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Reaction of quinine, 9-epiquinine and their acetates in superacid in the presence of hydrogen peroxide: an access to new fluorhydrins and/or ketones

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Abstract—In HF–SbF_5, in the presence of H_2O_2 (source of OH^+ equivalent) quinine **1a** yields 10-keto derivatives **4a** and **5a** and cyclic ether **3** as the major product. In the same conditions **1b**, **2a**, and **2b** give the 10-keto and 10-fluoro-3-hydroxy analogs.

1. Introduction

We have previously reported the reactivity of Cinchona alkaloids (quinine, quinidine), their 9-epimers and the corresponding acetates in superacid HF–SbF_5 in the presence of chloride ion. Except for quinine **1a**, leading to ether **3** previously obtained,[1] all other substrates yielded new *gem*-difluorinated products.[2,3]

In our search for new derivatives, we have studied the reactivity of quinine derivatives in HF–SbF_5 in the presence of hydrogen peroxide H_2O_2, an equivalent source of 'OH^+' in the reaction conditions.[4]

2. Reaction of quinine 1a, epiquinine 2a, and acetates 1b and 2b

2.1. Results

The experimental procedure is as follows: to a mixture of HF–SbF_5 (12 mL, 7:1 molar ratio) and 80% H_2O_2 (3 equiv), maintained at −35 °C in a Teflon® flask, was added a quinine derivative (500 mg, 1.37 mmol). The mixture was magnetically stirred at the same temperature for 3 min. After usual work-up, flash-chromatography and preparative TLC over SiO_2 yielded the products.

Except for quinine **1a** yielding ether **3** previously described as the major product in HF–SbF_5, Table 1 shows that all substrates gave ketones and fluorhydrins. The determination of structure of these new compounds was made by ^1H and ^{13}C NMR analysis, resonances being assigned from DEPT, COSY, HMQC data.[5] Acylation of ketones **4a** and **5a** yielded the corresponding acetates **4b** and **5b** respectively, also obtained from quinine acetate **1b** (Fig. 1).

2.2. Structure determination

2.2.1. Compounds 4b and 5b. For both compounds **4b** and **5b** the molecular weight $[M+H]^+$ (383 g mol^{-1}) implies the formal addition of one oxygen atom. The ^1H NMR spectra showed that the quinoline moiety did not appear to be modified when compared to compound **1b** and changes were observed in the quinuclidine part with the disappearance of the vinylic group at C-3 carbon. The presence of a singlet for a methyl group at 2.12 ppm in ^1H NMR spectra and of a quaternary carbon at 210 ppm in ^{13}C NMR spectra was

Table 1.

Entry	Substrate	Products (yields %)(molar ratio)
1	**1a**	**3**(35) + **4a**(5) + **5a**(5)
2	**1b**	**4b**(20) + **5b**(20) + **6b**[a](20) + **7b**[a](10)
3	**2a**	(**8a** + **9a**)(12)(1/1) + (**10a**[a] + **11a**[a])(25)(2/1)
4	**2b**	(**8b** + **9b**)(30)(1/1) + **10b**[a](33) + **11b**[a](17)

[a] 4/1 (Molar ratio).

