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238. **Goro Kobayashi, Sunao Furukawa, Yoshiro Matsuda, and Yuko Washida**[*1]: Studies of Indole Derivatives. Ⅳ.[*2] Reaction of Indolylmagnesium Bromide with Ketenethioacetals.

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Several 2-methylthio-2-(3-indolyl)acrylic acid derivatives (Ⅲ) 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 known[1] and the usefulness of ketenethioacetals as an electrophilic reagent has been experimented in substitution reaction of amines and active methylene compounds with them.[2~4]

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 (Ⅱa) in dry tetrahydrofuran gave methyl 1-methoxycarbonyl-2-methylthio-2-(3-indolyl)-acrylate (Ⅲa) in 42.3% yield. Ⅲa had an empirical formula $C_{15}H_{15}O_4NS$ 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 Ⅲa and sodium hydroxide was refluxed for 30 min., 3-acetylindole (Ⅳ), m.p. 189°, was obtained. Ⅳ was shown to be identical with authentic 3-acetylindole prepared by Majima's method.[5]

Under the same reaction condition to give Ⅲa, 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 Ⅲd with 5% sodium hydroxide solution gave the corresponded compounds Ⅴ[6] and Ⅵ.

The reaction of Ⅰa and Ⅰb with methyl 1-cyano-2,2-bismethylthioacrylate (Ⅱb) in boiling dry tetrahydrofuran gave Ⅶa and Ⅶb. Ⅶa had an empirical formula $C_{14}H_{12}ON_2S_2$ and was crystallized from methanol, m.p. 190°. Treatment of Ⅶa with sodium methoxide in methanol gave Ⅷ, which was shown to be identical with 3-(ω-cyano-ω-methoxycarbonyl-acetyl)indole prepared by treatment of Ⅲb with sodium methoxide in methanol. These facts obviously showed that Ⅶa was 3-substituted indole. Ⅶb had an empirical formula $C_{15}H_{14}ON_2S_2$ 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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[*2] Part Ⅲ: Yakugaku Zasshi, **86**, 1156 (1966).

[*3] Tetramethylsilan.

1) A.H. Salway: J. Chem. Soc., **103**, 353 (1913); R. Majima, T. Hoshino: Chem. Ber., **58**, 2042 (1925); J.W. Baker: J. Chem. Soc., **1947**, 558, etc.

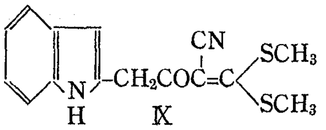
2) R. Gompper, W. Töpfl: Chem. Ber., **95**, 2861 (1962).

3) Y. Kuwayama, S. Kataoka: Yakugaku Zasshi, **85**, 387 (1965).

4) G. Kobayashi, S. Furukawa, Y. Matsuda: Yakugaku Zasshi, **86**, 1152 (1966).

5) R. Majima, M. Kotake: Chem. Ber., **55**, 3865 (1922).

6) H. Fischer, K. Pistor: Chem. Ber., **56**, 2313 (1923) reported m.p. 214°.



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of 2-methylindole). From the facts mentiond above, VIIb was formulated as 2-methyl-3-(1-cyano-2,2-bismethylthioacryl)indole rather than a structural isomer IX, 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 ketenethioacetals with amines and active methylene compounds.[2~4)]

