Communications to the Editor

[Chem. Pharm. Bull. 33(4)1763—1765(1985)]

SYNTHESIS OF FAGARIDINE, A PHENOLIC BENZO[*c*]PHENANTHRIDINE ALKALOID

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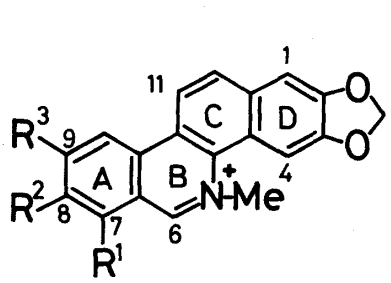
Regioselective demethylation of oxychelerythrine (5), derived from berberine (4), with *p*-toluenesulfonic acid in refluxing toluene gave oxyfagaridine (6), which was converted into fagaridine (1) in good yields by successive reduction and oxidation.

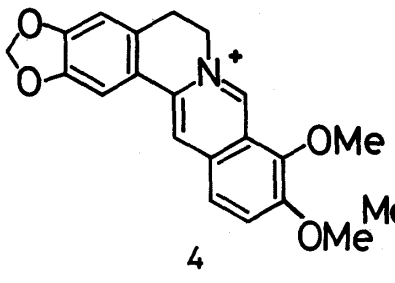
KEYWORDS——— fagaridine; oxyfagaridine; phenolic benzo[*c*]-phenanthridine alkaloid; berberine; oxychelerythrine; regioselective demethylation

Fully aromatized 2,3,7,8-tetraoxygenated benzo[*c*]phenanthridine alkaloid, fagaridine (1),[1] isolated from the root bark of *Fagara xanthoxyloides*, has been shown to possess a phenolic hydroxy group at C-7 position on ring A by comparison of its proton nuclear magnetic resonance spectrum with those of chelerythrine (2) and nitidine (3). This phenolic benzo[*c*]phenanthridine alkaloid has also been isolated from *Zanthoxylum tsihanimposa*[2] and *F. tessmannii*.[3] However, no report has so far been made on the unambiguous determination of the position of the phenolic hydroxy group in fagaridine (1).[4]

Recently we have developed a novel and efficient method[7] for a synthesis of chelerythrine (2), a benzo[*c*]phenanthridine alkaloid from the corresponding protoberberine alkaloid, berberine (4), *via* oxychelerythrine (5) according to a



1: R^1=OH, R^2=OMe, R^3=H
2: R^1=R^2=OMe, R^3=H
3: R^1=H, R^2=R^3=OMe



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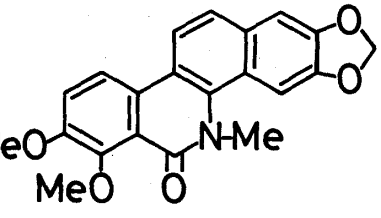

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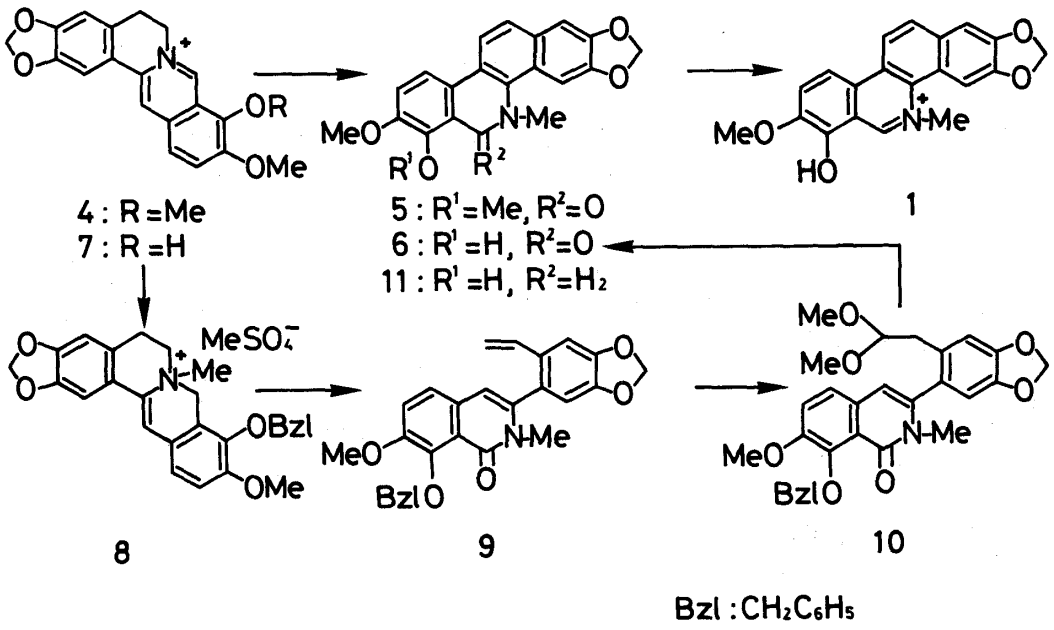
biogenetic route. We now report a first synthesis of fagaridine (1) from berberine (4) through a regioselective demethylation of C-7 methoxy group in oxychelerythrine (5).

