

Short Communication

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PREPARATION OF CONESSINE ANALOGUES FOR AMOEBIC DYSENTERY

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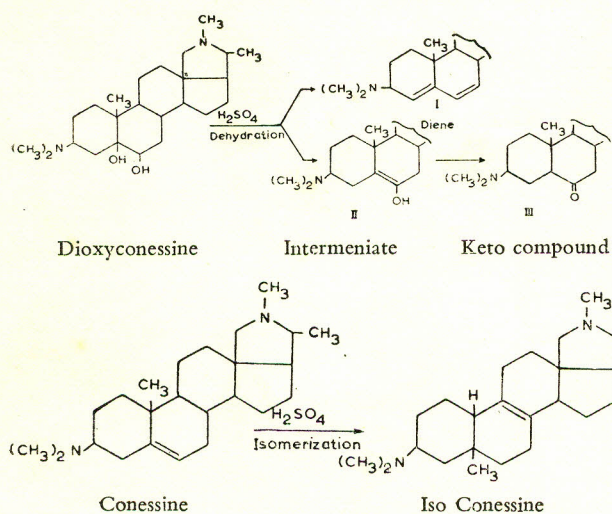
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Conessine,¹ the main alkaloid from *Holarrhena antidysenterica*, is effective² for the treatment of amoebic dysentery. Conessine, a ditertiaryamine, has a steroidal skeleton³ with a double bond at 5:6 position.⁴

When dioxyconessine (3 β -dimethylamine conane-5 α , 6 β -diol)⁵ is dehydrated with sulphuric acid, it yields two compounds namely 3 β -dimethylamine-4:6-diene with conjugated double bond in two different rings (I) as proved by its UV study⁶ and by hydrogenation when it yields dihydroconessine. The other compound obtained at the same time is 3 β -dimethylamine conane-6-one (III).⁷

In this reaction, migration of C-methyl from position 10 to position 5 does not occur due to the formation of conjugated double bond in the former case, and in the keto compound the formation of ketone at position 6 checks the migration of C-methyl as compared to conessine. Moreover, conessine on treatment with sulphuric acid gives isoconessine in which the migration of C-methyl to position 5 and the double bond at 8:9 occur.⁸



The oily substance obtained by Bertho⁹ yielded a different hydriodide, m.p. 268°C, while the hydriodides of the bases obtained as a result of dehydration of dioxyconessine have m.p.s. 247 and 349°C.

That the reaction of β -oxyconessine¹⁰ with H_2SO_4 and H_2O_2 under reflux yields a diene is very doubtful. The presence of H_2O_2 in the reaction mixture will hydroxylate one or both the double bonds if they were created.

Bertho's oil yielded a substance described as a diene (m.p. 116°C) on the basis of UV study indicate that the two double bonds in conjugation are in two different rings.⁹ Neither a hydriodide was formed of this base to characterize and compare with hydriodide of Bertho's oil, nor hydrogenated to yield dihydroconessine to prove its structure as the requisite diene.

Further, oxidation¹¹ of 6-acetoxy-3 β -dimethylaminocon-6-one enine with osmium tetroxide and treatment of the gum with 2N H_2SO_4 yields 3 β -dimethylaminocon-4:6-diene (m.p. 116°C) involves several steps without purification of the intermediate reaction products. Hence, it is not free of doubts to state categorically the main compound which yields this substance.

Since the position of the double bond and C-methyl in conessine molecule is very labile, if at all it is a conjugated diene, it should be a compound where the positions of double bonds and C-methyl may be different.

The products of dehydration of dioxyconessine can be put to the pharmacological effect on *Entamoeba histolytica*—the cause of amoebic dysentery—from the point of view of a compound in one case where two double bonds are present and in the second where a ketonic group is available in comparison with the effect of conessine which contains only one double bond in the steroidal moiety.

Experimental

Action of H_2SO_4 (concd) on Dioxyconessine. Dioxyconessine (0.5 g) was dissolved by adding in small portions of the substance at a time to 3 ml H_2SO_4 (concd) (d 1.84) while keeping the temperature between 0–5°C. The thick brown viscous liquid thus obtained was poured on crushed ice, basified with 30% NaOH and the product was taken up in light petroleum (b.p. 62–82°C), washed thrice with small amount of water. The solution was dried. (Na_2SO_4) filtered and the solvent removed in vacuum when 0.385 g oily base was obtained. The base was dissolved in 30% acetic acid and (concd) KI was added to get an oily hydriodide which was crystallized from methanol–water mixture (2:100), m.p. 247°C, yield 0.2 g. Small portions of this hydriodide when crystallized with ethanol or methanol separately did not change the m.p. The base from hydriodide was liberated and obtained through petroleum ether as an oil. (Found C, 81.3; H, 10.78; N, 7.93. Calc for $C_{24}H_{38}N_2$: C, 81.35; H, 10.76; N, 7.9%)

The UV study of the oily base showed λ_{EtOH}^{max} 244 nm in agreement with the conjugated double bonds at 4:5 and 6:7 positions.

Hydrogenation of the Oily Base. Oily base (0.2 g) in acetic acid (10 ml) was shaken in hydrogen atmosphere in the presence of 15% palladium charcoal (0.3 g). After 8 hr adsorption of hydrogen (32 cm³, calculated for two double bonds 25 cm³), the base was isolated in the usual way by crystallization with acetone, m.p. 105°C (yield 0.18 g). It showed no depres-

sion in m.p. with an authentic specimen of dihydroconessine obtained by hydrogenating conessine.

The base recovered from the mother liquor of hydriodide was taken up in light petroleum (b.p. 62–82°C). The solution concentrated to about 10 ml and poured over a column of alumina, 5 g (according to Brockmann, E. Merck). The column was eluted with more light petroleum till no more substance came in the eluent. The light petroleum eluent was kept aside and was not worked up further. The column was next eluted with ether till exhausted. The ethereal solution on evaporation gave a residue crystallized with acetone, m.p. 190–203°C (yield 10 mg). (Found: C, 77.45; H, 10.68; N, 7.61; O, 4.26. Calc. for $C_{24}H_{40}N_2O$; C, 77.41; H, 10.75; N, 7.53; O, 4.24%).

The IR spectrum gave a peak at 1701 cm^{-1} showing a ketonic group. The compound gave a hydriodide, m.p. 349°C, and 2:4-dinitrophenylhydroxone, m.p. 248–25°C (dec.).

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