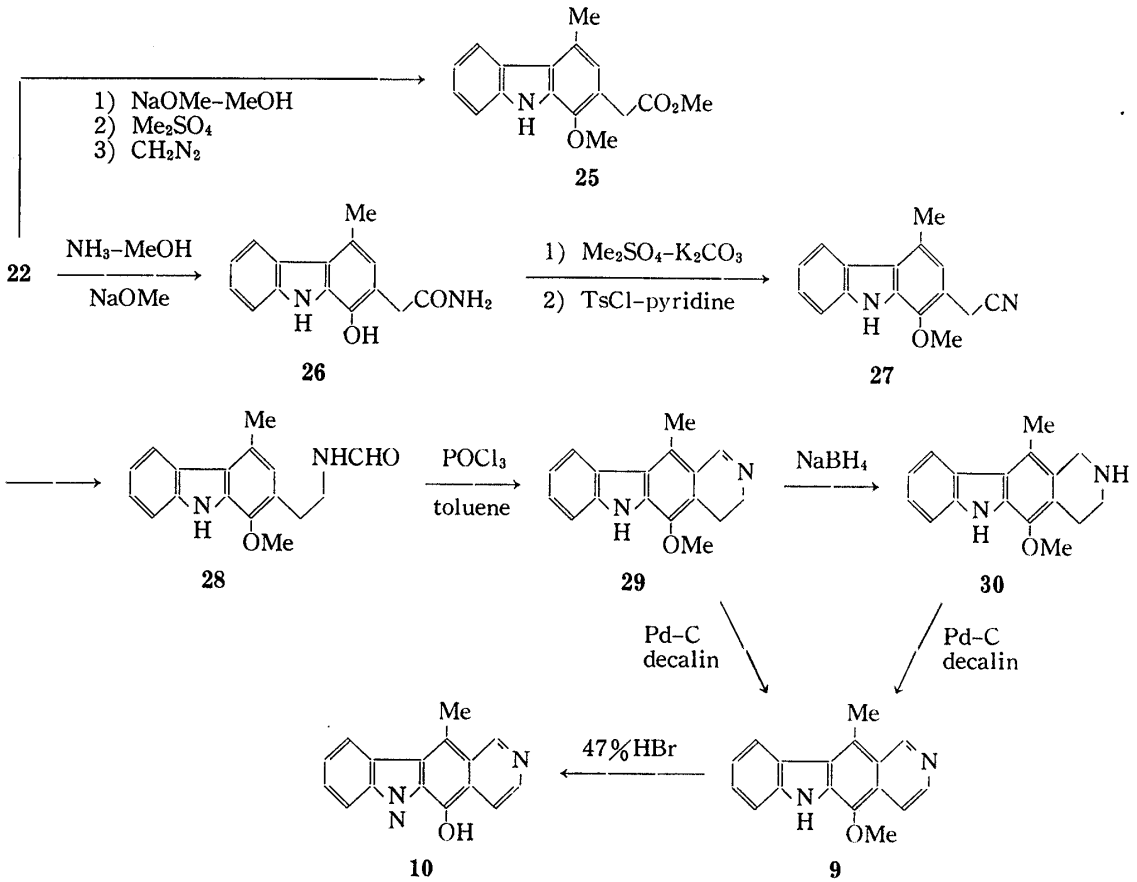


Chart 6

The next step, cleavage of the lactone ring in **22** to **25**, again gave an unsatisfactory result, so **22** was treated with sodium methoxide in methanol at room temperature, followed by methylation to give **25** in only 51% yield. This compound can, of course, be converted to **27**, but a more efficient transformation from **22** to **27** *via* **26** was established after several trials. When **22** was treated with methanolic ammonia containing sodium methoxide in a sealed tube at 60—65°, the cleavage of the lactone ring occurred quite smoothly and gave the hydroxyamide (**26**) almost quantitatively. Methylation of **26** with dimethyl sulfate in the presence of potassium carbonate in 50% aqueous acetone and dehydration with *p*-toluenesulfonyl chloride in refluxing pyridine gave the nitrile (**27**) in 88% yield.