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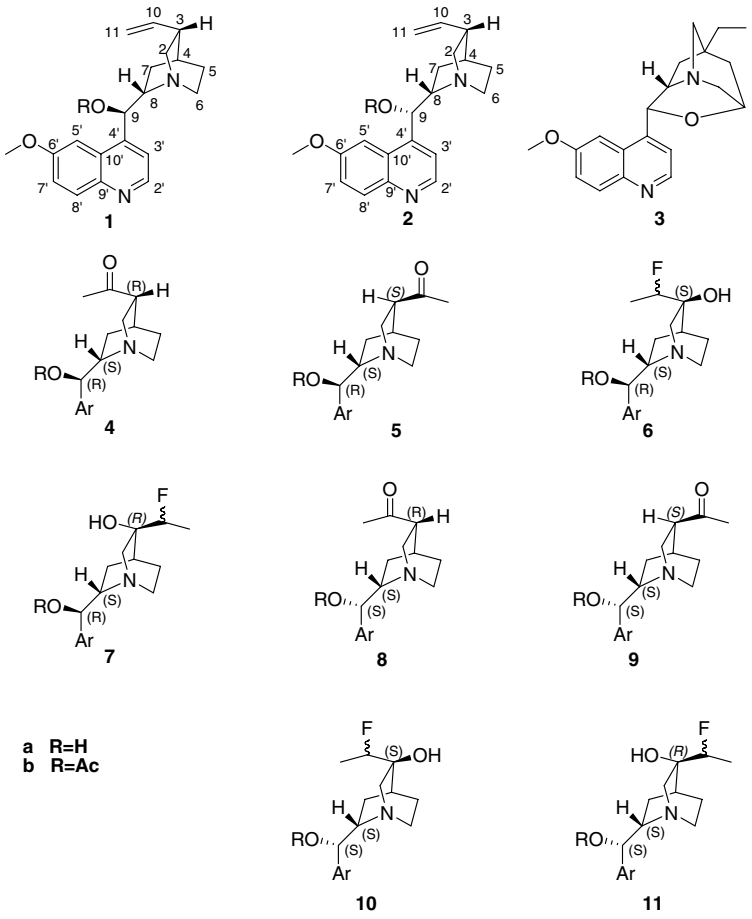


Figure 1.

in accordance with the presence of a methylketone in both products. Compounds **4b** and **5b** only differ from the configuration at C-3. In ^{1}H NMR spectra, a W-coupling between H-2a and H-6a for both compounds permits to identify H-2a. For compound **5b** a cis coupling ($J = 7.3$ Hz) between H-2a and H-3 determines the configuration at C-3 in this compound and consequently that of compound **4b** (Fig. 2).

This assignment was confirmed in ^{13}C NMR by the chemical shifts of C-5 and C-7 carbons, C-7 carbon (25.9 ppm) in compound **4b** being more shielded than C-5 carbon (27.7 ppm), for compound **5b** the reverse being observed (29.5 and 22.6 ppm, respectively). This feature was previously observed in the quinidine series with the acetyl and the difluoroethyl groups exerting a similar effect.[3]

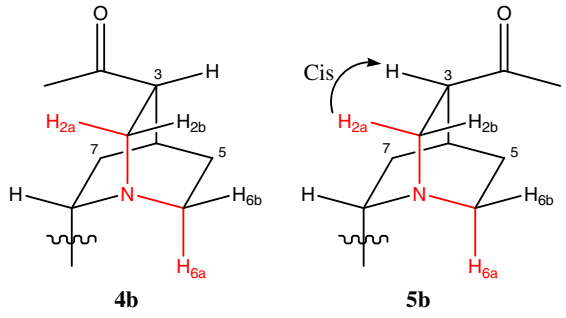
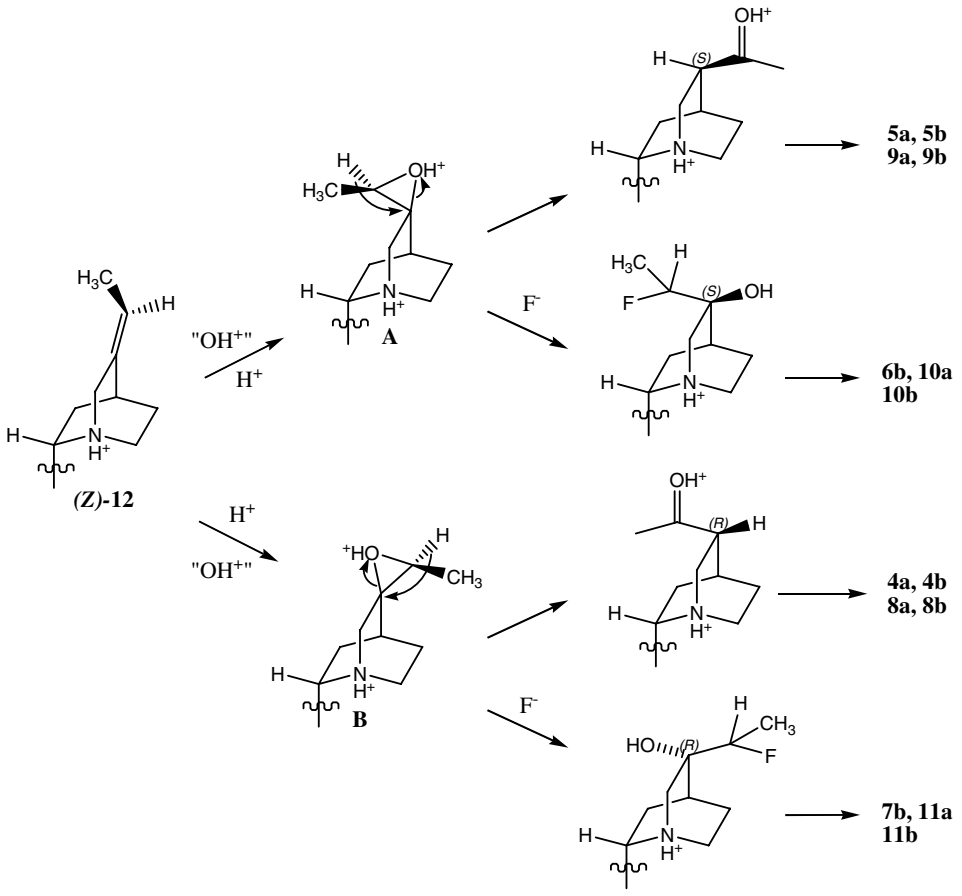


