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Studies on Organosulfur Compounds. X.[1] Dechlorination during 4(3*H*)-Quinazolinone Cyclization Process[2]

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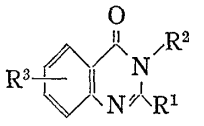
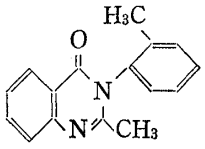
In order to clarify in more detail the dechlorination of the chlorine-substituent in 4(3*H*)-quinazolinone in the course of the quinazolinone cyclization process, some further experiments have been carried out by the modified Willgerodt–Kindler reaction condition and the modified Niementowski reaction. The results obtained proved that the dechlorination occurred at the cyclization step in the modified Niementowski reaction.

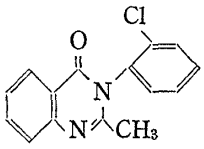
Since Gujral and his co-workers[4] first reported that some kinds of 4(3*H*)-quinazolinone derivatives exhibited a potent hypnotic action in experimental animals, much attention has been focussed on these compounds. Numerous 4(3*H*)-quinazolinone derivatives, particularly those with 2,3-disubstituents, have been prepared for the screening of biological activity.

2-Methyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (methaqualone)[5] and 2-methyl-3-(*o*-chlorophenyl)-4(3*H*)-quinazolinone (mecloqualone)[5] have been utilized in therapy as a hypnotic.





methaqualone



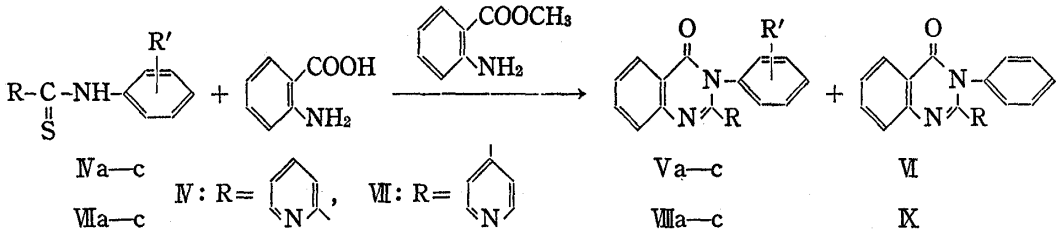
mecloqualone

Our previous paper[6] reported convenient synthetic methods to obtain 2-heterocyclic substituted 4(3*H*)-quinazolinones under the modified Willgerodt-Kindler reaction condition and the modified Niementowski reaction,[7,8] and for pharmacological activities[9] of these compounds were evaluated.

During the course of the synthesis of the Mecloqualone-like compounds, such as 2-pyridyl-3-(*o*-chlorophenyl)-4(3*H*)-quinazolinones, we had occasion to witness a new dechlorination during the quinazolinone cyclization process.[9] However, detailed investigation on this phenomenon was not referred in that paper. For example, attempts to obtain 2-(4-pyridyl)-3-(*o*- or *m*-chlorophenyl)-4(3*H*)-quinazolinone (VIIIa—b) using 4-picoline (II) and *o*- or *m*-chloroaniline (IIIa—b) as an aromatic amine, and anthranilic acid in the presence of sulfur

1) Part IX: T. Hisano and M. Tamayama, *Yakugaku Zasshi*, **93**, 1356 (1973).
2) A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, Kumamoto, December 1972.
3) Location: *Oe-hon-machi, Kumamoto, 862, Japan.*
4) M.L. Gujral, P.N. Saxena, and R.S. Tiwari, *Indian J. Med. Res.*, **43**, 637 (1955); M.L. Gujral, P.N. Saxena, and B.K. Khanna, *J. Indian Med. Profess.*, **3**, 1098 (1956); M.L. Gujral, K.N. Sacreen, and R.P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957).
5) G.B. Jackman, V. Petrow, and O. Stephensor, *J. Pharm. Pharmacol.*, **12**, 529 (1960); J. Klosa, *J. Prakt. Chem.*, **14**, 84 (1961).
6) *a*) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2625 (1971); *b*) T. Hisano, T. Nishi, and M. Ichikawa, *Yakugaku Zasshi*, **92**, 582 (1972).
7) V. Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).
8) M.M. Endicott, E. Wick, M.L. Mercury, and M. Sherrill, *J. Am. Chem. Soc.*, **68**, 1299 (1946).
9) T. Hisano, M. Ichikawa, G. Kito, and T. Nishi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2575 (1972).

Method A (modified Niementowski reaction)



Method B (modified Willgerodt-Kindler reaction condition)

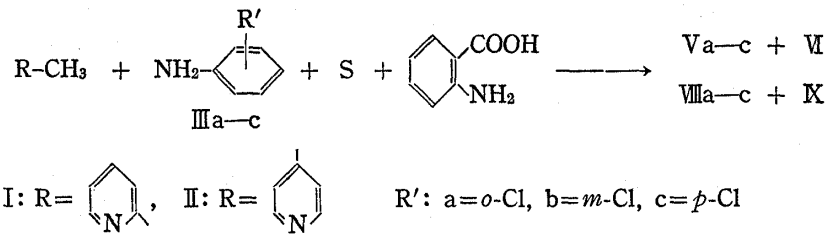
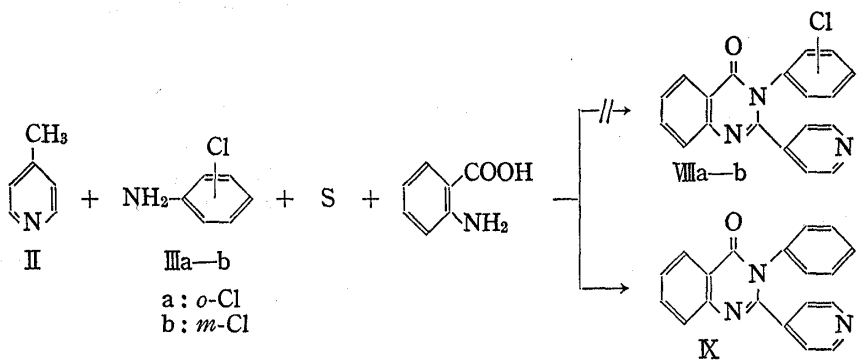


