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Rearrangement and fluorination of quinidinone in superacid

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Abstract

In HF/SbF_5 at −78 °C, quinidinone **1** yields fluoroketone **3** (50% yield). The reaction implies a cyclic carboxonium ion as an intermediate, which reacts through a concerted rearrangement and fluorination to yield ketone **3**.

Keywords: Superacids; Cinchona alkaloids; Fluorination; Rearrangement; Carboxonium ion

1. Introduction

Since the early 1970s we have studied the reactivity of natural products in the HF/SbF_5 system. Under these superacidic conditions these compounds are (poly)protonated and reactions, not observed with conventional acids, can be performed in good yields [1–5].

We have previously reported the reactivity of quinidine and its acetate in superacid in the presence of carbon tetrachloride or hydrogen peroxide [4]. In our search for new fluorinated compounds, which can have biological or catalytic activities, we have studied the reaction of quinidinone **1** in HF/SbF_5 and compared it with the reactivity of quinidine acetate **2** in the same conditions (Fig. 1).

2. Results and discussion

2.1. Results

Quinidinone **1** has been prepared by oxidation of quinine or quinidine according to Woodward procedure [6]. Table 1 shows that at −30 °C, whatever the acidity is, quinidinone **1** leads to a complex mixture. At −78 °C, at the highest acidity (entry 3), starting material **1** is recovered. At the same temperature to a lower acidity (entry 4), the sole compound **3** (50%) could be separated from the complex mixture.

The mass spectra of compound **3** showed that the molecular weight (342 g mol^{-1}) implies the formal addition of hydrogen fluoride, HF. Determination of structure and conformation of compound **3** was made by extensive NMR analysis. In summary ^1H and ^{13}C resonances were assigned from DEPT, COSY, NOESY, HMQC and HMBC data.

Whereas the quinoline moiety appeared not to be modified when compared with quinidinone **1**, significant changes were observed in the upper part in the ^1H and ^{13}C NMR spectra of compound **3**:

- Disappearance of vinylic protons and presence of an ethyl group bonded to a quaternary carbon.
- Presence of a CHF group characterized in ^1H NMR by a doublet at 4.74 ppm ($^2J_{HF}$ = 49.0 Hz). In ^{13}C NMR six carbon atoms are coupled with the fluorine atom: C4 ($^1J_{CF}$ = 175 Hz), C3 quaternary carbon ($^2J_{CF}$ = 19 Hz), C5 ($^2J_{CF}$ = 23 Hz), C6 ($^3J_{CF}$ = 1 Hz), C2 ($^3J_{CF}$ = 4 Hz) and the methylene of the ethyl group C10 ($^3J_{CF}$ = 1 Hz).

These ^1H and ^{13}C resonances are in agreement with a rearrangement to an azabicyclo[3,2,1]octane different of that observed in quinidine series [4].

It should be pointed out that (W) couplings between H8, H2exo and H2endo, H4 have determined (*S*) configuration at C4.

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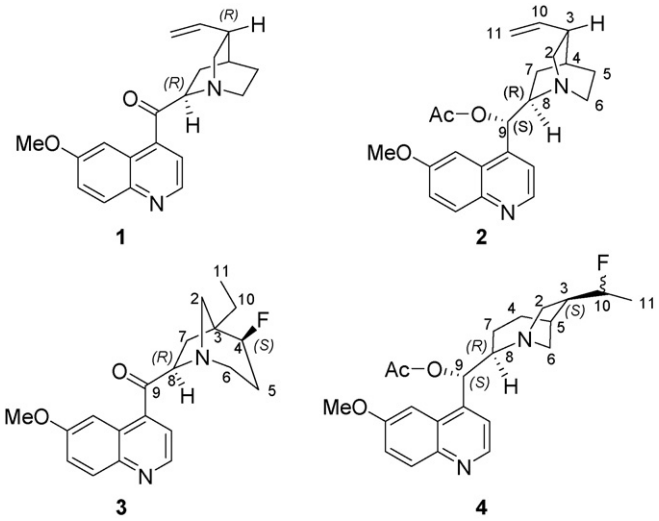

Fig. 1. Structures of compounds **1**–**4**.

Table 1
Reactivity of quinidinone **1** in HF/SbF_5

Entry	Temperature (°C)	HF/SbF_5 (molar ratio)	Time (s)	Product(s)
1	−30	3.6/1	30	Complex mixture
2	−30	7/1	30	Complex mixture
3	−78	3.6/1	30	**1** (90%)
4	−78	25/1	30	**3** (50%)

The structure of compound **3** was confirmed by X-ray analysis (Fig. 2).

