[Chem. Pharm. Bull. 22(11)2624—2634(1974)]

UDC 547.833.04 : 547.379.1.04

Heterocyclic Ketenethioacetal Derivatives. IV.[1] Reactions of 1,2,3,4-Tetrahydro-1,3-dioxoisoquinoline and 1,2,3,4-Tetrahydro-1,4-dioxoisoquinoline with Ketenethioacetals and Reaction of These Products

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(Received May 8, 1974)

Reaction of 1,3-dioxo- or 1,4-dioxo-1,2,3,4-tetrahydroisoquinolines (Ia, b, c) with ketenethioacetals (IIa, b, c, d, e, f) gave the corresponding substitution products (IIIa, b, c, d, e, f, IVa, b, V, VI, VII, IX, X) of methylthio group in ketenethioacetal derivatives in a good yield. The application of these reactions afforded pyrano[2,3-*c*]isoquinoline and pyrrolo[1,2-*b*]isoquinoline derivatives.

The reaction of IIIa, b, IVa, or IVb with amines afforded recyclized products, 2-benzopyrano[3,4-*b*]pyridine derivatives (XIIIa, b, c, d). The reaction of VII and IX with amines gave amino derivatives (XVIa, b, c) which were the replaced products of methylthio groups of VII and IX. The reaction of X with aminoacetal afforded an amino-acetal derivative (XVII) which was treated with hydrochloric acid to give a cyclized product (XVIII). The reaction of IX or XVIc with ethyl orthoformate or formic acid gave pyrimidine derivatives (XXa, b, XXI).

It is well known that ketenethioacetals are attacked by nucleophilic reagents with replacement of either one or two methylthio groups attached to the same carbon atom by such groups as amines or active methylene compounds.[3]

Our previous studies on the ketenethioacetals showed that the reaction of oxindole, indoxyl, and indole derivatives with some ketenethioacetals afforded 2-methylthio-2-(3-oxindolyl)acrylic acid,[3j] 2-(2-cyano-2-methoxycarbonyl-1-methylthiovinyl)-3-hydroxyindole,[3s] and 3-(2-cyano-1-methylthiovinyl)indole derivatives[3i,r] in the presence of sodium hydride as a base.

The present paper deals with the reaction of 1,2,3,4-tetrahydro-1,3-dioxoisoquinoline (Ia), 1,2,3,4-tetrahydro-2-methyl-1,3-dioxoisoquinoline (Ib), and 1,2,3,4-tetrahydro-1,4-

1) K. Mizuyama, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **94**, 702 (1974).

2) Location: *1–14, Bunkyo-machi, Nagasaki, 852, Japan.*

3) *a*) H.D. Edwards and J.D. Kendall, U.S. Patent 2533233 (1950); *b*) R. Gompper and W. Töpfel, *Chem. Ber.*, **95**, 2861, 2871, 2881 (1962); *c*) J.K. Williams, *J. Am. Chem. Soc.*, **84**, 3478 (1962); *d*) R. Gompper and R. Kung, *Chem. Ber.*, **99**, 2900 (1966); *e*) A. Dornow and K. Dehmer, *Chem. Ber.*, **100**, 2577 (1967); *f*) R. Gompper and H. Schaefer, *Chem. Ber.*, **100**, 591 (1967); *g*) V.J. Gante and G. Mohr, *Angew. Chem.*, **83**, 886 (1971); *h*) M. Yokoyama and S. Hong, *Bull. Chem. Soc. Japan.*, **46**, 699 (1973); *i*) G. Kobayashi, S. Furukawa, Y. Matsuda, and Y. Washida, *Chem. Pharm. Bull.* (Tokyo), **15**, 187 (1967); *j*) G. Kobayashi, S. Furukawa, Y. Matsuda, and Y. Washida, *Yakugaku Zasshi*, **87**, 857 (1967); *k*) G. Kobayashi, S. Furukawa, Y. Matsuda, M. Nakamura, and R. Natsuki, *Yakugaku Zasshi*, **87**, 1044 (1967); *l*) G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *Yakugaku Zasshi*, **89**, 203 (1969); *m*) G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki, and S. Matsunaga, *Chem. Pharm. Bull.* (Tokyo), **18**, 124 (1970); *n*) G. Kobayashi, Y. Matsuda, R. Natsuki, and M. Sone, *Chem. Pharm. Bull.* (Tokyo), **20**, 657 (1972); *o*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 1468 (1972); *p*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 713 (1972); *q*) G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, and M. Sone, *Yakugaku Zasshi*, **93**, 612 (1973); *r*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **93**, 836 (1973); *s*) Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1658 (1973); *t*) S. Harry, B. Bernd, and G. Karl, *Z. Chem.*, 13, 294 (1973) [*Chem. Abstr.*, **80**, 3361 (1974)].

dioxoisoquinoline (Ic) with some ketenethioacetals as an electrophilic reagent, together with cyclization of the reaction products.

Reactions of Ia or Ib with ketenethioacetals, methyl 2-cyano-3,3-bis (methylthio)acrylate[3b] (IIa), 1-nitro-2,2-bis(methylthio)ethylene[3f] (IIb), 1,2,3,4-tetrahydro-3-bis (methylthio) methylene-1,4-dioxoisoquinoline[4](IIc), and N-bis(methylthio)methylene-*p*-toluenesulfonamide[5] (IId), in the presence of potassium carbonate in dimethyl sulfoxide gave the corresponding substitution products (IIIa, b, c, d, e, f) of methylthio group in ketenethioacetal derivatives in good yields. The reaction of Ib with 2-cyano-3,3-bis (methylthio) acrylamide[3b] (IIe), followed by refluxing in methanol, afforded a cyclized product, 2-cyano-3,5,6-trihydro-5-methyl-1-methylthio-3, 6-dioxopyrano[2,3-*c*]isoquinoline (IVa). This compound (IVa) was also obtained by the treatment of IIIa with acetic acid on a steam bath. In a similar manner the treatment of IIIb with acetic acid gave IVb in a good yield.

In a similar manner, the reaction of Ic with IIb in the presence of sodium hydride in anhydrous tetrahydrofuran gave 1,2,3,4-tetrahydro-3-(1-methylthio-2-nitroethylidene)-1, 4-dioxoisoquinoline (V) in a good yield. The reaction of Ic with IIc also gave the corresponding substitution product (VI) of methylthio group.

