DOUBLE ANNELATION OF THE ENAMINE-IMINES, ISOQUINOLINE AND β-CARBOLINE DERIVATIVES, WITH 6-METHYLPYRAN-2-ONE-3,5-DICARBOXYLATES

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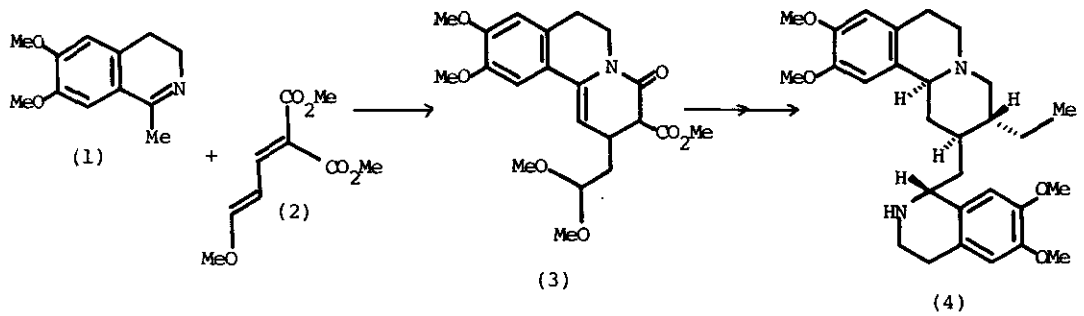
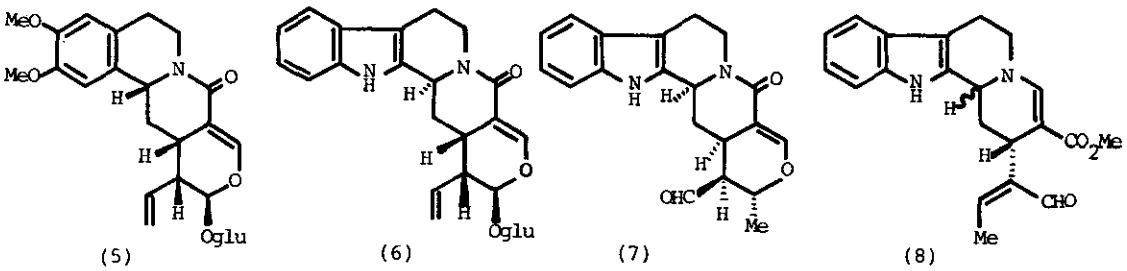
Abstract —— 6-Methylpyran-2-one-3,5-dicarboxylates (11a and 11b) were synthesized by the reaction of dimethyl methoxymethylenemalonate (9) and acetoacetates in the presence of sodium hydride followed by the acidic treatment. Reaction of the enamine-imines (1, 12 and 16) with the pyran-2-ones (11a and 11b) produced the tetra-(15a and 15b) and pentacyclic compounds (17a and 17b) by the double annelation. The epoxyetheno-bridge was reductively cleaved at pH 3 giving the benzo-(18) and indoloquinolizidines (19).

Recently, we developed a new construction method of benzo- and indoloquinolizidine ring system utilizing the enamine-imine character of 1-alkyl-3,4-dihydroisoquinolines and -β-carbolines. Namely (±)-emetine (4) was effectively synthesized *via* the acetal (3) prepared by the reaction of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) and the unsaturated diester (2)[1]. This annelation was further applied to the synthesis of several alkaloids, for example (±)-tubulosine[2], (±)-corynantheine[3], (±)-ajmalicine[3], and (±)-camptothecin[4].

Attempting the synthesis of unusual alkaloids, alangiside (5)[5], strictosamide (6)[6], naucleidinal (7)[7], and vallesiachotamin (8)[8], proper Michael acceptors having eight carbon units have been searched. In this communication, we would like to report a novel double annelation of the enamine-imines (1, 12 and 16) with 6-methylpyran-2-one-3,5-dicarboxylates (11a and 11b).

