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Synthesis of Organosulfur Compounds. III.[1] Application of Thiopicolinanilide Series for the Niementowski Synthesis

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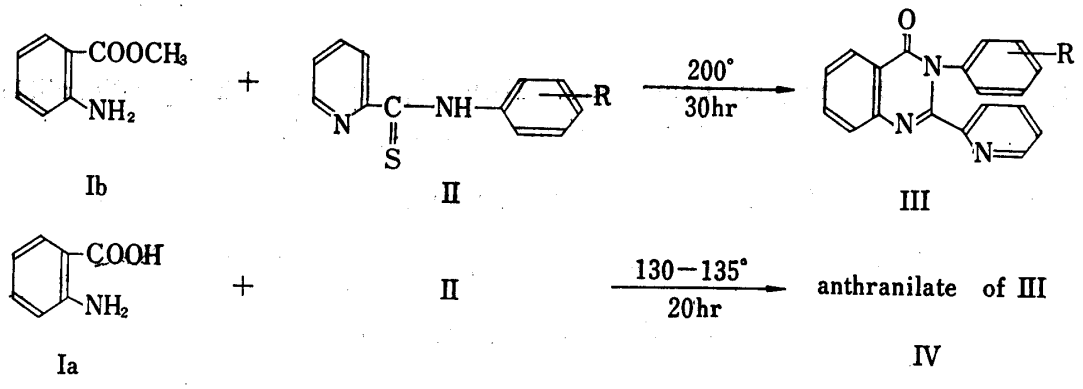
The most common synthesis of 4(3H)-quinazolinones is effected in a reaction which was first described by Niementowski.[3] When anthranilic acid is heated with excess of formamide at 120°, a nearly quantitative conversion to 4(3H)-quinazolinone is achieved. This reaction has also been adapted to benzamide series as well as to aliphatic amides.[4] As a rule, a higher temperature or longer reaction time is required for the reaction with the former. However, it has been reported by Sherrill, *et al.*[5] to be able to raise the yields of 2-phenyl-4(3H)-quinazolinone 20% to 50%, replacing benzamide with thiobenzamide for considering extremely low yield with benzamide. Still less, a satisfactory synthetic method on 4(3H)-quinazolinone derivatives having a heterocyclic substituent at the C_2- or C_3-position has never been found a way out.

In connection with the matters, we have attempted to carry out 4(3H)-quinazolinone cyclization using thiopicolinanilide derivatives originally in our laboratory.[6] The previous report has involved for the thiopicolinanilides to exhibit a considerable reactivity in the range of 160° to 180° for the azole formation with a bifunctional group, such as *o*-phenylenediamine or *o*-aminophenol.[1]

As an experiment of 4(3H)-quinazolinone formation, if a condensation of anthranilic acid with the thioanilide series is carried out in the same range of reaction temperature, it appears that an intereference with the reaction may be due to decarboxylation of the acid. Our experiments could be found in fact that the yield of the 4(3H)-quinazolinone was unable to be raised above 20%, in spite of various examinations on the correlation between a reaction temperature and time, while an ester of anthranilic acid was condensed with the thioanilide series at least above 200° to give the quinazolones in below 20% yields. As a rule, the formation of anthranilate of the formed 4(3H)-quinazolinone exclusively offered during reaction for the employ of anthranilic acid as above. However, such salt was warmed with 5% caustic alkaline solution to be able to be led to the corresponding 4(3H)-quinazolinone in about 60% yield. This evidence undertakes to make a structure of the salt more clear. The structures of 4(3H)-quinazolinone derivatives (III-type) obtained from methyl anthranilate and their salts(IV-type) from anthranilic acid as mentioned above were determined by elemental analyses and infrared absorption spectra observation, respectively (Fig. 2, Table II and III).

These results evoked an interest that a complete reaction may be attributed to certain catalyses in the course of this reacion. Therefore, we have attempted to find out an active catalyst in such a way that is reached without the formation of such salt in the employ of anthranilic acid.

