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STUDIES ON THE SYNTHESIS OF QUINOLINE COMPOUNDS. I.

Syntheses of 3,3′-Dicarboxy-1,1′-diethyl-4,4′-dioxo-1,1′-,4,4′-tetrahydrobiquinolines

by

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SYNOPSIS

The synthesis of 3, 3′-dicarboxy-1, 1′-diethyl-4, 4′-dioxo-1, 1′, 4, 4′-tetrahydrobiquinolines and related compounds is described. Several diaminobiphenyls were condensed with 2 molar of diethyl ethoxymethylenemalonate to give bis[2, 2-di(ethoxycarbonyl)-vinylamino]biphenyls in high yield. The products were subjected to thermal cyclization at 260°C, and di(ethoxycarbonyl)dihydroxybiquinolines were obtained also in good yield. Subsequent hydrolysis of ethoxycarbonyl group and N-alkylation resulted in the desired product.

1. INTRODUCTION

Oxolinic acid[1], nalidixic acid[2], and pyromidic acid[3] are the well known antibacterials for Gram negative bacteria. These compounds contain a common 3-carboxy-1-ethyl-4-oxo-1,4-dihydropyridine moiety in their molecule. In order to improve the antibacterial capacity of this type of compounds, we started the synthesis of poly-cyclic heteroaromatics containing this part. In this paper, we wish to describe the synthesis of 3,3′-dicarboxy-1, 1′-diethyl-4,4′-dioxo-1,1′,4,4′-tetrahydrobiquinolines, in which two of the structure mentioned was connected by carbon or hetero-atoms.

2. RESULTS AND DISCUSSIONS

The Gould-Jacobs reaction[4] was employed as the ring formation method, which consists of the condensation of aromatic amines with diethyl ethoxymethylenemalonate (EMME) followed by a thermal cyclization of the resulted arylaminomethylenemalonate losing ethanol. Thus, we chose diaminobiphenyls (1) as the starting material (Fig. 1).

Condensation of several aromatic diamines (1) with 2 molar of diethyl ethoxymethylenemalonate was performed in refluxing methanol to give bis(enaminomalonate) (2) in high yield (61–95%) after recrystalization. A marked difference in the reaction time was observed depending on the structure of 1. Thus, dienamine formation of 1d was complete in 5 min, though 5 h's heating was required for others to avoid the generation of monoenamine. Preference of enamine form was presented by NMR Spectra of 2 which showed a NH signal as a doublet, coupled with an adjacent olefinic proton. The double cyclization

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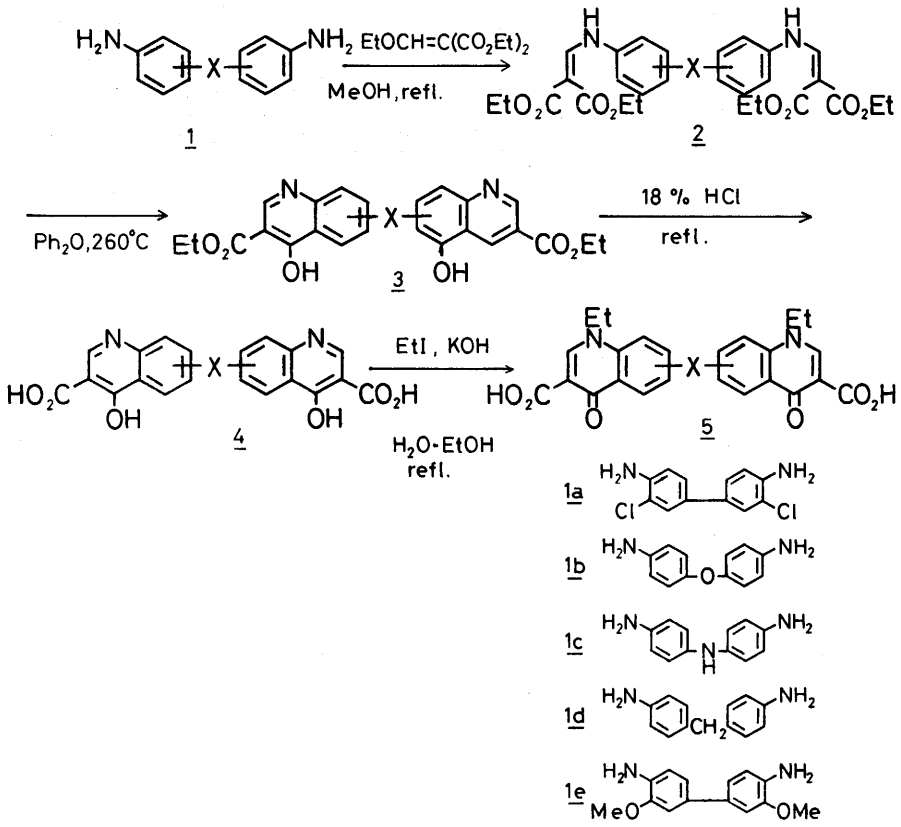

