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 studies[4,5] 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

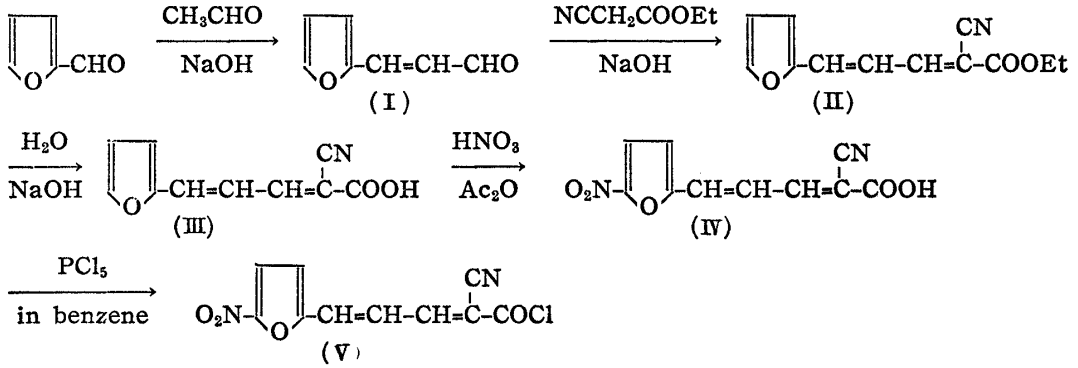

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TABLE. I.

Compd. No.	Prepn. proc.	Yield* (%)	R	R′	m.p. (°C)	Crystn. solvent	Appearance	Formula	Analyses (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
(VI)	A	52	H	H	199 (dec.)	Dioxane	Brown Powder	$C_{10}H_7O_4N_3$	51.51	51.38	3.03	3.13	18.02	18.12
(VII)	〃	48	〃	CH_3	236 (〃)	〃	〃	$C_{11}H_9O_4N_3$	53.44	53.21	3.67	3.73	17.00	17.24
(VIII)	〃	52	〃	C_2H_5	234 (〃)	〃	Yellow needles	$C_{12}H_{11}O_4N_3$	55.17	55.35	4.24	4.31	16.09	16.32
(IX)	B	55	C_2H_5	〃	132～133	MeOH	〃	$C_{14}H_{15}O_4N_3$	58.12	57.97	5.23	5.46	14.53	14.72
(X)	〃	63	H	C_3H_7	207 (dec.)	〃	〃	$C_{13}H_{13}O_4N_3$	56.72	56.58	4.76	4.84	15.27	15.50
(XI)	〃	52	C_3H_7	〃	92～93	〃	Yellow plates	$C_{16}H_{19}O_4N_3$	60.55	60.60	6.04	6.13	13.24	13.28
(XII)	〃	58	H	iso-C_3H_7	205 (dec.)	〃	Yellow needles	$C_{13}H_{13}O_4N_3$	56.72	56.89	4.76	4.62	15.27	15.35
(XIII)	〃	58	〃	C_4H_9	173～174	〃	〃	$C_{14}H_{15}O_4N_3$	58.12	58.31	5.23	5.37	14.53	14.82
(XIV)	〃	55	C_4H_9	〃	100～101	〃	Yellow prisms	$C_{18}H_{23}O_4N_3$	62.59	62.31	6.71	6.58	12.17	12.46
(XV)	〃	58	H	iso-C_4H_9	171～172	〃	Yellow needles	$C_{14}H_{15}O_4N_3$	58.12	58.21	5.23	5.44	14.53	14.79
(XVI)	〃	55	〃	sec-C_4H_9	149～151	〃	Yellow plates	$C_{14}H_{15}O_4N_3$	58.12	58.48	5.23	5.27	14.53	14.19
(XVII)	〃	58	〃	iso-C_5H_{11}	165～166	〃	〃	$C_{15}H_{17}O_4N_3$	59.36	59.70	5.55	5.80	13.86	13.73
(XVIII)	〃	55	iso-C_5H_{11}	〃	97～98	〃	〃	$C_{20}H_{27}O_4N_3$	64.34	64.60	7.29	7.22	11.26	11.41
(XIX)	〃	62	H		204 (dec.)	Dioxane	Fine yellow needles	$C_{17}H_{13}O_4N_3$	63.15	63.42	4.05	4.18	13.00	13.16
(XX)	C	77	〃		275 (〃)	〃	Fine yellow prisms	$C_{16}H_{11}O_4N_3$	62.13	61.93	3.59	3.44	13.59	13.88
(XXI)	〃	76	〃		281 (〃)	〃	Fine yellow plates	$C_{17}H_{13}O_4N_3$	63.15	63.34	4.05	4.18	13.00	13.12
(XXII)	〃	78	〃		238 (〃)	〃	Fine yellow needles	$C_{17}H_{13}O_4N_3$	63.15	63.48	4.05	4.03	13.00	13.15
(XXIII)	〃	72	〃		273 (〃)	〃	Fine red needles	$C_{16}H_{11}O_5N_3$	59.08	58.84	3.41	3.34	12.92	13.26
(XXIV)	〃	70	〃		255 (〃)	〃	Orange yellow needles	$C_{16}H_{11}O_5N_3$	59.08	59.12	3.41	3.46	12.92	13.03
(XXV)	〃	77	〃		262 (〃)	〃	Fine red needles	$C_{17}H_{13}O_5N_3$	60.17	60.21	3.86	3.77	12.39	12.59
(XXVI)	〃	74	〃		249 (〃)	〃	Fine yellow plates	$C_{16}H_{10}O_4N_3Cl$	55.96	55.74	2.96	2.86	12.24	12.20
(XXVII)	〃	76	〃		272 (〃)	〃	〃	$C_{16}H_{10}O_4N_3Br$	49.50	49.61	2.60	2.74	10.83	10.91

