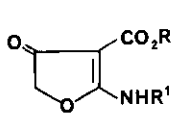
SYNTHESIS OF SUBSTITUTED 4,5-DIHYDRO-4-OXO-2-[(2-TRANS-PHENYLCYCLOPROPYL)AMINO]-3-FURANCARBOXYLIC ACIDS AND ETHYL ESTERS

Vassil St. Georgiev*, Robert A. Mack, and C. Richard Kinsolving

Department of Organic Chemistry, Pennwalt Corporation,
Pharmaceutical Division, Rochester, New York 14623, U.S.A.

Abstract - The synthesis and biological activity of a series of novel 4,5-dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic acids and their ethyl esters, is described. When tested in broth and agar dilution tests, some of the title compounds exerted in vitro antimicrobial activity against a number of gram-positive and gram-negative bacteria, as well as in vitro antifungal activity against dermatophyte and yeast fungi.

A number of 2-[(N-substituted)amino]-4,5-dihydro-4-oxo-3-furancarboxylic acids (1) and their esters have been previously prepared as intermediates in the synthesis of various naturally occurring furoquinolines (2) [1-6], or as products of a heterocyclization reaction that involved a cyclic C-O - insertion of an isocyanate synthon [7].



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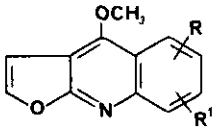

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In addition, the synthesis of ethyl 2-ethoxy-4,5-dihydro-4-oxo-3-furancarboxylate (3) was described by Mulholland et al. [8] as part of the preparation of tetronic acid [2,4(3H,5H)-furandione] (4).

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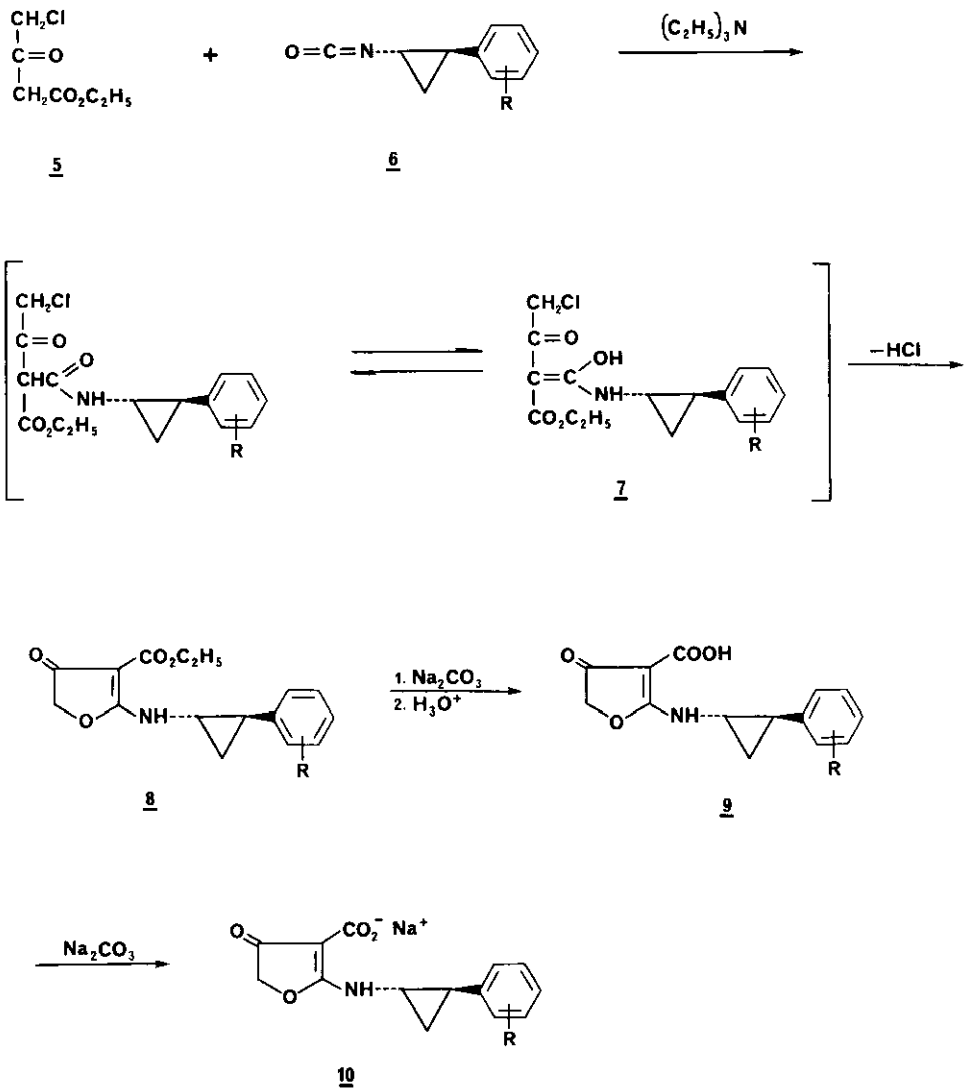
In the present study, we wish to report the synthesis and biological activity of a series of novel substituted 4,5-dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic acids and their ethyl esters. The preparation of compounds 8 and 9 involved a base-catalyzed cyclocondensation of ethyl 4-chloroacetoacetate (5) with an appropriately substituted trans-phenylcyclopropyl isocyanate (6). The reaction most likely proceeded through the intermediacy of the ketene N-acetal 7 and a C-O -insertion into the ring [7], to give the desired ethyl 4,5-dihydro-4-oxo-2-[(2-trans-phenylcyc-

