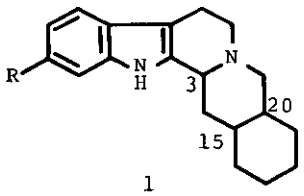
STEREOSELECTIVE SYNTHESIS OF YOHIMBANE AND ALLOYOHIMBANE

Toshio Suzuki, Akiko Tomino, and Katsuo Unno
Department of Pharmacy, Akita University Hospital, Hondo, Akita 010, Japan
Tetsuji Kametani*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

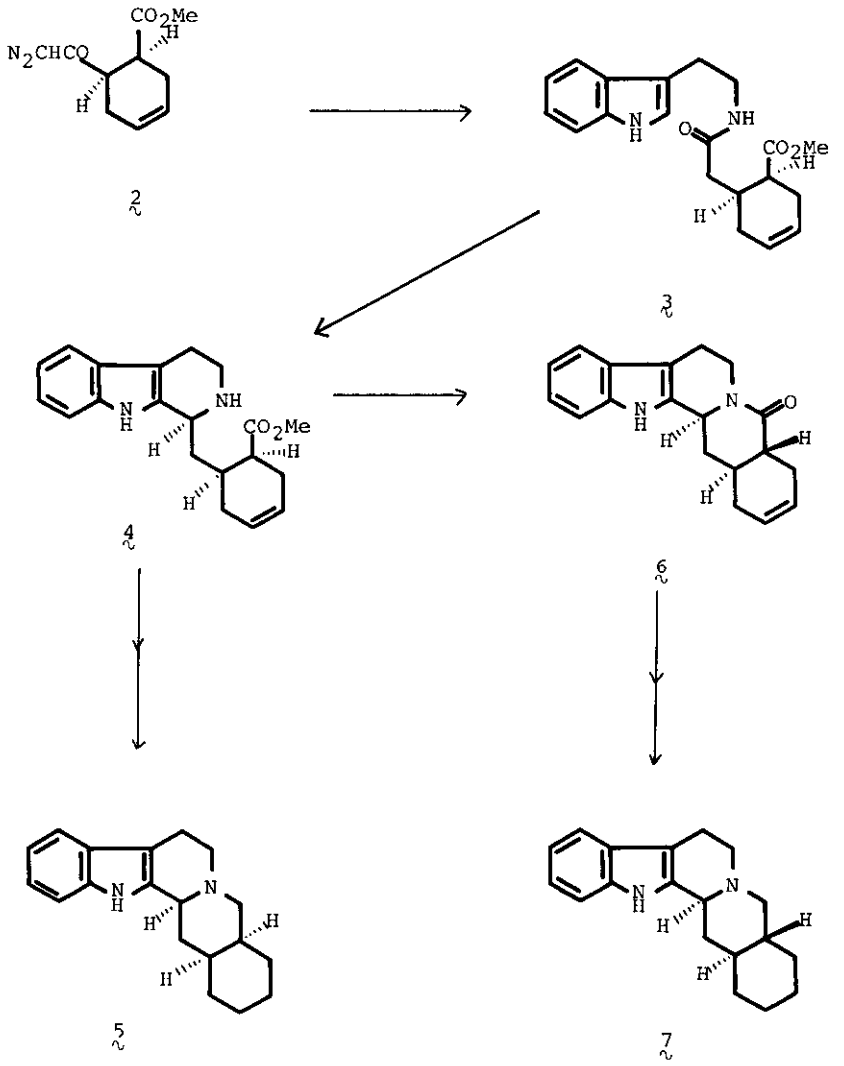
Abstract —— A general method for the stereoselective synthesis of yohimbane and alloyohimbane is described. The preparation of pentacyclic ring systems as contained in yohimbine and reserpine showed should make possible the synthesis of such alkaloids by this method.

In the field of alkaloid chemistry the basic pentacyclic skeleton of the yohimbane family is a familiar structure (1). Changes in the geometry of the hydrogen atoms attached to certain vital centers (positions 3, 15, 20) completely alter the properties of the individual members of this family.



1

In addition to this, one can position various functional group about the structure and by having the proper stereochemical form many compounds of medicinal interest such as yohimbine[1] and reserpine[2] are obtained. Our proposed synthetic scheme involved Wolff[3] rearrangement of the diazoketone (2) with tryptamine to give the amide (3). Subsequent cyclization and reduction should produce 4, and after formation of D ring, catalytic hydrogenation followed by lithium aluminum reduction would give alloyohimbane (5). On the other hand, epimerization of the methyl ester group in 4 and subsequent formation of the lactam would afford 6 leading to yohimbane (7).