The reaction of Ic with 2-cyano-3,3-bis(methylthio)acrylonitrile (IIf) in the presence of potassium carbonate in dimethyl sulfoxide gave a crystalline powder (VII), mp>300°, in 80% yield. Elemental analysis of this product corresponded to $C_{14}H_9O_2N_3S$. The infrared (IR) spectrum of VII showed absorptions at 3485,

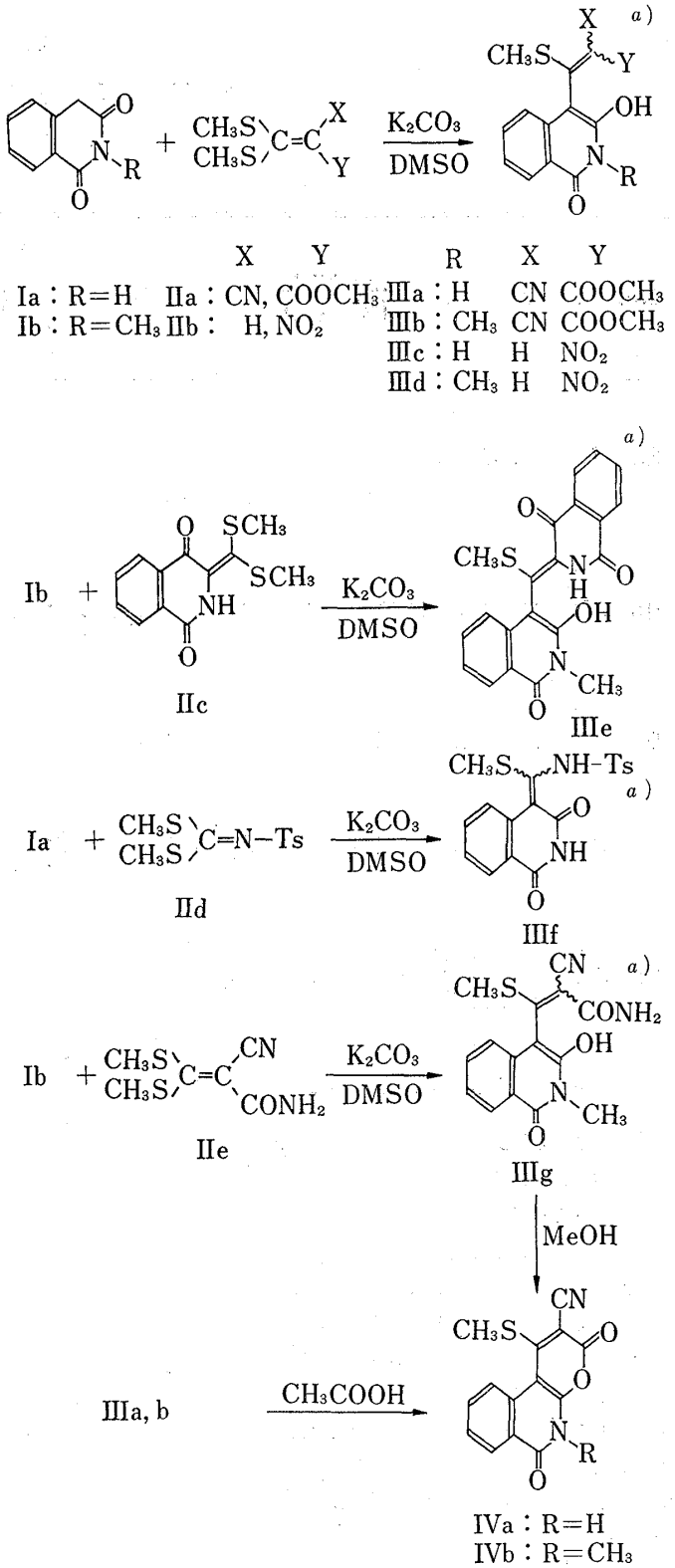
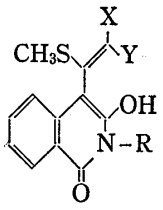


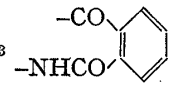
Chart 1

a) Geometrical isomers of III, V, VI, and XII were not examined in this paper, but details these geometrical isomers will be published in other paper.

4) S. Ueno, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **94**, 607 (1974).
5) *a*) R. Kuwayama and S. Kataoka, *Yakugaku Zasshi*, **85**, 391 (1965); *b*) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).

TABLE I



No.	R	X	Y	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR ppm
IIIa	H	CN	$COOCH_3$	193	75	$C_{15}H_{12}O_4N_2S$	56.96 (56.56)	3.82 (3.83)	8.85 (8.45)	CN2220 CO1700	228(4.35) 308(4.29)	a) Ⓣ SCH_3 2.12 (3H, s) OCH_3 3.08 (3H, s)
IIIb	CH_3	CN	$COOCH_3$	150	70	$C_{16}H_{14}O_4N_2S$	58.18 (58.01)	4.27 (4.28)	8.48 (8.21)	CN2200 CO1715	310(4.30)	a) Ⓒ SCH_3 2.60 (3H, s) NCH_3 2.76 (3H, s) OCH_3 3.82 (3H, s)
IIIc	H	H	NO_2	165	50	$C_{12}H_{10}O_4N_2S$	51.80 (51.83)	3.62 (3.49)	10.07 (9.85)	NH3260 CO1680	224(4.43) 308(3.98) 356(4.03)	
IIId	CH_3	H	NO_2	144	45	$C_{13}H_{12}O_4N_2S$	53.43 (53.40)	4.14 (4.19)	9.59 (9.49)	CO1690	227(4.46) 310(4.05) 360(4.03)	a) Ⓣ SCH_3 3.30 (3H, s) NCH_3 3.96 (3H, s)
IIIe	CH_3			227	80	$C_{21}H_{16}O_4N_2S$	64.28 (63.97)	4.11 (4.06)	7.14 (7.08)	NH3230 CO 1675 1638	304(4.12) 370(4.21)	a) Ⓣ SCH_3 2.79 (3H, s) NCH_3 4.25 (3H, s)

a) Ⓣ: CF_3COOH, Ⓒ: $CDCl_3$

3370, and 3300 cm^{-1} due to amino group, at 2220 cm^{-1} due to cyano group, and at 1690 cm^{-1} due to carbonyl group. The ultraviolet (UV) spectrum of VII revealed maxima at 243, 314, 336, and 460 nm. The nuclear magnetic resonance (NMR) spectrum (in CF_3COOH) of VII exhibited three-proton singlet at 3.20 ppm assignable to a methyl proton of methylthio group. From these spectroscopic and elemental analytical data, this compound (VII), was found to be a cyclized product, 3-amino-2-cyano 5,10-dihydro-1-methylthio-5,10-dioxopyrrolo[1,2-*b*] isoquinoline, which was methylated by methyl iodide in the presence of potassium carbonate.