The conversion of **27** into 5-methoxy-3,4-dihydroellipticine (**29**) readily proceeded without any complications as described above. Dehydrogenation of **29** with palladium on charcoal in refluxing decalin gave 5-methoxyellipticine (**9**), though in only 46% yield. The yield of **9** was slightly improved to 52% by treatment of **29** with active manganese dioxide[17] in refluxing dioxane. A more satisfactory result was obtained by two-step transformation *via* the tetrahydro compound (**30**),[18] so **29** was reduced with sodium borohydride in methanol to give **30**, which was dehydrogenated, without purification, with palladium on charcoal in decalin at 170° and gave **9** in 66% yield.

5-Hydroxyellipticine (**10**) was readily obtained as the hydrobromide by demethylation with refluxing 47% aqueous hydrobromic acid in 85% yield.

Pharmacological tests of the four 5-modified ellipticine analogs (**7**—**10**) synthesized here are currently under way and the results will be reported elsewhere.

Experimental

4-(3-Indolyl)-1-methylsulfinyl-1-methylthiopentan-2-one (**12**)——An anhydrous THF (80 ml) solution of MMTS (8.1 g, 65 mmol) was added dropwise at room temperature to stirred sodium hydride prepared from a 50% dispersion (11.2 g, 0.23 mol) by washing with hexane. After 1.5 hr, an anhydrous THF (40 ml) solution of ethyl 3-(3-indolyl)butyrate (**11**) (10 g, 43 mmol) was added dropwise, and then the resulting mixture was heated under reflux for 1.5 hr. The solvent was concentrated *in vacuo*, and the residue was neutralized with saturated NH_4Cl solution and extracted with EtOAc. The extracts were washed with water, dried (Na_2SO_4), and concentrated to leave crude **12** as a pale brown oil (11.82 g, 88.4%), which was used for the next reaction without further purification. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3250, 1730, 1700, 1040.

4-Methyl-1,1-bismethylthio-2-oxo-1,2,3,4-tetrahydrocarbazole (**13**)——A solution of **12** (0.26 g, 0.84 mmol) and anhydrous TsOH (17 mg) in THF (4.5 ml) and benzene (1.2 ml) was heated at 60° for 3 hr. After neutralization with saturated $NaHCO_3$ solution, the mixture was concentrated *in vacuo* to remove the solvents and the residue was extracted with CH_2Cl_2. The extracts were washed with water, dried (Na_2SO_4), and concentrated to leave an oil, which was purified by passage in EtOAc–hexane (1 : 3) through a silica gel column to give **13** as an oil (0.2 g, 81%), which crystallized on scratching in EtOH. Recrystallization from EtOH gave colorless prisms, mp 99—102°. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3400, 1710. MS *m/e* (%): 291 (M^+, 4.3), 243 (100). NMR ($CDCl_3$) δ: 1.36 (3H, d, $J=7$ Hz), 1.87 (3H, s), 2.07 (3H, s), 2.59—2.81 (1H, m), 3.39—3.65 (2H, m), 7.04—7.62 (4H, m), 8.38 (1H, br. s). *Anal.* Calcd for $C_{15}H_{17}NOS_2$: C, 61.85; H, 5.88; N, 4.81; S, 21.97. Found: C, 61.78; H, 6.00; N, 4.77; S, 22.22.

***tert*-Butyl 2-Hydroxy-4-methyl-1,1-bismethylthio-1,2,3,4-tetrahydrocarbazole-2-acetate** (**14**)——A toluene (30 ml) solution of *tert*-butyl acetate (19.97 g, 0.17 mol) was added dropwise to a stirred solution of lithium diisopropylamide prepared from a 15% hexane solution of butyl lithium (73.5 ml, 0.17 mol) and a toluene (50 ml) solution of diisopropylamine (19.13 g, 0.19 mol) below −70°. After 30 min, the solution was allowed to warm to −40°, and a toluene (40 ml) solution of **13** (8.35 g, 29 mmol) was added dropwise. The mixture was stirred for 1 hr at room temperature, then poured into saturated NH_4Cl solution, and extracted with toluene. The extracts were dried (Na_2SO_4), concentrated *in vacuo*, and then purified by passage in EtOAc–hexane (1 : 5) through a silica gel column to give **14** (an oil, 11.36 g, 97.3%) as a 1 : 2 diastereomeric mixture. IR ν_{max}^{Nujol} cm^{-1}: 3370, 1700. MS *m/e* (%): 407 (M^+, 10), 360 (48), 341 (16), 334 (10), 304 (100), 285 (43), 256 (89), 238 (67), 214 (100). NMR ($CDCl_3$) δ: 1.45—1.60 (12H, m), 2.01 (1H, s), 2.04 (2H, s), 2.11 (1H, s), 2.17—2.23 (1H, m), 2.38 (2H, s), 2.48—3.41 (4H, m), 4.68 (0.33H, s), 4.92 (0.67H, s), 7.08—7.68 (4H, m), 8.32 (1H, br. s).

