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Favorsky Rearrangements

XI. Some Notes on the Mechanism of the Rearrangement of Polybromoketones

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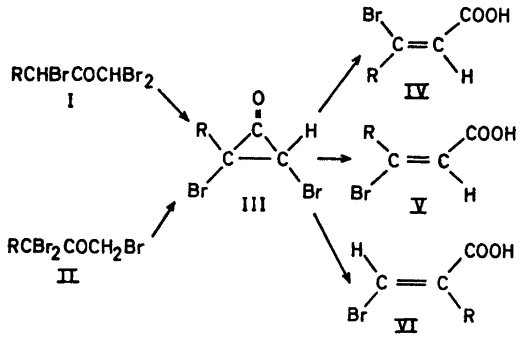
2-Bromo-4,4-dimethyl-*trans*-2-pentenoic acid (IX) can be prepared by the Favorsky rearrangement of 1,1,3-tribromo-4,4-dimethylpentanone-2 (VII). In addition to the cyclopropanone mechanism, a semibenzilic acid and a ketocarbene mechanism are discussed for the Favorsky rearrangement of tri- and tetrahalo ketones. The experimental data are in agreement only with a cyclopropanone mechanism.

The bromination of mixed methyl ketones gave a mixture of the two tribromo isomers, I and II, see Scheme 1, and it was not possible to separate



SCHEME 1

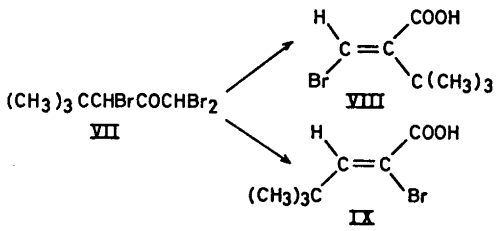
these two isomers by distillation.[1,2] When this mixture was used as starting material in the Favorsky rearrangement, the reaction yielded three acids, all of which gave a singlet (with observed β-coupling) for the ethylenic protons when analyzed by NMR. From this it could be concluded that all three acids

are 3-bromosubstituted acids.[2] In 2-bromosubstituted acids the signals from the ethylenic protons would be multiplets, and no multiplets could be detected in the region of ethylenic protons.[2] The percentages of the three components in the crude extracts were determined by NMR although only one of the three isomers was isolated, acid IV, see Scheme 1.[2]

From the δ-values of the ethylenic protons it could be determined that two of the acids contained an α-proton and the third had a *cis*-β-proton. The three components were acids IV, V, and VI; see Scheme 1.[2]

This method for structure determination was proposed by the present author from analyses of the spectra of *cis*- and *trans*-3-haloacrylic acids.[3] In addition to the structure determination cited above, it has been used later in the determination of *cis*- and *trans*-2,3-dibromo- and 3,3-dibromo-2-enoic acids,[4] the corresponding chloro acids,[5] and *cis*- and *trans*-2-cyano-3-alkoxy-3-alkylacrylic acids.[6]

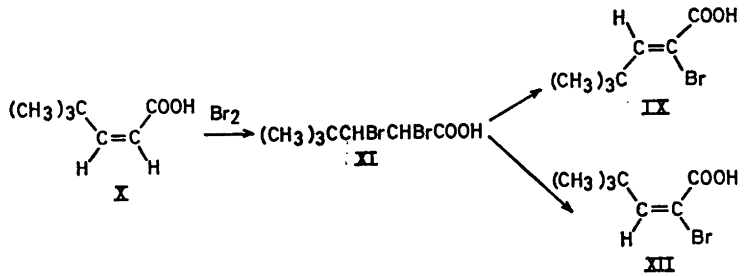
4,4-Dimethylpentanone-2 was an exception to this general behaviour. From the bromination only the 1,1,3-tribromo isomer (VII) was obtained,



SCHEME 2

see Scheme 2, and the Favorsky rearrangement of this compound gave only one acid.[2] From the NMR-spectrum it could be seen that it contained a *cis*-β-proton, and by analogy with other tribromo ketones, which gave only 3-bromosubstituted acids, the structure VIII, *trans*-3-bromo-2-*tert*.butylacrylic acid was proposed for this acid.[2]

However, in this separate case, acid IX, 2-bromo-4,4-dimethyl-*trans*-2-pentenoic acid, has a *cis*-β-proton, which contrary to the lower homologues



SCHEME 3

would be a singlet too. Therefore it is desirable to get a chemical proof for the structure determination of the acid obtained from the rearrangement of ketone VII.

