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Synthesis and X-ray diffraction structure of a novel steroid-pyrrolidinoisoquinoline alkaloid hybrid

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A novel steroid – pyrrolidinoisoquinoline alkaloid hybrid has been successfully synthesized by Diels-Alder reaction N-acyliminium ion cyclization sequence.

Keywords: Hybrid, steroid, pyrrolidinoisoquinoline alkaloid, N-acyliminium ion, Diels-Alder reaction

Novel molecules which may exhibit biological activity have always attracted the attention of synthetic chemists. Nature is playing a pivotal role in providing enticing molecules through mixed biosynthetic routes. For example, Taipaienine[1] **1** is a combination of 12-nor-17α-homo-steroid and an alkaloid. Rubivirine[2] **2** and Solanidine[3] **3** are illustrative examples of steroid-alkaloid conjugates. Ritterazine[4] **4** is yet another example of molecular entity having a dimeric steroidal-alkaloid structure (Figure 1).

Newer molecular entities can be generated by combining structural features of two or more different class of compounds. Molecules generated in this way are commonly referred to in the literature as 'hybrids'[5] or 'conjugates. Among these hybrids, steroidal hybrids[6] are unique due to their broad biological activity profile and their ability to penetrate the cell membrane. Reports[7] dealing with steroid-alkaloid hybrid have particularly captured our attention. The biological activity associated with pyrrolidino-isoquinoline alkaloid[8] prompted us to synthesize its steroidal analogue.

Results and Discussion

In this paper, we wish to report a novel steroid-pyrrolidino-isoquinoline alkaloid hybrid. Our strategy is based on Diels-Alder reaction followed by N-acylinimium ion cyclization[9]. The retrosynthetic approach of our scheme is depicted below in Figure 2.

In light of the estrogen-anthracenedione hybrid work, reported by De Riccardis *et al.*[10], we decided to synthesize a novel molecular entity through the fusion of pregnenolone[11] and hexahydropyrroloisoquinoline[12] moieties. In this context, diene **7** was prepared from 16 –DPA, **9** (Scheme I) following the method reported by Wu and Yang group[13]. Diels-Alder addition of diene **7** (1 mmol) and maleimide **8** (1mmol), followed by acid hydrolysis of the cycloadduct resulted into a mixture of presumably two isomeric polycyclic keto-imide **6**. Since all our efforts to resolve the mixture were unsuccessful, it was thought desirable to subject the keto-imide **6** to borohydride reduction[9,12,14] with a hope that the two components may separate at latter stage.

Our choice of reducing the keto-imide was governed by the fact that N-(2'-phenylethyl)-α-hydroxy lactams derivable from such amides are known for elaboration to 13-aza-steroid ring[15] system on acid catalyzed cyclization. The keto-imide **6** was, therefore, reduced to a diol **10** which was subsequently subjected to acid catalyzed cyclization. The resultant molecular entity was then crystallized from pet ether-ethyl acetate (3:2) which resulted into a colorless crystalline compound[16] **5** (Scheme II).

Having synthesized a molecule with the gross features of the desired steroid-pyrrololidinoisoquino line alkaloid hybrid; the most difficult and challenging task before us was to establish the stereochemistry at all new stereocenters generated during the process. Based on the literature available[17], it was expected that between C_{24} and C_{25} carbonyls, the latter one will preferentially get reduced upon borohydride reduction and this selectivity could be attributed to the steric hindrance offered by the C_{15} methylene protons of ring D. Literature[13,18] lends support for the α-orientation of C_{17} hydrogen, and the stereochemistry of the hydroxyl