Chart 1

under the modified Willgerodt–Kindler reaction condition (Chart 1, method A) resulted in the formation of 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (IX) as a dechlorinated compound instead of the expected chlorine-substituted compound (VIIIa—b) in both cases.



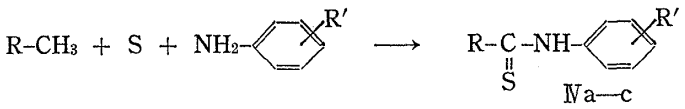
Some further experiments have now been carried out in order to clarify in more detail this dechlorination phenomenon, limitations, scope, and, if possible, to find some evidence for the mechanism of quinazolinone cyclization process. For this purpose, two general approaches, which seemed to be considerably different in the synthetic process, as shown in Chart 1, were used and comparative studies were made to determine the mechanism of dechlorination in the course of cyclization.

Chlorothiopicolinanilides (IVa—c), required as the starting material for the present work, were prepared by the modified Willgerodt–Kindler reaction[10] of the appropriate chloroaniline (IIIa—c) with 2-picoline (I) in the presence of sulfur. In this synthetic step of IVa—c, it was ascertained in all our experiments that dechlorination did not occur, although the yield of each product (IVa—c) was different (Table I).

IVa—c obtained by the above procedure were used for the reaction[6b] with anthranilic acid in the presence of methyl anthranilate. From the reaction of IVa with anthranilic acid, a small amount of 2-(2-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (VI) was unexpectedly separated as the dechlorinated compound instead of the expected 2-(2-pyridyl)-3-(*o*-chlorophenyl)-4(3*H*)-quinazolinone (Va) as the chlorine-substituted compound. In a similar reac-

10) *a*) B. Emmert and M. Groll, *Chem. Ber.*, **86**, 208 (1953); *b*) H. Saikachi and T. Hisano, *Yakugaku Zasshi*, **81**, 64 (1961); H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **7**, 716 (1959).

Table I. Chlorothiopicolinanilides

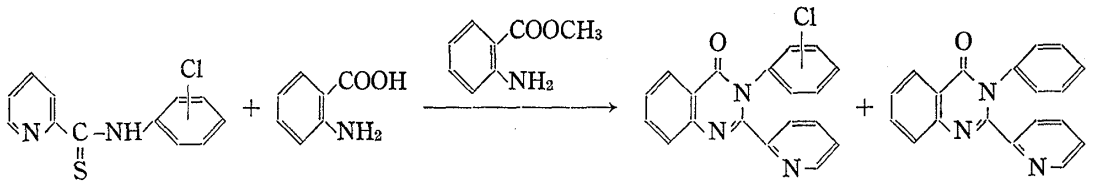


Compd. No.	R	R′			mp (°C)	Yield (%)	Appearance[a]	Formula	Analysis (%) Calcd. (Found)		
		o-	*m*-	*p*-					C	H	N
IVa		Cl	H	H	125	49	orange prisms	$C_{12}H_9N_2SCl$	57.95 (57.83)	3.65 (3.59)	11.26 (11.19)
IVb		H	Cl	H	98[b]	68	orange prisms	$C_{12}H_9N_2SCl$	57.95 (57.81)	3.65 (3.55)	11.26 (11.32)
IVc		H	H	Cl	87	40	orange prisms	$C_{12}H_9N_2SCl$	57.95 (57.86)	3.65 (3.57)	11.26 (11.20)

a) All the compounds were recrystallized from EtOH.
b) Reported[c] mp96—98°.
c) T. Hisano and Y. Yabuta, *Chem. Pharm. Bull.* (Tokyo), **21**, 511 (1973).

tion of IVb, the chlorine-substituted compound (Vb) and the dechlorinated compound (VI) were obtained in 30 and 10% yield, respectively. Further, in that of IVc, the chlorine-substituted compound (Vc) was obtained in 34.1% yield and the dechlorinated compound (VI) was isolated in a small amount (1.2%) (Table II).

Table II. 2-(2-Pyridyl)-3-aryl-4(3*H*)-quinazolinones



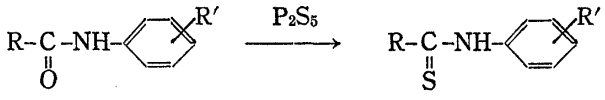
IVa—c Va—c VI

Starting material	Product[a] V	mp (°C)	Yield[b] (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	VI	mp (°C)	Yield[b] (%)
IVa	Va	—	—	$C_{19}H_{12}ON_3Cl$	—	—	—	VI	162[c]	7.4
IVb	Vb	155	30.0	$C_{19}H_{12}ON_3Cl$	68.37 (68.64)	3.62 (3.41)	12.59 (12.31)	VI	162[c]	10.0
IVc	Vc	195	34.1	$C_{19}H_{12}ON_3Cl$	68.37 (68.45)	3.62 (3.41)	12.59 (12.28)	VI	162[c]	1.2

a) All the compounds were recrystallized from benzene–petr. benzine (1:2) as colorless prisms.
b) Calcd. on the basis of authrauilic acid.
c) Reported[9] mp 162°.

