Synthesis of Benzimidazo-substituted 3-Quinolinecarboxylic Acids as Antibacterial Agents

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The 6- and 7-(1-ethylbenzimidazolyl)-substituted 1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids were synthesized. Antibacterial activity was tested *in vitro*. Only one of the new compounds prepared showed slight antibacterial activity against one of the strains tested. So, they are of no interest as antibacterial agents.

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Introduction.

During the last 25 years, Oxolinic **1**, Nalidixic **2** and Pipemidic **3** acids have been widely used as lead compounds in the research of new antibacterial agents [1], becoming an antibacterial agents group commonly named the quinolone chemotherapeutics [2]. The presence of 6 and 7 substituents increases activity, being the most active structure the one which bear a fluorine atom at position 6 and a piperazine ring at position 7 of the quinolone ring as shown in the QSAR study made by Fujita on this group of drugs [3]. In recent studies the mechanism of action of the quinolones was elucidated. These agents were shown to be specific inhibitors of the A subunit of the bacterial topoisomerase DNA gyrase [4].

On the other hand, benzimidazole group appears in some anthelmintic agents as Thiabendazole **4**, Parbendazole **5** and Mebendazole **6** [5], as well as in some inmunostimulant agents as Procodazol **7** [6] and Dibazol **8** [7].

In this paper our aim is to synthesize 4-oxoquinoline-3-carboxylic acids which, in a first approximation, bear on its structures, a benzimidazole moiety at positions 6- or 7-, as **9**, in order to know the influence of this heterocyclic system on the antibacterial activity and their behaviour as inmunomodulators.

Chart 1

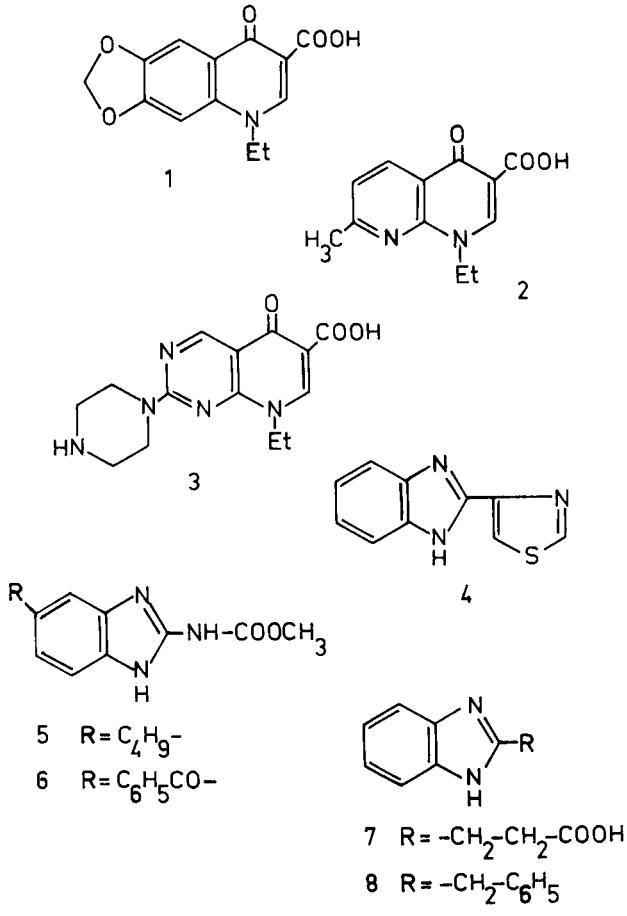
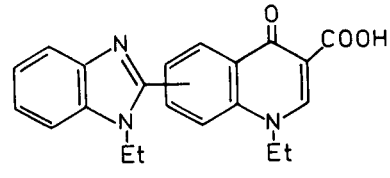


