Memoirs Kyushu Inst. Tech.
(Eng.) No. 14, 1984, pp. 29–34

STUDIES ON THE SYNTHESIS OF QUINOLINE COMPOUNDS. IV.*

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

by

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(Received November 18, 1983)

SYNOPSIS

A synthesis of 3, 3′-dicarboxy-1, 1′-diethyl-4, 4′-dioxo-1, 1′, 4, 4′-tetrahydropolymethylenedioxydiquinolines is described. Dinitropolymethylenedioxydibenzenes were prepared from nitrophenols and dibromoalkanes in the presence of potassium carbonate. The nitro compounds were reduced with stannous chloride to give diamine derivatives, which, in turn, without isolation were condensed with diethyl ethoxymethylenemalonate. The thermal cyclization of the enamines gave polymethylenedioxydiquinolines. Hydrolysis of ethoxycarbonyl group and N-ethylation afforded the desired products.

1. INTRODUCTION

In course of our recent synthetic investigation directed to biologically active compounds, we have prepared various derivatives of 3-carboxy-1-ethyl-4-oxo-1, 4-dihydropyridines. They include tricyclic fused aromatic compounds with one or two pyridine part[1),2)], and biquinolines connected by carbon or heteroatoms[3)].

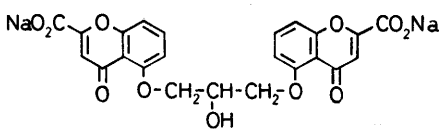

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Fig. 1 The structure of DSCG.

Disodium cromogrycate (DSCG, I) is a known compound of antiallergy activity. It consists of two chromone moiety bonded through glycerol part by ether lincage. As a further synthetic study of pyridine derivatives, we were interested in the compound with two 3-carboxy-1-ethyl-4-oxo-1, 4-dihydroquinolines settled in a similar manner as chromones in DSCG. The present paper describes the preparation of this new heteroaromatic compounds.

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* Part III of this series; Ichiro HIRAO, Masahiko YAMAGUCHI, Nobuo TZKDVUJI, and Yasushi KAWAZOE, Memoirs of the Kyushu Institute of Technology, Engineering, 14, 23 (1984).

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2. RESULTS AND DICCUSSIONS

The formation of quinoline ring was planned to perform by Gould-Jacobs reaction[4] as was in the other work of this series.[1),2),3)] At first, we examined the synthesis by the coupling reaction of 2 molar of hydroxyquinolines (II) with dibromoalkanes. Thus, 3-carboxy-1-ethyl-4, 5-dihydroxyquinoline was prepared from m-aminophenol by the condensation with diethyl ethoxymethylenemalonate followed by the thermal cyclization. N-Alkylation of the product gave 3-ethoxycarbonyl-1-ethyl-5-hydroxy-4-oxo-1, 4-dihydroquinoline (II). Though II was allowed to react with 1, 2-dibromoethane, desired product was isolated quite in low yield (Fig. 2).

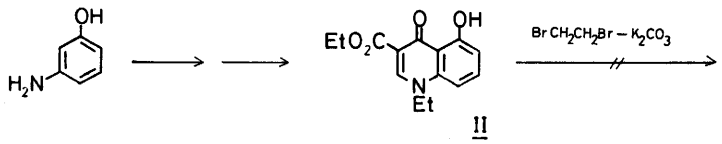
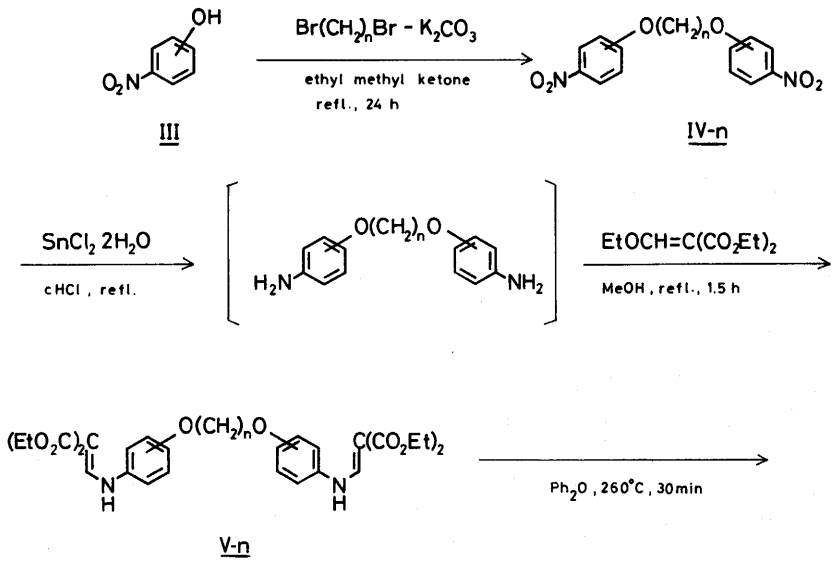


Fig. 2 The synthesis of polymethylenedioxydiquinolines (Route I).

