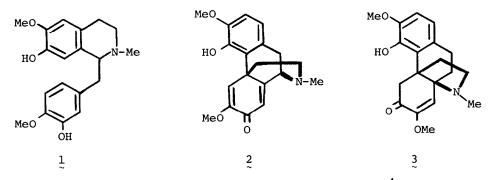
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SYNTHESIS OF MORPHINE ALKALOID ANALOGS. HASUBANANS AND 9,17-SECOMORPHINANS.¹

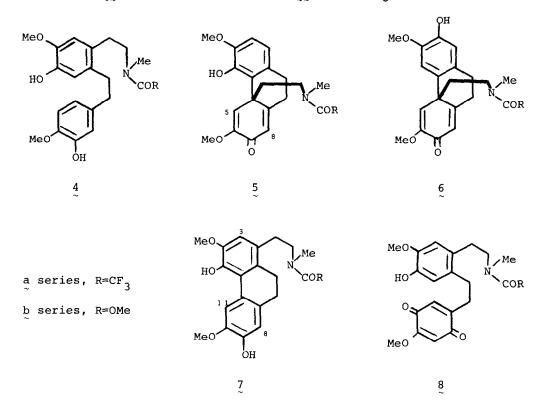
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Abstract: Oxidative coupling of N-trifluoroacetyl- and N-methoxycarbonylsecoreticulines with thallium(III) trifluoroacetate afforded the corresponding N-acylsecosalutaridines in 15-24% yield. The latter compounds were converted to alkaloids of the hasubanan and 9,17-secomorphine classes.

We have previously shown that the key step in morphine alkaloid biosynthesis, <u>para-ortho</u> oxidative coupling of reticuline (1) to salutaridine (2), can be mimicked in the laboratory in reasonable yield when thallium(III) trifluoroacetate (TTFA) is utilized as oxidant, thus affording an efficient synthetic approach to the morphine alkaloids.^{2,3} We wish now to report that TTFA mediated coupling of N-acylsecoreticuline derivatives yields the corresponding secosalutaridines, which serve as convenient precursors to hasubanan [<u>e.g.</u>, (±)-cepharamine (3)] and 9,17-secomorphinan derivatives.



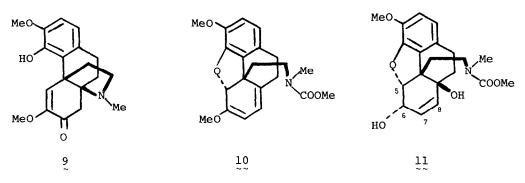
The N-trifluoroacetylsecoreticuline 4a (mp 94-95°; lit⁴, oil) was prepared⁴ in two steps from (±)-reticuline⁵ (1). Oxidation of 4a with 1 mol equiv of TTFA in anhydrous CH_2Cl_2 (~10⁻³M) at 25° for 2 hr afforded a 15% yield of N-trifluoroacetylsecosalutaridine (5a) [mp 174-175.5°; ir 5.90, 5.96, 6.08µ; nmr (CDCl₃) δ 7.30 (s, H-5), 6.74 (d, J=8.5), 6.64 (d, J=8.5), 6.35 (s, H-8)].^{6a} Also isolated from the coupling reaction were the secopallidine derivative 6a (3%; spectra in agreement with lit⁴), the secoisoboldine derivative 7a [5%, mp 140-141°; nmr (CDCl₃) δ 8.02 (s, H-11), 6.78 (s, H-8), 6.56 (s, H-3); m/e 425 (M⁺), 285 (base peak)],^{6a} the quinone 8a [10%; orange needles, mp 157-158°; nmr (CDCl₃) δ 6.70, 6.62, 6.47, 5.91; m/e 441 (M⁺), 153 (base peak)],^{6a} and recovered starting material 4a (33%). In contrast to these results, treatment of 4a with 3.5 mol equiv of VOCl₃ in $CH_2Cl_2(\sim 10^{-3}M; 2 hr at -78°, 1.5 hr at 25° and 1 hr at reflux) afforded$ $\frac{6a}{2}$ (45%), $\frac{7a}{2}$ (46%), and recovered $\frac{4a}{2}$ (5%), but no detectable amount of secosalutaridine 5a. Kametani and coworkers⁴ have similarly reported isolating only secopallidine 6a (26%) from oxidation of 4a with VOCl₃ in ether.⁷