Similarly the reaction of Ic with IIe afforded two products, IX and X. IX, obtained in 20% yield, had empirical formula of $C_{14}H_{11}O_3N_3S$. Its UV spectrum was similar to that of the corresponding compound, VII. IX was also obtained by the treatment of VII with conc. sulfuric acid. From its spectral data and elemental analysis, 3-amino-2-carbamoyl-5,10-dihydro-1-methylthio-5,10-dioxopyrrolo[1,2-*b*]isoquinoline was assigned to this compound (IX). These results supported formula VII as the correct structure. X, obtained in 60% yield, did not melt below 300°, and its elemental analysis corresponded to $C_{14}H_9O_2N_3S$. Its IR spectrum showed absorptions at 3200 cm^{-1} due to amino group and at 2200 cm^{-1} due to cyano group. Its UV spectrum revealed maxima at 231, 265, 322, and 397 nm, and its NMR spectrum exhibited three-proton singlet at 3.01 ppm assignable to a methyl proton of the methylthio group. From these spectral data and elemental analysis, this compound (X) was found to be 2-cyano-3,9-dihydro-1-methylthio-3,10-dioxopyrido[3,2-*c*]isoquinoline. Treatment of X with conc. sulfuric acid gave an amide (XI).

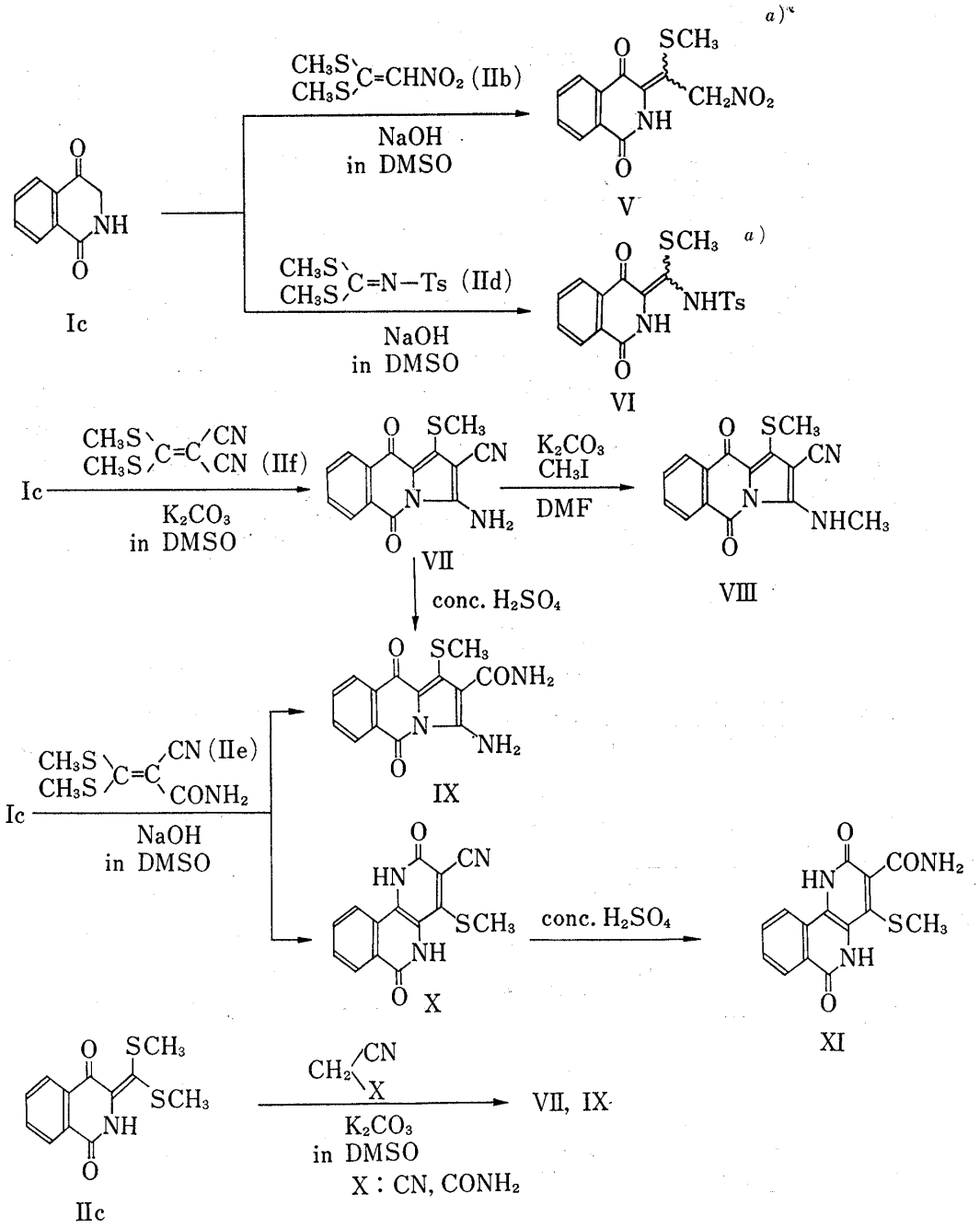


Chart 2

a) Geometrical isomers of III, V, VI, and XII were not examined in this paper, but details these geometrical isomers will be published in other paper.

These pyrrolo[1,2-*b*]isoquinolines (VII, IX) were also obtained by the reaction of IIc with malononitrile or cyanoacetamide in the presence of potassium carbonate in dimethyl sulfoxide.

Since IIIa and IIIb have an active methylthio group, the reaction of IIIa and IIIb with amines was examined. The reaction of IIIa and IIIb with amine (morpholine, piperidine, pyrrolidine) in methanol under refluxing did not give any product formed by replacement of methylthio group. This reaction afforded compounds (XIIa, b, c, d) which were complexes of IIIa and amines. The treatment of XII with 10% hydrochloric acid in dimethyl sulfoxide gave the starting materials, IIIa and IIIb, in a good yield. When acetic acid was used instead of methanol, the reaction of IIIa with morpholine did not give XIIa, but afforded white needles, mp 222°, in 80% yield. Elemental analysis of this product corresponded to $C_{17}H_{16}O_3N_2S$, its IR spectrum showed an absorption at 1720 cm^{-1} due to carbonyl group and did

