Bridged Quinuclidines: Synthesis of 5-Azatricyclo[3.2.1.$0^{2,7}$]octane. Incorporation of a Bridged Quinuclidine Into The Cinchona Alkaloid Skeleton [1a,†]

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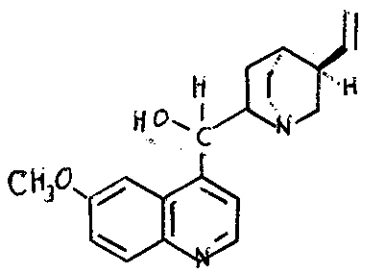
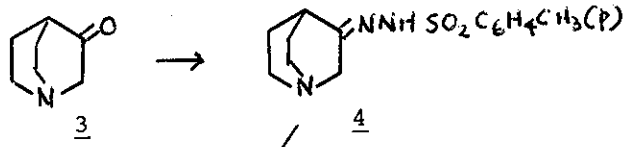
Incorporation of a bridged quinuclidine into the cinchona alkaloid skeleton is discussed.

More than twenty years after the completion of the synthesis of quinine (1) and quinidine (2) by Woodward and Doering,[2] a resurgence of interest in the chemistry of the Cinchona alkaloids has occurred and recently several new syntheses have been reported.[3] With the emergence of resistant strains of P. falciparum, the antimalarial activity of quinine and its analogues is becoming more important.[3] Therefore ,we were interested in synthesizing quinine analogue 20, incorporating a bridged quinuclidine moiety such as 5 in such a manner that the vinyl feature in the Cinchona alkaloids would be replaced by a carbon-carbon bridge at that site.

The parent novel tricyclo base ring system 5-azatricyclo[3.2.1.$0^{2,7}$]octane (5) was synthesized by transannular carbene insertion.[4] The readily available 3-quinuclidone was converted to tosylhydrazone 4 which was decomposed via the sodium salt by heating in ethylene glycol. It had been reported that under these conditions there was formed a mixture containing equal amounts



1 8(S),9(R)
2 8(R),9(S)



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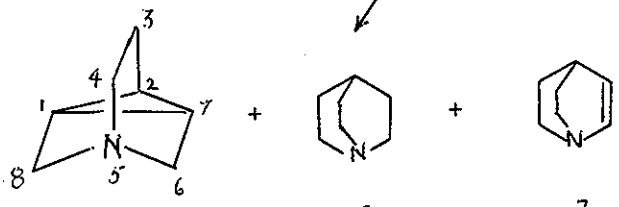

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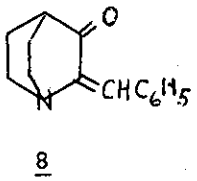

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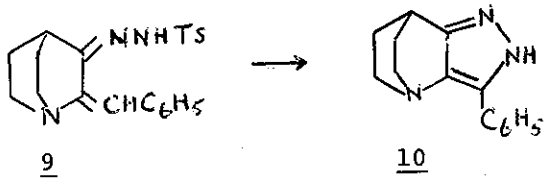

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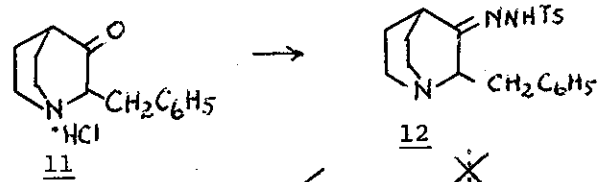
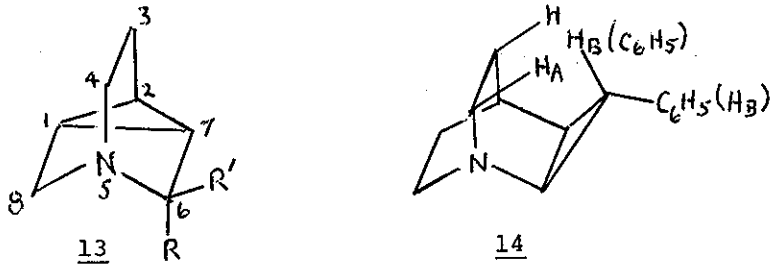


