## Communications to the Editor

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# 1,6-DIHYDRO-3(2*H*)-PYRIDINONES AS SYNTHETIC INTERMEDIATES. STEREOSELECTIVE SYNTHESIS OF (±)-CORYNANTHEIDOL AND (±)-QUININE

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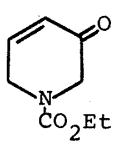
A new synthetic method is described for the *cis*-3,4-disubstituted piperidine compounds starting from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (1). Total synthesis of (±)-corynantheidol (3) and formal synthesis of (±)-quinine (4) were accomplished by an application of this method.

KEYWORDS —— dihydropyridinone; Claisen rearrangement; hydroboration-oxidation; oxymercuration-demercuration; *cis*-3,4-disubstituted piperidine; meroquinene; indole alkaloid; corynantheidol; quinine

Since the first preparation of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinone (1) was reported,[1] we have been demonstrating various alkaloid syntheses using the dihydropyridinone as a common synthon.[2] At present we are beginning to synthesize many alkaloids and related compounds bearing the *cis*-3,4-disubstituted piperidine moiety, e.g. reserpine, corynantheidine, and quinine, utilizing the same synthon. Here we wish to present a new method for construction of the piperidine (2) with functionalized *cis*-dialkyl pendants at 3- and 4-position, and its application to a new stereoselective synthesis of (±)-corynantheidol (3) and (±)-quinine (4).



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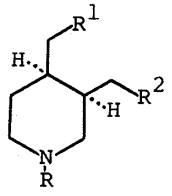

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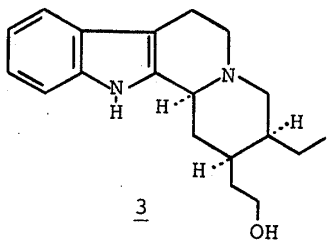

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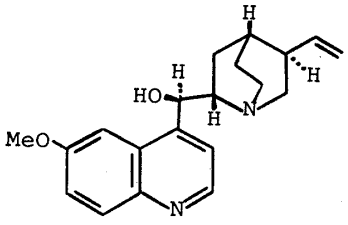

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It had been found that ethyl 3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (5) gave the 3-hydroxy compound (6) along with a small amount of the 4-hydroxy one (7) by the hydroboration-oxidation process.[2b] Oxymercuration-demercuration of 5, however, yielded an approximately equal amount of 6 and 7, and furthermore, epoxidation of 5 followed by reduction with diborane afforded 7 as a major isomer in 49% yield (see Table). Replacement of the nitrogen protective group of 7 from ethyl ester into benzyl ester was performed by basic hydrolysis and subsequent treatment with carbobenzoxy chloride, yielding 8 from 5 in overall yield of 32%. The compound 8 was also obtained in overall 36% yield by initial conversion of 5 into the benzyl urethane (10) *via* the amine (9) and subsequent epoxidation followed by reduction with diborane.

