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STUDIES ON THE SYNTHESES OF HETROCYCLIC AND NATURAL COMPOUNDS. PART 948[1]. A SIMPLE AND CONVENIENT SYNTHESIS OF YOHIMBANE AND ALLOYOHIMBANE[2]

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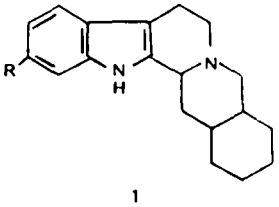
Abstract — A simple method for the stereoselective synthesis of yohimbane (7) and alloyohimbane (5) via the diazoketone (2) from the anhydride (8), a symmetrical starting material, was examined. The preparation of pentacyclic ring systems contained in yohimbine and reserpine would be possible for the synthesis of such alkaloids by this method.

In the field of the indole 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 at 3, 15, and 20 positions completely alter the properties of the individual members of this family. In addition to this, one can introduce various functional group on the structure (1) and many compounds of medicinal interest such as yohimbine[3] and reserpine[4] having the proper stereochemical form would be obtained.



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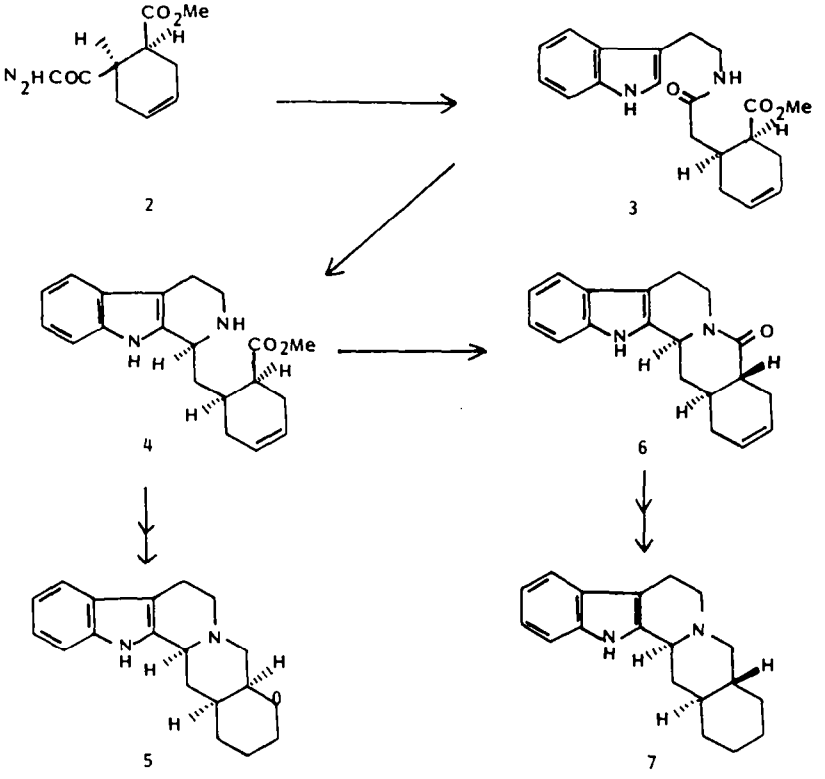
In our continuous efforts[5] towards the total synthesis of yohimbine and reserpine, we have required a synthesis of dehydrooxoyohimbane (6) and dehydrooxoalloyohimbane (14) which could be potential intermediates for yohimbine and reserpine. Our proposed synthetic scheme involved Wolff rearrangement 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 hydrogenetion followed by lithium aluminum hydride reduction would give alloyohimbane (5). In this case alkaline treatment of 3 afforded the imide (10). On the other hand, epimerization of the methyl ester group in 4 followed by formation of the lactam would afford 6, leading to yohimbane (7).

