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Synthesis of 3,3′-Biquinazoline-4,4′-diones and 1,3,4-Oxadiazoles from Isatoic Anhydride

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Treatment of isatoic anhydrides with hydrazine hydrate gave 1,2-bis-(*o*-aminobenzoyl)-hydrazines (IIa—c). The reaction of IIa, b with ethoxymethylenemalononitrile, ethyl ethoxymethylenecyanoacetate or triethyl orthoformate afforded new 3,3′-bisquinazoline-4,4′-diones (IIIa, b and IVa—d) in good yields. On the other hand, the reaction of IIa—c with polyphosphoric acid furnished 2,5-diaryl-1,3,4-oxadiazole derivatives in high yields.

Keywords——3,3′-biquinazoline-4,4-diones; 1,3,4-oxadiazoles; isatoic anhydride; hydrazine hydrate; ethoxymethylenemalononitrile; triethyl orthoformate; polyphosphoric acid

Owing to the interesting antimalarial,[2] antibacterial[3] and antiviral[4] activities displayed by the certain derivatives of 3,4-dihydro-4-oxoquinazoline, the syntheses of this series have extensively been studied.[5] Recent paper[6] from our laboratory described a new synthesis of 3,4-dihydro-4-oxoquinazoline derivatives by the reaction of 2-aminobenzamides with ethoxymethylenemalononitrile (EMMN) or ethyl ethoxymethylenecyanoacetate (EMCA). As a continuing program on the synthesis of 3,4-dihydro-4-oxoquinazoline derivatives, we report here the synthesis of a new dimeric derivatives of 3,4-dihydro-4-oxoquinazolines, 3,3′-biquinazoline-4,4′-diones, which is of particular interest because of its potential physiological activity due to the 3,4-dihydro-4-oxoquinazoline structure.

It has been well established that isatoic anhydride (Ia) react with various amines to give the corresponding *o*-aminobenzamide derivatives,[7] however, the reaction of Ia with hydrazine hydrate has not previously been reported. When Ia was treated with hydrazine hydrate (molar ratio 1: 1), a small amounts of 1,2-bis-(*o*-aminobenzoyl)hydrazine (IIa) was obtained instead of the expected *o*-aminobenzhydrazide, while the reaction of Ia with hydrazine hydrate (mole ratio 1: 2) afforded IIa in 48% yield. The structure of IIa was established by its satisfactory spectral data and elemental analysis. In particular, the infrared (IR) spectrum revealed the amino absorption bands at 3280, 3380, 3420 and 3480 cm^{-1} and the carboxamide absorption bands at 1640 and 1660 cm^{-1}. This reaction was equally applicable to other isatoic anhydrides. Namely, the reaction of 5-chloroisatoic anhydride (Ib) and N-methylisatoic anhydride (Ic) with two moles of hydrazine hydrate gave the corresponding 1,2-bis-(*o*-aminobenzoyl)hydrazine derivatives (IIb and IIc) in good yields, respectively.

The bis-*o*-aminobenzamide compounds (IIa—c) prepared were found to be the versatile synthetic intermediate for the preparation of [3,3′-biquinazoline]-4,4′-diones. For example, the reaction of IIa with two moles of EMMN or EMCA under the similar conditions described in

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[1] Location: *Shirokane 5-9-1, Minato-ku, Tokyo, 108, Japan.*
[2] R.I. Hewitt, W.S. Wallace, E.R. Gill, and J.H. Williams, *Am. J. Trop. Med. Hyg.*, **1**, 768 (1952).
[3] *a*) D. Libermann and F. Boyer, *Compt. Rend.*, **227**, 377 (1948); *b*) D. Libermann, U.S. Patent 2522831 (1950) [*C.A.*, **45**, 312 (1951)].
[4] L. Weinstein, T.W. Chang, and J.B. Hudson, *Antibiot. Chemotherapy*, **7**, 443 (1957).
[5] W.L.F. Armarego, "The Chemistry of Heterocyclic Compounds, Fused Pyrimidines: Part I, Quinazolines" (Ed. D.J. Brown), John Wiley and Sons, 1967, p. 87 and p. 490.
[6] K. Nagahara, K. Takagi, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1310 (1976).
[7] *a*) R. Staiger and E. Miller, *J. Org. Chem.*, **24**, 1214 (1956); *b*) R. Clark and E. Wagner, *ibid.*, **9**, 55 (1944); *c*) R. Staiger and E. Wagner, *ibid.*, **18**, 1427 (1953).

