

Synthesis of Functionalized Indoles by Diels-Alder Reaction Utilizing the Diene Generated by the Alkylation of *N*-Methyl-3-thioacetylpyrrole

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Cycloaddition reaction of 3-vinylpyrroles, generated by the alkylation of 1-methyl-3-thioacetylpyrrole, with dienophiles provided functionalized indoles.

Keywords cycloaddition; 3-vinylpyrrole; 1-methyl-3-thioacetylpyrrole; alkylation; dienophile; indole

Recently, we reported that functionalized carbazoles can be synthesized by Diels-Alder reaction of the sulfur substituted 3-vinylindoles **2**, generated by the alkylation of thioacetylindole (**1**), with several dienophiles.¹⁾ We also found

that such behavior is observed in thioacetylpyrroles. This paper describes the synthesis of indoles having various substituents by means of Diels-Alder reactions of the sulfur substituted 3-vinylpyrrole **7**, generated *in situ* by the

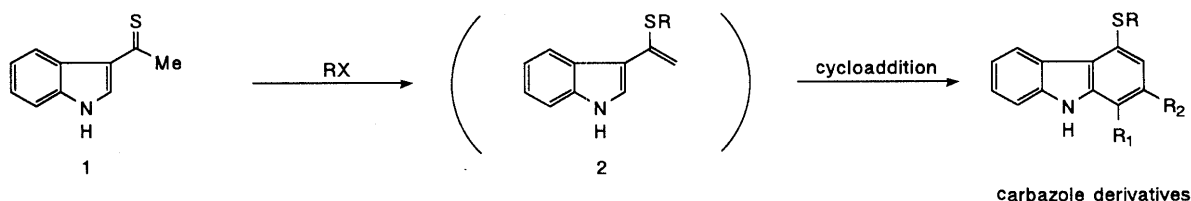
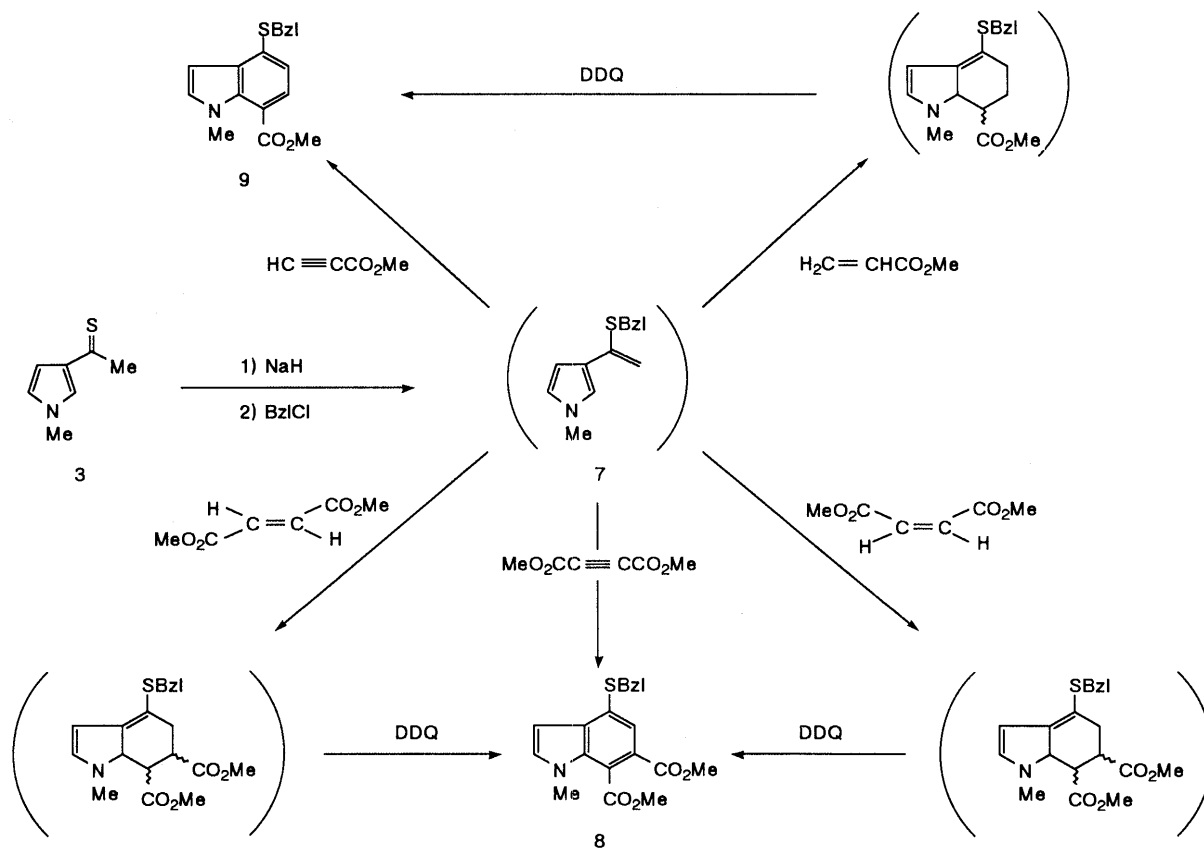
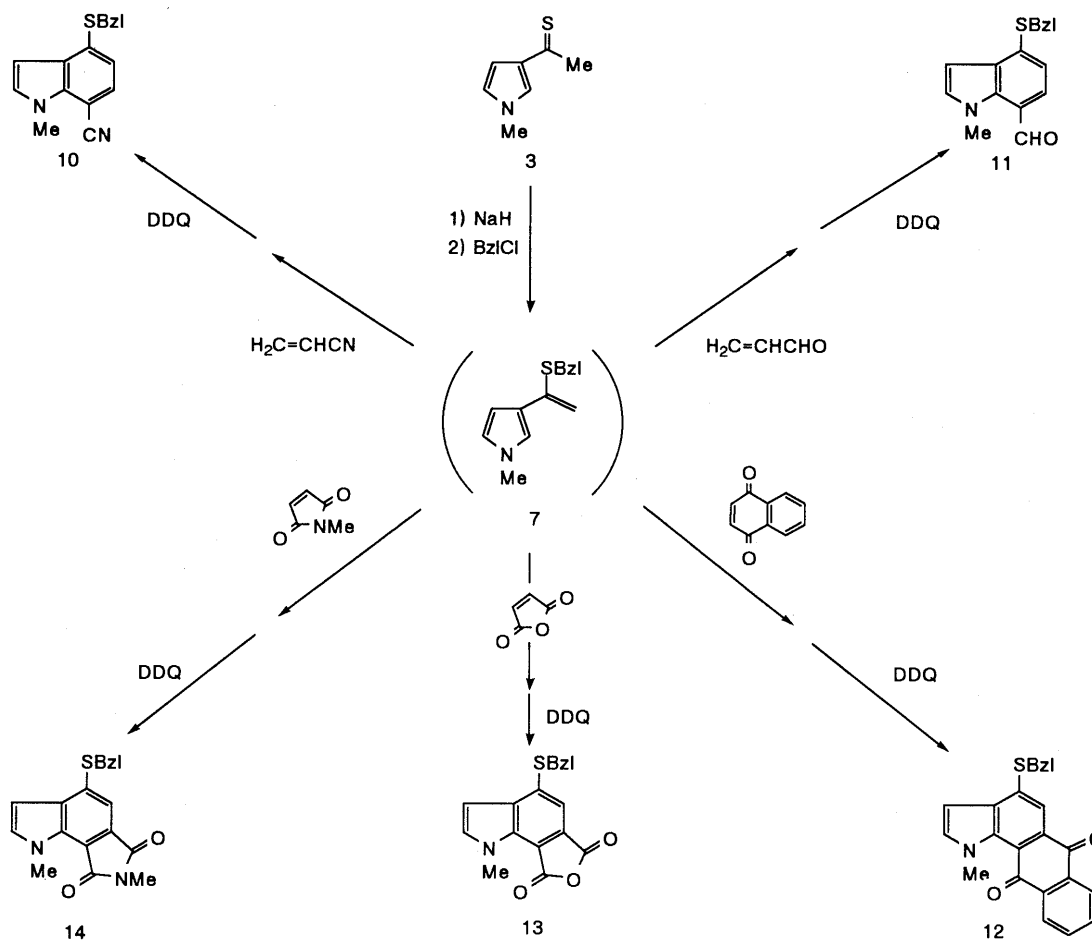


Chart 1





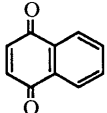

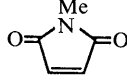
alkylation of the 3-thioacetylpyrrole **3**, with dienophiles.