Wolff[6] rearrangement of the diazoketone (2)[7], derived via the half ester (9) from the anhydride (8), with tryptamine in the presence of freshly made silver oxide at room temperature for 20 min furnished the amide (3) in 80.6 % yield [ν_{max} ($CHCl_3$) 3460, 1720 and 1650 cm^{-1}]. Ring closure of the amide (3) was effected by refluxing with phosphorous oxychloride, and subsequent methanolic sodium borohydride reduction afforded the unexpected trans fused D/E lactam (6), m.p. 200-202° [ν_{max} ($CHCl_3$) 3460 and 1620 cm^{-1}] by way of 4 in 39.2 % yield, together with β-carboline derivative (4), m.p. 205-206° [ν_{max} (KBr) 3450 and 1700 cm^{-1}] in 46.3 % yield. The lactam (6) was hydrogenated over 5 % Pd-C in methanol to afford oxoyohimbane (12)[8]. This unexpected compound (6) presumably resulted from partial epimerization of the methyl ester group followed by cyclization of the resultant trans methyl ester

during sodium borohydride reduction and aqueous treatment. On the other hand lithium aluminum hydride reduction of the lactam (6) to give 12 whose IR spectrum showed Bohlmann bands[9]. respectively, by comparison of their IR and NMR spectra with those of authentic samples kindly donated by Professor Ninomiya. Since compound 12



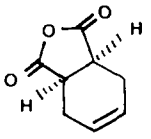
The synthesis of alloyohimbane (5)[8,10] was also carried out as follows. Thus, treatment of 11 with excess potassium carbonate in dry methanol brought about cyclization without epimerization of the methyl ester group to form the cis fused D/E lactam (13), m.p. 200 - 202° [ν_{max} ($CHCl_3$) 3460 and 1620 cm^{-1}] in 60.5 % yield. On the other hand, treatment of 4 hydrochloride with 0.4 % methanolic potassium carbonate gave exclusively the trans fused D/E lactam (6). Under this condition none of the cis fused D/E lactam (13) was detected. The cis fused D/E lactam (13) was not epimerized under such conditions, the result of which suggests that epimerization would occur first and then cyclization would proceed. Catalytic hydrogenation of the lactam (13) in the presence of 5 % Pd-C gave oxoalloyohimbane (14) in almost quantitative yield, m.p. 222 - 224° [ν_{max} ($CHCl_3$) 3460 and 1625 cm^{-1}]. The lactam (14) was reduced by lithium aluminum hydride to afford the amine (5). Compounds (11) and (5) were shown to be oxoyohimbane and alloyohimbane, has already been converted into yohimbane (7) by Ninomiya and his co-workers, we have achieved an alternative formal total synthesis of 7.

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

Thus synthetic route has been proven to be useful for the synthesis of yohimbane-type such as yohimbine, reserpine, and also corynanthe-type alkaloids because of the formation of compounds containing a double bond between C_{17} and C_{18} positions. 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.

EXPERIMENTAL

M.p.s are uncorrected and were determined on Yazawa microapparatus. IR spectra were recorded with Shimazu IR-400 spectrophotometer, NMR spectra with JEOL JNM-PMX-60 spectrometer using TMS as an internal standard, and mas



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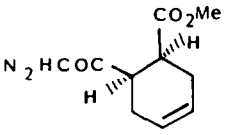

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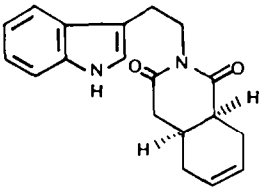

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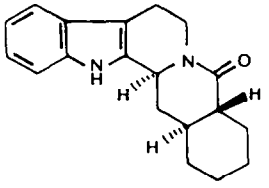

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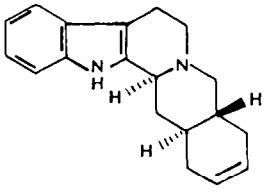

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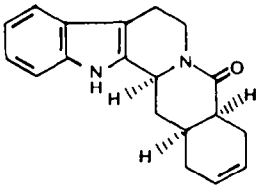

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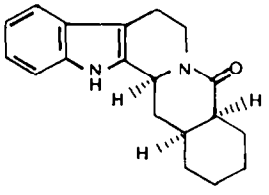

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spectra were taken with JEOL-MJS-OISG spectrometer.

Arndt-Eistert Reaction of Diazoketone (2) with Tryptamine. A mixture of the diazoketone (2) (4 g), tryptamine (3.7 g), freshly prepared silver oxide (2 g) and dioxane (50 ml) was stirred for 20 min at room temperature under nitrogen and the mixture was filtered through short silica gel pad. The filtrate was condensed to leave a residue which was subjected to chromatography on silica gel (100 g). The elution with $CHCl_3$ afforded the amide (3) (5.27 g) as a pale brown syrup; IR ($CHCl_3$) 3460 (NH), 1720 (CO) and 1650 cm^{-1} (CO); NMR ($CDCl_3$) : 3.57 (3H, s, OCH_3), 5.53 (2H, br s, olefinic H), 6.82 7.67 (5H, m, ArH), 8.50 8.83 (1H, br s, NH, exchanged with D_2O); mass (m/e) 340 (M^+).

