AN APPROACH TO THE SYNTHESIS OF THE NON-TRYPTAMINE MOIETY OF RESERPINE BY DIELS-ALDER REACTION

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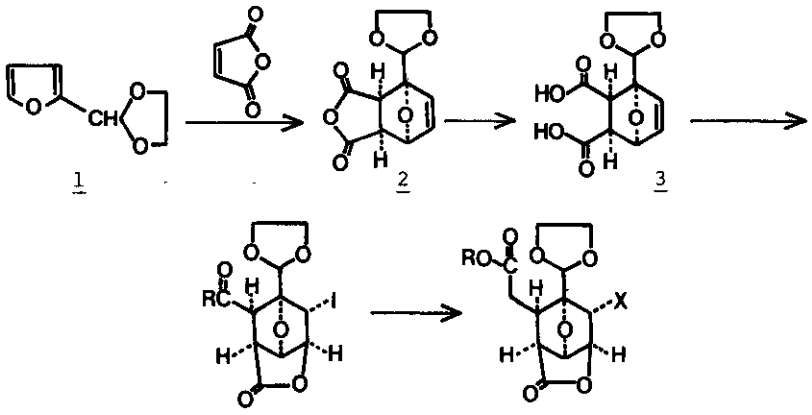
Abstract-----Diels-Alder adduct 2 between furfural ethylene acetal 1 and maleic anhydride has been converted into the tricyclic acetal 10b which would be a promising intermediate for the construction of the non-tryptamine moiety of the Rauwolfia alkaloids, such as reserpine(13).

Recent reports[1] on the synthetic approach to the Rauwolfia alkaloids employing Diels-Alder reaction prompts us to publish our own results on the same subject.

Diels-Alder reaction between an equimolar amount of furfural ethylene acetal 1 and maleic anhydride in ether at room temperature for 24 h allowed exclusive formation of the endo-adduct 2, mp 98∿99 °C, in 30 % yield[2]: IR(Nujol) 1860, 1800 cm^{-1}; NMR($CDCl_3$) δ 4.0(2H, m), 4.15(4H, m), 5.5(1H, m), 5.6(1H, s), 6.7(2H, s). Hydrolysis of 2 with water formed the acid 3 which, without further purification, on treatment with potassium triiodide in sodium bicarbonate solution gave the iodo-lactone[3] 4, mp 188∿190 °C, in 97.2 % yield: IR(Nujol) 1780, 1710 cm^{-1}; NMR($CDCl_3$+CF_3CO_2H) δ 3.2(1H, d, J=11 Hz), 3.6(1H, dd, J=5, 11 Hz), 4.15(4H, s), 4.6(1H, s), 5.1(1H, br.d, J=5 Hz), 5.25(1H, br.s), 5.45(1H, s); MS(m/e) 383(M^++1), 382(M^+), 338, 266, 73(100 %). Treatment of 4 with oxalyl chloride followed by diazomethane afforded the diazoketone 6, mp 161∿163 °C, in 92 % overall yield: IR(Nujol) 2100, 1790, 1625 cm^{-1}; NMR($CDCl_3$) δ 2.8∿3.6(2H, m), 4.1(4H, br.s), 4.7∿5.0(2H, m), 5.2(1H, br.s), 5.5(1H, s), 5.6(1H, s); MS(m/e) 406(M^+), 352, 73(100 %). The diazoketone 6 upon treatment with methanol in the presence of freshly prepared silver oxide initiated the rearrangement to furnish the methyl ester 7a, mp 109∿110 °C, in 63.4 % yield: IR(Nujol) 1780, 1735 cm^{-1}; NMR($CDCl_3$) δ 2.5∿3.0(4H, m), 3.75(3H, s), 4.05(4H, br.s), 4.2(1H, s), 4.8(1H, m), 5.1(1H, br.s), 5.4(1H, s); MS(m/e) 410(M^+), 379, 283,

