Memoirs Kyushu Inst. Tech.
(Eng.) No. 14, 1984, pp. 23–27

STUDIES ON THE SYNTHESIS OF QUINOLINE COMPOUNDS. III.*

Syntheses of Tricyclic Aromatic Compounds with Two Parts of 3-Carboxy-1-ethyl-4-oxo-1,4-dihydropyridine

by

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(Received November 18, 1983)

SYNOPSIS

Tricyclic fused aromatic compounds possessing two parts of 3-carboxy-1-ethyl-4-oxo-1, 4-dihydropyridine moiety were synthesized. The reaction of phenylenediamines with diethyl ethoxymethylenemalonate afforded bis(vinylamino)benzenes in high yield. These compounds were heated at 260°C and converted to di(ethoxycarbonyl)pyridoquinolines. Hydrolysis of ethoxycarbonyl group and N-ethylation with ethyl iodide resulted in the desire compounds.

1. INTRODUCTION

In the preceding paper[1], we have reported the synthesis of tricyclic fused aromatic compounds containing 3-carboxy-1-ethyl-4-oxo-1, 4-dihydropyridine moiety starting from bicyclic aromatic mono amines. And it was found that 7-carboxy-9-ethyl-6-oxo-6, 9-dihydroquino[7, 8-d][2, 1, 3]thiadiazole had a strong antibacterial activity against several microorganisms. Encouraged by this result, we have continued the synthetic investigation of the tricyclic aromatic compounds. In this paper, we wished to describe the preparation of another tricyclic compounds with two 3-carboxy-1-ethyl-4-oxo-1, 4-dihydropyridine parts starting from mono cyclic aromatic diamines constructing two pyridine moiety by the Gould-Yacobs reaction[2] (Fig. 1).

2. RESULTS AND DICCUSSIONS

Condensation of 2 molar of diethyl ethoxymethylenemalonate with several derivatives of phenylenediamines (1) were performed in refluxing methanol to give dienamines (2) in high yield (61–82%) after recrystalization. Then, 2 were subjected to thermal cyclization at 260°C for 30 min and doubly cyclized pyridoquinolines (3) were obtained. In case of 3a and 3b, two regioisomers were possible depending on the direction of the cyclization. Single isomer, however, was isolated in either case. The examination of ^{1}H–NMR spectra of 3a showed a couple of doublets (J = 9 Hz) and the structure was determined to be as

* Part II of this series; Ichiro HIRAO, Masahiko YAMAGUCHI, Nobuo TAKEFUJI, and Yuzo FUJIKURA, Memoirs of the Kyushu Institute of Technology, Engineering, 14, 17 (1984).

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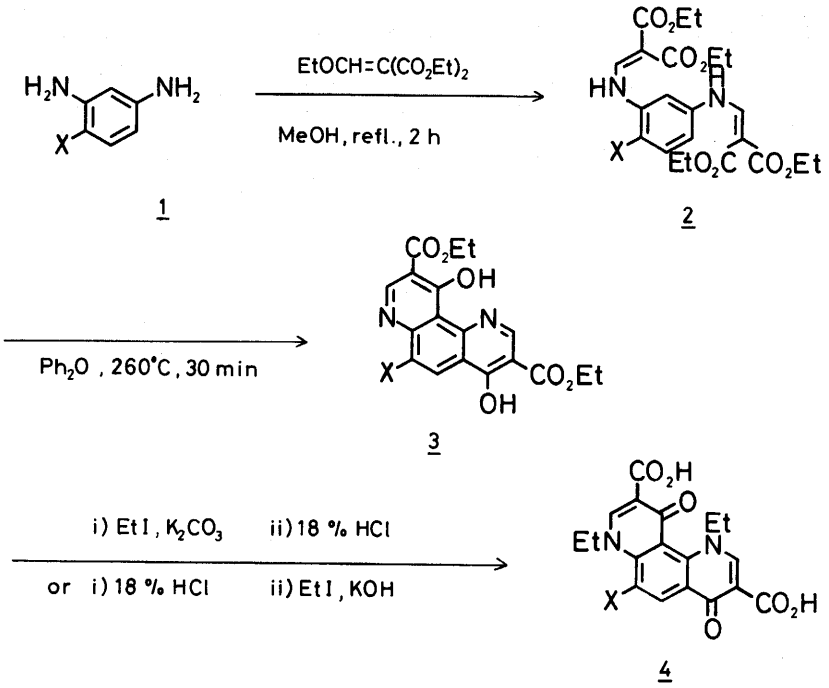
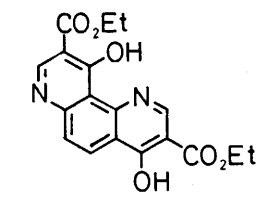