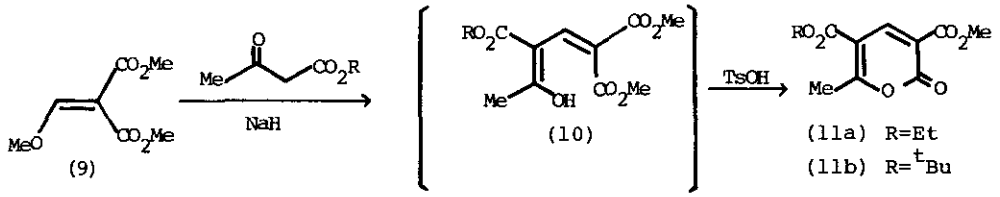


(1) (2) (3) (4)



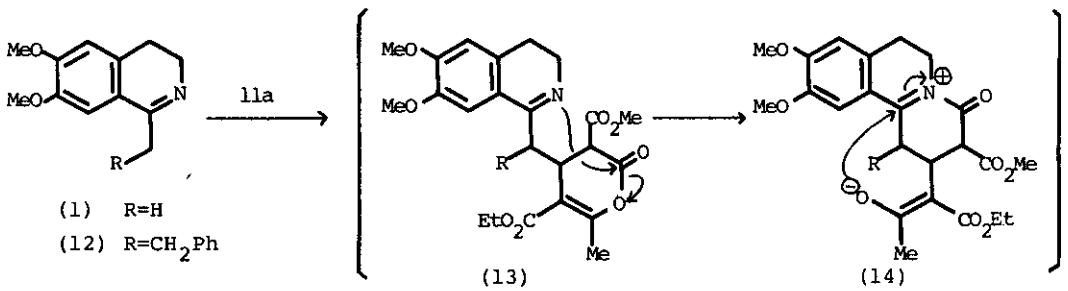
(5) (6) (7) (8)

Dimethyl methoxymethylenemalonate (9) was reacted for 3 hr with ethyl acetoacetate in the presence of 1.2 equivalent of sodium hydride in benzene at room temperature. Treatment of the crude product with p-toluenesulfonic acid in benzene for 24 hr, followed by purification using a column chromatography on silica gel gave a pyran-2-one (11a) as crystalls, mp 89 - 90°C, whose structure was determined by mass m/e 240 (M^+), UV λ_{max} (MeOH) 210, 247 and 325 nm, IR ν_{max} ($CHCl_3$) 1760, 1720 and 1605 cm^{-1}, and NMR spectrum δ ($CDCl_3$) 2.72 (3H, s, 6-Me) and 3.90 (3H, s, OMe). The corresponding 5-tert.-butoxycarbonyl compound (11b), mp 116 - 117°C, was prepared by the similar reaction. The cyclization would proceed through the Michael adduct (10) and this procedure provides an alternative route to the pyran-2-one derivatives[9].



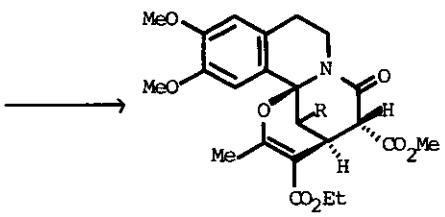
(9) (10) (11a) R=Et (11b) R=^{t}Bu

It was observed that these pyran-2-ones acted as a good Michael acceptor and double annelation interestingly took place on the reaction with the enamine-imines. Thus after reaction of the 3,4-dihydroisoquinoline (1) and the above pyran-2-one (11a) for 2 hr in acetonitrile at room temperature, disappearance of the starting materials and formation of two products were detected by tlc analysis. Further stirring the mixture for 12 hr at the same temperature, followed by a short column (silica gel) purification furnished the tetracyclic compound (15a) as crystalls, mp 126 - 127°C, in 82.5 % yield. UV (MeOH) spectrum of the product, m/e 444 (M^+), showed absorptions at 230, 240 and 280 nm. In the IR ($CHCl_3$) spectrum, three carbonyl absorptions were observed at 1728, 1700 and 1645 cm^{-1}, while NMR ($CDCl_3$) spectrum indicated three O-methyl groups at 3.73, 3.87 and 3.89, one O-ethyl group at 4.23 and 1.32 and one methyl group at 2.28 ppm. The above spectral data supported the tetracyclic structure (15a) and the stereochemistry between C_2 and C_3 positions was postulated from the thermodynamic consideration. Reaction of the pyran-2-one

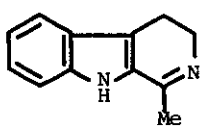


(1) R=H
(12) R=CH_2Ph

(13) (14)

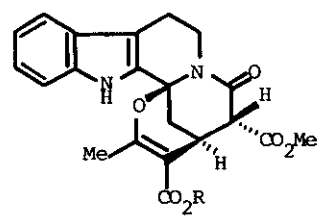


(15a) R=H
(15b) R=CH_2Ph



(16)

