SYNTHESIS UTILIZING β-CARBONYL SYSTEM. IV
A NOVEL CYCLIZATION OF 1,9-DIIMINO-3,7-DICARBONYL AND -3,5,7-TRICARBONYL COMPOUNDS

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Bis-(3-methyl-5-isoxazolylmethyl) ketone (1) was converted into 1,9-diimino-3,7-dicarbonyl compounds (3 and 7), which were cyclized to 8-isoquinolinols (5 and 10) by hydrochloric acid in high yields. The compound (12) containing a sterically crowded 1,9-diimino-3,5,7-tricarbonyl system was prepared from the methyl analogue (11) of the ketone (1). The cyclization of 12 afforded the 4-pyridone (13) exclusively.

In continuation of our studies on the preparation of bis-isoxazole-ketones[1], we now wish to report the behavior of these ketones toward hydrogenolysis and subsequent recyclization under acidic media.

Partial hydrogenation of the ketone (1)[2] using platinum

oxide gave the carbinol (2a) [bp 140∿145°(0.15 mm); IR(liquid): 3350 cm^{-1}] first, whereas uptake of 3 mol equiv of hydrogen led it to the diimino-diketo-alcohol (3a) in 96.4% yield. This produced the 8-isoquinolinol (5a) hydrochloride [mp>270°; IR(nujol): 1660 and 1610 cm^{-1}; NMR(d_6-DMSO-TFA)τ: 2.08∿2.82(4H), 6.74(3H,s) and 7.34(3H,s); UVλ_{max}^{EtOH}nm(ε): 376(5600), 308(3200), 247(sh)(16800), 235(sh)(21200) and 226(26400); $\lambda_{max}^{EtOH-0.1N\ NaOH}$nm(ε): 370(5900), 328(4300) and 250(12500)[3]; m/e 173(M^+-HCl)] on refluxing in dilute hydrochloric acid for a short time.

In the same manner as with 2a, the carbinol (2b)[4] was converted into 3b [mp 123∿124°; IR(nujol): 3330, 3150, 1640 and 1595 cm^{-1}; NMR($CDCl_3$)τ: 2.70(5H,s), 5.14(2H,s), 7.21(4H,s) and 8.26(6H,s); m/e 302(M^+)] which, on treatment with dilute hydrochloric acid at room temperature, gave the 8-isoquinolone (4b) hydrochloride [mp 304∿305°(dec); IR(nujol): 3280, 3200, 1705 and 1640 cm^{-1}; NMR(d_6-DMSO) τ: 6.38(2H,s), 6.65(2H,s), 7.05(3H,s) and 7.29(3H,s); m/e 267(M^+-HCl)] in 46.6% overall yield from 2b. Also obtained in 18.1% yield was the 8-isoquinolinol (5b) hydrochloride [mp 304∿306°; IR (nujol): 1660 and 1620 cm^{-1}; nmr(d_6-DMSO-TFA)τ: 2.20∿2.60(8H), 6.73(3H,s), and 7.33(3H,s); m/e 249(M^+-HCl)].

An attempt to obtain the diimino-triketone (8) by acid treatment of the diimino-diketo-ketal (7) [mp 175∿176°; IR(nujol): 3300, 3150, 1620 and 1600 cm^{-1}; NMR($CDCl_3$)τ: 0.08(2H,bs), 4.80(2H,s) 4.90(2H,bs), 6.01(4H,s), 7.20(4H,s) and 8.08(6H,s); m/e 268(M^+)] which was derived from 1 by the conventional ketalization followed by hydrogenolysis resulted in the formation of the 6-isoquinolone-ketal (9) [mp 201∿203°(dec); IR(nujol): 3500∿2500(br) and 1620

cm^{-1}; UV $\lambda_{max.}^{EtOH}$ nm(ε): 325(5400), 275(5400), 244(51400) and 223(19700); $\lambda_{max.}^{EtOH-0.1N\ NaOH}$ nm(ε): 340(7200), 258(27000); NMR(d_6-DMSO) τ: 2.79 (1H,s), 3.36(1H,d,J= 2Hz), 3.40(1H,d,J= 2Hz), 5.93(2H, t,J= 5Hz), 6.23(2H,t,J= 5 Hz), 7.04(3H,s) and 7.55(3H,s); m/e 233(M^+)] in 73.8 % yield accompanied with trace amonuts of the 6,8-isoquinolinediol (10) [mp 188∿190°(dec); IR(nujol) 3500∿3200 and 1660 cm ; UV $\lambda_{max.}^{EtOH}$ nm(ε): 328(4500), 278(7300), 264(8500), 245(31600) and 220 (14000); $\lambda_{max.}^{EtOH-0.1N\ NaOH}$ nm(ε): 345(5000), 300(5000), 275(sh)(16400) and 263(22000), m/e 189(M^+)].

