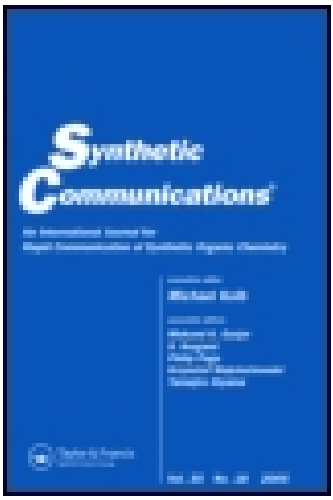

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Synthesis of 3-Methoxy-5-methyl Anthranilic Acid: A Key Intermediate in the Synthesis of Anticoccidial and Antitumour Antibiotics Isolated from the Strains of Streptomyces

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SYNTHETIC COMMUNICATIONS, 23(4), 509-515 (1993)

SYNTHESIS OF 3-METHOXY-5-METHYL ANTHRANILIC ACID: A KEY INTERMEDIATE IN THE SYNTHESIS OF ANTICOCCIDIAL AND ANTITUMOUR ANTIBIOTICS ISOLATED FROM THE STRAINS OF STREPTOMYCES

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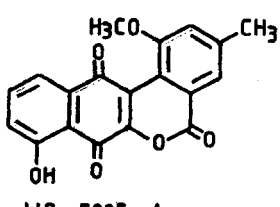
Abstract: An efficient synthesis of 3-methoxy-5-methyl anthranilic acid, a key intermediate in the synthesis of anticoccidial and antitumour antibiotics isolated from the strains of streptomyces by catalytic carbonylation route is described.

3-Methoxy-5-methyl anthranilic acid 3 constitutes ring 'D' in various antibiotics viz., WS-5995-B & WS-5995-C[1] (anticoccidials) and Gilvocarcin-M[2], Albacaricin-M[3] and Virenomycin-M[4] (antitumours).



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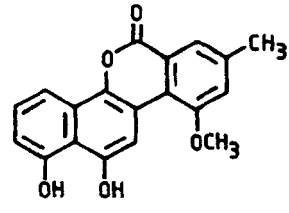

Aglycone of Gilvocarcin-M

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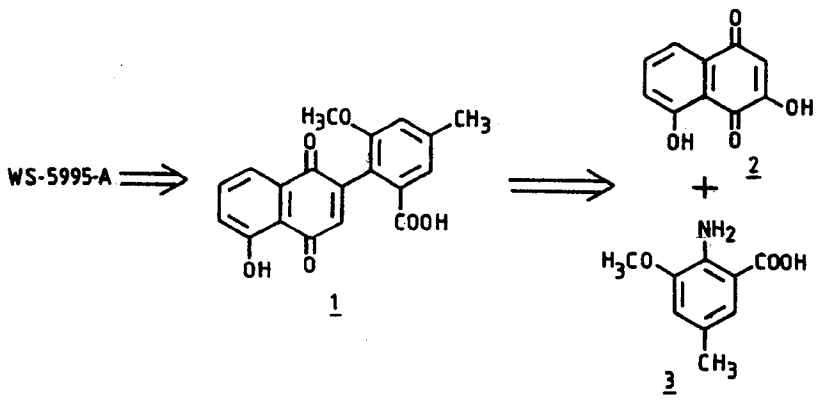
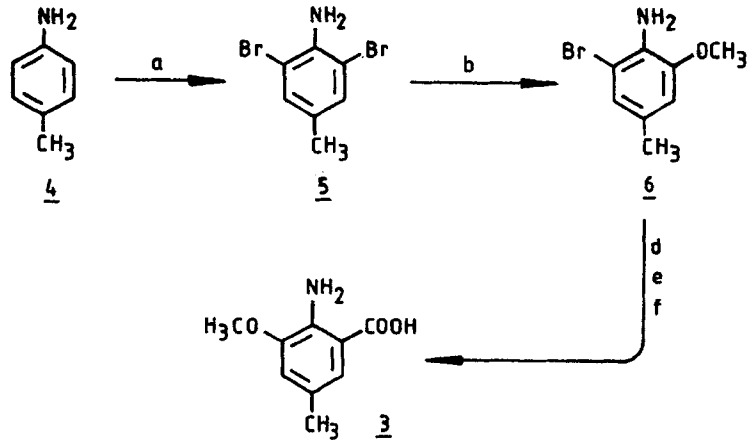
The basic skeleton of these antibiotics could be derived from the corresponding anthranilic acid, through diazocoupling.



The reported syntheses by Ikushima[5] and Mcenzie[6] involve tideous and multistep routes. Ikushima reported its synthesis starting from vanillin, via introduction of amino group and involves protection of carboxyl group as an oxazoline ring. The overall yield of this 8 step sequence is 0.7%. Though Mcenzie's method involves shorter sequence, the yields were poorer in carbonation step with an overall yield of 36%. In view of the importance of synthon 3 and the drawbacks associated with the earlier methods, it is necessary to develop a new methodology with improved yields.