Further confirmation of this observation was tested by trying to condense chlorothioisonicotinanilides (VIIa—c) with anthranilic acid but the synthetic method by the modified Willgerodt–Kindler reaction could not be applied to the preparation of VIIa—c, since the yield of VIIa—c was too poor to obtain them as the starting materials for the present work. It has already been shown[1] that the reaction of 4-picoline (II) with substituted anilines in the presence of sulfur mainly gave benzothiazole derivatives. Therefore, chlorothioisonicotin-

Table III. Chlorothioisonicotinanilides



VIIa—c

Compd. No.	R	R′ o-	R′ m-	R′ p-	mp (°C)	Yield (%)	Appearance[a]	Formula	Analysis (%) Calcd. (Found) C	H	N
VIIa		Cl	H	H	146	43	orange prisms	$C_{12}H_9N_2SCl$	57.95 (58.20)	3.65 (3.57)	11.26 (11.15)
VIIb		H	Cl	H	169[b]	62	orange prisms	$C_{12}H_9N_2SCl$	57.95 (58.02)	3.65 (3.56)	11.26 (11.27)
VIIc		H	H	Cl	201	65	orange prisms	$C_{12}H_9N_2SCl$	57.95 (58.00)	3.65 (3.67)	11.26 (11.06)

a) All the compounds were recrystallized from benzene.
b) Reported[1] mp 169°.

anilides (VIIa—c) required as the starting materials for this study were prepared by the Jacobson method.[11] The results are summarized in Table III.

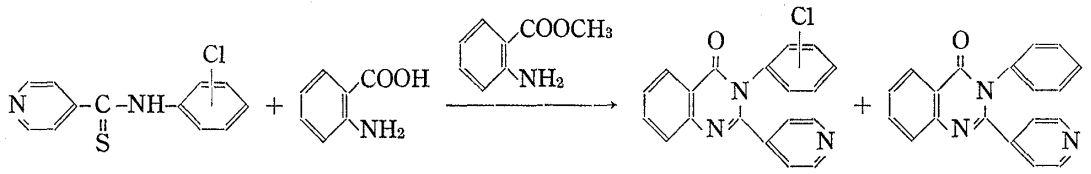
The reaction of VIIa—c with anthranilic acid was carried out by quite the same reaction sequence as described above. The results using VIIa—c were similar to those obtained with IVa—c. Namely, from the reaction of VIIa with anthranilic acid, only 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (IX) was obtained as the dechlorinated compound in 9.4% yield. On the other hand, in a similar reaction of VIIb or VIIc, the product was a mixture of the chlorine-substituted and dechlorinated compounds in both cases. Therefore, these mixtures were analyzed by gas chromatography. The gas chromatographic analyses indicated the presence of 2-(4-pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (VIIIb) as the chlorine-substituted compound in 31.4% yield and 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (IX) as the dechlorinated compound in 17.7% yield from VIIb, and 2-(4-pyridyl)-3-(*p*-chlorophenyl)-4(3*H*)-quinazolinone (VIIIc) as the chlorine-substituted compound in 44.3% yield and 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (IX) as the dechlorinated compound in 4.7% yield from VIIc.

As the next step to examine the behavior of the chlorine substituent, one-step cyclization of 4(3*H*)-quinazolinone derivatives by the modified Willgerodt–Kindler reaction was carried out. 2-Picoline (I) was heated with IIIa—c and anthranilic acid in the presence of sulfur, and the reaction gave 4(3*H*)-quinazolinone derivatives. Namely, from the reaction of IIIa, only the dechlorinated compound (VI) was obtained in 15.1% yield. On the other hand, in a similar reaction of IIIb, the chlorine-substituted compound (Vb) and the dechlorinated compound (VI) were obtained in 7.5 and 11.7% yield, respectively. Further, in that of IIIc, the chlorine-substituted compound (Vc) was obtained in 10.8% yield and the dechlorinated compound (VI) was isolated in 2.1% yield.

In a similar reaction of 4-picoline (II), IIIa gave only the dechlorinated compound (IX) in 31.1% yield, while in that of IIIb or IIIc, the product was a mixture of the chlorine-substituted (VIIIb or VIIIc) and dechlorinated compound (IX). Therefore, these mixtures were analyzed by gas chromatography as mentioned above.

11) P. Jacobson, *Chem. Ber.*, **19**, 1067 (1886).

