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Sulfur-Assisted Synthesis of Functionalized Carbazoles

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Cycloaddition reactions of 3-vinylindoles, generated by the alkylation of 3-thioacetylindole, with dienophiles to give functionalized carbazoles were explored.

Keywords cycloaddition; 3-vinylindole; 3-thioacetylindole; alkylation; dienophile; carbazole

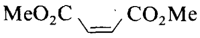
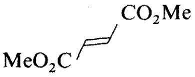
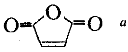
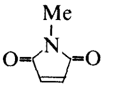
There is considerable interest in 2- and 3-vinylindoles both as a building blocks to synthesize functionalized carbazoles by [4+2]cycloaddition reaction and to improve our knowledge of cycloaddition pathways with vinylheterocycles and dienophiles.[1] This paper describes the preparation of 3-vinylindoles assisted with sulfur substituents and subsequent [4+2]cycloaddition reaction with dienophiles to give functionalized carbazoles.

We found that the alkylation of 3-thioacetylindole (**1**), prepared by the reaction of 3-acetylindole with Lawesson's reagent,[2] with 3-bromo-1-phenylpropene afforded the sulfur substituted 3-vinylindole **3**. Although **3** is not stable enough for complete purification, it undergoes thio-Claisen rearrangement to give **4**. Generation of a fairly stable 3-vinylindole such as **3** prompted us to examine its use for the synthesis of functionalized carbazoles through cycloaddition reactions with dienophiles.

A preliminary study was done on the reaction of the 3-vinylindoles **5** and **6**, generated by the reaction of the anion of **1** with methyl iodide *in situ*, with dimethyl acetylenedicarboxylate to yield the carbazoles **8** and **7** in yields of 67% and a trace amount. Compound **7** was also identified by transformation to **8** by methylation with methyl iodide and sodium hydride.

Reactivities of a 3-vinylindole with dienophiles were investigated with the S-benzyl derivative **9** because methylation of **1** has less selectivity, as shown above. Reactions were generally carried out in a fused glass tube at 100 °C under a nitrogen atmosphere for an appropriate time, and the results are shown in Table I and Chart 2. Among the cycloadducts, compound **12** is an unstable oil and has the absorptions at 3400, 1730, and 1600 cm^{-1} in the infrared (IR) spectrum. The structure of **12** was identified by transformation to **10** by reaction with active MnO_2. Though **13** has absorptions at 3350, 1730, and 1635 cm^{-1} in the IR spectrum, the proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed that it is a isomeric mixture in a ratio of 2 : 1 in the case of the reaction with dimethyl maleate

Table I. Cycloaddition Reaction of the Diene (**9**) with Dienophiles

Dienophile	Temperature (°C)	Time (h)	Product	Yield (%)
$MeO_2CC \equiv CCO_2Me$	100	5	**10**	70
$HC \equiv CCO_2Me$	100	24	**11**	9.3
	100	24	**12** + **13**	52.6 21.4
	100	24	**12** + **13**	83 Trace
 [a,b]	0	3	**16**	23
 [a]	0→r.t.	5	**17**	17

a) Reactions were carried out at atmospheric pressure. *b*) Obtained by the oxidation of the addition product **15** with active MnO_2 without purification, because the adduct **15** was unstable. r.t. = room temperature.

