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Reaction of 3-Ethoxycarbonyl-2-methylthiothiazolo[2,3-*a*]isoquinolinium Sulfate with Active Methyl and Methylene Compounds

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The reaction of 3-ethoxycarbonyl-2-methylthiothiazolo[2,3-*a*]isoquinolinium sulfate (II) with various active methyl and methylene compounds in the presence of a base afforded mesoionic compound (V, VI) substituted by methylthio group with active methylene and pyrrolo[2,1-*a*]isoquinoline (=benzoindolizine) derivatives (III, IV, VII, VIII, IX, Xa,b, XI) with opening of the thiazole ring and formation of a pyrrole ring. 1,3-Diethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (Xb) was converted to 1-ethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (XII) by the treatment with polyphosphoric acid (PPA).

There have been many reports on the syntheses and reactions of mesoionic compounds since Earl and Mackney[2] found that treatment of N-nitroso-N-phenylglycine with acetic anhydride gave an anhydro compound, Sydnone, by intramolecular dehydration. A review of these results was published by Ohta and Kato.[3] We have examined the reactivities of methylthio groups in various heterocyclic ketenethioacetal derivatives, having electron-attracting groups at β-position.[4]

Concerning the synthesis of 3-acyl-thiazolo[2,3-*a*]isoquinolinium-2-thione, Kröhnke, *et al.*[5] had already reported a method of treatment of N-acylisoquinolinium salts with carbon disulfide in the presence of a base and also the alkylation of mesoionic compounds. It was reported that the reaction of 3-(*p*-nitrophenyl)-2-methylthiothiazolo[2,3-*a*]isoquinolinium iodide with amines produced mesoionic imidazo [2.1-a] isoquinolinium thiones, substituted with a methylthio group.[6] However, there has been no report on the reaction of 3-acyl-2-methylthiothiazolo[2,3-*a*]isoquinolinium salt with active methyl and methylene compounds except for the analogous reaction[7] of 2-methylthio-1,3,4-triazolo[5,1-*a*]isoquinolinium iodide with active methylene compounds (malononitrile, methyl cyanoacetate). The present paper is on the interesting reaction of 3-ethoxycarbonyl-2-methylthiothiazolo[2,3-*a*]isoquinolinium sulfate (II) with active methyl and methylene compounds.

We recently reported briefly that the reaction of II with active methyl compounds (nitromethane, acetophenone) in the presence of powdered potassium hydroxide in dimethyl sulfoxide afforded corresponding pyrrolo[2,1-*a*]isoquinoline derivatives (III and IV) with opening of the thiazole ring and formation of a pyrrole ring, in 36 and 18% yield, respectively. A possible mechanism for this reaction was also reported.[8]