not show the absorption of cyano group at 2220 cm^{-1} present in IIIa. Its UV spectrum revealed maxima at 256, 304, and 360, and its NMR spectrum (in CF_3COOH) showed a singlet peak of methyl protons at 2.84 ppm (3H, SCH_3) and revealed newly a singlet peak of an aromatic proton at 6.80 ppm (1H). From these spectroscopic data and elemental analysis, this compound (XIIIa), was found to be a recyclized product, 1-methylthio-3-morpholino-6-oxo-2-benzopyrano[3,4-*b*]pyridine. The teratment of XIIIa with 10% potassium hydroxide gave 3-(*o*-carboxyphenyl)-1,2-dihydro-4-methylthio-6-morpholino-2-oxopyridine (XIV) in which the pyrone ring was opened by a base. This product was recyclized with acetic acid to the parent compound (XIIIa) in a good yield. In a similar manner, the reaction of IIIa or IIIb with other amines (piperidine, pyrrolidine, dimethylamine) in acetic acid under refluxing gave 3-amino-1-methylthio-6-oxo-2-benzopyrano[3,4-*b*]pyridine derivatives (XIIIb, c, d). These compounds (XIIIa, b, c, d) were also obtained by the reaction of IVa and IVb with amines and compound (XII) with amines under similar conditions. In a similar rearrangement reaction, we reported previously that the reaction of methyl 1,2,3,4-tetrahydro-2-methyl-1,3-dioxoisoquinoline-4-dithiocarboxylate with methyl bromoacetate in the presence of sodium hydride resulted in the formation of methyl 1-(methylthio)thieno[3,4-*c*]isocoumarin-3-carboxylate.[6]

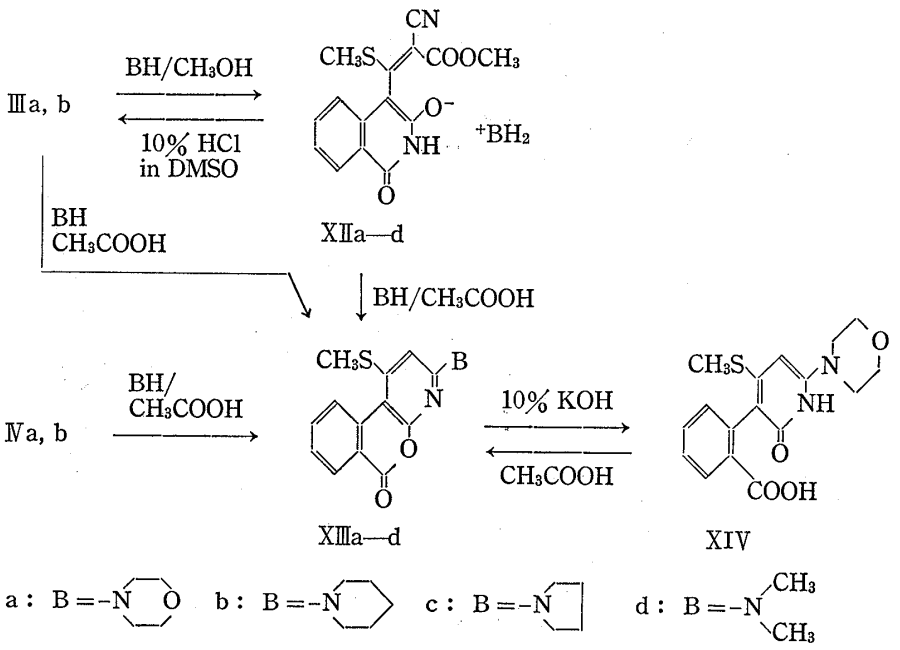


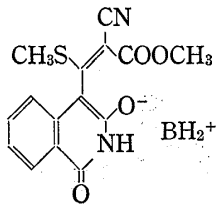
Chart 3

It has been reported that the methylthio group on the heterocyclic ring reacts with a nucleophile to give the corresponding replacement products,[7] but there has been no report on the reaction of methylthio group on the pyrrole ring having amino group at α-position with nucleophiles. We experimented the reaction of compounds (VII and IX) with amines. The reaction of VII and IX with amines (aniline, morpholine) gave amine derivatives (XVIa,

6) G. Kobayashi, Y. Matsuda, R. Natsuki, and S. Ueno, *Yakugaku Zasshi*, **93**, 322 (1973).

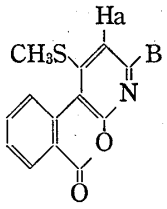
7) *a*) L.C. King, *J. Org. Chem.*, **20**, 448 (1955); *b*) M.R. Atkinson, *J. Chem. Soc.*, **1956**, 3847; *c*) G.G. DeAngelis and H.J. Hess, *Tetrahedron Letters*, **1969**, 1451; *d*) G. Kobayashi, Y. Matsuda, and R. Natsuki, *Yakugaku Zasshi*, **91**, 1275 (1971); *e*) M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1667 (1973); *f*) M. Sone, Y. Tominaga, R. Natsuki, Y. Mastuda, and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1008 (1973); *g*) G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, T. Okamura, and A. Itamura, *Yakugaku Zasshi*, **93**, 964 (1973); *h*) Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1523 (1973).

TABLE II

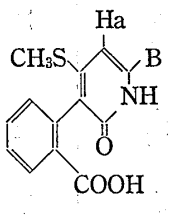


No.	B	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
XIIa		218	85	$C_{19}H_{21}O_5N_3S$	56.57 (56.37)	5.25 (5.22)	10.42 (10.21)	CN 2217 CO 1704	227(4.48) 306(4.51) 396(3.77)
XIIb		217	75	$C_{20}H_{23}O_4N_3S$	59.84 (59.69)	5.78 (5.64)	10.47 (10.62)	CN 2200 CO 1710	227(4.46) 306(4.53) 398(3.74)
XIIc		220	80	$C_{19}H_{21}O_4N_3S$	58.91 (58.65)	5.46 (5.44)	10.85 (10.73)	CN 2200 CO 1710	227(4.46) 306(4.53) 396(3.72)
XIId		203	80	$C_{17}H_{19}O_4N_3S$	56.50 (56.16)	5.30 (5.20)	11.63 (11.59)	CN 2200 CO 1713	227(4.45) 306(4.50) 396(3.70)

