SYNTHESIS OF 1-BENZAZOCIN-5-ONE DERIVATIVES FROM A 1,2,3,4-TETRAHYDROCYCLOPENT[b]INDOLE; A SYNTHETIC APPROACH TO MITOMYCINS

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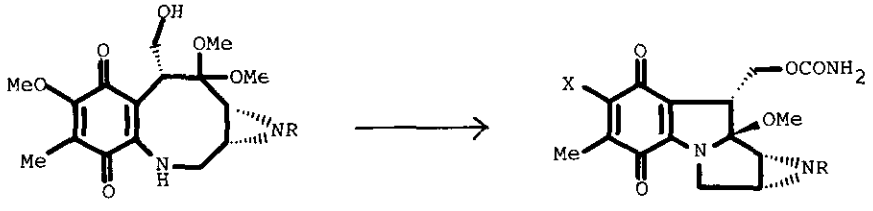
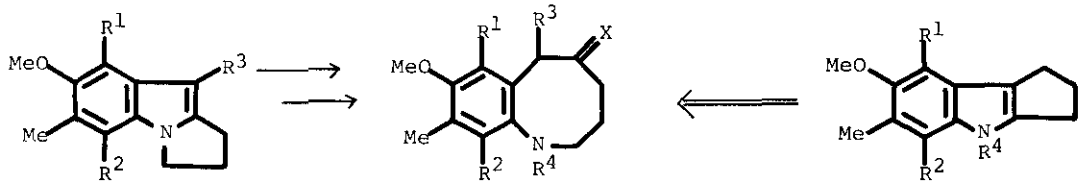
Abstract —— *Photo-oxygenation of* 4-benzyl-1,2,3,4-tetrahydro-5,7-dimethoxy-6-methylcyclopent[b]indole (14), derived from 2,4-dimethoxy-3-methylacetanilide (6) in eight steps, gave, in excellent yield, 1-benzyl-1,2,3,4,5,6-hexahydro-2,5-diketo-8,10-dimethoxy-9-methyl-1-benzazocine (15), which was converted to 1-benzyl-1,2,3,4,5,6-hexahydro-2-keto-5,5,8,10-tetramethoxy-9-methyl-6-methylene-1-benzazocine (19).

Recently Kishi and co-workers have ingeniously accomplished the first total synthesis of mitomycins, potent antitumor antibiotics, namely mitomycin A (2a), mitomycin C (2b) and porfiromycin (2c), with transannular cyclisation of 1-benzazocin-5-one derivatives (1) as the key step.[1] We have independently studied the conversion of 2,3-dihydro-1H-pyrrolo[1,2-a]indoles (3) into 1-benzazocin-5-ones (4) and the transannular reactions thereof.[2] Further, we investigated the synthesis of 1-benzazocines from smaller ring fused systems and wish to report transformation of a 1,2,3,4-tetrahydrocyclopent[b]indole (5) into benzazocin-5-one derivatives (4) using dye sensitized photo-oxygenation.



