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Synthesis of the 6- and 7-Hydroxylated Cocaines and Pseudococaines

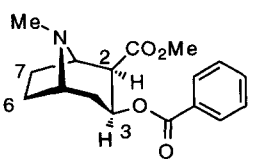
A. P. Kozikowski,*[a] D. Simoni,[b] S. Manfredini,[c] M. Roberti,[d] and J. Stoelwinder[e]

[a]Georgetown University Medical Center, Institute for Cognitive and Computational Sciences, 3970 Reservoir Road N. W., Washington, DC 20007-2197, [b]Istituto Farmacochimico, Università di Palermo, [c]Dipartimento di Scienze Farmaceutiche, Università di Ferrara, [d]Dipartimento di Scienze Farmaceutiche, Università di Bologna, Italy, and [e]Mayo Clinic Jacksonville, Jacksonville, Florida

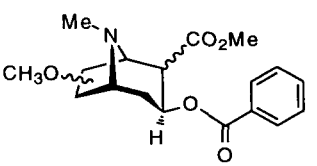
Abstract: In efforts aimed at further exploration of our finding that functionalization of the two-carbon bridge of cocaine can lead to a weak antagonist of cocaine, we report a route to the 6- and 7-hydroxylated analogues by use of the Willstätter synthesis. The hydroxylated derivatives can in principle be used to gain access to a diverse library of 6- and 7-functionalized cocaine analogues.

The tropane alkaloids comprise a group of over a hundred natural products occurring principally in the *Solanaceae* family.[1] Many of these natural alkaloids, such as atropine, anisodamine, scopolamine, anisodine, baogongteng A, and cocaine, bear some oxygen substituent on the tropane skeleton: hydroxy, epoxy, acetoxy, benzoyloxy, and other esters groups are frequently present at the C-2, C-3, and C-6 carbon atoms. While some of these natural products are of pharmacological interest and, in fact, clinically useful, cocaine in particular is currently the focus of intensive studies for reasons relating to both health and societal concerns. Specifically, the discovery of cocaine antagonists or partial agonists may offer a strategy in the quest to identify agents for the treatment of substance abuse.[2]

Results from our laboratory have demonstrated that methoxylation of cocaine's two-carbon bridge leads to compounds of pharmacological interest, for at least one of these methoxylated analogues was found capable of countering to a minor extent the effects of cocaine on dopamine reuptake.[3] This finding thus supports the idea that it may be possible to design a functional antagonist of cocaine through appropriate structural modifications of cocaine.[4]

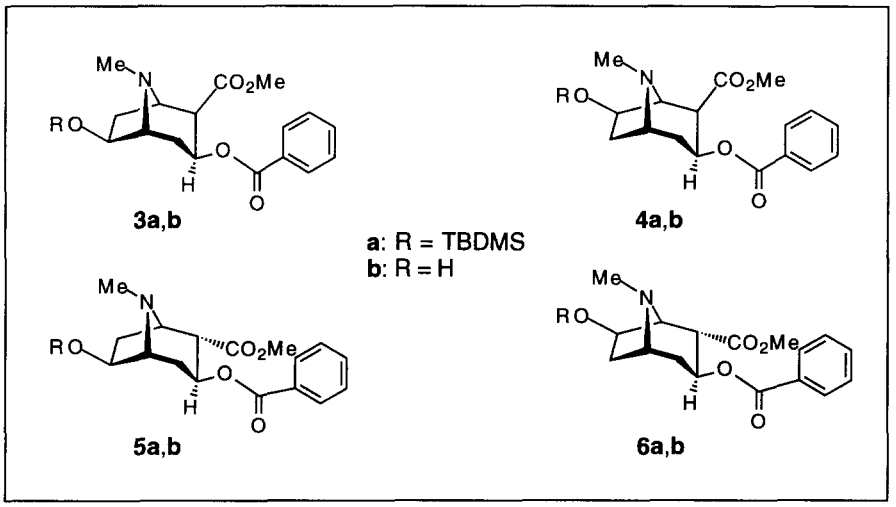


(-)-cocaine (**1**)



6- and 7-methoxylated cocaines and pseudococaines (**2**)

As a part of our continuing investigation aimed at exploring the biological effect of diverse modifications to the 6- and 7-positions of cocaine, we desired access to 6- and 7-hydroxylated cocaine analogues **3b** and **4b** as well as to their stereoisomers **5b** and **6b**. In spite of the fact that tropane alkaloids bearing oxygen substitution on the two-carbon bridge are well represented in nature, a search of the literature failed to reveal any general methodologies for the synthesis of the 6- and 7-hydroxylated cocaine derivatives. In this Letter we accordingly disclose a simple and regioselective preparation of 6- and 7-hydroxycocaines **3b** and **4b** and their pseudo-analogues **5b** and **6b**.