TABLE III



XIII

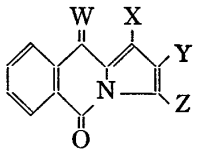


XIV

No.	B	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR (CF_3COOH) ppm
XIIIa		222	80	$C_{17}H_{16}O_3N_2S$	62.19 (62.25)	4.91 (4.99)	8.53 (8.67)	CO 1728	256[a] 304 360	SCH_3 2.84 (3H, s) Ha 6.80 (1H, s)
XIIIb		221	80	$C_{18}H_{18}O_2N_2S$	66.24 (66.12)	5.56 (5.65)	8.58 (8.31)	CO 1728	224[a] 254 307 366	SCH_3 2.83 (3H, s) Ha 6.84 (1H, s)
XIIIc		234	75	$C_{17}H_{16}O_2N_2S$	65.37 (65.09)	5.16 (5.20)	8.97 (8.85)	CO 1728	255[a] 304 327 367	SCH_3 2.81 (3H, s) Ha 6.53 (1H, s)
XIIId		212	75	$C_{15}H_{14}O_2N_2S$	62.93 (63.03)	4.93 (4.79)	9.79 (9.85)	CO 1720 1714	224(4.35) 254(4.37) 303(4.20) 324(4.12) 365(4.19)	SCH_3 2.84 (3H, s) NCH_3 3.48 (6H, s) Ha 6.64 (1H, s)
XIV		269	65	$C_{17}H_{18}O_4N_2S$	58.95 (58.73)	5.24 (5.18)	8.09 (8.00)	CO 1730 1655	244[a] 340	SCH_3 2.42 (3H, s) Ha 6.28 (1H, s)

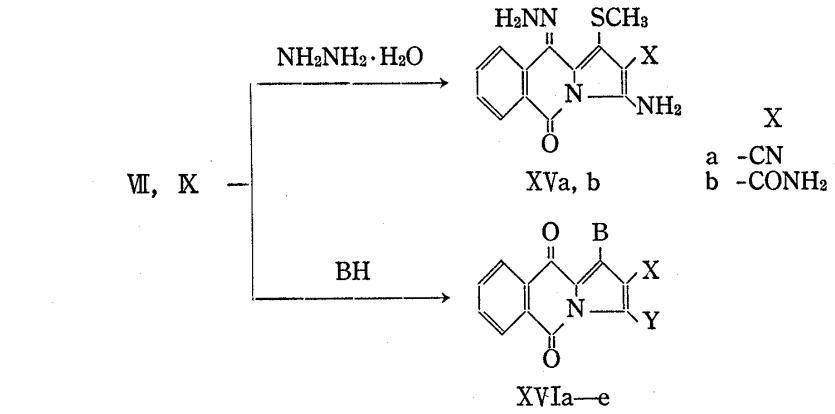
a) Concentration is unknown because of insufficient solubility.

TABLE IV



No.	W	X	Y	Z	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
XVa	NNH_2	SCH_3	CN	NH_2	265	75	$C_{14}H_{11}ON_5S$	56.56 (56.85)	3.73 (3.91)	23.56 (23.73)	NH 3300 CN 2200	251(4.30) 270(4.24) 345(3.71)
XVb	NNH_2	SCH_3	$CONH_2$	NH_2	293	70	$C_{14}H_{13}O_2N_5S$	53.33 (53.05)	4.16 (4.21)	22.22 (21.79)	NH 3400 3310 CO 1665	250[a] 286
XVIa	O	NH- 	$CONH_2$	NH_2	282	60	$C_{19}H_{14}O_3N_4$	65.89 (65.88)	4.07 (4.02)	16.18 (16.07)	NH 3500 3480 CO 1705	234[a] 268 344
XVIb	O		CN	NH_2	283	55	$C_{17}H_{14}O_3N_4$	63.35 (63.51)	4.38 (4.57)	17.38 (17.59)	NH 3420 CN 2208 CO 1676	234[a] 265 350 453
XVIc	O		$CONH_2$	NH_2	282	60	$C_{17}H_{16}O_4N_4$	59.99 (59.71)	4.74 (4.69)	16.46 (16.12)	NH 3480 3360 CO 1695	238(4.46) 340(3.87) 462(4.08)
XVId	O	$NHCH_2CH(OEt)_2$	CN	$NHCH_2CH(OEt)_2$	124	60	$C_{25}H_{32}O_6N_4$	61.96 (61.80)	6.66 (6.64)	11.56 (11.82)	NH 3400 CN 2195 CO 1675	233(4.53) 265(4.39) 340(4.07) 453(4.14)
XVIe	O	$NHCH_2CH(OEt)_2$	$CONH_2$	$NHCH_2CH(OEt)_2$	238	60	$C_{25}H_{34}O_7N_4$	59.74 (59.59)	6.82 (6.87)	11.15 (11.39)	NH 3330 CO 1665	230(4.52) 265(4.29) 354(4.12) 460(4.11)

a) Concentration is unknown because of insufficient solubility.



	B	X	Y
XVIa	–NH–	$-CONH_2$	$-NH_2$
XVIb	–N O	–CN	$-NH_2$
XVIc	–N O	$-CONH_2$	$-NH_2$
XVId	$-NHCH_2CH(OEt)_2$	–CN	$-NHCH_2CH(OEt)_2$
XVIe	$-NHCH_2CH(OEt)_2$	$-CONH_2$	$-NHCH_2CH(OEt)_2$