TABLE IV. 2-(4-Pyridyl)-3-aryl-4(3*H*)-quinazolinones

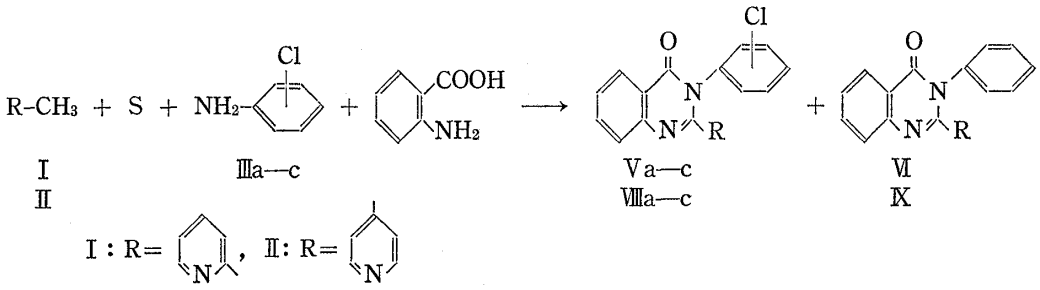


VIIa—c VIIIa—c IX

Starting material	Product VIII	mp (°C)	Yield (%)	Formula	Appearance	Analysis (%) Calcd. (Found) C	H	N	IX	mp (°C)	Yield (%)
VIIa	VIIIa	—	—	$C_{19}H_{12}ON_3Cl$	—	—	—	—	IX	159[a]	9.4
VIIb	VIIIb	175[b]	31.4	$C_{19}H_{12}ON_3Cl$	colorless needles	68.37 (68.20)	3.62 (3.43)	12.59 (12.63)	IX	159[a]	17.7
VIIc	VIIIc	228	44.3	$C_{19}H_{12}ON_3Cl$	colorless needles	68.37 (68.65)	3.62 (3.41)	12.59 (12.31)	IX	159[a]	4.7

a) Reprted[9] mp 159°.
b) Reported[9] mp 179°.

TABLE V. 2-Pyridyl-3-aryl-4(3*H*)-quinazolinones



I II IIIa—c Va—c VIIIa—c VI IX

I : R= , II: R=

Starting material	Prodxct	mp (°C)	Yield (%)		mp (°C)	Yield (%)
I+IIIa	Va	—	—	VI	162	15.1
I+IIIb	Vb	155	7.5	VI	162	11.7
I+IIIc	Vc	195	10.8	VI	162	2.1
II+IIIa	VIIIa	—	—	IX	159	31.1
II+IIIb	VIIIb	175	16.8	IX	159	11.3
II+IIIc	VIIIc	228	19.5	IX	159	3.7

As a second step in this work, it seemed of interest to investigate in more detail the mechanism of 4(3*H*)-quinazolinone ring formation in one-step by method B and the condensation process of active methyl group in the pyridine ring, aromatic amine with anthranilic acid in the presence of sulfur at an elevated temperature under the modified Willgerodt–Kindler reaction condition. Furthermore, this condensation offers some interesting problems from the mechanistic and preparative views, especially in connection with the modified Niementowski reaction. For the sake of convenience, according to the numerous variations reported for the modified Niementowski 4(3*H*)-quinazolinone synthesis,[12] we assumed the possibility of 4(3*H*)-quinazolinone ring formation process, and the combination of reactants used in our

12) T. Hisano, *Org. Prep. Proced. Int.*, 5, 145 (1973).

experiment with method B was classified into three categories, processes A, B, and C. That is to say, there are three possible processes involving anthranilic acid in this reaction. In each process, the work was carried out by the combination of each reactant which might react with each other in the stepwise process, and we examined in what step the dechlorination reaction occurred (Chart 2).