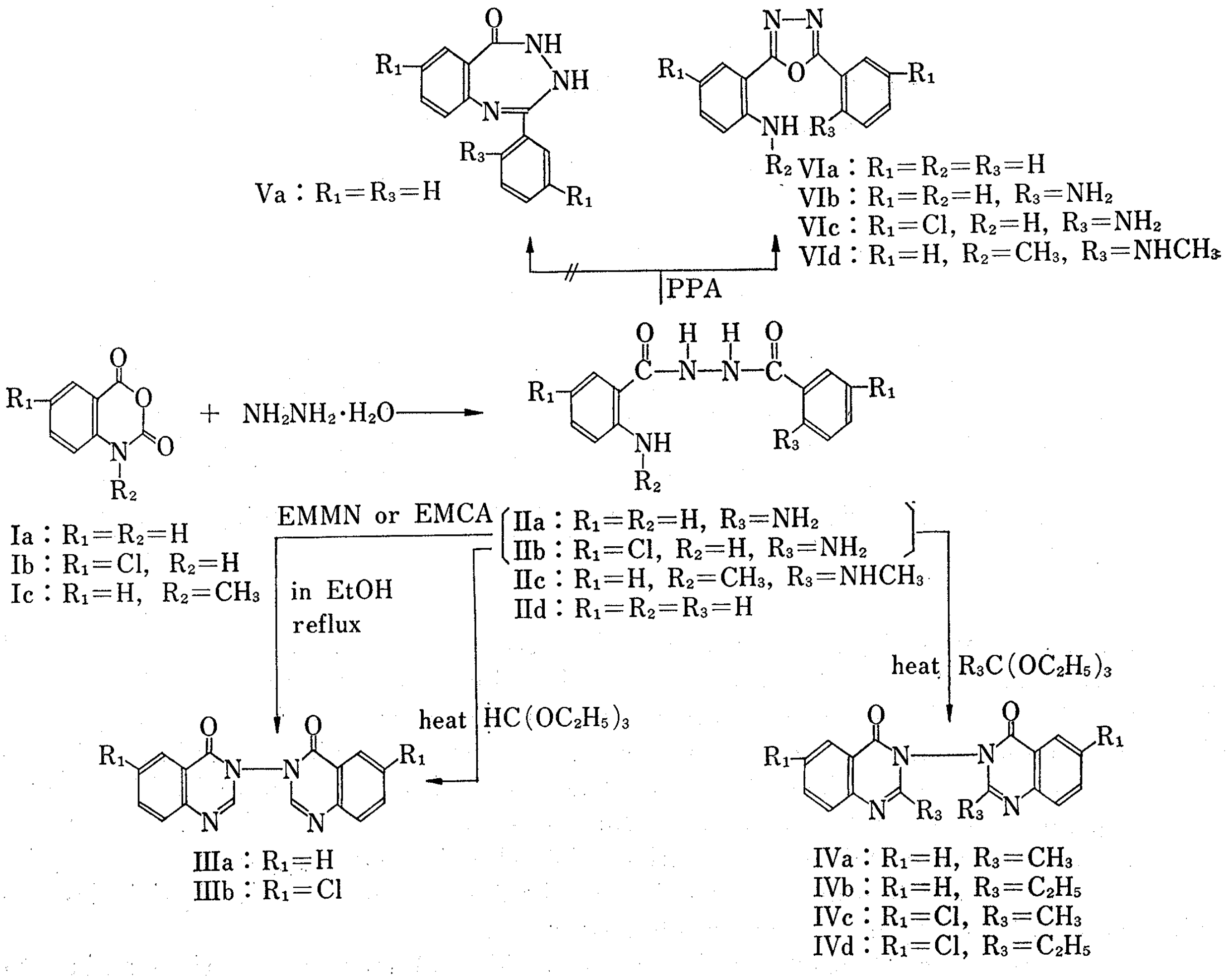


Chart 1

the preceding paper[6] gave 3,3'-biquinazoline-4,4'-dione (IIIa) in 41 and 25% yield, respectively. The structures of IIIa was assigned by its IR spectrum (1695 and 1710 cm^{-1} (C=O) and 1605 cm^{-1} (C=N)) and mass spectrum (*m/e* 290), and confirmed by the satisfactory elemental analysis. Similarly, the treatment of IIb with EMMN or EMCA afforded the corresponding 3,3'-biquinazoline-6,6'-dichloro-4,4'-dione (IIIb). In contrast with the above results, the compound (IIc) did not react with these reagents and the starting material being recovered.

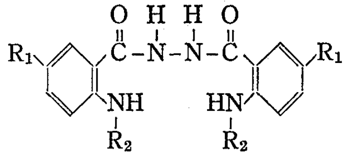
The cyclization of IIa, b to IIIa, b was also achieved on using ortho esters as one carbon reagents. Thus the reaction of IIa with excess triethyl orthoformate at 150° for 10 hr gave

Table I. Infrared Spectral Data

Product	IR $\nu_{\max}^{\text{KBr}}$ (cm^{-1})			
	$\nu_{\text{N-H}}$	ν_{CONH}	$\nu_{\text{C=O}}$	$\nu_{\text{C=N}}$
IIa	3480, 3420, 3380, 3280	1660, 1640	—	—
IIb	3480, 3360, 3300	1660, 1630	—	—
IIc	3360, 3300	1660, 1630	—	—
IIIa	—	—	1710, 1695	1605