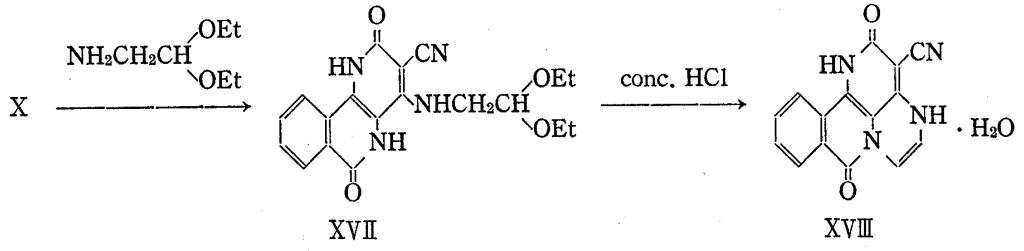


Chart 4

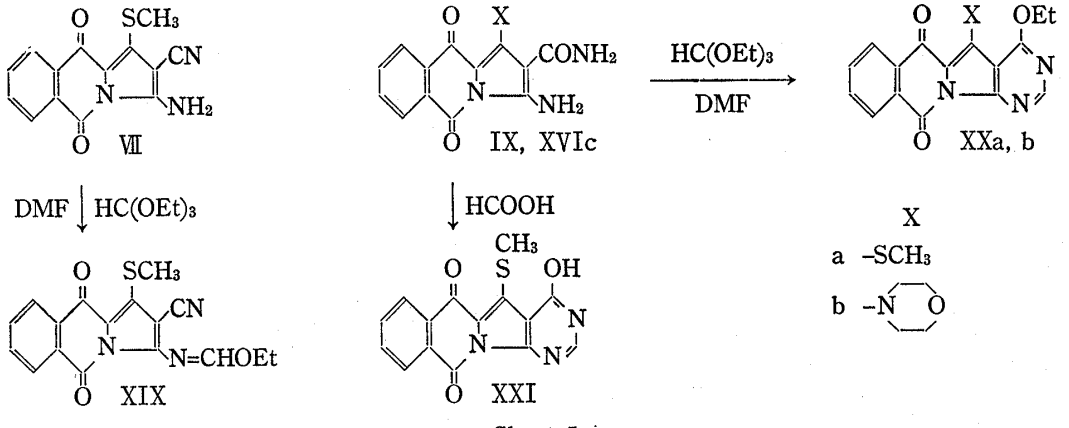


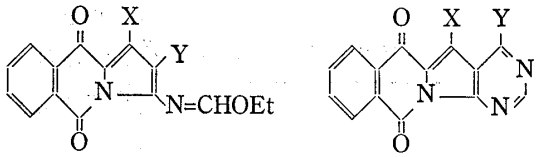
Chart 5

b, c) which were the replaced products of methylthio group of VII and IX in a good yield. When VII and IX were reacted with aminoacetal, they gave diaminoacetal derivatives (XVId, e) which were the replaced products of both the methylthio and the amino groups of VII and IX, but the reaction of VII and IX with hydrazine hydrate did not give a replaced product, this reaction affording hydrazone derivatives (XVa, b).

The reaction of X with aminoacetal afforded an aminoacetal derivative (XVII) which was treated with hydrochloric acid to give a cyclized product, XVIII. Reactions similar to this can often be seen in the reaction of aminoacetals.

The compounds with *o*-aminonitrile or *o*-aminoamide are useful synthetic intermediate for pyrimidine derivatives. The compounds (VII, IX, and XVIIc) also have a similar system.

TABLE V



No.	X	Y	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (logε)	NMR ppm
XIX	SCH_3	CN	227	60	$C_{17}H_{13}O_3N_3S$	60.17 (60.38)	3.86 (3.92)	12.39 (12.11)	CN 2218 CO 1720 1650	245(4.46) 312(4.02) 440(3.93)	©[a] CCH_3 1.48 (3H, t) SCH_3 2.84 (3H, s) OCH_2 4.58 (2H, q)
XXa	SCH_3	OEt	>300	70	$C_{17}H_{13}O_3N_3S$	60.17 (60.00)	3.86 (3.84)	12.39 (12.59)	CO 1710 1675	247[b] 291 316 440	Ⓣ[a] CCH_3 1.65 (3H, t) SCH_3 2.90 (3H, s) OCH_2 4.48 (2H, q)
XXb		OEt	>300	65	$C_{20}H_{18}O_4N_4$	63.48 (63.32)	4.80 (4.99)	14.81 (15.04)	CO 1708 1674	250(4.46) 293(3.93) 316(3.91) 472(4.16)	Ⓣ[a] CCH_3 1.58 (3H, t)
XXI	SCH_3	OH	>300	70	$C_{15}H_9O_3N_3S$	57.88 (58.16)	2.91 (3.06)	13.50 (13.70)	CO 1708 1690	243[b] 455	Ⓣ[a] SCH_3 2.87 (3H, s)

a) ©: $CDCl_3$, Ⓣ: CF_3COOH
b) Concentration is unknwon because of insufficient solubility.

The reaction of VII with ethyl orthoformate in dimethylformamide gave only a condensation product (XIX). When the reaction of IX or XVc under a similar condition gave pyrimidine derivatives (XXa, b) in good yields. Similarly, the treatment of IX with formic acid afforded a pyrimidine derivative (XXI).

Experimental

Reaction of 1,2,3,4-Tetrahydro-1,3-dioxoisoquinolines (Ia, b) with Ketenethioacetal Derivatives——To a solution of 0.001 mole of Ia or Ib and 0.003 mole of K_2CO_3 in 20 ml of Me_2SO, 0.001 mole of ketenethioacetal derivative (methyl 2-cyano-3,3-bis(methylthio)acrylate, 1-nitro-2,2-bis(methylthio)ethylene, 5-bis(methylthio)methylene-3-methyl-4-oxothiazolidine-2-thione, 1,2,3,4-tetrahydro-3-bis(methylthio)methylene-1,4-dioxoisoquinoline, or N-bis(methylthio)methylene-*p*-toluenesulfonamide), was added with stirring at room temperature. The mixture was stirred at room temperature for 3 hr, by which the mixture turned resddish brown. The mixture was poured into ice water, acidified with 10% HCl solution, the precipitate was collected by filtration, washed with water, and recrystallized from MeOH or acetone to give monosubstitute of methylthio group of ketenethioacetal in a high yield such as 70—80% yield. The result is shown in Table I.

2-Cyano-1-methylthio-5,6-dihydro-3,6-dioxo-3H-pyrano[2,3-*c*]isoquinolines (IVa, b)——a) To a solution of 1 g of IIIg in 50 ml of MeOH, 5 ml of 10% HCl was added and the mixture was refluxed for 1 hr. When cooled, the precipitate was collected by filtration, washed with water, and recrystallized from Methylcellosolve (IVa) or benzene (IVb).

b) A solution of 1 g of IIIa or IIIb in 50 ml of AcOH was refluxed for 3 hr. When cooled, the solution was poured into ice water. The precipitate was collected by filtration, washed with water, and recrystallized from Methylcellosolve or benzene to give IVa or IVb in good yield. IVa: mp>300°, *Anal.* Calcd. for $C_{14}H_8O_3N_2S$: C, 59.16; H, 2.84; N, 9.86. Found: C, 59.36; H, 2.94; N, 9.74. IR(KBr) cm^{-1}: 2200 (CN), 1738, 1645 (CO). UV λ_{max}^{EtOH} nm: 245, 265, 285, 405. NMR (CF_3COOH): 3.06 ppm (3H, singlet, SCH_3). IVb: mp 250°, *Anal.* Calcd. for $C_{15}H_{10}O_3N_2S$: C, 60.40; H, 3.38; N, 9.39. Found: C, 60.58; H, 3.27; N,

9.59. IR(KBr) cm^{-1}: 2205 (CN), 1732, 1670 (CO). UV λ_{max}^{EtOH} nm (log ε): 228 (4.31), 310 (4.05). NMR (CF_3-COOH) ppm: 2.93 (3H, singlet, SCH_3), 3.88 (3H, singlet, NCH_3).