1 a R=Me
b R=$(CH_2)_3OAc$

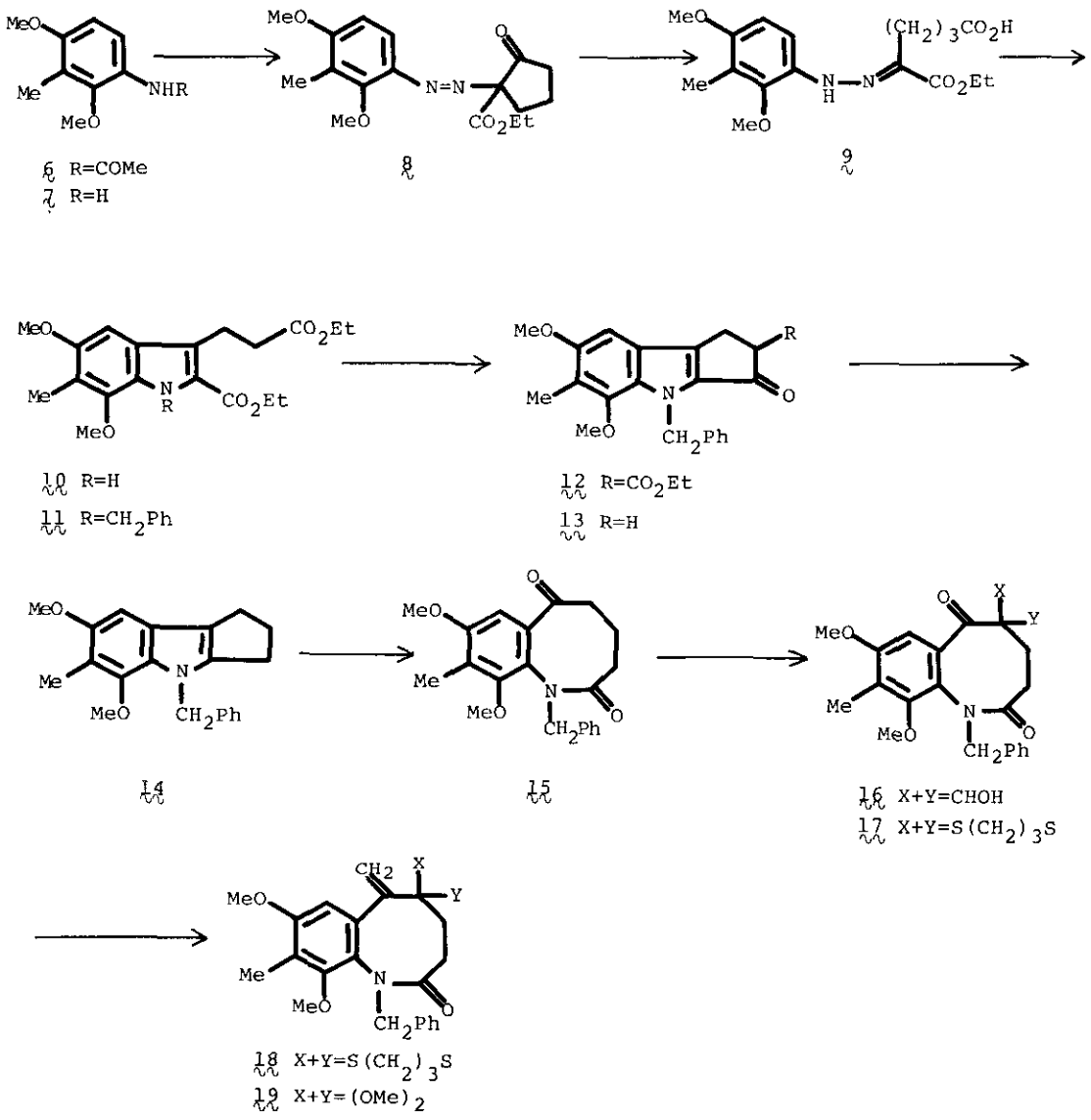
2 a X=OMe, R=H Mitomycin A
b X=NH_2, R=H Mitomycin C
c X=NH_2, R=Me Porfiromycin