11 12



13 14

a) R = $CH_2C_6H_5$, R' = H

b) R = H, R' = $CH_2C_6H_5$

of quinuclidine (6) and dehydroquinuclidine (7).[5] However, we separated (vpc) a 12:2:1 mixture of bases 5, 6, and 7 respectively. Decomposition of the potassium salt prepared from 4 with potassium t-butoxide in refluxing diglyme gave a 9:1 mixture of 5 and 6 (69% combined yield). Isolation of 5 was facilitated with the oxalate salt, mp 168.5-170°,[6] from which the desired free base 5 was obtained as an hygroscopic, low melting, volatile solid; ν_{max}(neat) 3045 cm^{-1} (cyclopropyl CH); PMR (CCl_4,δ) 0.78 (tt, $J_{H_1H_2}$= 8 Hz, $J_{H_2H_7}$= 8 Hz, $J_{H_2H_3}$= 2.5 Hz, 1 H, H-2), 1.34 (broad d, $J_{H_1H_2}$ and $J_{H_2H_7}$ = 8 Hz, 2H, H-1 and H-7), 1.71 (m, 2H, H-3), 2.50-2.85 (complex m, 6H, CH_2N); picrate, mp 286-289°(dec.).[6]

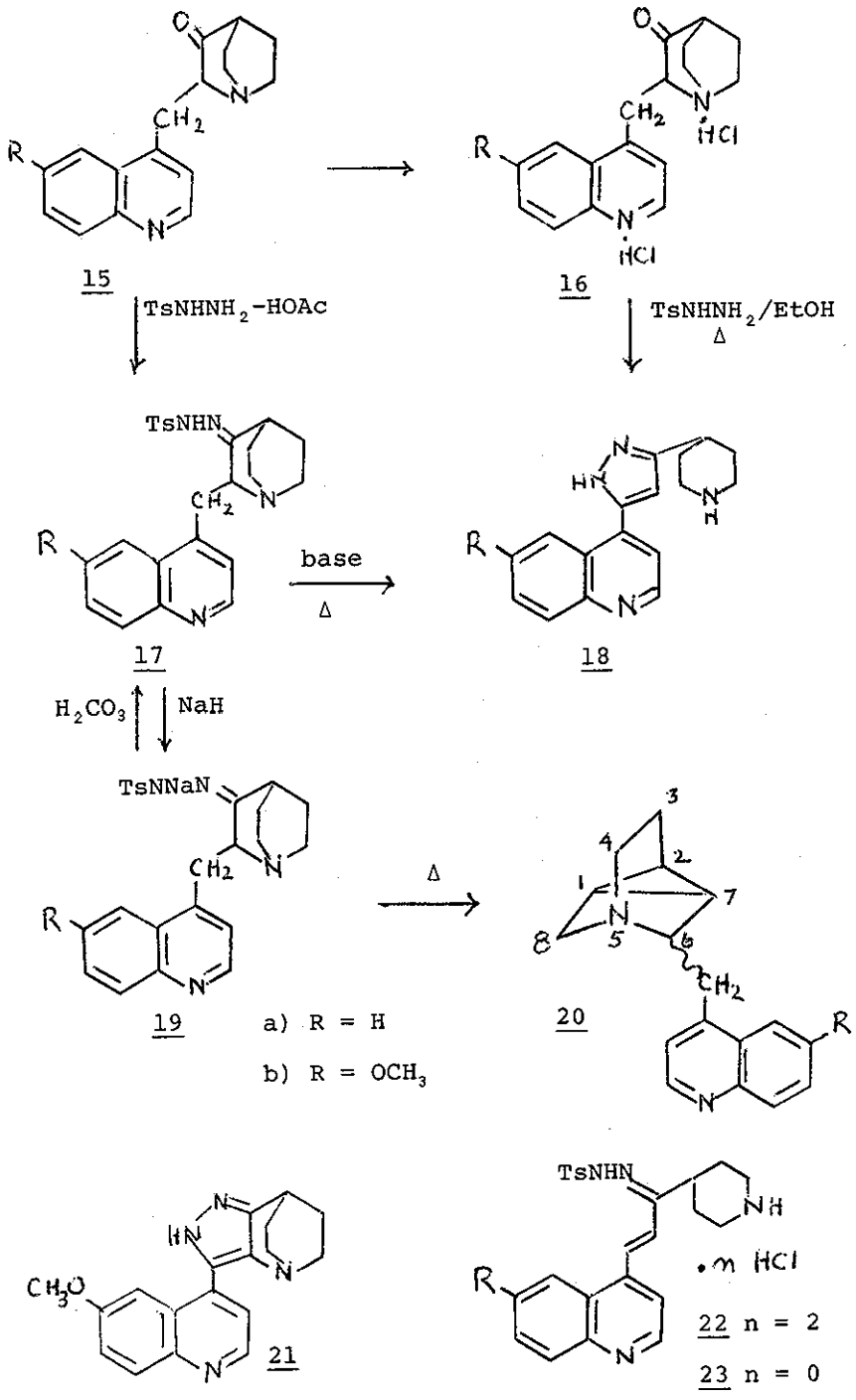
Although the carbene derived from 4 was conveniently effective for synthesis of the parent ring system, derivatives substituted alpha to the carbene center present yet another potential site for insertion. Therefore, decomposition of α-benzylidine and α-benzyl-tosylhydrazones 9 and 11 was investigated. 2-Benzylidine-3-quinuclidone 8 [7] was converted into tosylhydrazone 9, mp 218-219°(dec), decomposition of which (potassium t-butoxide, refluxing diglyme) led not to transannular insertion but to pyrazole 10 (60%) isolated as an etherate, mp 179.5-180.5°; M^+, m/e 225 ($C_{14}H_{15}N_3$ = 225). The intermediacy of a diazoalkane in this cyclization is suggested by previous observations [8] on the formation of 3(5)-phenylpyrazole from cinnamaldehyde benzenesulfonylhydrazone.

