UDC 615.778.5 : 547.831.2+547.552

10. **Haruo Saikachi and Takuzo Hisano :** Synthetic Studies on Fungicidal Agent. IX. Reaction of Quinaldine and Aromatic Primary Amines in the Presence of Sulfur.

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Previous papers[1] described the behavior of 2-picoline and 4-picoline possessing one active methyl group in the pyridine ring upon treatment with aromatic primary amines in the presence of sulfur at elevated temperature. Some works[2] concerning experimental chemotherapeutic studies of quinaldine derivatives have also appeared.

It has been well known[3] that the reactivity of the methyl group in quinaldine resembles that of both 2- and 4-picolines by possessing a polarizable nitrogen in the pyridine ring. On the basis of such facts, the condensation of quinaldine with aromatic primary amines was carried out in the presence of sulfur to obtain both the corresponding N-(2-quinolinecarbothionoyl)anilines and 2-(2-quinolyl)benzothiazoles, for the purpose of microbiological screening in this laboratory.

According to Emmert and Holz,[4] the use of 2-naphthylamine as the amino component in this reaction afforded 2-(2-quinolyl)naphtho-thiazole and not N-(2-quinolinecarbothionoyl)naphthylamine. Thus in the condensation of active methyl component with aromatic primary amine, products vary even under very close conditions. This fact suggests that the reaction itself may considerably be dependent on the characteristics of the amino components. Therefore, in order to investigate in greater detail the behavior of other aromatic amines in this reaction, the following seven aromatic primary amines were used : Aniline (I), *p*-toluidine (II), *p*-anisidine (III), *p*-phenetidine (IV), *p*-isopropoxyaniline (V), *p*-propoxyaniline (VI), and *p*-butoxyaniline (VII).

In the first phase of this work, a mixture of quinaldine, one of the aromatic amines mentioned above, and sulfur in molar ratio of about 1:1.5:2.5 was reacted over a narrow temperature range (160~165°) for 20~25 hours. As shown in Table I, among the above amino components, (I), (II), (III), (VI), and (VII) predominantly gave the corresponding N-(2-quinolinecarbothionoyl)anilines, (VIII), (X), (XII), (XVIII) and (XX), accompanied with formation of the corresponding 2-(2-quinolyl)benzothiazoles, (IX), (XI), (XIII), (XIX) and (XXI), in a very poor yield. On the other hand, both (IV) and (V) gave only the corresponding N-(2-quinolinecarbothionoyl)aniline type compounds (XIV and XVI) and all attempts to isolate the corresponding 2-(2-quinolyl)benzothiazoles from the reaction mixtures were unsuccessful. Hence, a further approach was separately made to prepare the desired benzothiazoles which could not be obtained by the above procedure. For this purpose, oxidative thiazole ring formation of (XIV) and (XVI) with potassium ferricyanide were undertaken in alkaline medium.

Above experimental results suggested that the possibility of thiazole ring formation in the course of the condensation, apart from electronic discussions on the problem, might be influenced to some extent by the substituent in the *para*-position of the aromatic primary amino group.

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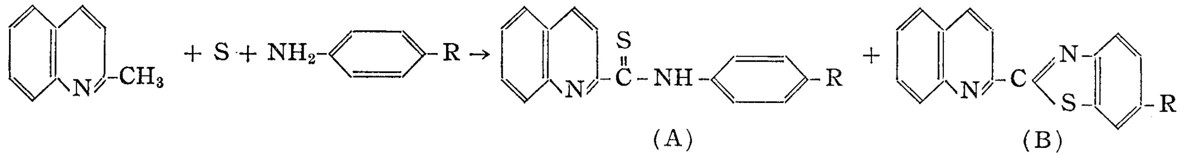
Experimental

Condensation of Quinaldine with Aromatic Primary Amines—The following general procedure was used for condensation of compounds listed in Table I.

a) N-(2-Quinolinecarbothionoyl)anilines : A mixture of 3.6 g. (0.025 mole) of quinaldine (b.p. 114~115°), 0.038 mole of aromatic primary amines, and 2.0 g. (0.063 mole) of S was refluxed in an oil bath at 160~165° for 20 hr. H_2S gas evolved vigorously during the period of this reaction. After gas evolution became weak, the reaction mixture was submitted to vacuum distillation to remove unchanged amine and quinaldine. The residue was extracted with about 300 cc. (3×100 cc.) of hot 10% NaOH solution. After cool the orange crystalline mass that deposited from the combined alkaline extracts was collected by suction and recrystallized several times from EtOH.

b) 2-(2-Quinolyl)benzothiazole : In the above procedure, the alkali-insoluble residue was purified by three recrystallizations from EtOH and the product was obtained in a very poor yield.

Table I.



Type-A compounds*

Compound No.	R	Formula	m.p. (°C)	Yield[a] (%)	Analysis (%) Calcd. N	Analysis (%) Found N
(VIII)	H	$C_{16}H_{12}N_2S$	109.0~110.0	66.7	10.59	10.49
(X)	CH_3	$C_{17}H_{14}N_2S$	117.0~118.5	63.2	10.06	9.85
(XII)	OCH_3	$C_{17}H_{14}N_2SO$	116.0~117.0	59.4	9.52	9.83
(XIV)	OC_2H_5	$C_{18}H_{16}N_2SO$	114.5~115.5	75.3	9.08	8.98
(XVI)	iso-OC_3H_7	$C_{19}H_{18}N_2SO$	87.0~ 87.5	76.5	8.68	8.97
(XVIII)	OC_3H_7	$C_{19}H_{18}N_2SO$	96.5~ 98.5	55.6	8.68	8.85
(XX)	OC_4H_9	$C_{20}H_{20}N_2S$	92.5~ 94.0	50.0	8.32	8.58

* All are orange needle crystals.