***tert*-Butyl 4-Methyl-1-methylthiocarbazole-2-acetate** (**15**)——A solution of **14** (462 mg, 1.14 mmol) and AcOH (0.35 ml) in xylene (6 ml) was heated under reflux for 10 hr. The solution was concentrated *in vacuo* to leave a solid (385 mg), which was chromatographed on a silica gel column with CH_2Cl_2–hexane (4 : 1) to

give colorless prisms, mp 171.5—173.5°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1700. MS *m/e* (%): 341 (M^+, 62), 285 (100), 270 (9), 240 (87). NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.32 (3H, s), 2.82 (3H, s), 4.01 (2H, s), 7.21 (1H, s), 7.25—7.48 (3H, m), 8.08 (1H, d, J=8 Hz), 8.64 (1H, br. s). *Anal.* Calcd for $C_{20}H_{23}NO_2S$: C, 70.36; H, 6.79; N, 4.10; S, 9.38. Found: C, 70.37; H, 6.86; N, 4.00; S, 9.43.

Methyl 4-Methyl-1-methylthiocarbazole-2-acetate (16)——A MeOH (280 ml) solution of **15** (5.81 g, 17 mmol) and TsOH monohydrate (654 mg) was heated under reflux for 20 hr. After removal of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), and concentrated to leave a pale yellow solid. Recrystallization from MeOH gave **16** (4.98 g, 98%) as colorless plates, mp 140—140.5°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3400, 1730, 1720. MS *m/e* (%): 299 (M^+, 100), 284 (4), 252 (30), 240 (40), 224 (30). NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.83 (3H, s), 3.72 (3H, s), 4.12 (2H, s), 7.16 (1H, s), 7.24—7.48 (3H, m), 8.12 (1H, d, J=8 Hz), 8.66 (1H, br. s). *Anal.* Calcd for $C_{17}H_{17}NO_2S$: C, 68.21; H, 5.72; N, 4.86; S, 10.69. Found: C, 68.29; H, 5.73; N, 4.65; S, 10.78.

4-Methyl-1-methylthiocarbazole-2-acetonitrile (18)——A solution of **16** (1.5 g, 5 mmol) in saturated methanolic ammonia (150 ml) containing NaOMe (250 mg) was heated at 60—65° in a sealed tube for 68 hr. After removal of the solvent *in vacuo*, the residue was triturated in water, and an insoluble solid was collected by filtration and dried to give crude 4-methyl-1-methylthiocarbazole-2-acetamide (**17**) (1.38 g, 96.6%) as colorless needles, mp 241—243° (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3380, 3340, 3180, 1650. MS *m/e* (%): 284 (M^+, 100), 266 (3), 252 (8), 240 (61), 224 (36), 196 (35), 194 (34), 180 (33).

A pyridine (70 ml) solution of crude **17** (3.88 g, 14 mmol) and *p*-toluenesulfonyl chloride (6.22 g, 33 mmol) was heated under reflux for 1.5 hr. Water (9 ml) was added to the solution, and the mixture was heated at 60° for 30 min then cooled. After dilution with benzene, the solution was washed with 6 N HCl and water, dried (Na_2SO_4), and concentrated *in vacuo* to leave **18** (3.7 g) as a crude solid. Recrystallization from EtOH gave colorless prisms (3.4 g, 93.5%), mp 171—173°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 2250. MS *m/e* (%): 266 (M^+, 100), 251 (84), 224 (27). NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.86 (3H, s), 4.17 (2H, s), 7.13 (1H, s), 7.19—7.53 (3H, m), 8.15 (1H, d, J=8 Hz), 8.68 (1H, br. s). *Anal.* Calcd for $C_{16}H_{14}N_2S$: C, 72.16; H, 5.30; N, 10.52; S, 12.02. Found: C, 72.06; H, 5.20; N, 10.34; S, 12.06.

