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SYNTHESES OF THE BASIC STRUCTURES OF CORYNOLINE AND RELATED ALKALOIDS

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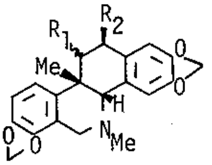
Syntheses of the compounds (XII, VII, and XI) having the basic structures of corynoline (Ia) and related alkaloids (Ib and Ic) are described.

Synthetic approach to corynoline (Ia)[1] and related alkaloids[2], 11-epicorynoline (Ib), 12-hydroxycorynoline (Ic), and 6-oxocorynoline, which are representatives of the hydrobenzo[c]phenanthridine alkaloids popular in Corydalis plants, is almost unexploited, except the work[3] by Onda and his coworkers who succeeded in a conversion of a protoberberine alkaloid into an analogue of corynoline.

In the course of study aiming at total syntheses of these alkaloids, the present investigation was undertaken in order to establish the stereospecific synthetic route toward these alkaloids by preparing the compounds (XII, VII, and XI) which have the basic structures of alkaloids, especially employing the enamide photo-



(Ia) R_1= ''''OH, R_2= -H

(Ib) R_1= ◂OH, R_2= -H

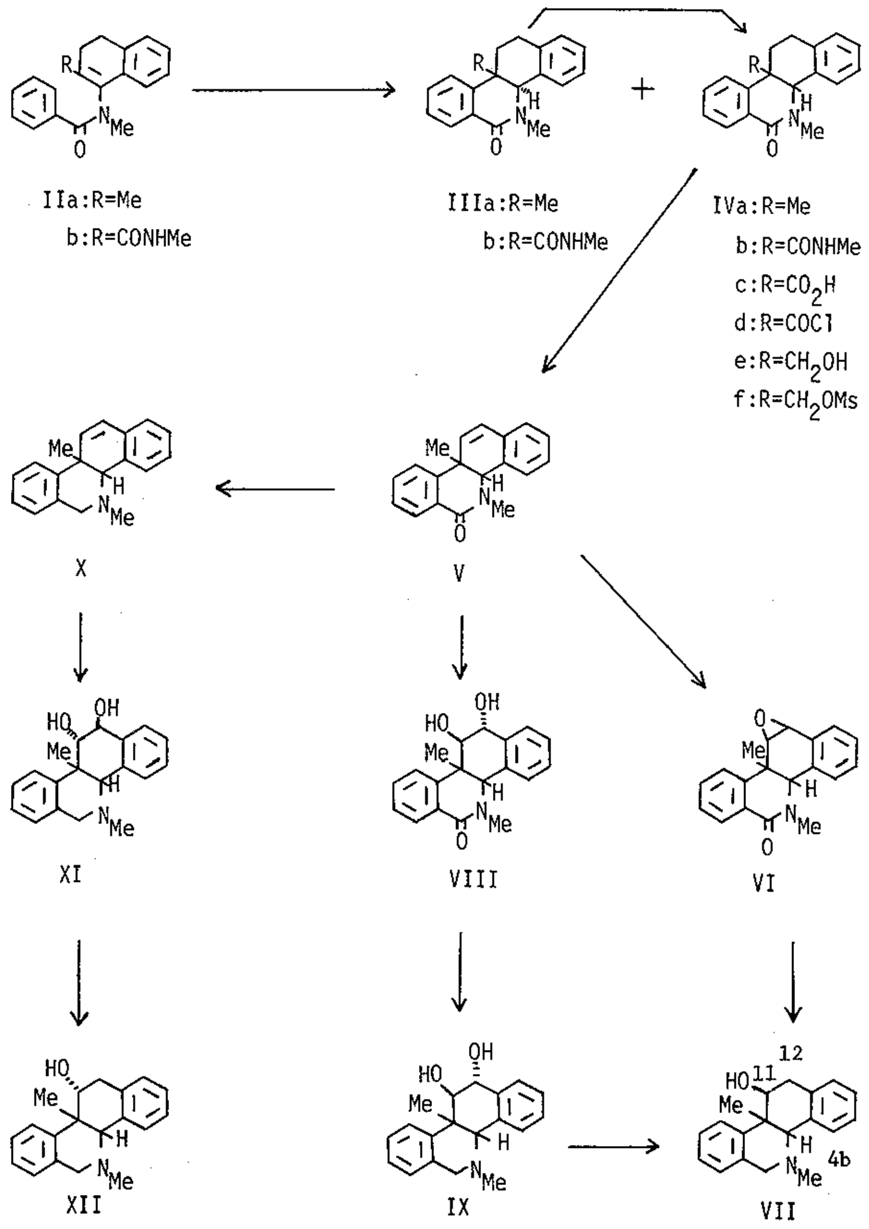
(Ic) R_1= ''''OH, R_2= -OH

cyclisation.[4] A methanolic solution (0.02 M) of the enamide (IIa), which was prepared from 2-methyl-1-tetralone, was irradiated with a low pressure mercury lamp at room temperature for 40 hr. Chromatography of the reaction mixture on alumina afforded a mixture of isomeric products, the trans-lactam (IIIa), m.p. 133-134°(1 %) and the cis-lactam (IVa), m.p. 158-159° (7 %). Furthermore, it is found that prolonged irradiation (70 hr) of the enamide (IIa) and also irradiation of the trans-lactam (IIIa) yielded the cis-lactam (IVa) as a sole product.[5]

