# AN APPROACH TO THE SKELETON OF RAUWOLFIA ALKALOIDS. A GENERAL SYNTHESIS OF 3,8-EPOXY-7-KETO-6-OXABICYCLO-[3.2.1]OCTANE DERIVATIVES

Toshio Suzuki, Akiko Tomino, Seiko Kagaya, and Katsuo Unno

Department of Pharmacy, Akita University Hospital,

Hondo, Akita, Japan

Tetsuji Kametani*

Pharmaceutical Institute, Tohoku University,

Aobayama, Sendai 980, Japan

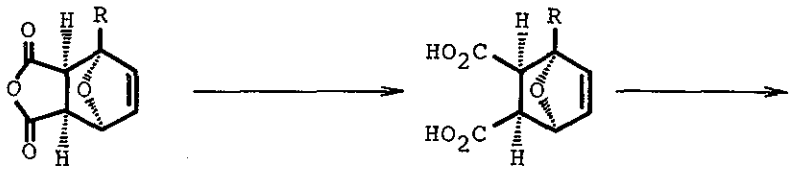
Hydrolysis of the Diels-Alder adducts (1) and (2), followed by halolactonization, gave 4-bromo-(6) and 4-iodo-3-methoxycarbonyloxymethyl-3,8-epoxy-7-keto-6-oxabicyclo[3.2.1]octane-2-carboxylic acid (8), respectively. Arndt-Eistert reaction of the acid chloride (14), derived from 6, provided the methyl ester (16). The intermediate diazoketone (15) was also transformed to the amides (17) and (18) by condensation with tryptamine and 6-methoxytryptamine, respectively, both of which would be key intermediates for the synthesis of Rauwolfia alkaloids, deserpidine (12) and reserpine (13)

It is well known that halolactonization[1] has provided a useful method for the conversion of unsaturated acids to halolactones and has been applied for the synthesis of natural products[2]. As a preliminary experiment in a synthetic approach to reserpine,

we have examined the synthesis of the halolactones (6) and (8) which would be very useful compounds for constructing the complicated ring systems, especially for the synthesis of Rauwoldia alkaloids.

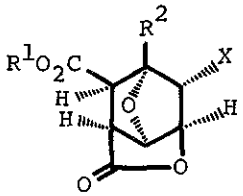
Diels-Alder adduct[3] (1) which was easily obtained from furan and maleic anhydride was chosen as a starting material. Hydrolysis of the anhydride (1) with water at room temperature afforded the dicarboxylic acid (4), m.p. 141-143°, in 90.3 % yield; $\nu_{max}^{KBr}$ 1710 $cm^{-1}$ (C=O); nmr δ ($CDCl_3$ + $CD_3OD$) 2.77 (2H, br s), 5.18 (2H, s), 6.40 (2H, s), whose halolactonization with 0.8 N sodium hydroxide solution, sodium bicarbonate and bromine for 2 h at room temperature gave the bromolactone (6), m.p. 125-127°, in 70 % yield. Treatment of the carboxylic acid (6) with an excess of diazomethane in ether provided the methyl ester (7), m.p. 161-164°, in quantitative yield, $\nu_{max}^{KBr}$ 1790 (C=O), 1730 $cm^{-1}$ (C=O); nmr δ ($CDCl_3$) 3.80 (3H, s, $OCH_3$), 4.27 (1H, s, >CH-O-), 4.73 (1H, s, >CH-O-), 4.73 (1H, s, CH-O-), 6.08 (1H, br s, >CH-O-CO-).

Since we have succeeded in the synthesis of the model compound, we applied this method to the another derivative (2). Namely, Diels-Alder reaction[4] of freshly distilled furfuryl alcohol with maleic anhydride in the presence of a catalytic amount of hydroquinone in dry benzene yielded the adduct (2), m.p. 79-81°, in 60 % yield. This anhydride was easily converted to lactone carboxylic acid (10) as a solid [ $\nu_{max}^{KBr}$ 1775 (C=O), 1750 $cm^{-1}$ (C=O)] by setting aside at room temperature, which was also characterized as a benzyl ester (11) [ $\nu_{max}^{KBr}$ 1780 (C=O), 1730 (C=O) 1630 $cm^{-1}$

