Synthesis of Antimicrobial Agents. VII.1) Synthesis and Antibacterial Activities of Furo[2,3-g]quinoline Derivatives2)

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(Received March 24, 1984)

As part of a series of studies on the synthesis of new antibacterial agents, tetracyclic compounds having a furo[2,3-g]quinoline moiety as a common structural unit were synthesized, and their antibacterial activities were examined. Among them, 3-methyl-7-oxo-2,3-dihydro-7H-furo[2,3-h]pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (4c) exhibited the most potent antibacterial activity against Gram-positive and -negative organisms, including Pseudomonas aeruginosa, and it showed low acute toxicity to mice.

Keywords—[1]benzofuro[4,5,6-i]quinolizine; furo[2,3-h]pyrido[1,2,3-de][1,4]benzoxazine; oxazine ring; piperidine ring; pyridine ring formation; antibacterial activity; acute toxicity

Since nalidixic acid3) was found to have potent activities against Gram-negative bacteria not including Pseudomonas aeruginosa, many compounds having a 4-oxopyridine-3-carboxylic acid moiety as a partial structure have been synthesized. Among these compounds, droxacin4) and flumequine,4) whose structures consist of three condensed rings, are known to have high antibacterial activities. In this connection, we reported that furo[3,2-b][1,8]-naphthyridine derivatives5) exhibited more potent antibacterial activities and a broader spectrum of activity than other fused 1,8-naphthyridine analogues.

In the course of our studies on the synthesis of antibacterial agents, our interest was directed to furo[2,3-g]quinoline derivatives fused with piperidine or 1,4-oxazine rings at the ij-bonds of the quinoline nucleus. The present paper is concerned with the synthesis of 2,3-dihydro-7-oxo-1H,7H-benzofuro[4,5,6-i]quinolizine-6-carboxylic acid (4a), its 3-methyl derivative (4b), 2,3-dihydro-3-methyl-7-oxo-7H-furo[2,3-h]pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (4c) and the corresponding 10,11-dihydro derivatives (6a—c), and with their antibacterial activities.

![Fig. 1](image)

These structures were designed for the following reasons. a) Linear-type compounds in which a furan5) or thiazole6,7) ring is fused with the quinoline ring at the g-bond or with the 1,8-naphthyridine ring at the b-bond showed high antibacterial activities. b) Introduction of substituents on the 5-membered rings of the thiazoloquinoline derivatives decreased the
antibacterial activities.\textsuperscript{a} c) Reduction of the bulkiness of the N-substituent by cyclization of the N-alkyl group to the peri-position of the quinoline ring may affect the antibacterial activities.

**Chemistry**

**The Target Compounds**

The secondary amines (1a—c) were heated with diethyl ethoxymethylenemalonate (EMME) to afford the corresponding condensates (2a—c). Thermal cyclization of 2a—c in polyphosphoric ester (PPE) gave the esters (3a—c). The esters thus obtained were hydrolyzed by HCl to give the desired carboxylic acids (4a—c).

The 2,3-dihydrofuro derivatives (6a—c) were obtained by catalytic reduction of the esters (3a—c) using Pd-C as a catalyst, followed by hydrolysis of the resulting 2,3-dihydrofuro esters (5a—c) with 10% NaOH.

![Chart 1](image)

**Intermediates of Benzofuro[4,5,6-ij]quinolizine Derivatives**

5-Aminobenzofuran (7)\textsuperscript{a} was used as the starting material for the synthesis of the 2,3-dihydro-7-oxo-1H,7H-benzofuro[4,5,6-ij]quinolizine-6-carboxylic acid derivatives (4a—b) and the corresponding 2,3-dihydrofuro derivatives (6a, b). Compound 7 was heated with methyl acrylate or crotonic acid to give the condensate 8 or 11, respectively. In the case of the ester (8), the amino group was protected by treatment with p-toluensulfonyl chloride in pyridine to give the tosylate (9), which was hydrolyzed with KOH to the carboxylic acid (10). Treatment of 10 with PCl\textsubscript{5}, followed by AlCl\textsubscript{3} gave the cyclized compound (12a). Compound 12b was obtained by heating 11 in polyphosphoric acid (PPA). The oxo group of the tricyclic compounds (12a, b) thus obtained was reduced to a methylene group with LiAlH\textsubscript{4} to give the desired intermediates (1a, b).