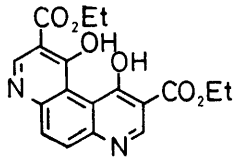
1a 1b 1c 1d 1e

Fig. 1 The synthesis of tricyclic fused aromaitc compounds.

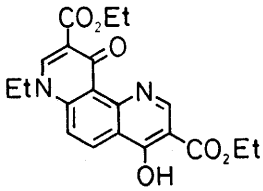
depicted in the following Fig. 2. Though we could not confirm the arrangement of 3b by spectral data, we tentatively assigned the structure as shown in Fig. 2. The presumption might be supported by the facts that the formation of tricyclic fused aromatics by the Gould-Jacobs reaction[1),3)] very often resulted in the molecules with a bent-shape, and not a linear-shape. The final steps consisted of the hydrolysis of ethoxycarbonyl group with 18% hydrochloric acid at refluxing temperature, and N-ethylation with ethyl iodide, which led to 4. In case of 3a, b, e N-alkylation using potassium carbonate preceded the hydrolysis step. On the other hand, 3c and 3d were subjected at first to hydrolysis and the N-alkylation with ethyl iodide and potassium hydroxide came to the last step. In either case, the results were not very different. It was also observed that, in the present synthesis, the N-alkylation process gave mono alkylated product (4a), or no ethylated compound as was 3c. Though the precise reason is not fully clear, the steric hindrance around the



3a



3b



4a

Fig. 2 The structure of 3a, 3b, and 4a.

nitrogen atom might account for the results*.

The antibacterial activities of the compounds (4) toward several microorganisms were tested. No significant activity, however, was observed.

We thank Mr. F. Iino and Mr. N. Morishita for the help in the present study. We are also indebted to Dr. Ueno and his staff of Ueno Pharmaceutical Company, Ltd., for the assay. The research reported in this paper was partially aided by a Grant-in-Aid for Scientific Research No. 57470063 from the Ministry of Education, Science and Culture.

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 spectrometer. The mass spectra were obtained on a Shimazu mass spectrometer, LKD-9000.

1, 3-Bis[(2, 2-di(ethoxycarbonyl)vinylamino]benzene (2a). A solution of m-phenylenediamine (1.08 g, 10 mmol) and diethyl ethoxymethylenemalonate (4.32 g, 20 mmol) in methanol (10 ml) was heated at reflux for 2 h. On cooling, the precipitated products was filtered and dried. Recrystalization from methanol gave 2a (3.64 g, 82%), mp 109°C. IR(KBr) 3400–3300, 1680, and 1640 cm^{-1}. Found: C, 58.72; H, 6.34; N, 6.31%. Calcd for $C_{22}H_{28}O_8N_2$: C, 58.93; H, 6.25; N, 6.25%.

The following compounds (2b–2e) were synthesized by a similar procedure.

2b. 61%, mp 162.5°C (EtOH). IR(KBr) 3300, 1670, and 1630 cm^{-1}. NMR($CDCl_3$) δ 7.40 (4H, s), 8.35 (2H, d), and 10.71 (2H, d). MS m/e 448(M^+).

2c. 82%, mp 144°C (MeOH). IR(KBr) 1690 and 1640 cm^{-1}. Found: C, 59.94; H, 6.66; N, 6.16%. Calcd for $C_{23}H_{30}O_8N_2$: C, 59.74; H, 6.49; N, 6.06%.