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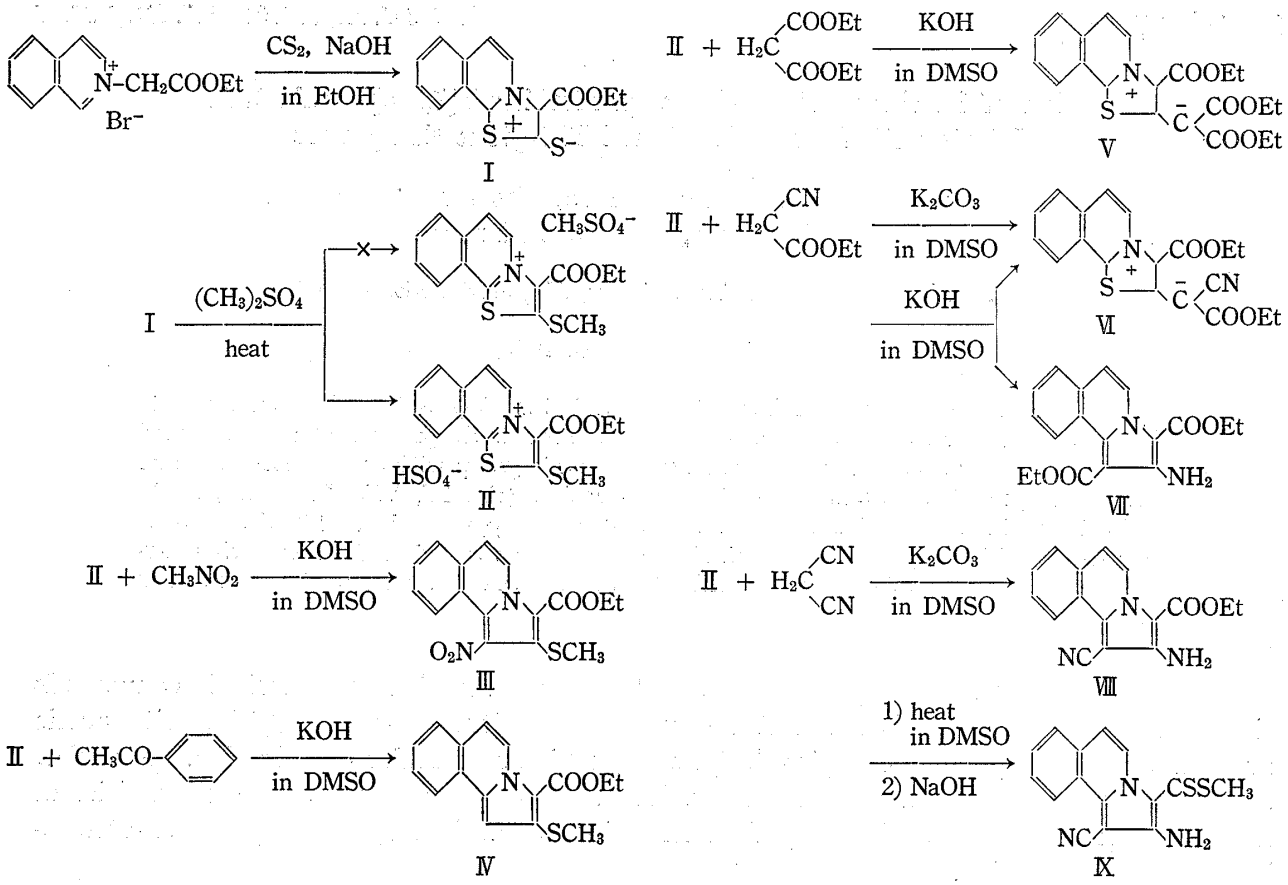

Chart 1

Chart 2

In a similar manner, the reaction of II with diethyl malonate gave the mesoionic compound (V) which was substituted with a methylthio group at 2-position of II. The nuclear magnetic resonance (NMR) spectrum of V showed no signal for a methylthio group and its infrared (IR) spectrum exhibited absorptions due to carbonyl groups at 1605 and 1670 cm^{-1}. The reaction of II with ethyl cyanoacetate in the presence of potassium carbonate in dimethyl sulfoxide at room temperature afforded similar mesoionic compound (VI). On the other hand, when II was allowed to react with ethyl cyanoacetate in the presence of powdered potassium hydroxide in dimethyl sulfoxide, two products were separated by column chromatography over aluminum oxide. The first product was found to be 2-amino-1,3-diethoxycarbonylpyrrolo[2,1-*a*]isoquinoline (VII) from elemental analysis, and NMR and IR spectra. The IR spectrum of this product exhibited absorptions due to amino group at 3270 and 3480 cm^{-1}. The second product was proved to be VI on the basis of analytical data, and from IR and ultraviolet (UV) spectra.

