A ROUTE FOR TOTAL SYNTHESIS OF CHELIDONINE GROUP OF ALKALOIDS.

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A potential synthetic route (V ⟶ III) for total synthesis of chelidonine (I) and homochelidonine (II)[1] was developed using the model compounds (V ∼ X).

We have previously succeeded in total synthesis of corynolines.[2] As a continuation of our synthetic study on hexahydrobenzo[c]phenanthridine alkaloids which consist of corynoline and chelidonine groups, the present investigation was undertaken to establish a synthetic route for the alkaloids of chelidonine type, which have previously been synthesized only by Oppolzer.[3] We now describe a synthetic route with a great potentiality of application to to total synthesis of natural alkaloids.

The starting benzo[c]phenanthridone (VI), mp 176-177°, was readily prepared by photocyclization of the enamide (V)[4], mp 144-146°, in 50 % yield [irradiation; 0.02M MeOH-Et_2O solution, a low pressure mercury lamp, 10 hr.].

For further conversion of the lactam (VI) into the 11α-hydroxyamine (III), which is a target compound in this study and has a basic structure required for chelidonine group of alkaloids, we took advantage of diverse reactivity of the oxidizing agent, $Pb(OAc)_4$. Oxidation of the lactam (VI) and related compounds was extensively examined and found that the oxidation proceeded in various ways depending on the condition employed. Thus, treatment of VI with this reagent in benzene at 50° brought about dehydrogenation[5] to afford the aromatized lactam (VII), mp 187.5-189°, which was further oxygenated with $Pb(OAc)_4$[6a] to give the 12-acetoxylactam (VIII)[6b], mp 202.5-203°, when treated under refluxing temperature for 5 hr. [VIII; ir ν max 1760 cm^{-1}; nmr δ 7.88 (1H, s, 11-H) and 2.50 (3H, s, COMe)]. After hydrolysis of VIII into the 12-hydroxylactam (IX), treatment with $Pb(OAc)_4$ in acetic acid converted IX into the corresponding ortho-quinone (X)[7] in 95 % yield [X; red-brown crystal; mp 280°(dec); ir (nujol) ν max 1690, 1675 and 1660 cm^{-1})].

Lithium aluminum hydride reduction of the quinone (X) followed by catalytic hydrogenation of a double bond at ring junction [PtO_2 in EtOH] afforded the BC-cis diol (XI)[8] in 23 % yield upon chromatographic separation. The structure of the diol (XI) was deduced from its spectral evidences, [XI; ir ν max 3600 and 3400 cm^{-1}; nmr δ 4.51-4.26 (2H, m, 11-H and 12-H), which was reduced to two

sets of peaks (d, J=3.5Hz, 12-H) and (d, J=3.5Hz, 11-H) upon double irradiation of the 10b-H signal, 3.47 (1H, d, J=4Hz, 4b-H) and 3.01 (1H, t-like, J=4Hz, 10b-H)].

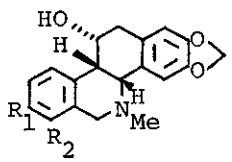
Further structure determination and conversion into the model compound (III) of chelidonine were carried out as follows. Hydrogenolysis[9] of the trans-diol (XI) [40% Pd-C in 10% HCl, 70% $HClO_4$ added, under 5-6 atm.] yielded a mixture of products (IV, XII and XIII) which were separated on the preparative t.l.c.; [the 11β-alcohol (IV); 25 % yield, ir ν max 3600 cm^{-1}; nmr δ 4.63 (1H, t-d, J=8, 6Hz , 11-H), 3.67 (1H, br s, 4b-H) and 2.98 (1H, d-d, J=8, 4Hz , 10b-H); the 11β,12β-cis-diol (XII); 13 %, ir ν max 3600 cm^{-1}; nmr δ 4.82 (1H, d, J=4.5Hz, 12-H), 4.62 (1H, d-d, J=8, 4.5Hz , 11-H), 3.64 (1H, d, J=5Hz, 4b-H) and 3.30 (1H, d-d, J=8, 5Hz , 10b-H) and the saturated amine (XIII); mass spectrum m/e 309 (M^+)].

Although the structures of these products were readily assignable from these spectral data, we carried out chemical conversions into various stereoisomers (III, XVII and XVIII) to make sure of these assignments. Acetylation[10] of the trans-diol (XI) with Ac_2O in $CHCl_3$ at room temperature afforded the 12-monoacetylated product (XIV) [ir ν max 1720 cm^{-1}; nmr δ 5.93 (1H, d, J=7Hz, 12-H) and 4.55 (1H, d-d, J=10, 7Hz , 11-H)], which was then mesylated[11] to yield the corresponding 11-mesylate (XV) [ir ν max 1730, 1360 and 1170 cm^{-1}]. Hydrolysis with 5% KOH-MeOH under reflux for 1 hr. converted the mesylate (XV) into the 11-hydroxy-12-methoxyamine (XVI) in 60% yield from XI [XVI; ir ν max 3200 cm^{-1}(very broad);

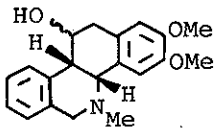
nmr δ 4.32 (2H, m, 11-H and 12-H), 3.97, 3.90, 3.67 (each 3H, s, OMe × 3) and 3.33 (1H, m, W1/2=4.5Hz, 10b-H)]. The formation of XVI can be explained as follows[12]; the elimination of a 11β-mesyloxy group which is facilitated by alkali and the neighboring group participation by an 12α-oxygen function onto the 11-position would occur to form an 11α,12α-epoxide which, though not detected, would undergo spontaneous ring opening by the attack of a solvent to form the diol 12-monomethyl ether (XVI).

