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SYNTHESIS OF RING SYSTEM RELATED TO.HASUBANAN ALKALOID

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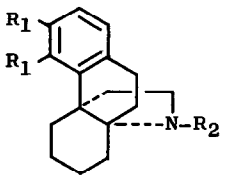
Alkaloids containing hasubanan framework (I) were isolated from various Stephania species and the complete constitutions were settled recently[1]. In this paper the authors wish to communicate the synthesis of dl-N-methyl-hasubanan derivative[*1].

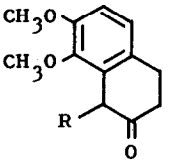
Condensation of pyrrolidine enamine of 7,8-dimethoxy-2-tetralone (II)[2] with ethyl bromoacetate, followed by hydrolysis, afforded the keto ester (III), m.p. 68-68.5°, $C_{16}H_{20}O_5$. By treatment with 1-diethylamino-3-butanone methiodide and potassium ethoxide[3], the keto ester (III) was converted into the keto lactone (IV), m.p. 160-163°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767 (lactone); 1722 (ketone), $C_{18}H_{20}O_5$. Ketalization of the keto lactone (IV) by ethylene glycol in the presence of p-toluenesulfonic acid in benzene gave the ketal lactone (V), m.p. 194-196°, $C_{20}H_{24}O_6$, which on treatment with the mixture of methylamine and methylamine hydrochloride in aq. dioxane[*2] gave the keto lactam (VI), m.p. 170-172°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1718 (ketone); 1675 (lactam), NMR ($CDCl_3$) τ : 7.20 ($N-CH_3$), $C_{19}H_{23}O_4N$, along with the O-demethylated keto lactam (VII)[*3], m.p. 247-250°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (hydroxyl); 1715 (ketone); 1675 (lactam), $C_{18}H_{21}O_4N$.

Huang Minlon reduction of the keto lactam (VI) afforded the lactam (VIII), m.p. 187.5-190°, $C_{19}H_{25}O_3N$, and the O-demethylated product (IX)[*3], m.p. 167-170°, $C_{18}H_{23}O_3N$. Methylation of IX with methyl iodide and potassium carbonate



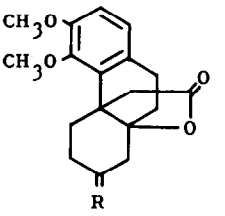
I $R_1 = R_2 = H$

XI $R_1 = OCH_3$, $R_2 = CH_3$



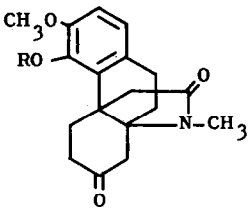
II $R = H$

III $R = CH_2CO_2C_2H_5$



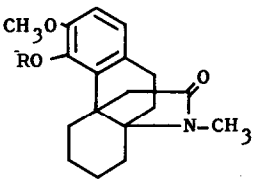
IV $R = O$

V $R =$ 



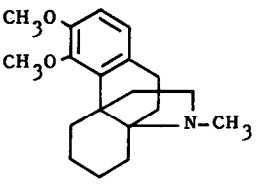
VI $R = CH_3$

VII $R = H$



VIII $R = CH_3$

IX $R = H$



X

in acetone gave VIII. Treatment of the lactam (VIII) with lithium aluminum hydride gave the dl-3,4-dimethoxy-N-methylhasubanan (X) as a colorless oily substance, which was characterized as its hydrobromide, m.p. 242-250°, $C_{19}H_{27}O_2N.HBr$. The over-all yield of X from II was approximately 2.2 % .

The racemic product (X) and the 3,4-dimethoxy-N-methylhasubanan (XI)[4] derived from naturally occuring hasubanan alkaloids were found to be identical in terms of their IR spectra (in $CHCl_3$), NMR spectra (in $CDCl_3$), and the thin layer chromatographic behaviors.

The synthesis of dl-hasubanan derivative by the above route points to the accessibility of similar racemic hasubanan derivatives.

*1 All compounds given by formulas in this communication gave satisfactory elementary analyses.

*2 The expectation that the keto lactone (IV) could be transformed into the keto lactam (VI) was not fulfilled, and the experimental condition will be presented in the full paper.

*3 M. Gates, et al. (J. Am. Chem. Soc., 78, 1380 (1956).) and M. Tomita et al[4]. have reported that the methoxyl group at C-4 position in morphinan and hasubanan series alkaloids was demethylated under alkaline condition. Furthermore, VII and IX showed a strong blue color with 2,6-dichloroquinone-4-chloroimide suggesting hydroxyl groups should be situated at C-4 position (cf. homostephanoline[1a] which has hydroxyl group at C-3 position was negative to the reagent).

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