Dihydrooxoyohimbane (6) and 1-(1,2,3,6-Tetrahydro-2-methoxycarbonylbenzyl)-1,2,3,4-tetrahydro-β-carboline (4) Hydrochloride. A mixture of the amide (3) (2 g) and freshly distilled phosphorous oxychloride (4 ml) in dry benzene (20 ml) was refluxed for 3 h under nitrogen. The solvent and an excess of phophorous oxychloride were evaporated completely in vacuo to leave a residue which was washed with ether to give the 3,4-dihydro-β-carboline hydrochloride. This hydrochloride was used in the following reaction without further purification.

The crude hydrochloride was dissolved in MeOH (20 ml) whose solution was treated with sodium borohydride (1 g) and the resulting mixture was stirred for 10 min at room temperature. An excess of sodium borohydride was decomposed by an addition of AcOH (5 drops) and the solvent was evaporated to leave a residue which was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$ and then evaporated to leave a yellowish brown syrup (2.2 g) which was subjectied to chromatography on silica gel (30 g). Elution with $CHCl_3$ and evaporation of the eluate left a pale brown syrup (674 mg) which was triturated with MeOH to give dehydrooxoyohimbane (6) as colorless needles, m.p. 202°(from MeOH) (Calc. for $C_{10}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found : C, 78.15;

H, 6.87; N, 9.57 %): IR ($CHCl_3$) 3460 (NH) and 1620 cm^{-1} (CO); NMR ($CDCl_3$) δ 4.57 4.93 (1H, m, C_{20}-H), 5.07 (1H, dd, J = 8 and 2 Hz, C_3-H), 5.50 (2H, br s, olefinic H), 6.90 7.70 (4H, m, ArH), 8.57 8.90 (1H, br s, NH, exchanged with D_2O); mass (m/e) 292 (M^+). Elution with MeOH-$CHCl_3$ (v/v 98 : 2) gave tetrahydro-β-carboline (4), whose hydrochloride (880 mg) afforded colorless prisms, m.p. 205 206° (from MeOH) (Calc. for $C_{20}H_{25}N_2O_2Cl$: C, 66.56; H, 6.98; N, 7.76. Found : C, 66.15; H, 7.05; N, 7.68 %); IR ($CHCl_3$) 3450 (NH) and 1700 cm^{-1} (CO); NMR ($CDCl_3$ + CD_3OD) δ 3.63 (3H, s, OCH_3), 5.63 (2H, br s, olefinic H), 6.83 7.58 (4H, m, ArH); mass (m/e) 324 (M^+).

Oxoyohimbane (11). Dehydrooxoyohimbane (6) (50 mg) was hydrogenated over 5 % Pd C (100 mg) in MeOH (15 ml) at room temperature. Catalyst was filtered and washed with Et_2O. Evaporation of the solvent gave oxoyohimbane (11) (46 mg), m.p. 200 202°; mass (m/e) 294 (M^+). IR ($CHCl_3$) and NMR ($CDCl_3$ + CD_3OD) spectra were identical with those of an authentic sample[8].

17,18-Dehydroyohimbane (12). To an ice cooled suspension of lithium aluminum hydride (20 mg) in dry THF (1 ml) was added a solution of dehydrooxoyohimbane (29 mg) in dry THF (1 ml) under nitrogen. The mixture was refluxed with stirring for 3 h and quenched with Et_2O saturated with H_2O. Ethereal layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with birne, dried over $MgSO_4$ and then evaporated to leave a residue which was purified by preparative thin layer chromatography ($CHCl_3$-MeOH 9.5 : 0.5 v/v) to give 17,18-dehydroyohimbane (12) (27 mg) as a pale yellow syrup; IR ($CHCl_3$) 3460 (NH) and 2850 2725 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 5.45 (2H, br s, olefinic H), 6.82 7.45 (4H, m, ArH), 7.53 7.77 (1H, br s, NH, exchanged with D_2O); mass (m/e) 278 (M^+).

