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THE TOTAL SYNTHESIS OF dl-CEPHARAMINE

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Isolations and structure establishments of several alkaloids possessing a modified morphinan skeleton from the Stephania species (Menispermaceae) have been reported[1] and cepharamine (1)[2] is a member of these new type alkaloids. This communication concerns the total synthesis of dl-cepharamine.

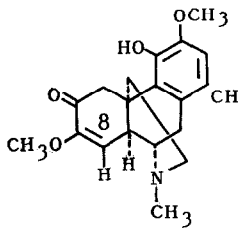
The synthesis of the skeletal ring system, hasubanan (2), has been described in a previous publication.[3] In the present synthesis, an alternative route which involves a modified Robinson annelation reaction, was effectively employed in the construction of the ring system. The pyrrolidinenamine of 7,8-dimethoxy-2-tetralon (3)[4] was condensed with iodoacetonitrile (or chloroacetonitrile) in acetonitrile, followed by hydrolysis, to give the keto nitrile (4)*1, m.p. 73-76°, ν_{max} 2270 cm^{-1}. Reaction of 4 with methyl vinyl ketone in anhydrous methanol[5] at the presence of catalytic amount of sodium hydroxide afforded the two epimeric alcohols (5) which without separation were transformed into the keto lactam (6), m.p. 270°, ν_{max} 3410 and 1690 cm^{-1}, by treatment with sodium ethoxide in refluxing ethanol. The ketal lactam (7), m.p. 255-259°, ν_{max} 3410 and 1685 cm^{-1} formed by ketalization of 6, was methylated with methyl iodide and sodium hydride to give the N-methyl ketal lactam (8), m.p. 177°, ν_{max} 1672 cm^{-1} which is identical with an authentic sample derived from the N-methyl keto lactam (9) reported in the previous report.[3]

Partial demethylation of 8 was carried out according to the procedure,

*1 Satisfactory analyses of crystalline compounds in this communication were obtained and all compounds revealed the reasonable i.r. and n.m.r. spectra for the structures, respectively. All i.r. spectra were measured in chloroform.

previously reported in the morphine synthesis,[6] the compound being heated with potassium hydroxide and hydrazine hydrate in diethylene glycol. The resulting phenol (10), m.p. 225°, ν_{max} 3500 cm^{-1} was then acetylated to the ketal acetate (11), b.p. 200/2x10^{-4} mm. Hg which was hydrolysed to afford the keto acetate (12) m.p. 249-251.5°, ν_{max} 1672 and 1719 cm^{-1}. Bromination of 12 with two equivalent of bromine in acetic acid gave the dibromo ketone which without purification was treated with freshly fused sodium acetate in acetic acid[7] to afford crystals consisting of the α-diketone (13) and the compound with an unidentified structure Enolmethylation of this mixture with methanol and boron trifluoride[8] afforded dl-oxocepharamine acetate (14), m.p. 267°, ν_{max} 1684 and 1640 cm^{-1}, n.m.r. τ (in $CDCl_3$), 4.55 (1H, singlet, olefinic proton), in ca 10% yield from the compound (12).*2 Reduction of 14 with lithium aluminum hydride in a mixture of tetrahydrofuran and ether, and the successive dimethylsulfoxide-dicyclohexylcarbodiimide-phosphoric acid oxidation[9] afforded dl-cepharamine (15) as an oil, which

*2 Direction of enolmethylation of the diketone seemed to depend on the structure of the five-membered nitrogen heterocycle. We, therefore, examined this by using the following model compounds. In sinomenine series, the analogous two isomers, (16) and (17) have been reported and the remarkable chemical shift difference between the signal due to the C_5 olefinic proton (3.25 τ, 1H, singlet) and that due to the C_8 olefinic proton (4.50 τ, 1H, doublet) has been observed.[10] On the analogy of these observations, the relative intensity of the olefinic proton signal of each isomer will be useful in estimating the ratio of two isomeric products generated from enolmethylation of the diketone. Enolmethylation of 18 possessing a lactam ring, gave a mixture consisting of the compound (20, 4.49 τ, singlet) and the compound (22, 4.15 τ, singlet), in a ratio of 4:1, whereas that of the compound (19) possessing an ethanamine structure, afforded nearly exclusively the compound (23, 3.85 τ, singlet) (the compound 21, 4.35 τ, singlet): unpublished results.



