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REACTION OF METHYL TETRONATE WITH 3,4-DIHYDRO-6,7-DIMETHOXY-2-METHYLISOQUINOLINIUM IODIDE

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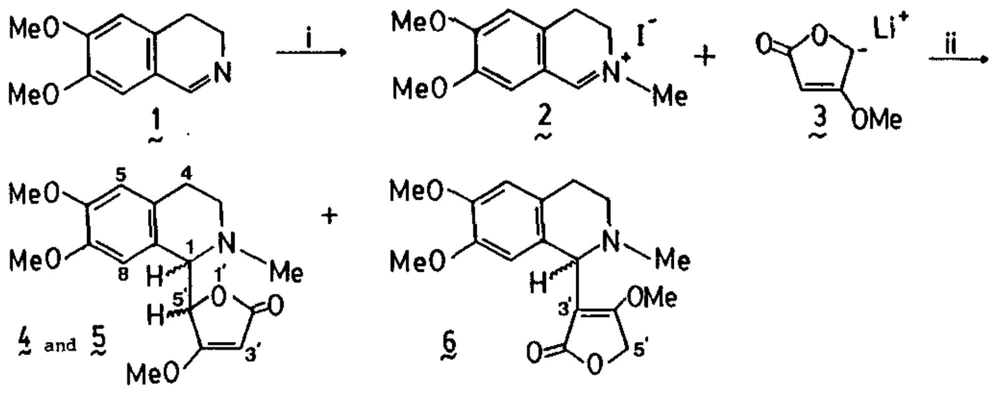
Abstract —— The lithium salt of methyl tetronate adds to 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide and affords a mixture of three coupled products. Zinc chloride has been found to suppress formation of one of these isomers. These compounds may be thought of as precursors to a new class of C-nucleosides.

Recent work has shown that imines react readily with phthalide anions. In the case of acyclic imines the products are 4-hydroxyisoquinolones, carrying substituents at C-2 and C-3[1,2]. When the imine is a 3,4-dihydroisoquinoline the products are 13-hydroxy-8-oxoprotoberberines[3]. It has been shown also that phthalide anions react with 3,4-dihydro-2-methylisoquinolinium salts to form 1,2,3,4-tetrahydro-2-methyl-1-phthalidylisoquinolines[4]. We report here the results of an investigation of the reaction of a butenolide (a non-aromatic analog of phthalide) with 3,4-dihydro-6,7-dimethoxyisoquinoline (1) and its N-methyliminium salt (2). Pelter et al.[5] have shown that 4-methoxybutenolide (methyl tetronate) can be deprotonated at C-5 using lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -77°C, and that the anion, 3, so formed reacted with aromatic aldehydes or with D_2O at C-5. On the other hand Miyata and Schmidt[6] have reported that 5-alkylated methyl tetronates deprotonate and react preferentially at C-3 with a variety of electrophiles.

In the present study we have found that butenolide itself decomposes to intractable material upon treatment with LDA in THF even at -100°C. Anion 3 prepared as described below did not react with the imine 1, but added readily to the iminium salt 2 to yield a mixture of three products, 4, 5, and 6 (see Scheme 1).

In a typical procedure n-BuLi was added dropwise over a 3-min period to a solution of diisopropylamine in THF (freshly distilled from $LiAlH_4$ under N_2) at 0°C. After 10 min, the solution was



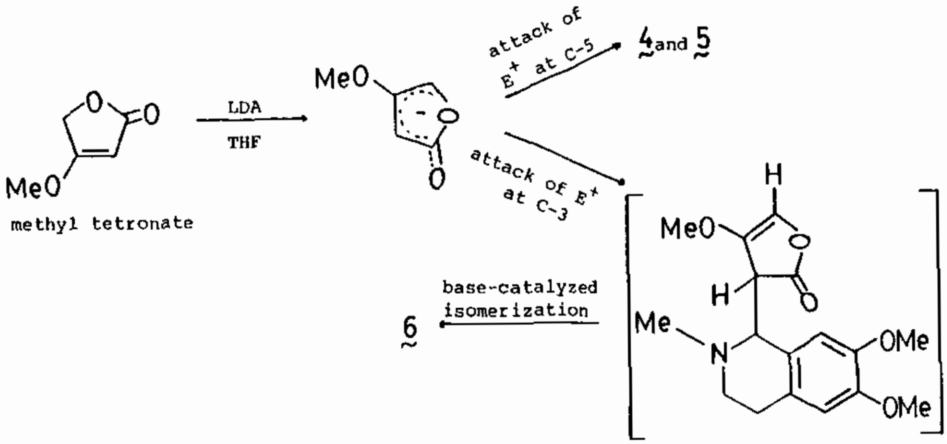
i MeI in THF.

ii THF, kept at -42°C for ∿3 h, then at ∿20°C overnight; the tetronate anion was prepared from methyl tetronate using LDA in THF.

