On the features of reactivity of 8-[(1*E*)-2-phenylethenyl]-substituted thebaine and codeinone derivatives

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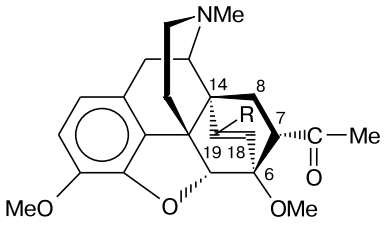
An improved method for the synthesis of 8-[(1*E*)-2-phenylethenyl]codeinone dimethyl ketal was described. The ability of [(1*E*)-2-phenylethenyl] substituent to stabilize effectively the π-system of the ring *C* is responsible for the essential difference in both the reactivity and the compositions of products formed in the reactions of the corresponding substituted and unsubstituted codeinone and thebaine derivatives.

Key words: morphinan alkaloids, 8-[(1*E*)-2-phenylethenyl]codeinone dimethyl ketal, 8-[(1*E*)-2-phenylethenyl]thebaine, hydrolysis, dehydrobromination.

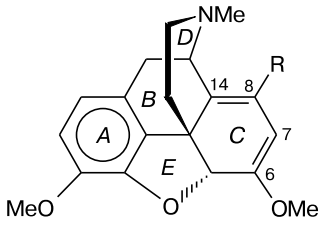
Thevinone (**1a**) is a key intermediate on the synthetic route from natural alkaloid thebaine (**2a**) toward orvinols (**3a**), so called "semi-synthetic" opioid derivatives exhibiting marked affinity to opioid receptors (*e.g.*, buprenorphine, diprenorphine, ethorphine, dihydroethorphine).[1,2] Therefore, compounds **3a** for decades are the subjects for intense search for potent analgetics for treatment of severe and chronic pain with decreased level of unwanted side effects. Compound **1a** is formed by [4+2] cycloaddition of $AcCH{=}CH_2$ to diene system of **2a** and serve as the starting compound for the synthesis of large scope of thevinols **3b**, *O*-demethylation of the latter leading to compounds **3a**. A variety of compounds **3b** and **3a** resulted mainly from altering the substituents R^2 and R^3. However, recently, modification of the C(6)—C(14)-etheno or -ethano bridge of compounds **3** became of interest. Functionalization of these positions can be achieved by either preliminary introduction of the substituent at the positions 7 or 8 of diene **2a** (which correspond to positions 18 and 19 of adduct **1a**) followed by [4+2] cycloaddition[3] or by modification of the ethene bridge in the Diels—Alder adduct.[4,5]

Recently, in the framework of the design of novel procedures for the modification of the *C* ring of the morphinan alkaloids, we carried out the Pd-catalyzed Heck reaction of codeine (**4a**) and PhCH=CHBr to give 7,8-dihydro-8β-[(1*E*)-2-phenylethenyl]codeinone (**5a**), from which 8-[(1*E*)-2-phenylethenyl]codeinone dimethyl ketal (**6a**) was synthesized in four steps.[6] It was found that ketal **6a** bearing conjugated diene system reacts with dienophiles to give adducts **7** including 19-[(1*E*)-2-phenylethenyl]thevinone (**1b**) (in the reaction with $AcCH{=}CH_2$) instead of the expected 7,8-fused compounds. The use of ketal **6a** as "masked" 8-[(1*E*)-2-phenylethenyl]thebaine (**2b**) opens the route toward derivatives of compounds **3** substituted at the position 19. Moreover, the hydrolysis of ketal **6a** and subsequent reduction of the carbonyl group afforded 8-[(1*E*)-2-phenylethenyl]codeinone (**4b**), which in the "ordinary" Diels—Alder reaction gives derivatives with the additional cycle fused to the *C* ring at the positions C(7)—C(8).[6]

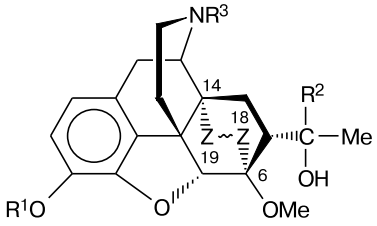
Thus, ketal **6a** is the key intermediate toward both the 7,8-fused derivatives of morphinan alkaloids and de-



1a,b



2a,b



3a,b

1, **2:** R = H (**a**), *trans*-CH=CHPh (**b**)
3: R^1 = H (**a**), Me (**b**); Z~Z = CH_2CH_2, CH=CH

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rivatives of thevinols and orvinols **3** substituted at the position 19.