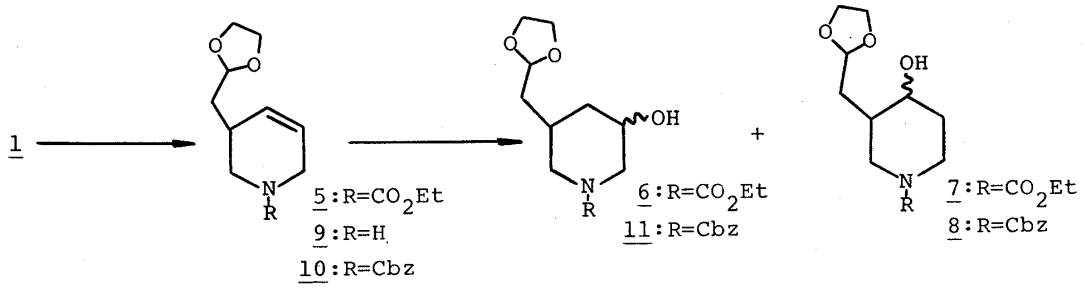
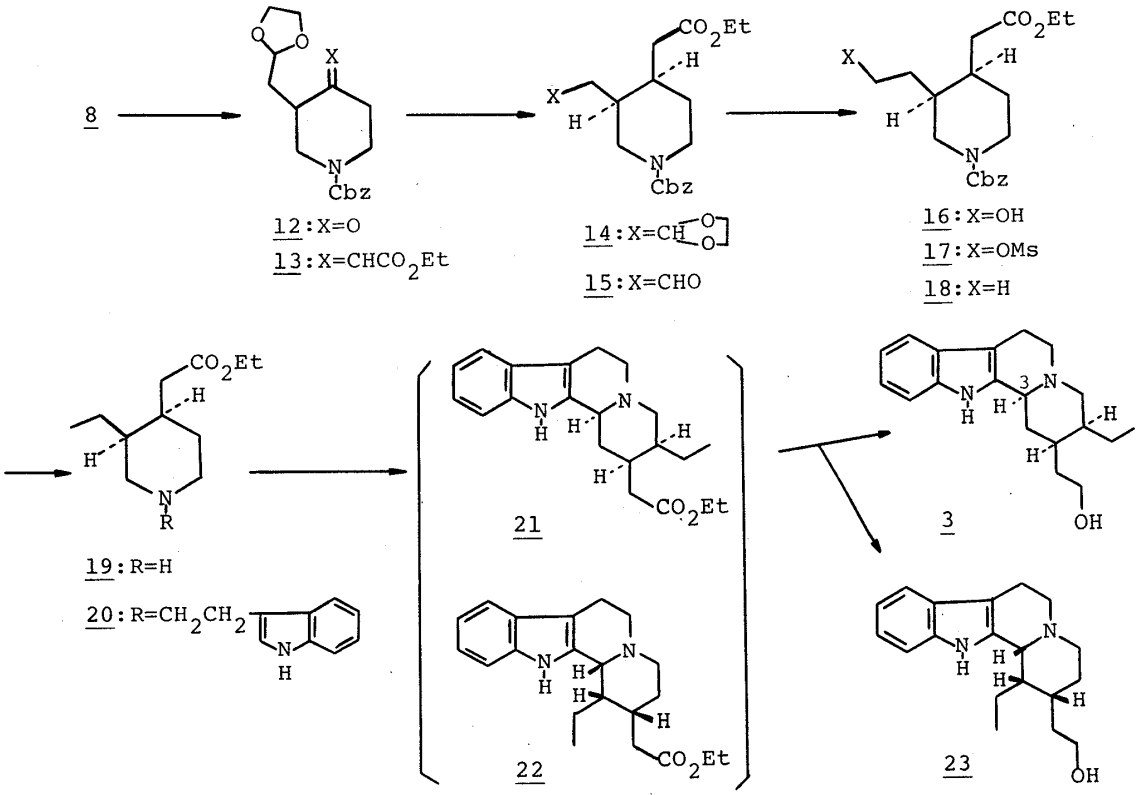



Table. Hydration of the Olefin (5) into 6 and 7

| Entry | Conditions | Products (%) 6 | 7 |
|---|---|---|---|
| 1[2b] | 1) $B_2H_6$/THF 0°C 3 h<br>2) $H_2O_2$, aq. NaOH 0°C 3 h | 52 | 13 |
| 2 | 1) $Hg(OAc)_2$/THF-$H_2O$ r.t. 13 h<br>2) $NaBH_4$, aq. NaOH r.t. 30 min | 40 | 38 |
| 3 | 1) MCPBA/$CH_2Cl_2$ r.t. 15 h<br>2) $B_2H_6$, $NaBH_4$/THF r.t. 3 h | 32 | 49 |

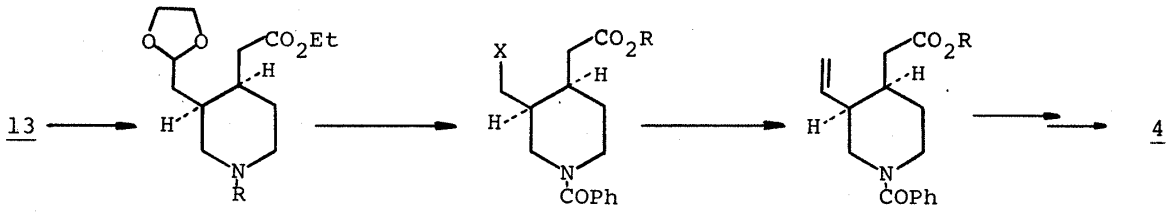
Oxidation of 8 with PCC[3] afforded the ketone (12), which was condensed with the ylid of triethyl phosphonoacetate in benzene to give the unsaturated ester (13) [60% yield from 8; mp 78-80°C]. Catalytic hydrogenation of 13 over platinum oxide in ethyl acetate gave the saturated ester (14) as a single stereoisomer in 93% yield. From the inspection of the Dreiding model it is clear that the hydrogenation proceeded exclusively from the side opposite to the adjacent bulky