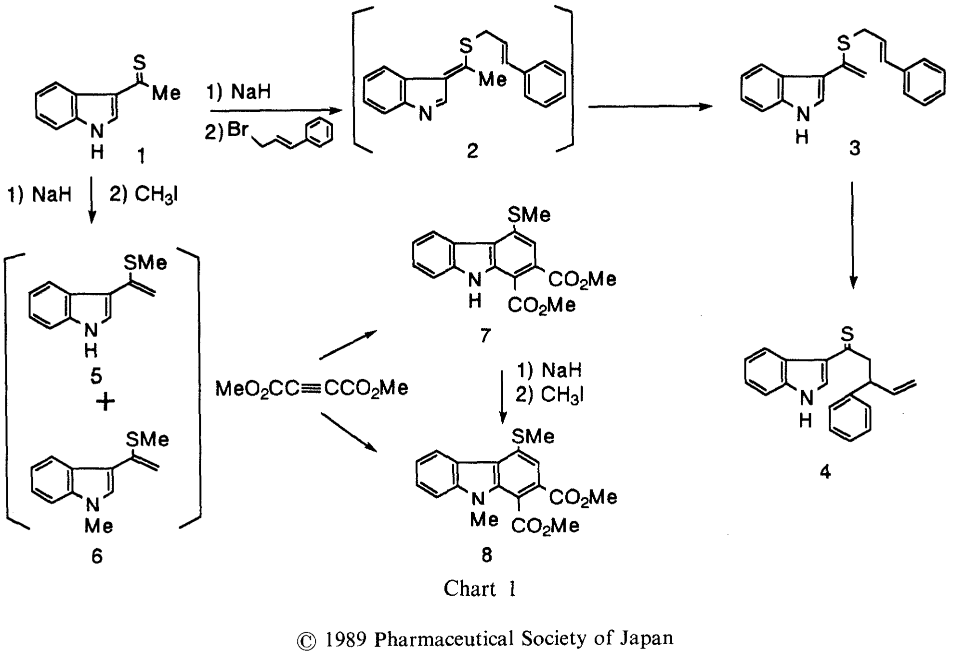


Chart 1

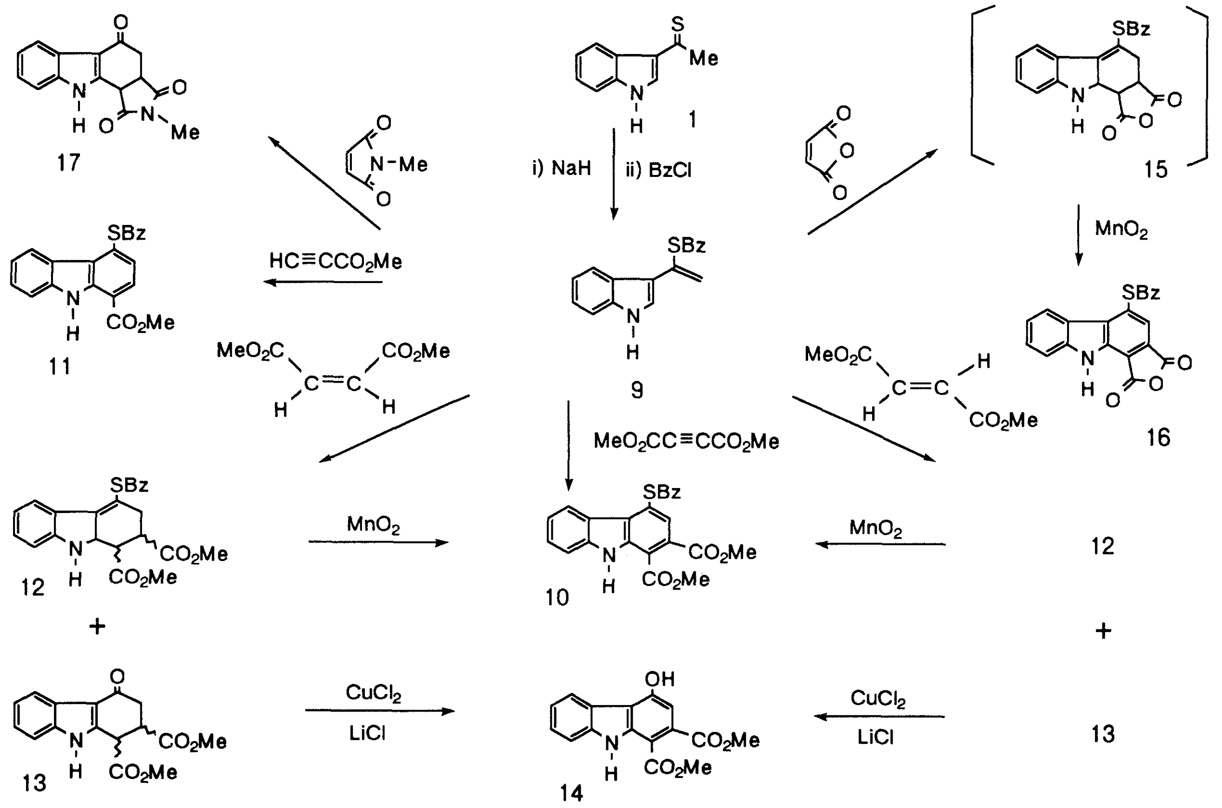


Chart 2

and 1.5 : 1 in the case of the reaction with dimethyl fumarate. Treatment of the mixture of **13** with $CuCl_2$ and LiCl afforded **14**. Further, the cycloaddition product **15** produced by the reaction with maleic anhydride was transformed immediately to **16** by the addition of active MnO_2 to the reaction solution because **15** was very unstable.

Further studies on the application of these reactions for the synthesis of natural products are under way.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer, ^1H-NMR spectra with a JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard, and mass spectra (MS) with a JEOL JMS-d 300 spectrometer. Elementary analyses were done by Ms. A. Sakamoto and Ms. S. Okamura, Kissei Pharmaceutical Company Ltd., Japan. Wako Silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin layer chromatography (TLC), respectively.

3-Thioacetylindole (1) Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (20.17 g), was slowly added to a solution of 3-acetylindole (14.31 g) in 1,2-dimethoxyethane (DME) (270 ml) with ice cooling and the whole was stirred at room temperature under a nitrogen atmosphere with shielding from light for 24 h. The reaction mixture was poured into water, and then extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried and concentrated. The residue was recrystallized from chloroform–acetone to yield 13.34 g (84.7%) of **1** as red needles, mp 144—145 °C. IR (KBr) cm^{-1}: 3100, 1470, 1410, 1310, 1220. ^1H-NMR (CD_3COCD_3) δ: 3.07 (3H, s, -Me), 7.24—7.33 (2H, m, C-5H and C-6H), 7.05—7.57 (1H, m, C-4H), 8.46 (1H, d, $J=3.42$ Hz, C-2H), 8.89—8.94 (1H, m, C-7H), 11.29 (1H, br, -NH). MS *m/z*: 175 (M^+). *Anal.* Calcd for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.34; H, 5.11; N, 7.75.