Type-B compounds*

Compound No.	R	Formula	m.p. (°C)	Appearance	Yield[a] (%)	Analysis (%) Calcd. N	Analysis (%) Found N
(IX)	H	$C_{16}H_{10}N_2S$	198.0~200.0[b]	colorless prisms	3.0	10.68	10.64
(XI)	CH_3	$C_{17}H_{12}N_2S$	220.0~221.5[b]	colorless plates	4.3	10.13	9.82
(XIII)	OCH_3	$C_{17}H_{12}N_2SO$	194.0~195.5	〃	5.5	9.58	9.71
(XV)	OC_2H_5	$C_{18}H_{14}N_2SO$	172.0~173.0	colorless needles	[c]	9.15	9.20
(XVII)	iso-OC_3H_7	$C_{19}H_{16}N_2SO$	135.5~136.5	colorless prisms	[c]	8.74	9.00
(XIX)	OC_3H_7	$C_{19}H_{16}N_2SO$	191.0~192.0	colorless needles	8.8	8.74	9.06
(XXI)	OC_4H_9	$C_{20}H_{18}N_2SO$	158.0~159.5	colorless prisms	14.3	8.37	8.61

All melting points are not corrected and all products were recrystallized from EtOH.

a) Calculated on the basis of quinaldine.

b) Both (IX) and (XI) were also identified by oxidation of (VIII) and (X), respectively.

c) (XV) and (XVII) were prepared from (XIV) and (XVI) by oxidation in alkaline medium with $K_3Fe(CN)_6$.

2-(2-Quinolyl)-6-ethoxybenzothiazole (XV)—To a stirred solution of 1.0 g. of (XIV) and 8.0 g. of NaOH in 110 cc. of water at 50~60°, a saturated solution of 44 g. of powdered $K_3Fe(CN)_6$ in 70 cc. of water was added dropwise. After completion of the addition, the mixture was treated for an additional 1 hr., and 30 g. of K_2CO_3 was added to the reaction mixture. After some time the final reaction mixture was extracted with about 400 cc. of ether (4×100 cc.). The combined organic extract was dried over Na_2SO_4 and filtered. Removal of the solvent gave a crude crystalline mass which was purified by three recrystallizations from EtOH.

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Summary

Condensation of quinaldine with seven kinds of aromatic primary amines in the presence of sulfur was carried out at an elevated temperature. With the exception of *p*-phenetidine and *p*-isopropoxyaniline, which yielded only the corresponding thioanilides, these amines gave N-(2-quinolinecarbothionoyl)anilines and also 2-(2-quinolyl)benzothiazoles, without much difference in the yield. The results of microbiological screening will be reported elsewhere in due course.

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11. **Haruo Saikachi**[*1] **and Keizo Suzuki**[*2] : Syhthesis of Furan Derivatives. XXIII. 4-(5-Nitrofurfurylidene)-2-cyanocrotonamides.

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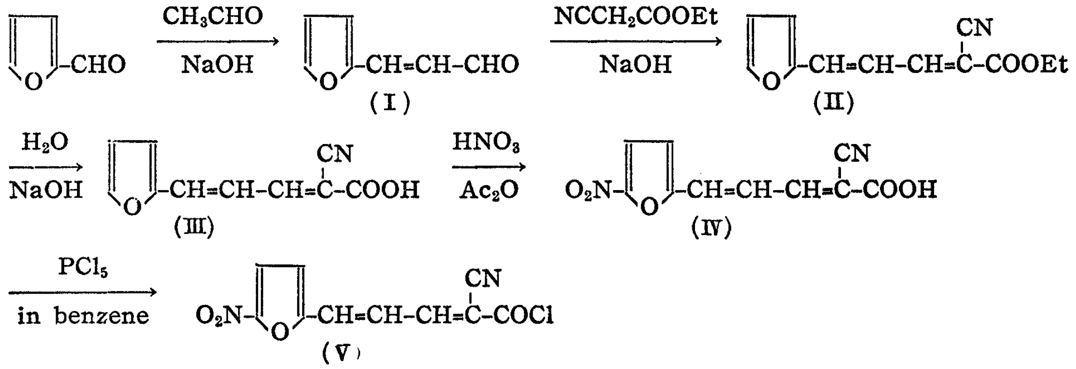
In the preceding parts of this series, syntheses and antibacterial activity were reported on 3-(5-nitro-2-furyl)acrylamides,1) 2-cyano-3-(5-nitro-2-furyl)acrylamides,2) and 2-methyl-3-(5-nitro-2-furyl)acrylamides.3) From the earlier results, a few 3-(5-nitro-2-furyl)acrylamides exhibited excellent antibacterial activity, but the mechanism of antibacterial action has not yet been clarified satisfactorily. It may be concluded on the basis of past studies4,5) that the introduction of a conjugated double bond between the nitrofuryl and the end group in the side chain might enhance the antibacterial activity to some extent. Therefore, an attempt was made to extend the conjugated double bond in the side chain.

The starting material, 3-(2-furyl)acrolein (I), was prepared by the condensation of furfural and acetaldehyde. Condensation of (I) with ethyl cyanoacetate in alkaline medium gave ethyl 4-furfurylidene-2-cyanocrotonate (II) in a good yield, and (II) easily underwent hydrolysis on being heated in alkaline solution to form 4-furfurylidene-2-cyanocrotonic acid (III). Nitration of (III) with a cold mixture of concentrated nitric acid and acetic anhydride afforded the corresponding 4-(5-nitrofurfurylidene)-2-cyanorotonic acid (IV), and (IV) gave 4-(5-nitrofurfurylidene)-2-cyanocrotonoyl chloride (V) on heating



[*1] Katakasu, Fukuoka (西海枝東雄).

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