11a or 11b

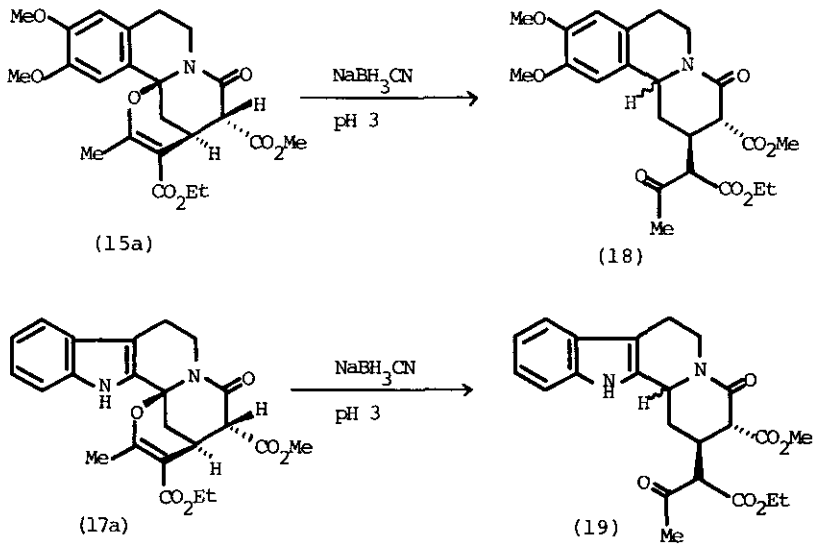


(17a) R=Et
(17b) R=^{t}Bu

(11a) with the 1-phenethylisoquinoline (12) quantitatively produced the corresponding product (15b), mp 74 - 75°C, m/e 535 (M^+); UV λ_{max}(MeOH) 236 and 281nm; IR ν_{max} ($CHCl_3$) 1745, 1705, 1660 and 1635 cm^{-1}; NMR δ ($CDCl_3$) 2.27 ppm (3H, s, Me), whose stereochemistry at the C_1 position was obscure. It is probable that carbonyl group in the dihydropyran ring (13) is the most electrophilic and the ring closure of the resulting zwitter ion (14) affords the tetracyclic compound.

On the treatment of 3,4-dihydro-1-methyl-β-carboline (16) with the pyran-2-ones (11a and 11b) under the same reaction conditions, the pentacyclic compounds, (17a), mp 139 - 141°[m/e 424 (M^+); UV λ_{max} (MeOH) 223, 267 and 282 nm; IR ν_{max} ($CHCl_3$) 3460 (NH), 1730, 1700, 1660 and 1620 cm^{-1}; NMR δ ($CDCl_3$) 2.25 (3H, s, Me) and 3.67 ppm (3H, s, OMe)] and (17b), mp 164 - 166°C [m/e 452 (M^+); UV λ_{max} (MeOH) 220 and 268 nm; IR ν_{max} ($CHCl_3$) 3470 (NH), 1740, 1700, 1655 and 1620 cm^{-1}; NMR δ ($CDCl_3$) 1.53 (9H, s, ^{t}Bu), 2.23 (3H, s, Me) and 3.70 ppm (3H, s, OMe)] were obtained in 54.6 % and 65.3 % yield, respectively.

The epoxyetheno-bridge was easily cleaved by the action of 2N-hydrochloric acid and the imine formed was immediately reduced with sodium cyanoborohydride[10]. Thus the reduction of the tetracyclic compound (15a) with sodium cyanoborohydride at pH 3 in methanol and hydrochloric acid at the ambient temperature formed the β-keto-ester (18), m/e 447 (M^+); IR ν_{max} ($CHCl_3$) 1740, 1720 (sh) and 1638 cm^{-1}, as a mixture of stereoisomers in 92.5 % yield. Similarly, the pentacyclic compound was converted to the indolo[a]quinolizidin-4-one (19), m/e 426; IR ν_{max} ($CHCl_3$) 1735, 1720 (sh) and 1635 cm^{-1}, in 81.6 % yield.



The above method must be useful for the synthesis of the framework of the aforementioned alkaloids. Furthermore the pentacyclic lactam (17b) was transformed to (±)-camptothecin as reported in the following paper.

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