1) Part II: T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, **91**, 727(1971).
2) Location: *Oe-hon-machi, Kumamoto.*
3) V. Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).
4) J.F. Meyer and E.C. Wagner, *J. Org. Chem.*, **8**, 239 (1943).
5) M.M. Endicott, E. Wick, M.L. Mercury and M.L. Sherrill, *J. Am. Chem. Soc.*, **68**, 1299 (1946).
6) H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **7**, 349 (1959).



R=a: H, b: *o*-CH_3, c: *m*-CH_3, d: *p*-CH_3, e: *o*-OCH_3, f: *p*-OCH_3, g: *p*-OC_2H_5, h: *p*-$COOC_2H_5$

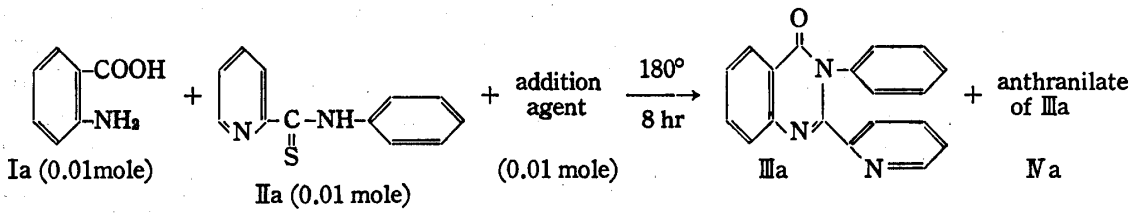
Chart 1

In order to protect anthranilic acid from decarboxylation at higher temperature, the amines as shown in Table I were previously added to a mixture of anthranilic acid and the thioanilide. Herewith, a close correlation between a reaction temperature and time was investigated throughout the reaction.

Addition Agents to the Condensation of Anthranilic Acid (I_a) with Thiopicolinanilide Series (II)

Pyridine, N,N-dimethylaniline, aniline,and methyl anthranilate were employed for the condensation as a basic addition agent, in addition to benzyl alcohol, methyl benzoate and nitrobenzene. Consequently, it is seemed advisable to consider that such basic agents as having an amino group may form presumably an intermediary amidine[7,8] upon the interaction with II, but in particular, we did not check it up in this paper.

TABLE I. Effect of Addition Agents in 4(3H)-Quinazolinone Cyclization



Addition agent	Pyridine	N,N-Dimethyl-aniline	Aniline	Methyl anthranilate	Nitro-benzene	Benzyl alcohol	Methyl benzoate
Total yield[a] (%)	15.2	14.0	31.8	38.0	23.4	1.2	7.2

a) The salt (IVa) hydrolyzed was applied to the total yield, as described in experimental.

As indicated in Table I, methyl anthranilate (I_b) has a good result for the quinazolone cyclization at least in our experiment. It is seemed that I_b catalytically participates in this reaction, because methyl anthranilate is quite indifferent to the quinazolone cyclization under such reaction condition as mentioned above, and afterwards, we observed that rather excess of I_b resulted in inhibiting the formation of III.

Thereupon, in our search for the reaction condition of the cyclization in the presence of methyl anthranilate, it was proved that increase in molar concentration of II_a progressively raised product(III_a).

7) H. Saikachi and T. Hisano, *Yakugaku Zasshi*, **81**, 64 (1961).
8) S. Tanimoto, S. Shimojo and R. Oda, *J. Soc. Org. Syn. Chem.* (Japan), **26**, 151 (1968).

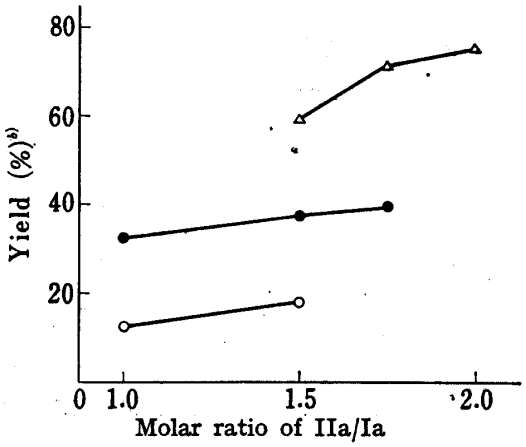


Fig. 1. Quantitative Correlation between Ia[a] and IIa on the 4(3H)-Quinazolinone (IIIa) formed in Duration of Eight Hours

reaction temperature: ○: 160°, ●: 180°, △: 190°
a) 0.01 mole of I was employed in all reactions.
b) calculated on a basis of Ia