2-(2-Formamidoethyl)-4-methyl-1-methylthiocarbazole (19)——$AlCl_3$ (6.46 g, 49 mmol) was added in portions to a stirred suspension of $LiAlH_4$ (1.7 g, 45 mmol) in ether (120 ml) at 0°. Stirring was continued at 0° for 30 min and at room temperature for 30 min, and then **18** (3.26 g, 12 mmol) in THF (60 ml) was added dropwise. The resulting mixture was stirred for 2 hr at room temperature and cooled at 0°. The excess hydride was carefully destroyed by adding water (4 ml) dropwise. After addition of excess 10% NaOH solution, MeOH was added till the emulsified inorganic salts precipitated as a colorless powder, which was filtered off with suction. The filtrate was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2, washed with water, and dried (K_2CO_3). Removal of the solvent *in vacuo* left the crude amine (3.85 g), which was dissolved in ethyl formate (70 ml) and heated under reflux for 15.5 hr. After removal of the excess formate *in vacuo*, the residual crude **19** (3.56 g) was recrystallized from EtOH to give colorless prisms (3.36 g, 91.8%), mp 167—169°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3175, 1680. MS *m/e* (%): 298 (M^+, 54), 253 (19), 240 (48), 238 (100), 223 (25), 196 (29). NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.83 (3H, s), 3.28 (2H, t, J=7 Hz), 3.44—3.76 (2H, m), 5.71 (1H, br. s), 6.92—8.08 (5H, m), 8.14 (1H, s), 8.75 (1H, br. s). *Anal.* Calcd for $C_{17}H_{18}N_2OS$: C, 68.44; H, 6.08; N, 9.39; S, 10.73. Found: C, 68.49; H, 6.14; N, 9.54; S, 10.80.

11-Methyl-5-methylthio-3,4-dihydro-6*H*-pyrido[4,3-*b*]carbazole (20)——A toluene (19 ml) solution of **19** (118 mg, 0.4 mmol) and $POCl_3$ (0.5 ml) was heated under reflux for 30 min. After removal of the solvent *in vacuo*, dilute NH_4OH solution was added to the residue, and the mixture was extracted with $CHCl_3$. The extracts were washed with water, dried (K_2CO_3), and concentrated *in vacuo* to leave a solid (110 mg), which was purified by passage in $CHCl_3$ through an alumina column to give **20** (102 mg, 91.9%). Recrystallization from DMF gave colorless prisms, mp 274—275.5° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1620, 1585, 1565. MS *m/e* (%): 280 (M^+, 100), 265 (20), 247 (9), 232 (41), 204 (13). NMR ($CDCl_3$) δ: 2.30 (3H, s), 3.01 (3H, s), 3.17 (2H, t, J=8 Hz), 3.77 (2H, dt, J=2, 7 Hz), 7.26—7.51 (3H, m), 8.19 (1H, d, J=8 Hz), 8.88 (2H, t, J=2 Hz). *Anal.* Calcd for $C_{17}H_{16}N_2S$: C, 72.84; H, 5.75; N, 9.99; S, 11.42. Found: C, 72.63; H, 5.74; N, 9.82; S, 11.33.

11-Methyl-5-methylthio-6*H*-pyrido[4,3-*b*]carbazole (7)——A suspension of **20** (1.375 g, 4.9 mmol) and 10% Pd-C (5.53 g) in decalin (130 ml) was heated under reflux for 4 hr under an argon atmosphere. The catalyst was filtered off and washed thoroughly with $CHCl_3$–MeOH (5: 1), and the filtrates were concentrated *in vacuo* to leave a yellow solid, which was purified by passage in $CHCl_3$ through an alumina column to give **7** (0.86 g, 63.1%). Recrystallization from xylene gave yellow needles, mp 269.5—271° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1600, 1490, 1240, 740. MS *m/e* (%): 278 (M^+, 71), 263 (100). NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.34 (3H, s), 7.28—7.40 (1H, m), 7.52—7.61 (2H, m), 8.37 (1H, d, J=9 Hz), 8.41 (1H, d, J=6 Hz), 8.60 (1H, d, J=6 Hz), 8.87 (1H, br. s), 9.73 (1H, s). *Anal.* Calcd for $C_{17}H_{14}N_2S$: C, 73.36; H, 5.07; N, 10.07; S, 11.50. Found: C, 73.30; H, 5.02; N, 10.00; S, 11.62.

