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STUDIES ON THE SYNTHESIS OF QUINOLINE COMPOUNDS. II.*

Syntheses of Tricyclic Derivatives of 3-Carboxy-1-ethyl-4-oxo-1,4-dihydroquinolines

by

Ichiro HIRAO, Masahiko YAMAGUCHI, Nobuo TAKEFUJI
and Yuzo FUJIKURA**

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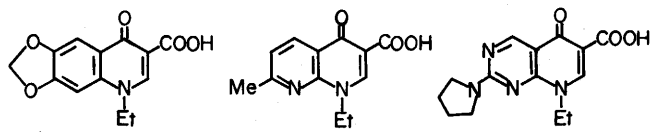
SYNOPSIS

An investigation on the synthesis of tricyclic fused aromatics containing 3-carboxy-1-ethyl-4-oxo-1, 4-dihydroquinoline moiety is described. Several bicyclic aromatic amines were condensed with diethyl ethoxymethylenemalonate to give 2, 2-di(ethoxycarbonyl)-vinylamino compounds. The thermal cyclization of the enamines resulted in 3-ethoxycarbonyl-4-hydroxyquinolines. Subsequent N-ethylation and hydrolysis of ester part led to the desired quinolines. A number of ester and amide derivatives were also synthesized. One of the products, 7-carboxy-9-ethyl-6-oxo-6, 9-dihydroquino [7,8–d] [2, 1, 3] thiadiazole was a strong antibacterium.

1. INTRODUCTION

These are several antibacterial aromatic compounds (1, 2, 3)[1] which contain a common 1-ethyl-3-carboxy-4-oxo-1, 4-dihydropyridine moiety in their structure. In connection with our synthetic investigation directed to biologically active compounds[2], it seemed to be of interest to prepare polyfused heteroaromatics possessing this part in the molecule.



Oxolinic acid (1) Nalidixic acid (2) Piromidic acid (3)

Fig. 1 The structure of 1, 2, and 3.

The Gould-Yacobs reaction[3] is a powerful synthetic tool for the preparation of 4-hydroxy-3-carboxyquinoline derivatives. It consists of the condensation of aromatic amines with diethyl ethoxymethylene-malonate (EMME) followed by a thermal cyclization. In the present study, a synthesis of tricyclic aromatic compounds with 1-ethyl-4-oxo-

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** Department of Industrial Chemistry.

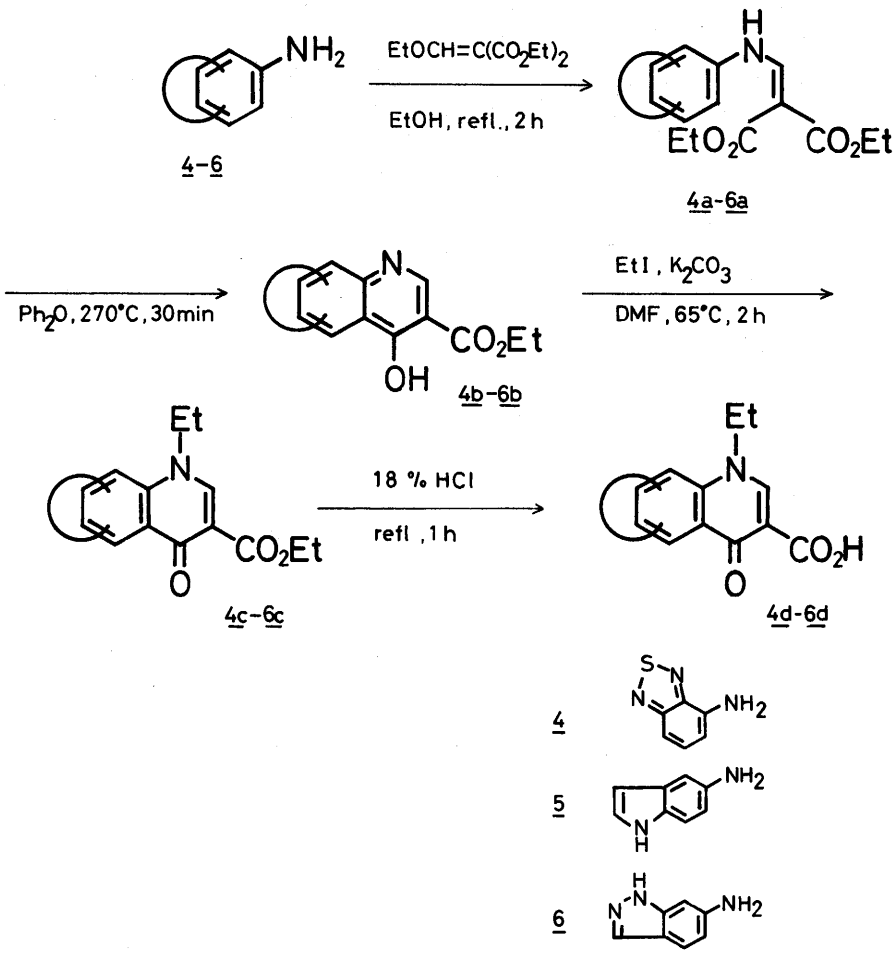
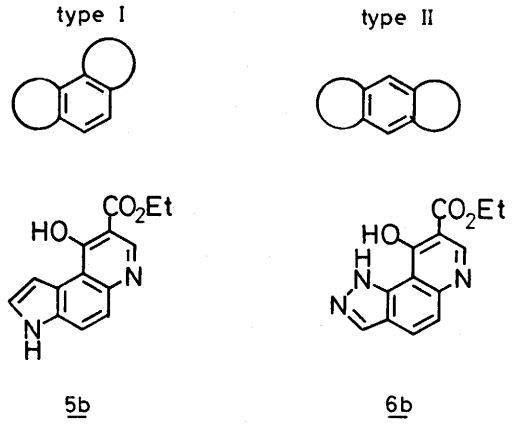


