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Rearrangement of quinine in superacid: an efficient access to a novel chiral heterocyclic system

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Abstract—In superacid, quinine rearranges to yield a novel oxazapolycyclic compound.

We have previously reported novel and selective reactions carried out in superacid HF–SbF_5 on various polyfunctional natural products.[1] Under these superacidic conditions the substrates being (poly)protonated, their reactivity is dramatically modified when compared to what is observed in conventional acids. Reactivity of terpenoids and alkaloids in superacids is well documented.[2,3] The high acidity of the medium and its low nucleophilicity limit secondary processes to yield compounds that are not formed in usual acids.

Cinchona alkaloids quinine and quinidine are known to be cleaved in acetic acid to yield quinicine (Fig. 1).[4]

We would like to report in this paper a novel rearrangement of quinine in superacid.

Results

The experimental procedure is as follows: to a mixture of HF–SbF_5 (45 mL, 7:1 molar ratio) maintained at −30°C in Teflon® flask was added quinine hydrochloride **1**-HCl (1.377 g, 3.81 mmol). The mixture was magnetically stirred at the same temperature for 5 min. After usual work-up, flash-chromatography over silica gel, yielded compound **2** (1.099g, 89%) (Fig. 1). Mass spectroscopy of compound **2** shows that the molecular weight (324) is identical to that of quinine. Determination of structure and conformation of compound **2** was made by extensive NMR analysis. In summary, ^1H and ^{13}C resonances were assigned from DEPT, COSY, NOESY, HMQC and HMBC data.[5]

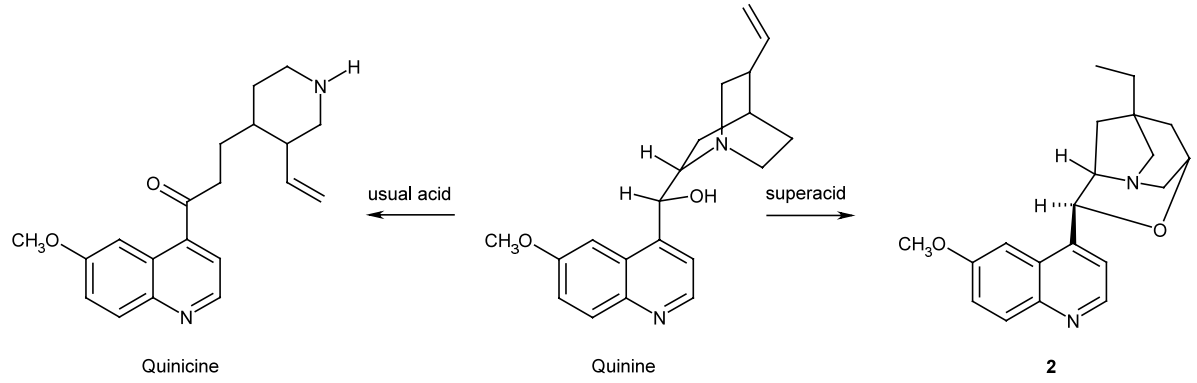

Figure 1.

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Whereas the quinoline moiety appears not to be modified, when compared to quinine, significant changes are observed in upper part in ^{1}H and ^{13}C NMR of compound **2**:

– disappearance of vinylic protons and presence of an ethyl group bounded to a quaternary carbon.
– five carbon atoms (2 CH_2, 3 CH) are bearing an heteroatom (not including the methoxy group), besides three additional CH_2.

Long range couplings have been observed between H_{2a}–H_{9b}, H_{2b}–H_{10a}, H_{7b}–H_{9a}, H_{9a}–H_{10b} and NOE interactions as indicated in Fig. 2.

It should be pointed out that NOE between $H_{3'}$ and H_{2b} and between $H_{5'}$ and H_3 and H_4 favor an *anti* conformation, with the 6′-methoxy quinoline in horizontal position due to the reduced rotation mobility about $C_{4'}$–C_4 single bond as indicated.[6]

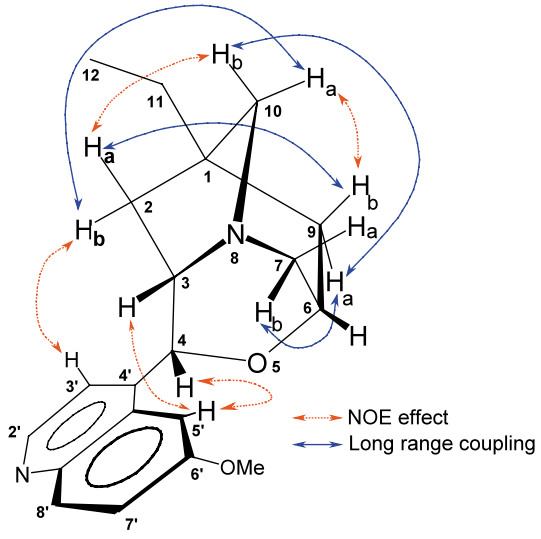


Figure 2.