17,18-Dehydrooxoalloyohimbane (13). To a stirred solution of tetrahydro-β-carboline (4) hydrochloride (33 mg) in absolute MeOH(1 ml) was added K_2CO_3 (25 mg) at room temperature and the mixture was stirred for 1.5 h at room temperautre under nitrogen. The mixture was poured into Et_2O. The ethereal layer was washed with brine, dried over $MgSO_4$ and then evaporated to leave a residue which was purified by preparative thin layer chromatography ($CHCl_3$-MeOH 9.5 : 0.5 v/v) to give 17,18-dehydrooxoyohimbane (18 mg), m.p. 200 202° (from MeOH) (Calc. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found : C, 78.04; H, 7.02; N, 9.52 %); IR ($CHCl_3$) 3460 (NH) and 1620 cm^{-1} (CO); NMR ($CDCl_3$) δ 4.70 5.25 (2H, m, C_3-H and C_{20}-H), 5.65 (2H, br s, olefinic H), 6.93 7.57 (4H, m, ArH), 7.87 8.10 (1H, br s, NH, exchanged with D_2O); mass (m/e) 292 (M^+).

Oxoalloyohimbane (14). The lactam (13) (130 mg) was hydrogenated over 5 % Pd-C (130 mg) in MeOH (25 ml) at room temperature. Catalyst was filtered and washed with MeOH and Et_2O. Evaporation of the solvent gave oxoalloyohimbane (14) (129 mg), m.p. 222 224° (from MeOH) (Calc. for $C_{19}H_{22}N_2O$; C, 77.52; H, 7.53; N, 9.52. Found : C, 77.57, H, 7.56; N, 9.42 %); IR ($CHCl_3$) 3460 (NH) and 1625 cm^{-1} (CO); NMR ($CDCl_3$ + CD_3OD) δ 4.63 5.00 (1H, m, C_{20}-H), 5.03 (1H, dd, J = 8 and 2 Hz, C_3-H), 6.87 7.50 (4H, m, ArH), 9.50 9.77 (1H, br s, NH); mass (m/e) 294 (M^+).

Alloyohimbane (5). To an ice-cooled suspension of lithium aluminum hydride (50 mg) in dry THF (2 ml) was added dropwise with stirring a solution of oxoyohimbane (34 mg) in dry THF (2 ml) under nitrogen. The mixture was refluxed for 3 h and then quenched with Et_2O saturated with H_2O. The ethereal layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over K_2CO_3 and then evaporated to leave a crystalline residue which was purified by preparative thin layer chromatography ($CHCl_3$-MeOH 9.5 : 0.5 v/v) to give alloyohimbane (5) (17 mg); IR ($CHCl_3$) 3470 (NH) and 2950 2750 cm^{-1} (Bohlmann bands); mass (m/e) 280 (M^+). IR($CHCl_3$) and NMR ($CDCl_3$) spectra were identical with those of an authentic sample[8].

17,18-Dehydrooxoyohimbane (6) from 4. A mixture of 4 (65 mg), K_2CO_3 (8 mg) and absolute MeOH (2 ml) was stirred for 4 h at room temperature under nitrogen. The mixture was poured into Et_2O and the solvent was washed with a small amount of brine, dried over $MgSO_4$ and then eva-

porated to give a residue, which was subjected to chromatography on silica gel (5 g). The elution with $CHCl_3$ afforded 6 (45 mg), whose IR ($CHCl_3$) and NMR ($CDCl_3$) spectra were identical with those of an authentic sample[8].

N-(Indolylethyl)-homophthalimide (10). To a solution of 3 (500 mg) in absolute MeOH (5 ml) was added K_2CO_3 (400 mg) at room temperature under nitrogen. The mixture was stirred for 25 h at room temperature and then diluted with $CHCl_3$. The mixture was washed with brine, dried over $MgSO_4$ and then evaporated to leave a crystalline residue which was filtered and washed with Et_2O to give the imide (10) (248 mg) as colorless needles, m.p. 235 - 236°(from MeOH) (Calc. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found : C, 74.12; H, 6.29; N, 9.00 %); IR (KBr) 3340 (NH) and 1665 cm^{-1} (CO); NMR ($CDCl_3$ + CD_3OD) δ4.08 (1H, d, J = 10 Hz, NCOCH), 5.67 (2H, br s, olefinic H), 6.93 7.08 (5H, m, ArH), mass (m/e) 308 (M^+).

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