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

Seiichi Takano*, Fumitaka Ito, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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 reports1 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 % yield2; IR(Nujol) 1860, 1800 cm⁻¹; NMR(CDCl₃) 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 4, mp 188-190 °C, in 97.2 % yield: IR(Nujol) 1780, 1710 cm⁻¹; NMR(CDCl₃+CF₃CO₂H) 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 5, mp 161-163 °C, in 92 % overall yield: IR(Nujol) 2100, 1790, 1625 cm⁻¹; NMR(CDCl₃) 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 5 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(CDCl₃) 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(CDC\(_3\)) 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
\(\pm\)106 °C, IR(neat) 1770, 1730 cm\(^{-1}\); NMR(CDC\(_3\)) 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(CDC\(_3\)) 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).

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(CDC\(_3\)) 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(CDC\(_3\)) 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\(^+\)),

\[ \text{Scheme 1} \]

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87(100 %), and 9c, oil, IR(neat) 1780, 1730 cm\(^{-1}\); NMR(CDCl\(_3\)) \(\delta\) 2.0\(^{\sim}\)2.2(2H, m), 2.1(3H, s), 2.18(3H, s), 2.4\(^{\sim}\)3.0(4H, m), 3.7(3H, s), 3.8\(^{\sim}\)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 solvolysed to the corresponding methoxy compounds, 10a, oil, in 47 % yield: IR(neat) 3450, 1785, 1715 cm\(^{-1}\); NMR(CDCl\(_3\)) \(\delta\) 2.3\(^{\sim}\)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\(_3\)) \(\delta\) 2.0(2H, br.s), 2.4\(^{\sim}\)3.0(4H, m), 3.6(3H, s), 3.75(3H, s), 3.7\(^{\sim}\)4.1(5H, m), 4.65\(^{\sim}\)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.

![Scheme 2](image)

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).

![Scheme 3](image)
Reference and Notes


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.


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