Oxychelerythrine (5), easily derived from berberine (4),[7] was heated in toluene under reflux in the presence of *p*-toluenesulfonic acid for 3 h to give oxyfagaridine (6) [94%; mp 246-247°C; *m/z* 349 (M^+); ν 3450, 1630; δ ($CDCl_3$) 7.89, 7.48 (2H, AB-q, *J*=9), 7.56, 7.28 (2H, AB-q, *J*=9), 7.44, 7.10 (each 1H, each s), 6.08 (2H, s), 3.98, 3.85 (each 3H, each s), 3.31 (1H, s)]. The structure of 6 was unambiguously established by an alternative synthesis according to our method[7,8] developed recently. The methosulfate (8), derived from berberrubine (7),[9] successively underwent the Hofmann elimination and oxidation leading to the enamide (9). Upon treatment with thallium trinitrate in methanol, the enamide (9) provided the acetal (10), hydrolysis of which with 10% hydrochloric acid effected deacetalization, ring closure, dehydration, and debenzylation to furnish oxyfagaridine (6).

Reduction of 6 with lithium aluminum hydride in dry tetrahydrofuran followed by sodium borohydride in methanol at room temperature yielded dihydrofagaridine (11) [79%; mp 239-240°C; *m/z* 335 (M^+); ν 3500; δ (DMSO-d_6) 8.76 (1H, s), 7.75, 7.53 (2H, AB-q, *J*=9), 7.52, 7.28 (each 1H, each s), 7.31, 6.97 (2H, AB-q, *J*=9), 6.13 (2H, s), 4.16 (2H, s), 3.86, 2.49 (each 3H, each s)]. Finally, dihydrofagaridine (11) was oxidized with iodine in refluxing ethanol in the presence of potassium acetate, producing fagaridine iodide, which was subsequently treated with silver chloride to give fagaridine chloride (1) [77%; mp 206-208°C; *m/z* 334,



333 (base peak); ν 3400; δ (CF_3COOD) 9.81 (1H, s), 8.58, 8.08 (2H, AB-q, J=9), 8.45, 8.23 (2H, AB-q, J=9), 8.05, 7.53 (each 1H, each s), 6.26 (2H, s), 5.04, 4.22 (each 3H, each s)]. The spectral data of the synthetic fagaridine were in good agreement with those of natural fagaridine.

Thus, we have accomplished a first and efficient synthesis of fagaridine (]), a phenolic benzo[*c*]phenanthridine alkaloid from berberine (4), a protoberberine alkaloid, and the present synthesis established the correct structure of fagaridine (]).

REFERENCES AND NOTES

1) F.G. Torto, I.A. Mensah, and I. Baxter, *Phytochemistry*, 12, 2315 (1973).
2) N. Decaudain, N. Kunesch, and J. Poisson, *Ann. Pharm. Fr.*, 35, 521 (1977).
3) I.A. Mensah and E.A. Sofowora, *Planta Medica*, 35, 94 (1979).
4) On treatment with diazomethane, fagaridine (]) afforded chelerythrine (4),[1] and fagaridine (]) was shown to be not identical with *N*-methyldecarine,[5] the phenolic hydroxy group of which was proved to be on C-8 position.[6] The structure of], therefore, seems to be correct although direct proof is lacking.
5) P.G. Waterman, *Phytochemistry*, 14, 843 (1975).
6) H. Ishii, T. Ishikawa, and Y. Ichikawa, *Chem. Pharm. Bull.*, 26, 514 (1978); S.V. Kessar, Y.P. Gupta, T. Mohammad, A. Khurana, and K.K. Sawal, *Heterocycles*, 22, 2723 (1984).
7) M. Hanaoka, T. Motonishi, and C, Mukai, *J. Chem. Soc., Chem. Commun.*, 1984, 718.
8) M. Hanaoka, H. Yamagishi, M. Marutani, and C. Mukai, *Tetrahedron Letters*, 25, 5169 (1984).
9) E. Späth and G. Burger, *Ber.*, 59, 1486 (1926).

(Received February 18, 1985)