First, the thioacetylpyrroles **3**, **4**, **5**, and **6** were synthesized by the reaction of corresponding acetylpyrroles with Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide,²⁾ to examine their reactivity. A preliminary study was done on the reaction of the 3-vinylpyrrole **7**, generated *in situ* by the reaction of 1-methyl-3-thioacetylpyrrole (**3**) with benzyl chloride, with dimethyl acetylenedicarboxylate in tetrahydrofuran (THF). The indole **8** was obtained in 30.5% overall yield from 3-acetyl-1-methylpyrrole. In general, the cycloaddition reactions of the vinylpyrrole **7** with dienophiles were carried out in a fused glass tube at 100 °C in THF or MeCN under a nitrogen atmosphere for an appropriate time, and the results are summarized in Charts 2 and 3 and Table I.

Among the cycloadducts, products of the reactions of the diene **7** with dimethyl maleate, dimethyl fumarate, methyl acrylate, acrylonitrile, acrolein, 1,4-naphthoquinone, maleic anhydride, and *N*-methylmaleinimide were directly transformed to the corresponding indoles by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), though the products were not purified because of their instability. In these reactions, we also observed significant changes of the cycloadduct yields in the reactions with dimethyl acetylenedicarboxylate, methyl propiolate, and acrolein (Table I).

Although the reactivities of the thioacetylpyrroles **4**, **5**, and **6** for cycloaddition were investigated, in addition to that of **3**, the results were unsatisfactory. That is, the re-

TABLE I. Cycloaddition Reaction of the Diene **7** with Dienophiles

Dienophile	Time (h)	Product	Solvent	Yield (%) ^{a)}
MeO ₂ C≡CCO ₂ Me	24	8	THF	30.5
			MeCN	10.0
MeO ₂ C-C=C(H)-CO ₂ Me	48	8 ^{b)}	THF	29.7
H-C=C(H)-CO ₂ Me	48	8 ^{b)}	THF	16.7
MeO ₂ C-C=C(H)-CO ₂ Me				
HC≡CCO ₂ Me	24	9	THF	10.4
			MeCN	31.4
H ₂ C=CHCO ₂ Me	48	9 ^{b)}	THF	13.6
H ₂ C=CHCN	48	10 ^{b)}	THF	19.6
H ₂ C=CHCHO	48	11 ^{b)}	THF	Trace
			MeCN	20.4
	48	12 ^{b)}	THF	21.1
	48	13 ^{b)}	THF	8.0
	48	14 ^{b)}	THF	15.7

a) Overall yield from 3-acetyl-1-methylpyrrole. b) Obtained by the oxidation of the cycloaddition product without purification.

action of dimethyl acetylenedicarboxylate with the solution obtained from the reaction of **4** with NaH followed by the treatment with benzyl chloride gave only a trace amount of

