SYNTHESES OF (±)-DIHYDROLYCORICIDINES FROM THE COMMON INTERMEDIATE TO ETHANOPHENANTHRIDINE ALKALOIDS

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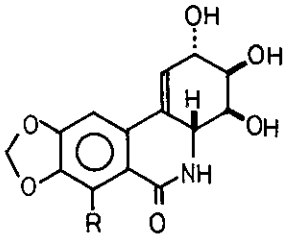
The common intermediate (6) to 11-oxygenated ethanophenanthridine alkaloids was converted in a stereospecific manner to the lactam-diacetate (12), from which the carboxylic function was selectively removed by alkaline hydrolysis and photolysis of the hydrolysate furnishing cis- and trans-(±)-dihydrolycoricidines, (15) and (16). This method, photoremoval of a carboxylic group via the corresponding anion, was shown to be a useful tool by several model experiments.

Lycoricidine[1] (1) and narciclasine[2] (2), the antimitotic and growth-inhibiting substances occurring in some Amaryllidaceae plants, are synthesized in plants from the ethanophenanthridine

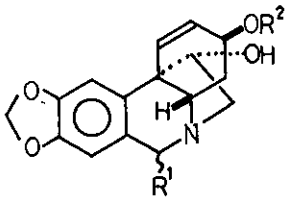
alkaloid, 11-hydroxyvittatine (3)[3]. Here we report the syntheses of dihydrolycoricidines, (15) and (16), from the bicyclic compound (6)[4] which was the key synthetic intermediate to various 11-oxygenated ethanophenanthridine alkaloids such as haemanthamine (4a)[4], haemanthidine (5)[5], and crinamine (4b)[6], by this novel procedure (photo-removal of a carboxylic group via the corresponding anion).

Treatment of 6 with methyl chloroformate and KOH in CH_3CN at room temperature for 30 min followed by hydrolysis with 10% KOH in methanol afforded the keto-acid (7) which on oxidation with H_2O_2-NaOH gave the urethan-acid (8)[7] (68% from 6), m.p. 196-199° On treatment with N-bromosuccinimide in CH_2Cl_2, 8 was converted into the bromo-lactone (9) (77%), m.p. 144-146°, which was dehydrobrominated to 10 by 1,5-diazabicyclo[5.4.0]undecene-5 in toluene at 100°C. Osmium tetraoxide oxidation of 10 followed by acetylation of the resulting glycol afforded the diacetate (11) (58%, from 9), m.p. 245-247°, in which the new glycol function should have been introduced from the opposite side of the lactonic function. Application of the modified Bischler-Napieralski cyclization[8] to this urethan-acetate (11) furnished the lactam-acetate (12) (60%), m.p.>300°, which should have the same stereochemistry with that of lycoricidine except the additional carboxyl function instead of the double bond. Removal of this function was achieved as follows.

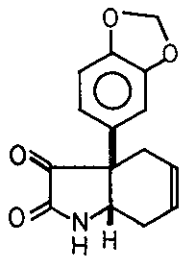
The model compounds, (17)[8] and (19)[8], were smoothly decarboxylated on irradiation in 0.1N NaOH with medidum pressure mercury lamp for 15 min to give (18)[9], m.p. 302-305°, and (20), m.p.>300°



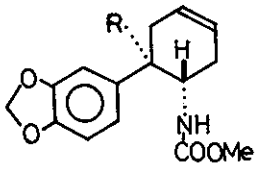
1 R=H
2 R=OH



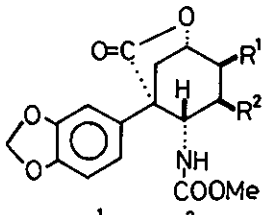
3 $R^1=R^2=H$
4a $R^1=H$, $R^2=Me$
4b $R^1=H$, α=OMe instead of β-OR^2
5 $R^1=OH$, $R^2=Me$