**Intermediates of Furo[2,3-h]pyrido[1,2,3-de][1,4]benzoxazine Derivatives**

4-Hydroxybenzofuran-6-carboxylic acid (13)\textsuperscript{a} was used as a starting material for the synthesis of 2,3-dihydro-7-oxo-7'H-furo[2,3-h]pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid derivatives. Nitration of 13 was conducted by using various nitrating agents, among which aluminum nitrate nonahydrate was the most efficient. After decarboxylation of 14 and successive acetylation of the hydroxyl group of 15, catalytic reduction of 16 by the method
of Hill\textsuperscript{10} afforded the cyclized furo[2,3-\textit{h}][1,4]benzoxazine derivative (1e), which was used for the condensation reaction with EMME without further purification.

**Biological Studies**

The target compounds (4a—c and 6a—c) prepared in this work were tested for \textit{in vitro}
antibacterial activities (MIC, \( \mu g/ml \)) and acute toxicity (LD\(_{50}, \mu g/kg \)) on intravenous administration to mice. These results are presented in Table I. Droxicin was chosen as a reference compound because of its structural resemblance to the test compounds. The furo derivatives (4a – c) showed higher activity than the corresponding 2,3-dihydrofuro derivatives (6a – c). Antibacterial activity was little affected by the introduction of a methyl group at the 3-position. Compound 4c exhibited the highest antimicrobial activity against Gram-positive and -negative pathogens tested, including \( P.s. \) aeruginosa. In addition, replacement of methylene (Y) in 4b by oxygen (Y) in 4c significantly decreased the acute toxicity to mice.

**Experimental**

\( N\)-(5-Benzofuryl)-N-tosyl-\( \beta \)-alanine (10) — A mixture of 5-aminobenzofuran (10 g), methyl acrylate (6.8 g) and a catalytic amount of AcOH (0.1 ml) was heated under reflux for 20 h, then concentrated in vacuo. The oily residue was dissolved in pyridine (100 ml). p-Toluenesulfonyl chloride (17 g) was added portionwise to the solution at room temperature during 30 min, then the reaction mixture was heated at 80–90°C for 1 h with stirring. After being cooled, the solution was poured into ice-water (200 ml) and extracted with ether. The ether layer was washed successively with 10\(^\circ\) \( \text{HCl} \), 5\(^\circ\) \( \text{KOH} \) and water. After evaporation of the solvent, the crude product was purified by silica-gel column chromatography using CHCl\(_3\) as an eluent to give the oily methyl ester (9). A solution of the ester in 10\(^\circ\) \( \text{KOH} \) (40 ml) and 80\(^\circ\) \( \text{MeOH} \) (100 ml) was stirred for 1 h at room temperature. The reaction mixture was poured into ice-water (200 ml), then neutralized with 10\(^\circ\) \( \text{HCl} \) and extracted with CHCl\(_3\). After removal of the solvent, the residue was purified by silica-gel column chromatography using CHCl\(_3\) as an eluent to give 10 (4.8 g, 18\(^\circ\)), mp 129–130°C. Anal. Calcd for \( C_{15}H_{12}N_2O_5 \): C, 60.15; H, 4.76; N, 3.89. Found: C, 59.84; H, 4.82; N, 3.92.

9-Oxo-6,7,8,9-tetrahydrofuro[3,2-f]quinoline (12a) — Phosphorus pentachloride (3.0 g) was added to a solution of 10 (5.4 g) in benzene (30 ml) at 0–5°C, and the mixture was heated at 100°C for 30 min. Aluminum chloride (2.5 g) was added to the solution at 5°C during 30 min. The whole was stirred for 3 h at room temperature, then most of the benzene solution was removed by decantation, and water was added to the residue, which was extracted with CHCl\(_3\). The combined benzene and CHCl\(_3\) solution was washed with water and concentrated to dryness. The crude product was subjected to silica-gel column chromatography using CHCl\(_3\) as an eluent to give 12a (1.5 g, 54\(^\circ\)), mp 130–134°C. Anal. Calcd for \( C_{15}H_{12}N_2O_5 \): C, 70.57; H, 4.84; N, 7.47. Found: C, 70.54; H, 4.87; N, 7.38.

