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# A VERSATILE APPROACH TO THE 8- AND 9-AZASTEROID SYSTEM. ANGULAR METHYLATION AT C-10 AND C-13[1]

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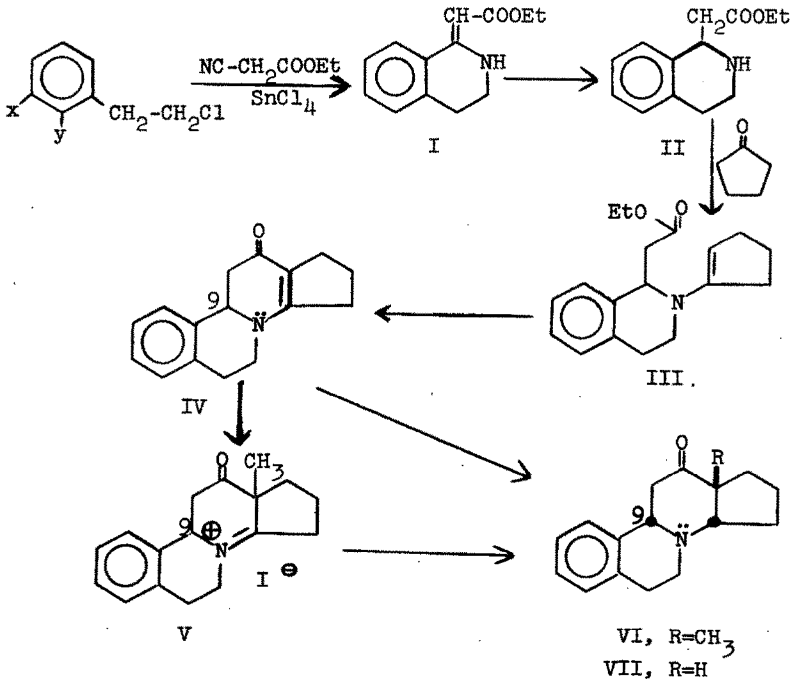
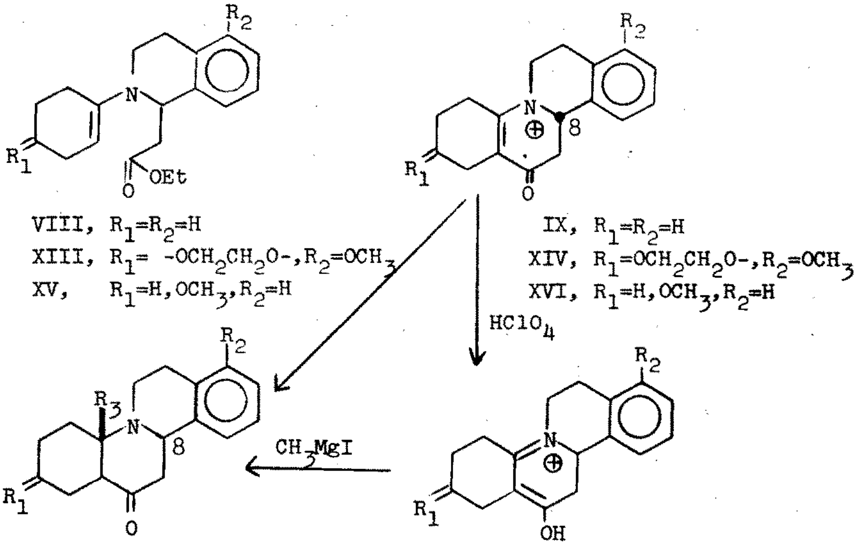
Recently, the total synthesis of an 8-azasteroid was reported,[2] and represented the first successful attempt to prepare azasteroids containing nitrogen at a bridgehead position. We wish to report a route to both the 8- and 9-azasteroids by exemplifying the method with suitable models. It is anticipated that the necessary modifications would be applicable to these models so that this technique would lead to the aza analogs of the natural steroids. The scheme was initiated by condensing phenylethyl chloride (**X=Y=H**) with ethyl cyanoacetate using stannic chloride.[3] The resulting dihydroisoquinoline,[4] I was rapidly hydrogenated to the tetrahydroisoquinoline ester, II [b.p. 120°(0.5 mm), $n_D^{25}$ 1.5350, $\nu_{max}^{film}$ 1740, 3333 cm$^{-1}$]. Treatment of the latter with cyclopentanone in refluxing toluene gave the enamine, III ($\nu_{max}^{CCl_4}$ 1741, 1637 cm$^{-1}$) which, without further purification, was cyclized in hot ethylene glycol[5] to the enaminoketone, IV m.p.[160-161°, $\nu_{max}^{CHCl_3}$ 1626, 1565 cm$^{-1}$, $\lambda_{max}^{Hex}$ 310 (4.08), proton at C-9, 5.22$\tau$]. Reduction of IV with lithium aluminum hydride resulted in the ketone, VII [m.p. 106-107°, $\nu_{max}^{CCl_4}$ 1720, 2809, 2770 cm$^{-1}$, proton at C-9, 6.22$\tau$(quartet)]. The trans-quinolizidine structure is assigned to VII on the basis of the infrared[6] and n.m.r. data.[7]

Base-catalyzed equilibration of VII gave complete recovery of starting material, suggesting that the CD ring fusion was cis[8]. Treatment of IV with excess methyl iodide gave only the C-alkylated compound, V [m.p. 279-280° $\nu_{max}^{nujol}$ 1721, 1665 cm$^{-1}$, $\lambda_{max}^{H_2O}$ 270 (2·62)] along with unreacted starting material. Subjecting V to catalytic reduction resulted in VI [m.p. 110-112°; $\nu_{max}^{CCl_4}$ 1722, 2804



2764 cm$^{-1}$; proton at C-9, 6.21τ(quartet); methyl at 8.83τ(singlet).] The CD fusion was shown to be cis[9] and the methyl group shown to occupy an axial position[10] by measuring its upfield n.m.r. shift in benzene (compared to chloroform).