4,4-Dimethyl-*cis*-2-pentenoic acid, X (Scheme 3), was prepared by the Favorsky rearrangement of 1,3-dibromo-4,4-dimethylpentanone-2.[7] 2,3-Dibromo-4,4-dimethylvaleric acid (XI) was obtained by the addition of bromine to this acid. Treatment of 2,3-dibromo acids with base is known to give mixtures of 2-bromo-*trans*-2-enoic acids and 2-bromo-*cis*-2-enoic acids.[2,8,9] The 2,3-dibromo acid XI was treated with potassium hydroxide, and from this reaction a yellow oil was obtained in 43 % yield, which was analyzed by NMR. These analyses showed that it consisted of 2-bromo-4,4-dimethyl-*trans*-2-pentenoic acid (IX) and the corresponding *cis*-acid XII (Scheme 3) in the approximate ratio 3:1. Acid IX partly crystallized and was isolated in 24 % yield. By IR, NMR, and mixed melting point analyses, this acid was proved to be identical with the acid prepared by the Favorsky rearrangement.

DISCUSSION OF THE MECHANISM

The cyclopropanone mechanism

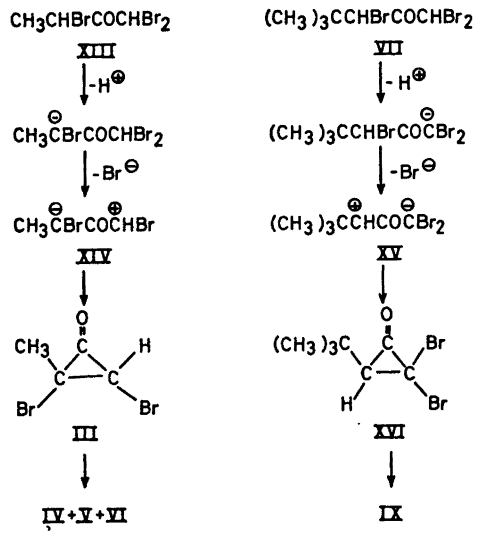
The formation of 2-bromo-4,4-dimethyl-*trans*-2-pentenoic acid (IX) from the rearrangement of 1,1,3-tribromo-4,4-dimethylpentanone-2 (VII) gave interesting information of the mechanism of the rearrangement.

The currently accepted theory for the mechanism involves the formation and cleavage of a symmetrical intermediate. The nature of this intermediate as either a cyclopropanone or an open dipolar ion has been subjected to much discussion.[10-15] It is of special interest to note that one cyclopropanone has recently been prepared. This rearranged easily and the reaction was found to give the same products as those from the Favorsky rearrangement.[16]

However, the discussion and all experiments concern the mechanism for the rearrangements of monohaloketones. Therefore it was of interest to note that the rearrangement of 1,1-dichloro-3-bromoacetone and 1,1-dibromo-3-chloroacetone gave the same rearranged product. 1,1,3-Tribromo- and 1,3,3-tribromobutanone-2 were also found to give the same proportion of products. These data are in agreement only with a symmetrical intermediate of the reaction, in the case of tribromobutanone-2, the cyclopropanone III, R = CH_3; see Scheme 1.[17]

The formation of the cyclopropanone III (or its delocalized analogue XIV), the two first steps in the rearrangement of 1,1,3-tribromobutanone-2 (XIII) are summarized in Scheme 4. From this it can be seen that a proton from the secondary CHBr-group is expelled together with one of the two bromines in the primary $CHBr_2$-group.

A comparison with the same steps in the rearrangement of 1,1,3-tribromo-4,4-dimethylpentanone-2, VII, *shows that this rearrangement follows an alternative route*. If we assume a cyclopropanone to be an intermediate, the rearrangement can be visualized in Scheme 4. Unlike the rearrangement of XIII, in this case it is a proton from the primary $CHBr_2$-group and a bromine from



SCHEME 4

the secondary CHBr-group which are expelled in the formation of the cyclopropanone XVI or its delocalized analogue XV.