1-(3-Indolyl)-1-(3-phenyl-2-propenylthio)ethylene (3) and 1-(3-Indolyl)-3-phenyl-4-pentene-1-thione (4) A solution of thioacetylindole (**1**) (176 mg, 1 mmol) in tetrahydrofuran (THF, 0.5 ml) was slowly added to a suspension of NaH (52 mg, 1.3 mmol) in THF (3 ml) at −20 °C with stirring under a nitrogen atmosphere. After 5 min, the temperature of the mixture was lowered to −78 °C, then a solution of cinnamyl bromide (217 mg, 1.1 mmol) in THF (0.5 ml) was added, and the whole was allowed to warm to room temperature, then poured into water, and extracted with ether. The organic layer was washed with brine, then dried and concentrated to give **3**, mp 110 °C, light grey needles (CH_2Cl_2–hexane). IR (Nujol) cm^{-1}: 3430, 1590. ^1H-NMR (CD_3COCD_3) δ: 3.63 (2H, d, $J=$ 6.83 Hz, $-CH_2-$), 5.3 (1H, s, C-$2H_a$), 5.61 (1H, s, C-$2H_b$), 6.36 (1H, dd, $J=$ 6.83, 15.62 Hz, C-2′H), 6.50 (1H, d, $J=15.62$ Hz, C-3′H), 7.07—7.20 (2H, m, indole C-5,6H), 7.21—7.40 (5H, m, phenyl-H), 7.47 (1H, d, $J=7.57$ Hz, indole C-4H), 7.59 (1H, d, $J=2.68$ Hz, indole C-2H), 7.90 (1H, d, $J=$ 7.57 Hz, indole C-7H), 10.5 (1H, br, indole NH). MS *m/z*: 291 (M^+). The crude **3** obtained from the above reaction (without purification) and $CaCO_3$ (300 mg) were dissolved in DME (15 ml) and H_2O (5 ml), and the whole was heated at 80 °C for 1.5 h, then poured into water, and extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with chloroform–hexane (1 : 1) gave 150 mg (51%) of **4** as a red oil. IR (neat) cm^{-1}: 3370, 1635, 1600. ^1H-NMR (CD_3COCD_3) δ: 3.74 (1H, d, $J=7.57$ Hz, $-CH_2-$), 3.75 (1H, d, $J=7.33$ Hz, $-CH_2-$), 4.23—4.31 (1H, m, methin H), 4.91—5.02 (2H, m, vinyl-*endo* H), 6.03—6.20 (1H, m, olefinic H), 7.10—7.54 (8H, m, phenyl and indole C-4,5,6H), 8.46 (1H, d, $J=3.17$ Hz, indole C-2H), 8.95 (1H, d, $J=7.32$ Hz, indole C-7H), and 11.28 (1H, br, -NH). MS *m/z*: 291 (M^+).