11-Methyl-6*H*-pyrido[4,3-*b*]carbazole (8)[19]——A suspension of **7** (102 mg, 0.37 mmol) and Raney Ni (W-7) (1 g) in xylene (30 ml) was heated under reflux for 50 min. The catalyst was filtered off and washed thoroughly with MeOH, and the filtrates were concentrated *in vacuo* to leave a yellow solid, which was purified by passage through an alumina column. Elution with $CHCl_3$ gave **8** (52 mg, 61%), which was recrystallized from MeOH–H_2O to give yellow needles, mp 271.5—274° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1630, 1600, 1250. MS *m/e*

(%): 232 (M^+, 100). NMR ($CDCl_3$) δ: 3.34 (3H, s), 7.34 (1H, t, $J=8$ Hz), 7.47—7.59 (3H, m), 7.72 (1H, d, $J=6$ Hz), 8.24 (1H, br. s), 8.39 (1H, d, $J=8$ Hz), 8.45 (1H, d, $J=6$ Hz), 9.73 (1H, s). *Anal.* Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.63; H, 5.23; N, 12.11.

Methyl 2-Hydroxy-4-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole-2-acetate (**21**)——A MeOH (12 ml) solution of **14** (489 mg, 1.2 mmol) and TsOH monohydrate (108 mg) was heated at 50° for 22.5 hr. After neutralization with saturated $NaHCO_3$ solution, the mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated to leave an oil (379 mg), which was purified by passage through a silica gel column. Elution with EtOAc–hexane (1:2) gave a solid of **21** (300 mg, 87%) as a 1:2 diastereomeric mixture. Colorless needles, mp 129—142° (80% aqueous MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3500, 3450, 3275, 1730, 1660. MS *m/e* (%): 287 (M^+, 28), 269 (21), 256 (10), 237 (34), 214 (31), 209 (100), 196 (23), 143 (57). NMR ($CDCl_3$) δ: 1.57 (1H, d, $J=8$ Hz), 1.64 (2H, d, $J=7$ Hz), 1.96—2.99 (4H, m), 3.26—3.60 (1H, m), 3.69 (2H, s), 3.79 (1H, s), 4.34 (0.67H, br. s), 4.99 (0.33H, br. s), 7.06—7.52 (3H, m), 7.84 (1H, d, $J=8$ Hz), 9.49 (1H, br. s). *Anal.* Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.08; H, 6.05; N, 4.75.

5-Methyl-2,3-dihydrofuro[2,3-*a*]carbazol-2-one (**22**)——a) A xylene (500 ml) solution of **21** (10.03 g, 35 mmol) and TsOH monohydrate (4.97 g) was heated under reflux for 18.5 hr. The solution was diluted with EtOAc, washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated *in vacuo*. The residual solid was washed with Et_2O to give crude **22** (4.15 g, 50%). Recrystallization from EtOAc gave pale brown plates, mp 269—270.5° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3310, 1770. MS *m/e* (%): 237 (M^+, 47), 209 (100), 180 (29). NMR ($CDCl_3$) δ: 2.88 (3H, s), 3.92 (2H, s), 6.94 (1H, s), 7.20—7.56 (3H, m), 8.18 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 75.83; H, 4.65; N, 5.61. Found: C, 75.93; H, 4.67; N, 5.90.

b) A toluene (5 ml) solution of **24b** (51 mg, 0.19 mmol) and TsOH monohydrate (30 mg) was heated under reflux for 16.5 hr. Work-up as described above gave **22** (37 mg, 81%).

c) Deacetylation of **23** (231 mg, 0.702 mmol) with NaH in benzene gave a mixture of **24a** and **24b** (192 mg) (see below), which was treated with TsOH in toluene as described above to give **22** (106 mg, 63.9%).