Now it is of interest to discuss why a 1,1,3-tribromo-2-one can form a cyclopropanone in two different ways. One reason can be the shielding effect of the large *tert.* butyl group on the secondary proton. Bromination experiments of 4,4-dimethylpentanone-2 showed that in contradistinction to other methyl ketones, no 1,1,3,3-tetrabromo compound could be prepared from this ketone although forced conditions were used.[2] This property was interpreted as a consequence of steric hindrance of the *tert.* butyl group.

The problem can also be discussed from another point of view. In the *tert.* butyl case (VII) the steric repulsion in the secondary CHBr-group is much greater than in the methyl case (XIII). Therefore in compound VII the gain of steric energy is greater when the secondary bromine is expelled as compared with one of the primary bromines. In the butanone-2 case (XIII) the conditions are the opposite.

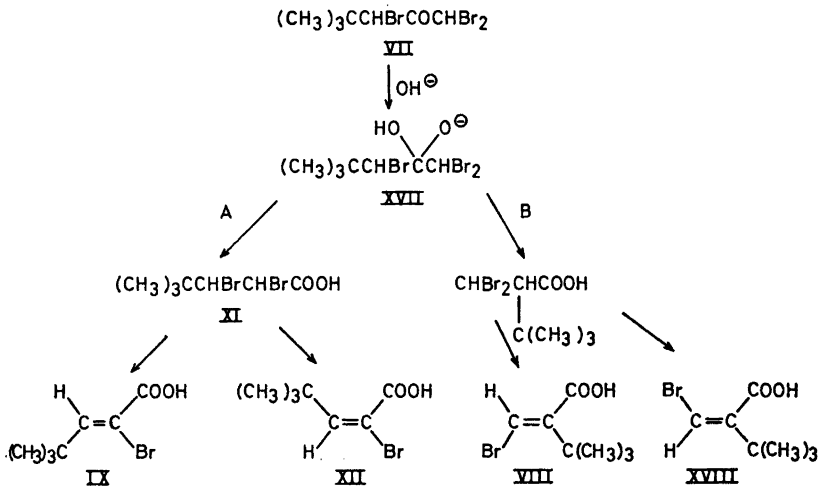
More information about these problems can be obtained when the rearrangements are performed in heavy water. Here the speed of deuteration can be compared with the speed of rearrangement. This reveals which is the rate determining step of the reaction.

In addition to the symmetrical cyclopropanone mechanism, two other mechanisms can be discussed for the rearrangement of a polybromo ketone; a semibenzilic acid mechanism and a mechanism involving a ketocarbene.

The semibenzilic acid mechanism

Conia and Salaün have recently reported that the rearrangement of bromocyclobutanone seems to follow a semibenzilic acid mechanism.[18]

As mentioned above, 1,1,3-tribromo-4,4-dimethylpentanone-2 (VII) was found to react abnormally in a cyclopropanone mechanism. Therefore, it is of interest to discuss if this tribromoketone can follow an alternative mechanism.



SCHEME 5

If we assume that the rearrangement of the tribromo ketone VII follows a semibenzilic acid mechanism, Scheme 5 summarizes the situation. The anion XVII can lose either a primary (route A) or the secondary bromine (route B). In route A, 2,3-dibromo-4,4-dimethylvaleric acid (XI) is an intermediate. It has been mentioned above that treatment of this acid with base yielded both 2-bromo-4,4-dimethyl-*trans*-2-pentenoic acid, IX, and the *cis*-acid XII (ratio 3:1). Unlike the elimination reaction the Favorsky rearrangement has geometric specificity, and this makes the semibenzilic acid mechanism less plausible. However, as long as the elimination of both diastereoisomers of acid XI (*erythro* and *threo*) has not been studied in separate syntheses, this is of limited importance. The products according to route B would be the two isomeric 3-bromosubstituted acids VIII and XVIII; see Scheme 5.