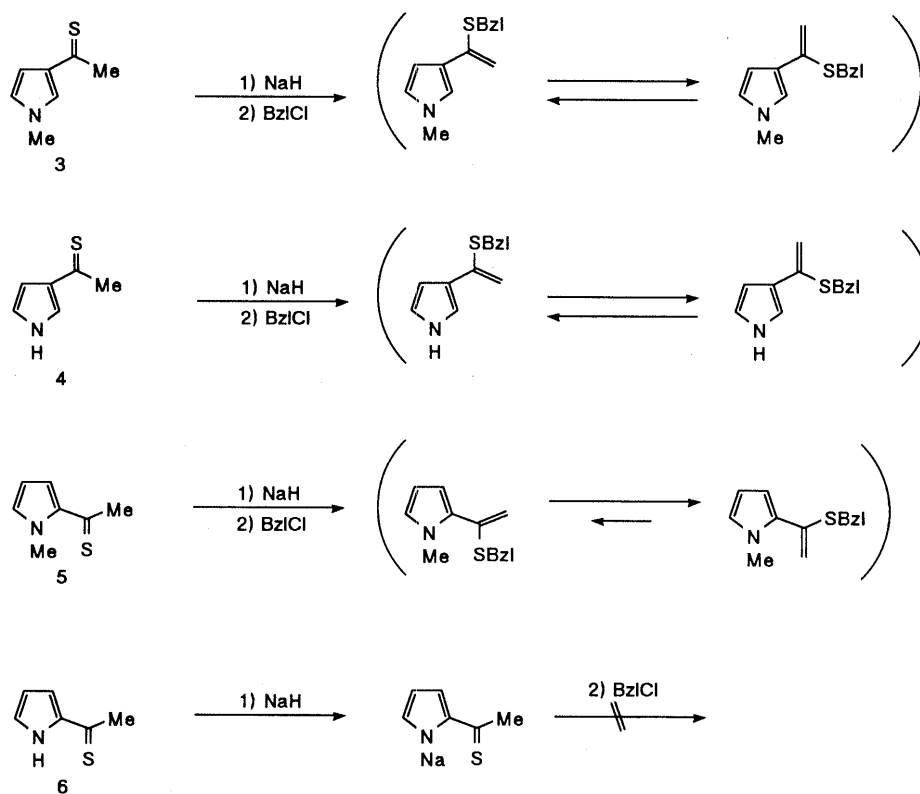


Chart 4

the cycloadduct (not investigated further). The poor result in this reaction may be due to the lability of the vinylpyrrole produced from **4**. Similar treatment of an anion from **5** with benzyl chloride followed by reaction with dimethyl acetylenedicarboxylate did not afford any cycloaddition product. The inertness of the vinylpyrrole generated from **5** to cycloaddition may be due to the predominance of the transoid form of the diene in the solution owing to steric interaction between the N-Me and S-benzyl groups. Further, the reaction of benzyl chloride with an anion derived from the thioacetylpyrrole **6** by treatment with NaH did not give any alkylation product.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 or a JASCO IR-700 spectrometer, ^1H -nuclear magnetic resonance (^1H -NMR) spectra with a JEOL JNM-GX 270 or a JEOL JNM-EX 90 or a Varian T-60 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., Matsumoto, 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.

1-Methyl-3-thioacetylpyrrole (3) Lawesson's reagent (2425 mg, 6 mmol) was slowly added to a solution of 3-acetyl-1-methylpyrrole (615 mg, 5 mmol) in THF (15 ml) and the whole was stirred at room temperature under a nitrogen atmosphere with shielding from light for 30 min. Hexane (24 ml) was added to the reaction mixture and the insoluble precipitate was filtered off. The filtrate was poured into water and extracted with hexane. The organic layer was washed with saturated aqueous NaHCO_3 and brine, and then dried and concentrated. The residue was used without purification for the synthesis of the diene **7**. An analytic sample was obtained by silica gel column chromatography of the above residue to give 605 mg (87%) of **3** from the chloroform-hexane (1:1) eluate as deep red plates (petroleum ether), mp 42–44 °C. ^1H -NMR (acetone- d_6) δ : 2.84 (3H, s, Me), 3.72 (3H, s, N-Me), 6.70 (2H, m, pyrrole H), 7.59 (1H, m,

pyrrole H). MS m/z Calcd for $\text{C}_7\text{H}_9\text{NS}$ (M^+): 139.0456. Found: 139.0468.

3-Thioacetylpyrrole (4) Lawesson's reagent (484 mg, 1.2 mmol) was slowly added to a solution of 3-acetylpyrrole (109 mg, 1 mmol) in THF (5 ml) and the whole was stirred at room temperature under a nitrogen atmosphere with shielding from light for 1 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with saturated aqueous NaHCO_3 and brine, and then dried and concentrated. The residue was subjected to silica gel column chromatography to yield **4** from the benzene eluate in a quantitative yield as orange plates, mp 74–75 °C (benzene-hexane). ^1H -NMR (acetone- d_6) δ : 2.90 (3H, s, Me), 6.73 (2H, m, pyrrole H), 7.67 (1H, m, pyrrole H), 10.80 (1H, br, NH). MS m/z Calcd for $\text{C}_6\text{H}_7\text{NS}$ (M^+): 125.0298. Found: 125.0288.