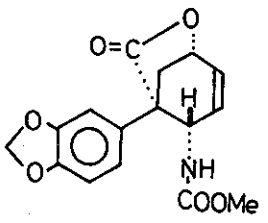
6



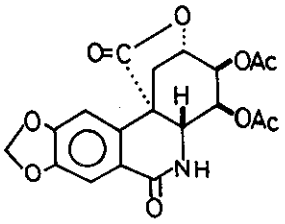
7 R=COCOOH
8 R=COOH



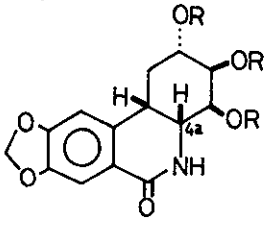
9 $R^1=Br$, $R^2=H$
11 $R^1=R^2=OAc$



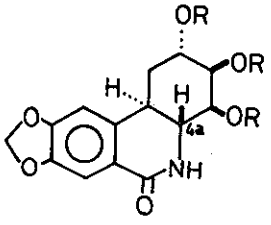
10



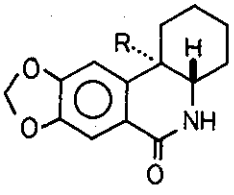
12



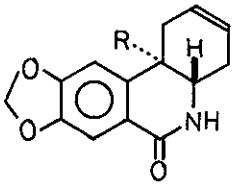
13 R=Ac
15 R=H



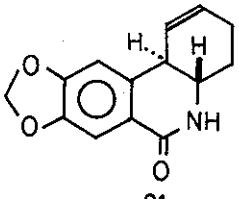
14 R=Ac
16 R=H



17 R=COOH
18 R=H



19 R=COOH
20 R=H



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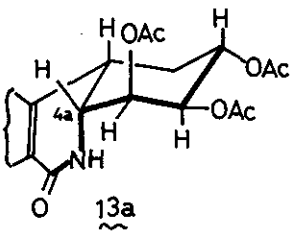
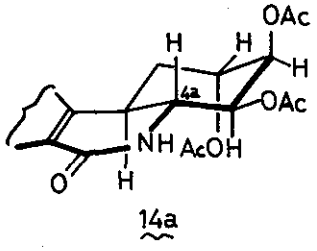
in almost quantitative yields, respectively, while the corresponding free acids were difficult to decarboxylate. Simplicity of the procedure and high yield of the product suggest that this decarboxylation method is advantageous over the other methods.

Thus lactam-acetate (12) was hydrolysed by 0.1N NaOH and irradiation of the hydrolysate as above for 30 min, followed by acetylation (Ac_2O-Py) of the product to furnish, in contrast to the model compounds which gave only A/B-trans isomers, 1:1 mixture of cis- and trans-dihydrolycoricidine triacetate (43%), [(13), m.p. 289-291°, and (14) m.p.>300°] which were separated by column chromatography and proved respectively to be identical (IR and NMR in $CDCl_3$, and TLC) with the corresponding specimens obtained by hydrogenation (H_2/Pd-C) of natural lycoricidine triacetate.[10] Their stereochemistries were elucidated from the NMR spectra: C_{4a}-H signal of 13 appeared as a triplet (J=3 Hz) at δ3.93 and that of 14 showed quartet (J=10 and 12 Hz) at δ3.77 ppm indicating that they have the configuration (13a) and (14a) respectively.[11]

Hydrolysis of 13 and 14 with *MeOH-NH₃* furnished cis- and trans-(±)-dihydrolycoricidine[12] [(15), m.p.>300°, and (16), m.p.>300°], respectively.



13a



14a

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References and Footnotes

1. T. Okamoto, Y. Torii, and Y. Isogai, *Chem. and Pharm. Bull. (Japan)*, 16, 1860 (1968).
2. G. Ceriotti, *Nature*, 213, 595 (1967); F. Piozzi, C. Fuganti, R. Mondelli, and G. Ceriotti, *Tetrahedron*, 24. 1119 (1968); A. Immirzi and C. Fuganti, *J. C. S. Chem. Comm.*, 240 (1972).
3. C. Fuganti, *Gazz. Chim. Ital.*, 103, 1255 (1973).
4. Y. Tsuda and K. Isobe, *Chem. Comm.*, 1555 (1971).
5. Y. Tsuda, A. Ukai, and K. Isobe, *Tetrahedron Letters*, 3153 (1972).
6. K. Isobe, J. Taga, and Y. Tsuda, *Tetrahedron Letters*, 2331 (1976).
7. All compounds reported had spectroscopic properties in accord with their assigned structures.
8. Y. Tsuda, K. Isobe, J. Toda, and J. Taga, *Heterocycles*, 5, 157 (1976).
9. This was identified by hydrogenation of (21) reported by Ohta and Kimoto [*Chem. and Pharm. Bull. (Japan)*, 24, 2969 (1976)].
10. Hydrogenation of the natural lycoricidine triacetate yielded a 4:1 mixture of cis- and trans-dihydro derivatives which were hydrolysed respectively to dihydrolycoricidines (cis-isomer, m.p. 292-293°, and trans-isomer, amorphous).

11. For dihydronarciclasines, C_{4a}-H for cis-isomer (δ3.89, t, J=3.6 Hz) and that for trans-isomer (δ3.73, q, J=10.7 and 12.5 Hz) were described [A. Mondon and K. Krohn, *Chem. Ber.*, 108, 445 (1975)].

12. Okamoto et al. [*Chem. and Pharm. Bull. (Japan)*, 16, 1860 (1968)] reported dihydrolycoricidine, m.p. 258-261°, which was now proved, by IR comparisons, to consist of the cis-isomer (15) contaminated with a small amount of the trans-isomer (16).

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