1,2-Dimethoxycarbonyl-4-methylthiocarbazole (7) and 1,2-Dimethoxycarbonyl-4-methylthio-*N*-methylcarbazole (8) A solution of thioacetylindole (**1**) (1.76 g, 10 mmol) in THF (15 ml) was added to a suspension of NaH (600 mg, 15 mmol) in THF (30 ml) with stirring at −20 °C under a nitrogen atmosphere. After 20 min, a solution of MeI (3.12 g, 22 mmol) in THF (2 ml) was added to the mixture, and the whole was stirred for 30 min to give **6** and a trace of **5**. A solution of dimethyl acetylenedicarboxylate (1.7 g, 12 mmol) in THF (2 ml) was added to the above mixture, and the whole was heated at 50 °C for 5 h. After the reaction, aqueous NH_4Cl was added, and the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with chloroform–hexane (2 : 1) gave 2.29 g (67%) of **8** and a trace of **7**. Treatment of **7** with NaH and MeI in THF afforded **8** as light greenish needles. **7**: mp 136.5—137 °C, white needles (ether). IR (Nujol) cm^{-1}: 3420, 1720, 1700. ^1H-NMR (CD_3COCD_3) δ: 2.81 (3H, s, S-Me), 3.90 (3H, s, CO_2Me), 3.96 (3H, s, CO_2Me), 7.22 (1H, s, C-3H), 7.33 (1H, dd, $J=8.06$, 8.3 Hz, C-7H), 7.52 (1H, t, J=8.3 Hz, C-6H), 7.75 (1H, d, J=8.3 Hz, C-5H), 8.46 (1H, d, J=8.06 Hz, C-8H), 10.97 (1H, br, –NH). MS *m/z*: 329 (M$^+$). **8**: mp 162—163 °C, light greenish needles (benzene–hexane). IR (Nujol) cm^{-1}: 3400, 1720. ^{1}H-NMR (CD$_3$COCD$_3$) δ: 2.77 (3H, s, S-Me), 3.89 (3H, s, N-Me or CO$_2$Me), 3.93 (3H, s, N-Me or CO$_2$Me), 4.02 (3H, s, N-Me or CO$_2$Me), 7.35 (1H, t, J=8.05 Hz, C-6 or C-7H), 7.60 (1H, t, J=8.05 Hz, C-6 or C-7H), 7.67 (1H, d, J=8.05 Hz, C-5H), 7.68 (1H, s, C-3H), 8.56 (1H, d, J=8.05 Hz, C-8H). MS *m/z*: 343 (M$^+$). *Anal.* Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.82; H, 4.97; N, 3.87.

Synthesis of the Diene 9 A solution of 3-thioacetylindole (**1**) (875 mg, 5 mmol) in THF (15 ml) was added to a suspension of NaH (240 mg, 6 mmol) in THF (30 ml) with stirring at −15 °C under a nitrogen atmosphere. After 30 min, benzyl chloride (700 mg, 5.5 mmol) in THF (2 ml) was added to the mixture, and the whole was stirred at room temperature for 6 h. The resultant solution of the diene **9** was used without purification for the reaction with dienophiles under the conditions described in Table I.

