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Studies on Indole Derivatives. XXII.[1] Synthesis and Reactions of Methyl 3-(2-Substituted 3-indolyl)thio-2-cyano-3-methylthioacrylates

In a continuation of our previous studies of the ketenethioacetals, the authors have been reported the synthesis of several heterocyclic compounds.[2] Recently, thiophene synthesis by various methods has been reported.[3]

The reaction of 3-iodoindole with methyl 2-cyano-3-mercapto-3-(methylthio)acrylate (II) in the presence of potassium hydroxide in water gave yellow crystals of mp 154—156°, the physical data of which suggest a novel ketenethioacetal derivative (IIIa) (Yield 65%). Similarly the reaction of 2-substituted 3-iodoindole with II gave also ketenethioacetals (IIIb, IIIc) (IIIb; mp 196°, IIIc; mp 158°).

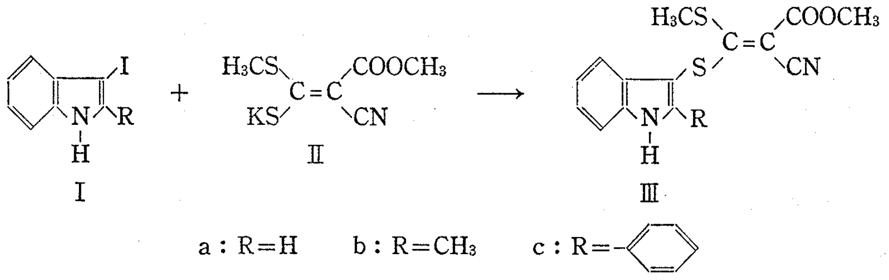

Chart 1

Treatment of IIIa with 10% hydrochloric acid in methanol under refluxing for 10 min gave red needles (IVa), $C_{14}H_{12}O_2N_2S_2 \cdot HCl$ (mass spectrum *m/e*: 304 (M^+)), mp 300°, in good yield. The infrared (IR) spectrum of IVa showed absorptions at 3200—3280 cm^{-1} (shoulder) due to NH, at 1690 cm^{-1} due to a carbonyl group, and 1660 and 1610 cm^{-1} due to C=N. This IR spectrum did not show any absorption of a cyano group at 2200 cm^{-1} present in IIIa. The ultraviolet (UV) spectrum revealed maxima at 234 ($\varepsilon=4.66$) and 280 ($\varepsilon=4.39$) and these absorption was not similar to that of the parent compound (IIIa) (287 ($\varepsilon=4.12$), 325 ($\varepsilon=4.16$)). From these spectroscopic data and elemental analysis, this compound, IVa, was found to be a cyclized product, 3-imino-4-methoxycarbonyl-5-(methylthio)thiophene-2-spiro-3-(3*H*-indole). In a similar manner as above, treatment of other compounds (IIIb, IIIc) with 10% hydrochloric acid gave spiro compounds (IVb, IVc) in good yield (IVb; mp 300°, *Anal.* Calcd. for $C_{15}H_{14}O_2N_2S_2 \cdot HCl$: C, 50.73; H, 4.23; N, 7.89. Found: C, 50.76; H, 4.17; N, 8.06. IR

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1) Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, submitted.

2) *a*) G. Kobayashi, S. Furukawa, Y. Matsuda, and Y. Washida, *Yakugaku Zasshi*, **87**, 857 (1967); *b*) G. Kobayashi, S. Furukawa, Y. Matsuda, M. Nakamura, and R. Natsuki, *Yakugaku Zasshi*, **87**, 1044 (1967); *c*) G. Kobayashi, S. Furukawa, Y. Matsuda, and R. Natsuki, *Yakugaku Zasshi*, **88**, 767 (1968); *d*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **91**, 203 (1971); *e*) G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki, and S. Matsunaga, *Chem. Pharm. Bull.* (Tokyo), **18**, 124 (1970); *f*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 713 (1972); *g*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 1468 (1972).

3) *a*) R. Gompper, E. Kutter, and W. Töpfl, *Ann.*, **659**, 90 (1962); *b*) J.B. Hendrickson, R. Rees, and J.F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964); *c*) H. Wynberg and H.J. Kooreman, *J. Am. Chem. Soc.*, **87**, 1739 (1965); *d*) E.J. Smutny, *J. Am. Chem. Soc.*, **91**, 208 (1969); *e*) S. Rajappa and B.G. Advani, *Tetrahedron Letters*, **1969**, 5067; *f*) M. Takaku, Y. Hayashi, and H. Nozaki, *Bull. Chem. Soc. Japan*, **43**, 1917 (1970); *g*) I.T. Kay and N. Punja, *J. Chem. Soc.* (*C*), **1970**, 2409; *h*) R. Laliberté and G. Médawa, *Can. J. Chem.*, **48**, 2709 (1970); *i*) K. Hirai and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 2194 (1971).