In the present work we report the shorter and more efficient synthetic pathway toward ketal **6a** and describe the role of the (1*E*)-2-phenylethenyl moiety at the position C(8) as structural factor that significantly effects the chemical behavior of the corresponding derivatives and, specifically, brings about unique properties of ketal **6a**.

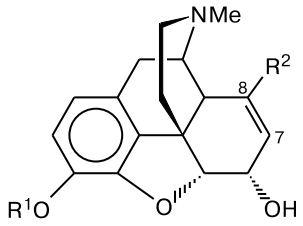
Results and Discussion

According to the known procedure,[6] ketal **6a** was prepared form ketone **5a** in four steps, which include transformation of **5a** by the action of $HC(OMe)_3$ in MeOH into ketal **5b**, treatment of **5b** with TsOH in anhydrous conditions to give enol ether **8**, conversion of the later by treatment with MeOBr in MeOH into bromide **5c**, which in the reaction with Bu^{t}OK in DMSO at ambient temperature afforded ketal **6a**.

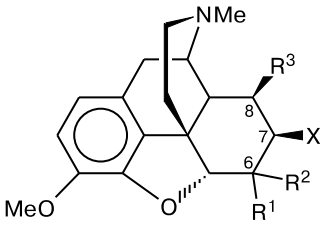
We managed to shorten the synthetic route and prepare ether **8** from ketone **5a** in one step in 82% yield. The modified procedure involved treatment of ketone **5a** with the excess of sodium hydride in DMF at ambient temperature followed by alkylation of the sodium enolate with dimethyl sulfate at −5 °C. Besides the reducing the synthetic route, the essential advantage of the developed procedure to produce ketal **6a** is that the only step of the four on the pathway from codeine (**4a**) to ketal **6a**, which required purification of the intermediate is the reaction **4a** → **5a**, while next three steps can be carried out without purification of the intermediates; compound **6a** can easily be purified by recrystallization.

If required, ketal **6a** can be used for the synthesis of compound **2b**, which is the substituted analog of **2a**.[6] Although, it is not mandatory because Diels—Alder adducts **7** substituted at the position 19 can be prepared directly from compound **6a**. It was suggested[6] that formation of adducts **7** in the reactions of dimethyl ketal **6a** with dienophiles instead of the expected 7,8-fused compounds is due to triene **2b** that formed from **6a** by elimination of MeOH under reaction conditions used (reflux in toluene). In this case, triene **2b** is the true substrate of cycloaddition.

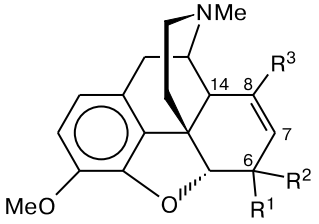
We studied in detail the composition of the reaction mixture formed upon refluxing ketal **6a** in toluene without dienophile. Indeed, triene **2b** was formed under these conditions. After 5 h, the reaction reached the equilibrium with **6a** : **2b** = 1 : 4. Ease of methanol elimination in this case can obviously be explained by the gain upon the formation of extended system of the conjugated π-bonds in compound **2b**, which included diene fragment of the ring *C* and phenylethenyl moiety in the position C(8). Thus, the presence in the codeinone derivatives of the type of ketal **6a** the substituents at the position C(8) capable of effective π,π-conjugation with the C—C multiple bonds of the ring *C* turned them into "masked" thebaine derivatives. Conversely, equilibrium between compounds **6a** and **2b** upon refluxing in toluene suggests that the presence of above-mentioned substituents at position C(8) of diene **2a**



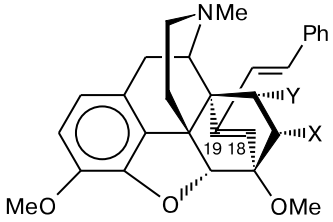
4a—c



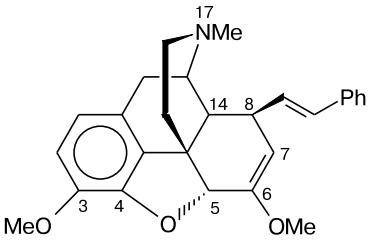
5a—d



6a—d



7



8

4: R^1 = Me, R^2 = H (**a**); R^1 = Me, R^2 = *trans*-CH=CHPh (**b**); $R^1 = R^2$ = H (**c**)
5: $R^1 + R^2$ = O; R^3 = *trans*-CH=CHPh, X = H (**a**); $R^1 = R^2$ = OMe; R^3 = *trans*-CH=CHPh, X = H (**b**); $R^1 = R^2$ = OMe, R^3 = *trans*-CH=CHPh, X = Br (**c**); $R^1 = R^2$ = OMe, R^3 = H, X = Br (**d**)
6: $R^1 = R^2$ = OMe, R^3 = *trans*-CH=CHPh (**a**); $R^1 + R^2$ = O, R^3 = *trans*-CH=CHPh (**b**); $R^1 = R^2$ = OMe, R^3 = H (**c**); $R^1 + R^2$ = O, R^3 = H (**d**)