Thus Wolff[3] rearrangement of the diazoketone (2), derived from the anhydride (8) according to the known procedure,[4] with tryptamine in the presence of freshly made silver oxide at room temperature for 20 min furnished the amide (3) in 80.6 %, ir ($CHCl_3$) 3460, 1720 and 1650 cm^{-1}, δ 3.57 (3H, s, CO_2CH_3), 5.53 (2H, br s, olefinic protons), mass m/e 340 (M^+). Closure of the C ring was effected by refluxing with

phosphrous oxychloride, and subsequent methanolic sodium borohydride reduction afforded the unexpected trans fused D/E lactam (6)[5,6] in 39.2 %, mp 200 ∿ 202°, ir ($CHCl_3$) 3460 and 1620 cm^{-1}, δ 4.57 ∿ 4.93 (1H, m, C_{20}-H), 5.07 (1H, d, d, J = 8, 2 Hz, C_3-H), 5.50 (2H, br s, olefinic protons), mass m/e 292 (M^+), together with the ester (4) in 46.3 %, hydrochloride of 4[5], mp 205 ∿ 206°, ir (KBr) 3450 and 1700 cm^{-1}, δ 3.63 (3H, s, OCH_3), 5.63 (2H, br s, olefinic protons), mass m/e 324 (M^+). The lactam (6) was hydrogenated over 5 % Pd-C in methanol to afford oxoyohimbane (9)[7].

The synthesis of alloyohimbane (5)[8] was also carried out as follows.

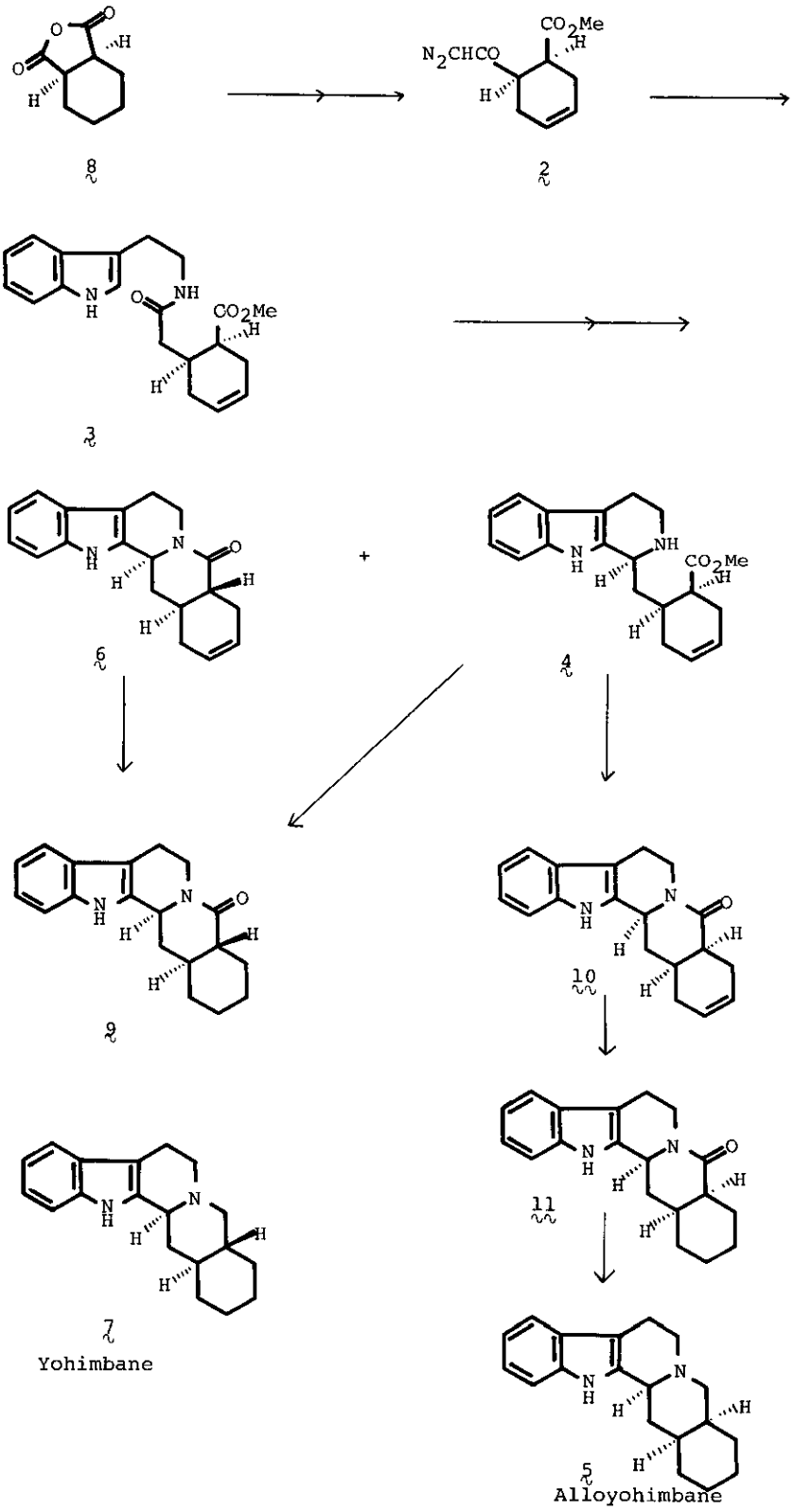
Thus, treatment of 4 with excess potassium carbonate in dry MeOH brought about cyclization, without epimerization of the methyl ester group, to form the cis fused D/E lactam (10)[8] in 60.5 %, mp 200 ∿ 202°, ir ($CHCl_3$) 3460 and 1620 cm^{-1}, δ 4.70 ∿ 5.25 (2H, m, C_{15}-H and C_{20}-H), 5.65 (2H, br s, olefinic protons), mass m/e 292 (M^+).