The reaction of II with malononitrile in the presence of potassium carbonate in dimethyl sulfoxide afforded a similarly cyclized product, 2-amino-1-cyano-3-ethoxycarbonylpyrrolo[2,1-*a*]isoquinoline (VIII), whose IR spectrum showed absorptions due to amino group at 3280 and 3360 cm^{-1}, due to cyano group at 2190 cm^{-1}, and due to carbonyl group at 1670 cm^{-1}. When the solution of II and malononitrile in dimethyl sulfoxide was heated on a boiling water-bath and the solution treated with sodium hydroxide solution, followed by neutralization with 10%-hydrochloric acid, the yellow precipitates were obtained as the product. This product was proved to be 2-amino-1-cyano-3-(methylthio)thiocarbonylpyrrolo[2,1-*a*]isoquinoline (IX) by elemental analysis and from spectral data. Its NMR spectrum (in CF_3COOH) displayed the signal of methylthio group at 2.88 ppm (3H) as a singlet and its mass spectrum exhibited a molecular ion peak (*m/e*=297).

The reaction of II with acetylacetone in the presence of potassium carbonate in dimethyl sulfoxide afforded two products. One product appeared in a basic solution was found to be 1-acetyl-3-ethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (Xa) on the basis of its analytical data and NMR spectrum (in $CDCl_3$) which showed a singlet peak of methylthio group at 2.41 ppm (3H) and the structure of this product was supported by its mass spectrum (*m*/*e*=327). The second product appeared in a neutral solution was proved to be 1-acetyl-3-