* Calcd. on the basis of 4-(5-nitrofurfurylidene)-2-cyanocrotonoyl chloride used.

TABLE II. Minimum Bacteriostatic Concentration (Unit 10,000)

Compd. No.	*Staph. aureus*	*E. coli*	Compd. No.	*Staph. aurens*	*E. coli*	Compd. No.	*Staph. aureus*	*E. coli*	Compd. No.	*Staph. aureus*	*E. coli*
(VI)	<1	<1	(XI)	2	<1	(XIX)	<1	<1	(XXIV)	<1	<1
(VII)	2	<1	(XII)	<1	<1	(XX)	<1	<1	(XXV)	<1	<1
(VIII)	3	2	(XIII)	2	<1	(XXI)	<1	<1	(XXVI)	<1	<1
(IX)	1	<1	(XIV)	2	<1	(XXII)	<1	<1	(XXVII)	<1	<1
(X)	<1	<1	(XVI)	<1	<1	(XXIII)	<1	<1	Furacin	14	14

with phosphorus pentachloride in dry benzene medium.

By condensation of the acid chloride (V) with various amines, 22 kinds of corresponding derivatives were obtained (Table I). These amides were screened for bacteriological activity (Table II). As seen from Table II, not all amides showed the intended effect, which may have been due to their low solubility.

Experimental

Ethyl 4-Furfurylidene-2-cyanocrotonate (II)—To a solution of 113 g. (2.0 moles) of 3-(2-furyl)-acrolein, 225 g. (2.0 moles) of ethyl cyanoacetate, and 200 cc. of MeOH, about 30 cc. of 10% methanolic NaOH was added dropwise while cooling and stirring. After a few minutes, the reaction mixture became yellow and turbid. After allowing the reaction mixture to stand for 1 hr., the precipitate was collected by suction and washed with 30% cold MeOH solution. Recrystallization of the crude product from MeOH gave 160 g. (80%) of pale yellow needles, m.p. 107~108°. *Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45. Found : C, 66.57; H, 5.21; N, 6.73.