should facilitate ready conversion of these compounds into the corresponding codeinone derivatives under the action of compounds HX with sufficient acidity. Moreover, it is natural to expect that the compounds bearing 8-phenylethenyl substituent could easier be involved in the reactions proceeding *via* formation of carbocation at C(8) atom.

Therefore, with the task to determine how strong could be the effect of 2-phenylethenyl substituent at the C(8) atom in the corresponding chemical transformations of the compound of this series, we studied the reaction, which resulted in the formation of the π-system in the ring *C* capable of effective conjugation with the 8-(2-phenylethenyl) group, namely, elimination of HBr from bromide **5c** and hydrolysis of ketal **6a**. In addition, the chemical behavior of 8-(2-phenylethenyl)-substituted derivatives was compared with previously described properties of the corresponding compounds unsubstituted at the C(8) atom. Both studied reactions are of practical interest due to the relevance to the synthesis of opium alkaloid thebaine (**2a**), which is the most valuable from the synthetic point of view and is very scarce due to low natural content (and consequently its derivatives) from more affordable row materials — morphine (**4c**) or codeine (**4a**). For this reason, both the elimination of HBr from bromide **5d** and hydrolysis (acidolysis) of codeinone dimethyl ketal (**6c**) were studied in detail in the framework of the developed earlier procedure for the preparation of **2a** from codeinone (**6d**), which is readily available from **4a**.[7,8]

Ketal **6c** can be synthesized from bromide **5d** by both the prolonged refluxing with potassium *tert*-amylate in *tert*-amyl alcohol[7] and the action of Bu^{t}OK in DMSO at 60 °C.[8] Similar reaction of 8-[(1*E*)-2-phenylethenyl]-substituted bromide **5c** with Bu^{t}OK in DMSO proceeded at ambient temperature to give ketal **6a**.[6]

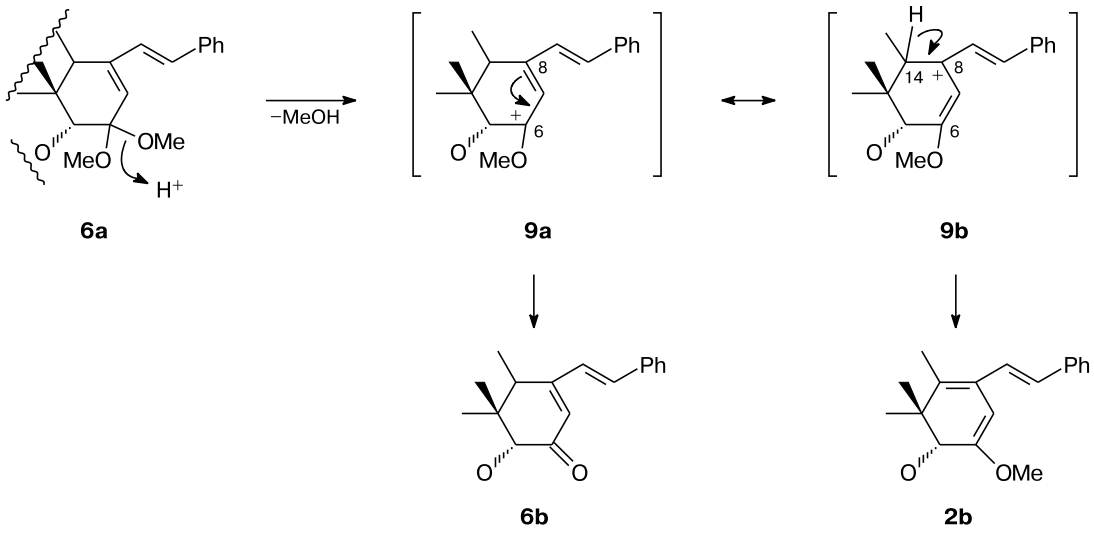
Reaction of bromide **5d** with Bu^{t}OK in DMSO at higher temperature (120 °C) afforded thebaine (**2a**) in nearly quantitative yield.[8] However, reaction of bromide **5c** with Bu^{t}OK under the same conditions resulted in a complex product mixture. Probably, these conditions is too severe for triene **2b**.