IIIb	—	—	1710, 1695	1610
IVa	—	—	1710, 1695	1620sh, 1605
IVb	—	—	1710, 1695	1610sh, 1600
IVc	—	—	1710, 1690	1610
IVd	—	—	1705, 1695	1610

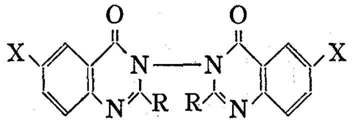
IIIa in 48% yield. Similarly, the reaction of IIa with triethyl orthoacetate and triethyl orthopropionate gave the corresponding 2,2′-dialkyl-3,3′-biquinazoline-4,4′-diones (IVa, b) in good yields, respectively. Moreover, the reaction of IIb with triethyl orthoacetate and triethyl orthopropionate under the similar conditions afforded the corresponding 2,2′-dialkyl-3,3′-biquinazoline-6,6′-dichloro-4,4′-diones (IVc, d) in high yields, respectively.

Table II. 1,2-Bis-(*o*-aminobenzoyl)hydrazines



No.	R_1	R_2	mp (°C)	Recryst. solvent	Appearance	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Mass (M^+)
IIa	H	H	203—205	DMF+H_2O	Powders	48	$C_{14}H_{14}N_4O_2$	62.22 (62.22)	5.22 (5.24)	20.74 (20.80)	270
IIb	Cl	H	252—253	DMF+H_2O	Powders	44	$C_{14}H_{12}Cl_2N_4O_2$	49.58 (49.79)	3.57 (3.60)	16.52 (16.75)	338, 340
IIc	H	CH_3	187—189	DMF+H_2O	Needles	73	$C_{16}H_{18}N_4O_2$	64.41 (64.54)	6.08 (6.12)	18.78 (18.94)	298

