APORPHINES VI.<sup>1</sup> A NOVEL SYNTHESIS OF 7-HYDROXYAPORPHINE, 7-HYDROXYNORAPORPHINE AND 6a,7-DEHYDRONORAPORPHINE

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A number of examples of the 7-hydroxyaporphine system can be found in naturally occurring alkaloids. Structure determinations and physical data have been described for norushinsunine (normicheline, michelalbine) (I, R = H), ushinsunine (micheline) (I, R =  $CH_3$ )<sup>3,4,5,6</sup> and guatterine II.<sup>6</sup> Synthetic methods for the elaboration of such alkaloids have not been reported.



We wish to report in this communication a novel synthesis of 7-hydroxyaporphine (IIIa) and 7-hydroxynoraporphine (IIIb) by a route which involves simultaneous protection of the labile hydroxyl group and the secondary amino group via the 1-aryl-3H-oxazolo[4,3-a]isoquinoline-3-one (VII), a series of selective reductions (VII  $\rightarrow$  VIII  $\rightarrow$  IX) and Pschorr cyclization leading to the oxazoloaporphine (X). This versatile intermediate (X) was utilized to prepare the 7-hydroxyaporphines (IIIa, IIIb) and 6a,7-dehydronoraporphine (IV) as shown in Scheme 1. The synthesis of the related 1-(1,2,3,4-tetrahydroisoquinoly1)carbinol system via such an oxazolidone has recently been described.<sup>7</sup> Scheme 1



Oxidation of 1-(2-nitrobenzyl)isoquinoline<sup>8</sup> with sodium dichromate in glacial acetic acid provided 1-(2-nitrobenzoyl)isoquinoline (V, mp 167-169°, v<sup>Nujol</sup> 1670 cm<sup>-1</sup>) in 90% yield. Reduction of V with sodium borohydride in absolute alcohol gave the carbinol (VI, mp 145-147°,  $v^{
m Nujol}$  $3200 \text{ cm}^{-1}$ ) in 85% yield. Phosgene in dichloromethane at 0-5° in the presence of triethylamine reacted readily with VI yielding the oxazolidaone (VII, mp 195-198°,  $v^{\text{KBr}}$  1750 cm<sup>-1</sup>) in 91% yield. Selective reduction of the nitro group in VII was accomplished in 70% yield with 10% palladium and hydrogen in tetrahydrofuran and acetic acid to give VIII [mp 158-161°,  $\lambda_{max}^{EtOH}$  250 mµ ( $\epsilon$  = 22,000), 260 ( $\varepsilon$  = 20,000), 345 ( $\varepsilon$  = 8,850);  $v^{\text{KBr}}$  1755 cm<sup>-1</sup>, 3230, 3270, 3350]. Further reduction of VIII with platinum oxide and hydrogen at room temperature in tetrahydrofuran and acetic acid for 14 hr led to a 70% yield of IX [mp 204-205°,  $\lambda_{max}^{EtOH}$  230 mµ (shoulder  $\epsilon = 16,350$ ), 290 ( $\epsilon$  = 5,830); v<sup>KBr</sup> 1735 cm<sup>-1</sup>, 3360, 3465]. The nmr spectrum of IX showed a singlet at 6 5.31 (amino) which exchanged with D<sub>2</sub>O, a pair of doublets at  $\delta$  5.53 and 6.22 (J = 8.5 Hz) which characterized the benzylic proton and the 1-proton of the isoquinoline nucleus, and multiplets at  $\delta$ 2.6-3.3 which were assigned to the 3- and 4-protons. Examination of Dreiding models of IX reveals that only the cis reduction product is stereochemically oriented to undergo cyclization to X. Standard conditions<sup>9</sup> for the Pschorr ring closure of IX afforded the oxazoloaporphine [X, mp 255-260°,  $\lambda_{max}^{EtOH}$ 270 mµ ( $\epsilon$  = 19,850);  $v^{\text{KBr}}$  1740 cm<sup>-1</sup>] in 30% yield.

Hydrolysis of X with trifluoroacetic acid led exclusively to the 6a,7-dehydronoraporphine IV [isolated as the hydroiodide, mp 250° dec,  $\lambda_{max}^{EtOH}$  255 mµ ( $\epsilon$  = 41,300), 323 ( $\epsilon$  = 8,700)]. Reduction of X with lithium aluminum hydride in tetrahydrofuran gave 7-hydroxyaporphine (IIIa) which was isolated and characterized as the hydroiodide salt in 35% yield [mp 205° dec,  $\lambda_{max}^{EtOH}$  270 mµ ( $\varepsilon = 17,480$ );  $\nu_{kBr}^{KBr}$  3370 cm<sup>-1</sup>]. Further proof for the structure of IIIa is afforded by its mass spectrum. The parent peak is observed at m/e 251 and principal secondary peak at m/e 233 is indicative of the dehydrated product. The absence of any of the dehydro product in IIIa is indicated by the absence of any UV absorption bands at 255 mµ which are diagnostic for the 6a,7-dehydroaporphine system, <sup>10</sup> as shown also in IV.

Treatment of X with methyllithium in dry ether resulted in the isolation of IIIb as the free base [mp 198-200° dec,  $\lambda_{max}^{\text{EtOH}}$  270 mµ ( $\varepsilon = 18,150$ );  $\nu^{\text{KBr}}$  3500-3300 cm<sup>-1</sup> (broad OH), 3275 (weak NH)]. The mass spectrum showed a parent peak m/e 237 and a peak at m/e 219 again indicative of the dehydrated product. The structural assignment for IIIb is further supported by the nmr spectrum which suggests a *cis* arrangement of the hydrogen atoms at 6a and 7. Protons at C-7 are shown as a signal at 6 4.56 d (J<sub>6a,7</sub> = 3.5 Hz). The small coupling constant indicates the dihedral angle between the two methine protons is small. This condition is fulfilled when the protons are in a *cis* orientation and therefore the conformation of the hydroxyl group is determined, e.g., HO  $(H_a) = 3.5 Hz$ . Similar spectroscopic evidence was presented by

Harris and Geissman<sup>6</sup> for assignment of the stereochemistry of the 7-hydroxyl group in ushinsunine I ( $R = CH_3$ ). Satisfactory elemental analyses were obtained for all new compounds reported in this communication.

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