substituent to give only the *cis*-3,4-disubstituted piperidine as depicted in 14. The acetal group of 14 was hydrolyzed with 1% hydrochloric acid in acetone to give the aldehyde (15), which was reduced with sodium borohydride in methanol into the alcohol (16) in 91% yield from 14. Mesylation of 16 followed by reduction with zinc-sodium iodide in boiling 1,2-dimethoxyethane[4] furnished 18 *via* 17 in 71% yield. Hydrogenolysis of 18 over 5% palladium on carbon in ethanol yielded the amine (19) [84% yield; ν 3300, 1720; δ 0.90 (3H, t, $J$ = 6 Hz), 1.23 (3H, t, $J$ = 7 Hz), 2.00 (1H, s), 2.23 (2H, d, $J$ = 1.5 Hz), 4.06 (2H, q, $J$ = 7 Hz)], which was found to be identical with (+)-cincholoipon ethyl ester[5] by means of TLC and IR comparison. In this stage the stereochemistry of the product (14) obtained on the hydrogenation of 13 was completely confirmed.

On condensation with tryptophyl bromide[6] in dioxane the secondary amine (19) was converted into the tertiary amine (20) in 88% yield. Oxidative cyclization[7] of 20 using mercuric acetate-EDTA·2Na and subsequent sodium borohydride reduction yielded an inseparable mixture of the cyclized products (21 and 22) in total 37% yield. The mixture was reduced with lithium aluminum hydride in ether to furnish (±)-corynantheidol (3) [52% yield; mp 162-164°C; ν 3470, 3300, 2790, 2730; δ 0.92 (3H, t, $J$ = 6 Hz), 3.75 (2H, t, $J$ = 7 Hz), 7.0-7.5 (4H), 7.88 (1H, br s); *m/e* 298 ($M^+$), 297 (base), 225, 184, 170] and its structural isomer[8] (23) [34% yield; mp 137-140°C; ν 3460, 3300, 2800, 2760; δ 0.83 (3H, t, $J$ = 7 Hz), 3.47 (1H, s), 3.78 (2H, t, $J$ = 7 Hz), 7.0-7.5 (4H), 7.59 (1H, br s); *m/e* 298 ($M^+$), 297 (base), 253, 197, 184, 170]. The synthetic (±)-corynantheidol was proved by the spectral comparison to be identical with the authentic sample.

On the other hand, hydrogenation of 13 over 5% palladium on carbon in ethanol gave the saturated amine (24) as a sole isomer in 78% yield. The benzamide (25), prepared in the usual manner from 24 in 99% yield, was subjected to an acidic hydrolysis to afford the aldehyde (26), which was reduced with sodium borohydride in ethanol to the alcohol (27) [97% yield from 24; ν 3400, 1720, 1615; δ 1.25 (3H, t, $J$ = 7 Hz), 2.03 (1H, s), 2.31 (2H, br), 4.13 (2H, q, $J$ = 7 Hz), 7.39 (5H, s); *m/e* 319 ($M^+$), 105 (base)]. Chlorination of 27 with phosphorus oxychloride in pyridine followed by basic hydrolysis provided the carboxylic acid (29) [79% yield; mp 110-114°C; ν 3600-2400, 1705, 1615; δ 2.27 (2H, br), 7.27 (5H, s), 9.91 (1H, s); *m/e* 309 ($M^+$), 105 (base)]. According to the known method,[9] 29 was converted into




24: R=H
25: R=COPh

26: R=Et, X=CHO
27: R=Et, X=$CH_2OH$
28: R=Et, X=$CH_2Cl$
29: R=H, X=$CH_2Cl$

30: R=H
31: R=Me

(±)-*N*-benzoylmeroquinene methyl ester (31) [56% yield; ν 1725, 1616; δ 2.26 (2H, br), 3.66 (3H, s), 4.9-5.2 (2H, m), 5.79 (1H, ddd, *J* = 16, 11, 9 Hz), 7.34 (5H, s); *m/e* 287 ($M^+$), 105 (base)], which was proved by TLC, IR, and $^1$H-NMR comparison to be identical with (+)-*N*-benzoylmeroquinene methyl ester.[10] Since the ester (31) has already been transformed into (±)-quinine (4),[11] the present synthesis of 31 constitutes a formal synthesis of (±)-quinine (4).

Thus, we have established a novel and stereoselective method for construction of the piperidine bearing functionalized alkyl substituents at the 3- and 4-positions with the *cis* relationship. By applying the method to alkaloid syntheses, (±)-corynantheidol (3) and (±)-quinine (4) have been synthesized. The successive synthetic studies on more complex alkaloids are now in progress.

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