1,2,3,4-Tetrahydro-3-(1-methylthio-2-nitroethylene)-1,4-dioxoisoquinoline (V)——To a solution of 1.6 g of Ic in 30 ml of Me_2SO, 1 g of powdered NaOH and 1.6 g of 1-nitro-2,2-bis(methylthio)ethylene were added. The mixture was stirred at room temperature for 3 hr when the mixture turned reddish brown. The mixture was poured into ice water and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from acetone to give a yellow needles, mp 170°, in 60% yield.

1,2,3,4-Tetrahydro-3-[methylthio(*p*-toluenesulfonylamino)methylene]-1,4-dioxoisoquinoline (VI)——To a solution of 1.6 g of Ic in 30 ml of Me_2SO, 1 g of powdered NaOH and 2.7 g N-bis(methylthio)methylene-*p*-toluenesulfonamide were added. The mixture stirred at room temperature for 3 hr. The mixture was poured into ice water and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from acetone to yellow crystals, mp 204°, in 65% yield. *Anal.* Calcd. for $C_{18}H_{19}O_4N_2S_2$: C, 55.67; H, 4.15; N, 7.21. Found: C, 55.67; H, 4.16; N, 7.25. IR(KBr) cm^{-1}: 3240 (NH), 1665 (CO). UV λ_{max}^{EtOH} nm (log ε): 263 (4.01), 344 (3.86), 450 (3.66).

3-Amino-2-cyano-5,10-dihydro-1-methylthio-5,10-dioxo-pyrrolo[1,2-*b*]isoquinoline (VII)——To a solution of 1.8 g of 2-cyano-3,3-bis(methylthio)acrylonitrile and 1.6 g of Ic in 20 ml of dimethylformamide, 1.5 g of K_2CO_3 was added with stirred for 3 hr at the same temperature. The reaction mixture was poured into 100 ml of ice water and acidified with 10% HCl solution. The precipitate was collected by filtration, washed with water, and recrystallized from a mixture of Methylcellosolve and dimethylformamide, to mp >300°. *Anal.* Calcd. for $C_{14}H_9O_2N_3S$: C, 59.36; H, 3.20; N, 14.84. Found: C, 59.39; H, 3.19; N, 14.92. IR(KBr) cm^{-1}: 3485, 3370 (NH), 2220 (CN), 1690 (CO). UV λ_{max}^{EtOH} nm: 243, 314, 336, 460. NMR (CF_3-COOH): 3.20 ppm (3H, singlet, SCH_3).

2-Cyano-5,10-dihydro-3-methylamino-1-methylthio-5,10-dioxopyrrolo[1,2-*b*]isoquinoline (VIII)——To a solution of 1.4 g of VII in 20 ml of dimethylformamide, 1.3 g of K_2CO_3 and 2.4 g of CH_3I was added and the mixture was heated on a steam bath for 3 hr. When cooled, the reaction mixture was poured into 100 ml of ice water and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from benzene to red crystals, mp 260°, in 60% yield. *Anal.* Calcd. for $C_{15}H_{11}O_2N_3S$: C, 60.60; H, 3.73; N, 14.14. Found: C, 60.30; H, 3.78; N, 14.24. IR(KBr) cm^{-1}: 3350 (NH), 2220 (CN), 1675 (CO). UV λ_{max}^{EtOH} nm (log ε): 237 (4.44), 314 (3.90), 335 (3.98), 467 (4.07). NMR (CF_3COOH) ppm: 3.15 (3H, singlet, SCH_3), 3.70 (3H, singlet, NCH_3).

3-Amino-2-carbamoyl-5,10-dihydro-1-methylthio-5,10-dioxopyrrolo[1,2-*b*]isoquinoline (IX)——a) To a solution of 1.6 g of Ic and 1.8 g of 2-cyano-3,3-bis(methylthio)acrylamide in 50 ml of Me_2SO, 1 g of powdered NaOH was added and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into 100 ml of ice water and acidified with 10% HCl. The precipitate was collected by filtration, washed with water, and recrystallized from Methylcellosove to red crystals, mp 288°, in 80% yield. *Anal.* Calcd. for $C_{14}H_{17}O_3N_3S$: C, 55.81; H, 3.68; N, 13.95. Found: C, 55.81; H, 3.68; N, 14.00. IR(KBr) cm^{-1}: 3460, 3360, 3200 (NH), 1700 (CO). UV λ_{max}^{EtOH} nm: 238, 290, 314, 470. NMR(CF_3COOH) ppm: 2.92 (3H, singlet, SCH_3). b) A mixture of 1 g of VII and 20 ml of conc. H_2SO_4 was heated on a steam bath for 2 hr, cooled, and poured into 100 ml of ice water. The precipitate was collected by filtration and recrystallized from Methylcellosolve to give the same product as above in 60% yield.

3-Cyano-1,2,5,6-tetrahydro-4-methylthio-2,6-dioxopyrido[3,2-*c*]isoquinoline (X)——To a solution of 1.6 g of Ic and 1.9 g of 2-cyano-3,3-bis(methylthio)acrylamide in 50 ml of Me_2SO, 2 g of powdered NaOH was added, the mixture was stirred at room temperature for 3 hr, and poured into 100 ml of ice water. The precipitate was collected by filtration and recrystallized from dimethylformamide to give a yellow powder, mp>300°, in 60% yield. *Anal.* Calcd. for $C_{14}H_9O_2N_3S$: C, 59.36; H, 3.20; N, 14.84. Found: C, 58.97; H, 3.32; N, 14.93. IR(KBr) cm^{-1}: 3200 (NH), 2220 (CN). UV λ_{max}^{EtOH} nm: 231, 265, 322, 397. NMR (CF_3-COOH) ppm: 3.01 (3H, singlet, SCH_3).

3-Carbamoyl-1,2,5,6-tetrahydro-4-methylthio-2,6-dioxopyrido[3,2-*c*]isoquinoline (XI)——A mixture of 0.5 g of X and 10 ml conc. H_2SO_4 was heated on a steam bath for 2 hr, cooled, and poured into 100 ml of ice water. The precipitate was collected by filtration and recrystallized from dimethylformamide to yellow crystals, mp>300°, in 70% yield. *Anal.* Calcd. for $C_{14}H_{11}O_3N_3S$: C, 55.81; H, 3.68; N, 13.95. Found: C, 55.70; H, 3.85; N, 13.51. IR(KBr) cm^{-1}: 3200 (NH). UV λ_{max}^{EtOH} nm: 225, 357, 374. NMR (CF_3COOH) ppm: 2.71 (3H, singlet, SCH_3).

