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Favorsky Rearrangements

XV.* Products and By-products from the Rearrangement of Tetrahalo Ketones

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Treatment of 1,1,3,3-tetrahalo-2-ones with aqueous sodium carbonate or sodium bicarbonate yielded a mixture of acidic components, which could be separated by TLC and most of the main components identified by NMR and mass spectrometry. All the tetrahalo ketones studied yielded the expected Favorsky product, 3,3-dihaloacrylic acids (I). In addition, the tetrachloro and tetrabromo ketones yielded in general 2-hydroxy-3,3-dihalo carboxylic acids (II) and 2,2-dihalo acids (III); the latter formed in a haloform fission. From the treatment of 1,1,3,3-tetrachloroacetone a small amount of chloranilic acid (VIa) could be isolated, while 1,1,3,3-tetraiodo acetone yielded 2,3,3-triiodoacrylic acid (VIIc), iodopropiolic acid (IX), and *cis*-3-iodoacrylic acid (VIIIc). The mechanisms for the formation of the various acids are discussed.

The Favorsky rearrangement has been carefully studied for mono-, di-, and trihalo ketones, see Refs. 1 and 2 for comprehensive articles in this field. But up to now only two articles seem to have been published concerning the rearrangement of tetrahalo ketones.[3,4] The present authors have found that the Favorsky rearrangement of a number of 1,1,3,3-tetrabromo-2-ones gave 3,3-dibromo-2-alkylacrylic acids.[3] From studies of the rearrangement of 1,1-dichloro-3,3-dibromo-2-butanone a carbene mechanism could be excluded.[4]

It is well known that both chloro and bromo ketones can be used as starting material in the Favorsky rearrangements,[1] but Loftfield and Schaad reported that chloro ketones should be preferred due to unwanted side reactions in the rearrangement of the bromo ketones.[5,6] From the rearrangement of 1,1,3-trihaloacetones Rappe found that the chloro and bromo isomers gave about the same yield.[7,8]

Very recently Nace and Olsen reported the first (and only) example of a rearrangement of an iodo ketone. They studied the rearrangement of 2α-

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iodo-, 2α-bromo-, and 2α-chlorocholestan-3-one, and they found that the nature of the halogen has little effect on the yield of rearranged product.[9] From kinetic measurements of the increasing amount of halide ions in the reaction mixture the authors found that the order of reactivity was iodo> bromo>chloro.

In the present investigation we have studied the rearrangement of 1,1,3,3-tetrachloro-, 1,1,3,3-tetrabromo-, and 1,1,3,3-tetraiodoacetone, 1,1,3,3-tetrachloro-, 1,1,3,3-tetrabromo-, and 1,1-dichloro-3,3-dibromo-2-butanone. The acidic products were analyzed by means of thin layer chromatography (TLC), NMR and mass spectrometry, and special attention was paid to the identification of the observed by-products.

Rearrangement of 1,1,3,3-tetrachloroacetone. The commercial sample of 1,1,3,3-tetrachloroacetone was carefully purified by distillation on a spinning band column. By mass spectrometry it could be shown that it did not contain any chloranil or chloranilic acid. (It is possible to prepare 1,1,3,3-tetrachloroacetone from chloranil.[10]) The crude mixture of acidic products were isolated as an ethereal extraction residue and this was analyzed by NMR and TLC. It contained at least five components, Ia—Va; in NMR we obtained a spectrum with five singlets. The ratio for the compounds Ia:IIa:IIIa:IV:V was estimated to be 1.0:6.9:2.1:2.5:1.4. From the acidic extract we isolated chloranilic acid VIa as yellow-reddish crystals or its dark brown-violet sodium salt in less than 1 % yield. The disodium salt was also found to crystallize directly from the basic extract. The identification was done by mass spectrum, the authentic sample prepared according to Graebe.[11] Since VIa contained no protons on carbon atoms and since it did not move on TLC, it was not among the (at least) five components detected by NMR and TLC.

By comparison with authentic samples it could be established that Ia, IIa, and IIIa were 3,3-dichloroacrylic acid, 2-hydroxy-3,3-dichloropropionic acid, and dichloroacetic acid, respectively. For the preparation of 2-hydroxy-3,3-dichloroacetic acid, see below. The two components IV and V are still unknown.