The model system for the 9-azasteroids was investigated by treatment of the isoquinoline ester II with cyclohexanone in refluxing toluene and obtaining the enamine, VIII ($\nu_{max}^{CCl_4}$ 1744, 1640 cm$^{-1}$). The latter was cyclized in hot ethylene glycol to the corresponding enaminoketone IX [m.p. 170-171°, $\nu_{max}^{CHCl_3}$ 1616, 1560 cm$^{-1}$, $\lambda_{max}^{Hex}$ 312 (4.05); proton at C-8, 5.30τ]. The perchlorate X [m.p. 231-232°, $\nu_{max}^{KBr}$ 3110, 1642] gave, upon addition with methyl magnesium iodide, a 35% yield of the angularly methylated compound XI [m.p. 144-145°, $\nu_{max}^{CCl_4}$ 1719 cm$^{-1}$; methyl signal, 9.07τ(singlet); proton at C-8, 5.80τ]. The field position of the C-8 proton suggests that the molecule, XI, possesses the <u>cis</u>-quinolizidine[7] in



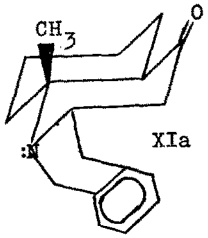
VIII, $R_1=R_2=H$
XIII, $R_1=-OCH_2CH_2O-, R_2=OCH_3$
XV, $R_1=H, OCH_3, R_2=H$

IX, $R_1=R_2=H$
XIV, $R_1=OCH_2CH_2O-, R_2=OCH_3$
XVI, $R_1=H, OCH_3, R_2=H$

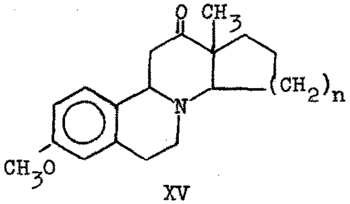
XI $R_1=R_2=H, R_3=CH_3$
XII $R_1=R_2=R_3=H$

X $R_1=R_2=H$

one of its two possible conformations (XIa). That the methyl group is axial is supported by the fact that XI was also isolated as a mixture of two isomers (methyl signals at 9.01τ and 9.07τ) which upon base-catalyzed equilibration showed only the higher field signal.



XIa



XV

Treatment of IX with excess lithium aluminum hydride in tetrahydrofuran gave the ketone XII [m.p. 130-131°, $\nu_{max}^{CCl_4}$ 1720, 2835, 2764 cm$^{-1}$; proton at C-8, 6.17$\tau$ (quartet)] which possesses the trans-quinolizidine system, and the thermodynamically more stable AB-trans fusion (complete recovery after basic equilibration).

In order to test further the feasibility of this approach, starting materials containing the necessary 3-and 17-substituents of the natural steroids were investigated. The isoquinoline ester derived from 2-methoxyphenylethyl chloride (X=H, Y=$OCH_3$) was prepared [m.p. 70-72°, $\nu_{max}^{CCl_4}$ 3335, 1650, 1610, 1570 cm$^{-1}$)] and reduced to the tetrahydroisoquinoline ester (viscous oil, $\nu_{max}^{CCl_4}$ 3336, 1738 cm$^{-1}$), which gave the enamine, XIII ($\nu_{max}^{CCl_4}$ 1739, 1641 cm$^{-1}$) when heated with the mono-dioxolane of 1,4-cyclohexanedione[11]. Cyclization in ethylene glycol gave the enaminoketone, XIV [m.p. 181-182°, $\nu_{max}^{nujol}$ 1615, 1559 cm$^{-1}$, $\lambda_{max}^{Hex}$ 312 (4.08), proton at C-8, 5.25$\tau$ (quartet)]. In another experiment, 4-methoxycyclohexanone was condensed with the isoquinoline ester, II, to give the enamine, XV, which was readily converted to the methoxy-substituted enaminoketone, XVI [m.p. 159-160°, $\nu_{max}^{CHCl_3}$ 1616, 1562 cm$^{-1}$, $\lambda_{max}^{Hex}$ 314(3.99)].

From the foregoing results, it is evident that angular methylation of IV and IX, coupled with the cyclizations leading to the naminoketones, provide a highly useful approach to a series of 8- and 9-azasteroids. By showing that the 3- and 17-substituents (the D-ring can be constructed from the methoxy-substituted aromatic ring by known methods[12]) are readily introduced (XIV), a route is open to the 9-aza analogs of the natural steroids. Alternatively, initiating the synthetic scheme with m-methoxyphenylethyl chloride ($X=OCH_3$, Y=H), and various substituted cyclopentanones and cyclohexanones, a series of 8-azasteroids (with or without the 12-keto function) and their D-homo derivatives (XVII) should also be accessible. Although the reactions described here are more in the nature of a progress report than a completed study, the novelty of the approach appears to justify reporting it at this time. Many other obvious modifications of this approach, too numerous to mention are currently being studied.

## References

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