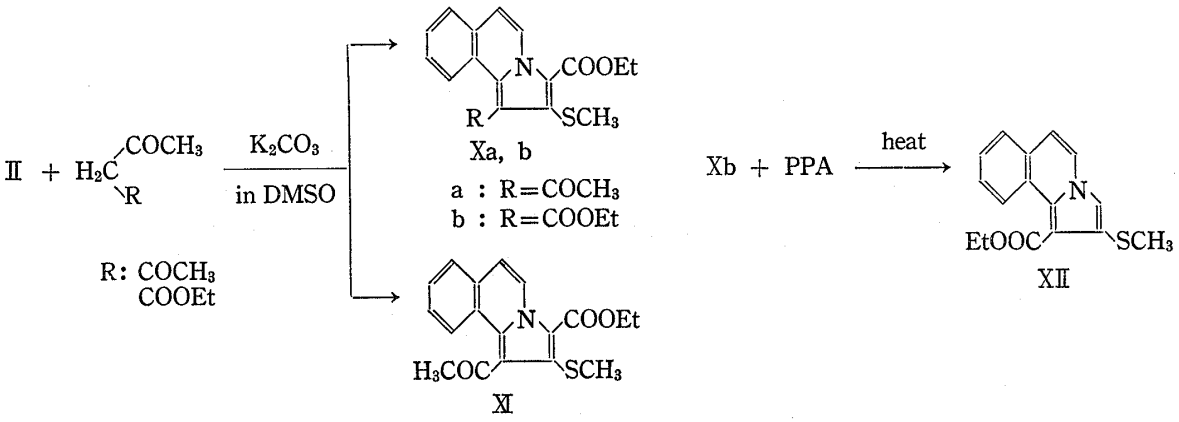

Chart 3

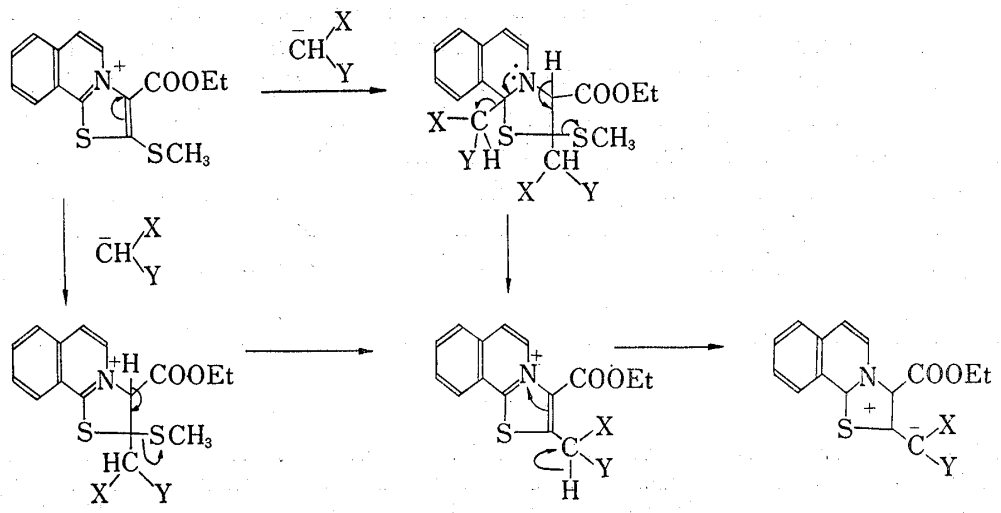

Chart 4

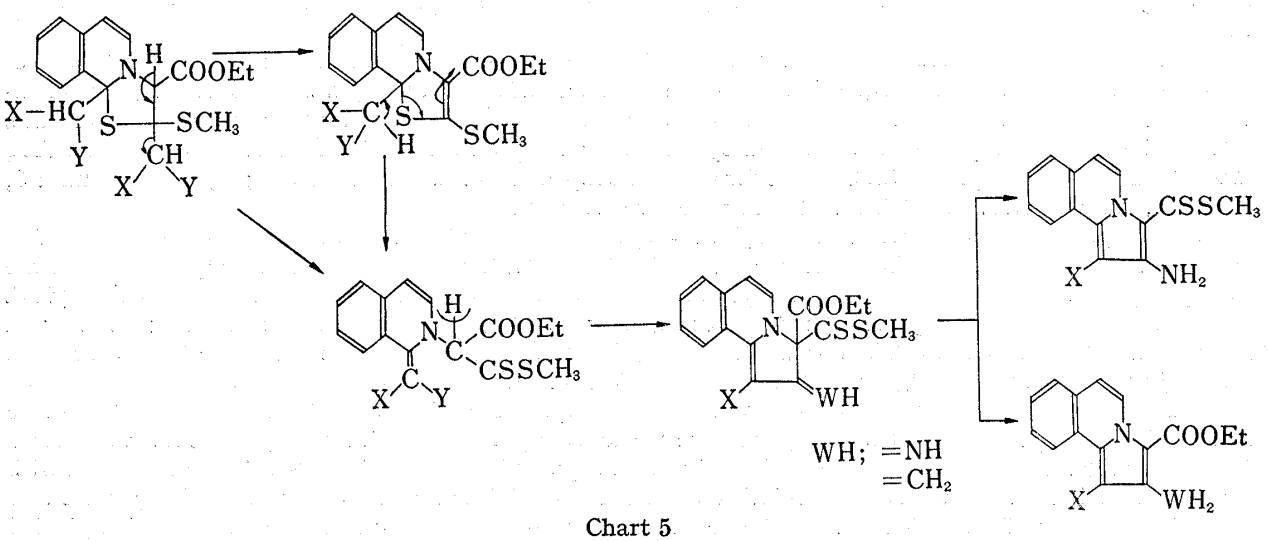

Chart 5

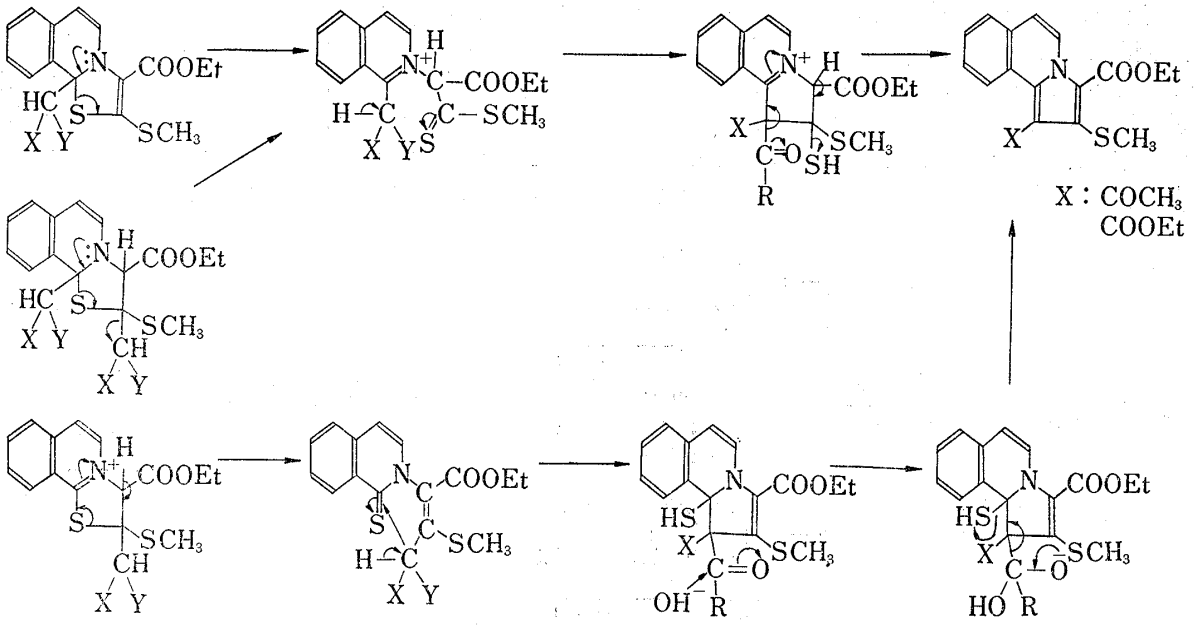

Chart 6

ethoxycarbonyl-2-methylpyrrolo[2,1-*a*]isoquinoline (XI) by its elemental analysis and from spectral data, and its NMR spectrum (in $CDCl_3$) showed a singlet peak of methyl group at 2.57 ppm (3H). The molecular weight of this compound was determined by mass spectrum. Analogous to the above reaction, II was allowed to react with ethyl acetoacetate in the presence of potassium carbonate (or potassium hydroxide) in dimethyl sulfoxide to produce only 1,3-diethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (Xb) of mp 87—88°, in 15% (or 35%) yield. On treatment with polyphosphoric acid, Xb was converted to 1-ethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (XII), accompanying decarboxylation at C-3-position, and the NMR spectrum (in $CDCl_3$) of XII indicated the C-3-proton at 6.82 ppm (1H) as a singlet.

Possible mechanisms for these reactions are outlined in Charts 4, 5, and 6.

Experimental

All melting points were determined in a capillary and are uncorrected. IR spectra were recorded in KBr pellets on a Nippon-Bunko IRA-2 spectrometer. UV absorption spectra were determined in 95% EtOH on a Hitachi EP-S2 spectrometer. NMR spectra were obtained with a JNM ps-100 (100 Mcps) spectrometer with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were recorded on a JEOL JMS-OlSG double-focus mass spectrometer, using a direct sample insertion into the ion source in all cases.

3-Ethoxycarbonylthiazolo[2,3-*a*]isoquinolinium-2-thione (I)——To a mixture of 2.96 g (0.01 mol) of N-ethoxycarbonylmethyleneisoquinolinium bromide and 3 g (0.04 mol) of CS_2 in 50 ml of EtOH, a large excess of 50% NaOH solution was added and the reaction mixture was stirred for 2 hr at room temperature. The precipitate that appeared was collected by filtration and recrystallized from benzene to yellow needles, mp 214—217°, in 80% yield, *Anal.* Calcd. for $C_{14}H_{13}O_2NS_2$=291.25: C, 57.73; H, 4.50; N, 4.82. Found: C, 58.08; H, 4.29; N, 4.77. IR (KBr): 1670 cm^{-1} (ester carbonyl).