Methyl 2-Acetoxy-4-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole-2-acetate (**23**)——A solution of **21** (2 g, 7 mmol) in Ac_2O (50 ml) was heated under reflux for 3 hr. The solution was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), and concentrated *in vacuo* to leave a solid (2.239 g), which was recrystallized from MeOH to give colorless prisms of **23** as a diastereomeric mixture. The mother liquor was chromatographed on a silica gel column, and elution with $CHCl_3$ gave further **23** (total 2.089 g, 91%). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1740, 1720, 1660. MS *m/e* (%): 329 (M^+, 6), 298 (3), 269 (4), 237 (3), 209 (100). *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.75; H, 5.85; N, 4.31.

Methyl (*E*)-4-Methyl-1-oxo-1,2,3,4-tetrahydrocarbazol-2-ylideneacetate (**24a**) **and Methyl (*Z*)-4-Methyl-1-oxo-1,2,3,4-tetrahydrocarbazol-2-ylideneacetate** (**24b**)——A benzene (10 ml) solution of **23** (502 mg, 1.5 mmol) was added dropwise to a stirred suspension of NaH (111 mg, 4.6 mmol) in benzene (20 ml) at room temperature. Stirring was continued for 2 hr, and then the mixture was poured into saturated NH_4Cl solution. The benzene layer was separated, washed with water, dried (Na_2SO_4), and concentrated to leave a solid, which was recrystallized from MeOH to give **24b** (226 mg) as pale yellow needles. The mother liquor was chromatographed on a silica gel column. Elution with $CHCl_3$ gave **24a** (21 mg, 5%) and an additional amount (62 mg) of **24b** (total 288 mg, 70%). Physical data are given below. **24a**——Pale yellow needles, mp 164—166° (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3240, 1710, 1650, 1610. MS *m/e* (%): 269 (M^+, 82), 254 (13), 238 (17), 222 (93), 210 (48), 209 (100). NMR ($CDCl_3$) δ: 1.47 (3H, d, $J=7$ Hz), 3.50—3.78 (3H, m), 3.82 (3H, s), 6.95 (1H, s), 7.11—7.47 (3H, m), 7.26 (1H, d, $J=8$ Hz), 9.30 (1H, br. s). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.34; H, 5.65; N, 5.28. **24b**——Pale yellow needles, mp 200—202° (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1720, 1640. MS *m/e* (%): 269 (M^+, 100), 254 (36), 238 (14), 222 (59), 210 (53). NMR ($CDCl_3$) δ: 1.49 (3H, d, $J=7$ Hz), 2.72 (1H, dd, $J=4$, 14 Hz), 3.15 (1H, ddd, $J=2$, 4, 14 Hz), 3.38—3.63 (1H, m), 3.78 (3H, s), 6.19 (1H, s), 6.94—7.74 (4H, m), 9.94 (1H, br. s). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.34; H, 5.56; N, 5.20.

1-Hydroxy-4-methylcarbazole-2-acetamide (**26**)——A solution of **22** (1.511 g, 6.38 mmol) in saturated methanolic ammonia (150 ml) containing NaOMe (0.24 g) was heated at 60—65° in a sealed tube for 13 hr. After removal of the solvent, the residue was dissolved in EtOAc, washed with 2 N HCl and water, dried (Na_2SO_4), and concentrated to leave a solid, which was washed with Et_2O to give crude **26** (1.542 g, 95.2%). Recrystallization from EtOAc–hexane gave colorless plates, mp 195—197° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3130, 1640. MS *m/e* (%): 254 (M^+, 33), 237 (33), 209 (100), 180 (24). NMR ($CDCl_3$) δ: 2.73 (3H, s), 3.69 (2H, s), 6.69 (1H, s), 7.05—7.51 (3H, m), 8.07 (1H, d, $J=8$ Hz). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.64; H, 5.56; N, 10.97.