73(100 %). Similar treatment of 6 with β,β,β-trichloroethanol afforded the β,β,β-trichloroethyl ester 7b, mp 117∿118 °C, in 52 % yield: IR(Nujol) 1785, 1750 cm^{-1}; NMR($CDCl_3$) δ 2.65∿3.1(4H, m), 4.1(4H, br.s), 4.25(1H, s), 4.85(2H, s), 4.9(1H, m), 5.15(1H, br.s), 5.45(1H, s); MS(m/e) 532(M^++6), 531, 530, 529, 528, 527, 526(M^+), 73(100 %). Reductive deiodination of 7a using Raney nickel catalyst(W-2) in refluxing methanol in the presence of pyridine[4] gave the deiodo compound 7c: mp 105 ∿106 °C, IR(neat) 1770, 1730 cm^{-1}; NMR($CDCl_3$) δ 2.0(2H, m), 2.4∿3.0(4H, m), 3.7(3H, s), 4.05(4H, br.s), 4.8(2H, m), 5.35(1H, s); MS(m/e) 285(M^++1), 73(100 %), in 84.2 % yield, while upon the same treatment 7b, gave the β,β-dichloroethyl ester 7d, oil: IR(neat) 1780, 1740 cm^{-1}; NMR($CDCl_3$) δ 2.0(2H, m), 2.4∿3.0(4H, m), 4.05(4H, br.s), 4.5(2H, d, J=6 Hz), 4.8(2H, m), 5.4(1H, s), 5.9(1H, t, J=6 Hz); MS(m/e) 368(M^++2), 366(M^+), 253, 73(100 %), in 72.5 % *via* concomitant dechlorination(Scheme 1).



1 2 3

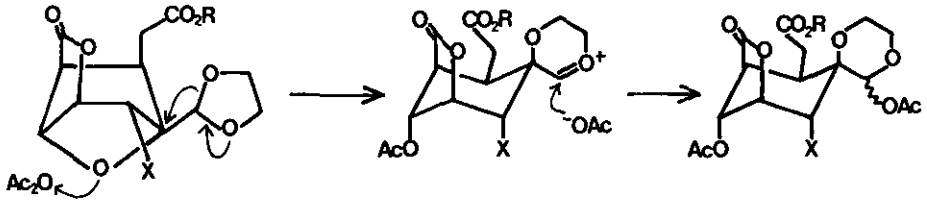
4: R=OH
5: R=Cl
6: R=CHN_2

7a: R=Me, X=I
b: R=CH_2CCl_3, X=I
c: R=Me, X=H
d: R=CH_2CHCl_2, X=H

Scheme 1

Treatment of 7a with acetic anhydride in the presence of catalytic amount of concd sulfuric acid[5] at 50 °C allowed regioselective cleavage of the ether ring accompanied by rearrangement of the dioxolane ring into the dioxane ring to form a diastereomeric mixture(1:1) of the acetates 9a, oil, in 94 % yield: IR(neat) 1780, 1720 cm^{-1}; NMR($CDCl_3$) δ 2.1(3H, s), 2.18(3H, d), 2.6(2H, m), 2.9(2H, br.d), 3.75(3H, s), 3.8∿4.4(4H, m), 4.2(1H, s), 4.8(1H, m), 5.2(1H, br.s), 6.4(1H, d); MS(m/e) 513(M^++1), 385, 88(100 %). Similarly, 7b and 7c gave 9b, oil, IR(neat) 1780, 1730 cm^{-1}; NMR($CDCl_3$) δ 2.1(3H, s), 2.24(3H, d), 2.7∿3.1(4H, m), 3.9∿4.2(4H, m), 4.3(1H, s), 4.9(2H, s), 4.9(1H, s), 5.2(1H, s), 6.45(1H, d); MS(m/e) 569(M^+),