3-Ethoxycarbonyl-2-methylthiothiozolo[2,3-*a*]isoquinolinium Sulfate Hydrate (II)——A mixture of I and Me_2SO_4 was heated on a boiling water bath. After 1—2 min, the mixture was thermally reacted and the freshly appeared yellow precipitate was recrystallized from acetone to colorless needles, mp 210°, in 95% yield. *Anal.* Calcd. for $C_{15}H_{16}O_7NS_3$=418.28: C, 43.06; H, 3.86; N, 3.35; S, 22.98. Found: C, 42.85; H, 4.03; N, 3.18; S, 22.48. NMR (δ in CF_3COOH): 2.95 ppm (3H, singlet, SCH_3). IR (KBr): 1705 cm^{-1} (ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (4.33), 224 (4.35), 265 (4.53), 354 (4.18).

3-Ethoxycarbonyl-2-methylthio-1-nitropyrrolo[2,1-*a*]isoquinoline (III)——A mixture of 0.83 g (0.002 mol) of II, 0.25 g (0.004 mol) of CH_3NO_2 and a large excess of powdered KOH in Me_2SO (30 ml) was stirred for 12 hr at room temperature. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% HCl solution. After the reaction mixture was extracted with benzene, the solvent was evaporated and the residue (orange oil) was chromatographed over Al_2O_3, using ether as solvent. The first fraction yielded

yellow crystals, which were recrystallized from ether to yellow leaflets, mp 115—116°, in 36% yield. *Anal.* Calcd. for $C_{16}H_{14}O_4NS$=330.29: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.08; H, 4.28; N, 8.53. NMR (δ in $CDCl_3$): 2.49 ppm (3H, singlet, SCH_3). IR (KBr) cm^{-1}: 1339 and 1505 (nitro), 1690 (ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (4.42), 257 (4.45), 279 (4.55), 340 (3.89), 390 (3.58). Mass Spectrum: 330 (M^+).

3-Ethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (IV)——The same method as for III, using II and CH_3CO–Ph, and the same chromatography afforded pale yellow crystals, which were recrystallized from ether to colorless needles, mp 120—121°, in 18% yield. *Anal.* Calcd. for $C_{16}H_{15}O_2NS$=285.29: C, 67.36; H, 5.30; N, 4.91; S, 11.21. Found: C, 66.94; H, 5.27; N, 4.78; S, 10.96. NMR (δ in $CDCl_3$) ppm: 2.53 (3H, singlet, SCH_3), 6.78 (1H, singlet, C-1-proton). IR (KBr): 1675 cm^{-1} (ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (3.86), 288 (4.41), 318 (3.91), 330 (3.86), 351 (3.71), 369 (3.79). Mass Spectrum: 285 (M^+).

Substituted Mesoionic Compound (V)——To a solution of 0.83 g (0.002 mol) of II and 0.64 g (0.004 mol) of diethyl malonate in Me_2SO (30 ml), a large excess of powdered KOH was added and the mixture was stirred for 2.5 hr at room temperature. The reaction mixture was poured into ice-water with vigorous stirring and extracted with $CHCl_3$. After evaporation of $CHCl_3$, the red oily residue was purified by chromatography over Al_2O_3 with benzene. The first fraction afforded orange crystals, whose recrystallization from acetone gave orange needles, mp 219—220°, in 25% yield. *Anal.* Calcd. for $C_{21}H_{21}O_6NS$=415.39; C, 60.72; H, 5.10; N, 3.37. Found: C, 61.00; H, 5.06; N, 3.30. IR (KBr) cm^{-1}: 1605, 1670 (ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 224 (4.38), 256 (4.48), 314 (4.36), 360 (3.96), 390 (4.02), 456 (4.07).