6-[2,2-Bis(ethoxy carbonyl)ethenyl]-6,7,8,9-tetrahydrofuro[3,2-f]quinoline (2a) — A mixture of 12a (1.0 g) and LiAlH\(_4\) (0.4 g) in tetrahydrofuran (THF) (100 ml) was heated under reflux for 1 h. Excess LiAlH\(_4\) was decomposed by adding water cautiously. The solvent was evaporated off. The residue was mixed with CHCl\(_3\) and water. The CHCl\(_3\) layer was separated, washed and dried. After removal of the solvent, the residue was subjected to silica-gel column chromatography using CHCl\(_3\) as an eluent to give 1a as an oil (0.8 g). EMME (1.1 g) was added to the oily intermediate (1a) and the mixture was heated at 120–125°C for 1.5 h, then cooled. The reaction mixture was triturated with ether. The insoluble material was collected by filtration and recrystallized from petroleum ether to give 2a (1.0 g, 55\(^\circ\)) as colorless needles, mp 83–84°C. Anal. Calcd for \( C_{19}H_{23}N_2O_5 \): C, 66.45; H, 6.16; N, 4.07. Found: C, 66.44; H, 6.19; N, 4.14.

Ethyl 2,3-Dihydro-7-oxo-1H,7H-benzofuro[4,5,6-ij]quinoline-6-carboxylate (3a) — A mixture of 2a (5.0 g) and PPE (4.5 g) was heated at 120°C for 20 min. After the mixture had cooled, water was added to the viscous oil and stirring was continued until a homogeneous suspension was formed. The product was extracted with CHCl\(_3\). The CHCl\(_3\) solution was washed with water, dried over Na\(_2\)SO\(_4\) and concentrated to dryness. The residue was recrystallized from EtOH to give 3a (3.4 g, 79\(^\circ\)) as colorless needles, mp 256–259°C. Anal. Calcd for \( C_{21}H_{25}N_2O_5 \): C, 68.67; H, 5.08; N, 4.70. Found: C, 68.57; H, 5.21; N, 5.09.

7-Methyl-9-oxo-6,7,8,9-tetrahydrofuro[3,2-f]quinoline (12b) — A solution of 5-aminobenzofuran (9.0 g) and crotonic acid (6.4 g) in benzene (35 ml) was heated under reflux for 16 h. Benzene (35 ml) and 2.5\(^\circ\) \( \text{KOH} \) (175 ml) were added to the cooled reaction mixture with stirring. The aqueous layer was separated, neutralized with conc. HCl and extracted with CHCl\(_3\). The CHCl\(_3\) solution was washed with water, dried over Na\(_2\)SO\(_4\) and concentrated to dryness. PPA (40 g) was added to the residue and the mixture was heated at 110–115°C for 30 min with stirring. Water (200 ml) was added to the cooled viscous oil and the product was extracted with CHCl\(_3\). The crude product obtained from the CHCl\(_3\) extract was purified by silica-gel column chromatography using CHCl\(_3\) as an eluent to give 12b (2.9 g, 21\(^\circ\)) as light yellow needles, mp 108–110°C. Anal. Calcd for \( C_{19}H_{21}N_2O_5 \): C, 71.63; H, 5.50; N, 6.95. Found: C, 71.42; H, 5.63; N, 6.79.

Ethyl 2,3-Dihydro-3-methyl-7-oxo-1H,7H-benzofuro[4,5,6-ij]quinoline-6-carboxylate (3b) — A mixture of 12b (3.0 g) and LiAlH\(_4\) (1.5 g) in THF (150 ml) was heated under reflux for 2 h. Excess LiAlH\(_4\) was decomposed by adding water cautiously, and the solvent was evaporated off. The residue was mixed with CHCl\(_3\) and water. EMME (3.2 g) was added to the crude product (1b) obtained from the separated CHCl\(_3\) layer. The mixture was heated at 120–130°C for 2.5 h, followed by addition of PPE (50 g), and the whole was heated at 120°C for an additional 20 min.
Water was added to the cooled reaction mixture and the product was extracted with CHCl₃. The crude 3b obtained from the CHCl₃ extract was recrystallized from EtOH to afford 3b (2.2 g, 47%) as colorless prisms, mp 260—262 °C. Anal. Calcd for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.49. Found: C, 69.78; H, 5.60; N, 4.64.