Figure 2.

2.2.2. Compounds 6b and 7b. For both compounds the molecular weight $[M+H]^{+}$ (403 g mol^{-1}) implies the formal addition of FOH. Compounds **6b** (20%) and **7b** (10%) are both mixtures of stereoisomers differing from the configuration at C-10. In ^{1}H NMR spectra of compounds **6b** and **7b** major changes are observed only in the quinuclidine ring when compared to compound **1b**: disappearance of the vinylic group and presence of a CH_3–CHF group.

For example, in compounds **7b**, the major isomer gives in ^{1}H NMR a doublet of quadruplets at 4.81 ppm ($J_1 = 45.9$ Hz and $J_2 = 6.3$ Hz) for C10-H and a doublet of doublets at 1.32 ppm ($J_1 = 25.0$ Hz and $J_2 = 6.3$ Hz) for the methyl group. In ^{13}C NMR spectrum of compounds **7b**, the major one exhibits the expected couplings for C-10 ($^{1}J_{CF} = 168.7$ Hz), C-11 ($^{2}J_{CF} = 23.2$ Hz), C-3 ($^{2}J_{CF} = 18.7$ Hz), C-4 ($^{3}J_{CF} = 4.9$ Hz), and C-2 ($^{3}J_{CF} = 4.9$ Hz). A mixture of isomers **6b** exhibit very close signals for the CH_3–CHF group in ^{1}H and ^{13}C NMR spectra. Furthermore, in ^{1}H NMR of compounds **7b** a NOESY interaction between H-10 and one hydrogen at C-5 determines the configuration at C-3 in these compounds and consequently in their isomers **6b**.



Scheme 1.

For epiquinine derivatives, the determination of the structure of alcohols **8a**, **9a**, **10a**, and **11a** and of acetates **8b**, **9b**, **10b**, and **11b** have been carried out similarly.

2.3. Reaction mechanism

Formation of fluorhydrins and ketones implies initial isomerization of the C10–C11 double bond to the exocyclic (*Z* or *E*) C3–C10 one. For proof, when the reaction is carried out either with acetate **1b** or $\Delta^{3,10}$-isoquinine acetate (*Z*+*E*)-**12**,[6] the same products are obtained.

Reaction of the electrophile 'OH^+' with the C10–C11 double bond can be ruled out, protonated terminal epoxide would have led to an aldehyde.

