FACILE PREPARATION OF TWO 5-(α-ACETOXYETHYL)-3-QUINUCLIDINONES VIA INTRAMOLECULAR FUNCTIONALIZATION ‡

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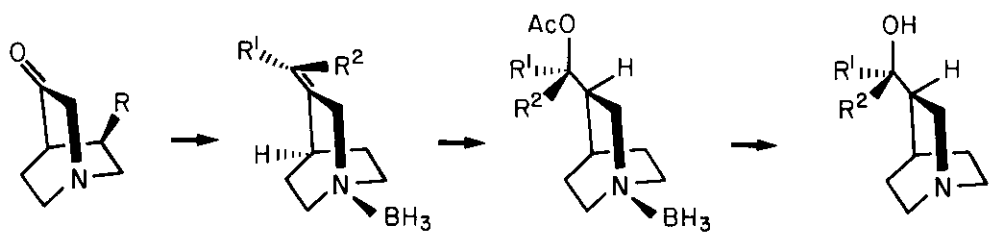
Abstract - Two title compounds with three adjacent chiral centers have been prepared as diastereomerically-pure racemates of known stereochemistry, suitable for use as synthetic intermediates in Cinchona alkaloid synthesis. Stereochemical control of C-4 in the quinuclidine skeleton was established using intramolecular attack by the C-3 substituent of stereoisomerically-pure threo or erythro 3-(α-hydroxyethyl)quinuclidine via Barton oxidation.

In the preceding communication, we defined two methodological requisites of a new synthetic strategy for completely stereocontrolled synthesis of Cinchona alkaloids having an intact quinuclidine ring system. As a consequence of that strategy, we undertook an extended synthetic investigation of quinuclidine systems, derivable from prochiral 3-quinuclidinone. We detailed several diastereocontrolled preparations of functionalized quinuclidines, utilizing quinuclidine-N-boranes as intermediates. These species allowed selective functionalization via N-protection and facilitated isolation/purification and characterization of products. Two useful intermediates were prepared, using diastereocontrolled methodology. Thus, in ~50% overall yield from 3-quinuclidinone (1 with R=H), threo and erythro 3-(α-hydroxyethyl)quinuclidine, (2a) and (2b) respectively, were obtained (Scheme 1), each as a diastereomer-pure material.



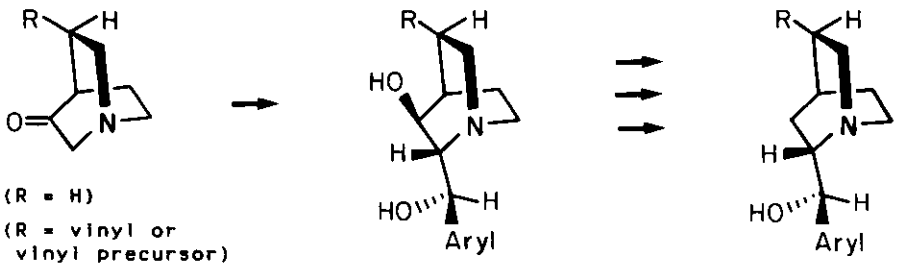
1 (R = H)

2a (R^1 = CH_3, R^2 = H)
2b (R^1 = H, R^2 = CH_3)

Scheme 1

‡ Dedicated to Gilbert Stork on the occasion of his sixty-fifth birthday

Recently, we reported[2] a successful model study of the kinetic, stereocontrolled construction of the C-8/C-9 bond of Cinchona alkaloids. The procedure established requisite erythro stereochemistry at these vicinal centers during bond formation. In the model study (Scheme 2), kinetic aldol condensation followed by in situ reduction of the intermediate β-ketoalkoxide were realized in a high yield preparation of erythro-2-(α-hydroxybenzyl)quinuclidine. 3-Quinuclidinone (1, where R = H) was used as enolate precursor and benzaldehyde as trapping electrophile. Application of the methodology to quinine synthesis would require 1 (R = vinyl or vinyl precursor), which is a 5-substituted 3-quinuclidinone (IUPAC numbering) or 3-substituted 7-quinuclidinone (quinine numbering).



