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Synthesis and Antimicrobial Activity of Benzofuran-Carboxamide Derivatives

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Abstract□The reaction of the sodium salts of 4-methoxy and 4,7-dimethoxy 6-hydroxybenzofuran-5-carboxylic acid with ethyl chloroformate yields the corresponding dicarbethoxy derivatives. The N-substituted amides were obtained by treating the latter compounds with amines. The corresponding hydrazides were synthesized by the reaction of hydrazine hydrate on the dicarbethoxy derivatives which spontaneously cyclized to 5-substituted-2,3-dihydro-1,3,4-oxadiazol-2-one. Also the reaction with phenyl hydrazine has been studied. The dicarbethoxy derivatives and N-substituted amides were tested against Gram positive and Gram negative bacteria *in vitro*. Most of the compounds possess moderate or slight activity against Gram positive bacteria.

Keywords□Benzofuran-carboxamide, antimicrobial activity.

Some hydrazides possess activity against *Mycobacterium tuberculosis*[1,2]. Also substituted salicylamides possess antifungal[3,4], antibacterial[3,5], insecticidal[6], pesticidal[1,7] and molluscicidal properties[8]. These findings stimulated the interest for the synthesis of a new series of compounds for antimicrobial evaluation.

The naturally occurring furochromones "visnagin and Khellin" are oxidized with hydrogen peroxide in presence of alkali forming 4-methoxy-(**Ia**) and 4,7-dimethoxy-6-hydroxybenzofuran-5-carboxylic acid (**Ib**). On treating the sodium salts of **Ia** or **Ib** with ethyl chloroformate in dry acetone the corresponding dicarbethoxy derivatives (**IIa,b**) were obtained.

The reaction of amines *i.e.* p-bromoaniline, m-anisidine, p-toluidine, 2-aminopyrazine, 2-benzimidazolamine with **IIa** and **b** proceeds *via* the initial hydrolysis of ester group at the 6-position by stirring the reaction mixture at room temperature to form **IIIa** and **b**. However, refluxing the reaction mixture leads to the formation of the N-substituted amides (**IVa-g**) by a further rupture of the COO-CO-groups.

Similarly, phenyl hydrazine yields the corresponding hydrazide **IVh.**

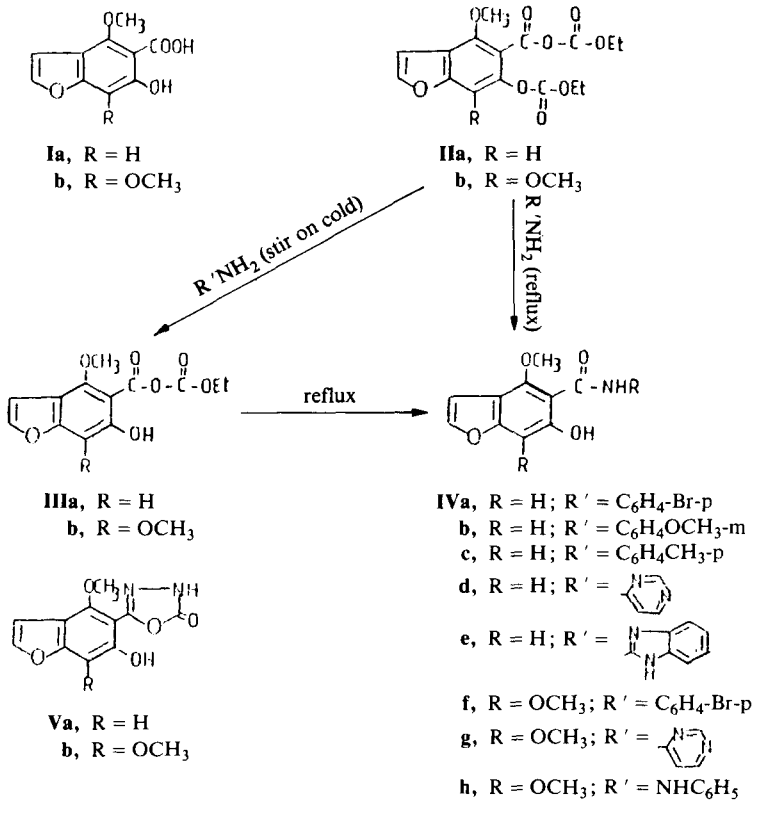
On the other hand, the reaction of **IIa** and **b** with hydrazine hydrate proceeds also *via* the initial hydrolysis of the ester group at the 6-position followed by the formation of the hydrazide which spontaneously cyclized to the corresponding 5-substituted-2,3-dihydro-1,3,4-oxadiazol-2-one (**Va,b**).