Reaction of (*Z*)-isomer **12** with the electrophile 'OH^+' equivalent yields protonated epoxides **A** and **B**. Isomerization of protonated epoxides **A** and **B** gives ketones **5a**, **5b**, **9a**, **9b** and ketones **4a**, **4b**, **8a**, **8b**, respectively and their trans opening with a fluoride ion yields fluorhydrins **6b**, **10a**, **10b** and **7b**, **11a**, **11b**. Reaction of (*E*)-isomer **12** will similarly lead to the same ketones and diastereoisomeric fluorhydrins (Scheme 1).

It should be pointed out that no oxidation is observed at the benzylic position. The oxidation would imply formation of the corresponding carbenium ion[8] which is disfavored by the protonation of both quinoline moiety and nitrogen quinuclidyl group.

3. Conclusion

Quinine derivatives have been reported as active molecules against malaria or catalysts in a variety of enantioselective reactions: hydrogenation, fluorination, dihydroxylation, and desymmetrization of prochiral anhydrides.[7] In this report, we have synthesized fluorhydrins and ketones which can have new biological or catalytic activities.

References and notes

1. Thibaudeau, S.; Violeau, B.; Martin-Mingot, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2002**, *43*, 8773–8775.
2. Debarge, S.; Thibaudeau, S.; Violeau, B.; Martin-Mingot, A.; Jouannetaud, M. P.; Jacquesy, J. C.; Cousson, A. *Tetrahedron* **2005**, *61*, 2065–2073.
3. Debarge, S.; Violeau, B.; Jouannetaud, M. P.; Jacquesy, J. C.; Cousson, A. *Tetrahedron* **2006**, *62*, 662–671.
4. (a) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley Interscience: New York, 1985; (b) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Vidal, Y. *Tetrahedron* **1990**, *46*, 815–826; (c) Jacquesy, J. C.; Berrier, C.; Gesson, J. P.; Jouannetaud, M. P. *Bull. Soc. Chim. Fr.* **1994**, *131*,

658–664; (d) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Lafitte, C.; Vidal, Y.; Zunino, F.; Fahy, J.; Duflos, A. *Tetrahedron* **1998**, *54*, 13761–13770; (e) Duflos, A.; Redoules, F.; Fahy, J.; Jacquesy, J. C.; Jouannetaud, M. P. *J. Nat. Prod.* **2001**, *64*, 193–195.