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

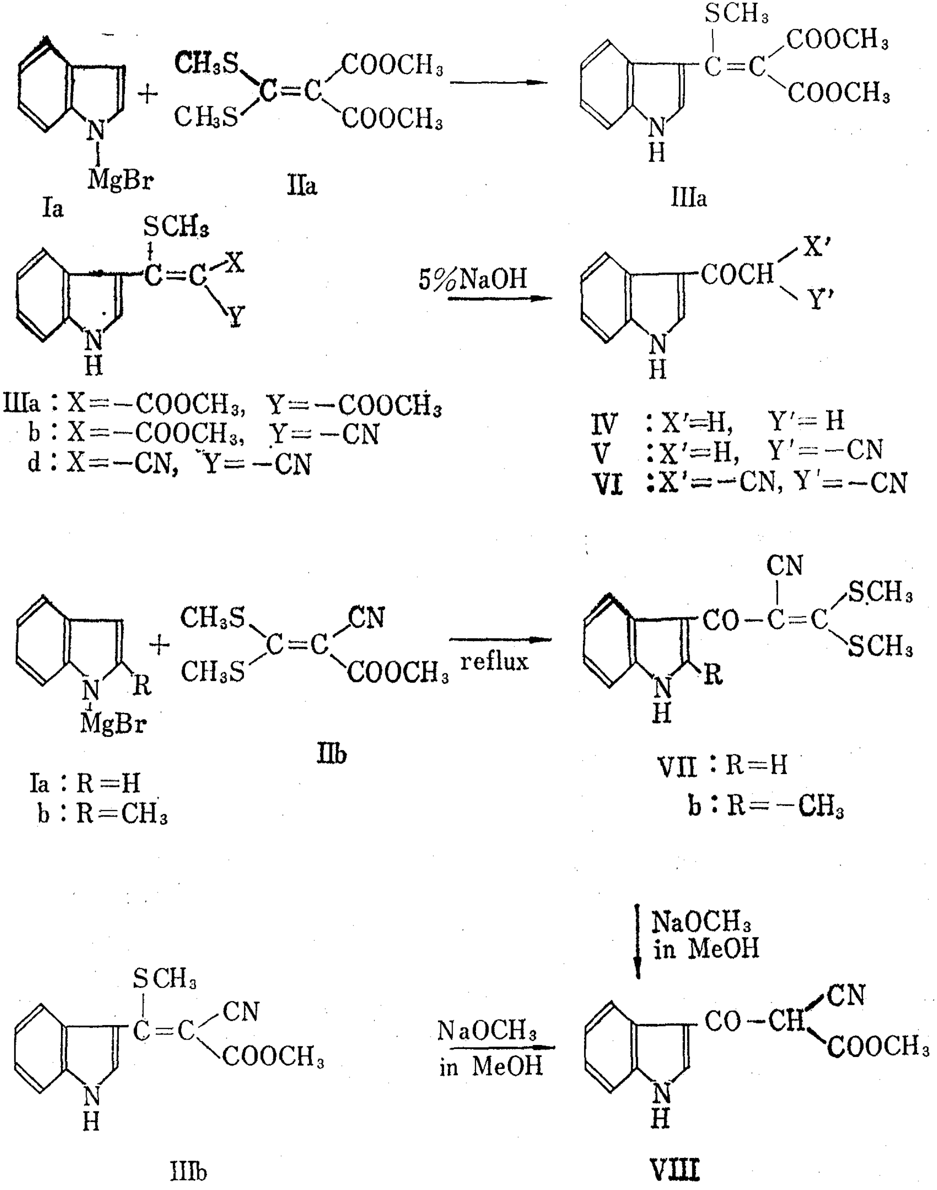
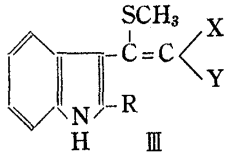


Chart 1.

Experimental

1) **Preparation of Ketenethioacetals (II)**——The procedures were carried out by the methods similar to those described by Gompper.[2)]

TABLE I.



Ⅲ

Na.	R	X	Y	m.p. (°C)	Yield (%)	Analysis (%)						IR (KBr) cm^{-1}
						Calcd.			Found			
						C	H	N	C	H	N	
a	H	-$COOCH_3$	-$COOCH_3$	132	42.3	59.01	4.95	4.85	58.76	4.85	5.00	$\nu_{C=O}$ 1680 1731 ν_{NH} 3390
b	H	-$COOCH_3$	-CN	133～134	46.1	61.76	4.44	10.29	61.89	4.32	9.92	$\nu_{C=O}$ 1705 $\nu_{C \equiv N}$ 2200 ν_{NH} 3320
c	H	-$COOC_2H_5$	-CN	172	40	62.93	4.93	9.79	63.03	4.83	9.83	$\nu_{C=O}$ 1688 $\nu_{C \equiv N}$ 2200 ν_{NH} 3350
d	H	-CN	-CN	183～184	50.5	65.26	3.79	17.57	65.42	3.89	17.63	$\nu_{C \equiv N}$ 2220 ν_{NH} 3320
e	-CH_3	-$COOCH_3$	-$COOCH_3$	129～132	23	60.18	5.37	4.39	59.85	5.14	4.73	$\nu_{C=O}$ 1700 ν_{NH} 3320
f	-CH_3	-$COOCH_3$	-CN	152～154	41	62.93	4.93	9.71	62.75	5.05	9.91	$\nu_{C=O}$ 1700 $\nu_{C \equiv N}$ 2200 ν_{NH} 3330
g	-ϕ	-$COOCH_3$	-CN	209～210	19	68.96	4.63	8.04	68.59	4.64	8.12	$\nu_{C=O}$ 1700 $\nu_{C \equiv N}$ 2200 ν_{NH} 3380

2) **Methyl 1-Methoxycarbonyl-2-methylthio-2-(3-indolyl)acrylate (IIIa)**——Indole (10 g.) dissolved in dry T.H.F.[*4] (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 indolylmagnesium bromide (Ia) was added dropwise, with vigorous mechanical stirring, to a solution of 20 g. of methyl 1-methoxycarbonyl-2,2-bismethylthioacrylate (Ⅱa) 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% hydrochloride and was repeatedly extracted with ether. The ethereal solution was dried (Na_2SO_4) and the ether was distilled off. The residue was diluted with cold benzene and filtrated to give 10 g. of Ⅲa, which was recrystallized from MeOH, m.p. 132°

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

3) **Methyl 1-Cyano-2-methylthio-2-(3-indolyl)acrylate (IIIb)**——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 (Ⅱb) (17.4 g.) to give 10.7 g. of Ⅲb, which was recrystallized from MeOH-isoPrOH, m.p. 133～134°. (Table I)