The results given in Table I show that all the compounds are inactive against Gram negative bacteria. It is obvious that most of the compounds possess slight activity except compound **IVb** which is

Table I. Antibacterial activity of benzofuran-carboxamide derivatives

Test Org.	IIa	IIb	IId	IVa	IVb	IVc	IVd	IVf	IVg	Va	Vb	Control
Bacillus subtilis	+	−	+	−	+	+	+	+	+	−	+	−
Pseudomonas	−	−	−	−	−	−	−	−	−	−	−	−
Aspergillus	+	−	+	−	+	+	−	−	+	−	+ +	−
Fusarium	+	−	+	−	+	+	−	−	+	−	+ +	−

The above estimation was based on the diameter of the inhibition zone formed. A control with acetone was also performed. −, no inhibition zone (12 m); +, slight inhibition zone (13-16m); + +, moderate inhibition zone (17-24m).



moderately active on *Fusarium.*

EXPERIMENTAL

Melting points are not corrected. The infrared spectra were carried out in potassium bromide on a Unicom Sp-2000 spectrophotometer. The ^{1}H-NMR spectra (at 100 MHz) on a FT 100, FA Jeol, Tokyo, using TMS as internal standard, and $CDCl_3$ as solvent. The ^{1}-NMR spectra were expressed in δ scale.

Preparation of the monocarbethoxy IIIa,b and dicarbethoxy IIa, b derivatives

Suspended was 0.001 mole of sodium salts of acid of Khellin or Visnagin in 30 m*l* dry acetone and 3 mg anhydrous potassium carbonate was added gradually while cooling and then was added 5 mg of ethyl chloroformate in 20 m*l* acetone. After 0.5 hr the reaction mixture was refluxed for 2 hrs, then filtered while hot and the excess acetone was evaporated to give **IIa** and **IIb** which were crystallized from the appropriate solvent.

IIa was crystallized from benzene as colorless needles, m.p. 90°C, yield Ca 70%. Calcd for $C_{16}H_{16}O_9$: C, 54.54; H, 4.54; Found C, 54.55; H, 4.51%. IR: 1800, 1780 cm^{-1} (COO-CO). ^{1}H-NMR: 7.63 and 6.9 (2H, furan, d, J = 2.1 Hz), 7.1 (1H, aromatic proton H_7, s), 4.4 (4H, $2CH_2$, q), 4.2 (3H, OCH_3, s) and 1.38 (6H, 2 CH_3, t).

IIb was crystallized from n-hexane as colorless crystals, m.p. 54-55 °C, yield Ca 75%. Calcd for $C_{17}H_{18}O_{10}$: C, 53.4; H, 4.71. Found C, 53.2; H, 4.61%. ^{1}H-NMR: 7.6 and 6.9 (2H, furan protons, d, J = 2.2 Hz), 4.4 (4H, 2 CH_2, q), 4.1 (6H, 2 × CH_3, s), 1.59 (6H, 2 CH_3, t).

Preparation of the N-substituted amides IVa-g

A mixture of **IIa** or **b** (0.001 mole) and 0.001 mole of amine *i.e.* p-bromoaniline, m-anisidine, p-toluidine, 2-amino pyrazine, 2-benzimidazolamine was stirred for 0.5 hr in ethanol (20 m*l*), filtered and crystallized from ethanol to give **IIIa** and **IIIb**, respectively.

When the above reaction mixture was refluxed for 2 hours then concentrated to about 10 m*l*, filtered and crystallized from the suitable solvent, it gave **IVa-g.**

IIIa was obtained as colorless crystals, m.p. 155-

58 °C, yield Ca 60%. Calcd for $C_{13}H_{12}O_7$: C, 55.71; H, 4.28. Found C, 55.44; H, 4.15%.

IIIb was obtained as pale yellow crystals, m.p. 128 °C, yield Ca 65%. Calcd for $C_{14}H_{14}O_8$: C, 54.19; H, 4.5. Found C, 54.15; H, 4.42%. IR: 3300-2800 (OH), 1775 and 1710 cm^{-1} (COO-CO). ^{1}H-NMR: 7.6 and 6.9 (2H, furan, d, J = 2.1), 4.4-4.32 (2H, CH_2, q), 4.1 (6H, 2 × OCH_3, s), 1.43-1.37 (3H, -CH_3, t).

IVa was crystallized from cyclohexane as colorless crystals, m.p. 120 °C, yield Ca 54%. Calcd for $C_{16}H_{12}BrNO_4$: C, 53.04; H, 3.31; N, 3.87; Br, 22.1, Found C, 53.2; H, 3.5; N, 3.6; Br, 21.9%.

IVb was crystallized from cyclohexane as colorless needles, m.p. 131 °C, yield Ca 60%. Calcd for $C_{17}H_{15}NO_5$: C, 65.18; H, 4.79; N, 4.47. Found C, 65.2; H, 5.2; N, 4.18%. IR: 3300 (OH), 3120 (NH), 1660 cm^{-1} (C = O group).

