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Studies on Organosulfur Compounds. XIV.[1] Sulfurations and Oxidations of 2,3-Disubstituted 4(3H)-Quinazolinones

Takuzo Hisano, Masataka Ichikawa, Keiji Muraoka, Yuko Yabuta, Yutaka Kido, and Motoo Shibata[2]

Faculty of Pharmaceutical Sciences, Kumamoto University[2]

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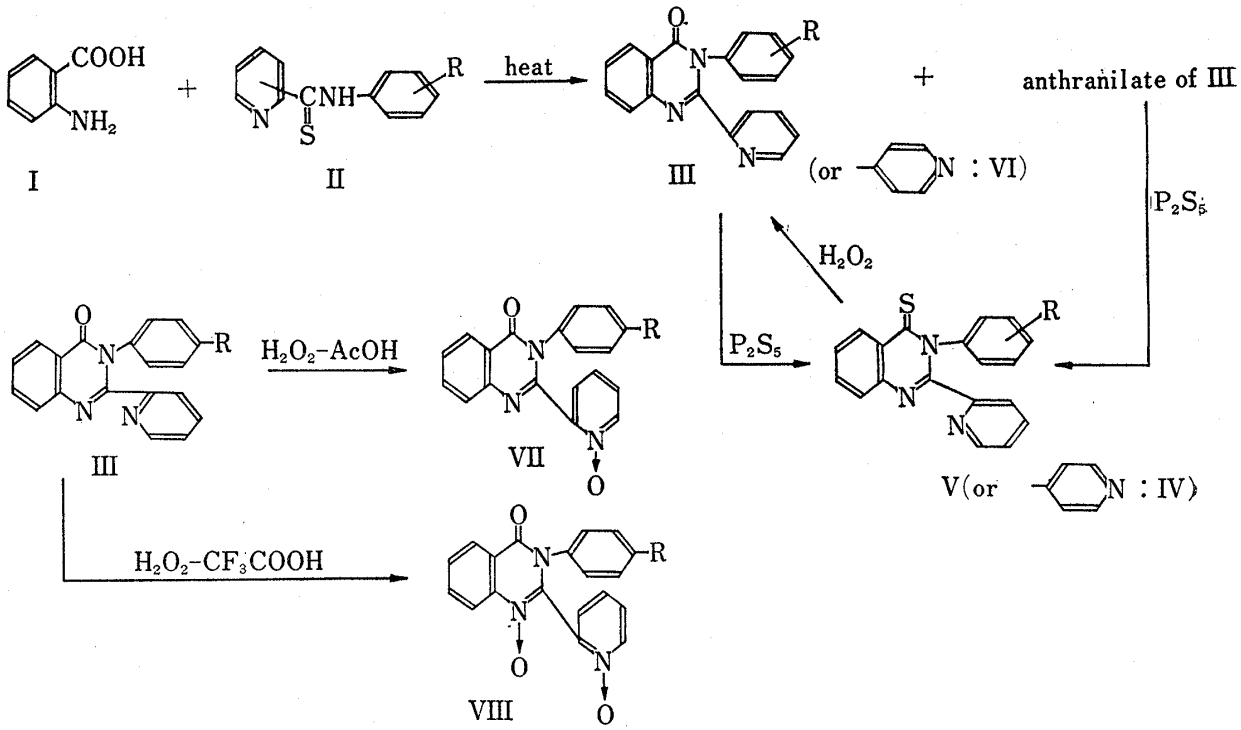
A series of 2-pyridyl-3-phenyl-4(3H)-quinazolinone and the anthranilate was reacted with phosphorus pentasulfide to give the corresponding 4(3H)-quinazolinethiones, which were oxidized with hydrogen peroxide to afford readily the above 4(3H)-quinazolinones. The hydrogen peroxide oxidation of them in trifluoroacetic acid gave the 1,1′-dioxide and that in acetic acid gave the 1′-oxide. The nuclear magnetic resonance spectra of oxidation products were compared. It was found that some 4(3H)-quinazolinethiones (Vc, VIa) were effective against several kinds of gram-positive bacteria, while exchange of the carbonyl group of 4(3H)-quinazolinone by thione resulted in a loss of action for central nervous system.

In the previous reports,[3] numerous 4(3H)-quinazolinones, particularly those with 2,3-disubstituents, have been prepared and evaluated for pharmacological activities. It was thereby demonstrated on the structure-activity relationship that 2-pyridyl and 4-pyridyl substitution at the 2-position of 4(3H)-quinazolinone ring are suitable for manifestation of hypnotic activity. Incidentally, Legrand[4] has reported that some of 4(3H)-quinazolinethiones possess hypnotic and antibacterial activities. It would be of interest that the 4(3H)-quinazolinones are compared with the corresponding 4(3H)-quinazolinethiones on pharmacological activities. The present paper deals with the synthesis of 2-pyridyl-3-substituted-phenyl-4(3H)-quinazolinethione derivatives and the reactivity of quinazolones for hydrogen peroxide oxidation. The 2-pyridyl-3-substituted-phenyl-4(3H)-quinazolinones (III and IV) prepared by methods already described[3] were fused with phosphorus pentasulfide at 180° to afford the corresponding 4(3H)-quinazolinethiones (V and VI) in 60 to 80% yield, while the 4(3H)-quinazolinones were reacted with phosphorus pentasulfide in xylene under refluxing to give the 4-thiones in a lower yield (50 to 55%). These products are listed in Table I.