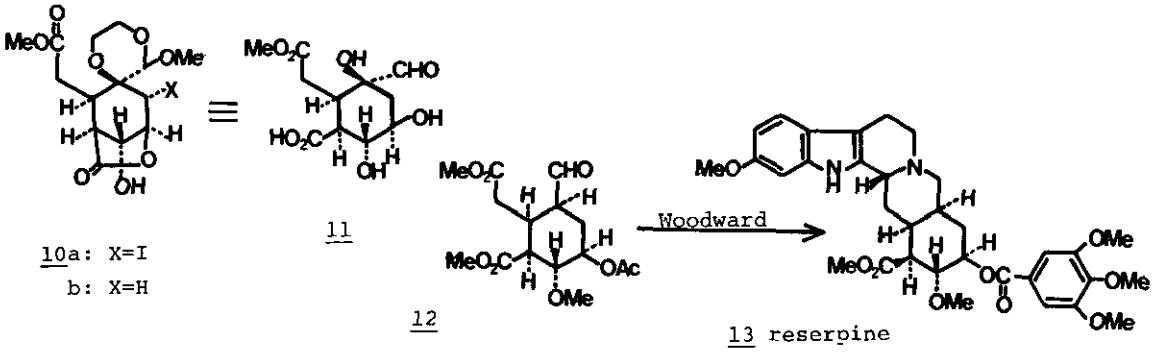
87(100 %), and 9c, oil, IR(neat) 1780, 1730 cm^{-1}; NMR($CDCl_3$) δ 2.0∿2.2(2H, m), 2.1(3H, s), 2.18(3H, s), 2.4∿3.0(4H, m), 3.7(3H, s), 3.8∿4.4(4H, m) 4.8(2H, m), 6.4(1H, s); MS(m/e) 387(M^++1), 87(100 %), in 94 and 79.4 % yield, respectively, Both of the epimeric diacetates, 9a and 9c were cleanly solvolyzed to the corresponding methoxy compounds, 10a, oil, in 47 % yield: IR(neat) 3450, 1785, 1715 cm^{-1}; NMR($CDCl_3$) δ 2.3∿2.7(2H, m), 2.9(2H, m), 3.4(3H, s), 3.4(1H, m), 3.75(3H, s), 4.25 (1H, s), 4.3(4H, br.s), 4.85(1H, m), 5.1(2H, m); MS(m/e) 412(M^+-32), 239(100 %), and 10b, oil, in 97 % yield: IR(neat) 3450, 1775, 1730 cm^{-1}; NMR($CDCl_3$) δ 2.0(2H, br.s), 2.4∿3.0(4H, m), 3.6(3H, s), 3.75(3H, s), 3.7∿4.1(5H, m), 4.65∿4.9(2H, m), 5.0(1H, s); MS(m/e) 317(M^++1), 183(100 %), each as a single stereoisomer by refluxing with methanol in the presence of a catalytic amount of p-toluenesulfonic acid. Consequently it is understood that the epimerization in both 9a and 9c could be ascribed to the anomeric acetal carbon and the ether cleavage reaction took a highly stereoselective sequence *via* Wagner-Meerwein type rearrangement to give the diacetates 9 presumably with the configuration as shown in Scheme 2.



7a, b, c 8 9a: R=Me, X=I; b: R=CH_2CCl_3, X=I; c: R=Me, X=H

Scheme 2

Since the acetal 10a may be looked upon as a hydroxy equivalent 11 of the key intermediate 12 of the *Woodward reserpine synthesis*[6], it would be a promising intermediate for the synthesis of the Rauwolfia alkaloids(Scheme 3).



10a: X=I; b: X=H 11 12 13 reserpine

Scheme 3

Reference and Notes

1) Suzuki, T.; Tomino, S.; Kagaya, S.; Kametani, T.; Ihara, M.; Takahashi, T. Heterocycles, 1978, 9, 1795 and related papers.

2) Prolonged reaction time allowed formation of the undesired exoisomer though total yield of the adducts increased(65 % yield after 4 days at room temperature; endo:exo=3:1).

3) Satisfactory analytical data were obtained for all new compounds.

4) Cf. Moriarty, R.M.; Chien, C.C.; Adams, T.B. J. Org. Chem., 1979, 44, 2206.

5) Cf. Kato, T.; Suzuki, T.; Ototani, N.; Kitahara, Y. Chem. Lett., 1976, 887.

6) Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. Tetrahedron, 1963, 19, 247.

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