IVc was crystallized from benzene as colorless crystals, m.p. 114.7 °C, yield Ca 65%. Calcd for $C_{17}H_{15}NO_4$: C, 68.69; H, 5.05, N, 4.41. Found C, 68.8; H, 5.20, N, 4.80%. ^{1}H-NMR: 13.6 (1H, OH, s), 10.24 (1H, NH, s), 7.5 and 6.8 (2H, furan, d), 7.4 and 7.1 (4H, aromatic, d), 6.8 (1H, C_7, s), 4.2 (3H, OCH_3, s), and 2.34 (3H, CH_3, s).

IVd was crystallized from cyclohexane as golden crystals, m.p. 178 °C, yield Ca 63%. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.86; N, 14.74. Found C, 59.11; H, 3.90; N, 14.35%.

IVe was crystallized from benzene as colorless powder, m.p. 129 °C, yield Ca 58%. Calcd for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.02; N, 13.0. Found C, 63.0; H, 4.3; N, 12.80%. IR: 3320 (OH), 3160 (NH), 1690 cm^{-1} (C = O).

IVf was crystallized from methanol as pale yellow crystals, m.p. 158 °C, yield Ca 60%. Calcd for $C_{17}H_{14}BrNO_5$: C, 52.04; H, 3.57; N, 3.57; Br, 20.41. Found C, 52.43; H, 3.77; N, 4.06, Br, 20.51%.

IVg was crystallized from methanol as colorless crystals, m.p. 147 °C, yield Ca 57%. Calcd for $C_{15}H_{13}O_5N_3$: C, 57.14; H, 4.14; N, 13.33. Found C, 57.23; H, 4.20; N, 13.50%.

Preparation of hydrazide derivative IVh

A mixture of **IIb** (0.001 mole) and phenyl-hydrazine (0.001 mole) was refluxed for 2 hr, filtered and crystallized from methanol, and it was obtained as golden crystals, m.p. 149 °C, yield Ca 60%. Calcd for $C_{17}H_{16}O_5N_2$: C, 64.97; H, 5.09; N, 4.46. Found C, 64.55; H, 4.88; N, 4.78. IR: 3330 (OH), 3160 (NH), 1640 cm^{-1} (C = O).

Preparation of 5-substituted 2,3-dihydro-1,3,4-oxadiazol-2-one (Va,b)

A mixture of **IIa** or **b** (0.01 mole) and hydrazine hydrate (0.01 mole) in 3 mole absolute ethanol was stirred for 1 hr, filtered off and crystallized from the proper solvent.

Va was crystallized from acetone as colorless crystals, m.p. 205 °C, yield Ca 65%. Calcd for $C_{11}H_8N_2O_5$: C, 53.22; H, 3.23; N, 11.29. Found C, 52.98; H, 3.01; N, 11.51%. IR: 3360 (OH), broad at 3200 (NH), 1710 (C = O, cyclic lactam), broad at 1630 cm^{-1} (CO-NH and C = N). ^{1}-NMR (DMSO): 13.5 (1H, OH, s), 9.4 (1H, NH, s), 6.95 (1H, aromatic proton H_7, s), 6.9, 6.4 (2H, 2 furan, d), 4.02 (3H, OCH_3, s).

Vb was crystallized from methanol as colorless needles, m.p. 200 °C, yield Ca 63%. Calcd for $C_{12}H_{10}N_2O_6$: C, 51.79; H, 3.59; N, 10.07. Found C, 52.23; H, 3.72; N, 9.71. ^{1}H-NMR (in DMSO); 9.9 (1H, OH, s), 7.87 (1H, NH aromatic, s), 7.8 and 7.1 (2H, furan, d, J = 2.1), 4.14, 4.09 (6H, 2 × CH_3, s).

Antimicrobial activity

The following microbial strains were used as target organisms. *Bacillus subtilis* (Gram + ve bacteria), *Pseudomonas putida* (Gram-ve bacteria), *Fusarium oxysporum* (pathogenic fungi), *Aspergilus sulphorous* (saprophytic fungus).

The compounds under investigation were insoluble in water, therefore they were dissolved in acetone 2g/liter and filtered through bacterial membrane filter (0.45 μm). The antimicrobial effect of the compounds was determined by the whole plate method[9]. A spore suspension of the test organisms was prepared and inoculated onto the surface of the solidified plate medium (pH = 7). 400 μg of each compound (dissolved in 0.2 m*l* of acetone) was added to each pit.

Incubation temperature was 35-37 °C for bacteria and 27.3 °C for fungi. The toxicity was measured after 24 and 48 hours for bacteria and 5-7 days for fungi.

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