As a rule, it is difficult to avoid the formation of anthranilates of the 4(3H)-quinazolinones during reaction arising from the employ of anthranilic acid in the quinazolinone synthesis[3a] as shown in Chart 1 and, moreover, the anthranilates are stable against hydrolysis. Therefore, we have attempted to find out such a way that is reached without the formation of such salt[3b] and to find out an utilization of the anthranilate formed. The sulfuration of anthranilates of 4(3H)-quinazolinones was thereupon carried out to react with phosphorus pentasulfide in xylene and the corresponding 4(3H)-quinazolinethiones were successfully obtained in about 50% yield. The structural assignment of this series was based on the satisfactory elemental analysis and the infrared (IR) spectrum (*e.g.*, a disappearance of the characteristic absorption band at near 1680 cm^{-1} assignable to the carbonyl group at the C_4-position of 4(3H)-quinazolinone nucleus.[3])

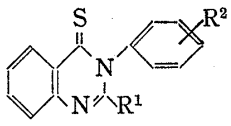
1) Part XIII: T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 1451 (1976).
2) Location: *Oe-honmachi, Kumamoto, 862, Japan.*
3) *a*) T. Hisano, T. Nishi, and M. Ichikawa, *Yakugaku Zasshi*, **92**, 582 (1972); *b*) T. Hisano, M. Ichikawa, G. Kito, and T. Nishi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2575 (1972); *c*) T. Hisano, M. Ichikawa, A. Nakagawa, and M. Tsuji, *Chem. Pharm. Bull.* (Tokyo), **23**, 1910 (1975).
4) M.L. Legrand, Fr. Patent 1451163 [*C. A.*, **66**, 115731 (1967)].



a : R=H, b : R=*o*-CH_3, c : R=*m*-CH_3, d : R=*p*-CH_3, e : R=*o*-OCH_3

Chart 1

TABLE I.



Compd. No.	R^1	R^2	mp[a] (°C)	Appearance[b]	Formula	Analysis (%) Calcd. (Found) C	H	N
Va	2-pyridyl	H	191—193	orange prisms	$C_{19}H_{13}N_3S$	72.36 (72.22)	4.15 (4.16)	13.32 (13.53)
Vb	2-pyridyl	*o*-CH_3	195—198	orange prisms	$C_{20}H_{15}N_3S$	72.92 (72.77)	4.59 (4.45)	12.76 (12.84)
Vc	2-pyridyl	*m*-CH_3	172—174	orange prisms		— (72.80)	— (4.63)	— (12.81)
Vd	2-pyridyl	*p*-CH_3	244—245	orange prisms		— (72.99)	— (4.55)	— (12.73)
VIa	4-pyridyl	H	175	orange prisms	$C_{19}H_{13}N_3S$	72.36 (71.99)	4.15 (4.14)	13.32 (12.97)
VIb	4-pyridyl	*o*-CH_3	168—170	orange prisms	$C_{20}H_{15}N_3S$	72.92 (73.06)	4.59 (4.43)	12.76 (12.83)
VIc	4-pyridyl	*m*-CH_3	170	orange needles		— (72.71)	— (4.42)	— (12.66)
VId	4-pyridyl	*p*-CH_3	188—190	orange prisms		— (73.20)	— (4.68)	— (12.57)
VIe	4-pyridyl	*o*-OCH_3	150	orange prisms	$C_{20}H_{15}ON_3S$	69.54 (69.52)	4.38 (4.49)	12.17 (12.25)

a) All melting points are uncorrected.
b) All compounds were recrystallized from EtOH.