2d. 65%, mp 134°C (MeOH). MS m/e 482(M^+). NMR($CDCl_3$) δ 1.2–1.5 (12H, m),

* Considering the steric hindrance around two nitrogen atoms, we tentatively determined the structure of the monoalkylated product (4a) to be as shown in Fig. 2.

4.0–4.5 (8H, m), 6.5–7.5 (3H, m), 8.43 (2H, d), and 11.30 (2H, d).

2e.[4] 74%, mp 137°C (MeOH). IR(KBr) 3350, 1680, and 1640 cm^{-1}. MS m/e 449(M^+). NMR(d_6-DMSO) δ 1.1–1.4 (12H, m), 4.0–4.4 (8H, m), 7.0–7.9 (3H, m), 9.02 (2H, brs), and 10.61 (2H, brs).

3, 9-Di(ethoxycarbonyl)-4, 10-dihydroxypyrido[2, 3-f]quinoline (3a)[3]. Compound (2a) (2.0 g, 4.5 mmol) was dissolved in diphenyl ether (40 ml) and the mixture was stirred at 270°C for 30 min. After cooling for 1–2 min, the solution was poured on n-hexane (280 ml), and the separated product was filtered. The solid was washed with n-hexane for several times and then with hot methanol to afford 3a in 79% yield (1.4 g), mp 270°C (dec.). IR(KBr) 3600–3300 and 1710 cm^{-1}. MS m/e 356(M^+). NMR(d_6-DMSO) δ 1.31 (6H, t, J=8 Hz), 4.27 (4H, q, J=7 Hz), 7.38 (1H, s), 7.54 (1H, d, J=9 Hz), 8.46 (1H, d, J=9 Hz), 8.54 (1H, s), 10.34 (1H, s), and 10.57 (1H, s).

3b. 94%, mp 268°C (2-methoxy-1-ethanol). IR(KBr) 3300 and 1700 cm^{-1}. MS m/e 356(M^+). NMR(d_6-DMSO) δ 1.33 (6H, t), 4.26 (4H, q), 8.12 (2H, s), 8.83 (2H, s), 10.41 (1H, s), and 10.65 (1H, s).

3c. 75%, mp 270°C (dec.). IR(KBr) 3600–3300 and 1710 cm^{-1}. MS m/e 370(M^+). NMR(d_6-DMSO) δ 1.27 (6H, t), 2.50 (3H, s), 4.20 (4H, q), 8.17 (1H, s), 8.40 (2H, s), 8.57 (1H, s), and 8.68 (1H, s).

3d. 90%, mp>300°C (DMF). IR(KBr) 3350 and 1690 cm^{-1}. MS m/e 390(M^+). NMR(d_6-DMSO) δ 1.31 (6H, t), 4.28 (4H, q), 8.4–8.8 (3H, m), and 14.0 (2H, brs).

3e. 49%, mp 227°C. IR(KBr) 3400 and 1720 cm^{-1}. MS m/e 357(M^+). NMR(d_6-DMSO) δ 1.28 (6H, t), 4.24 (4H, q), 7.2–8.5 (3H, m), and 10.6 (2H, brs).

3, 9-Di(ethoxycarbonyl)-7-ethyl-4-hydroxy-10-oxo-7, 10-dihydropyrido[2, 3-f]quinoline. A mixture of 3a (1.93 g, 5.4 mmol), ethyl iodide (4 ml, 54 mmol), and potassium carbonate (3.75 g, 27 mmol) in DMF (120 ml) was heated at 70°C for 2 h. On cooling, a small amount of water was added and the mixture was allowed to stand overnight. The precipitate was filtered and recrystalized from methanol to give the expected compound (1.04 g, 49%), mp>280°C. IR(KBr) 3500–3200, 1710, and 1620 cm^{-1}. MS m/e 384(M^+). NMR(d_6-DMSO) δ 1.72 (6H, t, J=7 Hz), 1.74 (3H, t, J=7 Hz), 4.59 (2H, q, J=7 Hz), 4.84 (4 H, q, J=7 Hz), 7.45 (1 H, d, J=9 Hz), 8.08 (1H, d, J=9 Hz), 8.41 (1H, s), and 8.63 (1H, s).

