

Favorsky Rearrangements

XII. The Mechanism of the Rearrangement of Bromocyclobutanone

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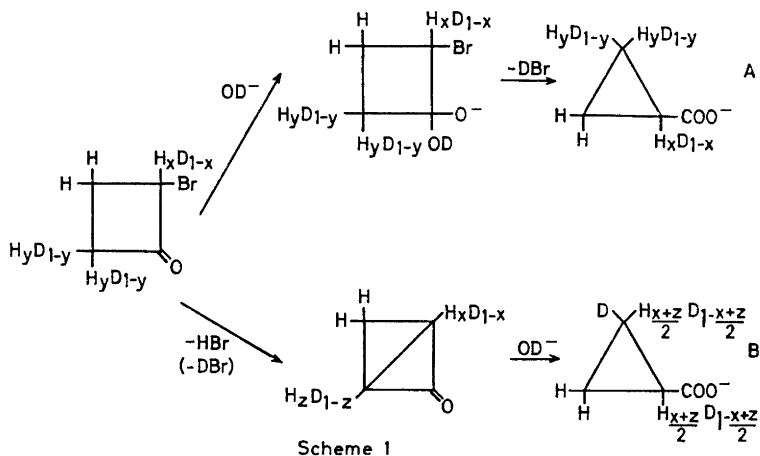
The rearrangement of bromocyclobutanone in deuterium oxide was studied. The sodium carbonate catalyzed rearrangement of bromocyclobutanone seems to proceed *via* a semibenzilic acid mechanism, the silver nitrate catalyzed rearrangement *via* a "push-pull" mechanism.

Conia and Ripoll recently found that by the action of sodium carbonate, silver nitrate or boiling water, bromocyclobutanone is rearranged, in good yield, to cyclopropanecarboxylic acid.¹ This is an example of a Favorsky rearrangement where a cyclopropane derivative is formed by a ring contraction of a cyclobutanone.

Later, Conia *et al.* studied the mechanism of this rearrangement.² They discuss four mechanisms: 1) the cyclopropanone mechanism 2) the semibenzilic acid mechanism 3) the ketene mechanism 4) the "push-pull" mechanism. The only mechanism which they consider to be in agreement with their experimental data is the semibenzilic acid mechanism. These authors suggest that this mechanism operates in the alkaline carbonate solution as well as in the rearrangement using silver nitrate or water only.^{2,3}

The semibenzilic acid mechanism includes an attack by hydroxylic ions, route A, Scheme 1. Therefore it seems a little doubtful that this mechanism can operate in the rearrangements where the bromoketone is rearranged by boiling water or silver nitrate; the pH of the solution at the end of these experiments was 1.¹

Conia and Ripoll excluded the ketene mechanism for stereochemical reasons, and the "push-pull" mechanism owing to the inability of silver ions to accelerate the rearrangement.² In order to distinguish between the cyclopropanone mechanism and the semibenzilic acid mechanism, Conia and Salaün studied the rearrangement in deuterium oxide.³ The ratio of α - and β -protons in the rearranged product was determined by NMR. The cyclopropanone mechanism would give a ratio $\beta\text{-H}/\alpha\text{-H} = 3$ and the semibenzilic acid mechanism $\beta\text{-H}/\alpha\text{-H} = 4$, see Scheme 1, $x = y = z = 1$. Conia and Salaün found



a value $\beta\text{-H}/\alpha\text{-H} = 5$, and on the basis of this determination they excluded the cyclopropanone mechanism.³

However, a more careful examination of the situation shows that this discussion is valid only in those cases, where only a small amount of protons is exchanged during the synthesis, x , y , and z are near 1. If the bromoketone is deuterated to a larger extent, other values of the ratio $\beta\text{-H}/\alpha\text{-H}$ are obtained. For instance the values $x = y = z = 0.5$ would give a ratio $\beta\text{-H}/\alpha\text{-H} = 5$ for the cyclopropanone mechanism. Due to the primary isotope effect, the cyclopropanone will be enriched in deuterium, $y > z$, see Scheme 1. A secondary isotope effect in the cleavage of the cyclopropanone is neglected.