Fig. 2 A synthesis of tricyclic derivatives of quinolines.

1, 4-dihydropyridine moiety using the Gould-Yacobs reaction (Fig. 2) and some results of the test of antibacterial activities are described.

2. RESULTS AND DISCCUSIONS

The reaction of aromatic mono amines (4–6) with EMME was performed in refluxing ethanol to give enaminomalonate (4a–6a) in good yield (66–75%). The Gould-Yacobs cyclization of these compounds (4a–6a) at 270°C in diphenyl ether resulted in tricyclic fused aromatics (4b–6b) with 3-ethoxycarbonyl-4-hydroxypyridine part in the molecule (50–69% yield). The ^{1}H-NMR spectra showed two singlets and a couple of doublets in aromatic region. As the coupling constant (J=9 Hz) indicated the presence of ortho protons, the arrangement of the three aromatic rings should be assigned as type I, and not type II (Fig. 3)[2),4),5),6)]. Alkylation of 4b–6b with ethyl iodide was performed in DMF in the presence of potassium carbonate to afford 1-ethyl-4-oxo derivatives (4c–6c) in 40–80% yield. Then, ethoxycarbonyl group was hydrolyzed under acidic condition and expected tricyclic aromatic compounds (4d–6d) with 1-ethyl-3-carboxy-4-oxo-1, 4-dihydropyridine moiety were obtained (45–88%).



5b 6b

Fig. 3 The structure of 5b and 6b.

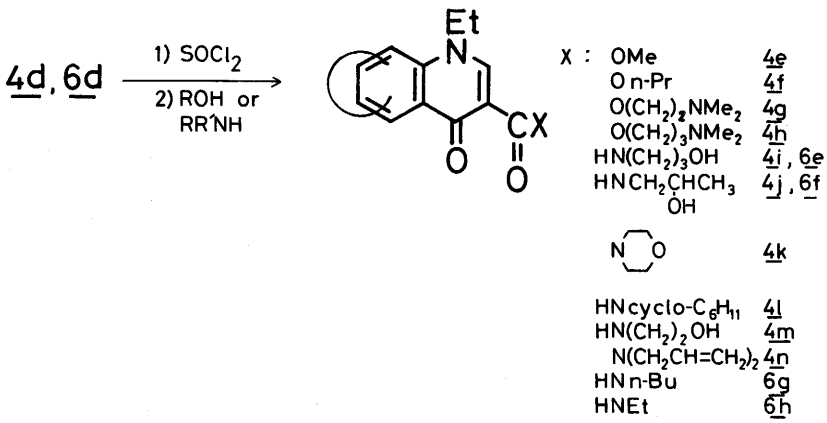


Fig. 4 The synthesis of ester and amide derivatives.