1a (R = H)

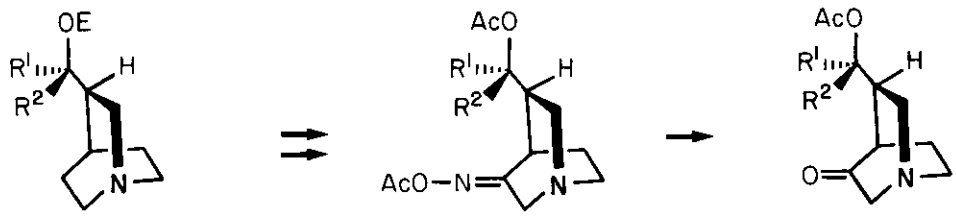
1b (R = vinyl or vinyl precursor)

Scheme 2

In the present communication, we report the facile, diastereocontrolled transformation of racemic compound 2a [or 2b] to the corresponding racemic title compound 5a [or 5b]. The relative stereochemistry at all centers of 5a and 5b is indicated in Scheme 3. We have used the C-3[3] α-hydroxyethyl group in compounds 2 to effect a selective intramolecular oxidation[4] of the bridge proximal to that C-3 substituent; only this bridge is capable of undergoing functionalization. (Note[3] that C-3 of compounds 2 corresponds to C-3 of quinine; after the intramolecular functionalization is completed, it is renumbered as C-5 in title compounds 5.) Our synthetic strategy for fixing the stereochemistry at carbon bridgehead C-4 is a communication of stereochemical information from C-3 to C-4. Thus, C-3 stereochemistry initially introduced at a prochiral center during preparation of 2 subsequently defines the bridgehead configuration during the conversion of 2 to 5. This strategy is a significant departure from classical synthetic methodology for constructing the quinuclidine part-structure of quinine. In the preceding communication, we noted serious limitations of a classical approach which employs synthesis of cis-3,4-disubstituted piperidines to establish relative stereochemistry at C-3/C-4[3] of quinine (corresponding to C-5/C-4[3] of the title compounds).

Alcohol 2a [or 2b] was converted to the corresponding nitrite ester 3a [or 3b], using methyllithium (1.1 equiv) followed by excess NOCl in THF at 0°C. The nitrite was isolated by partition between ether/aqueous $NaHCO_3$ and was used directly in the following Barton oxidation[4] sequence: the dried ethereal solution of 3a [or 3b] was diluted with dry toluene, ether was removed in vacuo, and benzene was added to make a solution (~10 mmol 3 : 50 ml of toluene : 150 ml of benzene) suitable for use in the next step. Photolysis of this solution was carried out at 4°C (450-watt Hanovia lamp with pyrex filter sleeve) until an aliquot showed no residual nitrite by ir (~3 h). The gummy precipitate was collected, the filtrates were concentrated

in vacuo, and the benzene-insoluble portion of the concentrate was combined with the original gummy precipitate. This material was washed with benzene, heated at reflux in isopropanol for 1 h, and isolated as an oily residue after evaporation of solvent and removal of residual volatiles at high vacuum. The resulting crude oxime-alcohol was acetylated using excess acetic anhydride/pyridine at 0-4°C for 18 h, and the expected diacetate was isolated after normal work-up. Solid 4a [or oily 4b] was obtained in 45-55% yield. Reductive cleavage of the O-acetyl-oximes afforded the corresponding ketones, using freshly prepared aqueous $TiCl_3$[5] (6 mole equiv) in acetone for 18 h at room temperature, with precipitation of TiO_2.[5] Aqueous K_2CO_3 was added until the solution was basic and the organic product isolated by extraction with CH_2Cl_2. Recrystallization from ether afforded 5a (mp 90-91°C) or 5b (mp 96-97°C) in ~40% overall yield from 2a or 2b, respectively.[6]



2a (R^1= CH_3, R^2= H, E = H)
2b (R^1= H, R^2= CH_3, E = H)
3a (R^1= CH_3, R^2= H, E = NO)
3b (R^1= H, R^2= CH_3, E = NO)

4a (R^1= CH_3, R^2= H)
4b (R^1= H, R^2= CH_3)

5a (R^1= CH_3, R^2= H)
5b (R^1= H, R^2= CH_3)

Scheme 3

It is expected that 5a, 5b, and/or materials derivable from them can be used in Scheme 2, as 1 (R = vinyl or vinyl precursor). As noted above, preparation of diastereomers 2 from prochiral precursors is compatible with complete stereocontrol (via enantioselection or resolution/recycling). Thus, formation of 5 by intramolecular functionalization of 2 completes this preliminary description of our strategy for a completely stereocontrolled synthesis of quinine.