(KBr) cm^{-1}: 3100—3200 (shoulder) (NH), 1680 (C=O), 1630 (C=N). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 232 (4.38), 280 (4.10), (IVc; mp 243°, *Anal.* Calcd. for $C_{20}H_{16}O_2N_2S_2 \cdot HCl \cdot 3/2H_2O$: C, 54.06; H, 4.51; N, 6.31. Found: C, 53.86; H, 4.35; N, 6.51. IR (KBr) cm^{-1}: 3200 (shoulder) (NH), 1669 (C=O), 1610 (C=N). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 231 (4.48), 265 (4.37), 300 (4.11)).

The compound (IVa) was added to a solution of 10% hydrochloric acid in methanol, and the mixture was refluxed for 5 hr on a steam bath. After cooling, the precipitate was collected by filtration and recrystallized from methanol to give white needles of V, $C_{13}H_{11}O_2NS_2$, mp 188°, in 60—80% yield. The mass spectrum of V showed a molecular ion peak at *m/e*: 277. Its nuclear magnetic resonance spectrum showed two three proton-singlets due to methylthio and methoxyl groups at 2.59 and 3.97 ppm. Its IR spectrum indicated absorption bands due to NH at 3440 cm^{-1} and due to a carbonyl band at 1670 cm^{-1}. Its UV spectrum revealed maxima at 236 (ε=4.57), 280 (ε=4.09), 326 (ε=4.03), 356 (ε=4.04). From these spectral data and elemental analysis, this compound, V, was found to be a rearranged product, 2-methylthio-3-(methoxycarbonyl)thieno[3,2-*b*]indole. This compound V was also obtained from IVb or IVc. In the case of 2-phenylindole derivatives, the reaction time was about 5 hr longer than those of other compound and benzoic was also obtained simultaneously in good yield.

A possible mechanism for the reaction is outlined in Chart 3.

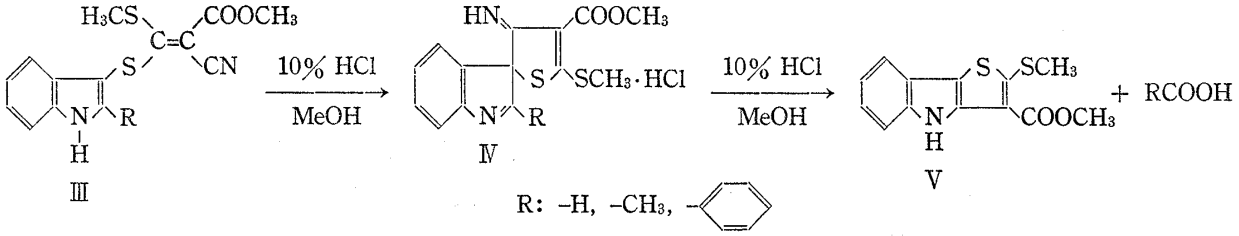

Chart 2

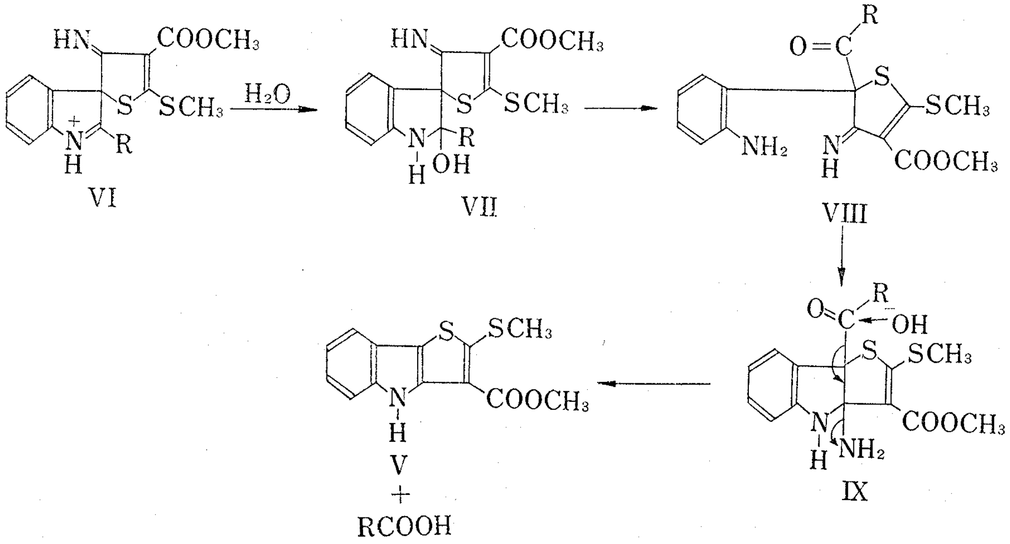

Chart 3

Details of chemical properties, synthesis, and other reactions of these compounds will be reported later.

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