On the other hand, the 4-thione compounds (V and VI) thus obtained were fairly readily oxidized by hydrogen peroxide in alkaline solution or in acetic acid to afford the 4(3H)-quinazolinones (III and IV). In this connection, the hydrogen peroxide oxidation of 2(2-pyridyl)-3-(*p*-tolyl)-4(3H)-quinazolinone (IIId) in trifluoroacetic acid was carried out and gave the di-oxide compound (VIIId), whose IR spectrum exhibited a characteristic absorption band at 1690 cm^{-1} assignable to the carbonyl group of 4(3H)-quinazolinone ring and at near 1250 cm^{-1} assignable to the N-oxide. Interestingly, the same oxidation of III in acetic acid gave the mono-oxide compounds (VII) similar to the IR spectrum of the above di-oxide. On the structural assignment as shown in Fig. 1, the nuclear magnetic resonance (NMR) spectrum of the di-oxide (VIIId) of 2-(2-pyridyl)-3-(*p*-tolyl)-4(3H)-quinazolinone was compared with its mono-oxide (VIId), referring to the NMR spectrum of 2-(2-pyridyl)-4-(*p*-tolyl)-4(3H)-quinazolinone (IIId). Namely, the mono-oxide showed one hydrogen peak as a doublet of doublets at τ: 1.84 attributable to a proton at the C_5-position of 4(3H)-quinazolinone nucleus[5] and the di-oxide twelve hydrogen peaks as complex multiplets at τ: 1.60—3.20, while that of 2-(2-pyridyl)-3-(*p*-tolyl)-4(3H)-quinazolinone produced a complex overlapping absorbance band at τ: 1.65—1.85 attributable to two hydrogens at the C_5-position of 4(3H)-quinazolinone nucleus and the α-position of 2-pyridyl group substituted in the second position of 4(3H)-quinazolinone ring. Katritzky, *et al.*[6] have reported that the absorbance band of α-proton of pyridine-N-oxide is shifted to a higher magnetic field as compared to that of pyridine nucleus, and we have also observed the similar shifts concerning β-substituted pyridine-N-oxides.[7] From these viewpoints, the NMR spectrum of the mono-oxide indicates that one hydrogen peak at the C_5-position of 4(3H)-quinazolinone nucleus appeared at τ: 1.84 as a doublet of doublets, because the absorbance band of the α-proton of 2-pyridyl group substituted in the second position of 4(3H)-quinazolinone ring was shifted to the higher field owing to the N-oxidation of the pyridyl substituent. The structure of the di-oxide is also assigned to the oxidation of nitrogen atom at the first position of the 4(3H)-quinazolinone nucleus and of the pyridyl substituent.

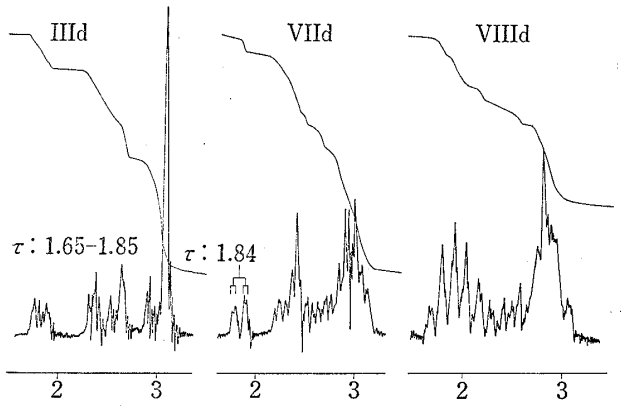


Fig. 1. NMR Spectra of IIId, VIId, and VIIId (60 Mc)

All of 4(3H)-quinazolinethiones did not show any activity for a central nervous system such as the 4(3H)-quinazolinone series,[3b,c] but 2-(2-pyridyl)-3-(*m*-tolyl)- (Vc) and 2-(4-pyridyl)-3-phenyl-4(3H)-quinazolinethione (VIa) were effective against several kinds of Gram-positive bacteria, the minimum growth-inhibitory concentrations on *Bacillus subtilis* and *cereus* cultivated in PW-agar medium at 37° for 24 hours and on *Penicillium chrysogenum* and *Saccharomyces cerevisiae* in Sabouraud medium were 100 μg/ml, respectively. It is suggested that there is a possibility that one or more members of this class of 4(3H)-quinazolinethiones will possess useful biologic properties.

Experimental

Most of all products are listed in Table I.

5) R.H. Bible, Jr., "Guide to the NMR Empirical Method, A Work Book," Plenum Press, New York, 1967 p. 22.
6) A.R. Katritzky and J.M. Langawski, *J. Chem. Soc.*, **1961**, 43.
7) T. Hisano, T. Matsuoka, and M. Ichikawa, *Org. Prep. Proc. Int.*, **6**, 243 (1974).

2-Pyridyl-3-substituted-phenyl-4(3H)-quinazolinethiones (V and VI)——1) A mixture of 0.005 mol of the 4(3H)-quinazolinone (III or IV) and 0.02 mol of P_2S_5 was heated at 180° for 4 hr. After the reaction was over, the reaction mixture was added to 8% NaOH aq. soln. and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with $NaHCO_3$ aq. soln. and H_2O, and then dried over anhyd. Na_2SO_4. After evaporation of $CHCl_3$, the residue was dissolved in a small amount of benzene and chromatographed over 30 g of Al_2O_3 (300 mesh). The product was eluted with benzene. The residue obtained from the first effluent fraction by evaporation was recrystallized, giving the product in 60—80% yield.