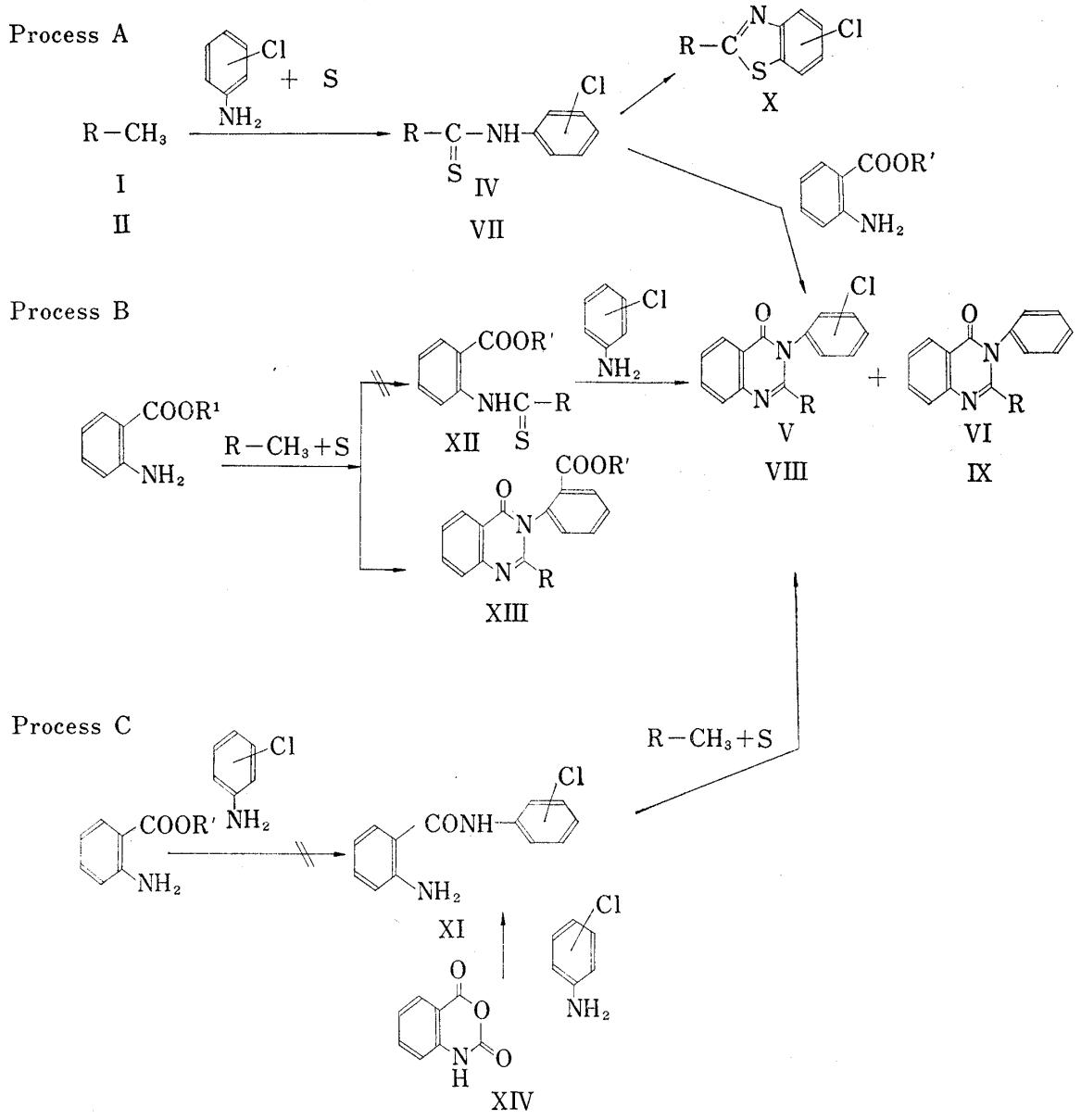


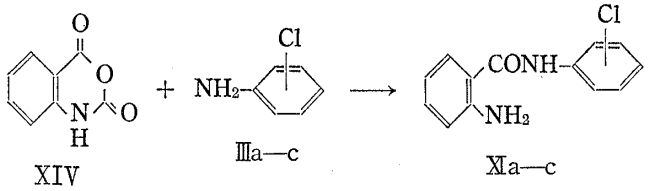
Chart 2

Process A was a similar combination as shown in method A, and was assumed to proceed by steps of (1) picolines (I or II) and chloroanilines (IIIa—c) react with sulfur to the corresponding chlorothiopicolinanilides (IVa—c or VIIa—c) and (2) condensation of IVa—c (or VIIa—c) with anthranilic acid to the 4(3*H*)-quinazolinone derivatives.

In process B, the reaction might be assumed to following the steps of (1) I (or II) and methyl anthranilate react with sulfur to methyl N-thiopicolinylanthranilate (XII) and (2) condensation of XII with chloroanilines (IIIa—c) to the 4(3*H*)-quinazolinones. In this procedure, the reaction of 2-picoline (I) with methyl anthranilate in the presence of sulfur unexpectedly resulted in the formation of 2-(2-pyridyl)-3-(*o*-methoxycarbonylphenyl)-4(3*H*)-quinazolinone (XIII) in about 20% yield instead of the expected methyl N-thiopicolinylanthranilate (XII).

In process C, the reaction might be assumed to proceed by the way of (1) methyl anthranilate reacts with chloroanilines (IIIa—c) to form anthranilanilides (XIa—c) and (2) condensation of XIa—c with I (or II) in the presence of sulfur to 4(3*H*)-quinazolinones. In this procedure, we assumed the formation of anthranilanilides (XIa—c) from the recation of methyl anthranilate with IIIa—c at an elevated temperature, but all attempts to isolate the products were unsuccessful. To examine the further possibility as mentioned above, preparation of XIa—c from isatoic anhydride (XIV) with IIIa—c was carried out, and then XIa—c was heated with I (or II) in the presence of sulfur to examine its behavior. The results obtained are summarized in Tables VI and VII.

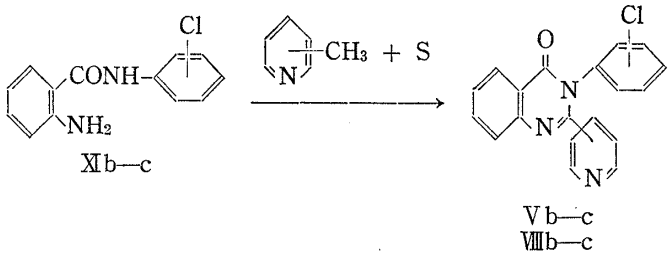
Table VI. Chloroanthranilanilides



Starting material				Product[a]						
								Analysis (%) Calcd. (Found)		
	o-	*m*-	*p*-	XI	mp (°C)	Yield (%)[b]	Formula	C	H	N
IIIa	Cl	H	H	XIa	—	—	$C_{13}H_{11}ON_2Cl$	—	—	—
IIIb	H	Cl	H	XIb	129—131[c]	60.8	$C_{13}H_{11}ON_2Cl$	63.29 (63.70)	4.49 (4.19)	11.36 (11.15)
IIIc	H	H	Cl	XIc	139—142	59.8	$C_{13}H_{11}ON_2Cl$	63.29 (63.59)	4.49 (4.56)	11.36 (11.72)

a) All the compounds were recrystallized from EtOH as colorless needles.
b) Calcd. on the basis of XIV.
c) Reported[9] mp 130—132°.