5. Selected spectral data are reported relative to tetramethylsilane (TMS) as the internal standard. Compound **4b**; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.43 (1H, d, $^{3}J_{HH} = 8.2$ Hz, H-9), 3.98 (3H, s, OMe), 3.52 (1H, q, $^{3}J_{HH} = 8.5$ Hz, H-8), 3.33 (1H, m, H-2a), 3.10 (1H, m, H-6), 2.69 (1H, m, H-2b), 2.62 (1H, m, H-6), 2.62 (1H, m, H-3), 2.31 (1H, m, H-4), 2.15 (3H, s, H-11), 2.08 (3H, s, CH_3COO), 1.75 (1H, m, H-5), 1.62 (1H, m, H-5), 1.62 (1H, m, H-7), 1.45 (2H, m, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.2 (C-10), 170.4 (COO), 74.0 (C-9), 58.1 (C-8), 56.0 (OCH_3), 51.1 (C-2), 49.7 (C-3), 42.7 (C-6), 29.5 (C-11), 27.7 (C-5), 25.9 (C-7), 25.8 (C-4), 21.4 (CH_3COO). Compound **5b**; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.53 (1H, d, $^{3}J_{HH} = 6.8$ Hz, H-9), 3.96 (3H, s, OMe), 3.33 (1H, q, $^{3}J_{HH} = 8.3$ Hz, H-8), 3.20 (1H, dd, $^{2}J_{HH} = 13.3$ Hz, $^{3}J_{HH} = 7.3$ Hz, H-2a), 3.05 (1H, m, H-6), 2.82 (1H, dd, $^{2}J_{HH} = 13.3$ Hz, $^{3}J_{HH} = 2.2$ Hz, H-2b), 2.72 (1H, m, H-6), 2.6 (1H, m, H-3), 2.26 (1H, m, H-4), 2.15 (3H, s, CH_3COO), 2.12 (3H, s, H-11), 1.77 (2H, m, H-7), 1.49 (2H, m, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz):δ 209.5 (C-10), 170.4 (COO), 74.0 (C-9), 59.4 (C-8), δ 56.1 (OCH_3), 51.6 (C-2), 49.1 (C-3), 43.0 (C-6), 29.5 (C-7), 29.4 (C-11), 25.6 (C-4), 22.6 (C-5), 21.5 (CH_3COO). Compound **6b**; major compound: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.55 (1H, d, $^{3}J_{HH} = 6.5$ Hz, H-9), 4.66 (1H, bd, $^{2}J_{HF} = 45.0$ Hz, H-10), 3.96 (3H, s, OMe), 3.26 (1H, q, $^{3}J_{HH} = 7.6$ Hz, H-8), 3.12 (1H, d, $^{2}J_{HH} = 13.7$ Hz, H-2), 3.08 (2H, m, H-6), 2.72 (1H, d, $^{2}J_{HH} = 13.7$ Hz, H-2), 2.15 (3H, s, CH_3COO), 2.12 (1H, m, H-5), 1.83 (1H, m, H-4), 1.71 (1H, m, H-7), 1.56 (1H, m, H-7), 1.46 (1H, m, H-5), 1.30 (3H, $^{3}J_{HF} = 25.0$, H-11); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1 (COO), 95.2 (d, $^{1}J_{CF} = 168.0$ Hz, C-10), 73.1 (C-9), δ 71.7 (d, $^{2}J_{CF} = 18.7$ Hz, C-3), 69.9 (d, $^{3}J_{CF} = 4.9$ Hz, C-2), δ 58.2 (C-8), δ 55.8 (OCH_3), δ 42.3 (C-6), δ 29.8 (d, $^{3}J_{CF} = 4.9$ Hz, C-4), 24.7 (C-7), 21.5 (CH_3COO), 21.4 (C-5), 15.3 (d, $^{2}J_{CF} = 23.2$ Hz, C11); ^{19}F NMR ($CDCl_3$, 282 MHz): −193.2 (m); minor compound: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.54 (1H, d, $^{3}J_{HH} = 6.3$ Hz, H-9), 4.62 (1H, bd, $^{2}J_{HF} = 45.0$ Hz, H-10), 3.96 (3H, s, OMe), 3.26 (1H, q, $^{3}J_{HH} = 7.6$ Hz, H-8), 2.78 (2H, m, H-6), 2.66 (1H, d, $^{2}J_{HH} = 14.4$ Hz, H-2), 2.50 (1H, d, $^{2}J_{HH} = 14.4$ Hz, H-2), 2.16 (3H, s, CH_3COO), 2.12 (1H, m, H-5), 1.83 (1H, m, H-4), 1.71 (1H, m, H-7), 1.56 (1H, m, H-7), 1.46 (1H, m, H-5), δ 1.30 (3H, $^{3}J_{HF} = 