3 4 5

Scheme 1

Alkaline hydrolysis of 2,4-dimethoxy-3-methylacetanilide (6)[3] quantitatively gave the amine (7), characterised as the hydrochloride,[4] mp 125 - 128° (sublimed), which was subjected to the Japp-Klingemann reaction[5] with 2-carboethoxycyclopentanone. After treatment of the resulting azo compound (8) with 10 % sodium hydroxide in aqueous dioxane at room temperature for 1 hr, the phenylhydrazone (9), mp 151 - 152°C, δ ($CDCl_3$) 1.35 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 2.20 (3H, s, ArMe), 3.78 (6H, s, 2 x OMe), 4.27 (2H, q, J = 7 Hz, OCH_2CH_3), 6.60 (1H, d, J = 9 Hz, ArH), 7.30 (1H, d, J = 9 Hz, ArH), and 11.83 (1H, br s, CO_2H); m/e 352 (M^+), was obtained in 61.9 % yield from 7. The acid (9) was reacted with dry hydrogen chloride in ethanol at 0° to 25°C for 3 hr to yield the indole (10), mp 92 - 93°, δ ($CDCl_3$) 1.22 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.43 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 2.28 (3H, s, ArMe), 3.87 (6H, s, 2 x OMe), 4.10 (2H, q, J = 7 Hz, OCH_2CH_3), 4.40 (2H, q, J = 7 Hz, OCH_2CH_3), 6.78 (1H, s, ArH), and 8.63 (1H, br s, NH); m/e 363 (M^+), in 65.0 % yield. After benzylation, with benzyl bromide in the presence of sodium hydride in dimethylformamide at room temperature, the diester (11), mp 92 - 93°, m/e 453 (M^+), which was formed in 87.4 %, was refluxed with sodium hydride in benzene for 16 hr to give, in 96 % yield, the β-ketoester (12), δ ($CDCl_3$) 1.28 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 2.25 (3H, s, ArMe), 3.62 (3H, s, OMe), 3.83 (3H, s, OMe), 4.23 (3H, q, J = 7 Hz, OCH_2CH_3), 5.68 (2H, s, NCH_2Ph), and 6.77 (1H, s, ArH); ν max ($CHCl_3$) 1727 and 1685 cm^{-1} (C=O); m/e 407 (M^+). Deethoxycarbonylation of 12 was carried out by heating with 10 % ethanolic sulphuric acid for 8 hr to afford the ketone (13), mp 162 - 163°, ν max ($CHCl_3$) 1670 cm^{-1} (C=O); m/e 335 (M^+), in 83.8 % yield. Wolff-Kishner reduction of the ketone (13), using hydrazine hydrate and potassium hydroxide in diethylene glycol[2] at 180 - 190° for 4 h, gave the cyclopent[b]indole (14) in 45.2 % yield, mp 105 - 106°, m/e 321 (M^+). Several other synthetic routes to cyclopent[b]indole derivatives were investigated and will be discussed elsewhere. Irradiation[6,7] of 14 with a 200-W halogen lamp, in the presence of Rose Bengal in a



Scheme 2

mixture of methanol and methylene chloride under an oxygen atmosphere at 24 - 25°C for 5 hr, formed the desired eight membered lactam (15) in 81.8 % yield, mp 155.5 - 156.5°; δ ($CDCl_3$) 2.25 (3H, s, ArMe), 3.75 (3H, s, OMe), 3.87 (3H, s, OMe), 4.12 and 5.75 (each 1H, each d, J = 14 Hz, NCH_2Ph); ν max ($CHCl_3$) 1650 cm^{-1} (C=O); m/e 353 (M^+). Treatment of this lactam (15) with ethyl formate in the presence of sodium hydride afforded the formyl ketone (16), which, without purification, was

converted into the cyclic thioketal (17), mp 174.5 - 175.5°, m/e 475 (M^+), in 55.6 % yield by reaction with propan-1,3-dithiol di-p-toluenesulfonate and potassium acetate in the usual manner.[8,9] Reaction of the thioketal (17) with triphenylmethylphosphonium bromide[10] in the presence of n-butyllithium in benzene at room temperature for 1 hr, gave the olefinic compound (18), δ ($CDCl_3$) 2.22 (3H, s, ArMe), 3.52 and 5.40 (each 1H, each s, $>C=CH_2$), 4.27 and 5.73 (each 1H, each d, J = 14 Hz, NCH_2Ph), and 6.45 (1H, s, ArH); ν max ($CHCl_3$) 1640 cm^{-1} (C=O); m/e 455 (M^+) and 258. Stirring 18 with mercuric chloride in anhydrous methanol[1] for 4 hr at room temperature furnished, in 64.6 % yield, the ketal (19) δ 2.25 (3H, s, ArMe), 3.05 and 3.17 (each 3H, each s, $>C<^{OMe}_{OMe}$), 3.27 and 4.97 (each 1H, each br s, $>C=CH_2$), 3.77 and 3.85 (each 3H, each s, 2 x OMe), 4.98 and 5.72 (each 1H, each d, J = 14 Hz, NCH_2Ph), and 6.33 (1H, s, ArH); m/e 411 (M^+). Further elaboration of these compounds towards mitomycins is under progress.

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