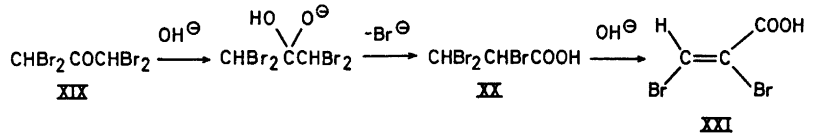
It is not clear whether route A or B would be favoured. In addition, the first step in the semibenzilic acid mechanism is formation of the anion XVII; see Scheme 5. This ion is more crowded than the starting tribromoketone VII, and it seems doubtful whether the reaction follows this mechanism in the case of the crowded tribromoketone VII, when it is known that in the case of other less crowded tribromoketones it follows the symmetrical cyclopropanone mechanism.

During the studies of the rearrangement of tetrabromo ketones, it was found that if a cyclopropanone was an intermediate in these reactions, this was cleaved in an abnormal way.[4] Therefore it is of interest to discuss whether the rearrangement of a 1,1,3,3-tetrahalo-2-one can follow a semibenzilic acid mechanism.

The Favorsky rearrangement of 1,1,3,3-tetrabromo-2-ones yields 2-alkyl-3,3-dibromoacrylic acids; in the case of 1,1,3,3-tetrabromoacetone, 3,3-dibromoacrylic acid.[4]

In the case of the higher tetrabromo ketones the situation with respect to an eventual semibenzilic acid mechanism is not clear. The question is still open whether a primary or a secondary bromine would be expelled from the intermediate anion.

Examination and discussion of the rearrangement of 1,1,3,3-tetrabromoacetone (XIX) gave valuable information. In Scheme 6 the rearrangement of



XIX XX XXI

SCHEME 6

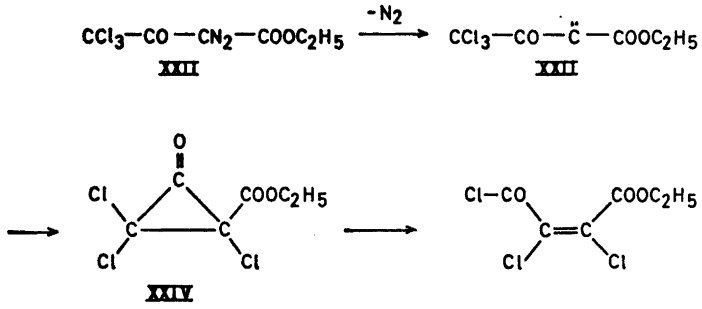
this compound according to a semibenzilic acid mechanism is shown. In this reaction 2,3,3-tribromopropionic acid (XX) would be an intermediate. However, treatment of this acid with base is known to give *cis*-2,3-dibromoacrylic acid (XXI).[4,19] Therefore a semibenzilic acid mechanism is ruled out in this case, and it seems plausible to assume that this mechanism is not valid for the rearrangement of other polybromo ketones.

The ketocarbene mechanism

The Wolff rearrangement, the rearrangement of a diazoketone to a saturated acid, is known to proceed in some cases *via* a ketocarbene; in most cases the loss of nitrogen from the diazoketone and migration to a ketene are considered as concerted processes.[20]

The rearrangement of trichloroacetyldiazoacetate XXII has been studied by Weygand and Koch; Scheme 7.[21] These authors suggest a ketocarbene, XXIII, as intermediate, and this is considered to rearrange to a chloro-substituted cyclopropanone intermediate, XXIV. As pointed out by Weygand and Koch this rearrangement is very like a Favorsky rearrangement.

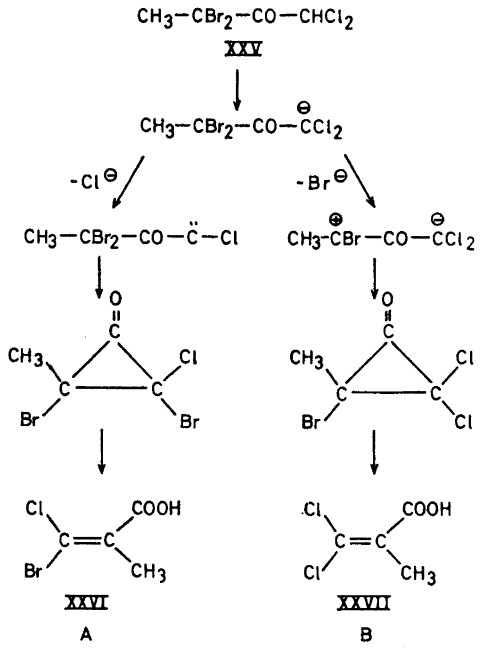
Hitherto it has only been little discussed, that a ketocarbene is a probable intermediate in the Favorsky rearrangement.[10,22] It may be of special interest to discuss it in connection with the rearrangement of polyhaloketones. As mentioned above, the rearrangement of both tri- and tetrabromo ketones is somewhat doubtful when applied to the cyclopropanone mechanism. In the ketocarbene mechanism a hydrogen and a halogen are lost from the same carbon.