General Procedure for the Cycloaddition Reaction of the Diene 9 with Dienophiles A solution of the diene **9** obtained by the reaction of **1** (5 mmol) with benzyl chloride was heated with a dienophile (7.5 mmol) in a fused glass tube under a nitrogen atmosphere under the appropriate conditions (Table I). The reaction mixture was poured into water, and the whole was extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. The residue was subjected to silica gel column chromatography using the appropriate solvents.

4-Benzylthio-1,2-dimethoxycarbonylcarbazole (10) The residue obtained from the reaction with the diene **9** and dimethyl acetylenedicarboxylate by the general procedure was subjected to silica gel column chromatography to yield 1.43 g (70%) of **10** from the chloroform eluate as colorless needles (benzene), mp 172—173 °C. IR (Nujol) cm^{-1}: 3425, 1705, 1595. ^{1}H-NMR (CD$_3$COCD$_3$) δ: 3.90 (3H, s, –CO$_2$Me), 3.96 (3H, s, –CO$_2$Me), 4.59 (2H, s, –CH$_2$Ph), 7.28—7.39 (4H, m, C-7H and S-benzyl aromatic H), 7.40 (1H, s, C-3H), 7.50 (1H, t, J=8.3 Hz, C-6H), 7.57 (2H, d, J=8.05 Hz, S-benzyl aromatic H), 7.73 (1H, d, J=8.3 Hz, C-5H), 8.49 (1H, d, J=7.81 Hz, C-8H), 10.94 (1H, br, –NH). MS *m/z*: 405 (M$^+$). *Anal.* Calcd for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45. Found: C, 68.29; H, 4.70; N, 3.25.

4-Benzylthio-1-methoxycarbonylcarbazole (11) The residue obtained from the reaction with the diene **9** and methyl acetylenecarboxylate by the general procedure was subjected to silica gel column chromatography to yield 162 mg (9.3%) of **11** from the chloroform–hexane (2 : 1) eluate as colorless needles (benzene), mp 168.5—170.5 °C. IR (Nujol) cm^{-1}: 3400, 1675, 1595. ^{1}H-NMR (CD$_3$COCD$_3$) δ: 3.96 (3H, s, –CO$_2$Me), 4.56 (2H, s, –CH$_2$Ph), 7.25—7.39 (4H, m, C-7H and S-benzyl aromatic H), 7.30 (1H, d, J=8.3 Hz, C-2H or C-3H), 7.47 (1H, t, J=8.3 Hz, C-6H), 7.55 (2H, d, J=8.05 Hz, S-benzyl aromatic H), 7.77 (1H, d, J=8.3 Hz, C-5H), 7.99 (1H, d, J=8.3 Hz, C-2H or C-3H), 8.48 (1H, d, J=8.05 Hz, C-8H), 10.94 (1H, br, –NH). MS *m/z*: 347 (M$^+$). *Anal.* Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.45; H, 4.82; N, 3.95.

Cycloaddition Reaction with the Diene 9 and Dimethyl Maleate The residue obtained from the reaction with the diene **9** and dimethyl maleate by the general procedure was subjected to silica gel column chromatography to yield 1.07 g (52.6%) of **12** and 320 mg (21.4%) of **13** from the chloroform–hexane (4 : 1) eluate. The condensation products **12** and **13** were quickly subjected to the following aromatization reactions because of their instability.

Aromatization of 12 A mixture of **12** (319 mg, 0.78 mmol) and active MnO$_2$ (1.04 g, 12 mmol) in benzene (6 ml) was refluxed for 1 h under a nitrogen atmosphere. Insoluble materials were filtered off through Celite. **10** was obtained as the precipitate when ether was added to the filtrate. The filtrate was subjected to silica gel column chromatography to give a further crop of **10** from the chloroform eluate. Total yield of **10** was 41% (130 mg).