Thus, we next turned to another synthetic route in which the ether formation was performed at the earlier stage. Nitrophenols (III) were treated with 1, ω-dibromoalkanes in ethyl methyl ketone in the presence of potassium carbonate and bis(aryloxy)alkanes (IV) were obtaned in good yield (38–95%). The use of dichloroalkanes in acetone[5] was not satisfactory in the present synthesis and only mono-aryloxylated alkanes were obtained even after 72 h's reaction. Next, the nitro compounds (IV) were reduced with stannous chloride in conc. hydrochloric acid. The resulted bianilines, without isolation, were condensed with diethyl ethoxymethylenemalonate (EMME) in 2-propanol at reflux for 1.5 h to give dienamines (V). The cyclization was performed in diphenyl ether at 270°C for 30 min in 49–87%. The thermal reaction of V–2c, however, resulted in decomposition and no cyclization product was obtained. Biquinolines (VI), thus obtained, was converted to acids (VII) by hydrolisis of ethoxycarbonyl group with potassium hydroxide (34–98%). Finally, N-alkylation of VII by ethyl iodide gave the desired products (VIII) in 30–84% yield (Fig. 3).



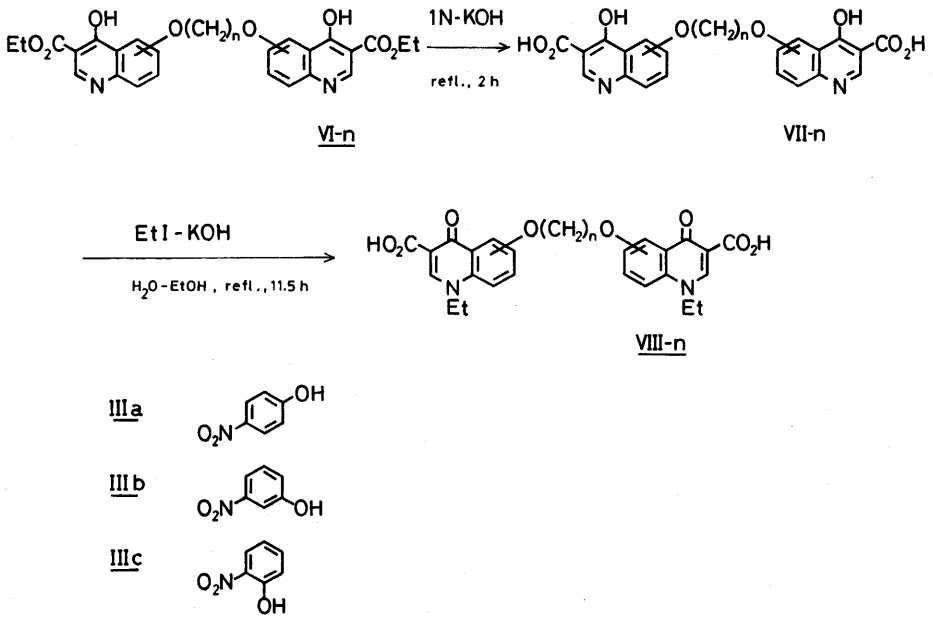


Fig. 3 The synthesis of polymethylenedioxydiquinolines (Route II).

In case of VI-2b, 3b, 4b, which were synthesized from m-nitrophenol (III-b), only one of two possible regioisomers was obtained. From the examination of IR spectra (790 cm^{-1}, 1, 2, 3-trisubstituted benzene) of VI-2b, the structure of these copounds were determined to be as follows and not VI-2b′ (Fig. 4).

