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THE TOTAL SYNTHESIS OF dl-HASUBANONINE

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Recent investigations[1] have indicated that a number of alkaloids possessing a modified morphinan skeleton occur in various Stephania species (Menispermaceae). Hasubanonine is a representative of these new type alkaloids and the authors have established the structure (1) for this alkaloid.[2]

In preceding papers, we reported the synthesis of the skeletal ring system of hasubanan alkaloids[3] and the total synthesis of dl-cepharamine which is the functionally least complicated one in this series of alkaloids.[4] This communication concerns with the total synthesis of dl-hasubanonine.

Oxidation of the compound (3), which was prepared from the keto lactam (2)[4], with $Pb(OAc)_4$-BF_3·etherate[5] in benzene at 50° for 2 hr. afforded the acetoxy ketone (4)*1, m.p. 235°, ν_{max} 1750, 1740 and 1685 cm^{-1}, n.m.r. τ 4.19 (1H, s.), in a 65% yield.*2 The acetoxy ketone (4) was transformed into the correspoding α-bromo ketone (5) (65% yield), m.p. 230-5°, ν_{max} 1758, 1750 and 1689 cm^{-1}, n.m.r. τ 5.47 (1H, q., δ_{AB}=8 cps., J=5 cps.), 4.07 (1H, s.), using 1.1 eq. pyridinehydrobromide-perbromide complex[6] in acetic acid at 50° for 2 hr.. The α-bromo ketone (5) was heated at 95-100° for 2 hr. in acetic acid with freshly fused sodium acetate[7] to give the rearranged enol

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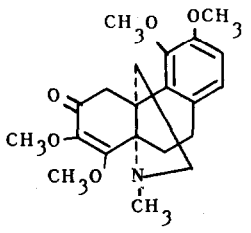
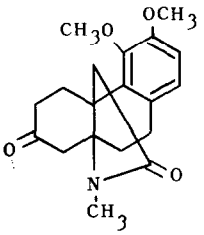
*1 All compounds reported in this communication gave satisfactory analyses. All i.r. and n.m.r. spectra were measured in $CHCl_3$ and $CDCl_3$, respectively.

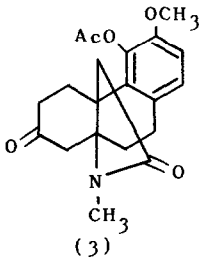
*2 Oxidation of the compound (2) under the same reaction condition gave a mixture of the compound (16), (17), and (18). Because of the poor yield of the desired compound (16), the compound (3) as the starting material was preferred for the present synthesis.



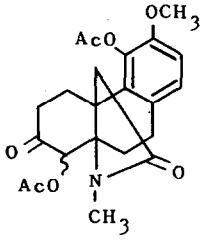
(1)



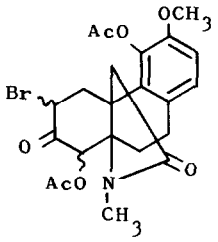
(2)



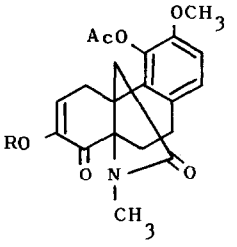
(3)



(4) (OAc=ax)

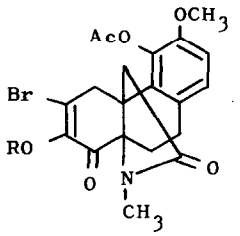


(5)



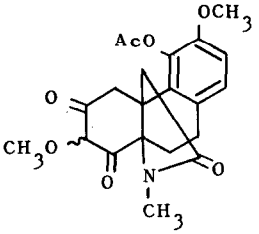
(6) (R=Ac)

(7) (R=H)

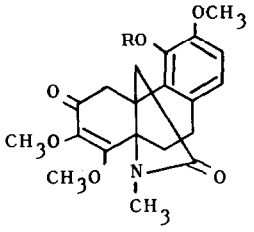


(8) (R=H)

(9) ($R=CH_3$)

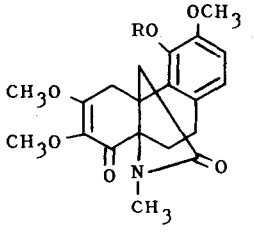


(10)



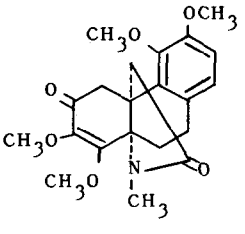
(11) ($R=CH_3$)

(13) (R=H)

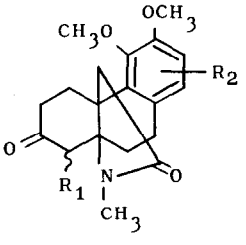


(12) ($R=CH_3$)

(14) (R=H)



(15)



(16) (R_1=OAc, R_2=H)

(17) ($R_1=R_2$=OAc)

(18) (R_1=H, R_2=OAc)

acetate (6), m.p. 208°, ν_{max} 1760 and 1687 cm^{-1}, n.m.r. τ 3.51 (1H, t., J= 5 cps.), in a 75% yield.

The partial hydrolysis of the enol acetate (6) was accomplished quantitatively by refluxing in 2% HCl-H_2O-acetone for 9 hr.. The resulting α-diketone (7), m.p. 222°, ν_{max} 3450, 1760, 1685, and 1654 cm^{-1}, n.m.r. τ 3.93 (1H, t., J=5cps.) was converted to the bromo compound (8), m.p. 250-2°, ν_{max} 3420, 1760, 1685, and 1643 cm^{-1}, by treatment with 1 eq. Br_2 in acetic acid for 2 hr. and thence to the corresponding methoxy compound (9), m.p. 192°, ν_{max} 1760, 1684, and 1629 cm^{-1}, by addition of an ethereal diazomethane solution to a methanol solution of the compound (8).

Treatment of the bromide (9) with 5% H_2SO_4-H_2O-1,2-dimethoxyethane in a sealed tube at 150-5° for 24 hr. afforded the desired β-diketone (10)[8], m.p. 264-7°, ν_{max} 3480, 3450, 1675, and 1621 cm^{-1}, in a 30% yield. Methylation of 10 with ethereal diazomethane, followed by column chromatography on silica gel gave non-phenolic and phenolic products. Fractional recrystallization of the non-phenolic products gave dl-16-oxohasubanonine (11), m.p. 177°, ν_{max} 1677 and 1615 cm^{-1}, n.m.r. τ 7.03 (N-Me), 6.33, 6.19, 6.08, and 5.90 (O-Me), and its isomer (12), m.p. 179-180°, ν_{max} 1680 and 1617 cm^{-1}, n.m.r. τ 6.99 (N-Me), 6.36, 6.15, 6.05, and 6.02 (O-Me), in ca. 1:1 ratio. The phenolic product was estimated to be a mixture of dl-aknadilactam (13)[9] and its isomer (14) in 1:1 ratio from the n.m.r. inspection, and the separation of the two components is currently in progress.

The desired product (11) was proved to be identical with an authentic sample of 16-oxohasubanonine (15), which was obtained from natural hasubanonine by oxidation with $KMnO_4$, in terms of their i.r., n.m.r., mass spectra and t.l.c. behaviors. Since $LiAlH_4$ reduction of 16-oxohasubanonine, followed by MnO_2 oxidation regenerated hasubanonine, the present synthesis amounts to the total synthesis of dl-hasubanonine.

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