Fig. 1 The syntheses of biquinolines and related compounds.

of 2 was effected by heating in diphenyl ether at 260°C, and high yield (81–99%) of biquinolines (3) were obtained. In general, the reaction was finished in 1 h. The ring formation of 2e, however, was relatively slow and it took 5 h for the completion. These tetracyclic heteroaromatics were quite insoluble to various organic solvents and often the recrystalization was a troublesome procedure. Next, 3 was treated with 18% hydrochloric acid at refluxing temperature for 1.5–2 h and diacid (4) was isolated in 45–93% yield. Finally, ethylation on nitrogen atom was performed by treating 4 and ethyl iodide using potassium hydroxide as the base at 75°C in ethanol-water.

The heteroaromatics (5a–e) prepared in the present study were tested for antimicrobial activities against several microorganism. No significant activity, however, was observed.

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3. EXPERIMENTAL

All the melting points are uncorrected. The IR spectra were taken on a JASCO IRA-2 grating infrared spectrometer. The NMR spectra were determined with a JEOL JNM-FX-60 or JNM-C-60HL spectrometer. The mass spectra were obtained on a Shimazu mass spectrometer, LKD-9000.

3,3′-Dichloro-4,4′-bis[2,2′-di(ethoxycarbonyl)vinylamino]biphenyl (2a). A mixture of 4,4′-diamino-3,3′-dichlorobiphenyl (5.06 g, 20 mmol) and diethyl ethoxymethylenemalonate (17.28 g, 80 mmol) in methanol (80 ml) was heated under reflux for 5 h. On cooling, the precipitated product was filtered and dried. Recrystalization from 2-methoxy-1-ethanol gave 2a (10.67 g, 91%), mp 200°C. IR(KBr) 3350, 1680, and 1640 cm^{-1}. NMR($CDCl_3$) δ 7.6–7.8 (6H, m), 8.41 (2H, d), and 10.88 (2H, d). MS m/e 592 (M^+).

8,8′-Dichloro-3,3′-di(ethoxycarbonyl)-4,4′-dihydroxy-6,6′-biquinoline (3a). A solution of 2a (3.3 g, 5.5 mmol) in diphenyl ether (100 ml) was heated at 250–260°C for 30 min, and the mixture was poured on n-hexane (700 ml). The pricipitate was filtered and washed with n-hexane for several times. Recrystalization from DMF gave 3a (2.5 g, 89%), mp > 300°C. NMR(d_6-DMSO) δ 6.8–8.6 (6H, m) and 14.0 (2H, brs). MS m/e 500(M^+).

8, 8′-Dichloro-3, 3′-dicarboxy-4, 4′-dioxo-1, 1′, 4, 4′-tetrahydro-6, 6′-biquinoline (4a). A solution of 3a (3.0 g, 6.0 mmol) in 18% hydrochloric acid (200 ml) was heated under reflux for 2 h. On cooling, the precipitated product was filtered to give 4a (2. 1g, 81%), mp > 300°C. IR(KBr) 2600–3500 cm^{-1}. NMR(d_6-DMSO) δ 6.8–8.6 (6H, m) and 12.85 (2H, brs). MS m/e 356(M^+-2CO_2).

8, 8′-Dichloro-3, 3′-dicarboxy-4, 4′-dioxo-1, 1′, 4, 4′-tetrahydrobiquinoline (5a). A mixture of 4a (2.0 g, 4.5 mmol), ethyl iodide (2.8 g, 18 mmol), and potassium hydroxide (1.0 g, 18 mmol) in water (10 ml) and ethanol (20 ml) was stirred at reflux for 1.5 h. Then, ethyl iodide (2.8 g, 18 mmol) and potassium hydroxide (1.0 g, 18 mmol) were added and heating was continued for another 10 h. After cooling, the solution was poured on excess dilute hydrochloric acid and the resulted mixture was allowed to stand overnight. The precipitated product was filtered and recrystalized from 2-methoxy-1-ethanol (2. 1 g, 93%). mp > 300°C. IR(KBr) 2700–3200 cm^{-1}. NMR(d_6-DMSO) δ 1.29 (6H, t), 4.29 (4H, q), 6.9–8.5 (6H, m), and 12.35 (2H, brs). MS m/e 500(M^+).

