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Novel Addition Reaction of Thebaine with Acetylenic Dienophiles: Construction of a New Morphine Skeleton

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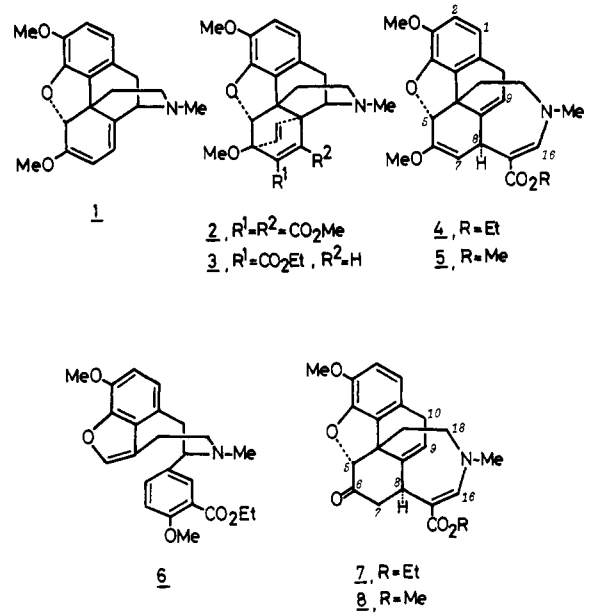
Thebaine (**1**), a unique morphine alkaloid, is too toxic to be used as an analgesic.[1] Owing to its diene structure, however, the Diels–Alder reactions of **1** with various dienophiles and chemical transformations of the resulting adducts have been extensively investigated.[2-9] Many of the compounds derived from **1** in this way show high analgesic activity.[3] During the course of our studies on chemical modifications of **1**, we have found that **1** undergoes abnormal addition reactions with acetylenic dienophiles in polar solvents, providing in high yields novel adducts derived from the morphine skeleton.

Rapoport and Sheldrick[10] reported that **1** and dimethyl acetylenedicarboxylate react smoothly in benzene at 50 °C to give the Diels–Alder adduct **2** in high yield, while the similar reaction of ethyl propiolate (EP) gives the adduct **3** only in very poor yield. In the latter case, the low reactivity was attributed to rapid polymerization of EP under the reaction conditions employed.[10] Therefore, we reexamined the same reaction under milder conditions by using various solvents. To our surprise, **1** was found to react very readily with EP in polar solvents even at room temperature. Thus, treatment of **1** (Chart I) with 1.5 equiv of EP in acetonitrile at room temperature (30 min) followed by evaporation in vacuo gave a quantitative yield of the cyrstalline adduct **4**, mp 168–170 °C (ethyl acetate).[11] The product **4** was also obtained in 64% yield by using CH_2Cl_2 as a solvent, although the similar reaction in benzene resulted in the formation of several minor products including **4** along with the recovery of large amounts of unreacted thebaine (**1**). The adduct **4** was totally different from the reported Diels–Alder adduct **3** (mp 130–131 °C).[10] While **3** is known to easily undergo the retro-Diels–Alder reaction at 140 °C to give **6**,[10] compound **4** is stable under the identical thermolytic conditions.