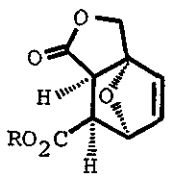


1 : R=H
2 : R=$CH_2OH$
3 : R=$CH_2OCO_2Me$

4 : R=H
5 : R=$CH_2OCO_2Me$



6 : $R^1$=H, $R^2$=H, X=Br
7 : $R^1$=Me, $R^2$=H, X=Br
8 : $R^1$=H, $R^2$=$CH_2OCO_2Me$, X=I
9 : $R^1$=Me, $R^2$=$CH_2OCO_2Me$, X=I



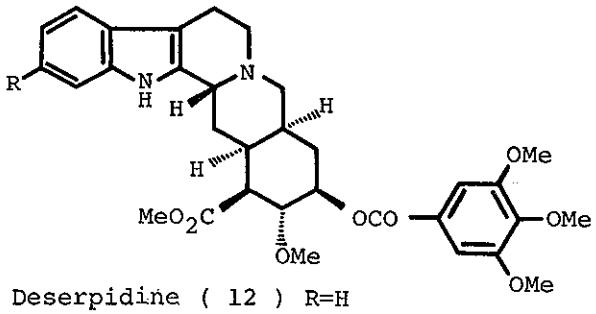
10 : R=H
11 : R=$CH_2Ph$

(C=C)] by treatment with silver oxide and benzyl bromide in dimethylformamide. Therefore, hydroxyl group in (2) was protected as the corresponding carbonate (3) [ $\nu_{max}^{CHCl_3}$ 1850 (anhydride C=O), 1770 (anhydride C=O), 1730 $cm^{-1}$ (C=O); nmr $\delta$ ($CDCl_3$) 3.73 (3H, s, $OC\underline{H}_3$)] by treatment with methyl chloroformate in dry pyridine at room temperature. Treatment of (3) with water at room temperature provided the dicarboxylic acid (5), $\nu_{max}^{CHCl_3}$ 1730 (C=O), 1710 $cm^{-1}$ (C=O); nmr $\delta$ ($CDCl_3$ + $CD_3OD$) 3.73 (3H, s, $OC\underline{H}_3$). Halolactonization of this dicarboxylic acid with 0.5 N sodium bicarbonate solution, potassium iodide and iodine afforded a crude product (8) which

was methylated with an excess of diazomethane in ether purification of this crude product with column chromatography on sileca gel afforded the pure iodolactone methyl ester (9) as an oil, $\nu_{max}^{CHCl_3}$ 1750 (C=O), 1730 (C=O), 1720 $cm^{-1}$ (C=O); nmr $\delta$ ($CDCl_3$) 3.69 (3H, s, $OC\underline{H}_3$), 3.79 (3H, s, $OC\underline{H}_3$), 6.40 (1H, br s, >C<u>H</u>-O-CO-). These three steps were carried out without purification and the overall yield of the methyl ester (8) from the starting anhydride (2) was about 40 %.

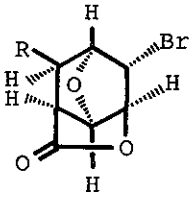
Now our attention was turned to the syntheses of the Rauwolfia alkaloids, deserpidine (12) and reserpine (13), which have been widely used as important drugs for the treatment of hypertensive, nervous and mental disorders. The first ingenious synthesis of reserpine by Woodward[5] and co-workers was unique up to the present. Recently, another group[6] also reported the synthesis of deserpidine. In our case, all what we have to do was an extension of one more carbon at $C_2$ position since the halolactones (6) and (8) elaborated well D ring of deserpidine and reserpine.

Thus, the reaction[7] of the bromolactone (6) with oxalyl chloride in refluxing dry benzene gave the acid chloride (14), whose treatment with an excess of diazomethane in ether provided the duazoketone (15), m.p. 146-150°, in quantitative yield, $\nu_{max}^{KBr}$ 2200 ($\overset{+}{N}\equiv N$), 1790 (C=O), 1630 $cm^{-1}$. This compound was refluxed for 3 h in absolute methanol in the presence of silver oxide made freshly to give, in 70 % yield, the methyl ester (16) as an oil after purification on silica gel chromatography, $\nu_{max}^{CHCl_3}$ 1780 (C=O), 1730 $cm^{-1}$ (C=O); nmr $\delta$ ($CDCl_3$) 2.62 (2H, s, $C\underline{H}_2CO_2CH_3$) 3.67 (3H, s, $CO_2C\underline{H}_3$), 4.23 (1H, br s, >C<u>H</u>-O-), 4.83 (1H, br s, >C<u>H</u>-O-), 6.0