The N-methoxycarbonylsecoreticuline 4b (mp 116-117°)^{6a} was prepared from 4a by hydrolysis and reacylation (K_2CO_3/CH_3OH , 25°, 12 hr; ClCOOCH $_3/(CH_3CH_2)_3N$, CHCl₃, 25°, 12 hr; 1% NaOH/CH $_3CH_2OH$, reflux, 1 hr; 96% overall). Analogous results were obtained upon coupling of 4b with TTFA under the same conditions as described for 4a. The desired secosalutaridine 5b (mp 200-202°)^{6a} was isolated in 24% yield, along with the corresponding secopallidine 6b (11%, oil),^{6b} secoisoboldine 7b (2%; oil),^{6b} quinone 8b (8%, mp 126-127°),^{6b} and recovered 4b (28%). Once again no secosalutaridine derivative could be detected upon oxidation of 4b with VOCl₃ under the conditions described above; isolated instead were 6b (51%), 7b (26%) and recovered 4b (10%).

The N-trifluoroacetyl group of dienone $\frac{4}{2}$ was hydrolized under mild conditions (K_2CO_3/CH_3OH , 25°, 2 hr) and the resulting amine underwent spontaneous cyclization to give a 75% yield of the hasubanan derivative 9 (picrate, ^{6a} mp 160-162°; lit, ⁸ picrate mp 156° dec). Enone 9 had been previously prepared in low

yield by photocyclization of a bromosecoreticuline derivative, and it has been converted by transetherification into (\pm) -cepharamine (3).⁸



Dienone 4b was reduced with NaBH₄ (CH₃OH, 25°, 1 hr) and the crude dienol was cyclized by sequential treatment⁹ with cold SOCl₂/pyridine followed by hot aqueous NaOH, to afford (±)-N-methoxycarbonyl-9,17-secothebaine (10) in 57% overall yield [mp 119-120°; nmr (CDCl₃) δ 6.59 (d, J=8.5), 6.55 (d, J=8.5), 5.51 (d, J=6, H-8), 5.50 (s, H-5), 5.00 (d, J=6, H-7); m/e 371 (M⁺), 282, 255, 116, 102 (base peak)].^{6a} All attempts to hydrolyze 10 to the corresponding secocodeinone derivative using methods developed¹⁰ for thebaine itself were unsuccessful. However, reaction of 10 with photochemically generated singlet oxygen (Rose Bengal, CHCl₃/CH₃OH, 12°) and immediate reduction of the crude product with NaBH₄ (CH₃OH, 25°, 15 min) gave (±)-N-methoxycarbonyl-14-hydroxy-9,17-secocodeine (11) in 40% yield [mp 149-150°; nmr (CDCl₃) δ 6.63 (d, J=8.5), 6.54 (d, J=8.5), 5.82 (br d, J=10, H-7), 5.54 (dd, J=10 and 3.5, H-8), 5.08 (m, H-5), 4.58 (m, H-6); m/e 375 (M⁺), 277, 276 (base peak), 244, 241].^{6b}

The stereochemistry assigned to 11 was confirmed by nmr decoupling experiments at 270 MHz. Successive irradiation of the signals assigned to H-7, H-8, and H-5 indicated that H-6 was axial and was coupled to four protons: vicinally coupled to the equatorial H-5 ($J_{5,6}$ =5.5 Hz), vicinally coupled to the vinyllic H-7 ($J_{6,7}$ =2 Hz), long-range coupled to the vinyllic H-8 ($J_{6,8}$ =3.5 Hz), and vicinally coupled to the adjacent OH (J=10 Hz). These values and assignments were in good agreement with those reported¹¹ for codeine and 14-hydroxycodeine.

The unique directing effect of Tl(III) for <u>para-ortho</u> oxidative coupling observed² in the reticuline system is thus extended to the seco derivatives, but somewhat surprisingly with little difference in either absolute or relative yields of the isomeric coupling products. The implications of these results in terms of the mode of action of TTFA in phenol coupling, as well as the extension of the method to the synthesis of other potentially useful morphine alkaloid analogs, are currently under study. Acknowledgement. This work was supported by Public Health Service Grant DA 01962 from the National Institute on Drug Abuse.

References and Notes

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