4-Hydroxy-5-nitrobenzofuran-6-carboxylic Acid (14) —— Aluminum nitrate nonahydrate (9.1 g) was added portionwise to a suspension of 13 (15.0 g) in AcOH (300 ml) at 20—25 °C during 1 h. After being stirred for an additional 1 h, the reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na₂SO₄ and concentrated until the product was deposited. The precipitate was collected by filtration and washed with ether to give 14 (6.8 g, 36%), mp 231—233 °C (dec.). Anal. Calcd for C₆H₅NO₄: C, 48.44; H, 2.26; N, 6.28. Found: C, 48.32; H, 2.33; N, 6.07.

4-Hydroxy-5-nitrobenzofuran (15) —— Copper powder (6 g) was added to a solution of 14 (6.7 g) in quinoline (70 ml) at 180 °C with vigorous stirring, and heating was continued for 10 min. AcOEt was added to the cooled reaction mixture and insoluble materials were filtered off. The filtrate was shaken with 3 n HCl to remove quinoline. The organic layer was washed with water, dried over Na₂SO₄ and concentrated to dryness. The residue was subjected to silica-gel column chromatography using benzene as an eluent to give 15 (3.1 g, 58%), mp 170 °C. Anal. Calcd for C₆H₅NO₄: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.42; H, 2.96; N, 7.63.

4-Acetonylxy-5-nitrobenzofuran (16) —— A mixture of 15 (1.05 g), K₂CO₃ (0.83 g), KI (0.20 g) and chloroacetic (1.0 ml) in aceton (20 ml) was heated under reflux for 1.5 h. The inorganic materials were removed by filtration, and the filtrate was concentrated to dryness. The residue was triturated with isopropyl ether and the resulting precipitate was collected by filtration to give 16 (1.19 g, 86%), mp 78 °C. Anal. Calcd for C₁₁H₉NO₄: C, 56.17; H, 3.86; N, 5.96. Found: C, 55.98; H, 3.69; N, 6.04.

Ethyl 3-Methyl-7-oxo-2,3-dihydro-7H-furo[2,3-a]pyrido[1,2,4-de][1,4]benzoxazine-6-carboxylate (3c) —— Compound 16 (1.6 g) was catalytically reduced in the presence of Raney Ni (2.0 ml) in EtOH (50 ml) at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated to dryness. EMME (1.6 g) was added to the oily

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<th>mp (°C)</th>
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residue and the mixture was heated at 120—130 °C for 40 min. PPE (25 g) was added to the reaction mixture and heating was continued at 130—140 °C for 1 h. After being cooled, the reaction mixture was poured into ice-water. The precipitate was collected by filtration and recrystallized from EtOH to give 3c (1.3 g, 61%), mp 235—237 °C. Anal. Calcd for C_{13}H_{14}NO_3: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.46; H, 4.88; N, 4.53.

6-Carboxylic Acids (4a—c): General Procedure—An ester (3a—c) was dissolved in 10 volumes of conc. HCl-AcOH (1:11) and heated under gentle reflux. After the reaction mixture had cooled, the precipitate was collected by filtration and recrystallized from N,N-dimethylformamide (DMF) to give the corresponding acid (4a—c) (Table II).

2,3-Dihydrofuro Derivatives (6a—c): General Procedure—An ester (3a—c) was hydrogenated in the presence of Pd-C in MeOH at atmospheric pressure. The dihydrofuro derivative (5a—c) thus obtained was hydrolyzed by heating in 10% NaOH to give the corresponding acid (6a—c) (Table III).

Acknowledgement The authors wish to thank Dr. Y. Osada and the staff of the Laboratory of Microbiology and the Analytical Section.

References and Notes

2) This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan. Tokyo, 1980, Abstr., p. 276.