238. Goro Kobayashi, Sunao Furukawa, Yoshiro Matsuda, and 
Yuko Washida*: Studies of Indole Derivatives. N.*

Reaction of Indolylmagnesium Bromide with 
Ketenethioacetals.

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Several 2-methylthio-2-(3-indolyl)acrylic acid derivatives (II) were prepared by reacting 
indolylmagnesium bromides (I) with ketenethioacetals (II).

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The reaction of indolylmagnesium halide with electrophile to give 3-substituted 
indole is well known1) and the usefulness of ketenethioacetals as an electrophilic reagent 
has been experimented in substitution reaction of amines and active methylene compounds 
with them.2-5)

In the course of our studies on indole derivatives, we found that the reaction of 
indolylmagnesium bromide (Ia) with methyl 1-methoxycarbonyl-2,2-bismethylthioacrylate 
(lla) in dry tetrahydrofuran gave methyl 1-methoxycarbonyl-2-methylthio-2-(3-indolyl)-
acrylate (lla) in 42.3% yield. lla had an empirical formula C_{11}H_{12}O_{2}NS and was crystallized 
from methanol, m.p. 132°, and its infrared spectrum showed a carbonyl absorption at 
1680, 1731 cm^{-1} and an indole N-H absorption at 3390 cm^{-1} (KBr). When the methanolic 
solution of lla and sodium hydroxide was refluxed for 30 min., 3-acetylindole (N), m.p. 
189°, was obtained. N was shown to be identical with authentic 3-acetylindole prepared 
by Majima's method.9)

Under the same reaction condition to give lla, indolyl- (Ia), 2-methylindolyl- (Ib) and 
2-phenylindolylmagnesium bromide (Ic) with ketenethioacetals (II) were subsequently 
converted into the corresponded 3-substituted indoles of general structure III (Table I).
Hydrolysis of IIIb and IIIc with 5% sodium hydroxide solution gave the corresponded 
compounds VIb and VIc.

The reaction of Ia and Ib with methyl 1-cyano-2,2-bismethylthioacrylate (IIb) in 
boiling dry tetrahydrofuran gave VIIIa and VIIIb. VIIIa had an empirical formula C_{11}H_{15}ON_{2}S_{2} 
and was crystallized from methanol, m.p. 190°. Treatment of VIIIa with sodium methoxide 
in methanol gave VIII, which was shown to be identical with 3-(w-cyano-w-methoxycarbonyl-
acetyl)indole prepared by treatment of IIIb with sodium methoxide in methanol. These 
facts obviously showed that VIIIa was 3-substituted indole. VIIIb had an empirical formula 
C_{11}H_{15}ON_{2}S_{2} and was crystallized from methanol, m.p. 187~189°, and its nuclear magnetic 
resonance spectrum in pyridine showed three different methyl signals as singlet at 2.00, 
2.40 and 2.58 p.p.m. (0 p.p.m. : TMS*3). The first signal at 2.00 p.p.m. was assigned 
as C-methyl protons, another 2.40 and 2.58 p.p.m. were assigned as S-methyl protons 
but its spectrum showed no characteristic signal in 6~7 p.p.m. region (3-position proton

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*3 Tetramethylsilanol.
of 2-methylindole). From the facts mentioned above, IIIb was formulated as 2-methyl-3-(1-cyano-2,2-bismethylthioacryl)indole rather than a structural isomer X, which could be obtained by the ester condensation reaction of the methyl group of 2-methylindole with IIb.

The reaction to give VII should be noted; that is, the ester condensation reaction occurred predominantly rather than the substitution reaction of the active bismethylthio groups of IIb, which fact was contrary to the observations obtained in the reaction of ketenethioacetics with amines and active methylene compounds.\(^{3-6}\)

In Chart 1, the results of all above reactions are summarized.