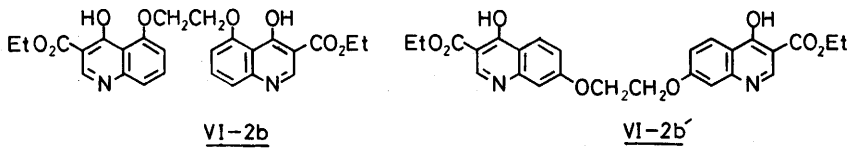


Fig. 4 The structure of VI-2b.

The compounds (VIII) synthesized in the present study were tested for antimicrobial activities against several microorganisms and analgesia but were inactive.

The authors are indebted to Dr. R. Ueno and his staff of Ueno Pharmaceutical Company, Ltd., for the assay. This work reported in this paper was partially supported by a Grant-in-Aid for Scientific Research No. 57470063 from the Ministry of Education, Science and Culture. We also thank Mr. T. Kimura and Mr. M. Higuchi for thier assistance in this study.

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-C-60HL spectrometer. The mass spectra were obtained on a Shimazu mass spectrometer, LKD-9000.

1, 1′-Dinitro-4, 4′-ethylenedioxydibenzene (IV-2a). A mixture of p-nitrophenol (13.9 g, 100 mmol), potassium carbonate (20.7 g, 150 mmol), and 1, 2-dibromoethane (4.3 ml, 50 mmol) in ethyl methyl ketone (100 ml) was heated under reflux for 24 h. After the

solvent removed in vacuo, ether and water were added to the residue. The precipitated product was filtered and washed with water and ether, and was dried. Recrystalization from methanol gave IV–2a (7.4 g, 43%), mp 145°C. MS m/e 304(M^+).

1, 1′-Bis[2, 2′-di(ethoxycarbonyl)vinylamino]-4, 4′-ethylenedioxydibenzene (V–2a). To the solution of stannous chloride dihydrate (54 g, 240 mmol) in conc. hydrochloric acid (42 ml) was added IV–2a (9.1 g, 30 mmol) and the temperature was raised slowly to 105°C. After cooled to room temperature, the mixture was poured on water and neutralized with dil. sodium hydroxide. The precipitate was filtered and dried. The solid was mixed with diethyl ethoxymethylenemalonate (12.9 g, 60 mmol) and 2-propanol (250 ml) and the suspension was heated at reflux for 1.5 h. The resulting mixture was filtered while hot. On cooling, the separated product was filtered and recrystalized from methanol to give V–2a (10.6 g, 64%), mp 146°C. NMR(d_6-DMSO) δ 4.47 (4H, s) and 11.8 (2H, s). MS m/e 586(M^+).

3, 3′-Di(ethoxycarbonyl)-4, 4′-dihydroxy-6, 6′-ethylenedioxydiquinoline (VI–2a). A mixture of V–2a (3.5 g, 6.0 mmol) in diphenyl ether (100 ml) was heated at 270°C for 30 min. After cooled for 1–2 min, the solution was poured on n-hexane (700 ml). The precipitate was filtered and washed with n-hexane for several times. The product was then washed with methanol and used for the next reaction without further purification (2.2 g, 75%), mp >300°C. NMR(d_6-DMSO) δ 1.28 (6H, t), 4.22 (4H, q), 4.47 (4H, s), 7.3–8.4 (10H, m), and 11.8 (2H, brs). MS m/e 492(M^+).

3, 3′-Dicarboxy-4, 4′-dihydroxy-6, 6′-ethylenedioxydiquinoline (VII–2a). A solution of VI–2a (3.9 g, 7.0 mmol) in 1N potassium hydroxide (100 ml) was refluxed for 2 h. After cooled to room temperature, the mixture was poured on excess dil. hydrochloric acid and liberated product was filtered. Recrystalization from DMF gave VII–2a (2.8 g, 98%), mp >300°C. IR(KBr) 3400–2500, 1700, and 780 cm^{-1}. NMR(d_6-DMSO) δ 4.54 (4H, s) and 7.4–8.7 (8H, m).

3, 3′-Dicaboxy-1, 1′-diethyl-4, 4′-dioxo-1, 1′, 4, 4′-tetrahydro-6, 6′-ethylenedioxydiquinoline (VIII–2a). A mixture of VII–2a (2.2 g, 5.0 mmol) and ethyl iodide (0.8 ml, 10 mmol) was heated at reflux in 1N potassium hydroxide (10 ml) and ethanol (20 ml) for 1.5 h. Then, another portion of ethyl iodide (0.8 ml, 10 mmol) and 1N potassium hydroxide (10 ml) was added and heating was continued for 10 h. On cooling, the reaction mixture was poured on dil. hydrochloric acid and the separated product was filtered and washed with water and methanol. Recrystalization from DMF afforded VIII–2a (2.1 g, 84%), mp >300°C. IR(KBr) 3300, 1710, and 800 cm^{-1}. NMR(d_6-DMSO) δ 1.36 (6H, t), 4.40 (4H, q), 4.53 (4H, s), and 7.5–8.9 (8H, m).