On the other hand, treatment of 4 with 5 % methanolic potassium carbonate gave only the trans fused D/E lactam (9)[9].

Catalytic hydrogenation of lactam (10) in the presence of 5 % Pd-C gave oxoalloyohimban (11)[5] in almost quantitative yield, mp 222 ∿ 224°, ir ($CHCl_3$) 2460 and 1625 cm^{-1}, δ 4.63 ∿ 5.0 (1H, m, C_{20}-H), 5.03 (1H, d, d, J = 2, 8 Hz, C_3-H), 6.78 ∿ 7.50 (4H, m, Ar-H), 9.50 ∿ 9.77 (1H, br s, NH), mass m/e 294 (M^+). The lactam (11) was reduced by lithium aluminum hydride to afford the amine (5). Compounds (9) and (5) were shown to be oxoyohimbane and alloyohimbane respectively, by comparison of their i.r. and n.m.r. spectra with those (kindly given by Professor Ninomiya) of authentic samples. Since 9 has already been converted into yohimbane (7) by Ninomiya and coworkers[7], we have achieved an alternative formal synthesis of 7.

Thus we have succeeded in a stereoselective synthesis of yohimbane and alloyohimbane starting from the same diazoketone.

This synthetic route should prove useful for the synthesis of yohimbane family alkaloids such as yohimbine, reserpine, and also corynanthe type alkaloids because of its production of compounds containing a double bond at C_{17} and C_{18}. This double bond could be manipulated to attach desired functional groups or could be used to bring about cleavage of the E ring after some modification.


8
2
3
6
4
9
10
11
7
Yohimbane
5
Alloyohimbane

ACKNOWLEDGEMENT

We thank Professor Ninomiya, Kobe Women's College of Pharmacy, for the ir and nmr spectral data for oxoyohimbane and alloyohimbane.

REFERENCES AND NOTES

1. For synthesis, see E. van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm and P. Aldrich, J. Amer. Chem. Soc., 1958, 80, 5006; L. Töke, K. Honty and Cs. Szántay, Chem. Ber., 1969, 102, 3248; G. Stork and R. N. Guthikonda, J. Amer. Chem. Soc., 1972, 94, 5109; T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi and K. Fukumoto, Chem. Pharm. Bull., 1975, 23, 2634; T. Kametani, Y. Hirai and K. Fukumoto, ibid., 1976, 24, 2500.

2. For synthesis, see R. B. Woodward, F. Bader, H. Bickel and R. Kierstead, Tetrahedron, 1958, 2, 1. For synthetic approaches, see Cs. Szántay, G. Blaskó, K. Honty, L. Szabó and L. Töke, Heterocycles, 1977, 7, 155; T. Suzuki, S. Kagaya, A. Tomino, K. Unno and T. Kametani, Heterocycles, 1978, 9, 1749; T. Suzuki, A. Tomino, S. Kagaya, K. Unno and T. Kametani, Heterocycles, in press.

3. L. Wolff, Ann., 1912, 394, 25.

4. F. V. Brutcher, Jr. and D. D. Rosenfeld, J. Org. Chem., 1964, 29, 3154.

5. This compound gave satisfactory elemental analysis.

6. This unexpected compound (6) presumably results from partial epimerization of the methyl ester group followed by cyclization of the resultant trans methyl ester derivative during sodium borohydride reduction and aqueous work-up.

7. I. Ninomiya, Y. Tada, T. Koguchi, O. Yamamoto and T. Naito, Heterocycles, 1978, 9, 1527.

8. For synthesis, see G. Stork and R. K. Hill, J. Amer. Chem. Soc., 1954, 76, 949; idem, J. Amer. Chem. Soc., 1957, 79, 495; G. C. Morrison, W. Cetenko and J. Shavel, Jr., J. Org. Chem., 1967, 32, 4089; A. Le Hir, R. Goutarel and M-M. Janot, Bull. Soc. Chim. France, 1952, 1091; I. Ninomiya, Y. Tada, T. Kiguchi, O. Yamamoto and T. Naito, Heterocycles, 1978, 9, 1527; L. Töke, K. Honty and Cs. Szantay, Chem. Ber., 1969, 102, 3248.

9. Under these conditions none of the cis fused D/E lactam (10) was detected. The cis fused D/E lactam (10) was not epimerized under such conditions suggesting that epimerization occurs first, followed by cyclisation.