Chart 2

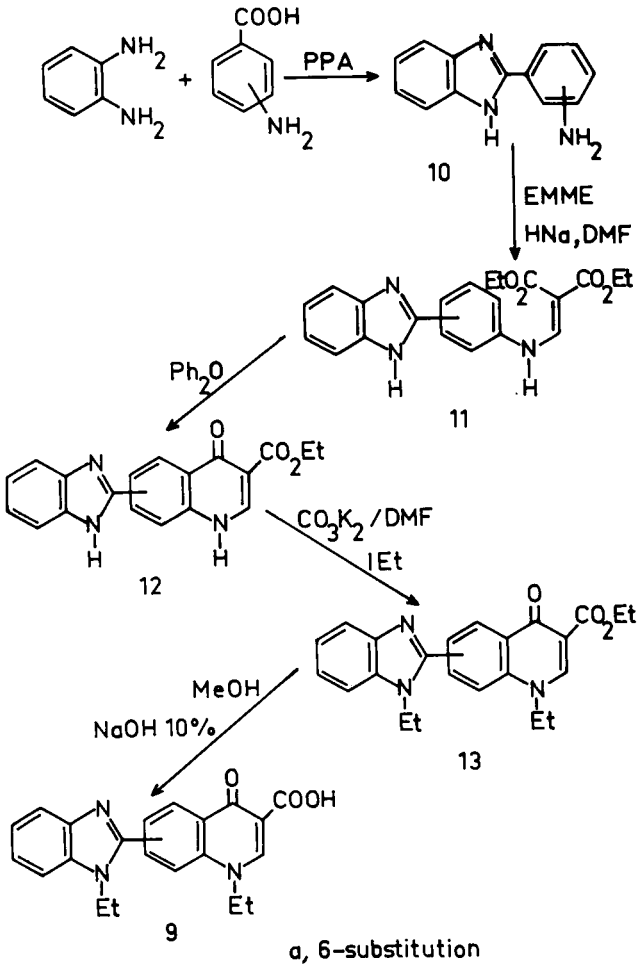


Chemistry.

Scheme 1 outlines the synthetic pathway used for the obtention of both quinoline derivatives **9a** and **9b** by application of the Gould-Jacobs synthesis [8]. Reaction of *o*-phenylenediamine with *p*- and *m*-aminobenzoic acids in polyphosphoric acid afforded 2-(4-aminophenyl)benzimidazole **10a** and 2-(3-aminophenyl)benzimidazole **10b** respectively.

The reaction of the latter compounds with diethyl ethoxymethylenemalonate (EMME) afforded the anilinomethylene malonates **11a** and **11b**, which were then converted into the corresponding quinolinecarboxylic esters **12a** and **12b** by thermal cyclization effected in boiling diphenyl ether, followed by *N*-ethylation on both nitrogen atoms, simultaneously as expected, with ethyl iodide in the presence of potassium carbonate in *N,N*-dimethylformamide.

Scheme 1



Successive alkaline hydrolysis in methanol afforded the desired quinoline-3-carboxylic acids **9a** and **9b**.

Cyclization of **11** to **12** was proved by the ^{1}H nmr spectra of **12** showing signals due to only one ethyl group instead of the two groups of **11**. At the same time, signal at 9.0 ppm (CH) moves to 9.7 (H_2-quinoline). Site of cyclization of **12b** was assigned comparing its spectrum with the **12a** one.

N-Ethylation on both nitrogen atoms of **13** was probed by the lack of N-H signals both in ir and nmr spectra together with broad signals of two slightly different ethyl groups in nmr.

The infrared spectra of compounds **9a** and **9b** show an absorption band at 1740 and 1720 cm^{-1}, respectively, due to the C=O stretching vibration, as well as the absorption band at 1610 (C=N) cm^{-1} on both isomers. In the nmr spectra signals due to ethyl groups (1.8 and 5.0 ppm) and benzimidazole moiety protons (8.0 ppm) appear at the same shifts. As expected, the position of the benzimidazole substitution at C-6 or C-7 leads to an upfield shifts of 0.1 and 0.3 ppm for H-5 and H-8 respectively in **9b** with regard to **9a**, while H-2 signal appears at the same shift in both cases.

Microbiology.

The 1-ethyl-1,4-dihydro-4-oxo-6-[2-(1-ethylbenzimidazolyl)]quinoline-3-carboxylic acid **9a** and its 7-analogue **9b** were tested *in vitro* for their antibacterial activity against a series of gram positive and gram negative strains (ATCC collection). *In vitro* bacterial susceptibility (minimal inhibitory concentration) was determined by the Chabbert dilution method using Mueller-Hinton liquid media. Only **9b** was slightly active against *Shigella dysenteriae* ATCC 13313 (333 μg/ml).