![Chemical structures](image)

**Experimental**

1) **Preparation of Ketenethioacetics (II)**—The procedures were carried out by the methods similar to those described by Gompper.\(^{3}\)
<table>
<thead>
<tr>
<th>Na.</th>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Calc'd.</th>
<th>Found</th>
</tr>
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</table>
| a   | H     | -COOCH₃ | -COOCH₃ | 132       | 42.3      | 4.95    | 4.85  | 5.00
|     |       |         |         |           |           |         |       | 1680 |
|     |       |         |         |           |           |         |       | 1731 |
|     |       |         |         |           |           |         |       | 3390 |
| b   | H     | -COOCH₃ | -CN     | 133~134   | 46.1      | 4.44    | 10.29 | 61.89 9.32 |
|     |       |         |         |           |           |         |       | 1705 |
|     |       |         |         |           |           |         |       | 2200 |
|     |       |         |         |           |           |         |       | 3320 |
| c   | H     | -COOC₅H₅ | -CN    | 172       | 40        | 4.93    | 9.79  | 63.03 4.83 |
|     |       |         |         |           |           |         |       | 1688 |
|     |       |         |         |           |           |         |       | 2200 |
|     |       |         |         |           |           |         |       | 3330 |
| d   | H     | -CN     | -CN     | 183~184   | 50.5      | 3.79    | 17.37 | 65.42 3.89 |
|     |       |         |         |           |           |         |       | 1763 |
|     |       |         |         |           |           |         |       | 3320 |
| e   | -CH₃  | -COOCH₃ | -COOCH₃ | 129~132   | 23        | 5.37    | 4.39  | 59.85 5.14 |
|     |       |         |         |           |           |         |       | 1700 |
|     |       |         |         |           |           |         |       | 3320 |
| f   | -CH₃  | -COOCH₃ | -CN     | 152~154   | 41        | 4.93    | 9.71  | 62.75 5.05 |
|     |       |         |         |           |           |         |       | 9.91   |
|     |       |         |         |           |           |         |       | 1700 |
|     |       |         |         |           |           |         |       | 2200 |
| g   | -φ    | -COOCH₃ | -CN     | 209~210   | 19        | 4.63    | 8.04  | 68.59 4.64 |
|     |       |         |         |           |           |         |       | 8.12  |

2) **Methyl 1-Methoxycarbonyl-2-methylthio-2-(3-indoly)acrylate (IIa)**—Indole (10 g.) dissolved in dry T.H.F.* (20 ml.) was added to the Grignard reagent prepared from magnesium (2.3 g.) and ethylbromide (10 g.) in dry T.H.F. (50 ml.), and the mixture was refluxed until the evolution of ethane ceased. The decanted solution of the indolymagnesium bromide (Ia) was added dropwise, with vigorous mechanical stirring, to a solution of 20 g. of methyl 1-methoxycarbonyl-2,2-bismethylthioacrylate (Ia) in dry T.H.F. (80 ml.), cooling in an ice-water during a period of 2 hr. After stirring at room temperature for an additional 1 hr., the mixture was refluxed for 1 hr. After cooling, the mixture was poured into an ice-water, acidified with 10% hydrochloric acid, and was repeatedly extracted with ether. The etheral solution was dried (Na₂SO₄) and the ether was distilled off. The residue was diluted with cold benzene and filtrated to give 10 g. of IIa, which was recrystallized from MeOH, m.p. 132°.

The materials from the mother liquor were chromatographed on alumina using benzene and then bcnene-acetone (1:1) for elution. The first fraction recovered 3 g. of III and the second afforded an additional 1 g. of IIa. (Table I)

3) **Methyl 1-Cyano-2-methylthio-2-(3-indoly)acrylate (IIb)**—Under the same procedure as in 2, indole (10 g.), Mg (2.3 g.) and ethylbromide (10 g.) reacted with methyl-1-cyano-2,2-bismethylthioacrylate (Ib) (17.4 g.) to give 10.7 g. of IIb, which was recrystallized from MeOH-isoproOH, m.p. 133~134°. (Table I)