Table 1. Minimal Inhibitory Concentration (μg/ml) of 4d

Test organisms	μg/ml
Staphylococcus aureus Smith	6.25
Staphylococcus epidermidis 12228	25
Seratia marcesens IID 620	3.13
Escherichia coli K–74	6.25
Proteus vulgaris IFO 3045	>25
Proteus mirabiris IFO 3849	>25
Proteus mirabiris I 37	25
Proteus molganii IFO 3168	6.25
Proteus rettgeri IFO 13501	0.39
Proteus inconstans IFO 12930	6.25
Enterobacter cloacae IID 977	6.25
Enterobacter aerogenes IID 972	3.13
Salmonella thyphimurium K–52	12.5
Salmonella pullorum Chuyu	3.13
Klebsiella pneumoniae IID 875	6.25
Pseudomonas aeruginosa K–81	>25

Sevaral amide and ester derivatives of 4d and 6d were also synthesized. Thus, acid chlorides were prepared by treating 4d or 6d with thionyl chloride at refluxing temperature and were directly reacted with amines or alcohols at 0°C to give 4e–n and 6e–h (Fig. 4).

The microbacterial activities of compounds (4d–n, 5d, 6d–h) toward several microorganisms were examined, and 7-carboxy-9-ethyl-6-oxo-6, 9-dihydroquino[7, 8-d][2, 1, 3] thiadiazole (4d) was found to be a strong antibacterium (Table 1). Though Kametani[4] have previously reported that 6d had activities, no significant activities were observed for the corresponding esters or amides (6e–h).

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3. EXPERIMENTAL

All the melting points are uncorrected. Elemental analyses were carried out with Yanagimoto CHN Corder, MT-2 type. The IR spectra were taken on a JASCO IRA-2 grating infrared spectrophotometer. The NMR spectra were determined with a JEOL JNM-FX-60 spectrometer. The mass spectra were obtained on a Shimazu mass spectrometer, LKD-9000.

4-[2, 2-Di(ethoxycarbonyl)vinylamino]-2, 1, 3-benzthiadiazole (4a). An ethanol (10 ml) solution of 4-amino-2, 1, 3-benzthiadiazole (4) (500 mg, 3.3 mmol) and diethyl ethoxymethylenemalonate (EMME) (713 mg, 3.3 mmol) was heated under reflux for 1 h. The hot solution was filtered, and, on cooling, a crude product separated. Recrystalization from methanol gave 4a (776 mg, 66%), mp 113.5°C. IR(KBr) 3300, 1680, and 1640 cm^{-1}. NMR($CDCl_3$) δ 1.2–1.5 (6H, m), 4.1–4.4 (4H, m), 7.2–7.6 (3H, m), 8.79 (1H, d, J=13 Hz), and 11.20 (1H, d, J=13 Hz). Found: C, 52.22; H, 4.67; N, 13.03%. Calcd for $C_{14}H_{15}O_4N_3S$: C, 52.34; H, 4.67; N, 13.08%.

The following compounds (5a, 6a) were synthesized according to the same procedures starting from 5-aminoindole (5) and 6-amino-1H-indazole (6).

5a. 68%, mp 118°C (MeOH). IR(KBr) 3300, 1720, and 1650 cm^{-1}. Found: C, 63.32; H, 5.96; N, 8.99%. Calcd for $C_{16}H_{18}O_4N_2$: C, 63.58; H, 5.96; N, 9.27%.

6a. 75%, mp 165°C (MeOH), lit.[5] 169°C.

7-Ethoxycarbonyl-6-hydroxyquino[7, 8-d][2, 1, 3]thiadiazole (4b). A solution of 4a (2.0 g, 6.2 mmol) in diphenyl ether (30 ml) was heated at 270°C for 30 min. After cooling for 5 min, the mixture was poured on n-hexane (250 ml). The precipitate filtered was washed with n-hexane for several times, and recrystalization from 2-ethoxy-1-ethanol gave 4b (0.97 g, 57%), mp 262°C. IR(KBr) 3400 and 1720 cm^{-1}. Found: C, 52.20; H, 3.31; N, 15.19%. Calcd for $C_{12}H_9O_3N_3S$: C, 52.36; H, 3.27; N, 15.27%.

The same procedure was employed for the synthesis of 5b and 6b.

5b. 50%, mp 298°C (dec.) (DMF). IR(KBr) 3400 and 1700 cm^{-1}. NMR(d_6-DMSO) δ 1.30 (3H, t, J=7 Hz), 4.22 (2H, q, J=7 Hz), 7.30 (1H, d, J=9 Hz), 7.4–7.6 (2H, m), 7.76 (1H, d, J=9 Hz), 8.44 (1H, s), 11.56 (1H, s), and 12.20 (1H, s). Found: C, 65.63; H, 4.65; N, 10.83%. Calcd for $C_{14}H_{14}O_4N_2$: C, 65.63; H, 4.69; N, 10.94%.