These unsuccessful results did not justify the extension of the synthesis to new compounds of the series.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and on an electrothermal melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer (potassium bromide pellets). The ^{1}H nmr spectra were recorded on a Perkin-Elmer R-12 60 MHz spectrometer in trifluoroacetic acid and chemical shifts are given in ppm (δ) relative to internal tetramethylsilane. The elemental analyses were performed by "Centro Nacional de Quimica Orgánica", Madrid.

General Procedure for the Reaction of *o*-Phenylenediamine with Aminobenzoic Acids.

A mixture of 18.5 g (0.17 mole) of *o*-phenylenediamine and 22.5 g (0.16 mole) of aminobenzoic acid in 250 g of polyphosphoric acid was heated with stirring in an oil bath at 180° for 5 hours, cooled to room temperature and poured into 500 ml of water. The resulting precipitate **10** was filtered off, stirred with aqueous 10% sodium hydroxide, filtered off and recrystallized from the appropriate solvent.

2-(4-Aminophenyl)benzimidazole **10a**.

This compound was obtained as white crystals (methanol/water) in 58% yield, mp 243-244° (lit [9], mp 240°); ir: ν 3440, 3360 (NH), 1620 (C=N), 1610, 1500, 1440 (Ar) cm^{-1}; ^{1}H nmr: δ 7.8-8.7 (m, 8H, aromatic H) ppm.

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.29; N, 20.08. Found: C, 74.36; H, 5.21; N, 20.20.

2-(3-Aminophenyl)benzimidazole **10b**.

This compound was obtained as white crystals (ethyl acetate) in 53% yield, mp 258-260° (lit [10], mp 251-252°); ir: ν 3460, 3360 (NH), 1620 (C=N), 1590 (Ar) cm^{-1}; ^{1}H nmr: δ 7.8-8.6 (m, 8H, aromatic H) ppm.

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.29; N, 20.08. Found: C, 74.90; H, 5.34; N, 19.89.

General Procedure for the Reaction of Aminophenylbenzimidazoles **10a** and **10b** with Diethyl Ethoxymethylenemalonate.

To a stirred mixture of 13 g (0.062 mole) of the corresponding 2-(aminophenyl)benzimidazole, 18.2 g (0.081 mole) of diethyl ethoxymethylenemalonate and 75 ml of *N,N*-dimethylformamide, 2.0 g (0.066 mole) of 80% sodium hydride was added portionwise

over a period of 10 minutes under ice-cooling. Stirring was continued for another 30 minutes in an ice bath and at room temperature for 16 hours. The resulting mixture was then poured into 250 ml of water containing 10 ml of acetic acid. The precipitate **11** was filtered off and recrystallized from the appropriate solvent.

Diethyl [4-(2-Benzimidazolyl)phenyl]aminomethylenemalonate **11a**.

This compound was obtained as white crystals (toluene) in 93% yield, mp 188-190°; ir: ν 3280 (NH), 1680 (C=O), 1630 (C=N), 1600 (Ar), 1250 (OEt) cm^{-1}; ^1H nmr: δ 1.5 (m, 6H, $2CH_3$), 4.7 (c, 4H, $2CH_2$), 7.8 (m, 6H, H-benzimidazole and H_2- and H_6-phenyl), 8.4 (m, 2H, H_3- and H_5-phenyl), 9.0 (s, 1H, CH), 9.2 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{21}H_{21}N_3O_4$: C, 66.47; H, 5.57; N, 11.07. Found: C, 66.74; H, 5.44; N, 11.01.

Diethyl [3-(2-Benzimidazolyl)phenyl]aminomethylenemalonate **11b**.

This compound was obtained as white crystals (benzene) in 55% yield, mp 195-197°; ir: ν 1700 (C=O), 1620 (C=N), 1590 (Ar), 1250 (OEt) cm^{-1}; ^1H nmr: δ 1.5 (m, 6H, $2CH_3$), 4.7 (m, 4H, $2CH_2$), 7.7-8.4 (broad m, 8H, aromatic-H), 8.9 (s, 1H, CH), 9.2 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{21}H_{21}N_3O_4$: C, 66.47; H, 5.57; N, 11.07. Found: C, 66.89; H, 5.66; N, 10.79.