1-Methoxy-4-methylcarbazole-2-acetonitrile (**27**)——A stirred solution of **26** (903 mg, 3.55 mmol) and Me_2SO_4 (3.99 g, 31.7 mmol) in 50% aqueous acetone containing K_2CO_3 (4.8 g, 34.8 mmol) was heated at 60° for 25 min. After removal of the acetone *in vacuo*, a precipitated solid was collected by filtration to give the 1-methoxy compound (917 mg, 96.3%), mp 221—222° (EtOH). This compound was heated with *p*-toluenesulfonyl chloride (1.562 g, 8.19 mmol) in pyridine (19 ml) under reflux for 1 hr. After addition of water (2 ml), the solution was heated at 60° for 30 min, then diluted with benzene, washed with 2 N HCl and water, dried (Na_2SO_4), and concentrated to leave a solid (912 mg), which was recrystallized from EtOH

to give **27** as pale yellow needles (779 mg, 87.7%), mp 144—146°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 2250. MS *m/e* (%): 250 (M^+, 73), 235 (100). NMR ($CDCl_3$) δ: 2.83 (3H, s), 3.88 (2H, s), 4.01 (3H, s), 6.97 (1H, s), 7.18—7.51 (3H, m), 8.15 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.78; H, 5.59; N, 11.11.

2-(2-Formamidoethyl)-1-methoxy-4-methylcarbazole (**28**)——Compound **27** (2.554 g, 10 mmol) was reduced with $LiAlH_4$–$AlCl_3$, followed by formylation with EtOCHO (70 ml) as described above to give **28** (2.668 g, 92.6%). Colorless prisms, mp 181—182° (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3330, 3300, 1660, 1640. MS *m/e* (%): 282 (M^+, 79), 237 (100), 224 (79), 222 (39), 209 (45), 194 (53), 180 (41). NMR ($CDCl_3$) δ: 2.79 (3H, s), 2.95 (2H, t, J=7 Hz), 3.42—3.76 (2H, m), 3.94 (3H, s), 5.94 (1H, br. s), 6.78 (1H, s), 7.15—7.53 (3H, m), 8.08—8.16 (2H, m), 8.34 (1H, br. s). *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.53; H, 6.50; N, 9.83.

5-Methoxy-11-methyl-3,4-dihydro-6*H*-pyrido[4,3-*b*]carbazole (**29**)——A toluene (80 ml) solution of **28** (548 mg, 1.9 mmol) and $POCl_3$ (3.3 g, 20 mmol) was heated under reflux for 30 min. After removal of the solvent *in vacuo*, the residue was neutralized with dilute NH_4OH solution and extracted with $CHCl_3$. The extracts were washed with water, dried (K_2CO_3), and concentrated to leave a solid, which was purified by passage in $CHCl_3$–MeOH (20: 1) through an alumina column to give crude **29** (412 mg, 80.3%). Recrystallization from MeOH gave pale yellow prisms, mp 255.5—257° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1620, 1600, 1565, 1500, 1130. MS *m/e* (%): 264 (M^+, 100), 249 (44). NMR ($CDCl_3$) δ: 2.87—3.01 (5H, m), 3.75 (2H, dt, J=2, 7 Hz), 3.93 (3H, s), 7.19—7.56 (3H, m), 8.18 (1H, d, J=8 Hz), 8.65 (1H, br. s), 8.87 (1H, t, J=2 Hz). *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.01; H, 5.99; N, 10.37.

5-Methoxy-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**9**)——a) $NaBH_4$ (136 mg, 3.6 mmol) was added to a stirred suspension of **29** (744 mg, 2.8 mmol) in MeOH (40 ml) and dioxane (6 ml). After 2.5 hr at room temperature, the excess hydride was decomposed with 2 N HCl and the solvents were evaporated off *in vacuo*. The residue was taken up in water, made basic with Na_2CO_3, and extracted with $CHCl_3$. The extracts were dried (K_2CO_3) and concentrated to leave **30** (820 mg) as a colorless solid, which was heated with 10% Pd–C (1.5 g) at 170° in decalin(70 ml) for 1.5 hr. Work-up as described above gave yellow needles, mp 232—235° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1640, 1620, 1600, 1440, 1240. MS *m/e* (%): 262 (M^+, 47), 247 (100). NMR ($CDCl_3$) δ: 3.28 (3H, s), 4.10 (3H, s), 7.29—7.37 (1H, m), 7.52—7.55 (2H, m), 7.97 (1H, d, J=6 Hz), 8.38 (1H, d, J=8 Hz), 8.49 (1H, d, J=6 Hz), 8.51 (1H, s), 9.69 (1H, s). *Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.64; H, 5.48; N, 10.50.

b) A dioxane (10 ml) solution of **29** (203 mg) was heated under reflux with active MnO_2 (498 mg) for 14 hr, then MnO_2 (308 mg) was added, and reflux was continued for 4 hr. After removal of the catalyst by filtration, the filtrate was concentrated to leave a solid, which was purified by passage through an alumina column to give **9** (104 mg, 51.8%).

c) A suspension of **29** (61 mg) and 10% Pd–C (120 mg) in decalin (6 ml) was heated under reflux for 2 hr. Work-up as described above gave **9** (28 mg, 46%).