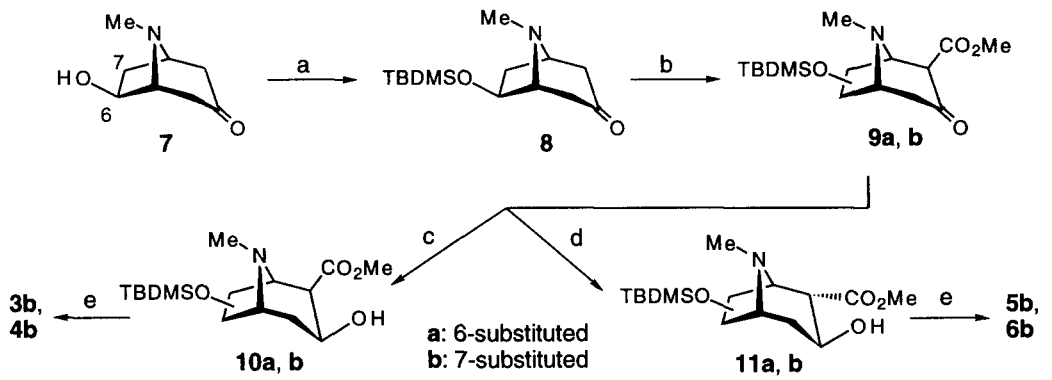
In our previous research on the methoxylated cocaine analogues, we demonstrated that chemistry developed nearly seven decades ago by Willstätter for the construction of cocaine itself could be used to gain access to these new structures.[3] Recently, we have also devised a methodology for procuring cocaine and its 6- and 7-methoxylated analogues in optically pure form by application of a PLE-catalyzed hydrolysis reaction to racemic cocaine and its analogues.[5] Accordingly, it appeared evident that ready access to the hydroxylated analogues **3b-6b** could be achieved by employing related chemistry. Specifically, simple demethylation of the already prepared methoxycocaines **2** was expected to yield **3b-6b**. Unfortunately, all attempts to perform the cleavage of the methyl ether group present in the starting methoxylated cocaines were unsuccessful, for the ester functions underwent cleavage more readily than the methyl group, thus producing inseparable mixtures.

Consequently, we devised an alternative methodology starting from the hydroxytropinone **7**, which is in turn easily transformed into the β-ketoesters **9a,b**, two promising precursors to the desired hydroxycocaines. Thus, compound **7** was prepared as described in the literature by using the classic Mannich type cyclization of acetonedicarboxylic acid with methylamine hydrochloride and 2-hydroxysuccindialdehyde in a citrate buffer solution.[6]

The hydroxytropinone **7** was protected as its *t*-butyldimethylsilyl ether, and intermediate **8** was then deprotonated with sodium hydride in the same manner as described by Carroll for tropinone.[7] The resulting

enolate was reacted with dimethyl carbonate to afford in 85% yield the corresponding carbomethoxylated derivatives **9a** and **9b** in a ratio of 45:55, respectively. Careful flash column chromatography allowed the separation of the two isomers. In view of the fact that the sodium amalgam reduction of 2-carbomethoxy-3-tropinone provides hitherto the best route to ecgonine methyl ester, the β-ketoesters **9a** and **9b** were reduced with sodium amalgam to generate the two alcohol derivatives **10a** and **10b** in yields of 17% and 23%, respectively. To prevent cleavage of the silyl protecting group, the pH of the reaction was carefully monitored using a pH meter supplied with a microelectrode. The reduction of the β-ketoesters **9a,b** was also attempted with sodium borohydride in methanol solution. After some experimentation aimed at optimizing the conditions so as to avoid cleavage of the TBDMS protecting group, the two pseudoecgonine methyl ester-like derivatives **11a** and **11b** were obtained in yields of 25% and 30%, respectively.

Scheme 1. Synthesis of the hydroxylated cocaine analogues.



Reagents: a) *tert*-butyldimethylsilyl chloride, imidazole, DMF; b) NaH, dimethyl carbonate; c) Na-Hg; d) $NaBH_4$, methanol; e) PhCOCl, DMAP; *n*-Bu_4NF.