General Procedure for the Cyclization of the Aminomethylenemalonates **11a** and **11b**.

Compound **11** (14 g, 0.036 mole) was added portionwise over a period of 1 hour to 100 ml of boiling diphenylether and the resulting solution was heated under reflux with stirring for 30 minutes. After cooling the mixture to room temperature, 300 ml of diethyl ether was added. The resulting precipitate **12** was filtered off and recrystallized from *N,N*-dimethylformamide.

1,4-Dihydro-4-oxo-6-(2-benzimidazolyl)quinoline-3-carboxylic Acid Ethyl Ester **12a**.

This compound was obtained as white crystals in 65% yield, mp 318°; ir: ν 3200 (NH), 1700 (C=O), 1630 (C=N), 1590 (Ar), 1200 (OEt) cm^{-1}; ^1H nmr: δ 1.6 (t, 3H, CH_3), 4.8 (c, 2H, CH_2), 8.0 (m, 4H, H-benzimidazole), 8.8 (m, 2H, H_7- and H_8-quinoline), 9.7 (m, 2H, H_2- and H_5-quinoline) ppm.

Anal. Calcd. for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.53; N, 12.60. Found: C, 68.10; H, 4.83; N, 12.64.

1,4-Dihydro-4-oxo-7-(2-benzimidazolyl)quinoline-3-carboxylic Acid Ethyl Ester **12b**.

This compound was obtained as white crystals in 85% yield, mp 328°; ir: ν 3200 (NH), 1700 (C=O), 1610 (C=N), 1540 (Ar), 1200 (OEt) cm^{-1}; ^1H nmr: δ 1.5 (t, 3H, CH_3), 4.7 (c, 2H, CH_2), 8.0 (m, 4H, H-benzimidazole), 8.4 (m, 1H, H_8-quinoline), 8.8 (m, 1H, H_6-quinoline), 9.1 (m, 1H, NH), 9.3 (m, 1H, H_5-quinoline), 9.7 (s, 1H, H_2-quinoline) ppm.

Anal. Calcd. for $C_{19}H_{15}N_3O_3 \cdot \frac{1}{2}\ C_3H_7NO$: C, 66.56; H, 5.04; H, 13.25. Found: C, 66.79; H, 5.18; N, 13.33.

General Procedure for the Ethylation of **12a-b**.

A slurry of 3.3 g (0.01 mole) of **12**, 2.8 g (0.015 mole) of anhydrous potassium carbonate in 50 ml of *N,N*-dimethylformamide was stirred and heated on a steam bath for 1 hour and then treated with a solution of 3.5 g (0.022 mole) of ethyl iodide in 5 ml of *N,N*-dimethylformamide. The resulting mixture was further stirred and heated for 2 hours and then concentrated to dryness. The residue was partitioned between chloroform and water. The organic phase was dried over magnesium sulphate and concentrated to dryness to give a solid residue, **13**, which was recrystallized from toluene.

1-Ethyl-1,4-dihydro-4-oxo-6-[2-(1-ethylbenzimidazolyl)]quinoline-3-carboxylic Acid Ethyl Ester **13a**.

This compound was obtained as white crystals in 51% yield, mp 203-204°; ir: ν 1730 (C=O), 1600 (C=N), 1450 (Ar), 1230 (OEt), 1090 (C-N) cm^{-1}; ^1H nmr: δ 1.7 (broad m, 9H, $3CH_3$), 4.9 (broad m, 6H, $3CH_2$), 8.0 (m, 4H, H-benzimidazole), 8.8 (m, 2H, H_7- and H_8-quinoline), 9.4 (s, 1H, H_5-quinoline), 9.75 (s, 1H, H_2-quinoline ppm.

Anal. Calcd. for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.78. Found: C, 71.26; H, 6.12; N, 10.65.

1-Ethyl-1,4-dihydro-4-oxo-7-[2-(1-ethylbenzimidazolyl)quinoline]-3-carboxylic Acid Ethyl Ester **13b**.