To study the influence of the functional group at the C9 position, we have studied the reactivity of quinidine acetate **2** under the same conditions of acidity and temperature. In HF/SbF_5 (25/1, molar ratio) at −78 °C, quinidine acetate **2** yielded compounds **4** (50%) as a mixture of monofluorinated diastereoisomers differing from the configuration at C10.

Structural determination of compounds **4** was made by ^1H and ^{13}C NMR analysis, resonances being assigned from DEPT, COSY and HMQC data. These data described in the experimental part are in agreement with a rearrangement of quinuclidine moiety in an azabicyclo[3,2,1]octane. An analogous rearrangement has been previously obtained with quinidine acetate in HF/SbF_5 in the presence of carbon tetrachloride or hydrogen peroxide [4].

This azabicyclo[3,2,1]octane is substituted by a fluoroethyl group CHF–CH_3 characterized in the ^1H NMR by a doublet of multiplet at 4.47 ppm ($^2J_{HF}$ = 48.1 Hz) and 4.31 ppm ($^2J_{HF}$ = 48.5 Hz) and a doublet of doublet at 1.56 ppm ($^3J_{HF}$ = 17.4 Hz, $^3J_{HH}$ = 6.2 Hz) and at 1.48 ppm ($^3J_{HF}$ = 17.2 Hz, $^3J_{HH}$ = 6.1 Hz). NOESY interaction between the hydrogen atom at C10 and a proton at C6 implies (*S*) configuration at C3. Consequently, the fluoroethyl group is *exo* in compounds **4**.

2.2. Reaction mechanism: formation of compounds *3* and *4*

Table 1 shows that the best yields of compound **3** are observed in HF/SbF_5 molar ratio 25/1 and at low temperature. The observed rearrangement implying initially the protonation of the C10–C11 double bond, the resulting ion A can be trapped by the neutral carbonyl group to yield a seven-membered carboxonium ion B [7]. At higher acidity (molar ratio 3.6/1) protonation of carbonyl group prevents the formation of cyclic carboxonium ion and no reaction occurs. The following rearrangement may account for the formation of ketone **3** through a concerted process: a 1,2-hydride shift from C3 to C10, concerted with the migration of the C4–C7 carbon bound to carbon C3, and nucleophilic attack of a fluoride ion at C4 leading to the precursor of compound **3** (Scheme 1).

To get a better understanding of the proposed mechanism, we have performed theoretical calculations at the density functional level [8]. We focused on relative energies of A, B and other isomeric structures. To save computer time, we chose to replace the aryl moiety by a methyl group. The main results of these calculations are presented in Fig. 3.

The secondary carbocation A initially formed can easily rearrange to the tertiary carbocation C. These two ions present several conformers due to the rotations about the C8–C9 and C3–C10 single bonds. To optimize their structures, we have

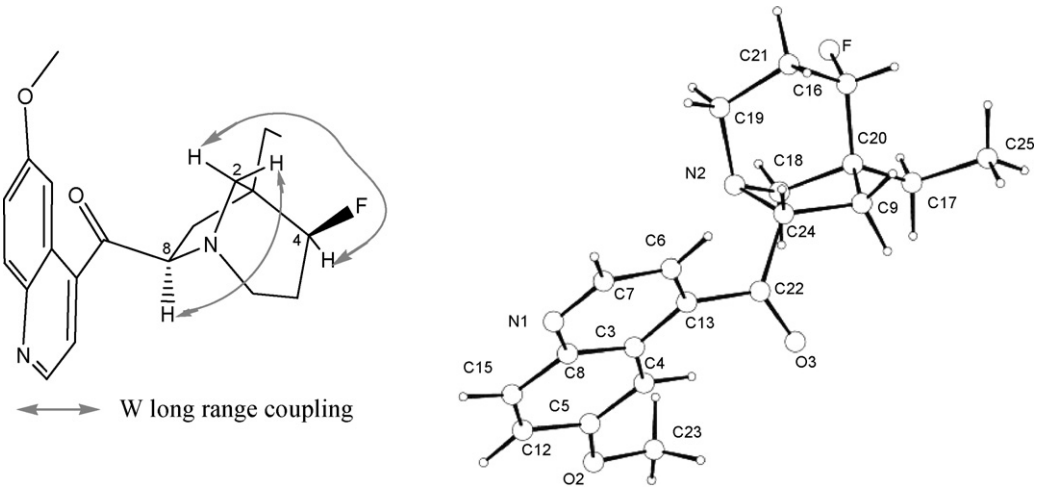

Fig. 2. NMR analysis and X-ray analysis of compound **3**.