1-Methyl-2-thioacetylpyrrole (5) Lawesson's reagent (967 mg, 2.4 mmol) was slowly added to a solution of 2-acetyl-1-methylpyrrole (246 mg, 2 mmol) in THF (10 ml) and the whole was stirred at room temperature under a nitrogen atmosphere with shielding from light for 3 h. *n*-Pentane was added to the reaction mixture and the insoluble precipitate were filtered off. The filtrate was poured into water and extracted with *n*-pentane. The organic layer was washed with saturated aqueous NaHCO_3 and brine, then dried and concentrated carefully at low temperature. The residue was subjected to silica gel column chromatography with *n*-pentane as an eluent to give 228 mg (82%) of **5** as deep red needles, mp 37–38 °C (petroleum ether). ^1H -NMR (acetone- d_6) δ : 2.93 (3H, s, Me), 4.03 (3H, s, NMe), 6.15 (1H, m, pyrrole H), 7.17 (2H, m, pyrrole H). MS m/z Calcd for $\text{C}_7\text{H}_9\text{NS}$ (M^+): 139.0456. Found: 139.0435.

2-Thioacetylpyrrole (6) Lawesson's reagent (484 mg, 1.2 mmol) was slowly added to a solution of 2-acetylpyrrole (109 mg, 1 mmol) in 1,2-dimethoxyethane (5 ml) and the whole was stirred at room temperature under a nitrogen atmosphere with shielding from light for 1 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with saturated aqueous NaHCO_3 and brine, then dried and concentrated. The residue was subjected to silica gel column chromatography to give **6** as a red oil from the chloroform eluate in a quantitative yield. ^1H -NMR (acetone- d_6) δ : 2.87 (3H, s, Me), 6.35 (1H, m, pyrrole H), 7.10 (1H, m, pyrrole H), 7.38 (1H, m, pyrrole H), 10.73 (1H, br, NH). MS m/z Calcd for $\text{C}_6\text{H}_7\text{NS}$ (M^+): 125.0298. Found: 125.0323.

Preparation of the Diene 7 A solution of 1-methyl-3-thioacetylpyrrole (**3**) (695 mg, 5 mmol) in MeCN or THF (5 ml) was added to a suspension of 60% NaH (200 mg, 5 mmol) and benzyl chloride (696 mg, 5.5 mmol) in MeCN or THF (35 ml) with stirring at –15 °C under a nitrogen

atmosphere and the whole was stirred at room temperature for 24 h to give the diene **7**, which 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 7 with Dienophiles A solution of the diene **7** prepared by the reaction of **3** (5 mmol) with benzyl chloride in the presence of NaH 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 ethyl acetate or chloroform. The organic layer was washed with brine, and then dried and concentrated. The residue was subjected to silica gel column chromatography using the appropriate solvent.

General Method for DDQ Oxidation of the Cycloadducts A benzene solution (50 ml) of the residue, obtained by applying the general procedure for the reaction of the diene **7** with dienophiles, was treated with DDQ (1.183 mg, 5 mmol) and the whole was stirred at room temperature for 1 h, then concentrated. CH_2Cl_2 (50 ml) was added to the residue and insoluble materials were filtered off. The filtrate was concentrated and subjected to silica gel column chromatography using an appropriate solvent.

4-Benzylthio-6,7-dimethoxycarbonyl-1-methylindole (8) The residue obtained from the reaction of the diene **7** with dimethyl acetylenedicarboxylate in THF by the general procedure in ethyl acetate was subjected to silica gel column chromatography to yield 562 mg (30.5% overall yield from 3-acetyl-1-methylpyrrole) of **8** from the chloroform-hexane (1:1) eluate as colorless needles (ether), mp 140–142°C. IR (Nujol) cm^{-1} : 1720, 1705. $^1\text{H-NMR}$ (acetone- d_6) δ : 3.82 (3H, s, NMe or CO_2Me), 3.86 (3H, s, NMe or CO_2Me), 3.96 (3H, s, NMe or CO_2Me), 4.34 (2H, s, benzyl H), 6.64 (1H, d, $J=3.18$ Hz, C-3 H), 7.20–7.33 (3H, m, aromatic H), 7.37–7.42 (2H, m, aromatic H), 7.50 (1H, d, $J=3.18$ Hz, C-2 H), 7.69 (1H, s, C-5 H), MS m/z : 369 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4\text{S}$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.82; H, 5.28; N, 3.65.