Compounds VIII–2b, VIII–3a–c, and VIII–4a–c were synthesized according to the similar procedure mentioned above from the corresponding nitrophenols and dibromoalkanes. The synthesis of VIII–2c, however, was unsuccessful and the physical data of the intermediates IV–2c and V–2c were presented.

IV–2b. 43%, mp 145°C. MS m/e 304(M^+).

V–2b. 48%, mp 96°C (MeOH). MS m/e 429(M^+).

VI–2b. 87%, mp 275°C. IR(KBr) 3350, 1690, and 790 cm^{-1}. NMR(d_6-DMSO) δ 1.28 (6H, t), 4.21 (4H, q), 4.40(4H, s), 6.6–8.4 (4H, m), and 11.69 (2H, brs). MS m/e 492(M^+).

VII–2b. 93%, mp >300°C (DMF). IR(KBr) 3400–2500, 1690, and 780 cm^{-1}. NMR(d_6-DMSO) δ 4.54 (4H, s) and 7.0–8.9 (8H, m). MS m/e 404(M^+–2O).

VIII–2b. 75%, mp 290°C (DMF). IR(KBr) 3300, 1700, and 800 cm^{-1}. NMR(d_6-DMSO) δ 1.36 (6H, t), 4.36 (4H, q), 4.59 (4H, s), 7.0–8.9 (8H, m), and 11.69 (2H, brs). MS m/e 476(M^+–O).

IV–2c. 35%, mp 162°C. MS m/e 304(M^+).

V-2c. 53%, mp 144°C (MeOH). MS m/e 584(M^+).

IV-3a. 90%, mp 130°C. IR(KBr) 1520 and 1340 cm^{-1}. MS m/e 318(M^+).

V-3a. 57%, mp 141°C. NMR(d_6-DMSO) δ 1.2–1.5 (12H, m), 2.1–2.4 (2H, m), 4.0–4.5 (12H, m) 6.8–7.3 (8H, m), 8.43 (2H, d), and 10.98 (2H, d). MS m/e 598(M^+).

VI-3a. 80%, mp 288°C. NMR(d_6-DMSO) δ 1.25 (6H, t), 2.1–2.4 (2H, m), 4.0–4.4 (8H, m), 6.9–8.4 (8H, m), and 11.8 (2H, brs). MS m/e 506(M^+).

VII-3a. 51%, mp 277°C (DMF). IR(KBr) 3400–2500 cm^{-1}. NMR(d_6-DMSO) δ 2.1–2.4 (2H, m), 4.0–4.5 (4H, m), 7.0–8.7 (2H, m), and 13.5 (2H, brs). MS m/e 362(M^+–$2CO_2$).

VIII-3a. 32%, mp 311°C (DMF). NMR(d_6-DMSO) δ 1.43 (6H, t), 2.1–2.4 (2H, m), 4.2–4.6 (8H, m), 7.4–8.9 (8H, m), and 13.0 (2H, brs). MS m/e 462(M^+–CO_2) and 418(M^+–$2CO_2$).

IV-3b. 87%, mp 122°C. IR(KBr) 1520 and 1340 cm^{-1}. MS m/e 318(M^+).

V-3b. 57%, mp 90°C. MS m/e 598(M^+).

VI-3b. 73%, mp 291°C. NMR(d_6-DMSO) δ 1.24 (6H, t), 2.1–2.3 (2H, m), 3.9–4.8 (8H, m), 6.6–8.5 (8H, m), and 11.8 (2H, brs). MS m/e 506(M^+).

VII-3b. 48%, mp 269°C (DMF). IR(KBr) 3400–2600 cm^{-1}. NMR(d_6-DMSO) δ 4.2–4.5 (4H, m) and 7.1–8.7 (8H, m). MS m/e 362(M^+–$2CO_2$).