In order to improve the yield of the cis-lactam (IVa), we prepared the enamide (IIb) and irradiated. The photocyclisation proceeded very smoothly to afford the trans-lactam (IIIb) in 77 % yield. Isomerisation of the trans-lactam (IIIb) to the cis-isomer (IVb) was readily accomplished in methanol either by irradiation[5] or by refluxing in the presence of acid (HCl) or base (KOH).

Hydrolysis with 20 % hydrochloric acid converted the trans-lactam (IIIb) into the cis-acid (IVc), which was then transformed into the 10b-methyllactam (IVa) via the acid chloride (IVd), the alcohol (IVe), and the mesylate (IVf) successively. The yield of the methyllactam (IVa) was 18 % from (IVb).

Dehydrogenation[3] of the lactam (IVa) with 2,3-dichloro-5,6-dicyanobenzoquinone afforded the 11,12-didehydrolactam (V) in 40 % yield, which was then treated with m-chloroperbenzoic acid


IIa:R=Me
b:R=CONHMe
IIIa:R=Me
b:R=CONHMe
IVa:R=Me
b:R=CONHMe
c:R=CO2H
d:R=COCl
e:R=CH2OH
f:R=CH2OMs
X
V
XI
VIII
VI
XII
IX
VII
12
11
4b

to give the homogeneous epoxide (VI) in 80 % yield, which contained n.m.r. peaks at δ4.41 (1H, s, 4b-H), 4.17 (1H, d, J=4Hz, 12-H), and 4.07 (1H, d, J=4Hz, 11-H), thus suggesting its β-orientation. The epoxide (VI) was reduced regiospecifically[3] with lithium aluminium hydride to afford the amino-alcohol (VII) as an oil, whose structure was determined from its i.r. absorption at 3620 cm^{-1} due to a non-bonded hydroxyl group and also from n.m.r. peaks at δ4.65 (1H, d-d, J=9.5 and 7Hzs, 11-H) and 3.32 (1H, s, 4b-H), thereby proved its stereochemistry identical with that of 11-epicorynoline (Ib)[2].

Treatment of the 11,12-didehydrolactam (V) with performic acid followed by alkali yielded the homogeneous trans-glycol (VIII) in 60 % yield, which was reduced with lithium aluminium hydride to give the aminoglycol (IX), δ 4.46 (2H, s, 11- and 12-H) and 3.22 (1H, s, 4b-H), which was then subjected to hydrogenolysis with 40 % palladium-charcoal, thus affording the amino-alcohol (VII) in 32 % yield, identical with the sample derived from (VI).

On the other hand, reduction of the lactam (V) with lithium aluminium hydride followed by treatment with performic acid afforded the aminoglycol (XI), m.p. 211-213°, in 33 % yield, δ5.06 (1H, m, $W_{h/2}$=5Hz, 12-H), 4.00 (1H, t, J=1.5Hz, 11-H), and 3.45 (1H, d, J=1.5 Hz, 4b-H), which is the basic structure of 12-hydroxycorynoline (Ic)[2].

Hydrogenolysis of the aminoglycol (XI) with 40 % palladium-charcoal afforded the corresponding amino-alcohol (XII) as an oil in 61 % yield, which exhibited an i.r. absorption of a bonded hydroxyl group at $\sim$3200 cm^{-1} (very broad) and n.m.r. peaks at δ4.20 (1H, m, 11-H), 3.34 (1H, s-like, 4b-H), and 3.27 (2H, d, J=4Hz, 12-H_2) which is the basic structure of corynoline (Ia)[1].

This marked difference observed on the behaviour of the lactam (V) and the amine (X) to peracid can be explained as follows; m-chloroperbenzoic acid or performic acid attacks a double bond of the lactam (V) from the less hindered β-side, thus affording the epoxide (VI) or the glycol (VIII) homogeneously. On the other hand, a bonding interaction between the basic nitrogen and an oxidising agent would make the attack of performic acid from the more hindered α-side possible in the amine (X), therefore affording the trans-diaxial-glycol (XI).

The above syntheses of the compounds (XII, VII, and XI) having the basic structures of the alkaloids offer the promising approach to total syntheses of natural alkaloids themselves, which are now under progress.

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