The residue obtained from the reaction of the diene **7** with dimethyl maleate in THF by the general procedure was oxidized with DDQ by the general method in ethyl acetate. The residue was subjected to silica gel column chromatography to yield 308 mg (16.7% overall yield from 3-acetyl-1-methylpyrrole) of **8** from the chloroform-hexane (1:1) eluate.

Reaction of the diene **7** with dimethyl fumarate in the same manner as described for the reaction with dimethyl maleate afforded 548 mg (29.7% overall yield from 3-acetyl-1-methylpyrrole) of **8**.

4-Benzylthio-7-methoxycarbonyl-1-methylindole (9) The residue obtained from the reaction of the diene **7** with methyl propiolate in MeCN by the general procedure in ethyl acetate was subjected to silica gel column chromatography to give 488 mg (31.4% overall yield from 3-acetyl-1-methylpyrrole) of **9** from the chloroform-hexane (1:1) eluate as colorless needles (ether), mp 122–122.5°C. IR (CHCl_3) cm^{-1} : 1700. $^1\text{H-NMR}$ (acetone- d_6) δ : 3.90 (3H, s, NMe or CO_2Me), 3.92 (3H, s, NMe or CO_2Me), 4.37 (2H, s, benzyl H), 6.61 (1H, d, $J=3.18$ Hz, C-3 H), 7.11 (1H, d, $J=7.81$ Hz, C-5 H or C-6 H), 7.24–7.34 (4H, m, C-2 H and aromatic H), 7.42–7.45 (2H, m, aromatic H), 7.56 (1H, d, $J=7.81$ Hz, C-5 H or C-6 H), MS m/z : 311 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_2\text{S}$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.40; H, 5.40; N, 4.48.

The residue obtained from the reaction of the diene **7** with methyl acrylate in THF by the general procedure was oxidized with DDQ by the general method in ethyl acetate. The residue was subjected to silica gel column chromatography to give 211 mg (13.6% overall yield from 3-acetyl-1-methylpyrrole) of **9** from the chloroform-hexane (1:1) eluate.

4-Benzylthio-7-cyano-1-methylindole (10) The residue obtained from the reaction of the diene **7** with acrylonitrile in THF by the general procedure was oxidized with DDQ by the general method in ethyl acetate. The residue was subjected to silica gel column chromatography to yield

272 mg (19.6% overall yield from 3-acetyl-1-methylpyrrole) of **10** from the chloroform-hexane (2:1) eluate as colorless plates (ether), mp 112–114°C. IR (KBr) cm^{-1} : 2210. $^1\text{H-NMR}$ (acetone- d_6) δ : 4.11 (3H, s, NMe), 4.40 (2H, s, benzyl H), 6.60 (1H, d, $J=3.29$ Hz, C-3 H), 7.14 (1H, d, $J=7.91$ Hz, C-5 H or C-6 H), 7.25–7.52 (7H, m, C-2 H, C-5 H or C-6 H and aromatic H), MS m/z : 278 (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{S}$: C, 73.35; H, 5.07; N, 10.06. Found: C, 73.22; H, 4.98; N, 9.91.