Thebaine (**2a**) is formed from dimethyl ketal **6c** under the action of $POCl_3$ in pyridine at 90 °C.[7] Diene **6a**, as it was mentioned above, readily afforded the corresponding derivative **2b** substituted at position 8 by refluxing in toluene.

Comparison of the results of hydrolysis of dimethyl ketals **6a** and **6c** provided even stronger evidence of the effect of the substituent at the C(8) atom. All attempts to synthesize compound **2a** by the acidolysis of dimethyl ketal **6c** were unsatisfactory from the practical point of view. The action of anhydrous TsOH and, conversely, aqueous acid (3 *M* AcOH) on dimethyl ketal **6c** resulted in ketone **6d** as the only product instead of **2a**. At the same time, hydrolysis of ketal **6c** by the action of TsOH with strictly controlled water content furnished the mixtures of compounds **2a** and **6d** in different ratios; besides, the maximum yield of **2a** (40%) was obtained in the presence of 3 mol.% of water.

In case of hydrolysis of ketal **6a**, the opposite pattern was observed. Hydrolysis of ketal **6a** in acetic acid gave triene **2b** (65%) as the main product; the yield of ketone **6b** was only 28%. Hydrolysis of ketal **6a** in 3.5% aqueous HCl afforded ketone **6b** in the yield of 75%, although, triene **2b** formed in significant amount (16%). However, preparative synthesis of **6b**, which is necessary for the synthesis of codeine **4b** substituted at the position 8 (see Ref. 6), requires the use of 20% aqueous HCl, under these conditions only traces of **2b** formed. These results can be explained as follows. According to the general mechanism of

Scheme 1



6a **9a** **9b**

6b **2b**

the ketal hydrolysis, in the acidic media, compound **6a** gives the C(6)-carbocation **9a**, which is prone to rearrangement into the C(8)-carbocation **9b** additionally stabilized by 8-[(1*E*)-2-phenylethenyl] moiety. In this case, formation of a mixture of two products is the result of the competitive processes of the nucleophilic attack of water on cation **9a** to give **6b** and the stabilization of cation **9b** by elimination of the proton from the position C(14) to give **2b** (Scheme 1). Possible attack of a water molecule on cation **9a** can be disregarded since it resulted in epimeric C(8) alcohols, which are, for the obvious reasons, in equilibrium with carbocation **9b** under acidic conditions of hydrolysis. In the case of ketal **6c**, which contains no substituent capable of addition stabilizing the carbocationic center at the C(8) atom, the formation of C(8)-cation analogous to **9b** is less favorable as compared with the corresponding C(6)-cation making the preparation of thebaine (**2a**) in preparative yields impossible.

In summary, the 8-[(1*E*)-2-phenylethenyl] moiety and, obviously, other substituents at the C(8) atom capable of effective π-conjugation can affect the chemical behavior of the codeinone and thebaine derivatives, which are the key intermediates in the synthesis of potent physiologically active compounds of orvinol and morphinone series.

Experimental

(5α,8β)-6,7-Didehydro-3,6-dimethoxy-17-methyl-8-[(1*E*)-2-phenylethenyl]-4,5-epoxymorphinan (8). To a solution of compound **5a** (2.67 g, 6.66 mmol) in anhydrous DMF (34 mL), NaH (0.40 g, 9.99 mmol, 60% dispersion in mineral oil) was added. The reaction mixture was stirred at ~20 °C until nearly clear solution was formed (20—30 min). The mixture was cooled to −10 °C, dimethyl sulfate (0.95 mL, 9.99 mmol) was added dropwise, and the reaction mixture was stirred at −5—0 °C for 1 h. Then the mixture was poured into the mixture of ice and 25% aqueous ammonia, stirred for 5 min, the products were extracted with diethyl ether (200 mL) with vigorous stirring for 30 min. The organic layer was separated, washed with water (2×100 mL), dried with Na_2SO_4, and the solvent was removed *in vacuo* to give compound **8** (2.25 g, purity ~95% according to the ^{1}H NMR data), foam, which crystallized at standing. The product can be used on the next steps without further purification. Analytically pure compound **8** was obtained by recrystallization from heptane—ethyl acetate (5 : 1), physicochemical characteristics and NMR ^{1}H spectra are identical to those given in literature.[6]

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