2) A suspension of 0.01 mol of the 4(3H)-quinazolinone (or anthranilate) and 0.02 mol of P_2S_5 in 30 ml of dry xylene was refluxed for 4 hr in an oil bath. After the reaction was over, the solvent was evaporated *in vacuo*. The residue was extracted with 200 ml of $CHCl_3$ and the $CHCl_3$ layer was washed with $NaHCO_3$ aq. soln. and H_2O, and then dried over anhyd. Na_2SO_4. After evaporation, the residue was chromatographed over and purified in the same manner as above, giving the product in 50—55% yield.

Oxidation of 2-Pyridyl-3-substituted-phenyl-4(3H)-quinazolinethiones with H_2O_2——1) To a solution of 0.001 mol of the 4(3H)-quinazolinethione in a mixture of 70 ml of EtOH and 20 ml of 0.2 N KOH, 10 ml of 3% H_2O_2 was added dropwise at room temperature and stirred for 30 min. After evaporation of EtOH *in vacuo*, the separated crystals were collected by suction and recrystallized to give the corresponding 4(3H)-quinazolinone in 80% yield, which was identical with the authentic sample[3] in all respects.

2) 1 g of the 4(3H)-quinazolinethione was added to a mixture of 0.95 ml of 30% H_2O_2 and 47 ml of CF_3COOH (or AcOH) at room temperature and the reaction mixture was occasionally shaked for 10 min. After the reaction was over, a small amount of H_2O was added to the reaction solution and then concentrated *in vacuo*. The residue was made alkaline with $NaHCO_3$ aq. soln. and then extracted with $CHCl_3$. After evaporation of $CHCl_3$, the residue was purified in the same manner as above to give the 4(3H)-quinazolinone in 60% yield.

N-Oxidation of 2-(2-Pyridyl)-3-(*p*-tolyl)-4(3H)-quinazolinone (IIId)——1) The 1,1′-Dioxide (VIIId): To a solution of 2 g (0.0063 mol) of IIId in 9.4 ml of CF_3COOH, 2.12 ml (0.019 mol) of 30% H_2O_2 was added at room temperature and then heated at 70° for 1 hr. After cooling, a small amount of H_2O was added to the reaction solution and concentrated *in vacuo*. The residue was made alkaline with $NaHCO_3$ aq. soln. and then extracted with $CHCl_3$. After evaporation of $CHCl_3$, the residue was dissolved in a small portion of $CHCl_3$ and applied to the top of a column packed with 25 g of Al_2O_3 (200 mesh), benzene being used as eluent. From the second eluted fraction, a colorless crystalline mass was obtained. Recrystallization from $(CH_3)_2CO$ gave colorless needles (VIIId), mp 255° (decomp.), in 20% yield. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O), 1249 (N→O). NMR [in $(CD_3)_2SO$, 60 Mc] τ: 7.81 (3H, s, $-CH_3$), 1.60—3.20 (12H, m). *Anal.* Calcd. for $C_{20}H_{15}O_3N_3$: C, 69.55; H, 4.38; N, 12.17. Found: C, 69.60; H, 4.42; N, 12.00.

2) The 1′-Oxides (VIIa, d): To a solution of 1 g (0.0031 mol) of IIId in 4.7 ml of AcOH, 0.5 ml of 30% H_2O_2 was added and then heated at 70° for 30 min. Additionally, 0.26 ml of 30% H_2O_2 was added and further heated at 70° for 6 hr. After cooling, a small amount of H_2O was added to the reaction solution and concentrated *in vacuo*. The residue was neutralized with 7% $NaHCO_3$ aq. soln. and extracted with dichloromethane. After evaporation of dichloromethane, the residue was recrystallized from $(CH_3)_2CO$, giving VIId (mp 223—225°) as colorless prisms in 34% yield. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O), 1269 (N→O). NMR (in $CDCl_3$, 60 Mc) τ: 7.77 (3H, s, $-CH_3$), 1.84 [1H, d-d broad, J=6.2 Hz, 4(3H)-quinazolinone C_5-H]. *Anal.* Calcd. for $C_{20}H_{15}O_2N_3$: C, 72.93; H, 4.59; N, 12.76. Found: C, 72.73; H, 4.73; N, 12.47.

2-(2-Pyridyl)-3-phenyl-4(3H)-quinazolinone (IIIa) was oxidized in the same manner as above to give the corresponding 1′-oxide (VIIa), mp 219—220°, as colorless prisms [$(CH_3)_2CO$] in 30% yield. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O), 1247 (N→O). NMR (in $CDCl_3$, 60 Mc) τ: 2.10—3.36 (12H, m), 1.87 [1H, d-d, J=6.2 Hz, 4(3H)-quinazolinone C_5-H].

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