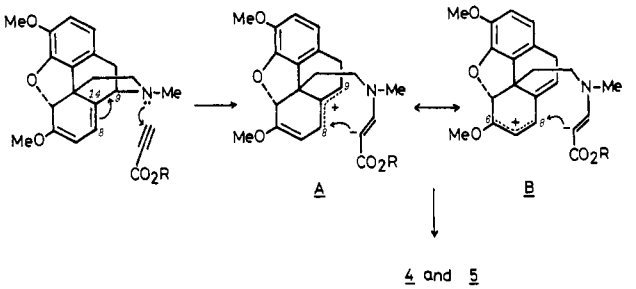
The structure of **4** was determined on the basis of its spectroscopic data and chemical conversions. Its nature as a 1:1 adduct was apparent from the elemental analysis and mass spectrum (M^+, m/e 409). The IR (Nujol) spectrum showed a characteristic absorption at 1680 cm^{-1} for a >NC=CCOOEt moiety. The ^1H NMR ($CDCl_3$) spectrum exhibited signals of the ethyl group at δ 1.28 (t, J = 6.8 Hz, 3 H) and 4.14 (q, J = 6.8 Hz, 2 H), three methyl groups at δ 2.91 (s, 3 H), 3.55 (s, 3 H), and 3.82 (s, 3 H), two methine protons at δ 4.50 (br d, J = 5.2 Hz, H-8) and 4.97 (d, J = 1.2 Hz, H-5), three olefinic protons at δ 5.25 (dd, J = 5.2, 1.2 Hz, H-7), 5.93 (dd, J = 5.4, 2.7 Hz, H-9), and 7.33 (s, H-16), and two aromatic protons at δ 6.65 (s, 2 H). The assignments were confirmed by the double-resonance decoupling experiments. The ^{13}C NMR ($CDCl_3$) spectrum showed signals of an ester carbonyl [δ169.3 (s)], 12 sp^2 carbons [δ150.5 (s), 150.5 (d), 144.5 (s), 142.3 (s), 141.0 (s), 133.7 (s), 128.3 (s), 124.5 (d), 118.6 (d), 111.8 (d), 104.5 (s), and 102.2 (d)], three methine carbons [δ86.1 (d), 38.4 (d), and 37.9 (s)], three methylene carbons [δ 59.5 (t), 54.4 (t), and 53.3 (t)], and four methyl carbons [δ56.2 (q), 50.2 (q), 44.2 (q), and 14.5 (q)]. From these data, **4** was concluded to be the novel 1:1 adduct derived from a morphine skeleton. The similar reaction of **1** with methyl propiolate (MP) in acetonitrile or methanol afforded the corresponding adduct **5**[11,12] in a quantitative yield.

Structure of these adducts was further confirmed by the following chemical conversions. While **4** (or **5**) was recovered unchanged from the catalytic hydrogenation (H_2, 5% Pd–C, ethyl acetate) or reductive treatment ($LiAlH_4$, THF, reflux), the enol ether functionality in **4** (or **5**) was exposed on mild acid hydrolysis (concentrated HCl–THF 20:80, 20 h, 25 °C) to give the ketone **7** (60%) [or **8**[13] (56%)], mp 170–172 °C (ethyl acetate):[11] MS, m/e 395 (M^+); IR (Nujol) 1735 and 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 6.9 Hz, 3 H), 1.68–2.00 (m, 2 H), 2.51

Chart I



Scheme I



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(11) Satisfactory combustion analyses were obtained for all new compounds.
(12) Compound **5**: mp 160–162 °C (ethyl acetate); *MS*, m/e 395 (M^+); IR (Nujol) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86–2.40 (m, 2 H), 2.91 (s, 3 H), 3.15–3.24 (m, 2 H), 3.55 (s, 3 H), 3.72 (s, 3 H), 3.82 (s, 3 H), 4.50 (br d, J = 5.2 Hz, H-8), 4.97 (d, J = 1.2 Hz, H-5), 5.25 (dd, J = 5.2, 1.2 Hz, H-7), 5.93 (dd, J = 5.4, 2.7 Hz, H-9), 6.65 (s, H-1 and H-2), and 7.33 (s, H-16); ^{13}C NMR ($CDCl_3$) δ29.4 (t), 37.9 (s), 38.4 (d), 44.3 (q), 50.2 (q), 51.0 (q), 53.1 (t), 54.4 (t), 56.2 (q), 86.1 (d), 102.2 (d), 104.4 (s), 111.8 (d), 118.6 (d), 124.5 (d), 128.3 (s), 133.6 (s), 140.9 (s), 142.3 (s), 144.6 (s), 150.5 (s), 150.7 (d), and 169.7 (s).