4-Benzylthio-7-formyl-1-methylindole (11) The residue obtained from the reaction of the diene **7** with acrolein in MeCN by the general procedure was oxidized with DDQ by the general method in ethyl acetate. The residue was subjected to silica gel column chromatography to give 286 mg (20.4% overall yield from 3-acetyl-1-methylpyrrole) of **11** from the chloroform-hexane (1:1) eluate as yellow needles (ether), mp 112–114°C. IR (CHCl_3) cm^{-1} : 1685. $^1\text{H-NMR}$ (acetone- d_6) δ : 4.15 (3H, s, NMe), 4.44 (2H, s, benzyl H), 6.62 (1H, d, $J=3.17$ Hz, C-3 H), 7.24 (1H, d, $J=7.81$ Hz, C-5 H or C-6 H), 7.26–7.37 (4H, m, C-2 H and aromatic H), 7.48–7.51 (2H, m, aromatic H), 7.70 (1H, d, $J=7.81$ Hz, C-5 H or C-6 H), 10.23 (1H, s, CHO), MS m/z : 281 (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NOS}$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.47; H, 5.50; N, 4.77.

4-Benzylthio-1-methylnaphth[2,3-g]indole-6,11-quinone (12) The residue obtained from the reaction of the diene **7** with 1,4-naphthoquinone in THF by the general procedure was oxidized with DDQ by the general method in chloroform. The residue was subjected to silica gel column chromatography to yield 404 mg (21.1% overall yield from 3-acetyl-1-methylpyrrole) of **12** from the chloroform-hexane (1:1) eluate as red needles (CH_2Cl_2 -ether), mp 170–172°C. IR (KBr) cm^{-1} : 1665. $^1\text{H-NMR}$ (CDCl_3) δ : 4.04 (3H, s, NMe), 4.42 (2H, s, benzyl H), 6.65 (1H, d, $J=3.18$ Hz, C-3H), 7.22–7.48 (6H, m, C-2 H and aromatic H), 7.68–7.75 (2H, m, aromatic H), 7.99 (1H, s, C-5H), 8.11–8.24 (2H, m, aromatic H), MS m/z : 383 (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{NO}_2\text{S}$: C, 75.17; H, 4.47; N, 3.65. Found: C, 75.22; H, 4.59; N, 3.58.

4-Benzylthio-1-methylindole-6,7-dicarboxylic Anhydride (13) The residue obtained from the reaction of the diene **7** with maleic anhydride in THF by the general procedure was oxidized with DDQ by the general method in ethyl acetate. The residue was subjected to silica gel column chromatography to yield 129 mg (8% overall yield from 3-acetyl-1-methylpyrrole) of **13** from the chloroform-hexane eluate as yellow needles (ether), mp 184–186°C. IR (KBr) cm^{-1} : 1821, 1759. $^1\text{H-NMR}$ (acetone- d_6) δ : 4.31 (3H, s, NMe), 4.60 (2H, s, benzyl H), 6.79 (1H, d, $J=3.29$ Hz, C-3 H), 7.30–7.50 (5H, m, aromatic H), 7.56 (1H, s, C-5 H), 7.66 (1H, d, $J=3.29$ Hz, C-2 H), MS m/z : 323 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_3\text{S}$: C, 66.86; H, 4.05; N, 4.33. Found: C, 66.67; H, 3.75; N, 4.28.

1,7-Dimethyl-4-benzylthiopyrrolo[3,4-g]indole-6,8-dione (14) The residue obtained from the reaction of the diene **7** with *N*-methylmaleinimide in THF by the general procedure was oxidized with DDQ by the general method in chloroform. The residue was subjected to silica gel column chromatography to yield 264 mg (15.7% overall yield from 3-acetyl-1-methylpyrrole) of **14** from the chloroform-hexane (1:1) eluate as yellow needles (CH_2Cl_2 -ether), mp 187–189°C. IR (KBr) cm^{-1} : 1753, 1697. $^1\text{H-NMR}$ (CDCl_3) δ : 3.16 (3H, s, NMe), 4.28 (3H, s, indole NMe), 4.35 (2H, s, benzyl H), 6.68 (1H, d, $J=3.3$ Hz, C-2 H), 7.23–7.45 (5H, m, aromatic H), 7.46 (1H, s, C-5 H), MS m/z : 336 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.80; H, 4.73; N, 8.30.

References

- 1) M. Murase, T. Hosaka, T. Koike, and S. Tobinaga, *Chem. Pharm. Bull.*, **37**, 1999 (1989).
- 2) M. C. Cava and M. I. Levinson, *Tetrahedron*, **22**, 5061 (1985).