On the other hand, the sterically hindered carbonyl group in the ketone (11) resisted to hydrogenation using platinum oxide, while smooth cleavage of the isoxazole ring occurred. Crude diimino-triketone (12) obtained was treated with the acid to yield the 4-pyridone (13) [mp 127∿129°; IR(nujol): 3270, 3170, 3055, 1740, 1710, 1635 and 1615 cm^{-1}; UV $\lambda_{max.}^{EtOH}$ nm(ε): 273(11400) and 219(16500); m/e 291(M^+), 262(M^+- C_2H_5), 234(M^+- COC_2H_5), 206(M^+- $CH_3CHCOC_2H_5$) and 178(M^+- $COCHCH_3COC_2H_5$)] exclusively.

Although such bis-isoxazole-ketones as 1 and 11 could not make the equivalents of linear β-pentaketones[5], the cyclization modes of 1,9-diimino-3,7-dicarbonyl and -3,5,7-tricarbonyl compounds are of interest in connection with the structures of some antibiotics originated from β-polyketides like bostrycoidin[6] and piericidins[7].

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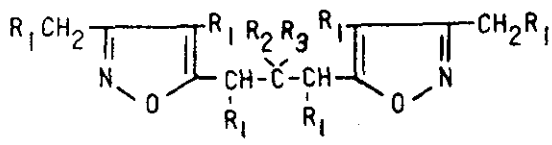
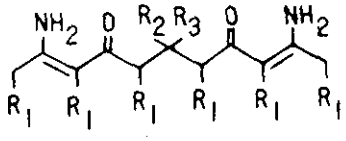
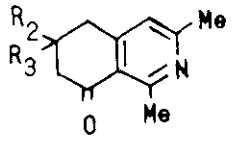


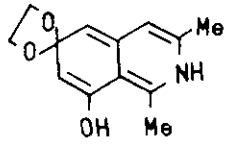
(1) R_1 = H, R_2,R_3 = O
(2a) R_1 = H, R_2 = H, R_3 = OH
(2b) R_1 = H, R_2 = C_6H_5, R_3 = OH
(6) R_1 = H, R_2,R_3 = 
(11) R_1 = Me, R_2,R_3 = O



(3a) R_1 = H, R_2 = H, R_3 = OH
(3b) R_1 = H, R_2 = C_6H_5, R_3 = OH
(7) R_1 = H, R_2,R_3 = 
(8) R_1 = H, R_2,R_3 = O
(12) R_1 = Me, R_2,R_3 = O



(4b) R_2 = C_6H_5, R_3 = OH



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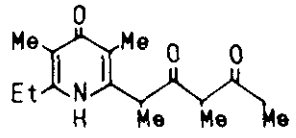

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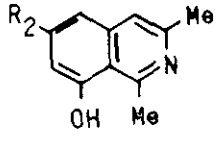
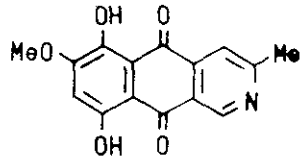
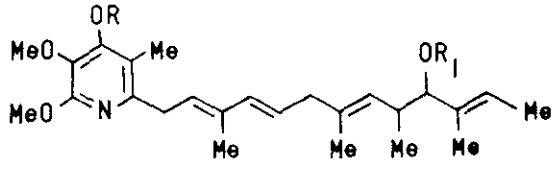


(5a) R_2 = H
(5b) R_2 = C_6H_5
(10) R_2 = OH



Bostrycoidin



Piericidins

laboratories for encouragement.

References and Notes

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4) This compound was obtained as a by-product of the reaction between 3-methyl-5-isoxazolylmethyl carbanion and methyl benzoate [mp 118∿119°; IR(nujol): 3400 cm^{-1}; NMR($CDCl_3$)τ: 7.80(6H,s), 6.64(4H,s), 4.35(2H,s) and 2.80∿2.60(5H); m/e 298(M^+)].

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