Reaction of IIc with Active Methylene Compounds——To a solution of 0.001 mole of IIc in 30 ml of Me_2SO, 0.002 mole of K_2CO_3 and 0.0015 mole active methylene compound (malononitrile, 2-cyanoacetamide, 2-cyano-N-benzylacetamide) were added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice water and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from Methylcellosolve or dimethylformamide to give the corresponding product in 70—90% yields.

Reaction of IIIa, b with Amines in MeOH——A solution of 0.002 mole of IIIa or IIIb and 0.004 mole of an amine (morpholine, piperidine, pyrrolidine, dimethylamine) in 50 ml of MeOH was refluxed on a steam bath for 30 min. After the solvent was evaporated, the residue was recrystallized from MeOH to give amine

complexes. This result is shown in Table II. These amine complexes returned to the material compounds (IIIa, b) by the treatment of 10% HCl in Me_2SO.

3-Amino-1-methylthio-6-oxobenzo-2-pyrano[3,4-*b*]pyridines (XIIIa—d)——A solution of 0.002 mole of IIIa and 0.008 mole of an amine (morpholine, piperidine, pyrrolidine, dimethylamine) in 20 ml of AcOH was refluxed for 3 hr. When cooled, the solvent was poured into ice water, the precipitate was collected by filtration, and recrystallized from Methylcellosolve to give 3-amino-6-oxobenzo-2-pyrano[3,4-*b*]pyridines (XIIIa—d) in 75—80% yield. These 3-aminobenzopyrano[2,3-*b*]pyridines were also obtained by the reaction of IIIb, IVa, IVb, or XII with amines under a similar condition. Average yield was about 75%. The result is shown in Table III.

Treatment of XIIIa with KOH——A solution of 0.5 g of XIIIa in 20 ml of 10% KOH solution was refluxed for 1 hr, cooled, and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from Methylcellosolve to give a ring-opened product, XIV, mp 265°, in 65% yield. *Anal.* Calcd. for $C_{17}H_{18}O_4N_2S$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.73; H, 5.18; N, 8.00. IR(KBr) cm^{-1}: 1730, 1655 (CO). UV λ_{max}^{EtOH} nm: 244, 340. NMR(CF_3COOH) ppm: 2.42 (3H, singlet, SCH_3), 6.28 (1H, singlet, aromatic proton).

3-Amino-10-hydrazo-5,10-dihydro-1-methylthio-5-oxopyrrolo[1,2-*b*]isoquinolines (XVa, b)——A mixture of 0.002 mole of VII or IX and 0.005 mole of hydrazine hydrate was heated at 150° for 1 hr. Ice water was added to the reaction mixture and the precipitate was collected by filtration to give hydrazone products. The result is shown in Table IV.

1,3-Diamino-5,10-dihydro-5,10-dioxopyrrolo[1,2-*b*]isoquinolines (XVIa—e)——A mixture of 0.002 mole of VII or IX, 0.005 mole of amine (aniline, morpholine, aminoacetal), and 10 ml of dimethylformamide was heated at 150° for 2 hr. When cooled, the reaction mixture was poured into ice water and the precipitate was collected by filtration. The products, XVIa, XVIb, XVIc, XVId, and XVIe were recrystallized from benzene, Methylcellosolve, or MeOH to give diamine products. The results are shown in Table IV.

4-[(2-Bisethoxyethyl)amino]-3-cyano-1,2,5,6-tetrahydro-2,6-dioxopyrido[3,2-*c*]isoquinoline (XVII)——A mixture of 0.002 mole of X and 0.005 mole of aminoacetal was heated at 150° for 1 hr, cooled, and 20 ml of MeOH was added to the solid. The product was collected by filtration and recrystallized from dimethylformamide to an aminoacetal derivative, mp>300°, in 85% yield. *Anal.* Calcd. for $C_{19}H_{20}O_4N_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 61.85; H, 5.43; N, 15.01. IR(KBr) cm^{-1}: 3360 (NH), 2200 (CN), 1690 (CO). UV λ_{max}^{EtOH} nm: 265, 277, 358, 374.

1,4,6a-Triazobenzanthrone Derivative (XVIII)——A mixture of 1 g of XVII and 50 ml of conc. HCl was heated on a steam bath for 4 hr, the solvent was evaporated under a reduced pressure, and residue was recrystallized from dimethylformamide to 1,4,6a-triazobenzanthrone derivative of mp>300° in 65% yield. *Anal.* Calcd. for $C_{15}H_{10}O_3N_4$: C, 61.22; H, 3.43; N, 19.04. Found: C, 60.83; H, 3.55; N, 18.89. IR(KBr) cm^{-1}: 3400 (OH), 3280 (NH), 2200 (CN), 1640 (CO). UV λ_{max}^{EtOH} nm: 225, 245, 372.

2-Cyano-3-ethoxymethyleneamino-5,10-dihydro-1-methylthio-5,10-dioxopyrrolo[1,2-*b*]isoquinoline (XIX)——A solution of 0.002 mole of VII and 0.008 mole of ethyl orthoformate in 20 ml of dimethylformamide was refluxed for 4 hr, the solvent was evaporated under a reduced pressure, and the residue was recrystallized from dimethylformamide to give a red crystal of mp 227° in 60% yield. *Anal.* Calcd. for $C_{17}H_{13}O_3N_3S$: C, 60.17; H, 3.86; N, 12.39. Found: C, 60.38; H, 3.92; N, 12.11. IR(KBr) cm^{-1}: 2218 (CN), 1720, 1650 (CO). UV λ_{max}^{EtOH} nm (log ε): 245 (4.46), 312 (4.02), 440 (3.93). NMR ($CDCl_3$) ppm: 2.84 (3H, singlet, SCH_3).

1-Ethoxy-6,11-dihydro-6,11-dioxopyrimido[4′,5′: 5,4]pyrrolo[1,2-*b*]isoquinolines (XXa, b)——A solution of 0.002 mole of IX or VIc and 0.008 mole of ethyl orthoformate in 20 ml of dimethylformamide was refluxed for 4 hr, the solvent was evaporated under a reduced pressure, and the residue was recrystallized from dimethylformamide to give a pyrimidine derivatives in a good yield. The result is shown in Table V.

6,11-Dihydro-1-hydroxy-12-methylthio-6,11-dioxopyrimido[4′,5′: 5,4]pyrrolo[1,2-*b*]isoquinoline (XXI)——A mixture of 0.5 g of IX and 25 ml of HCOOH (95%) was refluxed for 5 hr, cooled, and poured into ice water. The precipitate was collected by filtration and recrystallized from dimethylformamide to give a pyrimidine derivative in good yield. The result is shown in Table V.