6b. 69%, mp 318°C (dec.) (DMF), lit.[5] 302°C (dec.). NMR(d_6-DMSO) δ 1.32 (3H, t, J=7 Hz), 4.27 (2H, q, J=7 Hz), 7.35 (1H, d, J=9 Hz), 7.78 (1H, d, J=9 Hz), 8.03 (1H, s), and 8.18 (1H, s). Found: C, 60.51; H, 4.12; N, 16.29%. Calcd for $C_{13}H_{11}O_3N_3$: C, 60.70; H, 4.28; N, 16.34%.

7-Ethoxycarbonyl-9-ethyl-6-oxo-6, 9-dihydroquino[7, 8-d][2, 1, 3]thiadiazole (4c). A

mixture of 4b (2.75 g, 10 mmol), potassium carbonate (3.45 g, 25 mmol), and ethyl iodide (4.06 g, 25 mmol) in DMF (30 ml) was stirred at 65°C for 2 h. After cooling, insoluble materials were removed by filtration, and the solvent was evaporated in vacuo. To the residue was added water and the mixture was allowed to stand overnight. The separated product was filtered and recrystalization from methanol gave 4c (2.42 g, 80%), mp 173°C. IR(KBr) 1680 and 1640 cm^{-1}. NMR(d_6-DMSO) δ 1.44 (3H, t, J=8 Hz), 1.60 (3H, t, J=7 Hz), 4.42 (2H, q, J=8 Hz), 5.10 (2H, q, J=7 Hz), 7.83 (1H, d, J=9 Hz), 8.44 (1H, s), and 8.64 (1H, d, J=9 Hz). Found: C, 54.98; H, 4.29; N, 13.62%. Calcd for $C_{14}H_{13}O_3N_3S$: C, 55.45; H, 4.29; N, 13.86%.

Compounds (5c, 6c) were prepared by a similar procedure.

5c. 52%, mp 270°C (dec.) (MeOH). IR(KBr) 1710 and 1620 cm^{-1}. NMR($CDCl_3$) δ 1.44 (3H, t, J=8 Hz), 1.60 (3H, t, J=7 Hz), 4.42 (2H, q, J=8 Hz), 5.10 (2H, q, J=8 Hz), 5.10 (2H, q, J=7 Hz), 7.83 (2H, d, J=9 Hz), 8.44 (1H, s), and 8.64 (2H, d, J=9 Hz).

6c. 40%, mp 238°C (EtOH), lit.[5] 239°C. Found: C, 63.04; H, 5.36; N, 14.85%. Calcd for $C_{15}H_{15}O_3H_3$: C, 63.16; H, 5.26; N, 14.74%.

7-Carboxy-9-ethyl-6-oxo-6, 9-dihydroquino[7, 8-d][2, 1, 3]thiadiazole (4d). A solution of 4c (7.58 g, 25 mmol) in 18% hydrochloric acid (30 ml) was heated at reflux for 1 h, and the separated product was filtered. Recrystalization from DMF gave 4d (6.05 g, 88%); mp 305°C (dec.). IR(KBr) 3400, 1720, and 1620 cm^{-1}. Found: C, 53.45; H, 3.27; N, 15.14%. Calcd for $C_{12}H_9O_3N_3S$: C, 52.36; H, 3.27; N, 15.29%.

The same procedure was used for the preparation of 5d and 6d.

5d. 45%, mp 342°C (dec.) (2-methoxy-1-ethanol). IR(KBr) 3400–2800, 1700, and 1620 cm^{-1}. Found: C, 64.52; H, 4.75; N, 10.80%. Calcd for $C_{14}H_{12}O_3N_2$: C, 65.63; H, 4.69; N, 10.94%.

6d. 87%, mp 323°C (dec.) (DMF), lit.[5] >300°C. NMR(d_6-DMSO) δ 1.46 (3H, s), 4.69 (2H, q, J=7 Hz), 7.69 (1H, d, J=9 Hz), 8.30 (1H, s), 8.32 (1H, d, J=9 Hz), 9.07 (1H, s), 13.82 (1H, s), and 15.39 (1H, s). Found: C, 60.30; H, 4.28; N, 16.14%. Calcd for $C_{13}H_{11}O_3N_3$: C, 60.70; H, 4.28; N, 16.34%.