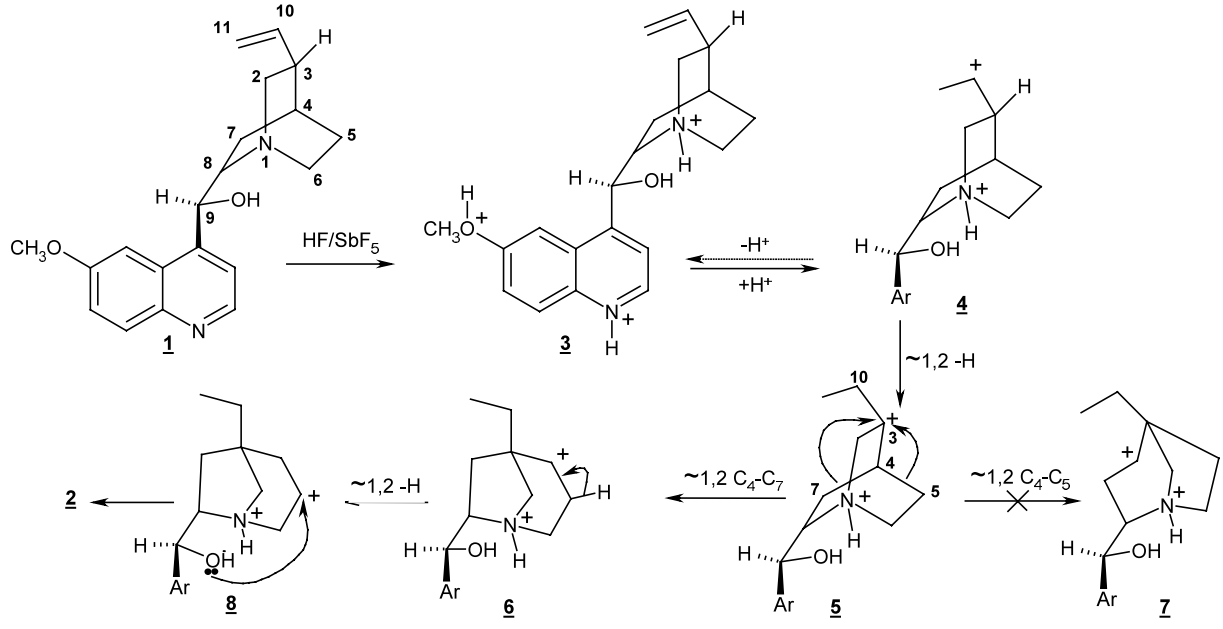
The structure of compound **2** has been confirmed by X-ray analysis.

Reaction mechanism

It should be pointed out that in the reaction conditions, quinine **1** is polyprotonated to yield ion **3**:

– diprotonation of quinoline moiety at nitrogen and at oxygen atom, thus minimizing the interaction of the two positive charges. As a result, this diprotonation disfavors formation of the benzylic ion by dehydration of the protonated hydroxyle (probably in equilibrium with neutral form).
– *N*-protonation of the quinuclidyl group.
– This following mechanism may be operative to explain the formation of compound **2** (Scheme 1).
– Protonation of the C_{10}–C_{11} double bond yields ion **4**. A mechanism (**4→5→6→8**), implying a 1, 2 hydride shift from C_3 to C_{10}, concerted with the migration of C_4–C_7 carbon bond to C_3, followed by a 1, 2 hydride shift, gives ion **8**, which is trapped by the neutral hydroxyl group to give ether **2**.
– A non-concerted rearrangement might yield either ion **6** or ion **7**, the latter would lead to a product which is not observed in the reaction.

Cinchona alkaloids and derivatives have been reported as catalysts or (co)catalysts in a variety of enantioselective reactions: hydrogenation,[7] fluorination,[8] dihydroxylation[9] and desymmetrization of prochiral anhydrides.[10] We can anticipate that the novel asymmetric system of compound **2** might be a potent chiral transmitter to perform various reactions with (high) enantioselectivity.



Scheme 1.

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5. Selected spectral data for compound **2**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $^3J_{H12-H11}=7.5$ Hz, 3H, CH_3, H-12), 1.21 (ddd, $^3J_{H2ax-H3}=12.5$ Hz $^2J=9.8$ Hz $^4J_{H2a-H9a}=2.8$ Hz, H, H-2a), 1.40 (m, 2H, CH_2, H-11), 1.82 (m, 1H, H-9$_a$), 1.84 (m, 1H, H-2$_b$), 1.93 (d broad, $^2J=13.7$ Hz, H-9$_b$), 2.72 (sl, 2H, CH_2, H-10), 2.82 (d broad, $^2J=14$ Hz, H-7$_a$), 3.96 (s, 3H, CH_3), 3.99 (d broad, $^2J=14$ Hz, H-7$_b$), 4.10 (d broad, $^3J_{H3-H2b}=9.7$ Hz, 1H, CH, H-3), 4.33 (s large, 1H, CH, H-6), 5.83 (s broad, 1H, CH, H-4), 7.20 (d, $^4J_{H5'-H7'}=2$ Hz, 1H, CH, H-5′), 7.36 (dd, $^3J_{H7'-H8'}=7.7$ Hz $^4J_{H7'-H5'}=2$ Hz, 1H, CH, H-7′), 7.66 (d, $^3J_{H3'-H2'}=4.4$ Hz, 1H, CH, H-3′), 8.03 (d, $^3J_{H8'-H7'}=7.7$ Hz, 1H, CH, H-8′), 8.78 (d, $^3J_{H2'-H3'}=4.4$ Hz, 1H, CH, H-2′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.8 (CH_3, C-12), 29.6 (CH_2, C-11), 38.4 (CH_2, C-2), 42.2 (C-1), 42.3 (CH_2, C-9), 54.4 (CH_2, C-7), 56.1 (O-CH_3), 63.9 (CH, C-3), 68.1 (CH_2, C-10), 68.7 (CH, C-4), 70.5(CH, C-6), 101.0 (CH, C-5′), 119.5 (CH, C-3′), 121.9 (CH, C-7′), 126.5 (CH, C-10′), 132.1 (CH, C-8′), 144.2 (C-4′), 144.4 (C-9′), 148.1 (CH, C-2′), 158.2 (C-6′).
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