

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

KATSUHIKO NAGAHARA and ATSUSHI TAKADA

*School of Pharmaceutical Science, Kitasato University<sup>1)</sup>*

(Received March 2, 1977)

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,<sup>2)</sup> antibacterial<sup>3)</sup> and antiviral<sup>4)</sup> activities displayed by the certain derivatives of 3,4-dihydro-4-oxoquinazoline, the syntheses of this series have extensively been studied.<sup>5)</sup> Recent paper<sup>6)</sup> 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,<sup>7)</sup> 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<sup>-1</sup> and the carboxamide absorption bands at 1640 and 1660 cm<sup>-1</sup>. 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

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).

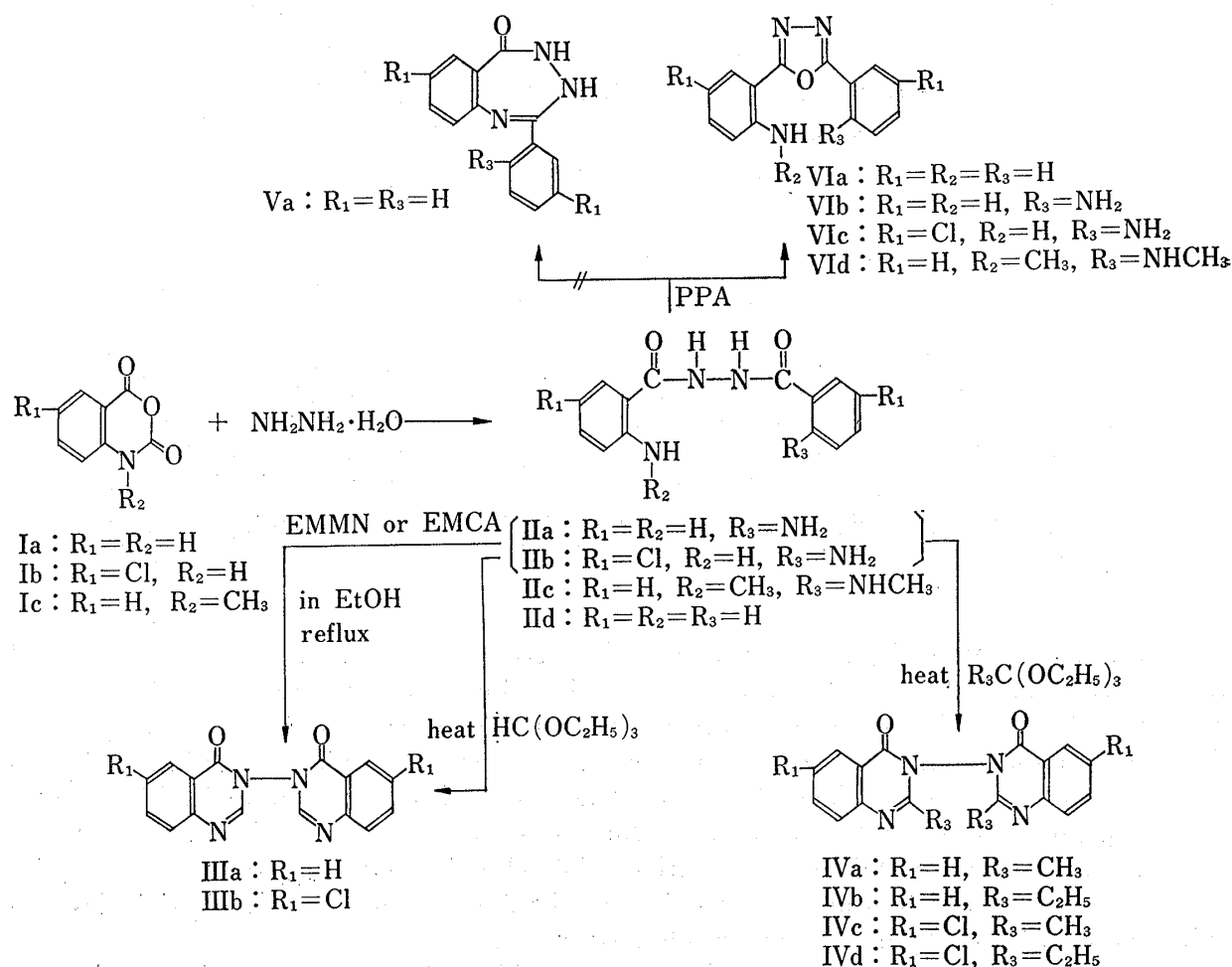


Chart 1

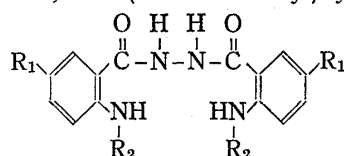
the preceding paper<sup>6</sup>) gave 3,3'-biquinazoline-4,4'-dione (IIIa) in 41 and 25% yield, respectively. The structure of IIIa was assigned by its IR spectrum (1695 and 1710  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ) and 1605  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ )) and mass spectrum ( $m/e$  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

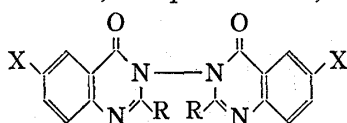
| Product | IR $\nu_{\text{max}}^{\text{KBr}}$ ( $\text{cm}^{-1}$ ) |                     |                    |                    |
|---------|---------------------------------------------------------|---------------------|--------------------|--------------------|
|         | $\nu_{\text{N-H}}$                                      | $\nu_{\text{CONH}}$ | $\nu_{\text{C=O}}$ | $\nu_{\text{C=N}}$ |
| 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 <sub>1</sub> | R <sub>2</sub>  | mp<br>(°C) | Recryst.<br>solvent  | Appearance | Yield<br>(%) | Formula                                                                       | Analysis (%)      |                |                  | Mass<br>(M <sup>+</sup> ) |
|-----|----------------|-----------------|------------|----------------------|------------|--------------|-------------------------------------------------------------------------------|-------------------|----------------|------------------|---------------------------|