Benzoylation of the β-hydroxy esters **10a,b** and **11a,b** was performed with benzoyl chloride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Finally, the TBDMS derivatives **3a-6a** were converted to the desired racemic alcohols **3b-6b** by reaction with tetra-*n*-butylammonium fluoride.

Structural assignments of the newly synthesized compounds **5b-6b** were based on ^1H and ^{13}C NMR analysis. Positions of all protons in the tropane ring were assigned on the basis of proton-decoupling experiments, starting from the diagnostic H-3 proton that appears as a multiplet in the 5.1-5.4 ppm region. Consequently, the H-6 and H-7 protons, linked to the hydroxy function, were easily attributed to the signal appearing in the 3.9-4.5 ppm region. The β stereochemistry of the hydroxy group in position 6 or 7 is based upon the identity of the starting hydroxytropinone **7** and was further confirmed by the lack of coupling between H-1/H-7 or H-5/H-6. A coupling constant of about 11 Hz between the H-2 and H-3 protons is diagnostic of the

pseudococaine-like structure; additionally, the ~3 Hz coupling between H-1 and H-2 further substantiates the *endo* stereochemistry of the carbomethoxy group.[8] These assignments were also corroborated by NOESY and COSY experiments and by comparison with other data on cocaine analogues previously reported by us.

In summation, the present work provides ready access to the 6- and 7-hydroxylated derivatives of cocaine. This methodology, when used in combination with our previously reported PLE-based method for achieving racemate resolution,[5] can thus be utilized in the creation of a diverse library of optically pure 6- and 7-substituted cocaine analogues through appropriate chemical manipulations of the OH group. These chemical studies and biological testing of the new cocaine derivatives reported herein will be published separately.

Acknowledgment. We are indebted to the National Institute on Drug Abuse for support of this work.

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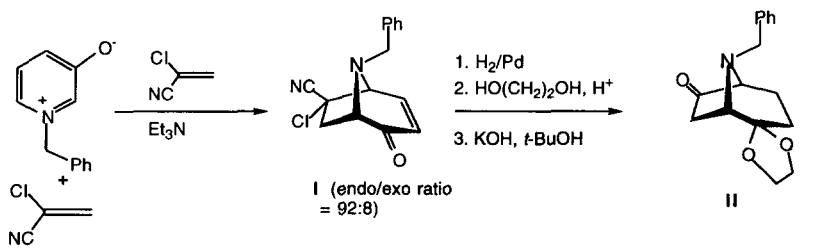
8. Spectral data for **5b** and **6b** follow: **5b**: oil; IR (film) 3450, 1740, 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71-1.95 (m, 2 H), 2.12-2.48 (m, 3 H), 2.64 (s, 3 H), 3.15 (dd, 1 H, *J* = 2.9, 11.1 Hz), 3.22 (m, 1 H), 3.59 (m, 1 H), 3.65 (s, 3 H), 4.33 (dd, 1 H, *J* = 2.1, 6.9 Hz), 5.35 (m, 1 H), 7.43 (m, 2 H), 7.55 (m, 1 H), 7.98 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.88, 34.47, 38.09, 43.42, 52.19, 61.53, 67.27, 67.86, 74.75, 128.41, 129.70, 130.16, 133.11, 165.57, 172.34.
6b: oil; IR (film) 3500, 1735, 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60-2.15 (m, 4 H), 2.35 (dd, 1 H, *J* = 7.4, 14.1 Hz), 2.61 (s, 3 H), 3.15 (dd, 1 H, *J* = 2.9, 10.9 Hz), 3.41 (m, 2 H), 3.67 (s, 3 H), 4.39 (dd, 1 H, *J* = 2.4 Hz, 7.2 Hz), 5.35 (m, 1 H), 7.42 (m, 2 H), 7.57 (m, 1 H), 7.98 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.58, 34.60, 41.15, 42.90, 52.27, 58.34, 67.97, 69.88, 72.27, 128.40, 129.67, 130.19, 133.07, 165.54, 172.35.
9. As another approach to the 6- and 7-functionalized analogues of cocaine and its Win derivatives, we note here that we have explored the "Katritzky-type " dipolar cycloaddition chemistry of 1-benzyl-3-oxidopyridinium with α-chloroacrylonitrile as dipolarophile to provide **I**, which has been further converted by standard chemistry to **II**. Additional details of this work will be reported separately.



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