Table VII. 2-Pyridyl-3-(chlorophenyl)-4(3*H*)-quinazolinones



Starting material	Product						
		mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found)		
					C	H	N
XIb + I	Vb	155	52.8	$C_{19}H_{12}ON_3Cl$	68.37 (68.57)	3.62 (3.46)	12.59 (12.39)
XIc + I	Vc	195	47.6	$C_{19}H_{12}ON_3Cl$	68.37 (68.64)	3.62 (3.19)	12.59 (12.83)
XIb + II	VIIIb	175	60.8	$C_{19}H_{12}ON_3Cl$	68.37 (68.19)	3.62 (3.28)	12.59 (12.19)
XIc + II	VIIIc	228	55.4	$C_{19}H_{12}ON_3Cl$	68.37 (68.21)	3.62 (3.35)	12.59 (12.65)

Discussion

In method A, it was ascertained that dechlorination did not occur at the synthetic step of IVa—c and that dechlorination occurred at the cyclization step of IVa—c with anthranilic acid to form 4(3*H*)-quinazolinones. In the case of method B, containing four reactants as the starting materials, a mixture of I (or II), IIIa—c, and anthranilic acid, was heated in the presence of sulfur, and gave an almost similar result as method A, but in this case, the yield of total 4(3*H*)-quinazolinones (chlorine-substituted and dechlorinated compound) seemed to be lower than that from method B, and it was observed that dechlorination did occur to give similar results as described for method A.

The results from the syntheses of 4(3*H*)-quinazolinones by methods A and B proved that *o*-chlorine substituent in the aniline ring was easily dechlorinated under these reaction conditions, and that *p*-chlorine substituent in the aniline ring exhibited resistance to dechlorination. Ease of dechlorination according to the difference in the position of chlorine atom in aniline decreases in the order of *ortho*, *meta*, and *para* positions in both cases.

On the other hand, in the course of method A, there is a possibility for the formation of an adduct intermediate such as α-pyridyl-α,α-bis(phenylamino)methanethiol[10b,13] by the reaction of thiopicolinanilide with anthranilic acid, and then from this compound, benzothiazole might be produced by elimination of anthranilic acid. At this point in the reaction of method A or B, the products were examined in further detail. As a result, the reaction of IIIb and II with anthranilic acid in the presence of sulfur gave simultaneously a small amount of 2-(4-pyridyl)-5-chlorobenzothiazole[14] (X), mp 180°, besides VIIIb and IX as the main products. This fact shows that 4(3*H*)-quinazolinone cyclization process is more preferential than the benzothiazole cyclization process from thiopicolinanilides under the modified Willgerodt–Kindler reaction condition. This observation was of interest in the light of the results obtained by the modified Willgerodt–Kindler reaction in our laboratory,[1] which indicated that, in the synthesis of thioisonicotinanilides by the modified Willgerodt–Kindler reaction, benzothiazoles which had undergone cyclization from the corresponding thioisonicotinanilides by dehydrogenation were the main products.

There are many reports on dehalogenation reaction. Toland and Campbell[15] reported that a reductive dechlorination occurred at an elevated temperature by hydrogen sulfide. Therefore, IVb or IVc with I was heated at 195° for 8 hr in the presence of sulfur, but in both cases only the starting materials were recovered. This result suggests that the dechlorination reaction does not occur after the cyclization reaction to form 4(3*H*)-quinazolinone ring. Further, in the synthesis of thiopicolinanilides as the starting material in method A, the dechlorinated thiopicolinanilides were not obtained.

These results suggested that, at least, the dechlorination occurred at the step of the cyclization reaction of thiopicolinanilides with anthranilic acid.

Next, for the purpose of clarifying in what step the dechlorination occurred in method B, first it was necessary to investigate what kind of reaction would occur during one-step cyclization under a mixture of four reactants, I (or II), IIIa—c, anthranilic acid, and sulfur. The reaction of method B, although of considerable synthetic importance, has not been referred to its mechanism in our previous paper.[9] Although anthranilic acid exhibits a different behavior depending on its nature and reaction conditions, there are three possible processes to form 4(3*H*)-quinazolinones involving anthranilic acid by one-step cyclization in our experiments as illustrated in Chart 2.

13) T. Hisano, *Yakugaku Zasshi*, **81**, 69 (1961).
14) Identification of this compound was made by mixed fusion and comparison of thin layer chromatography and infrared spectra (IR) with an authentic sample.[1]
15) W.G. Toland and R.W. Campbell, *J. Org Chem.*, **28**, 3124 (1963).

Process A (analogous to method A) was presumed to involve at first condensation of I (or II) with IIIa—c in the presence of sulfur, accompanied by elimination of hydrogen sulfide, and in the second step IVa—c (or VIIa—c) as the intermediate eventually converted to 4(3*H*)-quinazolinones by the modified Niementowski reaction in the presence of anthranilic acid.

Process B was presumed to involve at first condensation of I (or II) with methyl anthranilate in the presence of sulfur to give methyl N-thiopicolinylanthranilate (XII) as the intermediate, which in the second step eventually converted to 4(3*H*)-quinazolinones *via* N-thiopicolinoylanthranilanilides in the presence of IIIa—c, accompanied by elimination of hydrogen sulfide. To investigate this possibility to obtain XII, the reaction of I with methyl anthranilate in the presence of sulfur was carried out, but all attempts to isolate the desired XII were unsuccessful. The reaction of methyl anthranilate with I in the presence of suflur unexpectedly resulted in the formation of 2-(2-pyridyl)-3-(*o*-methoxycarbonylphenyl)-4(3*H*)-quinazolinone (XIII) in 20% yield in one-step. This finding suggests that the condensation does not proceed *via* XII, because XII should easily react with an excess IIIa—c to give the corresponding Va—c.