|     |                |                 |            |                      |            |              |                                                                               | Calcd.<br>(Found) | C              | H                | N                         |
| IIa | H              | H               | 203—205    | DMF+H <sub>2</sub> O | Powders    | 48           | C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>                 | 62.22<br>(62.22)  | 5.22<br>(5.24) | 20.74<br>(20.80) | 270                       |
| IIb | Cl             | H               | 252—253    | DMF+H <sub>2</sub> O | Powders    | 44           | C <sub>14</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> | 49.58<br>(49.79)  | 3.57<br>(3.60) | 16.52<br>(16.75) | 338, 340                  |
| IIc | H              | CH <sub>3</sub> | 187—189    | DMF+H <sub>2</sub> O | Needles    | 73           | C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>                 | 64.41<br>(64.54)  | 6.08<br>(6.12) | 18.78<br>(18.94) | 298                       |

TABLE III. 3,3'-Biquinazoline-4,4'-diones



| No.  | X  | R                             | Method <sup>a)</sup> | Reaction Condition |           | Yield<br>(%) | Mass<br>(M <sup>+</sup> ) | mp<br>(°C) |
|------|----|-------------------------------|----------------------|--------------------|-----------|--------------|---------------------------|------------|
|      |    |                               |                      | Temp. (°C)         | Time (hr) |              |                           |            |
| 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 <sub>3</sub>               |                      | 160—170            | 6.5       | 88           | 318                       | 195—196    |
| IVb  | H  | C <sub>2</sub> H <sub>5</sub> |                      | 160—170            | 11        | 83           | 346                       | 226—227    |
| IVc  | Cl | CH <sub>3</sub>               |                      | 160—170            | 6.5       | 61           | 386, 388                  | 264—266    |
| IVd  | Cl | C <sub>2</sub> H <sub>5</sub> |                      | 160—170            | 11        | 77           | 414, 416                  | 237—238    |