Then, this compound (XVI) was subjected to hydrogenolysis. [40% Pd-C, in 10% HCl, 70% $HClO_4$ added, under 5-6 atm., 72 hr.]. Upon chromatographic separation, three new products (III, XVII and XVIII) in 17, 38 and 8 % yields were obtained respectviely, along with the saturated amine (XIII; 8 %), [the 11α-alcohol (III); ir ν max 3200 cm^{-1} (very broad); nmr δ 4.34 (1H, m, W1/2=6Hz, 11-H), 3.64 (1H, d-d,like, J=3, 1.5Hz , 4b-H), 3.21 (2H, m, 12-H_2) and 3.04 (1H, t, J=3Hz, 10b-H); the 11α,12β-diol (XVII); ir ν max 3600 cm^{-1}; nmr δ 4.79 (1H, d, J=2Hz, 12-H), 4.07 (1H, m, W1/2=5Hz, 11-H), 3.56 (1H, m, W1/2=4Hz, 4b-H) and 3.31 (1H, t like, J=2Hz, 10b-H); the 11α,12α-diol (XVIII); ir ν max 3600 cm^{-1}; nmr δ 4.72 (1H, d, J=4.5Hz, 12-H), 4.27 (1H, m, W1/2=6Hz, 11-H), 3.62 (1H, m, W1/2=5Hz, 4b-H) and 3.13 (1H, t like, J=2.5Hz, 10b-H)].

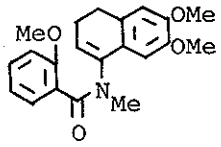
With pairs of stereoisomers, the epimeric 11-alcohols (IV and III), trans-diols (XI and XVII) and cis-diols (XII and XVIII) in hand for direct comparisons, we could establish their stereochemistry unambiguously. In addition, the corresponding acetonides were formed only from two cis-diols (XII and XVIII).



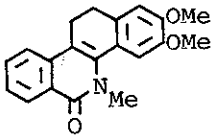
(I) $R_1+R_2=-OCH_2O-$
(II) $R_1=R_2=OMe$



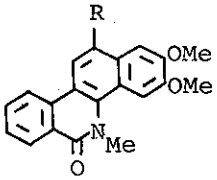
(III) 11α-OH
(IV) 11β-OH



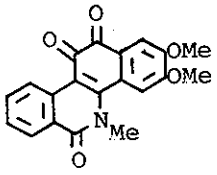
(V)



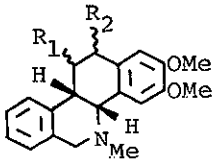
(VI)



(VII) R=H
(VIII) R=OAc
(IX) R=OH



(X)



(XI) R_1=▬OH, R_2=⋯OH
(XII) R_1=▬OH, R_2=▬OH
(XIII) $R_1=R_2$=H
(XIV) R_1=▬OH, R_2=⋯OAc
(XV) R_1=▬OMs, R_2=⋯OAc
(XVI) R_1=⋯OH, R_2=〰OMe
(XVII) R_1=⋯OH, R_2=▬OH
(XVIII) R_1=⋯OH, R_2=⋯OH

Thus, it was established that the compound (III) corresponds to the basic structure of chelidonine (I) and homochelidonine (II). Therefore, the route preparing the alcohol (III) from the o-quinone (X) via the compounds (XI, XIV, XV and XVI) can be a

potent one for total synthesis of these alkaloids, which is now extensively under way in our laboratory.

REFERENCES

Unless otherwise mentioned, ir spectra were measured in $CHCl_3$ and nmr spectra in $CDCl_3$ with TMS as internal standard.

1 M. Shamma, " The Isoquinoline Alkaloids ", Academic Press, New York, 1972, p315.

2 I. Ninomiya, O. Yamamoto, and T. Naito, J. C. S. Chem. Commun., 1976, 437.

3 W. Oppolzer and K. Keller, J. Amer. Chem. Soc., 1971, 93, 3836.

4 I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K. Harada, J. C. S. Perkin I, 1975, 762.

5 W. S. Johnson, A. D. Kemp, R. Pappo, J. Ackerman, and W. F. Johns, J. Amer. Chem. Soc., 1956, 78, 6312.

6a) L. F. Fieser and S. T. Putnam, J. Amer. Chem. Soc., 1947, 69, 1038; b) The position of an 12-acetoxy group was suggested on comparison with the corresponding 11-isomer; M. Onda, Y. Harigaya, and T. Suzuki, Heterocycles, 1976, 4, 1669.

7 R. R. Holmes, J. Conrady, J. Guthrie, and R. McKay, J. Amer. Chem. Soc., 1954, 76, 2400.

8 I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, J. C. S. Perkin I, 1973, 1696.

9 I. Ninomiya, O. Yamamoto, and T. Naito, Heterocycles, 1976, 5, 67.

10 E. Seoane, An. R. Soc. Esp. Fis. Quim. Madrid, Ser. B., 1965, 61, 755.

11 R. K. Crossland and K. L. Servis, J. Org. Chem., 1970, 35, 3195.

12 H. Osaka, Chem. and Pharm. Bull.(Tokyo), 1962, 10, 417.

Received, 19th May, 1977