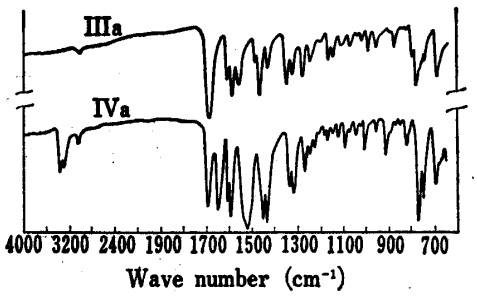
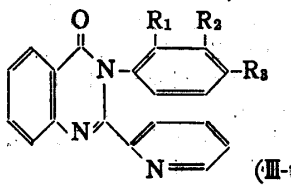


Fig. 2. Infrared Absorption Spectra (KBr)

Synthesis of 2-(2-Pyridyl)-3-substituted-4(3H)-quinazolinone Derivatives

Anthranilic acid was condensed with the thioanilides(II) in the presence of I_b, respectively. Table II lists the chemical properties of obtained 4(3H)-quinazolinone derivatives(III). Infrared (IR) spectrum(KBr) of III_a is compared with that of IV_a in Fig. 2. Both compounds show a characteristic absorption band at near 1680 cm^{-1} assignable to the carbonyl group at the C_4-position of 4(3H)-quinazolinone nucleus and the spectrum of IV_a an absorption band at near 3350 cm^{-1} attributable to the amino group of anthranilic acid forming the salt with III_a. All of the homologous series were observed in a similar manner as above.

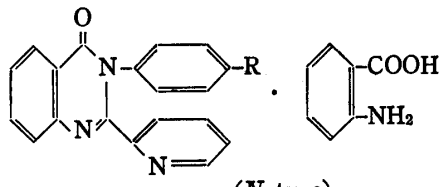
TABLE II



(III-type)

Compd. No.	R_1	R_2	R_3	mp (°C)	Appearance ( ): Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
IIIa	H	H	H	153	colourless amorphous (petr. benzine)	$C_{19}H_{13}ON_3$	76.25 (76.23)	4.35 (4.51)	14.05 (13.83)
IIId	H	H	CH_3	194	colourless prisms (petr. benzine)	$C_{20}H_{15}ON_3$	76.68 (76.91)	4.47 (4.83)	13.41 (13.00)
IIIf	H	H	OCH_3	212	colourless prisms (petr. benzine)	$C_{20}H_{15}O_2N_3$	72.95 (73.01)	4.26 (4.51)	12.77 (12.54)
IIIg	H	H	OC_2H_5	167	colourless prisms (petr. benzine)	$C_{21}H_{17}O_2N_3$	73.47 (73.51)	4.66 (5.02)	12.25 (11.88)
IIIh	H	H	$COOC_2H_5$	189.5	colourless needles (petr. benzine)	$C_{22}H_{17}O_3N_3$	71.15 (71.21)	4.58 (4.34)	11.32 (11.67)
IIIc	H	CH_3	H	133	colourless needles (petr. benzine)	$C_{20}H_{15}ON_3$	76.68 (76.64)	4.47 (4.72)	13.41 (13.39)
IIIb	CH_3	H	H	153	colourless needles (petr. benzine)	$C_{20}H_{15}ON_3$	76.68 (76.76)	4.47 (4.63)	13.41 (13.46)
IIIe	OCH_3	H	H	163	colourless needles (petr. benzine)	$C_{20}H_{15}O_2N_3$	72.95 (72.86)	4.26 (4.47)	12.77 (12.57)

TABLE III



(IV-type)