VIII-3b. 35%, mp 260°C (DMF). NMR(d_6-DMSO) δ 1.41 (6H, t), 4.0–4.7 (8H, m), 6.9–8.9 (8H, m), and 15.0 (2H, brs). MS m/e 462(M^+–CO_2) and 418 (M^+–$2CO_2$).

IV-3c. 87%, mp 112°C. IR(KBr) 1520 and 1340 cm^{-1}. MS m/e 318(M^+).

V-3c. 69%, mp 108°C. MS m/e 598(M^+).

VI-3c. 59%, mp 280°C. NMR(d_6-DMSO) δ 1.28 (6H, t), 3.9–4.6 (8H, m), 7.1–8.4 (8H, m), and 11.3 (2H, brs). MS m/e 506 (M^+).

VII-3c. 34%, mp 315°C (DMF). IR(KBr) 3400–2600 cm^{-1}. NMR(d_6-DMSO) δ 2.5–3.1 (2H, m), 4.4–4.7 (4H, m), 7.4–8.6 (8H, m), and 14.9 (2H, brs). MS m/e 362(M^+–$2CO_2$).

VIII-3c. 43%, mp 273°C (DMF). NMR(d_6-DMSO) δ 1.42 (6H, t), 2.5–3.1 (2H, m), 4.2–5.0 (8H, m), 7.3–8.8 (8H, m), and 14.8 (2H, brs). MS m/e 462(M^+–CO_2) and 418(M^+–$2CO_2$).

IV-4a. 90%, mp 145°C. IR(KBr) 1520 and 1340 cm^{-1}. MS m/e 322(M^+).

V-4a. 25%, mp 151°C. MS m/e 612(M^+).

VI-4a. 77%, mp 296°C. NMR(d_6-DMSO) δ 1.25 (6H, t), 3.9–4.4 (8H, m), 6.8–8.4 (8H, m), and 11.8 (2H, brs). MS m/e 520(M^+).

VII-4a. 46%, mp 287°C (DMF). NMR(d_6-DMSO) δ 6.6–8.7 (8H, m). MS m/e 376(M^+–$2CO_2$).

VIII-4a. 35%, mp 300°C (DMF). NMR(d_6-DMSO) δ 1.42 (6H, t), 4.0–4.7 (8H, m), 7.4–8.9 (8H, m), and 15.0 (2H, brs). MS m/e 476(M^+–CO_2) and 432(M^+–$2CO_2$).

IV-4b. 95%, mp 136°C. IR(KBr) 1520 and 1340 cm^{-1}. MS m/e 332(M^+).

V-4b. 65%, mp 125°C. MS m/e 613(M^+).

VI-4b. 88%, mp 301°C. NMR(d_6-DMSO) δ 1.33 (6H, t), 4.0–4.4 (8H, m), 6.6–8.4 (8H, m), and 11.7 (2H, brs). MS m/e 520(M^+).

VII-4b. 45%, mp 276°C (DMF). IR(KBr) 3400–2600 cm^{-1}. NMR(d_6-DMSO) δ 7.1–8.7 (8H, m). MS m/e 376(M^+–$2CO_2$).

VIII-4b. 40%, mp 312°C (DMF). NMR(d_6-DMSO) δ 1.34 (6H, t), 4.1–4.6 (8H, m), 7.1–8.9 (8H, m), and 15.1 (2H, brs). MS m/e 476(M^+–CO_2), and 432(M^+–$2CO_2$).

IV-4c. 95%, mp 123°C. IR(KBr) 1520 and 1340 cm^{-1}. MS m/e 332(M^+).

V-4c. 54%, mp 111°C. MS m/e 612(M^+).

VI-4c. 41%, mp 262°C. NMR(d_6-DMSO) δ 1.29 (6H, t), 4.0–4.4 (8H, m), 7.2–8.4 (8H, m), and 11.3 (2H, brs). MS m/e 520(M^+).

VII–4c. 35%, mp 311°C (DMF). IR(KBr) 3400–2600 cm^{-1}. NMR(d_6-DMSO) δ 7.4–8.6 (8H, m) and 15.0 (2H, brs). MS m/e 376(M^+-2CO_2).

VIII–4c. 30%, mp 290°C (DMF). NMR(d_6-DMSO) δ 1.41 (6H, t), 4.2–5.0 (8H, m), 7.3–8.8 (8H, m), and 14.9 (2H, brs). MS m/e 476(M^+-CO_2) and 432(M^+-2CO_2).

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