In process C, first the acid anilide such as anthranilanilide was presumed to be formed by the reaction of anthranilic acid with IIIa—c at an elevated temperature, and then this product was converted to the cyclization product of 4(3*H*)-quinazolinone by the elimination of hydrogen sulfide *via* N-thiopicolinoylanthranilanidide by the reaction of I (or II) with sulfur. To clarify this process, a mixture of anthranilic acid and IIIa—c was heated at an elevated temperature, but the expected product was not obtained. Chloroanthranilanilides (XIb—c) were prepared by the alternative route, but XIa could not be obtained by this reaction. These compounds (XIb—c) were heated at 170° for 8 hr with I (or II) in the presence of sulfur, and were converted only to the expected chlorine-substituted 4(3*H*)-quinazolinones. In this procedure, dechlorination did not occur at all. The results of these experiments demonstrate that XIa—c is not the sourse of process C in method B.

It was concluded from the results obtained in processes A, B, and C, and the separation of the chlorine-substituted benzothiazole (X) in the reaction of method B that there is a possibility of 4(3*H*)-quinazolinone ring formation only from process A. In other words, method B, as the one-step procedure for 4(3*H*)-quinazolinone ring formation, was presumed to proceed by the successive steps which contained the modified Willgerodt–Kindler reaction and the modified Niementowski reaction.

The present dechlorination phenomenon would perhaps occur at the last step in the modified Niementowski reaction but the mechanism whereby the dechlorination occurs is not yet clear. Further experimentation is necessary to explain fully this interesting observation.

Experimental

All melting points are uncorrected. IR spectra were recorded on Nippon Bunko DS-301 and Nippon Bunko IR-G spectrophotometer. Gas chromatographic analyses were performed with a Shimadzu GC-4APF gas chromatograph with a thermal conductivity detector, using 1.5% SE-30 on a column (3 m×4 mm).

2′-(3′ or 4′)Chlorothiopicolinanilide (IVa—c) (Table I)——A mixture of 12.7 g (0.10 mole) of *o*-(*m*- or *p*-)-chloroaniline (IIIa—c), 13.9 g (0.15 mole) of 2-picoline (I), and 8.0 g (0.25 mole) of S was heated in an oil bath at 170° for 10 hr. The unchanged I and IIIa—c were completely removed by vacuum distillation in an oil bath. The residue was extracted with hot 3N NaOH solution (200 ml×3), and the combined extracts were carefully acidified with dil. HCl; the yellowish orange crystalline mass which deposited was collected by suction and recrystallized from EtOH.

2′-(3′ or 4′)Chlorothioisonicotinanilide (VIIa—c) (Table III)——A mixture of 4.6 g (0.02 mole) of 2′-(3′ or 4′)chloroisonicotinanilide and 18 g (0.08 mole) of P_2S_5 was heated in an oil bath at 130° for 3 hr. The reaction mixture was extracted with 2N NaOH (500 ml) and the extract was filtered. The filtrate was carefully acidified with dil. HCl; the yellowish orange viscous precipitate was extracted with $CHCl_3$. The $CHCl_3$

layer was dried over anhyd. Na_2SO_4 and filtered. The solvent was removed from the filtrate by vacuum distillation, and the residue was recrystallized from benzene.

[I] **Method A (Modified Niementowski Reaction)**——General Method: A mixture of 4.37 g (0.0175 mole) of chlorothioanilide (IVa—c or VIIa—c), 1.37 g (0.01 mole) of anthranilic acid, and 1.51 g (0.01 mole) of methyl anthranilate was heated at 195° for 8 hr; H_2S gas evolved vigorously. The reaction mixture dissolved in a small portion of $CHCl_3$ was chromatographed over Al_2O_3 (200—300 mesh; 50 g). From the first effluent fraction, a crude crystalline mass was obtained and recrystallized from ether–petr. ether (1: 1).

Reaction of 3′-Chlorothiocolinanilide (IVb) with Anthranilic Acid——a) Separation of 2-(2-Pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (Vb): The crude crystals obtained in the above procedure were dissolved in $CHCl_3$ and chromatographed on silica gel (Wako-gel C-200; 70 g) using $CHCl_3$ as an eluant. From the first effluent fraction, 1.0 g (30.0%) of colorless prisms (Vb) (mp 155°) was obtained and recrystallized from benzene–petr. benzine (1: 2). IR ν_{max}^{KBr} cm^{-1}: 1665 ($\nu_{C=O}$). Positive to the Beilstein flame test. *Anal.* Calcd. for $C_{19}H_{12}ON_3Cl$: C, 68.37; H, 3.62; N, 12.59. Found: C, 68.64; H, 3.41; N, 12.31.

b) Separation of 2-(2-Pyridyl)-3-phenyl-4(3H)-quinazolinone (VI): From the second effluent fraction from the above procedure, 0.30 g (10.0%) of colorless amorphous substance of mp 162° was obtained, and recrystallized from benzene–petr. benzine (1: 2). Negative to the Beilstein flame test. This compound agreed with the authentic sample of VI by a mixed melting point and by IR spectral comparison.

