

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

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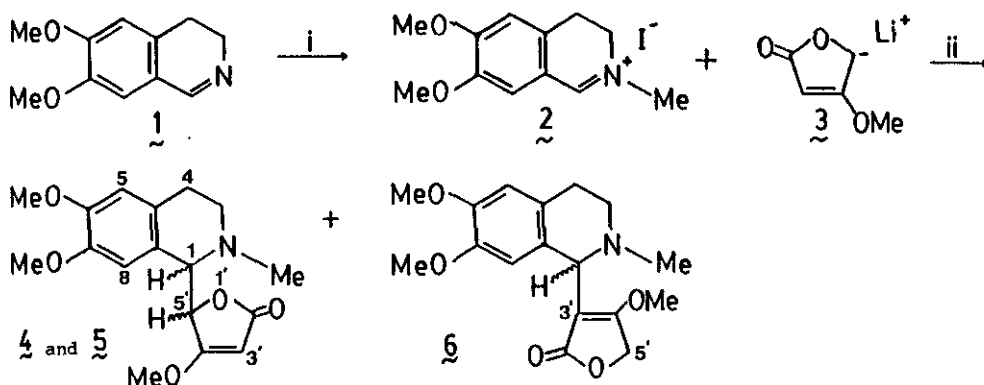
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Abstract — The lithium salt of methyl tetronate adds to 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide and affords a mixture of three coupled products. Zinc chloride has been found to suppress formation of one of these isomers. These compounds 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-oxoprotoberberines³. 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-phthalidylisoquinolines⁴. 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 D₂O at C-5. On the other hand Miyata and Schmidt⁶ 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 LiAlH₄ under N₂) at 0°C. After 10 min, the solution was



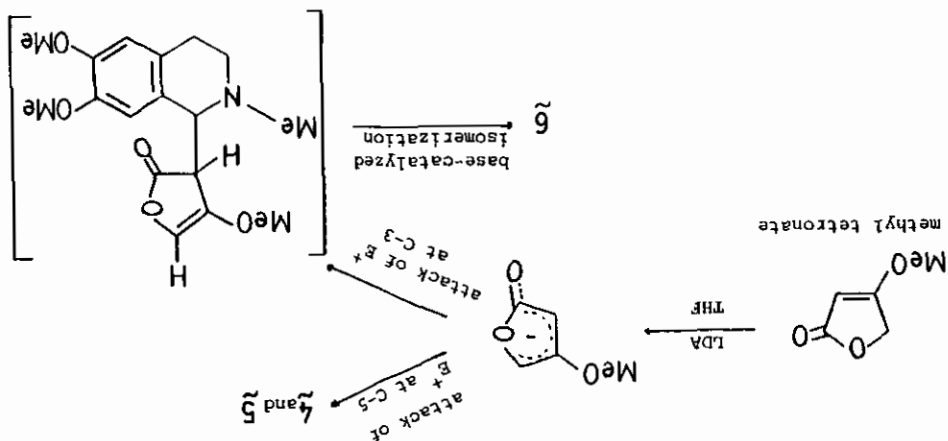
i MeI in THF.

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 data⁸. 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 ^1H -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



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 iminium 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. ^1H -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; $\nu_{\text{max}}^{\text{KBr}}$ 3100, 1735, 1620 cm^{-1} ; ^1H -nmr: δ 6.69 (1H, s, H-5 or H-8), 6.34 (1H, s, H-5 or H-8), 5.21 (1H, t, $J_{3',5'} = 1 \text{ Hz}$, $J_{1,5'} = 1 \text{ Hz}$, H-5'), 5.12 (1H, d, $J_{3',5'} = 1 \text{ Hz}$, H-3'), 3.98 (1H, broad s, H-1), 3.94 (3H, s, OMe), 3.78 (3H, s, OMe), 3.73 (3H, s, OMe), 3.08—3.24 (2H, m, 2 $\times$ H-3), 2.56—2.90 (2H, m, 2 $\times$ 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; $\nu_{\text{max}}^{\text{KBr}}$ 3100, 1720, 1620 cm^{-1} ; ^1H -nmr: δ 6.75 (1H, s, H-5 or H-8), 6.70 (1H, s, H-5 or H-8), 5.11 (1H, d, $J_{3',5'} = 1 \text{ Hz}$, H-3'), 5.07 (1H, dd, $J_{3',5'} = 1 \text{ Hz}$, $J_{1,5'} = 2 \text{ Hz}$, H-5'), 3.93 (1H, d, $J_{1,5'} = 2 \text{ Hz}$, H-1), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 2.97—3.13 (2H, m, 2 $\times$ H-3), 2.50—2.75 (2H, m, 2 $\times$ 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; $\nu_{\text{max}}^{\text{KBr}}$ 1725, 1650 cm^{-1} ; ^1H -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 $\times$ 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 $\times$ H-3), 2.44—2.81 (2H, m, 2 $\times$ 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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