4-Furfurylidene-2-cyanocrotonic Acid (III)—A mixture of 100 g. (0.46 mole) of (II) and 400 cc. of 10% NaOH solution was heated on a steam bath with occasional shaking. As soon as (II) dissolved, the reaction mixture was cooled with ice water and acidified to Congo Red with 10% H_2SO_4. The precipitated red (III) was collected by suction. Recrystallization of the crude product from MeOH gave 64 g. (74%) of a red crystalline powder, m.p. 224° (decomp.). *Anal.* Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.41. Found : C, 63.24; H, 3.65; N, 7.62.

4-(5-Nitrofurfurylidene)-2-cyanocrotonic Acid (IV)—The nitrating mixture was prepared by adding 88 g. (1.38 moles) of fuming nitric acid (sp. gr., 1.5) dropwise to 400 g. (3.9 moles) of Ac_2O at below 0° and 70 g. (0.37 mole) of (III) was added slowly to the nitrating mixture at below −5°. After stirring the reaction mixture for 1 hr., the yellow precipitate was collected on a sintered glass filter and washed well with cold water. Recrystallization of the crude product from dioxane gave 35 g. (40%) of yellow prisms, m.p. 234° (decomp.). *Anal.* Calcd. for $C_{10}H_6O_5N_2$: C, 51.29; H, 2.58; N, 11.96. Found : C, 51.38; H, 2.54; N, 11.72.

4-(5-Nitrofurfurylidene)-2-cyanocrotonoyl Chloride (V)—A mixture of 35 g. (0.15 mole) of (IV), 63 g. (0.3 mole) of PCl_5, and 250 cc. of benzene was refluxed until (IV) dissolved completely. The reaction mixture was evaporated under a reduced pressure and the crystalline residue was recrystallized from benzene to 28 g. (74%) of yellow needles, m.p. 148° (decomp.). *Anal.* Calcd. for $C_{10}H_5O_4N_2Cl$: C, 47.55; H, 1.99; N, 11.08. Found : C, 47.68; H, 1.85; N, 11.02.

Procedure A : 4-(5-Nitrofurfurylidene)-2-cyanocrotonamide (VI)—The preparation of compounds (VI) to (VIII) listed in Table I was as follows :

A small excess of dry NH_3 gas was bubbled while cooling through a solution of 2.5 g. (0.01 mole) of 4-(5-nitrofurfurylidene)-2-cyanocrotonoyl chloride in 60 cc. of dry acetone, until no more crystals deposited. After allowing the reaction mixture to stand in an ice-box for 3 hr., the crystalline product was collected and washed with cold water. Recrystallization of the crude product from dioxane gave 1.2 g. (52%) of brown powder, m.p. 199° (decomp.).

Procedure B : N,N-Diethyl-4-(5-nitrofurfurylidene)-2-cyanocrotonamide (IX)—The following procedure was used for the preparation of compounds (IX) to (XIX) listed in Table I.

A small excess of Et_2NH was added dropwise into a solution of 2.5 g. (0.01 mole) of (IV) in 60 cc. of dry acetone with cooling. After standing at room temperature for 3 hr., the reaction mixture was diluted with about 60 cc. of water. The precipitate was collected by suction and washed with cold water. The crude product recrystallized from MeOH to 1.6 g. (55%) of yellow needles, m.p. 132~133°.

Procedure C : N-Phenyl-4-(5-nitrofurfurylidene)-2-cyanocrotonamide (XX)—The preparation of compounds (XX) to (XXVII) listed in Table I was as follows :

A small excess of aniline was added dropwise into a solution of 2.5 g. (0.01 mole) of (IV) in 60 cc. of dry acetone while cooling. After standing at room temperature for 3 hr., the crystalline product was collected and washed with cold water. The crude product recrystallized from dioxane to 2.4 g. (77%) of fine yellow prisms, m.p. 275° (decomp.).

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Summary

Twenty-two kinds of 4-(5-nitrofurfurylidene)-2-cyanocrotonamides were prepared by condensation of 4-(5-nitrofurfurylidene)-2-cyanocrotonoyl chloride and various amines. These acid amides are almost insoluble in water and did not show the desired anti bacterial activity.

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