SYNTHESIS OF NEW CINCHONA AND QUININE ANALOGS[+]

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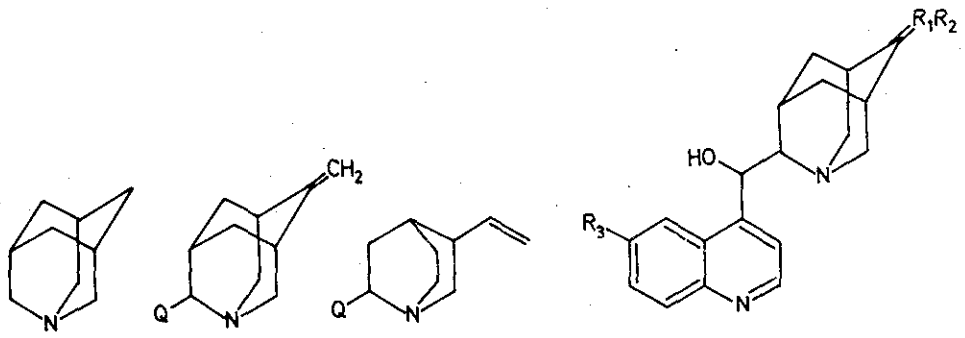
The total synthesis of quinine analogs 4a and 4b is described. The quinuclidine part in the naturally occurring compound has been replaced by the 1-aza-adamantane nucleus.

As part of a programme directed towards a rational total synthesis[1] of 1-aza-adamantanes several alkaloid analogs were prepared. Direct interest in this type of compound emerged from a consideration of the biological significance of quinuclidine[2] and the chemical curiosity of the adamantane[3] molecule. The result of a happy marriage between the two can be formally seen in the construction of 1-aza-adamantane 1. Members of the latter class of compounds also show interesting physicochemical behaviour.[4]

Comparison of 4-methylene-1-aza-adamantane 2 (Q=H) and the quinuclidine part of quinine 3 (Q=H) revealed a close correspondence between both structures. In view of the interesting biological properties of 1-amino-adamantanes the total synthesis of 4a was investigated. As a model compound the synthesis of the cinchona analog 5 was undertaken.

Starting from the readily available[5] aldehyde 7 a condensation

[+] Part VI in the series 1-Aza-adamantanes; for part V see ref.4.

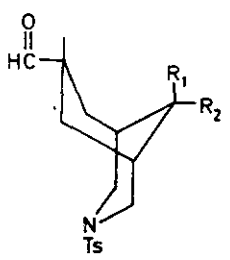


1 2 3

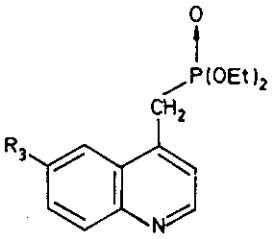
4 a $R_1R_2=CH_2$, $R_3=OCH_3$
b $R_1R_2=CH_2$, $R_3=H$
5 $R_1=R_2=R_3=H$
6 $R_1R_2=O$, $R_3=H$

of a modified quinoline derivative with 7 appeared obvious. The phosphonate 10 (1.1 eq DME), prepared from 4-chloromethyl-quinoline via coupling with the sodium salt of diethyl phosphite,[6] was converted to its Li salt by addition of n-BuLi (1.05 eq in DME) under argon at r.t., after which the aldehyde 7 (1.0 eq) was added. In view of the facile endo→exo isomerization of the $-\overset{H}{C}=O$ substituent in 7 and of the unstable character of the phosphonate anion of 10 the whole procedure had to be carried out in 20 min, after which 12 [mp 174-176°C ($J_{H_{10},H_{11}}$ = 16 Hz)] was obtained in 84% yield.[7] Conversion of 12 into the epoxide 15 proceeded quantitatively; however, neither the anticipated ring opening[8] under mildly acidic conditions nor a reductive cyclisation (sodium bis-(2-methoxy-ethoxy)aluminium hydride) could be effected. Refluxing 12 with (conc) HCl/acetic acid (1:1) afforded the cyclized material 16 in 89% yield, which according to the procedure[9] of

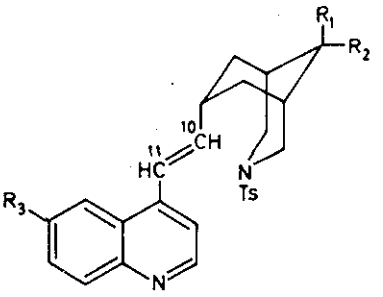
Uskoković[+] was converted into the OH-derivative 5 and obtained as a single stereo-isomer in 60% yield (pmr ($CDCl_3$) δ C<u>H</u>OH 5.83 d (J=7·5 Hz)).