SCHEME 7

Recently Conia and Salaün reported that 2-bromo-4,4-dimethylcyclobutanone, an α-bromoketone containing an α-hydrogen but no α′-hydrogen, does rearrange as easily as 2-bromo-3,3-dimethylcyclobutanone. According to Conia *et al.* this favours a semibenzilic acid mechanism rather than a cyclopropanone mechanism.[18] However, it can also favour a ketocarbene mechanism.

A good model substance for testing a ketocarbene mechanism is 1,1-dichloro-3,3-dibromobutanone-2. This substance was prepared by an Arndt-Eistert synthesis; this synthesis is described in a separate paper.[23]



SCHEME 8

1,1-Dichloro-3,3-dibromobutanone-2 (XXV) has only one α-proton. Analysis of the rearranged product shows which of the halogens is lost together with the proton, and Scheme 8 visualizes the situation. If a ketocarbene mechanism is operating, route A, the two geometrical isomers of acid XXVI or any other dihalo acid containing one chlorine and one bromine or two bromines are the only possible products. On the other hand, a cyclopropanone mechanism would result in the dichloro acid XXVII.

Elementary analyses of the isolated acid showed that it is a dichloro acid and the melting point (63—64.5°C) is in agreement with that of 3,3-dichloro-2-methylacrylic acid.[24] These data rule out a ketocarbene mechanism.

Although some objections can be raised against the cyclopropanone mechanism, it seems to be the most relevant for the rearrangements of tri- and tetrahalo ketones.

EXPERIMENTAL

4,4-Dimethyl-cis-*2-pentenoic acid* (X), was prepared according to Ref. 7, b.p. 60—61°C/0.8 mm, $n_D^{25} = 1.4432$.

2-Bromo-4,4-dimethyl-trans-*2-pentenoic acid* (IX). To 6.4 g of 4,4-dimethyl-*cis*-2-pentenoic acid dissolved in 100 ml of carbon tetrachloride was added 8.0 g of bromine. After 90 h, when the bromine colour had disappeared, the solvent was evaporated *in vacuo* yielding a faint yellow oil (8.3 g). This oil was treated with 10.0 g of potassium hydroxide dissolved in 100 ml of ethanol. Heat was evolved and potassium bromide separated at once. After 4 h, 200 ml of water was added, the aqueous phase extracted with ether (5 × 50 ml), the ether phase dried and the solvent evaporated yielding 4.5 g (43 %) of a yellow oil. This crude oil was analyzed by NMR and consisted of the two *cis-trans*-acids IX and XII and the ratio IX/XII was about 3:1. When the oil was left in a refrigerator (0°C) for one week, a crop of crystals separated; 2.5 g, m.p. 62—64°C, yield 24 %. Recrystallization from light petrol raised the m.p. to 68—69°C, lit. m.p. 69—70°C.[2]

1,1-Dichloro-3,3-dibromobutanone-2, XXV was prepared according to Ref. 23, m.p. 51—51.5°C.

3,3-Dichloro-2-methylacrylic acid (XXVII). 1.2 g of 1,1-dichloro-3,3-dibromobutanone-2 was treated at 80°C with 2.5 g of sodium bicarbonate in 30 ml of water for 4 h. The solution was worked up in the usual way.[4] From the acidic extracts 0.4 g of crystals, m.p. 55—57°C, were collected, yield 64 %. Recrystallization from light petrol raised the m.p. to 63—64.5°C. The m.p. of 3,3-dichloro-3-methylacrylic acid is quoted by Gottlieb as 64°C.[24] (Found: C 30.96; H 2.63; Cl 45.45. Calc. for $C_4H_4Cl_2O_2$: C 31.00; H 2.60; Cl 45.75).

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