Table III. 3,3′-Biquinazoline-4,4′-diones



No.	X	R	Method[a]	Reaction Condition Temp. (°C)	Time (hr)	Yield (%)	Mass (M^+)	mp (°C)
IIIa	H	H	A	100 (in EtOH)	6	41	290	293—295
			B	100 (in EtOH)	6	25		
			C	150	10	48		
IIIb	Cl	H	A	100 (in EtOH)	6	42	359, 361	$>$300
			B	100 (in EtOH)	6	50		
			C	150	10	49		
IVa	H	CH_3		160—170	6.5	88	318	195—196
IVb	H	C_2H_5		160—170	11	83	346	226—227
IVc	Cl	CH_3		160—170	6.5	61	386, 388	264—266
IVd	Cl	C_2H_5		160—170	11	77	414, 416	237—238

No.	Recryst. solvent	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	EtOH	Needles	$C_{16}H_{10}N_4O_2$	66.20	3.47	19.30	66.22	3.51	19.57
IIIb	DMF	Powders	$C_{16}H_8Cl_2N_4O_2$	53.50	2.25	15.60	53.72	2.51	15.82
IVa	EtOH	Plates	$C_{18}H_{14}N_4O_2$	67.91	4.43	17.60	67.81	4.45	17.71
IVb	DMF	Powders	$C_{20}H_{18}N_4O_2$	69.35	5.24	16.18	69.08	5.27	16.14
IVc	DMF	Powders	$C_{18}H_{12}Cl_2N_4O_2$	55.83	3.12	14.47	55.93	3.17	14.45
IVd	DMF	Powders	$C_{20}H_{16}Cl_2N_4O_2$	57.84	3.88	13.49	57.97	3.89	13.39

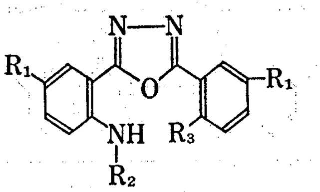
[a] See Experimental.

As described above, it was found that 3,3′-biquinazoline-4,4′-diones could be synthesized by the cyclization of 1,2-bis-(*o*-aminobenzoyl)hydrazines with the respective one carbon reagent, either EMMN and EMCA or ortho esters. Among them, the latter method seems to be quite general since the selection of appropriate ortho esters allows one to introduce practically any group into the 2-position of 3,3′-biquinazoline-4,4′-dione system as in the cases of IVa—d.

In addition to the synthesis of 3,3′-biquinazoline-4,4′-diones, we also investigated the reaction of bis-*o*-aminobenzamides with polyphosphoric acid (PPA) leading to 1,3,4-oxadiazole derivatives. Treatment of IIa with PPA at 150° for 1 hr afforded 2,5-di(2-aminophenyl)-1,3,4-oxadiazole (VIb). The structure of VIb was established by its satisfactory spectral data and elemental analysis. Langis[8] reported that the reaction of IId with PPA under the same conditions gave triazepine Va which has the same melting point with that of VIa, however, the absence of amide carbonyl absorption band in the IR spectra of VIa indicate that the reaction product obtained by Langis[8] is not triazepine Va, but VIa. In connection with the formation of 1,3,4-oxadiazoles, a similar reaction has been reported by Takahashi, *et al.*[9] in the reaction of 1-(*o*-aminobenzoyl)-2-(2-pyridinecarbonyl)hydrazine with PPA to give 2-(*o*-aminophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole. Additional 1,3,4-oxadiazole derivatives (VIb—d) were also prepared by the reaction of the corresponding 1,2-bis-*o*-aminobenzamides with PPA under the same conditions (Table IV).

The pharmacological evaluations of 3,3′-biquinazoline-4,4′-diones and 1,3,4-oxadiazoles prepared will be covered in a separate communication.