The rates of triethylamine-catalyzed hydrogen-deuterium exchange between deuterium oxide and a series of cyclic ketones have been studied. Among the ketones studied, cyclobutanone had the highest rate of exchange.⁴ In addition, α -bromoketones are known to be more easily deuterated than the parent ketones especially in the base catalyzed deuteration.^{5,6} Charpentier-Morize *et al.* have studied the Favorsky rearrangement of 1-chlorocyclohexyl methyl ketone, using sodium phenolate, in a mixture of dioxane and deuterated phenol.⁷ They found that the first step in this reaction is a rapid equilibrium ketone-deuterated ketone, followed by the slow formation of the cyclopropanone intermediate. The same results are reported by Ginsburg from the rearrangement of 2-chlorocyclohexanone.⁸

In view of these results and the objections above, it seems desirable to reinvestigate the rearrangement of bromocyclobutanone in deuterium oxide. Here special attention will be paid to the total amount of hydrogen exchanged during the syntheses.

A careful investigation of the degree of deuteration can be made by direct NMR-studies of the increasing OH-peak at $\delta = 4.7\text{--}5.2$ ppm. By comparison with blind tests of sodium carbonate in deuterium oxide and with rearranged products from ordinary water, the total amount of exchanged protons, as well as the amount of deuterium at the α - and β -carbons, was determined. A series of experiments was performed, and the results are collected in Table 1.

Table 1. Results from rearrangements of bromocyclobutanone in deuterium oxide.

Expt. No.	Base	Temp. °C	Time h	β -H/ α -H	-OH equiv.D	α -C equiv.H	β -C equiv.H
1	Na ₂ CO ₃	20	1/12	6.1	1.00	0.56	2.0 + 1.44
2	»	20	1 1/2	9.2	1.22	0.37	2.0 + 1.44
3	»	50	1/2	8.1	0.93	0.45	2.0 + 1.56
4	»	100	1/4	8.4	0.85	0.44	2.0 + 1.70
5	»	0	4 1/2	7.5	1.20	0.44	2.0 + 1.36
6	—	100	1	4.1	0.25	0.93	2.0 + 1.82
7	AgNO ₃	20	1 1/3	3.9	0	1.00	2.0 + 2.00

In one experiment, the rearrangement was effected in boiling deuterium oxide only (expt. 6), another in deuterated silver nitrate solution (expt. 7), and the rest in deuterium oxide at various temperatures using sodium carbonate as base. The reaction mixture is a two-phase system and the rate of reaction was found to be dependent on the degree of agitation. The reactions were interrupted when the heavier organic layer had disappeared. In expt. 1 the reaction was not complete when it was interrupted after 5 min.

In Table 1 it can be seen that the degree of deuteration is high, usually about 1.0–1.25 equiv. of protons being exchanged during the reactions. Higher temperatures gave somewhat lower values for the total amount of

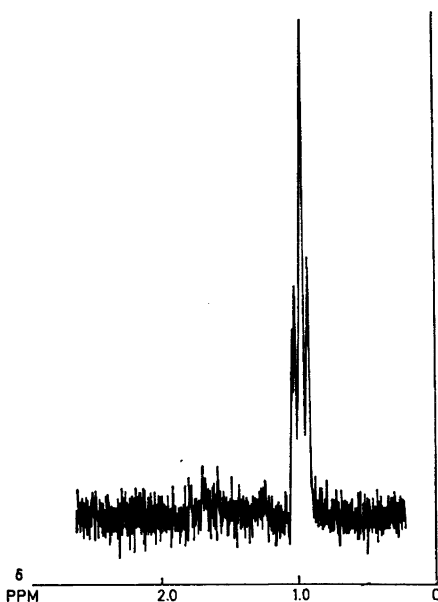


Fig. 1. NMR-spectrum of cyclopropane-carboxylic acid obtained from rearrangement with sodium carbonate in deuterium oxide.

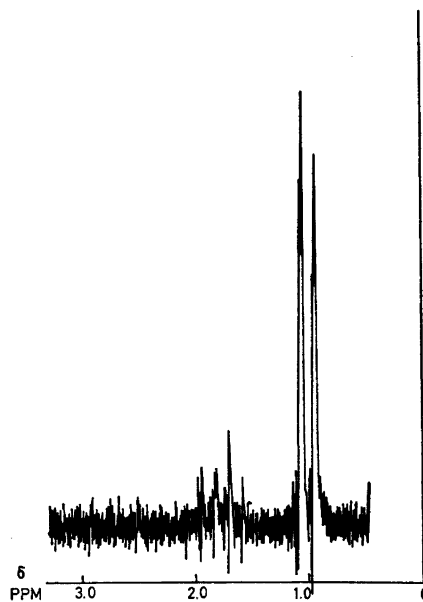


Fig. 2. NMR-spectrum of cyclopropane-carboxylic acid obtained from rearrangement with sodium carbonate in water.