9-Ethyl-7-methoxycarbonyl-6-oxo-6, 9-dihydroquino[7, 8-d][2, 1, 3]thiadiazole (4e). Under a nitrogen atomosphere 4d (1.0 g, 3.6 mmol) was treated with thionyl chloride (8 ml) under reflux for 30 min. Excess thionyl chloride was evaporated and the residue was dried for 3 h in vacuo. Acid chloride, thus obtained, was crushed to powder and excess methanol was added at 0°C. After strring for 1 h, water was added to the mixture, and the separated product was filtered. Recrystalization from methanol gave 4e (0.88 g 84%), mp 180°C. IR(KBr) 1680 and 1630 cm^{-1}. Found: C, 53.45; H, 3.75; N, 14.28%. Calcd for $C_{13}H_{11}O_3N_3S$: C, 53.98; H, 3.81; N, 14.53%.

Similarly, several acid derivatives (4f–n, 6e–h) were synthesized from 4d and 6d.

4f. 83%, mp 148°C (n-PrOH). IR(KBr) 1670 and 1630 cm^{-1}. Found: C, 56.86; H, 4.70; N, 13.25%. Calcd for $C_{15}H_{15}O_3N_3S$: C, 56.78; H, 4.74; N, 13.25%.

4g. 30%, mp 263°C (MeOH). IR(KBr) 1710 and 1640 cm^{-1}. MS m/e 346 (M^+).

4h. 32%, mp 153°C (dec.) (MeOH–H_2O). IR(KBr) 1710 and 1640 cm^{-1}. NMR($CDCl_3$) δ 1.60 (3H, t), 2.27 (6H, s), 4.47 (2H, t), 5.13 (2H, q), 7.90 (1H, d), 8.72 (1H, d), and 8.57 (1H, s). MS m/e 258 (M^+–$O(CH_2)_3NMe_2$).

4i. 20%, mp 189°C (EtOH). IR(KBr) 3600–3400, 3250, and 1660 cm^{-1}. MS m/e 332 (M^+) and 258(M^+–$NHCH_2CH_2CH_2OH$). Found: C, 53.87; H, 4.79; N, 16.79%. Calcd for $C_{15}H_{16}O_3N_4S$: C, 54.22; H, 4.82; N, 16.87%.

4j. 12%, mp 230°C (EtOH). IR(KBr) 3600–3200 and 1660 cm^{-1}. MS m/e 332(M^+) and 258(M^+–$NHCH_2CH(OH)CH_3$). Found: C, 53.97; H, 4.76; N, 16.86%. Calcd for $C_{15}H_{16}O_3N_4S$: C, 54.22: H, 4.82; N, 16.87%.

4k. 24%, mp 208°C (2-methoxy-1-ethanol). IR(KBr) 1640 cm^{-1}. MS m/e 334(M^+).

Found: C, 55.53; H, 4.54; N, 16.36%. Calcd for $C_{16}H_{16}O_2N_4S$: C, 55.81; H, 4.65; N, 16.28%.

4l. 50%, mp 160.5°C (MeOH). IR(KBr) 3400 and 1640 cm^{-1}. NMR($CDCl_3$) δ 1.24 (3H, t), 4.74 (2H, q), 7.63 (1H, d), 7.84 (1H, d), and 8.15 (1H, s). MS m/e 356(M^+) and 258(M^+–NHC_6H_{11}).

4m. 64%, mp 168°C (MeOH). IR(KBr) 3350 and 1660 cm^{-1}. MS m/e 258(M^+–$NH(CH_2)_2OH$).

4n. 75%, mp 144°C ($CHCl_3$–AcOEt). IR(KBr) 1640 cm^{-1}. NMR($CDCl_3$) δ 1.58 (3H, t), 3.96 (2H, d), 4.20 (2H, d), 5.10 (2H, q), 7.87 (1H, d), and 8.56 (1H, d).

6e. 66%, mp 218°C (n-PrOH). Found: C, 61.18; H, 6.04; N, 17.23%. Calcd for $C_{16}H_{18}O_3N_4$: C, 61.15; H, 5.73; N, 17.83%.

6f. 47%, mp 218°C (n-PrOH). Found: C, 61.42; H, 6.01; N, 17.55%. Calcd for $C_{16}H_{18}O_3N_4$: C, 61.15; H, 5.73; N, 17.83%.

6g. 56%, mp 196°C (MeOH). Found: C, 65.33; H, 6.56; N, 17.73%. Calcd for $C_{17}H_{20}O_2N_4$: C, 65.38; H, 6.41; N, 17.95%.

6h. 46%, mp 247°C (MeOH). Found: C, 63.34; H, 5.83; N, 19.69%. Calcd for $C_{15}H_{16}O_2N_4$: C, 63.38; H, 5.63; N, 19.72%.

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