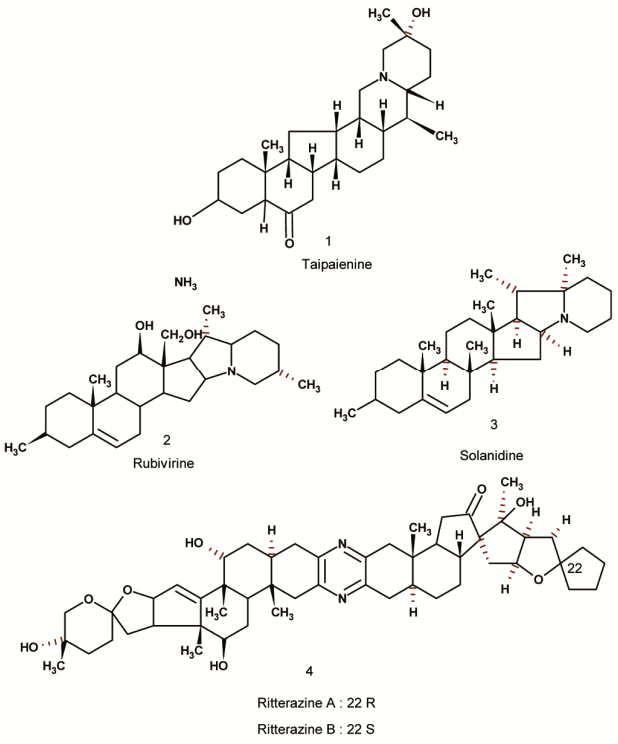


Figure 1

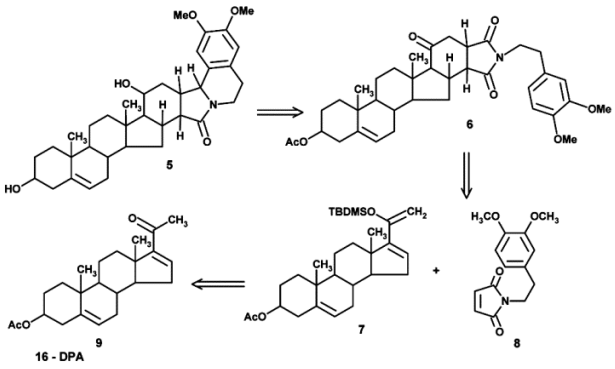


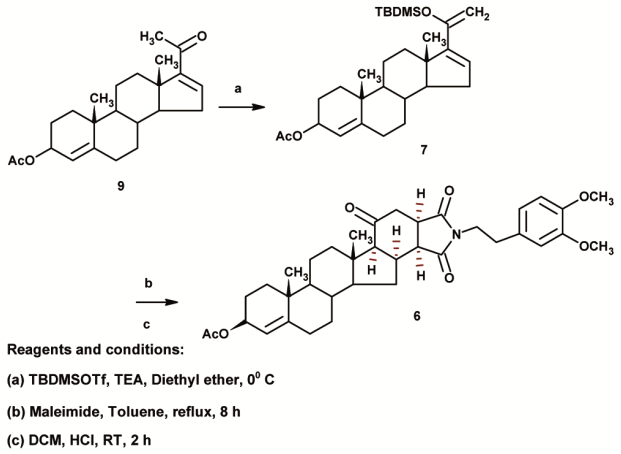
Figure 2

group located at C_{20} was similarly deduced to be α[19]. Taking steric repulsions into account, one may assume that the annulation of the acyliminium ion will proceed from the less hindered β face. The orientation of the hydrogen at the ring juncture (at C_{25}) will therefore be α[9,12,14]. Finally, the structure of hybrid **5** was unambiguously established by single crystal X-ray crystallography (Figure 3).

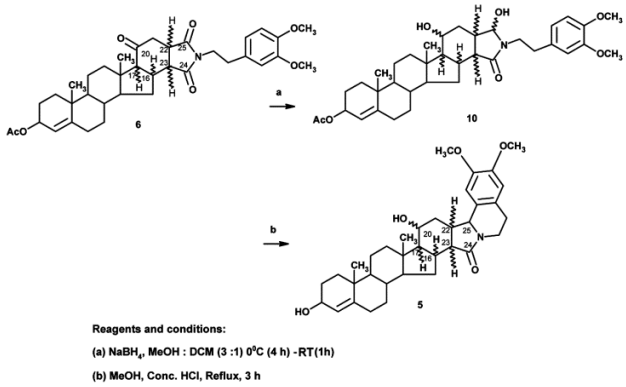
Experimental Section

Synthesis of steroidal diene 7

To an ice-cooled solution of **9** (0.712 g, 2 mmol) in anhydrous ether (30 ml) was added drop wise triethylamine (332 µl, 2.4 mmol) and *tert*-butyldimethylsilyl triflate (0.5 ml, 2.2 mmol). After stirring at 0°C for 15 minutes and then at RT for 30 minutes, the mixture was concentrated under reduced pressure, then passed through a pad of Al_2O_3 (petroleum ether as the eluant) to give compound **7** as a colorless solid[9].



Scheme I



Scheme II

Synthesis of cycloadduct 6

Maleimide **8** (0.370 g, 1.42 mmol) and steroidal diene **7** (0.669 g, 1.42 mmol) in toluene (40 mL) were refluxed for 8 h and allowed to cool to RT. The solvent was removed *in vacuo* to give cycloadduct which was used in the next step without purification.

Cycloadduct (1 g, 1.36 mmol) was dissolved in dichloromethane and treated with conc. HCl (0.5 ml). The resulting solution was then stirred at RT for 2 h. The solution was washed with saturated bicarbonate solution twice and then with water and brine solution, dried over Na_2SO_4 and concentrated *in vacuo* to give **6** which was purified by column chromatography (ethyl acetate: hexane 1/3).