Compd. No.	R	mp (°C)	Apperarance ( ): Recryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	H	260	colourless needles (EtOH)	$C_{19}H_{13}ON_3 \cdot C_7H_7O_2N$	71.56	4.58	12.84	71.66	4.70	13.07
IVd	CH_3	243	colourless needles (EtOH)	$C_{20}H_{15}ON_3 \cdot C_7H_7O_2N$	72.00	5.00	12.44	72.11	5.07	12.66
IVf	OCH_3	260	colourless needles (EtOH)	$C_{20}H_{15}O_2N_3 \cdot C_7H_7O_2N$	70.17	4.72	12.01	69.90	5.01	11.91
IVg	OC_2H_5	236	colourless needles (EtOH)	$C_{21}H_{17}O_2N_3 \cdot C_7H_7O_2N$	70.00	5.00	11.67	70.21	5.30	11.50

Experimental

Most of products are listed in Table II and III.

2-(2-Pyridyl)-3-substituted-4(3H)-quinazolinones (III)——Method A: 0.02 moles of I_b were heated with a slight excess of the thioanilide (II) at 200° for 30 hr. After cooling, the reaction mixture was dissolved in 40 ml of $CHCl_3$ and then applied to the top of a column packed with 70 g of Al_2O_3 (300 mesh). At first, the product (III) was eluted with $CHCl_3$. The fraction eluted was evaporated to leave a syrup. Resulting solid after cooling was recrystallized from petr. benzine, giving colourless crystals (III) in about 20% yield.

MethodB: A mixture of 0.01 mole of I_a and 0.02 moles of II was heated with 0.01 mole of I_b at 190° for 10 hr. After the reaction had been completed, the reaction mixture was dissolved in 20 ml of $CHCl_3$ and then kept over night up at below 5°. Separated crystals (IV) were filtered off, the filtrate was applied to the same column as method A and the first fraction was eluted with $CHCl_3$. The residue obtained from the fraction by evaporation was recrystallized from petr. benzine, giving the product (III) in about 60 to 80% yield, which were identical with the earlier product on the melting point test admixed and comparison of IR spectrum, respectively (Table II). The anthranilates (IV) as above were selectively obtained from the reaction with thiopicolin-*p*-substituted-anilides (II_a, $_d$, $_f$, and $_g$) and were identical with the subsequent anthranilates of III by admixed melting point test and comparison of IR spectrum, respectively.

Anthranilates (IV) of III——A mixture of 0.02 moles of I_a and 0.01 mole of II was heated at 130—135° for 20 hr, during which period the mixture were once dissolved and began to sublimate gradually. Then, the reaction solution occured to make solid to nearly complete reaction. The resulting solid was treated with a small amount of $CHCl_3$ at a room temperature and then kept over night up at below 10°. Separated crystals were filtered by suction and recrystallized to give the product (IV) in about 20% yield (Table III).

Hydrolyses of Anthranilates (IV)——0.5 g of IV was heated with 50 ml of 5% NaOH in EtOH–H_2O (7 : 3) at 80° for 2 hr and then evaporated *in vacuo*. To the residue added cold water and resulting solid was filtered by suction. Recrystallization gave III in about 60% yield, respectively, which was identical with their corresponding quinazolones by admixed melting point test.

2,3-Diphenyl-4(3H)-quinazolinone (V)——A mixture of 0.01 mole of I_a and 0.02 moles of thiobenzanilide was heated with 0.01 mole of Ib at 190° for 10 hr. The mixture after reaction was dissolved in 20 ml of $CHCl_3$ and applied to the same column as method A, during which period behaved itself in the same manner as III. Recrystallization from petr. benzine gave colourless needles (2.5 g), mp 159° (lit.: 156—157°).[9] *Anal.* Calcd. for $C_{20}H_{14}ON_4$: C, 80.53; H, 4.69; N, 9.39. Found: C, 80.75; H, 4.81; N, 9.18.

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9) D.T. Zentmyer and E.C. Wagner, *J. Org. Chem.*, 14, 967 (1949).