This compound was obtained as white crystals in 44% yield, mp 189-191°; ir: ν 1730 (C=O), 1615 (C=N), 1480 (Ar), 1220 (OEt) cm^{-1}; ^1H nmr: δ 1.7 (m, 9H, $3CH_3$), 4.7 (m, 6H, $3CH_2$), 8.0 (m, 4H, H-benzimidazole), 8.5 (d, 1H, H_8-quinoline), 9.0 (s, 1H, H_6-quinoline), 9.3 (d, 1H, H_5-quinoline), 9.7 (s, 1H, H_2-quinoline) ppm.

Anal. Calcd. for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.78. Found: C, 70.87; H, 5.68; N, 10. 97.

General Procedure for the Hydrolysis of Esters **13a-b**.

A mixture of 7.5 g (0.019 mole) of **13**, 28 ml of methanol and 28 ml of aqueous 10% sodium hydroxide was heated to reflux for 1 hour. The methanol was removed under reduced pressure and the residual solution was neutralized with aqueous 10% hydrochloric acid. The resulting solid was filtered off, washed with water and recrystallized from *N,N*-dimethylformamide.

1-Ethyl-1,4-dihydro-4-oxo-6-[2-(1-ethylbenzimidazolyl)]quinoline-3-carboxylic Acid **9a**.

This compound was obtained as white crystals in 57% yield, mp 258-260°; ir: ν 1740 (C=O), 1610 (C=N), 1470 (Ar) cm^{-1}; ^1H nmr: δ 1.8 (m, 6H, $2CH_3$), 5.0 (broad m, 4H, $2CH_2$), 8.0 (m, 4H, H-benzimidazole), 8.8 (m, 2H, H_7- and H_8-quinoline), 9.4 (s, 1H, H_5-quinoline), 9.8 (s, 1H, H_2-quinoline) ppm.

Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.29; N, 11.62. Found: C, 69.81; H, 5.26; N, 11.84.

1-Ethyl-1,4-dihydro-4-oxo-7-[2-(1-ethylbenzimidazolyl)]quinoline-3-carboxylic Acid **9b**.

This compound was obtained as white crystals in 74% yield, mp 325°; ir: ν 1720 (C=O), 1610 (C=N), 1450 (Ar) cm^{-1}; ^1H nmr: δ 1.8 (m, 6H, $2CH_3$), 5.0 (m, 4H, $2CH_2$), 8.0 (m, 4H, H-benzimidazole), 8.5 (m, 1H, H_8-quinoline), 9.0 (m, 1H, H_6-quinoline), 9.3 (d, 1H, H_5-quinoline), 9.8 (s, 1H, H_2-quinoline) ppm.

Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.29; N, 11.62. Found: C, 70.05; H, 5.49; N, 11.62.

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REFERENCES AND NOTES

[1] V. Cecchetti, S. Dominici, A. Fravolini and F. Schiaffella, *Eur. J. Med. Chem.*, **19**, 29 (1984).

[2] R. E. Bambury in Burgers Medicinal Chemistry, 4th Ed, Part **II**, M. E. Wolff, ed, John Wiley and Sons Inc., New York 1979, p 66.

[3] T. Fujita in Drug Design: Fact or Fantasy?, G. Jolles and K. R. H. Wooldridge, eds, Academic Press, London 1984, p 19.

[4] J. M. Domagala, L. D. Hanna, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez and M. Solomon, *J. Med. Chem.*, **29**, 394 (1986).

[5] A. Marxer, O. Schier in Progress in Drug Research, Vol **21**, Ernst Jucker, ed, Birkhause Verlag Basel, Stuttgart 1977, p 27.

[6] C. Fernandez, V. M. Escudero and M. Izquierdo, *Rev. Clin. Esp.*, **141**, 51 (1976).

[7] C. Fernandez, V. M. Escudero and M. Izquierdo, *Rev. Clin. Esp.*, **135**, 539 (1974).

[8] R. G. Gould and W. A. Jacobs, *J. Am. Chem. Soc.*, **61**, 2890 (1939).

[9] Kalle & Co., A.-G., British Patent 895,001; *Chem. Abstr.*, **57**, 14578 (1962).

[10] B. Miklaszewski and S. von Niementowski, *Chem. Ber.*, **34**, 2958 (1901).