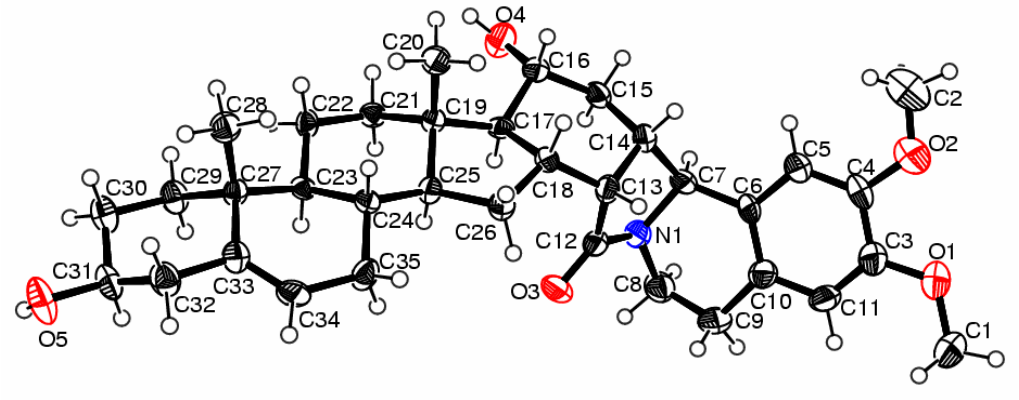


Figure 3 — ORTEP diagram of the X-ray structure of **5**

Acid catalysed cyclization of hydroxyl imide

The cyclo adduct **6** (0.36 g, 0.582 mmol) in MeOH: DCM (9 ml + 3 ml) at −10°C, with out further characterization, was treated with sodium borohydride (0.1 g, 2.64 mmol). After addition was complete, the mixture was stirred at 0°C for 4 h and then at RT for 1 h. Solvent was removed *in vacuo* and residue was diluted with water and extracted thrice with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatographic purification in ethyl acetate: hexane (1/4) gave imide alcohol as a colourless solid. The resulting hydroxy imide was carried forward to acid catalysed cyclization. Hydroxy imide (0.3 g, 0.484 mmol) was dissolved in dichloromethane and treated with (0.5 ml) conc. HCl. The resulting solution was then refluxed for 10 h. Reaction mixture was then poured over saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted thrice with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (EtOAc-hexane 3/7) gave unidentified mixture as colorless solid; whose fractional crystallization resulted into a crystalline compound which was unambiguously characterized as the required steroidal hybrid **5**.

Spectral data for compound 5

Colourless solid; m.p.> 200°C. IR (KBr): 3459, 2934, 1652, 1506, 1259, 1228, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.6 (1H, s), 6.5 (1H, s), 5.3 (1H, s), 4.2 (2H, m), 3.8 (3H, s), 3.8 (1H, s), 3.8 (3H, s), 3.5 (1H, m), 3.0 (2H, m), 2.5 (4H, m), 2.2 (4H, m), 1.9-1.0 (15 H, m), 1.0 (3H, s), 0.8 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 148.0, 147.5, 140.4, 127.5, 126.9, 121.7, 111.9, 107.5, 71.5, 70.8, 61.9, 59.4, 56.0, 55.8, 55.0, 50.2, 43.2, 42.2, 41.9, 39.9, 39.6, 38.9, 38.7, 38.0, 37.2, 36.5, 31.6, 31.5, 31.4, 27.1, 25.4, 20.5, 19.3, 12.3; HRMS: *m/z* Calcd for $C_{35}H_{48}NO_5$: $[M+1]^+$ 562.3532. Found: 562.3527.

Conclusion

Thus, a novel steroid-pyrrolidinoisoquinoline alkaloid hybrid with six new stereo-defined centers has been successfully synthesized *via* Diels-Alder reaction- N-acyliminium ion cyclization sequence. Absolute configuration of the hybrid molecule **5** has been established from its X-ray structure.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgments

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19 Some selected crystallographic data: Empirical formula $C_{35}H_{47}NO_5$, Crystal system, space group: Orthorhombic, P 21 21 21; Some of the important bond lengths: O(1)-C(3)-1.373(5); O(1)-C(1)- 1.426(5); O(2)-C(2)-1.315(6); O(2)-C(4)-1.368(6); O(3)-C(12)-1.225(4); O(4)-C(16)-1.427(5); O(4)-H(104)-0.86(6); O(5)-C(31)-1.442(5); O(5)-H(105) 0.76(5); N(1)-C(12)-1.361(5); N(1)-C(8)-1.444(5); N(1)-C(7)- 1.458(5).