lopropyl)amino]-3-furancarboxylate (8). Basic hydrolysis of the latter provided the corresponding free acid 9. Exposure of compound 9 to aqueous solution of sodium carbonate led to the preparation of the sodium salt 10 (Scheme 1).

Scheme 1



When tested for biological activity, the unsubstituted analogs 8a (R= H) and 9a (R= H) demonstrated antimicrobial and antifungal activities. Thus, in broth and agar dilution tests, compounds 8a and 9a exerted in vitro antimicrobial activity against a variety of gram-positive and gram-negative bacteria (Table 1), as well as antifungal activity against Candida albicans and two dermatophytes, Trichophyton mentagrophytes and Microsporum audouini (Table 2).

Table 1. *In vitro* Antimicrobial Activity of 4,5-Dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic Acids and Ethyl Esters

Broth and Agar Dilution Tests
(minimal inhibitory concentration, μg/ml)

Compd	Streptococcus pneumoniae	Streptococcus pyogenes	Neisseria gonorrhoeae	Haemophilus influenzae	Proteus vulgaris	Clostridium hystolyticum
8a	318.0 [a,b]	318.0 [a]	31.8 [b]	318.0 [b]	-	159.0 [a]
9a	69.0 [a] 460.0 [b]	460.0 [a,b]	46.0 [b]	230.0 [a] 69.0 [b]	690.0 [b]	-

[a] broth dilution test; [b] agar dilution test.

Table 2. *In vitro* Antifungal Activity of 4,5-Dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic Acids and Ethyl Esters

Broth and Agar Dilution Tests
(minimal inhibitory concentration, μg/ml)

Compd	Trichophyton mentagrophytes	Microsporum audouini	Candida albicans
8a	47.8 [a]	47.8 [a]	478.0 [a,b]
9a	-	230.0 [a]	690.0 [b] 460.0 [a]

[a] agar dilution test; [b] broth dilution test.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were obtained on a Nicolet MX-1 FT spectrometer as KBr discs. The ^{1}H-NMR spectra were taken on a Varian EM-360A (60 MHz) spectrometer using tetramethylsilane (Me_4Si) as an internal standard. All spectra were consistent with the assigned structures.