protons exchanged during the reaction. The high degree of deuteration is in contrast to the assumption made by Conia and Salaün.³ The NMR-spectrum of the product from the sodium carbonate-catalyzed rearrangement in deuterium oxide is also different from that of the rearrangement in ordinary water, see Figs. 1 and 2. The NMR-spectrum of undeuterated and deuterated products could be expected to be different, compare Conia and Salaün.³

It is evident from Table 1 that an unsymmetric mechanism operates in the reaction, as proposed by Conia *et al.*^{2,3} The α - and β -carbons are deuterated to a different extent; in a symmetric mechanism the degree of deuteration at these two atoms would be the same, see Scheme 1. In addition, the total amount of deuterium at the β -carbon is only about 0.3–0.6 equiv.; in the symmetric mechanism 1 equiv. of deuterium would be incorporated in the fission of the cyclopropanone ring, see Scheme 1, route B.

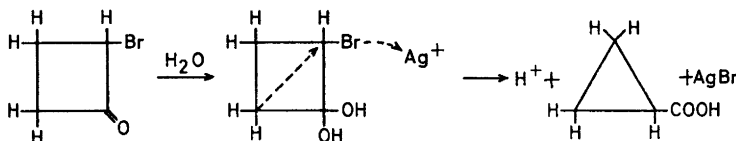
Additional proof was obtained by analyzing the ketonic component in expt. 1. The ratio of the four CH_2 - and the single CHBr -protons in this sample was found to be 6.5. This value is about the same as the ratio of α - and β -protons in the acid formed in the same experiment.

The rearrangement performed with silver nitrate was an exception to this general behaviour, see expt. 7, Table 1. Here no deuterium was found to be exchanged during the reaction. This indicates an alternative unsymmetric mechanism for this rearrangement.

As mentioned above, three unsymmetric mechanisms are discussed for the Favorsky rearrangement of this bromoketone.² The “push-pull” mechanism is discussed for the rearrangement using silver nitrate, but Conia and Ripoll excluded this mechanism owing to the inability of silver ions to accelerate the rearrangement.² Conia and Ripoll studied the rate of the reaction in a water-dioxane (1:1) solution by UV-techniques.

However, by weighing the precipitated silver bromide, we found that at 20°C the rearrangement was complete after 2 h in the case of silver nitrate. At the same temperature and using only water, no rearranged product could be detected after 24 h; undissolved bromoketone still persisted. *This indicates that addition of silver ions strongly accelerates the rate of rearrangement.* Therefore the “push-pull” mechanism seems plausible for this reaction.

The “push-pull” mechanism was originally proposed by Cope and Graham for the silver nitrate catalyzed rearrangement of 1-bromobicyclo[3,3,1]nonan-9-one.⁹ The first step in this mechanism is the addition of water (or deuterium oxide) to the carbonyl group. By an attack from the rear of the carbon, the bromine is “pushed” away, and at the same time the silver ion “pulls” the bromine from the molecule, see Scheme 2.



Scheme 2

The rearrangement described by Cope *et al.* is considered to be a type of quasi-Favorsky rearrangement. According to Bredt's rule the ketone is a very weak acid.⁹ In the other examples where silver (and mercuric) ions have been used to effect a Favorsky rearrangement, the ketone has no α -hydrogens at all; it is a real quasi-Favorsky mechanism.^{10,11} Therefore it is interesting to note that in the case of bromocyclobutanone it is a ketone with an unusual acidic α -proton, which is rearranged by the use of silver nitrate, according to a "push-pull" mechanism.

The mechanism for the rearrangement using pure water (or D₂O) is still unclear. Here also only a small amount of deuterium was found to be exchanged during the reaction, see expt. 6, Table 1. A "push-pull" mechanism seems most plausible, but the only ion, which can "pull" the bromine away from the molecule is the hydronium (or deuteronium) ion.

The results in this paper show that in the general base-catalyzed Favorsky rearrangement of bromocyclobutanone, the first step of the reaction is formation of an equilibrium ketone-deuterated ketone. This is in agreement with the observation by Charpentier-Morize *et al.*⁷ and Ginsburg.⁸

EXPERIMENTAL

Rearrangement of bromocyclobutanone. 0.20 g (1.34 mmole) of bromocyclobutanone was added to a well stirred solution of 0.156 g (1.48 mmole) of sodium carbonate or to 0.260 g (1.48 mmole) of silver nitrate dissolved in 2.0 ml of deuterium oxide. The time and temperature for the reactions are given in Table 1. The reaction mixture was analyzed directly by NMR. In expt. 1 the undissolved layer was extracted with carbon tetrachloride, and then the two phases were analyzed by NMR.

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