| No.  | Recryst.<br>solvent | Appearance | Formula                                                                       | Analysis (%) |      |       |       |      |       |
|------|---------------------|------------|-------------------------------------------------------------------------------|--------------|------|-------|-------|------|-------|
|      |                     |            |                                                                               | Calcd.       |      |       | Found |      |       |
|      |                     |            |                                                                               | C            | H    | N     | C     | H    | N     |
| IIIa | EtOH                | Needles    | C <sub>16</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub>                 | 66.20        | 3.47 | 19.30 | 66.22 | 3.51 | 19.57 |
| IIIb | DMF                 | Powders    | C <sub>16</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub>  | 53.50        | 2.25 | 15.60 | 53.72 | 2.51 | 15.82 |
| IVa  | EtOH                | Plates     | C <sub>18</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>                 | 67.91        | 4.43 | 17.60 | 67.81 | 4.45 | 17.71 |
| IVb  | DMF                 | Powders    | C <sub>20</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>                 | 69.35        | 5.24 | 16.18 | 69.08 | 5.27 | 16.14 |
| IVc  | DMF                 | Powders    | C <sub>18</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> | 55.83        | 3.12 | 14.47 | 55.93 | 3.17 | 14.45 |
| IVd  | DMF                 | Powders    | C <sub>20</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> | 57.84        | 3.88 | 13.49 | 57.97 | 3.89 | 13.39 |

<sup>a)</sup> 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<sup>8)</sup> reported that the reaction of IIc 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<sup>8)</sup> 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.*<sup>9)</sup> 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 <sub>1</sub> | R <sub>2</sub>  | R <sub>3</sub>    | mp<br>(°C)            | Appearance | Recryst.<br>solvt.     | Yield<br>(%) |
|-----|----------------|-----------------|-------------------|-----------------------|------------|------------------------|--------------|
| VIa | H              | H               | H                 | 167—168 <sup>a)</sup> | Needles    | EtOH                   | 48           |
| VIb | H              | H               | NH <sub>2</sub>   | 229—231               | Needles    | DMF+H <sub>2</sub> O   | 45           |
| VIc | Cl             | H               | NH <sub>2</sub>   | 259—260               | Powders    | EtOH                   | 47           |
| VIc | H              | CH <sub>3</sub> | NHCH <sub>3</sub> | 241—242               | Powders    | MeOH+CHCl <sub>3</sub> | 69           |

| No. | IR $\nu_{\text{max}}^{\text{KBr}}$ (cm <sup>-1</sup> ) |     | Formula | Analyses (%)      |   |   |
|-----|--------------------------------------------------------|-----|---------|-------------------|---|---|
|     | N—H                                                    | C=N |         | Calcd.<br>(Found) | C | H |

|     |                  |                  |                                                                  |                  |                |                  |
|-----|------------------|------------------|------------------------------------------------------------------|------------------|----------------|------------------|
| VIa | 3440, 3320       | 1630, 1610       | C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O                 | 70.87<br>(70.72) | 4.67<br>(4.66) | 17.71<br>(17.74) |
| VIb | 3450, 3380, 3350 | 1640, 1620, 1610 | C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O                 | 66.65<br>(66.71) | 4.79<br>(4.79) | 22.21<br>(22.50) |
| VIc | 3460, 3400, 3360 | 1610, 1600       | C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>4</sub> O | 52.35<br>(52.20) | 3.14<br>(3.14) | 17.45<br>(17.51) |
| VIc | 3340             | 1620, 1590       | C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> O                 | 68.55<br>(68.84) | 5.75<br>(5.66) | 19.99<br>(20.14) |

<sup>a)</sup> Lit.,<sup>8)</sup> 168—169°.

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<sup>10)</sup>

**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<sub>2</sub>O. The precipitates were filtered, washed with H<sub>2</sub>O, 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<sub>2</sub>CO<sub>3</sub> to give additional precipitates. The combined precipitates were washed with a small amount of H<sub>2</sub>O to give the corresponding 2,5-diaryl-1,3,4-oxadiazoles (VIa—d).

**Acknowledgement** We wish to thank Misses. N. Fushiki and Y. Kobayashi, the students of Kitasato University, for their skilled technical assistance, and also Dr. M. Takahashi of Ibaraki University for helpful suggestions.

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.).