Substituted Mesoionic Compound (VI)——A mixture of 0.83 g (0.002 mol) of II, 0.45 g (0.004 mol) of ethyl cyanoacetate, and a little excess of K_2CO_3 in Me_2SO (30 ml) was stirred for 4 hr at room temperature. The reaction mixture was poured into ice-water, neutralized with 10% HCl solution, and the precipitate that appeared was collected by filtration and recrystallized from acetone to give orange needles, mp 208°, in 45% yield. *Anal.* Calcd. for $C_{19}H_{16}O_4N_2S$=368.33: C, 61.95; H, 4.38; N, 7.61; S, 8.68. Found: C, 61.47; H, 4.30; N, 7.54; S, 8.78. IR (KBr) cm^{-1}: 1628, 1668 (ester carbonyl), 2175 (cyanogen). UV λ_{max}^{EtOH} nm (log ε): 224 (4.47), 252 (4.38), 311 (4.40), 345 (4.14), 440 (4.09). Mass Spectrum: 368 (M^+).

Reaction of II with Ethyl Cyanoacetate in the Presence of Powdered KOH——A mixture of 0.83 g (0.002 mol) of II, 0.45 g (0.004 mol) of ethyl cyanoacetate, and a large excess of powdered KOH was stirred for 2 hr at room temperature. The reaction mixture was poured into a large quantity of H_2O and neutralized with 10% HCl solution. Its extraction with benzene gave a red residual oil, which was chromatographed over Al_2O_3 with benzene. The residue from the first fraction was recrystallized from ether to 2-amino-1,3-diethoxycarbonylpyrrolo[2,1-*a*]isoquinoline (VII) as pale yellow needles, mp 82—85°, in 20% yield. *Anal.* Calcd. for $C_{18}H_{18}O_4N_2$=326.34: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.93; H, 5.40; N, 8.58. NMR (δ in $CDCl_3$): 6.00 ppm (2H, broad singlet, NH_2). IR (KBr) cm^{-1}: 1663 (ester carbonyl), 3270 and 3480 (amine). UV λ_{max}^{EtOH} nm (log ε): 220 (4.28), 279 (4.66), 306 (4.55), 342 (4.06). Mass Spectrum: 326 (M^+). Second fraction: 0.1 g (15%) of VI.

2-Amino-1-cyano-3-ethoxycarbonylpyrrolo[2,1-*a*]isoquinoline (VIII)——To a mixture of 0.83 g (0.002 mol) of II and 0.26 g (0.004 mol) of malononitrile in Me_2SO (30 ml), a little excess of K_2CO_3 was added at room temperature with stirring, the stirring was continued for 30 min, and the reaction mixture was poured into ice-water. The pale yellow precipitate that appeared was collected by filtration and recrystallized from acetone to give colorless needles, mp 178°, in 72% yield. *Anal.* Calcd. for $C_{16}H_{13}O_2N_3$=279.29: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.95; H, 4.65; N, 15.02. NMR (δ in $CDCl_3$): 5.12 ppm (2H, broad singlet, NH_2). IR (KBr) cm^{-1}: 1670 (ester carbonyl), 2190 (cyanogen), 3280 and 3360 (amine). UV λ_{max}^{EtOH} nm (log ε): 220 (4.17), 270 (4.67), 295 (4.58), 336 (4.01), 367 (3.76). Mass Spectrum: 279 (M^+).

2-Amino-1-cyano-3-(methylthio)thiocarbonylpyrrolo[2,1-*a*]isoquinoline (IX)——A solution of 0.83 g (0.002 mol) of II and 0.26 g (0.004 mol) of malononitrile in Me_2SO (30 ml) was heated on a boiling water bath for 5 min, standing at room temperature for 15 min, and the reaction solution was basified with conc. NaOH solution and poured into ice-water. The aqueous solution was neutralized with 10% HCl solution, the yellow precipitate was collected by filtration, and recrystallized from benzene to give yellow needles, mp 224—225°, in 65% yield. *Anal.* Calcd. for $C_{15}H_{11}N_3S_2$=297.26: C, 60.60; H, 3.73; N, 14.14; S, 21.53. Found: C, 60.56; H, 3.42; N, 14.29; S, 20.95. NMR (δ in CF_3COOH) ppm: 2.88 (3H, singlet, SCH_3), 6.88 (2H, singlet, NH_2). IR (KBr) cm^{-1}: 2200 (cyanogen), 3350 (amine). UV λ_{max}^{EtOH} nm (log ε): 220, 291, 413 (concentration is unknown because of insufficient solubility). Mass Spectrum: 297 (M^+).