The following compounds were synthesized from 3b and 3e, respectively.

2, 9-Di(ethoxycarbonyl)-4, 7-diethyl-1-1, 10-dioxo-1, 4, 7, 10-tetrahydropyrido[3, 2-f]quinoline. 58%, mp 270°C (2-methoxy-1-ethanol). IR(KBr) 1700 cm^{-1}. MS m/e 412(M^+). NMR(d_6-DMSO) δ 7.90 (1H, s) and 8.40 (1H, s).

3, 7-Di(ethoxycarbonyl)-1, 9-diethyl-4, 6-dioxo-1, 4, 6, 9-tetrahydro-1, 9, 10-triazaanthracene. 61%, mp 172°C (C_6H_6=n-C_6H_{14}). MS m/e 413(M^+). NMR(d_6-DMSO) δ 1.2–1.7 (12H, m), 4.1–4.6 (8H, m), and 6.8–9.2 (3H, m).

7-Ethyl-3, 9-dicarboxy-4-hydroxy-10-oxo-7, 10-dihydropyrido[2, 3-f] quinoline (4a). Ethylated product (9.6 g, 25 mmol) was dissolved in 18% hydrochloric acid (30 ml) and the solution was heated at reflux for 2 h. After cooling, a small amount of water was added and the suspension was allowed to stand sevaral hours. The separated product was filtered and washed with water. After dried, it was recrystalized from DMF to afford 4a (4.5 g, 56%), mp 351°C. IR(KBr) 3600–2400, 1710, and 1620 cm^{-1}. MS m/e 328(M^+). Found: C, 58.32, H, 3.67; N, 8.82%. Calcd for $C_{16}H_{12}O_6N_2$: C, 58.54; H, 3.66; N, 8.54%.

By a similar process, 4b and 4e were synthesized.

4b. mp>250°C (DMF). IR(KBr) 1700 cm^{-1}. MS m/e 356(M^+). NMR(d_6-DMSO) δ 1.50 (6H, t), 4.60 (4H, q), 8.30 (1H, s), and 8.90 (1H, s). Found: 60.67; H, 4.53; N, 7.86%. Calcd for $C_{18}H_{16}O_6N_2$: C, 59.87; H, 4.60; N, 7.85%.

4e. 10%, mp 200°C (MeOH). MS m/e 357(M^+). NMR(d_6-DMSO) δ 1.41 (6H, t), 4.42 (4H, q), 7.0–9.2 (3H, m), and 14.6 (2H, brs).

3, 8-Dicarboxy-1, 10-diethyl-4, 9-dioxo-1, 4, 7, 10-tetrahydro-1, 10-diazaphenanthrene (4d). Compound 3d was hydrolyzed according to the similar procedure as the synthesis of 4a. 92%, mp>300°C. IR(KBr) 3400–2500 cm^{-1}. MS m/e 246(M^+-2CO_2). The acid (1.0 g, 3 mmol), thus obtained, was mixed with ethyl iodide (0.48 ml, 6 mmol) in 10% aqueous potassium hydroxide (7 ml) and ethanol (21 ml). After refluxing for 1.5 h, another portion of ethyl iodide (0.48 ml, 6 mmol) and 10% aqueous potassium hydroxide (7 ml) was added. The refluxing was continued for 10 h. On cooling, the mixture was poured on excess dil. hydrochloric acid, and the suspension was settled overnight. The separated product was filtered and washed with water to give 4d (0.94 g, 81%), mp>300°C. IR(KBr) 3400–2500 cm^{-1}. MS m/e 390(M_+).

Similarly, 3c was hydrolized. 87%, mp>280°C. IR(KBr) 3600–2800 and 1700 cm^{-1}. MS m/e 194(M^+-2CO_2). The attempt, however, to alkylate the product was unsuccessful.

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