4) **Ethyl 1-Cyano-2-methylthio-2-(3-indolyl)acrylate (IIIc)**——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 (Ⅱc) (20 g.) to give 11 g. of Ⅲc, which was recrystallized from benzene, m.p. 172°. (Table I)

5) **1-Cyano-2-methylthio-2-(3-indolyl)acrylonitril (IIId)**——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 Ⅲd, which was recrystallized from benzene, m.p. 183～184°. (Table I)

6) **Methyl 1-Methoxycarbonyl-2-methylthio-2-(2-methylindol-3-yl)acrylate (IIIe)**——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 Ⅲe, which was recrystallized from MeOH, m.p. 129～132°. (Table I)

7) **Methyl 1-Cyano-2-methylthio-2-(2-methylindol-3-yl)acrylate (IIIf)**——Under the same procedure as in 2, 2-methylindole (13.1 g.),Mg (2.43 g.) and ethylbromide (10.9 g.) reacted with Ⅱb (20.3 g.) to give Ⅲf, which

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[*4] Tetrahydrofuran.

was recrystallized from MeOH, m.p. 152～154° (Table Ⅰ). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 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 (IIIg)**——Under the same procedure as in 2, 2-phenylindole (5.80 g.), Mg (0.73 g.) and ethylbromide (3.27 g.) reacted with Ⅱb (6.09 g.) to give 2 g. of Ⅲg, 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 (Na_2SO_4) and condensed. The residue was recrystallized from MeOH to give Ⅳ, m.p. 189° (0.3 g.). *Anal.* Calcd. for $C_{10}H_9ON$; 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-(ω-cyanoacetyl)indole (Ⅴ), which was recrystallized from MeOH, m.p. 238°. *Anal.* Calcd. for $C_{11}H_8ON_2$; C, 71.72; H, 4.38; N, 15.21. Found: C, 71.77; H, 4.26; N, 15.23. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 242.5(4.16), 259.5(4.07) (shoulder), 302.0(4.14). IR (KBr) cm^{-1}: $\nu_{C=O}$ 1640; $\nu_{C\equiv N}$ 2240; ν_{NH} 3270.

11) **Hydrolysis of (IIId)**——Under the same procedure as in 9, Ⅲb (0.5 g.) was treated with 5% sodium hydroxide (30 ml.) to give 3-(ω,ω-dicyanoacetyl)indole (Ⅵ), which was recrystallized from AcOEt, m.p. 236°. *Anal.* Calcd. for $C_{12}H_7ON_3$; C, 68.89; H, 3.37; N, 20.09. Found: C, 68.80; H, 3.32; N, 20.02. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 262(4.14) (shoulder), 270.5(4.16), 316(4.17). IR (KBr) cm^{-1}: $\nu_{C\equiv N}$ 2200, 2220; ν_{NH} 3300.

12) **3-(1-Cyano-2,2-bismethylthioacryl)indole (VIIa)**——Under the same procedure as in 2, a decanted 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 (Na_2SO_4) and condensed. The residue was recrystallized from MeOH to give 9 g. of Ⅶa, m.p. 190°. *Anal.* Calcd. for $C_{14}H_{12}ON_2S_2$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.86; H, 4.46; N, 9.49. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 277(4.12), 340(4.19), 393(4.12). IR (KBr) cm^{-1}: $\nu_{C=O}$ 1635; $\nu_{C\equiv N}$ 2200; ν_{NH} 3380.

13) **2-Methyl-3-(1-cyano-2,2-bismethylthioacryl)indole (VIIb)**——Under the same procedure as above, 2-methylindole (13.1 g.), Mg (2.43 g.) and ethylbromide (10.9 g.) reacted with Ⅱb (20.3 g.) to give 7.9 g. of Ⅶb, which was recrystallized from MeOH, m.p. 187～189°. *Anal.* Calcd. for $C_{15}H_{14}ON_2S_2$; C, 59.60; H, 4.67; N, 9.27. Found: C, 59.70; H, 4.55; N, 9.75. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 279(4.05), 286(4.01), 336(4.16), 398 (3.90). IR (KBr) cm^{-1}: $\nu_{C=O}$ 1640; $\nu_{C\equiv N}$ 2200; ν_{NH} 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 $NaOCH_3$**——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 $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and condensed. The residue was recrystallized from MeOH to give Ⅷ, m.p. 226° (0.2 g.). *Anal.* Calcd. for $C_{13}H_{10}O_3N_2$; C, 64.46; H, 4.16; N, 11.57. Found: C, 64.85; H, 4.13; N, 11.72. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 257.5(4.11), 271(3.99), 278 (4.03), 360(4.39). IR (KBr) cm^{-1}: $\nu_{C=O}$ 1637; $\nu_{C\equiv N}$ 2210; ν_{NH} 3420.

15) **Reaction of VIIa with $NaOCH_3$**——Under the same procedure as above, Ⅶa (0.1 g.) was treated with Na (0.08 g.) in abst. MeOH (5 ml.) to give Ⅷ, which was recrystallized from MeOH, m.p. 226°. Undepressed on admixture with a sample prepared above.

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