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AN APPROACH TO THE SYNTHESIS OF THE HASUBANAN CARBOCYCLIC SYSTEM

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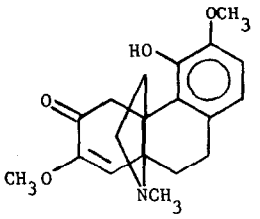
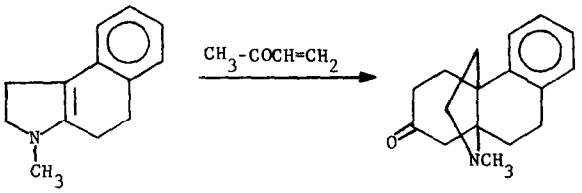
A growing number of alkaloids bearing a close structural relationship to the morphine bases have recently been isolated from various Stephania species of menispermaceous plants. To date six members of this class of hasubanan alkaloids have been characterized (1).



I

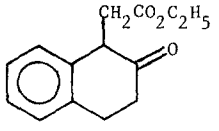
Cepharamine (I) (2), the functionally least complicated member of this class, illustrates the general oxygenation pattern which must be considered when designing a general synthesis of the hasubanan skeleton.



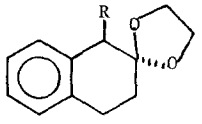
II III

Conceptionally, the simplest approach to examine as an efficient route to this carbocyclic skeleton is illustrated by the enamine annelation reaction shown above. In this communication the author wishes to report on the successful application of this annelation sequence to the synthesis of d,l-7-oxo-N-methylhasubanan (III) (4). During the course of this investigation several workers have succeeded in using this concept in the synthesis of the mesembrene (5), as well as the Erythrina alkaloid skeleton (6).

Reaction of the pyrrolidine enamine of 2-tetralone with ethyl bromoacetate in benzene followed by aqueous hydrolysis afforded the keto ester IV in 89% yield, bp 125-7° (0.08mm), IR (liquid film) 1721, 1734 cm^{-1} (7). Ketalization of this material with ethylene glycol in the presence of toluenesulfonic acid in benzene gave a quantative yield of the ketal ester V, bp 155° (0.03mm), IR (liquid film) 1730 cm^{-1}. Transformation of V into the corresponding N-methyl amide VI was accomplished using the method of Petit and Pouisson (8). This method, utilizing the lithium aluminum salt of methylamine, has proven very successful in this laboratory at preparing amides from hindered esters. Under these conditions the desired N-methyl amide was prepared in 61% yield, mp 127.5-129.5, IR ($CHCl_3$) 1661 cm^{-1}. Efforts to prepare this amide under milder conditions failed due to the hindered environment around the ester carbonyl function.

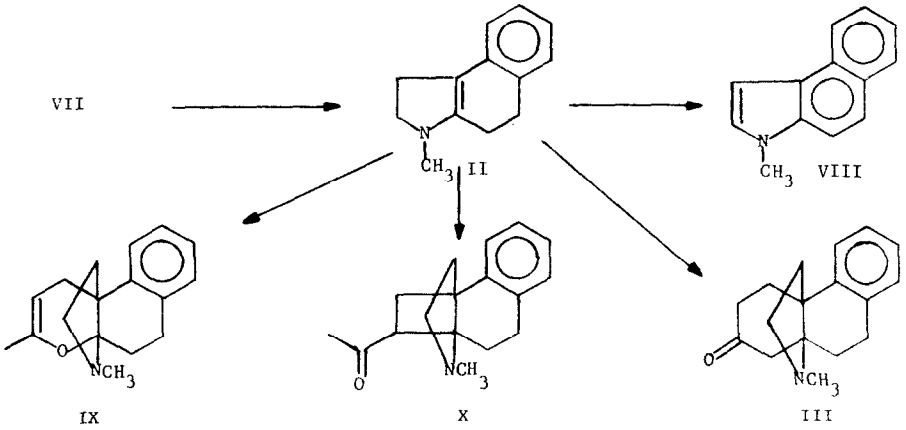


IV



V R=-$CH_2CO_2C_2H_5$
VI R=-$CH_2CONHCH_3$
VII R=-$CH_2CH_2NHCH_3$

Aluminum hydride reduction (9) of the ketal amide VI over a 24-hr. period gave the desired ketal amine VII, bp 117-120° (0.13mm), NMR ($CDCl_3$) δ: 1.08(N-H); 1.60 (N-CH_3); 3.97 ketal), in good yield.



Treatment of the ketal amine VII with aqueous acid followed by neutralization afforded a quantative yield of an oxygen sensitive oil exhibiting a strong IR band (liquid film) at 1628 cm^{-1} which is compatible with the conjugated enamine II (10). The NMR ($CDCl_3$) showed a sharp N-methyl resonance at 2.58 δ; the lack of any olefinic resonances in the region 3.3-6.3 δ rules against the alternative nonconjugated enamine. (11). Attempts to prepare a crystalline salt proved fruitless due to the extreme oxygen sensitivity of the compound. Direct proof of the tricyclic nature of the enamine II was obtained by dehydrogenation of the base with 10% palladium on charcoal in refluxing mesitylene. The resulting 3-methyl-1,2,4,5-tetrahydrobenz[e]indole VIII, mp 54-55.5°, NMR ($CDCl_3$) δ: 3.67 ($N\text{-}CH_3$); 6.97 (two-proton singlet); 7.2-8.3 (six-proton multiplet), was obtained in 75% yield. The mass spectrum showed a parent ion at m/e 181 ($C_{13}H_{11}N$) and additional ions at m/e 166 and 139. This mode of fragmentation has been substantiated for benz[e]indoles (12) and is not unlike that of 1-methylindole (13).

Due to the lability of the tricyclic base II the annelation reaction with methyl vinyl ketone was carried out without isolation of the enamine. Thus, the ketal amine was hydrolyzed with 6N H_2SO_4 in ethanol and the resulting solution was adjusted to PH 8-9 with 6N NaOH. The enamine, in this 1:1 mixture of ethanol-water, was heated to 75°, and an ethanolic solution of 1.4 equivalents of methyl vinyl ketone was added over a one-hour period; heating was continued for an additional three hours. The course of the reaction was followed by g.l.c.. It appears that the reaction of the enamine with unsaturated ketone was quite rapid. The reaction proceeded quite cleanly to produce two compounds having very similar retention times. The desired keto amine III was isolated as a colorless oil after chromatography on neutral alumina, IR($CHCl_3$) 1712 cm^{-1}, NMR ($CDCL_3$) 3.88 δ ($N\text{-}CH_3$). The mass spectrum of the crystalline, hygroscopic hydrochloride, mp 160-160.4° with decomposition (sealed cap.) showed a parent ion m/e 255 ($C_{17}H_{21}NO$) and additional ions at m/e 186 ($C_{13}H_{14}N$) and 185 ($C_{13}H_{13}N$). Confirmation of the structure of the keto amine III by an alternate synthesis similar to that reported by Tomita and coworkers (4) has been carried out (14).

The structure of the second product which is formed in this reaction is still in doubt. Based on the recent work of Fleming and Karger (15), the first-formed product in reactions of this type are dihydropyrans such as IX. Examination of the NMR spectrum of the crude reaction mixture suggests that the isomeric product is, in fact the cyclobutane isomer X.

A detailed study of this annelation reaction is now in progress, and its application to the synthesis of cepharamine is being pursued.

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