Addition Reaction of Thebaine and β-Dihydrothebaine with Phenylsulphonylpropadiene

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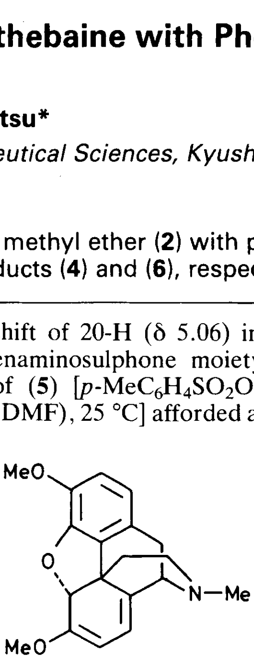
The addition reactions of thebaine (**1**) and β-dihydrothebaine methyl ether (**2**) with phenylsulphonylpropadiene (**3**) proceed very smoothly in polar solvents to provide novel adducts (**4**) and (**6**), respectively, in good yields.

Recently, we have found that the addition reactions of thebaine (**1**) with acetylenic dienophiles show a remarkable solvent dependency and give novel addition products in polar solvents.[1] This prompted us to investigate the addition reactions of (**1**) with various olefinic dienophiles[2,3] in different kinds of solvent. In this communication we report the facile addition reactions of (**1**) as well as β-dihydrothebaine methyl ether (**2**) with phenylsulphonylpropadiene (**3**)[4] in polar solvents *via* zwitterionic intermediates to give novel adducts in high yields.

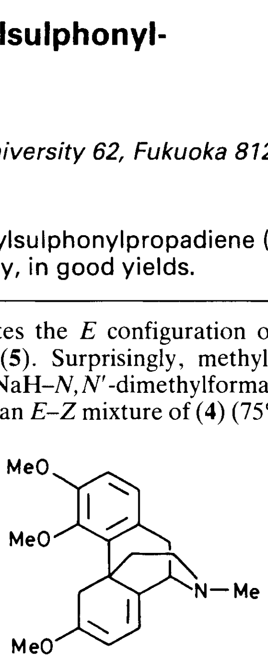
When (**1**) was allowed to react with (**3**) in methanol at room temperature, a smooth reaction occurred to give a quantitative yield of the crystalline adduct (**4**), m.p. 276 °C (decomp.), as an inseparable mixture (2:1) of *E* and *Z* isomers. The adduct (**4**),† in the same *E–Z* ratio, was obtained in 71% yield by using acetonitrile as a solvent, although the reaction in benzene even at refluxing temperature resulted in the recovery of mostly (**1**) and (**3**) together with several minor products.

The nature of (**4**) as a 1:1 adduct was apparent from the elemental analysis and mass spectrum [*m/z* 497 (M^+)]. The ^{1}H n.m.r. spectrum characteristically showed two broad singlets for 20-H at δ 5.14 (*E* isomer) and 4.72 (*Z* isomer), and two singlets for MeO (C-6) at δ 3.44 (*E* isomer) and 3.53 (*Z* isomer) in a 2:1 ratio, while the two other methyl groups appeared as 3-proton singlets at δ 2.77 (NMe) and 3.81 (OMe). Apparently, the downfield shift of the 20-H signal of the *E* isomer can be attributed to the deshielding effect of the nitrogen atom.[5]

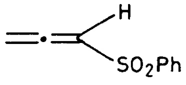
When an *E–Z* mixture of (**4**) was treated with conc. HCl–tetrahydrofuran (1:40), the ketone (**5**) (79%) was obtained as the sole thermodynamic product,[5] [m.p. 278—279 °C; *m/z* 477 (M^+); i.r. $\nu_{max.}$ 1728 cm^{-1}; ^{1}H n.m.r. δ 2.83 (s, NMe), 3.89 (s, OMe), and 5.06 (s, 20-H)]. The chemical shift of 20-H (δ 5.06) indicates the *E* configuration of the enaminosulphone moiety in (**5**). Surprisingly, methylation of (**5**) [p-MeC$_6$H$_4$SO$_2$OMe–NaH–*N,N'*-dimethylformamide (DMF), 25 °C] afforded again an *E–Z* mixture of (**4**) (75%) in