Reaction of II with Acetylacetone——A mixture of 0.83 g (0.002 mol) of II, 0.40 g (0.004 mol) of acetylacetone, and a small excess of K_2CO_3 in Me_2SO (30 ml) was stirred for 6 hr at room temperature, and poured into a large quantity of ice-water with vigorous stirring, and the yellow precipitate that appeared was collected by filtration. The filtrate was acidified with 10% HCl solution and allowed to stand for a few hours. Then the pale yellow precipitate that appeared was collected by filtration. The first precipitate was recrystallized from ether to give 1-acetyl-3-ethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (Xa) as colorless crystals, mp 104°, in 12% yield. *Anal.* Calcd. for $C_{18}H_{17}O_3NS$=327.32: C, 66.05; H, 5.24; N, 4.28. Found: C, 65.95; H, 5.31; N, 4.27. NMR (δ in $CDCl_3$) ppm: 2.40 (3H, singlet, SCH_3), 2.74 (3H, singlet, CH_3). IR (KBr): 1515—1700 cm^{-1} (broad, carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (4.28), 278 (4.64), 331 (3.95), 348 (4.07), 365 (4.10). Mass Spectrum: 327 (M^+). Recrystallization of the second precipitate from ether afforded 1-acetyl-3-ethoxycarbonyl-2-methylpyrrolo[2,1-*a*]isoquinoline (XI) as colorless needles, mp 143—146°, in 20% yield.

Anal. Calcd. for $C_{18}H_{17}O_3N$=295.32: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.34; H, 5.75; N, 4.49. NMR (δ in $CDCl_3$) ppm: 2.57 (3H, singlet, CH_3), 2.64 (3H, singlet, $COCH_3$). IR (KBr): 1610—1695 cm^{-1} (broad, carbonyl). UV λ_{max}^{EtOH} nm (log ε): 260 (4.12), 278 (4.73), 331 (3.92), 348 (4.07), 366 (4.13). Mass Spectrum: 295 (M^+).

1,3-Diethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (Xb)——The same treatment as for Xa, using II and ethyl acetoacetate, afforded Xb, recrystallized from ether as colorless needles, mp 87—89°, in 15% yield. When powdered KOH was used instead of K_2CO_3 in this reaction, the yield became 35%. *Anal.* Calcd. for $C_{19}H_{19}O_4NS$=357.35: C, 63.86; H, 5.36; N, 3.92; S, 8.95. Found: C, 63.81; H, 5.39; N, 3.74; S, 8.88. NMR (δ in $CDCl_3$): 2.48 ppm (3H, singlet, SCH_3). IR (KBr): 1676 and 1725 cm^{-1} (ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (4.24), 271 (4.64), 328 (3.93), 345 (4.01), 362 (4.03). Mass Spectrum: 357 (M^+).

1-Ethoxycarbonyl-2-methylthiopyrrolo[2,1-*a*]isoquinoline (XII)——A mixture of 0.54 g (0.002 mol) of Xb and 5 g of polyphosphoric acid (PPA) was heated on a boiling water bath for 2—3 hr. The reaction mixture was poured into ice-water, the white precipitate that appeared was collected by filtration and recrystallized from ether to give colorless needles, mp 131°, in 90% yield. *Anal.* Calcd. for $C_{16}H_{15}O_2NS$=285.29: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.06; H, 5.23; N, 4.71. NMR (δ in $CDCl_3$) ppm: 2.58 (3H, singlet, SCH_3), 6.82 (1H, singlet, C-3-proton). IR (KBr): 1662—1690 cm^{-1} (broad, ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (3.88), 289 (4.42). 318 (3.90), 330 (4.87), 350 (3.73), 369 (3.81).

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