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REFERENCES AND NOTES

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2. P.L. Stotter, M.D. Friedman, and D.E. Minter, J. Org. Chem., 1985, 50, 29.

3. Compounds 5 are correctly numbered 5-(α-acetoxyethyl)-3-quinuclidinones (using IUPAC nomenclature; this corresponds to 3-(α-acetoxyethyl)-7-quinuclidinones (using quinine numbering).

4a. Remote oxidations which involved heavy metal ions proved unsatisfactory, perhaps because of the excellent ligand properties of quinuclidines; little or no organic products could be recovered from final aqueous work-up using Ag_2O-Br_2 or $Pb(OAc)_4$; for which, see: R.A. Sneen and N.P. Matheny, J. Am. Chem. Soc., 1964, 86, 3906, 5503; M. Mihailovic and C. Cekovic, Synthesis, 1970, 209; and references cited therein.

4b. See, for example, D.H.R. Barton, J.M. Beaton, L.E. Geller, and M.M. Pechet, J. Am. Chem. Soc., 1960, 82, 2640; 1961, 83, 4076; D.H.R. Barton and J.M. Beaton, ibid., 1960, 82, 2641; 1961, 83, 4083; D.H.R. Barton, Pure Appl. Chem., 1968, 16, 1; R.H. Hesse, Adv. in Free Radical Chem., 1969, 3, 83, and references cited therein.

5a. A variety of different methods for oxime and/or O-acetyl-oxime cleavages were examined and proved unsatisfactory for these quinuclidinone derivatives: see, for example: C.H. DePuy and B.W. Ponder, J. Am. Chem. Soc., 1959, 81, 4629; Y. Yukawa, M. Sakai, and S. Suzuki, Bull. Chem. Soc., Japan, 1966, 39, 2266; S.H. Pines, J.M. Chemerda, and M.A. Kozlawski, J. Org. Chem., 1966, 31, 3446; R.E. Erickson, P.J. Andrulis, J.C. Collins, M.L. Lungli. and G.D. Muser, ibid., 1969, 34, 2961; E. J. Corey and J.E. Richman, J. Am. Chem. Soc., 1970, 92, 3276.

5b. Although not reported using O-acetyl-oximes as substrates, the $TiCl_3$ cleavage method for oximes proved very satisfactory: G.H. Timms and E. Wildsmith, Tetrahedron Lett., 1971, 195. [Considering the apparent difficulties we had encountered with metal complexes of quinuclidines,[4a] it is significant that titanium ions presented no complexation problems. We attribute the success of this reaction to the high affinity of Ti(IV) for oxygen and the very low solubility of the resulting TiO_2 precipitate.]

6. Yields and reaction conditions for conversions of 2 to 5 are not optimized.

7a. The analogous photolysis was also carried out using the nitrite derived from 2 (where R^1=R^2= H), 3-(hydroxymethyl)quinuclidine.[7b] Yields of crude oxime were substantially lower in this case than oximes derived from 2a and 2b. In all three cases, varying amounts of aromatic soluble materials were obtained, which appeared to contain the usual tetrahydrofuran by-products (tentatively assigned from nmr and physical properties). Aromatic soluble materials isolated from photolyses of compounds 2 also contained some methyl ketone (by nmr).

7b. When 3-(hydroxymethyl)quinuclidine was carried through the intramolecular functionalization scheme[7a] and the resulting 5-(acetoxymethyl)-3-quinuclidinone hydrolyzed, the isolated product was 5-(hydroxymethyl)-3-quinuclidinone,[7c] identical in all respects to a sample prepared by the method of Coffen.[7c]

7c. D.L. Coffen and T.E. McEntee, Jr., J. Chem. Soc., Chem. Commun., 1971, 539.

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