TABLE IV. 2,5-Diaryl-1,3,4-oxadiazoles



No.	R_1	R_2	R_3	mp (°C)	Appearance	Recryst. solvt.	Yield (%)
VIa	H	H	H	167—168[a]	Needles	EtOH	48
VIb	H	H	NH_2	229—231	Needles	$DMF+H_2O$	45
VIc	Cl	H	NH_2	259—260	Powders	EtOH	47
VId	H	CH_3	$NHCH_3$	241—242	Powders	$MeOH+CHCl_3$	69

No.	IR ν_{max}^{KBr} (cm^{-1}) N-H	IR ν_{max}^{KBr} (cm^{-1}) C=N	Formula	Analyses (%) Calcd. (Found) C	H	N
VIa	3440, 3320	1630, 1610	$C_{14}H_{11}N_3O$	70.87 (70.72)	4.67 (4.66)	17.71 (17.74)
VIb	3450, 3380, 3350	1640, 1620, 1610	$C_{14}H_{12}N_4O$	66.65 (66.71)	4.79 (4.79)	22.21 (22.50)
VIc	3460, 3400, 3360	1610, 1600	$C_{14}H_{10}Cl_2N_4O$	52.35 (52.20)	3.14 (3.14)	17.45 (17.51)
VId	3340	1620, 1590	$C_{16}H_{16}N_4O$	68.55 (68.84)	5.75 (5.66)	19.99 (20.14)

a) Lit.,[8] 168—169°.

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8) A.L. Langis, U.S. Patent 3542767 (1970) [*C.A.*, **74**, 88089 (1971)].

9) M. Takahashi, S. Onizawa, and T. Satoh, *Bull. Chem. Soc. Jpn.*, **47**, 2724 (1974).

Experimental[10]

1,2-Bis-(*o*-aminobenzoyl)hydrazines (IIa—c). General Procedure (see Table II)——To a solution of 0.1 mol of isatoic anhydride derivatives (Ia—c) in 80 ml of abs. EtOH or pyridine was added 0.06 mol of hydrazine hydrate and the mixture was refluxed. After cooling, the reaction mixture was evaporated, and the residue was solidified by the addition of H_2O. The precipitates were filtered, washed with H_2O, and recrystallized from a mixture of dimethylformamide (DMF) and water to give the corresponding 1,2-bis-(*o*-aminobenzoyl)-hydrazines (IIa—c).

3,3′-Biquinazoline-4,4′-diones (IIIa, b and IVa—d). General Procedures (see Table III)——Method A: To a solution of 0.0019 mol of 1,2-bis-(*o*-aminobenzoyl)hydrazines (IIa, b) in 20 ml of EtOH was added 0.0038 mol of EMMN and the mixture was refluxed. After cooling, the separated crystals were collected and recrystallized from proper solvent to give the corresponding 3,3′-biquinazoline-4,4′-diones (IIIa, b).

Method B (see Table III): To a solution of 0.0019 mol of IIa, b in 20 ml of EtOH was added 0.0038 mol of EMCA and the mixture was refluxed. After cooling, the reaction mixture was treated as described in the Method A to give IIIa, b.

Method C (see Table III): A mixture of 0.0037 mol of IIa, b and 17 ml of triethyl orthoformate was heated at 150°. After cooling, the precipitates were filtered, and recrystallized from proper solvent to give the corresponding 3,3′-biquinazoline-4,4′-diones (IIIa, b and IVa—d).

2,5-Diaryl-1,3,4-oxadiazoles (VIa—d). General Procedure (see Table IV)——A mixture of 5 g of IIa—d and 25 g of polyphosphoric acid was heated at 150—160° with gentle stirring for 1 hr. After cooling, the mixture was stirred into 100 ml of water, and the resulting precipitates were filtered off by suction. The filtrate was made alkaline with aqueous K_2CO_3 to give additional precipitates. The combined precipitates were washed with a small amount of H_2O to give the corresponding 2,5-diaryl-1,3,4-oxadiazoles (VIa—d).

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[10] All melting points are uncorrected. The IR spectra were recorded on a Japan Spectroscopic Model IRA-1 spectrometer. MS were obtained on a JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.).