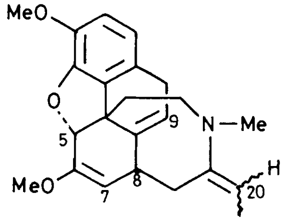
(**1**)



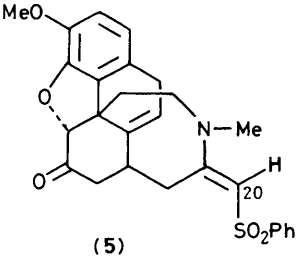
(**2**)



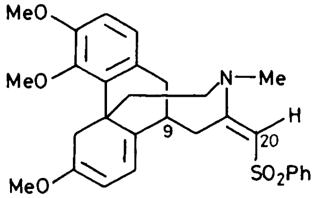
(**3**)



(**4**)



(**5**)



(**6**)

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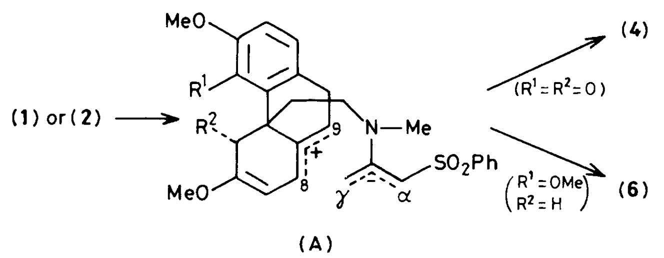
† Satisfactory analytical and spectral data (^{1}H, ^{13}C n.m.r., and mass spectra) were obtained for all new compounds.



Scheme 1

the same ratio (2 : 1). Therefore, the adduct (**4**) appeared to be an equilibrium mixture of *E–Z* isomers.[6]‡

In order to study the influence of the 4,5-ether bridge of (**1**) in these interesting reactions, the analogous reaction of β-dihydrothebaine methyl ether (**2**),§ which is free of the 4,5-ether bridge, was investigated. When equimolar amounts of (**2**) and (**3**) were mixed in methanol at room temperature, the crystalline adduct (**6**), m.p. 196—196.5 °C, was formed almost instantaneously in a quantitative yield [m/z 507 (M^+); ^{1}H n.m.r. δ 2.69 (s, 3H, NMe), 3.58 (s, 3H, OMe), 3.80 (s, 6H, 2 OMe), 4.84 (s, 20-H), 4.88 (dd, J 7, 1 Hz, 7-H), 5.48 (dd, J 7, 2 Hz, 8-H); ^{13}C n.m.r. δ 90.9 (d, C-7), 91.7 (d, C-8), 125.2 (d, C-20)]. The diene structure of (**6**) was confirmed by the similarity of its ^{1}H n.m.r. spectrum to that of (**2**) in the olefinic region, and the *E*-alkene geometry of the enaminosulphone moiety was based on the observation of nuclear Overhauser effects (16%) between NMe and 20-H.

The above results, including the remarkable solvent effects, can be most reasonably explained by the stepwise mechanism *via* ionic intermediates as shown in Scheme 1. The reaction may be initiated by the nucleophilic addition of either (**1**) or (**2**) to the central carbon of allene (**3**) followed by the cleavage of the C(9)–N bond to give the zwitterionic intermediates (A).[1] However, the cyclization of (A) seems to be strongly affected by the structure of substrates. While the intermediate (A) derived from (**1**) collapses at the sterically most favourable positions [C(γ) and C(8)] to give (**4**), in the reaction of (**2**) the same C(γ) carbon of the allyl anion attacks preferentially the C(9) position to give (**6**). This sharp contrast in the site-selectivity may be a result of the conformational difference between (**1**) and (**2**).

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‡ A Dreiding model shows that significant spatial overlap is expected between the lone-pair orbital of the nitrogen atom and the p orbital of the enol ether moiety in (**4**).

§ Compound (**2**) was synthesized from thebaine in 47% yield in four steps: i, Fe(CO)$_5$–benzene–*hν*; ii, Zn–AcOH; iii, *p*-MeC$_6$H$_4$-SO$_2$OMe–NaH–DMF; iv, Me$_3$N→O–benzene.