Reaction of 3′-Chlorothioisonicotinanilide (VIIb) with Anthranilic Acid——The reaction was carried out as in the foregoing general procedure. After the reaction had been completed, the reaction mixture was analyzed by gas chromatography, which indicated the presence of 2-(4-pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (VIIIb) as the chlorine-substituted 4(3*H*)-quinazolinone product obtained as 31.4% of colorless needles, mp 175°, and 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (IX) as the dechlorinated product obtained as 17.7% of colorless prisms, mp 159°.

[II] **Method B (Modified Willgerodt–Kindler Reaction Condition)**——General Method: A mixture of 3.72 g (0.04 mole) of I (or II), 5.10 g (0.04 mole) of IIIa—c, 5.48 g (0.04 mole) of anthranilic acid, and 3.84 g (0.12 mole) of S was heated at 195° for 8 hr. The reaction mixture was cooled, dissolved in $CHCl_3$, and the solution was purified by chromatography (Al_2O_3; 50 g) using $CHCl_3$ as an eluant. From the first effluent fraction, a crude crystalline mass was obtained, and recrystallized from ether–petr. ether (1: 1).

Reaction of 4-Picoline (II) and *m*-Chloroaniline (IIIb), with Anthranilic Acid in the Presence of Sulfur——The reaction was carried out by a similar procedure as in the foregoing general method B.

a) Separation of 2-(2-Pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (Vb): The crude crystalline mass obtained in the above procedure was dissolved in $CHCl_3$ and chromatographed over silica gel (Wako-gel C-200; 70 g) using $CHCl_3$ as an eluant. From the first effuent fraction, 1.0 g (7.5%) of colorless prisms (Vb), mp 155° was obtained and recrystallized from benzene–petr. benzine (1: 2). Positive to the Beilstein flame test. IR ν_{max}^{KBr} cm^{-1}: 1665 ($\nu_{C=O}$). This compound agreed with the authentic sample by mixed melting point and by IR spectral comparison.

b) Separation of 2-(2-Pyridyl)-3-phenyl-4(3*H*)-quinazolinone (VI): From the second effluent fraction from the above procedure, 1.4 g (11.7%) of colorless amorphous substance of mp 162° was obtained and recrystallized from benzene–petr. benzine (1: 2). Negative to the Beilstein flame test. This compound agreed with the authentic sample by mixed melting point and by IR spectral comparison.

Reaction of 4-Picoline (II) and *m*-Chloroaniline (IIIb) with Anthranilic Acid in the Presence of Sulfur——The reaction was carried out by a similar procedure as in the foregoing general method B. After the reaction had been completed, the reaction mixture was dissolved in a small portion of $CHCl_3$ and chromatographed over Al_2O_3 (50 g). From the first effluent fraction, a crude crystalline mass was obtained and recrystallized from ether–petr. ether (1: 1). The crude crystals were analyzed by gas chromatography which indicated the presence of 2-(4-pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (VIIIb) as the chlorine-substituted 4(3*H*)-quinazolinone product, obtained as colorless needles, mp 175°, in 16.8% yield, and 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (IX) as the dechlorinated product of mp 159°, in 11.3% yield.

[III] **Process B 2-(2-Pyridyl)-3-(*o*-methoxycarbonylphenyl)-4(3*H*)-quinazolinone (XIII)**——A mixture of 14 g (0.15 mole) of I, 15.1 g (0.10 mole) of methyl anthranilate, and 8.0 g (0.25 mole) of S was heated at 170° for 10 hr. After removal of unchanged I and methyl anthranilate *in vacuo*, the brown residue dissolved in a small portion of benzene was chromatographed over Al_2O_3 (130 g). From the first effluent fraction, 3.5 g (20.0%) of colorless plates, mp 190°, was obtained and recrystallized from EtOH. IR ν_{max}^{KBr} cm^{-1}: 1678, 1735 ($\nu_{C=O}$). *Anal.* Calcd. for $C_{21}H_{15}O_3N_3$: C, 70.58; H, 4.23; N, 11.76. Found; C, 70.61; H, 4.32; N, 11.71.

[IV] **Process C Chloroanthranilanilide (XIb—c) (Table VI)**——A mixture of 8.6 g (0.0675 mole) of IIIb—c and 10 g (0.0613 mole) of isatoic anhydride (XIV) was heated at 120° for 4 hr. The product was recrystallized from EtOH.

2-(2-Pyridyl)-3-(chlorophenyl)-4(3*H*)-quinazolinone (Vb—c) (Table VII) A mixture of 2.5 g (0.01 mole) of XIb—c, 1.4 g (0.015 mole) of I, and 0.8 g (0.025 mole) of S was heated at 195° for 8 hr. The reaction mixture was cooled, dissolved in $CHCl_3$, and the solution was chromatographed over Al_2O_3 (50 g), and eluted with $CHCl_3$. From the first effluent fraction, the solvent was evaporated in vacuum and the resulting solid was recrystallized from benzene–petr. benzine (1: 2) to colorless crystals (Vb—c). These crystals obtained agreed with Vb—c synthesized by method A, by mixed melting point and by IR spectral comparison.

2-(4-Pyridyl)-3-(chlorophenyl)-4(3*H*)-quinazolinone (VIIIb—c)——A mixture of 2.46 g (0.01 mole) of XIb—c, 1.4 g (0.015 mole) of II, and 0.8 g (0.025 mole) of S was treated by the general procedure of process C. The crystals obtained agreed with the samples of VIIIb—c synthesized by method A, by mixed melting point and by IR spectral comparison.

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