1,2-Dimethoxycarbonyl-4-hydroxycarbazole (14) A mixture of **13** (286 mg, 0.95 mmol), CuCl$_2$·2H$_2$O (305 mg, 1.8 mmol), and LiCl (74 mg, 1.76 mmol) in dimethylformamide (DMF) was heated at 90 °C with stirring for 1 h under a nitrogen atmosphere. The mixture was poured into water, and then the whole was filtered through Celite. The filtrate was extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. The residue was subjected to silica gel column chromatography to give 158 mg (56%) of **14** from the ether–hexane (1 : 1) eluate as light yellow needles (ether–hexane), mp 233 °C. IR (Nujol) cm^{-1}: 3350, 1705, 1665. ^{1}H-NMR (CD$_3$COCD$_3$) δ: 3.86 (3H, s, –CO$_2$Me), 3.93 (3H, s, –CO$_2$Me), 6.81 (1H, s, C-3H), 7.25 (1H, t, J=8.05 Hz, C-6H or C-7H), 7.44 (1H, t, J=8.05 Hz, C-6H or C-7H), 7.68 (1H, d, J=8.05 Hz, C-5H), 8.31 (1H, d, J=8.05 Hz, C-8H), 10.78 (1H, br, –NH). MS *m/z*: 299 (M$^+$). *Anal.* Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.18; H, 4.39; N, 4.77.

Cycloaddition Reaction with the Diene 9 and Dimethyl Fumarate A mixture of the diene **9** and dimethyl fumarate was treated as described for the reaction of dimethyl maleate to give 1.68 g (83%) of **12** and a trace amount of **13**. Subsequent aromatization reactions of **12** and **13** in the same manner afforded **10** and **14**.

4-Benzylthiocarbazole-1,2-dicarboxylic Anhydride (16) A mixture of the diene **9** obtained by the general method and maleic anhydride (735 mg, 7.5 mmol) was kept at 0 °C for 3 h, and then active MnO$_2$ (4.35 g) was added. The whole was stirred at room temperature for 20 h. Insoluble materials were filtered off through Celite, and then the filtrate was extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. Addition of chloroform to the residue caused precipitation of **16**. After separation of **16** by filtration, the mother liquor was subjected to silica gel column chromatography to give a further crop of **16** as orange needles (benzene), mp 276 °C. The combined yield of **16** was 23% (419 mg). IR (Nujol) cm^{-1}: 3400, 1830, 1755, 1585. ^{1}H-NMR (CD$_3$COCD$_3$) δ: 4.77 (2H, s, –CH$_2$Ph), 7.34—7.44 (3H, m, S-benzyl aromatic H), 7.43 (1H, t, J=7.81 Hz, C-7H), 7.64 (1H, dd, J=7.81, 8.06 Hz, C-6H), 7.65 (2H, d, J=7.32 Hz, S-benzyl aromatic H), 7.75 (1H, s, C-3H), 7.82 (1H, d, J=8.06 Hz, C-5H), 8.56 (1H, d, J=7.81 Hz, C-8H), 11.65 (1H, br, –NH). MS *m/z*: 359 (M$^+$). *Anal.* Calcd for $C_{21}H_{13}NO_3S$: C, 70.18; H, 3.65; N, 3.90. Found: C, 70.08; H, 3.65; N, 3.76.

2-Methyl-3a,4-dihydropyrrolo[3,4-*a*]carbazole-1,3,5-(10*H*,10b*H*)-trione (17) A mixture of the diene **9** prepared by the general method and *N*-methylmaleinimide (833 mg, 7.5 mmol) was kept at 0 °C for 5 h, then at room temperature overnight. Water was added to the mixture and the whole was extracted with AcOEt. The organic layer was washed with brine, then dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with 5% acetone in chloroform afforded 244 mg (17%) of **17** as light violet crystals (MeOH), mp 300 °C. IR (Nujol) cm^{-1}: 3250, 1780, 1690, 1625, 1580. ^{1}H-NMR (CDCl$_3$) δ: 2.93 (1H, dd, J=17.82, 9.03 Hz, C-4H$_a$), 3.00 (3H, s, N-Me), 3.32 (1H, dd, J=17.82, 2.20 Hz, C-4H$_b$), 3.70 (1H, ddd, J=9.03, 8.54, 2.2 Hz, C-3aH), 4.42 (1H, d, J=8.54 Hz, C-10bH), 7.26—7.43 (3H, m, C-6,7,8H), 8.25 (1H, d, J=8.3 Hz, C-9H), 9.04 (1H, br, –NH). MS *m/z*: 268 (M$^+$). *Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.86; H, 4.58; N, 10.47.

References

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