4) **Ethyl 1-Cyano-2-methylthio-2-(3-indoly)acrylate (IIc)**—Under the same procedure as in 2, indole (10 g.), Mg (2.3 g.) and ethylbromide (10 g.) reacted with ethyl 1-cyano-2,2-bismethylthioacrylate (Ic) (20 g.) to give 11 g. of IIc, which was recrystallized from benzene, m.p. 172°. (Table I)

5) **1-Cyano-2-methylthio-2-(3-indoly)acrylonitrile (IId)**—Under the same procedure as in 2, indole (10 g.), Mg (2.3 g.) and ethylbromide (10 g.) reacted with 1-cyano-2,2-bismethylthioacrylonitrile (IId) (14.8 g.) to give 10.5 g. of IId, which was recrystallized from benzene, m.p. 183~184°. (Table I)

6) **Methyl 1-Methoxycarbonyl-2-methylthio-2-(2-methylindol-3-yl)acrylate (IIe)**—Under the same procedure as in 2, 2-methylindole (3.9 g.), Mg (0.73 g.) and ethylbromide (3.3 g.) reacted with IIa (7.1 g.) to give 2.3 g. of Ile, which was recrystallized from MeOH, m.p. 129~132°. (Table I)

7) **Methyl 1-Cyano-2-methylthio-2-(2-methylindol-3-yl)acrylate (IIf)**—Under the same procedure as in 2, 2-methylindole (15.1 g.), Mg (2.49 g.) and ethylbromide (10.9 g.) reacted with IIb (20.3 g.) to give IIf, which

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*4 Tetrahydrofuran.
was recrystallized from MeOH, m.p. 152—154° (Table I). UV \( \lambda_{	ext{max}} \) mp (log e) : 279(4.04), 286(4.02), 321(4.15), 385(3.83). NMR singlet (3H) at 2.00 p.p.m. singlet (3H) at 2.30 p.p.m. singlet (3H) at 3.90 p.p.m.

8) **Methyl 1-Cyano-2-methylthio-2-(2-phenylindol-3-yl)acrylate (IIg)**—Under the same procedure as in 2, 2-phenylindole (5.80 g.), Mg (0.73 g.) and ethylbromide (3.27 g.) reacted with Ib (6.09 g.) to give 2 g. of IIg, which was recrystallized from MeOH, m.p. 209—210°. (Table I)

9) **Hydrolysis of (IIIa)**—IIIa (0.5 g.) dissolved in MeOH (50 ml.) was refluxed for 30 min. with 5% sodium hydroxide (30 ml.). After cooling, the mixture was acidified with 10% hydrochloride and repeatedly extracted with AcOEt. The AcOEt solution was dried (Na2SO4) and condensed. The residue was recrystallized from MeOH to give IVa, m.p. 180° (0.3 g.). Anal. Calcd. for C18H14ON; C, 75.45; H, 5.70; N, 8.80. Found : C, 75.18; H, 5.72; N, 8.89. This was identical with authentic 3-acetylindole prepared by Majima’s method.5)

10) **Hydrolysis of (IIIb)**—Under the same procedure as in 9, IIIb (0.5 g.) was treated with 5% sodium hydroxide (30 ml.) to give 3-(α-cyanoacetyl)indole (V), which was recrystallized from MeOH, m.p. 238°. Anal. Calcd. for C14H12On; C, 71.72; H, 4.38; N, 15.21. Found : C, 71.77; H, 4.26; N, 15.23. UV \( \lambda_{	ext{max}} \) mp (log e) : 242(5.14), 259(5.04) (shoulder), 302(0.414). IR (KBr) cm⁻¹ : \( \nu_{\text{C}=O} \) 1640; \( \nu_{\text{C}=N} \) 2240; \( \nu_{\text{NH}} \) 3270.