Hence, the α,β-unsaturated ketone 8 was catalytically reduced [7] and converted to hydrochloride 11, mp 168.5-174°(dec); ν_{max}(nujol) 2425 (broad, NH^+), 1740 cm^{-1}(C=O) as the necessary

precursor to tosylhydrazone 12, mp 156-157°(dec)[6], (prevention of base induced decomposition during tosylhydrazone formation). Decomposition of 12 as for the formation of 5 produced azatricyclooctane 13 in a mixture containing two dehydroquinuclidines. Silica gel chromatography afforded 13 as an oil (42% yield): ν_{max} (neat) 3075(sh), 3050(sh), 3020 cm^{-1}; PMR (CCl_4, δ) 0.82 (tt, $J_{H_1H_2}$= 8 Hz, $J_{H^2H^7}$ = 8 Hz, $J_{H^2H^3}$ = 3Hz, 1 H, H-2), 1.34 (broad doublet, $J_{H^1H^2}$ and $J_{H^2H^7}$ = 8 Hz, 2 H, H-1 and H-7), 1.42-1.77 (m, 2 H, H-3), 2.25 (q, 1 H, J_{gem}= 13.5 Hz, J_{vic}= 8 Hz, benzylic CH), 2.62 (q, J_{gem}= 13.5 Hz, J_{vic} = 6 Hz, benzylic CH), 2.6-3.0 (complex m, two CH_2N's), 2.96 (q, J_{vic}= 8 Hz, J_{vic}=6 Hz, H-6), 7.05 (m, 5 H, aromatic); M^+, m/e 199 ($C_{14}H_{17}N$ = 199); picrate, mp 166.5-167.5°[6]. Assignment of the proton resonances in 13 was corroborated by spin decoupling. Irradiation of the H-2 multiplet at 0.82 ppm collapsed the broad H-1 - H-7 doublet at 1.34 ppm, and the vicinal couplings of the benzylic proton quartets at 2.25 ppm and 2.62 ppm collapsed upon irradiation of the H-6 quartet at 2.96 ppm. Compound 13 appeared to be only one isomer, 13a or 13b, by TLC, VPC, and PMR, but as yet it has not been possible to ascertain the C-6 configuration with certainty. However, by comparison with previous observations on several substituted tricyclo[3.2.1.$0^{2,7}$]octane systems, the lack of coupling between H-6 and H-7 is strongly suggestive of the endo-7-benzyl structure 13a (exo C-6 H).[9,10] The formation of 13a may thence be rationalized on the basis that steric interactions (less on endo side) developing during the transition state may be responsible for giving the thermodynamically stable endo isomer.[10]

Cyclopropano-quinuclidine 14 which would have resulted from carbene insertion into the benzylic C-H bonds was not isolated from the reaction mixture. As is evident in a molecular model of the carbene, the two benzylic protons can achieve the same attitude and distance relative to the carbenic center as the two nearest syn transannular protons. However it is apparent that steric interactions bewtween H_A and H_B or the phenyl ring (see structure 14) would develop during the insertion process to inhibit the formation of 14.