5-Hydroxy-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**10**)——A solution of **9** (550 mg) in 47% HBr (25 ml) was heated under reflux for 25 min. After removal of the acid *in vacuo*, the residue was recrystallized from water to give the **10**·hydrobromide (594 mg, 84.9%) as pale orange plates, mp 313—318° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1640, 1600, 1240, 740. MS *m/e* (%): 248 (M^+, 100). NMR (MeOH-d_4) δ: 7.10 (1H, t, J=7 Hz), 7.29—7.43 (2H, m), 8.07 (1H, d, J=7 Hz), 8.20 (1H, d, J=8 Hz), 8.26 (1H, d, J=7 Hz), 9.69 (1H, s). *Anal.* Calcd for $C_{16}H_{13}N_2OBr \cdot 1/4H_2O$: C, 57.59; H, 4.00; N, 8.40. Found: C, 57.34; H, 3.85; N, 8.41.

Acknowledgement This work was supported by a Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture of Japan.

References and Notes

1) Preliminary communication: Y. Oikawa, M. Tanaka, H. Hirasawa, and O. Yonemitsu, *Heterocycles*, **15**, 207 (1981).
2) C.C.J. Culvenor and J.W. Loder, 152nd Am. Chem. Soc. Meeting, New York, N.Y., Sept., 1966, p. 29.
3) M. Sainsbury, *Syntheses*, **1977**, 437; M. Driver, I.T. Matthews, and M. Sainsbury, *J. Chem. Soc. Perkin I*, **1979**, 2506; M. Watanabe and V. Sniekus, *J. Am. Chem. Soc.*, **102**, 1457 (1980), and references cited therein.
4) J.B. LePecq, N.D. Xuong, C. Grosse, and C. Paoletti, *Proc. Natl. Acad. Sci. USA*, **71**, 5078 (1974).
5) C. Ducrocq, E. Bisagni, C. Rivalle, and J.M. Lhoste, *J. Chem. Soc. Perkin I*, **1979**, 142; E. Bisagni, C. Ducrocq, J.M. Lhoste, C. Rivalle, and A. Civier, *ibid.*, **1979**, 1706.
6) S.J. Martinez and J.A. Joule, *J. Chem. Soc. Chem. Comm.*, **1976**, 818; M. Driver and M. Sanisbury, *J. Chem. Soc. Perkin I*, **1979**, 2502.
7) Y. Oikawa and O. Yonemitsu, *Tetrahedron*, **30**, 2653 (1974).
8) Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **41**, 1118 (1976).
9) Y. Oikawa and O. Yonemitsu, *J. Chem. Soc. Perkin I*, **1976**, 1479.

10) Also known as formaldehyde dimethyldithioacetal *S*-oxide (FAMSO).
11) Y. Oikawa, H. Hirasawa, and O. Yonemitsu, *Tetrahedron Lett.*, **1978**, 1759.
12) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1971**, 3151; K. Ogura, S. Furukawa, and G. Tsuchihashi, *Chem. Lett.*, **1974**, 659.
13) Y. Oikawa and O. Yonemitsu, *Heterocycles*, **8**, 307 (1977).
14) It was unnecessary to separate the components because the asymmetric centers were lost at later steps.
15) R.F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955).
16) Dehydrogenation of **20** with manganese dioxide[17] in refluxing dioxane gave **7** in 46% yield, but attempts at DDQ dehydrogenation were unsuccessful.
17) *Cf.* A.J. Fatiadi, *Syntheses*, **1976**, 65.
18) *Cf.* F. LeGoffic, A. Gouyette, and A. Ahond, *Tetrahedron*, **29**, 3557 (1973).
19) J. Bergman and H. Goonewardena, *Acta Chem. Scand.*, **B 34**, 763 (1980).