11) **Hydrolysis of (IIIc)**—Under the same procedure as in 9, IIIb (0.5 g.) was treated with 5% sodium hydroxide (30 ml.) to give 3-(α,α-dicyanoacetyl)indole (VI), which was recrystallized from AcOEt, m.p. 236°. Anal. Calcd. for C14H10On; C, 68.89; H, 3.37; N, 20.09. Found : C, 68.80; H, 3.32; N, 20.02. UV \( \lambda_{	ext{max}} \) mp (log e) : 262(4.14) (shoulder), 270.5(4.16), 316(4.17). IR (KBr) cm⁻¹ : \( \nu_{\text{C}=O} \) 1635; \( \nu_{\text{C}=N} \) 2200, 2220; \( \nu_{\text{NH}} \) 3300.

12) **3-(1-Cyano-2,2-bis(methylthio)acryl)indole (VIIa)**—Under the same procedure as in 2, a deacetylated solution of Ia in dry T.H.F. prepared from indole (10 g.), Mg (2.3 g.) and ethylbromide (10 g.) was added dropwise with vigorous mechanical stirring to a boiling solution of IIb (17.3 g.) in T.H.F. The mixture was refluxed for an additional 5 hr. After cooling, the mixture was poured into ice-water, acidified with 10% hydrochloride and was repeatedly extracted with ether. The ethereal solution was dried (Na2SO4) and condensed. The residue was recrystallized from MeOH to give 9 g. of VIIa, m.p. 190°. Anal. Calcd. for C14H12N2S2; C, 58.33; H, 4.20; N, 9.72. Found : C, 58.86; H, 4.46; N, 9.49. UV \( \lambda_{	ext{max}} \) mp (log e) : 277(4.12), 340(4.19), 393(4.12). IR (KBr) cm⁻¹ : \( \nu_{\text{C}=O} \) 1635; \( \nu_{\text{C}=N} \) 1640; \( \nu_{\text{C}=S} \) 2200; \( \nu_{\text{NH}} \) 3380.

13) **2-Methyl-3-(1-cyano-2,2-bis(methylthio)acryl)indole (VIIb)**—Under the same procedure as above. 2-methylindole (13.1 g.), Mg (2.43 g.) and ethylbromide (10.9 g.) reacted with Ib (20.3 g.) to give 7.9 g. of VIIb, which was recrystallized from MeOH, m.p. 187—189°. Anal. Calcd. for C16H14N2S2; C, 59.60; H, 4.67; N, 9.27. Found : C, 59.70; H, 4.55; N, 9.75. UV \( \lambda_{	ext{max}} \) mp (log e) : 279(4.05), 286(4.01), 336(4.16), 398 (3.90). IR (KBr) cm⁻¹ : \( \nu_{\text{C}=O} \) 1640; \( \nu_{\text{C}=N} \) 2200; \( \nu_{\text{C}=S} \) 3340. NMR singlet (3H) at 2.00 p.p.m. singlet (3H) at 2.40 p.p.m. singlet (3H) at 2.58 p.p.m.

14) **Reaction of IIIb with NaOCl**—IIIb (0.5 g.) was refluxed for 2hr. with sodium methoxide solution from Na (0.04 g.) and abst. MeOH (10 ml.). After distilled off, the residue was acidified with 10% hydrochloride and repeatedly extracted with CHCl3. The CHCl3 solution was dried (Na2SO4) and condensed. The residue was recrystallized from MeOH to give VII, m.p. 226° (0.2 g.). Anal. Calcd. for C16H18ONCl; C, 64.46; H, 4.16; N, 11.57. Found : C, 64.85; H, 4.13; N, 11.72. UV \( \lambda_{	ext{max}} \) mp (log e) : 257.5(4.11), 271(3.99), 278 (4.03), 360(4.39). IR (KBr) cm⁻¹ : \( \nu_{\text{C}=O} \) 1637; \( \nu_{\text{C}=N} \) 2210; \( \nu_{\text{C}=S} \) 3420.

15) **Reaction of VIIa with NaOCl**—Under the same procedure as above. VIIa (0.1 g.) was treated with Na (0.08 g.) in abst. MeOH (5 ml.) to give VIIa, which was recrystallized from MeOH, m.p. 226°. Undepressed on admixture with a sample prepared above.

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