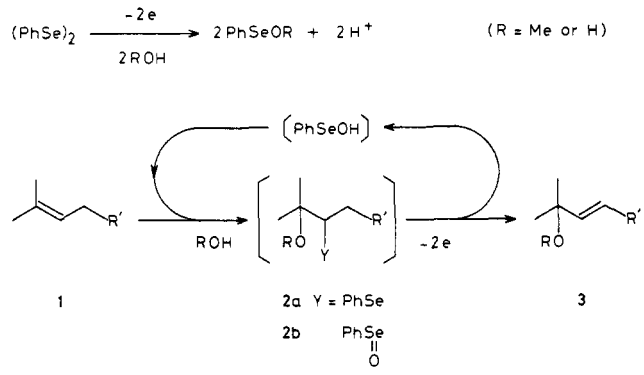
0002-7863/81/1503-4605$01.25/0

(dd, J = 14.2, 8.1 Hz, H-7β), 2.75 (dd, J = 14.2, 9.0 Hz, H-7α), 3.02 (s, 3 H), 3.20 (d-like m, 2 H-10), 3.40-3.50 (m, 2 H-18), 3.88 (s, 3 H), 4.15 (q, J = 6.9 Hz, 2 H), 4.39 (br t, J = 8.5 Hz, H-8), 5.05 (s, H-5), 5.90 (m, H-9), 6.69 (s, H-1 and 2), 7.42 (s, H-16). The ^{13}C NMR ($CDCl_3$) spectrum of **7** was very similar to that of **5** except for the new appearance in **7** of a carbonyl signal [δ205.8 (s, C-6)] and a methylene signal δ44.4 (t, C-7)] at the cost of two olefinic signals [δ102.2 (d) and 150.5 (s)] and a methyl signal [δ50.2 (q)] in **5**.

The above results can be most reasonably explained by the stepwise mechanism involving ionic species shown in Scheme I, which was also compatible with the observation of remarkable solvent effects. The reaction may be initiated by the nucleophilic addition of **1** to the electron-deficient acetylenes[14] followed by the cleavage of C(9)-N bond, which is stereoelectronically favored by its almost parallel arrangement to the p orbitals of adjacent C(8)=C(14) double bond. The sterically most favorable ring closure at C(8) position of the resulting intermeidates (A and/or B) leads to the formation of adducts **4** and **5**.

The facile formation of a new type of adduct of **1**, by using polar solvents, is most noteworthy. These results provide a further way for chemical modifications of **1** and stimulate the reexamination of cycloaddition reactions of **1** with various dienophiles in different solvents, which is currently under way in our laboratory.

Scheme I



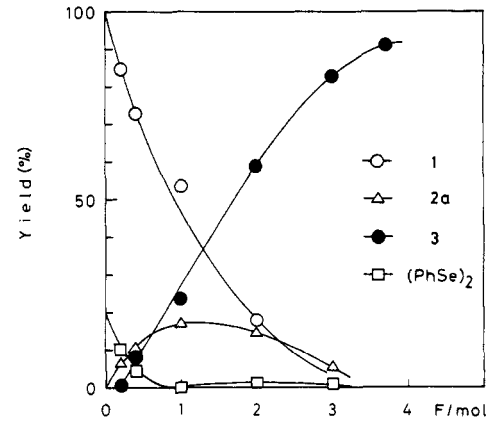


Figure 1. Electricity (F/mol of **1**) and yields of products [**2a** and **3**, R = $CH_2CMe(OAc)C{\equiv}CH$] in the presence of 10 mol % of diphenyl diselenide in MeOH at 60-63 °C.