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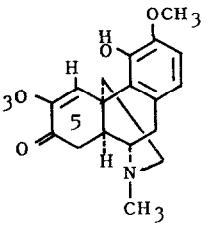

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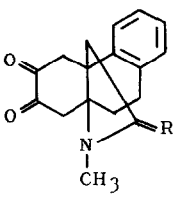

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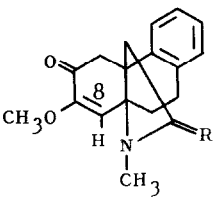
19: R=H_2



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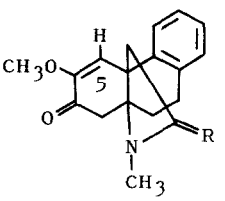
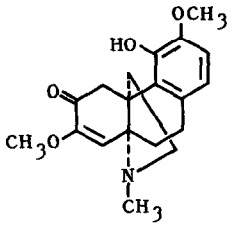


22: R=O
23: R=H_2



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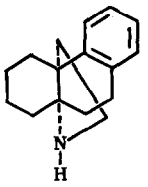

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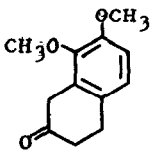

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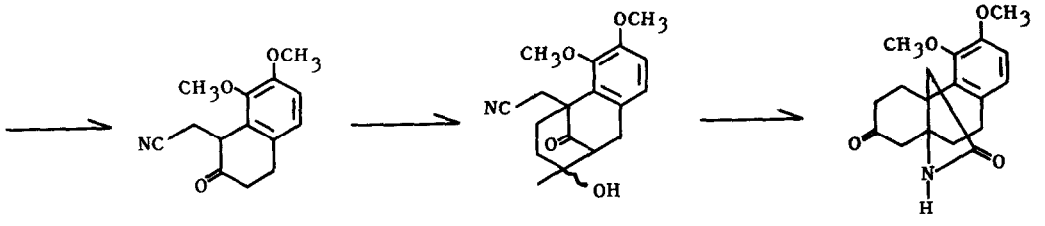

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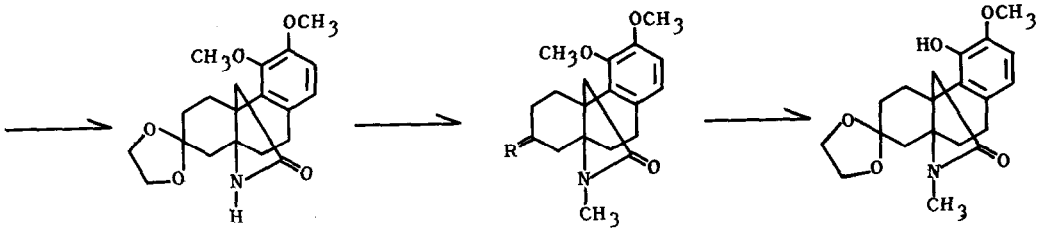
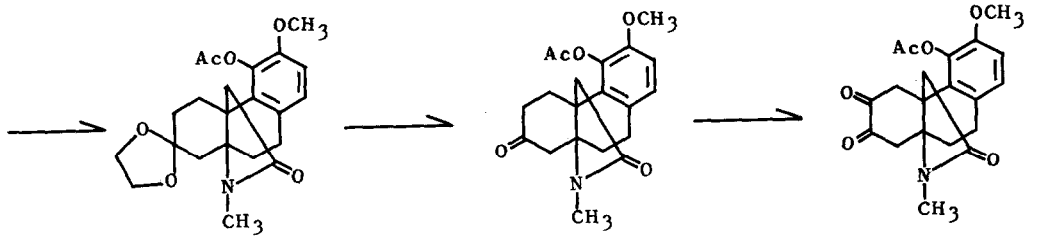
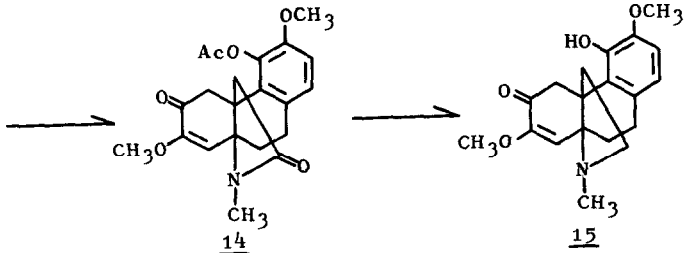


7 8 R= 9 R=O 10



11 12 13



14 15

was characterized as its hydrobromide, m.p. 243-246°. Both natural cepharamine and synthetic dl-cepharamine were found to be completely identical in terms of their i.r., n.m.r. and mass spectra, and t.l.c. behaviors.

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