Compounds 5b–5e were synthesized from 1b–1e according to the similar procedure, unless some comment was added.

2b. 61%, mp 80°C (n-hexane-C_6H_6). IR(KBr) 3200, 1680, and 1650 cm^{-1}. NMR($CDCl_3$) δ 7.3–7.7 (8H, m), 8.46 (2H, d), and 10.72 (2H, d). MS m/e 540(M^+).

3b. 86%, mp 282.5°C. IR(KBr) 3300 and 1700 cm^{-1}. MS m/e 448(M^+).

4b. 47%, mp 272°C. IR(KBr) 3350 and 1700 cm^{-1}.

5b. 38%, mp 227°C (DMF). IR(KBr) 3500–2700 and 1680 cm^{-1}. NMR (d_6-DMSO) δ 1.40 (6H, t), 4.60 (4H, q), and 8.0–9.1 (8H, m).

2c. 86%, mp 156°C (MeOH). IR(KBr) 3300, 1670, and 1640 cm^{-1}. NMR($CDCl_3$) δ 5.75 (1H, s), 7.04 (8H, s), 8.44 (2H, d), and 11.02 (2H, d). MS m/e 539(M^+).

3c. 96%, mp > 250°C (DMF). IR(KBr) 3100 and 1700 cm^{-1}. NMR(d_6-DMSO) δ 1.28 (6H, t), 4.16 (4H, q), and 7.5–8.4 (8H, m).

After the hydrolysis of 3c, the resulted 4c was used without purification.

5c. 54%, mp > 250°C (DMF). IR(KBr) 3500–2700 cm^{-1}. NMR(d_6-DMSO) δ 1.50 (6H, t), 4.50 (4H, q), and 7.6–8.9 (8H, m). MS m/e 447(M^+).

2d. In this case, the condensation reaction was completed in 5 min in 95% yield. mp 152°C (EtOH). IR(KBr) 3200, 1680, and 1640 cm^{-1}. NMR($CDCl_3$) δ 3.10 (2H, s), 8.45 (2H, d), and 10.95 (2H, d). MS m/e 538(M^+).

3d. 81%, mp 307.5°C. IR(KBr) 3300 and 1700 cm^{-1}. MS m/e 446(M^+).

4d. 55%, mp 296°C (DMF). IR(KBr) 3500–2700 and 1700 cm^{-1}. NMR(d_6-DMSO) δ 4.40 (2H, s), 7.7–7.9 (8H, m), and 15.1–15.3 (2H, m).

5d. 54%, mp 306.5°C (DMF). IR(KBr) 3500–2700 cm^{-1}. NMR(d_6-DMSO) δ 1.40 (6H, t), 4.40 (2H, s), 4.65 (4H, q), and 7.9–9.0 (8H, m).

2e. 89%, mp 169.5°C (2-methoxy-1-ethanol). IR(KBr) 3250, 1670, and 1640 cm^{-1}. NMR(d_6-DMSO) δ 4.02 (6H, s), 7.0–7.3 (6H, m), and 11.0–11.3 (2H, m). MS m/e

584(M^+).

3e. 89%, mp 298°C (DMF). IR(KBr) 3300 and 1680 cm^{-1}. NMR(d_6-DMSO) δ 4.10 (6H, s), 7.5–8.4 (6H, m), and 11.70 (2H, s). MS m/e 492(M^+). In the synthesis of 3e 5 h's heating was required for the completion of the reaction.

4e'. In this series, N-alkylation process precedented hydrolysis. Thus, 4e' corresponds to 1, 1'-diethyl-3, 3'-di(ethoxycarbonyl)-8, 8'-dimethoxy-4, 4'-dioxo-1, 1', 4, 4'-tetrahydro-6, 6'-biquinoline. 31%, mp 234°C (DMF). IR(KBr) 1680 cm^{-1}. NMR(d_6-DMSO) δ 4.07 (6H, s) and 7.5–8.5 (6H, m). MS m/e 548(M^+).

5e. 93%, mp>300°C (DMF). IR(KBr) 3500–2800 and 1700 cm^{-1}. NMR(d_6-DMSO) δ 1.40 (6H, t), 4.17 (6H, s), 4.80 (4H, q), and 7.8–8.8 (6H, m). MS m/e 492(M^+).

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