(13) Compound **8**: mp 231-233 °C (ethyl acetate); MS, m/e 381 (M^+); IR (Nujol) 1735 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68-2.00 (m, 2 H), 2.50 (dd, J = 13.8, 8.0 Hz, H-7β), 2.82 (dd, J = 13.8, 9.0 Hz, H-7α), 3.00 (s, 3 H), 3.18 (d-like m, 2 H), 3.40-3.60 (m, 2 H), 3.67 (s, 3 H), 3.86 (s, 3 H), 4.37 (br t, J = 8.5 Hz, H-8), 5.03 (s, H-5), 5.90 (m, H-9), 6.88 (s, H-1 and H-2), and 7.40 (s, H-16); ^{13}C NMR ($CDCl_3$) δ 29.2 (t), 37.4 (d), 37.4 (s), 41.5 (t), 44.5 (d) 51.1 (q), 53.3 (t), 54.2 (t), 56.5 (q), 89.4 (d), 105.4 (s), 112.8 (d), 119.6 (d), 126.3 (d), 126.3 (s), 132.2 (s), 138.5 (s), 142.3 (s), 143.9 (s), 150.6 (d), 169.4 (s), and 205.7 (s).

(14) Ethyl acrylate was found not to react with **1** in a similar way, but to give the Diels-Alder adduct under more drastic conditions.[3]

Generation and Recycle Use of Selenenylating Reagents in Electrochemical Oxyselenenylation-Deselenenylation of Olefins

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Oxyselenenylation-oxidative deselenenylation sequence provides double-bond transpositioned allylic alcohols and ethers from olefins.[1] The current method involves two steps: oxyselenenylation with PhSeX (X = Cl, Br, OR, and NR_2) followed by oxidation with O_3, $NaIO_4$, and peroxides (H_2O_2, t-BuOOH, m-CPBA) where stoichiometric amounts of PhSeX in the former step and large excess amount of oxidative reagents in the latter are required.[1,2] In principle, electrochemical transformation (**1** → **3**) must be realized since both oxyselenenylation and deselenenylation via selenoxide are oxidative processes.[3] Here, we describe a one-step preparation of allylic derivatives **3** from isoprenoids **1**, which is characterized by (1) electrochemical generation and recycled use of selenenylation reagents from a catalytic amount of diphenyl diselenide, (2) one-step preparation of allylic alcohols **3** (R = H) without use of phenylselenenic acid[4] and selenenamide,[5] and finally (3) deselenenylation in the absence of peroxides.

The reaction procedure requires a mixture of **5** (0.5 mmol), $(PhSe)_2$ (0.05 mmol), and $MgSO_4$ (2.5 mmol) in MeCN-H_2O (5:2) which is electrolyzed under a constant current (6.7 mA/cm^2, 4.2 F/mol) by using Pt foils as electrodes in an undivided cell at 66-68 °C, affording **14** (R = H, 89%). The results of the electrochemical transformation are summarized in Table I. Most of terminal ω double bonds of isoprenoids undergo regioselective oxyselenenylation-deselenenylation to give *trans*-allylic alcohols[6] in aqueous acetonitrile and methyl ethers[6] in methanol. Particularly noteworthy is the fact that the hydroxylative double-bond transposition (**1** → **3**, R = H) takes place efficiently in aqueous acetonitrile, which is an easier access to allylic alcohol **3** (R = H) than the known methods by phenylselenenic acid[4] and phenylselenenamide.[5] Acetoxyl, carbomethoxyl, ethynyl, and sulfonyl groups are inert in the electrolytic conditions. Enol acetate **10** was converted into α,β-unsaturated ketone **19** (81%) by this procedure. β-Pinene **11** provided **20a** and **20b** via oxyselenenylation involving ring opening of the cyclobutane skeleton[3b] → selenoxylation → [2,3]-sigmatropic rearrangement of the selenoxide.[1,7] This electrochemical reaction can be demonstrated by a one-step synthesis of *dl*-dihydroactinidiolide **21** (92%)[8] from

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(2) For instance, the transformation (**1** → **3** for citronellol, R = H) is performed by the action of 3 mol equiv of PhSeOH for hydroxyselenenylation followed by 5 mol equiv of t-BuOOH for deselenenylation via selenoxide: Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.

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(6) Purity of **3** was determined by HPLC (μ-Porasil, n-hexane-ethyl acetate 5:1). The coupling constants of the newly formed double bond (J, Hz) are as follows: **13**, 15.7; **14**, 15.6; **15**, 15.4; **16**, 15.4; **17** 15.1; **18**, 15.9; **19**, 15.9.

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