25.0$, H-11); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1 (COO), (C-8′), 91.7 (d, $^{1}J_{HF} = 172.3$ Hz, C-10), 73.1 (C-9), 72.2 (d, $^{2}J_{CF} = 19.2$ Hz, C-3), 61.0 (d, $^{3}J_{CF} = 4.4$ Hz, C-2), 58.6 (C-8), 55.8 (OCH_3), 42.3 (C-6), 29.5 (d, $^{3}J_{CF} = 3.8$ Hz, C-4), 24.9 (C-7), 21.5 (CH_3COO), 21.6 (C-5), 13.9 (d, $^{2}J_{CF} = 23.6$ Hz, C11); ^{19}F NMR ($CDCl_3$, 282 MHz): −183.6 (m). Compound **7b**; major compound: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.49 (1H, d, $^{3}J_{HH} = 7.4$ Hz, H-9), δ 4.81 (1H, dq, $^{2}J_{HF} = 45.9$ Hz, $^{3}J_{HH} = 6.3$ Hz, H-10), δ 3.92 (3H, s, OMe), δ 3.64 (1H, q, $^{3}J_{HH} = 8.1$ Hz, H-8), δ 3.11 (1H, m, H-6), δ 3.02 (1H, d, $^{2}J_{HH} = 14.3$ Hz, H-2), δ 2.74 (1H, d, $^{2}J_{HH} = 14.3$ Hz, H-2), δ 2.59 (1H, m, H-6), δ 2.13 (1H, m, H-7), δ 2.12(3H, s, CH_3COO), δ 1.86 (1H, m, H-4), δ 1.60 (1H, m, H-5), δ 1.44 (1H, m, H-5), δ 1.44 (1H, m, H-7), δ 1.32 (3H, dd, $^{3}J_{HF} = 25.0$ Hz, $^{3}J_{HH} = 6.3$ Hz, H-11); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5 (COO), 95.6 (d, $^{1}J_{CF} = 165.8$ Hz, C-10), 74.0 (C-9), 72.7 (d, $^{2}J_{CF} = 19.2$ Hz, C-3), 65.3 (d, $^{3}J_{CF} = 4.4$ Hz, C-2), 58.4 (C-8), δ 56.0 (OCH_3), 42.2 (C-6), δ 29.7 (d, $^{3}J_{CF} = 5.5$ Hz, C-4), 25.0 (C-7), 23.2 (C-5), 21.5 (CH_3COO), 15.3 (d, $^{3}J_{CF} = 23.6$ Hz, C11); ^{19}F NMR ($CDCl_3$, 282 MHz): −193.3 (m); minor compound: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.47 (1H, d, $^{3}J_{HH} = 7.5$ Hz, H-9), 4.75 (1H, dq, $^{2}J_{HF} = 47.4$ Hz, $^{3}J_{HH} = 6.3$ Hz, H-10), 3.97 (3H, s, OMe), 3.50 (1H, q, $^{3}J_{HH} = 8.5$ Hz, H-8), 3.33 (1H, m, H-6), 2.70 (1H, d, $^{2}J_{HH} = 14.4$ Hz, H-2), 2.59 (1H, m, H-6), 2.36 (1H, d, $^{2}J_{HH} = 14.4$ Hz, H-2), 2.19 (1H, m, H-4), 2.13 (1H, m, H-7), 2.11 (3H, s, CH_3COO), 1.60 (1H, m, H-5), 1.44 (1H, m, H-5), 1.44 (1H, m, H-7), 1.25 (3H, dd, $^{3}J_{HF} = 24.8$ Hz, $^{3}J_{HH} = 6.2$ Hz, H-11); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5 (COO), δ 91.0 (d, $^{1}J_{CF} = 172.3$ Hz, C-10), δ 74.0 (C-9), δ 73.1 (d, $^{2}J_{CF} = 18.7$ Hz, C-3), δ 60.8 (d, $^{3}J_{CF} = 4.4$ Hz, C-2), δ 58.1 (C-8), δ 56.0 (OCH_3), δ 51.0 (C-6), δ 29.4 (d, $^{3}J_{CF} = 6.0$ Hz, C-4), δ 25.0 (C-7), δ 23.2 (C-5), δ 21.5 (CH_3COO), δ 14.0 (d,$^{2}J_{CF} = 23.6$ Hz, C11); ^{19}F NMR ($CDCl_3$, 282 MHz): −183.4 (m).
6. Portlock, D.; Naskar, D.; West, L.; Seibel, W.; Gu, T.; Krauss, H.; Sean Peng, X.; Dybas, P.; Soyke, E.; Ashon, S.; Burton, J. *Tetrahedron Lett.* **2003**, *44*, 5365–5368.
7. Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, *7*, 961–998, and references cited therein.
8. Olah, G. A.; Parker, D. G.; Yoneda, N. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 909–931.