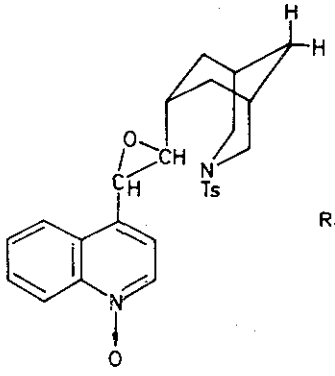
7 $R_1=R_2=H$
8 $R_1R_2=$ (-SCH_2CH_2S-)
9 $R_1=R_2=OCH_3$



10 $R_3=H$
11 $R_3=OCH_3$



12 $R_1=R_2=R_3=H$
13 $R_1=R_2=OCH_3$, $R_3=H$
14 $R_1=R_2=R_3=OCH_3$



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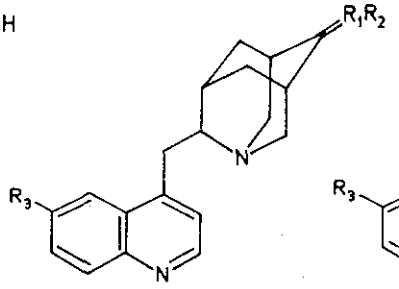
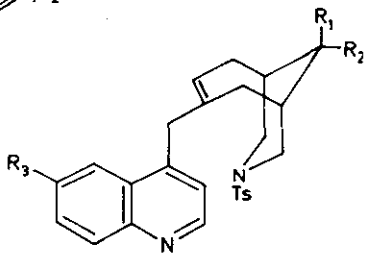


16 $R_1=R_2=R_3=H$
17 $R_1R_2=O$, $R_3=H$
18 $R_1R_2=O$, $R_3=OCH_3$
19 $R_1R_2=CH_2$, $R_3=H$
20 $R_1R_2=CH_2$, $R_3=OCH_3$



21 $R_1R_2=O$, $R_3=H$
22 $R_1R_2=O$, $R_3=OCH_3$
23 $R_1=R_2=OCH_3$, $R_3=H$

[+] We express our sincere gratitude to dr. M. Uskoković for communicating experimental details of the oxidation procedure prior to publication.

The successful conclusion of this reaction sequence prompted further exploration. Although it was possible to condense aldehyde 8 with the anion of 10 to the corresponding adduct (40% yield) a more attractive route was found by similarly reacting the corresponding aldehyde 9[10] to yield 13 (76%) [mp 180-183°C ($J_{H_{10},H_{11}}$ = 16 Hz)]. Ring closure (HCl-acetic acid 1:1, reflux), however, afforded only a small yield (8%) of the expected aza-adamantane 17 and a 43% yield of the rearranged aza-bicyclo[3,4,1]decene derivative 21 [mp 185-187°C, pmr ($CDCl_3$) δ 5·84 d (J=6 Hz)=CH]. The position of the double bond was established from the following pmr evidence: (i) no signals below δ=2·5 (ii) the appearance of the spectrum, especially the absorption of the N-CH_2 signals, strongly indicated a symmetric structure. Presumably an endo→ exo acid-catalyzed isomerization of the vinylquinoline moiety is taking place in 13 thereby rendering the ring closure impossible and thus favouring rearrangement of the protonated C=C bond. However, when the cyclization was carried out in CH_3OH/HCl no rearrangement was observed and the desired ketone 17 was obtained in 83% yield, [mp 149-151°C, pmr ($CDCl_3$) δ 3·52 s (ArCH_2)]. Although direct introduction of the 11-OH function via treatment with KO^{t}Bu-O_2-DMSO proceeded smoothly to afford 6 (pmr ($CDCl_3$) δ CHOH 5·80 d (J=8·5 Hz)), experimentally it proved to be easier to react 17 first with triphenyl methylphosphorane to afford 19 as an oil in 92% yield (pmr C_6D_6 δ 3.01 s (ArCH_2)) and then oxidize the latter compound to 4b [mp 163-165°C, pmr ($CDCl_3$) δ 5.74 CHOH d(J=8.5 Hz)] in 81% yield. This reaction sequence constitutes a total synthesis of new cinchona analogue.

In a similar fashion aldehyde 9 was condensed with phosphonate 11. The latter material was prepared from 6-methoxylepidine via SeO_2 oxidation (- $\overset{H}{C}$ = O), reduction with formaldehyde/KOH[11] ($-CH_2OH$), $SOCl_2/CHCl_3$ chlorination ($-CH_2Cl$) and reaction with $NaOP(OEt)_2$. Unexpectedly the adduct 14 [181-183°C, ($J_{H_{10},H_{11}}$ = 16 Hz)], obtained in 75% yield, underwent mainly rearrangement to 22 (55% yield), mp 216-218°C, upon treatment with MeOH-HCl at reflux while the cyclized product 18 was formed only in 33% yield.

However, after maintaining the reaction temperature at 34°C for 40 h, 18 was obtained in 85%, mp 134-136°C. Under these circumstances the rearrangement 14→22 was not observed. A variety of other acidic conditions to investigate this behaviour, for instance, reaction of 13 with p-TsOH (anh.)/C_6H_6 produced 23, mp 85-112°C (dec), did not lead to satisfactory results. Either decomposition occurred or the rearranged product was formed.[12]

Finally 18 was converted into the methylene derivative 20, (78% yield), [mp 117-119°C, pmr ($CDCl_3$) δ 3·37 s ($Ar\underline{CH}_2$)] and the latter compound oxidized to the quinine analogue 4a in 80% yield. According to pmr two isomers were formed. Separation on TLC, (Al_2O_3-CH_3CN) gave the major isomer [mp 191-194°C, pmr ($CDCl_3$) δ $C\underline{H}OH$ 5·60 d (J=7 Hz)].

Although the pmr-spectral data showed strong resemblance with those of cinchonine and quinine, in particular δ and J values recorded for $J_{C\underline{H},OH}$ the available spectroscopic data were not considered sufficient for a definite stereochemical assignment. A comparison of the solvent shifts did not add unequivocal evidence to settle this question. Further studies including X-ray analysis

and separation of optical isomers will therefore be pursued.

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12 Further studies on this interesting rearrangement will be published separately.

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