Scheme 1

cooled to -77°C and methyl tetronate in THF was added over an ∿10-min period. Methyl tetronate and the iminium salt 2 were prepared by conventional procedures[5,7]. After 10 min, the solution was transferred using a double needle to a well-stirred suspension of 2 in THF at -42°C. The mixture was stirred at -42°C for ∿3 h and was then allowed to warm slowly and kept at 20°C overnight. All of the operations were performed under an atmosphere of argon, and additions were made by a syringe through serum stoppers. The processed reaction mixture was purified on a silica gel column {9:1 (v/v) ethyl acetate—methanol} to afford 4 (26%), 5 (20%), and 6 (19%) in a combined yield of 65%. Compounds 4 and 5 are diastereomers; their relative configurations have not been established, however, their structural assignments seem secure on the basis of the nmr and other physical data[8]. Compound 6 differs from 4 and 5 in that it lacks the olefinic proton observed in the spectra of the other two. On the other hand its ^{1}H-nmr spectrum exhibits a two-proton signal (singlet) corresponding to the protons at C-5', whereas in the cases of 4 and 5 only a one-proton signal (doublet of doublets) is observed for C-5' at δ 5.21 and 5.07, respectively. Compounds 4 and 5 may be formed by direct attack of the electrophile at C-5 on the anion 3. A rationalization for the formation of 6 is not as straightforward. Compound 6 may arise directly from an anion formed initially by deprotonation at C-3, or, alternatively, from the same delocalized anion that affords 4 and 5 as shown in Scheme 2.

An interesting aspect was the observation that modification of the methyl tetronate anion by addition of zinc chloride prior to coupling with 2 decreased the overall yield (59%) and suppressed



Scheme 2

completely the formation of 6. Differences in the ability of zinc and lithium cations to complex intramolecularly may account for the observed behavior.

The new compounds are potentially useful in the synthesis of novel C-nucleosides, for example, by hydroxylation of the 3',4'-double bond followed by reduction. Also, the reactions of imimium salts with butenolides may prove useful in the construction of heterocyclic systems found amongst the alkaloids.

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8. Relevant physical data for compounds **4**, **5**, and **6** are given below. The composition of these compounds is supported by combustion analysis, and, in the case of **6** by high-resolution mass-spectral analysis. ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker CXP-200 spectrometer in CD_3CN and $CDCl_3$, respectively, with tetramethylsilane as the internal standard. Thin-layer chromatography was performed on glass plates precoated with Merck silica gel 60F-254 as the adsorbent, using 10:1 (v/v) chloroform—methanol.

Compound **4** has mp 163.5—164.5°C (recrystallized from acetone); R_f 0.46; ν_{max}^{KBr} 3100, 1735, 1620 cm^{-1}; ^{1}H-nmr: δ 6.69 (1H, s, H-5 or H-8), 6.34 (1H, s, H-5 or H-8), 5.21 (1H, t, $J_{3',5'}$ = 1 Hz, $J_{1,5'}$ = 1 Hz, H-5'), 5.12 (1H, d, $J_{3',5'}$ = 1 Hz, H-3'), 3.98 (1H, broad s, H-1), 3.94 (3H, s, OMe), 3.78 (3H, s, OMe), 3.73 (3H, s, OMe), 3.09—3.24 (2H, m, 2 x H-3), 2.56—2.90 (2H, m, 2 x H-4), 2.53 (3H, s, NMe); ^{13}C-nmr: δ 26.2 (C-4), 43.75 (NMe), 48.75 (C-3), 55.9, 56.3 (OMe's at C-6 and C-7), 59.2 (OMe at C-4'), 64.0 (C-1), 81.95 (C-5'), 90.7 (C-3'), 111.3, 112.1 (C-5 and C-8), 122.3, 129.6 (C-4a and C-8a), 146.9, 148.6 (C-6 and C-7), 171.8 (C-2'), 180.6 (C-4').

Compound **5** has mp 161—162°C (recrystallized from acetone); R_f 0.54; ν_{max}^{KBr} 3100, 1720, 1620 cm^{-1}; ^{1}H-nmr: δ 6.75 (1H, s, H-5 or H-8), 6.70 (1H, s, H-5 or H-8), 5.11 (1H, d, $J_{3',5'}$ = 1 Hz, H-3'), 5.07 (1H, dd, $J_{3',5'}$ = 1 Hz, $J_{1,5'}$ = 2 Hz, H-5'), 3.93 (1H, d, $J_{1,5'}$ = 2 Hz, H-1), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 2.97—3.13 (2H, m, 2 x H-3), 2.50—2.75 (2H, m, 2 x H-4), 2.44 (3H, s, NMe); ^{13}C-nmr: δ 27.35 (C-4), 44.5 (NMe), 50.7 (C-3), 56.0, 56.1 (OMe's at C-6 and C-7), 58.9 (OMe at C-4'), 64.1 (C-1), 81.8 (C-5'), 90.4 (C-3'), 110.1, 111.55 (C-5 and C-8), 124.3, 128.7 (C-4a and C-8a), 147.65, 148.1 (C-6 and C-7), 172.3 (C-2'), 181.2 (C-4').

Compound **6** has mp 139.5—140.5°C (recrystallized from ethyl acetate); R_f 0.39; ν_{max}^{KBr} 1725, 1650 cm^{-1}; ^{1}H-nmr: δ 6.66 (1H, s, H-5 or H-8), 6.41 (1H, s, H-5 or H-8), 4.84 (2H, s, 2 x H-5'), 4.21 (1H, s, H-1), 3.86 (3H, s, OMe), 3.80 (3H, s, OMe), 3.73 (3H, s, OMe), 2.88—3.13 (2H, m, 2 x H-3), 2.44—2.81 (2H, m, 2 x H-4), 2.32 (3H, s, NMe); ^{13}C-nmr: δ 28.9 (C-4), 43.9 (NMe), 52.8 (C-3), 56.0, 56.5 (OMe's at C-6 and C-7), 59.5 (OMe at C-4'), 60.0 (C-1), 65.9 (C-5'), 104.7 (C-3'), 110.7, 111.8 (C-5 and C-8), 126.8, 129.7 (C-4a and C-8a), 147.9, 148.2 (C-6 and C-7), 174.4, 175.1 (C-2' and C-4').

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