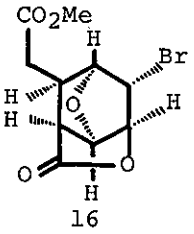
Deserpidine ( 12 ) R=H

Reserpine ( 13 ) R=OMe

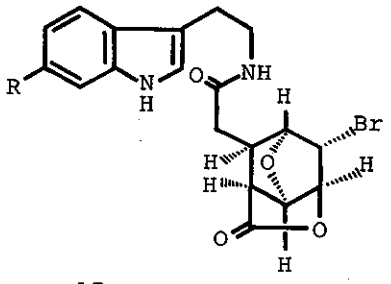


14 : R=COCl

15 : R=$COCHN_2$



16



17 : R=H

18 : R=OMe

(1H, br s, >C<u>H</u>-O-CO-).

On the other hand, refluxing the compound (15) with tryptamine and 6-methoxytryptamine in dioxane for 2.5 h in the presence of silver oxide prepared freshly afforded the desired amides (17) [$\nu_{max}^{CHCl_3}$ 3460 (indole NH), 1780 (C=O), 1650 $cm^{-1}$ (amide C=O); nmr ($CDCl_3$) 2.63-3.10 (4H, m, -NHCO-C<u>H</u>$_2$, Ar-C<u>H</u>$_2$-), 3.17-3.57 (4H, m, Ar-$CH_2$-C<u>H</u>$_2$-N, C<u>H</u>-CO-, C<u>H</u>Br-), 4.17 (1H, br s, C<u>H</u>-O-), 4.26 (1H, br s, C<u>H</u>-O-), 5.70 (1H, br s, -CON<u>H</u>, exchanged with $D_2O$) 5.95 (1H, d, J=3 Hz, C<u>H</u>-OCO-), 6.83-7.63 (5H, m, Ar<u>H</u>), 8.10 (1H, br s, indole N<u>H</u>, exchanged with $D_2O$); mass (m/e) 420 ($M^+$), 419, 418 ($M^+$), 417, 143 (base peak), 130] and (18) [$\nu_{max}^{CHCl_3}$ 3460 (indole NH), 1780 (C=O), 1650 $cm^{-1}$ (amide C=O); nmr δ ($CDCl_3$) 3.80 (3H, s, OC<u>H</u>$_3$), 4.16 (1H, br s, C<u>H</u>-O-), 4.25 (1H, br s, C<u>H</u>-O-), 5.95 (1H, br s, C<u>H</u>-O-), 6.80-7.60 (4H, m, Ar<u>H</u>); mass (m/e) 450 ($M^+$), 449, 458 ($M^+$), 173 (base peak), 160], respectively, in fairy good yield.

Thus, we could provide a simple and general method for the synthesis of 3,8-epoxy-7-keto-6-oxabicyclo[3.2.1]octane derivatives and the key intermediate for the synthesis of Rauwolfia alkaloids. The total synthesis of deserpidine (12), reserpine (13) and the other indole alkaloids according to this method is in progress in our laboratoly.

REFERENCES

1. H. O. House, Modern Synthetic Reactions, W. A. Benjamin, Inc. Menlo Park, California, 1972, 441 and references cited therein.

2. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Amer. Chem. Soc., 1969, 91, 5675; B. M. Trost and J. P. Genet, J. Amer. Chem. Soc., 1976, 98, 8516; S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, J. Amer. Chem. Soc., 1976, 98, 3028; S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, J. Amer. Chem. Soc., 1977, 99, 6066; W. C. Still and M. J. Schneider, J. Amer. Chem. Soc., 1977, 99, 948; R. F. Borch, A. J. Evans, and J. J. Wade, J. Amer. Chem. Soc., 1977, 99, 1617.

3. O. Diels and K. Alder, Ber., 1929, 62, 554.

4. M. C. Kloetzerl, Org. Reactions, 1948, 4, 1.

5. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, J. Amer. Chem. Soc., 1956, 78, 2023; idem, Tetrahedron, 1958, 2, 1.

6. C. Szántay, G. Blaskó, K. Honty, L. Szabó, and L. Töke, Heterocycles, 1977, 7, 155.

7. W. E. Bachmann and W. S. Struve, Org. Reactions, 1942, 1, 38.

Received, 9th June, 1978