Its synthesis begins with p-toluidine (Scheme 1). Bromination using bromine-dioxane complex gave the dibromo compound 5 quantitatively[7]. One of the bromines was selectively replaced by a methoxy group using equimolar proportion of sodium methoxide in the presence of cuprous iodide to give 6. It is conceived to introduce the carboxyl group through the carbonylation reaction

Scheme-I



Reagents and Conditions:

a. Bromine-dioxane complex/dioxane/5-10°C/1 hr
b. NaOMe/CuI/MeOH/DMF/100°C/1 hr
c. AC_2O/RT
d. Pd [o] Complex/CO (10 atm.)/Tributylamine/110°C/18 hr
e. 10% NaOH/100°C/1 hr

of bromo compound 6 using a suitable palladium catalyst. Thus, treatment of N-acetate of 6 with carbonmonoxide in the presence of $PdCl_2(TPP)_2$ catalyst at moderately low pressure (10 atm) gave the corresponding carboxylic acid in 80% yield. The acid was converted to the desired compound 3 in quantitative yields by alkaline hydrolysis. Thus, the synthesis of 3, an important synthon for the anticoccidial antibiotic, by a shorter sequence with improved yields is accomplished (50% overall yield).

EXPERIMENTAL

Preparation of 2,6-dibromo-p-toluidine 5. The bromine-dioxane complex was prepared by mixing equimolar amounts of the compo-

nents and quenching the hot product in ice water. The complex (25 g) was added over 15 min. to p-toluidine (10.7 g; 0.1 M), in dioxane (40 ml) at 5-10°C with stirring mechanically in a three necked flask. The resulting precipitate was filtered off, wahsed first with little water and later with dilute NaOH (20 ml) and again with water. It was crystallised from ethanol, m.p. 78°C (21.2 g, 80%) (lit.[7] 78°C).

Preparation of 2-bromo-6-methoxy-p-toluidine 6. Sodium (0.35 g; 0.005 M) was dissolved in methanol (10 ml) in a reaction vessel. To the sodium methoxide solution, 2,6-dibromo-p-toluidine (2.65 g; 0.01 M) and DMF (25 ml) were added and heated to refluxing temperature of 100°C, while methanol was allowed to distill out. Anhydrous cuprous iodide (1.9 g; 0.001 M) was added to the reaction mixture and heating continued for 1 hr. The cooled reaction mixture was poured into ice water and the resulting precipitate filtered, washed with water and with chloroform. The chloroform layer of the filtrate was separated. The aqueous layer was again extracted with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and the solvent evaporated. The residue, thus, obtained was purified by column chromatography over neutral alumina using hexane and benzene (1:1) as eluent. Low melting solid (1.72 g, 80%). IR ($CHCl_3$); 3350, 3260, 1150 & 1040 cm^{-1}; ^1H NMR ($CDCl_3$); (δ ppm): 2.31 (s, 3H, $-CH_3$); 3.87 (s, 3H, $-OCH_3$); 4.25 (br, 2H, D_2O exchanged), 6.5 (br.s, 1H, C_5-H, J=2Hz); 6.87 (br.s, 1H, C_3-H, J=2Hz). MS: m/e(%) 215, 217 (97, M^+); 200, 202(100), 172, 174 (35).

Preparation of N-acetyl-2-bromo-6-methoxy p-toluidine: To 2-bromo-6-methoxy p-toluidine (2.15 g; 0.001 M) were added acetic anhydride (1.53 g; 0.0015 M) and catalytic amount of sulfuric acid with stirring. After 5 min. the reaction mixture was treated with cold water. The resulting precipitate was filtered, washed with water, dried and crystallised from benzene/hexane (3:1) (2.55 g; 95%), m.p. 174°C. IR(KBr) 3220, 1660 and 1140 cm^{-1}. ^1H NMR ($CDCl_3$) (δ ppm): 2.06 (s, 3H, $-COCH_3$); 2.31 (s, 3H, $-CH_3$), 3.81 (s, 3H, $-OCH_3$); 6.68 (br.s, 1H, C_5-H, J=2Hz); 7.0 (br.s, 1H, C_3-H J=2Hz); 7.18 (br, 1H, D_2O exchanged). MS: m/e (%): 257, 259, (20, M^+), 215, 217 (100), 200, 202 (90), 178 (82), 43 (52).

Preparation of N-acetyl-3-methoxy-5-methyl anthranilic acid: Into an autoclave, N-acetyl-2-bromo-6-methoxy p-toluidine (2.57 g; 0.01 M), $PdCl_2(PPh_3)_2$ (8 mg; 0.001 M), triphenylphosphine (40 mg), tributyl amine (4.4 ml) and deoxygenated water (2 ml) were charged and pressurised with CO (10 atm). It was heated to 110°C and stirred for 18 hrs. to complete the reaction. The reaction mixture was cooled and diluted with water (10 ml) and filtered. The filtrate was acidified with 6N HCl. The resulting precipitate was filtered and washed with water. The solid, thus obtained, was dissolved in saturated $NaHCO_3$ solution to remove neutral impurities and reprecipitated with 6 N HCl (1.91 g; 86%). It was crystallised from ethanol. IR(KBr): 3200, 3000-2400 and 1670 cm^{-1}. ^1H NMR (DMSO-D_6): 2.18 (s, 3H, $-COCH_3$); 2.43 (s, 3H, $-CH_3$); 3.93 (s, 3H, $-OCH_3$); 7.0 (br.s, 1H, C_4-H, J=2Hz); 7.25 (br.s, 1H, C_6-H, J=2Hz). MS: m/e(%): 223 (30), 205 (14) 181 (100) 43 (70).

Preparation of 3-methoxy-5-methyl anthranilic acid 3: N-acetyl-3-methoxy-5-methyl anthranilic acid (0.72 g; 0.001 M) was dissolved in NaOH (10%, 5 ml) and refluxed for 1 hr. The reaction mixture was cooled and neutralised carefully with 5% HCl using pH meter. The resulting solid was filtered and washed thrice with water, dried and crystallised from ethanol, m.p. 170°C (lit.[5] 170°C) (0.15 g; 95%).

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