Ethyl 4,5-Dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylate (8a: R= H)
Under a nitrogen atmosphere, triethylamine (4.5 ml) was added dropwise over 15 min to a well-stirred solution of trans-phenylcyclopropyl isocyanate (5.45 g) and ethyl 4-chloroacetoacetate (4.50 g, 27.34 mmol) in petroleum ether-ethyl acetate (10:1), at 5-10°C (ice-water bath). During the addition a heavy precipitate formed. The reaction mixture was stirred at 0-5°C for 1 h, and the precipitate was filtered off under reduced pressure. The residual solid was stirred for 1 h in petroleum ether, then filtered off and stirred with 1 N hydrochloric acid for 1 h. The resulting cake was

rinsed with water and then sucked dry on the filter. Recrystallization from 2-propanol supplied 5.54 g of the title compound as white crystalline product melting at 140-142°C. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.08; H, 6.12; N, 4.95.

Ethyl 4,5-Dihydro-4-oxo-2-{[2-trans-(4-chlorophenyl)cyclopropyl]amino}-3-furancarboxylate (8b: R= Cl-4)

The title derivative was prepared by a procedure similar to that described for the synthesis of compound 8a, mp 146-148°C (2-propanol). Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.77; H, 5.01; Cl, 11.02; N, 4.35. Found: C, 59.78; H, 5.12; Cl, 11.38; N, 4.17.

Ethyl 4,5-Dihydro-4-oxo-2-{[2-trans-(4-methylphenyl)cyclopropyl]amino}-3-furancarboxylate (8c: R= CH_3-4)

Compound 8c was obtained by a procedure similar to that described for the synthesis of derivative 8a. It was hydrolyzed to the corresponding free acid 9c without further purification.

4,5-Dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic Acid (9a: R= H)

Ethyl 4,5-dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylate (8a) (15.50 g, 54 mmol) was added to a solution of sodium carbonate (11.45 g, 108 mmol) in 170 ml of water. Then, steam was passed through the reaction mixture for 2 hours. After refluxing for an additional 60 min, the reaction mixture was cooled to 5-10°C and filtered in order to remove some solid impurities. Acidification to pH 1 with concentrated hydrochloric acid precipitated the free acid 9a. The latter was recrystallized from ethanol to give 7.15 g of pure product, melting at 155-157°C. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.89; H, 5.05; N, 5.40. Found: C, 64.63; H, 4.98; N, 5.33.

4,5-Dihydro-4-oxo-2-{[2-trans-(4-chlorophenyl)cyclopropyl]amino}-3-furancarboxylic Acid (9b: R= Cl-4)

The title derivative was prepared by a procedure similar to that described for the synthesis of compound 9a, mp 173-175°C (ethanol). Anal. Calcd for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; Cl, 12.07; N, 4.77. Found: C, 57.03; H, 4.26; Cl, 12.07; N, 4.75.

4,5-Dihydro-4-oxo-2-{[2-trans-(4-methylphenyl)cyclopropyl]amino}-3-furancarboxylic Acid (9c: R= CH_3-4)

Compound 9c was obtained by a procedure similar to that described for the preparation of derivative 9a, mp 155-157°C. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 66.08; H, 5.60; N, 5.05.

4,5-Dihydro-4-oxo-2-[(2-trans-phenylcyclopropyl)amino]-3-furancarboxylic Acid Sodium Salt (10a: R= H)

The acid 9a (5.05 g, 19.5 mmol) was neutralized with sodium carbonate (2.56 g, 24.2 mmol) in 150 ml of water. The solution was warmed to 50°C, then filtered and concentrated to 50 ml under reduced pressure. The addition of a small amount of ethanol caused a rapid crystallization of the sodium salt 10a. Recrystallization from water provided 4.66 g of pure sodium salt as the monohydrate. Anal. Calcd for $C_{14}H_{14}NO_5Na$: C, 56.19; H, 4.72; N, 4.68; Na, 7.68. Found: C, 56.42; H, 4.76; N, 4.74; Na, 7.38.

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