Our investigations were extended to the synthesis of the analogous rubane systems 20. 3-Quinuclidones 15a [11] and 15b (mp 71.5-74°)[12] as hydrochloride salts 16 on treatment with p-toluenesulfonehydrazide (refluxing ethanol/water) did not yield the expected hydrazones 17 but rather pyrazoles 18a (35%), mp 261-263° (dec)[6], PMR(D_2O-DCl, internal standard DSS, δ) 6.67 (s, 1 H, pyrazole CH); λ_{max}^{EtOH} 231.5 (ε 34,400), 309 (ε 10,400) 315 nm (sh, ε 8,800); M^+, m/e 278 ($C_{17}H_{18}N_4$= 278), and 18b (22%), mp 231.5-232.5°[6]; λ_{max}^{EtOH} 205 (ε 25,700), 234 (ε 30,000), 300 (ε 6400) 338 nm (ε 6,300). The uv absorption of 18b shows a close similarity with that of the fused ring system 21; λ_{max}^{EtOH} 206 (ε 26,000), 233 (ε 34,000), 302 (ε 7,000), 338 nm (ε 7,400).[13] Formation of 18 was circumvented (15, p-toluenesulfonehydrazide, one equivalent acetic acid, two days at room temp.), and 17a (86%), mp 166.5-167.5°(dec) and 17b (80%), mp 165-166° (dec) were made available. Refluxing the rubane tosylhydrazones 17 in 10% aqueous potassium hydroxide also produced pyrazoles 18a (80%) and 18b (71%). Formation of the pyrazole ring system under both acidic


15
16
TsNHNH2-HOAc
TsNHNH2/EtOH
Δ
17
18
base
Δ
H2CO3
NaH
19
a) R = H
b) R = OCH3
20
21
22 n = 2
23 n = 0

and basic conditions probably proceeds through α,β-unsaturated tosylhydrazones 22 and 23, which decompose to 18 by cyclization-elimimination (or vice versa). The reaction is related to the well known rearrangement of the Cinchona alkaloids to toxines.[14]

Only by the decomposition of the dry sodium salts 19a,b (17 plus NaH) was it possible to obtain the desired bridged-quinuclidine rubanes 20a,b. Heating 19a as a dry powder at 310-320° gave the rubane 20a as an oil: ν_{max}(neat) 3030, 3010 cm^{-1}(sh); PMR ($CDCl_3$,δ) 0.91 (tt, $J_{H^1H^2}$=8 Hz, $J_{H^2H^7}$= 8 Hz, $J_{H^2H^3}$= 2.5 Hz, 1 H, H-2), 1.15-1.75 (complex m, 4 H, H-1, H-3, and H-7), 2.70-3.42 (complex m, 7H, CHN, 2 CH_2N's, and CH_2Ar), 7.23 (d, J=4.5 Hz, 1 H, aromatic H), 7.43-8.22 (complex m, 4 H, aromatic H), 8.73 (d, 1 H, J=4.5, aromatic H); M^+, m/e 250 ($C_{17}H_{18}N_2$ = 250). Decomposition of sodium salt 19b in refluxing diglyme gave rubane 20b (91%); mp 106.5-109°; M^+, m/e 280.1574 ($C_{18}H_{20}N_2O$ = 280.1576).

At this time the stereochemistry at C-6 in 20a,b has not been ascertained, because the PMR spectrum does not lend itself to such an analysis as was the case for 13a. But if the same factors and forces are operative here as in the benzyl substituted case 13a (vide supra), and it seems reasonable that they would be, then the endo configuration for the quinoline moieties (exo C6-H) would seem to be a palpable proposal for the structures 20a,b.

Also, during the decomposition of 17 dehydrorubanes are formed as evidenced by PMR, but these products were not investigated further.

We have succeeded in introducing the 5-azatricyclooctane

ring system 5 into the Cinchona alkaloid skeleton by remote functionalization. Currently, the introduction of an hydroxyl function at C-9 in 20 is under investigation using oxidative methods developed for the synthesis of the Cinchona alkaloids.[3)]

References

† Dedicated to Professor R. B. Woodward for his sixtieth birthday.

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