The molar ratio for the products given above refers to experiments with sodium carbonate as base. In experiments with sodium bicarbonate the same components were found, but the amount of the acids IIa, IIIa, and VIa was lower.

Rearrangement of 1,1,3,3-tetrabromoacetone. The present authors have found that from this ketone 3,3-dibromoacrylic acid could be isolated in 63 % yield using sodium bicarbonate and in only 12 % yield using sodium carbonate.[3] In the present investigation we have found by NMR and by TLC that the crude acidic extract from the treatment with sodium carbonate contained three components in the molar ratio 24:4:1. By comparison with authentic samples the components could be established as 3,3-dibromoacrylic acid (Ib) (main product), 2-hydroxy-3,3-dibromopropionic acid (IIb), and dibromoacetic acid (IIIb), respectively. All attempts to isolate bromanilic acid (VIb) were in vain.

Preparation and rearrangement of 1,1,3,3-tetraiodoacetone. 1,1,3,3-Tetraiodoacetone was prepared according to the method of Gupta *et al.*[12] with the modification that iodine was added prior to the addition of potassium permanganate.

In this way the yield was increased from 1 % to 10 %. A detailed description of the synthesis of polyiodo acetones will be given elsewhere. The halo ketone was analyzed by NMR and was found to consist of one single component. By mass spectrometry the calculated molecular peaks were obtained.

The rearrangement of 1,1,3,3-tetraiodoacetone using sodium carbonate yielded (after evaporation of the ether) a semisolid black-brown coloured acidic residue, the colour probably due to free iodine. The reaction was run for either 26 h or 95 h. TLC showed that at least three acids have been formed, the NMR-spectrum of the residue indicated only two components in the ratio 1.2:1.0. By comparison with authentic samples the two acids could be identified as 3,3-diiodoacrylic acid (Ic),[13] and 3-iodoacrylic acid.[14] Another acid, only detectable by TLC, was identified by its mass spectrum as 2,3,3-triiodoacrylic acid (VIIc).[13] Due to the absence of any other protons than in the carboxylic group, this acid gives no peaks in NMR. Iodopropiolic acid, which was shown to be formed from 3,3-diiodoacrylic acid under the rearrangement conditions, might also be expected to be present in the reaction mixture. However, authentic samples of 2,3,3-triiodoacrylic acid and iodopropiolic acid gave identical R_F-values and identical fragmentation patterns. Verification of the presence of iodopropiolic acid in the reaction mixture was thus not possible.

After treatment with boiling water the semisolid ethereal residue gave directly 15 % of pure 3,3-diiodoacrylic acid. The oily residue after this treatment was boiled with carbon tetrachloride. Upon cooling, crystals of 2,3,3-triiodoacrylic acid could be isolated.

The 3-iodoacrylic acid was of unknown configuration,[14] but NMR-analyses provided a possibility for a safe structure determination. For 3-chloro- and 3-bromoacrylic acid one of us has reported a coupling constant for the *cis*-acid of 8—8.5 Hz and for the *trans*-acid a constant of 14.5 Hz.[7] In the present case we found 9.1 Hz, in rather good agreement with the predicted value for the *cis*-isomer. It was found that the acid could be isomerized by a trace of bromine in direct sun-light. The other isomer gave a coupling constant of 14.9 Hz. Thus the acid previously described by Stolz is *cis*-3-iodoacrylic acid, VIIc,[14] compare also Bowden.[15]

Rearrangement of 1,1,3,3-tetrachloro-2-butanone. The starting ketone, which seems not to have been described before, was prepared by chlorination of 2-butanone and was purified by distillation in a spinning-band column. NMR indicated only one component. It crystallized when kept in a refrigerator, m.p. 8.5°C.

The tetrachloro ketone was reacted either with a 1.0 M sodium bicarbonate solution for 20 h or with a 1.0 M sodium carbonate solution for 4 h. Nearly the same amount of ethereal residue was isolated in the two reactions. By NMR, mass spectrometry, and TLC three components were identified, 3,3-dichloro-2-methacrylic acid (Id),[4] 2-hydroxy-3,3-dichloroisobutyric acid (IId),[16] and 2,2-dichloropropionic acid (IIId). From the bicarbonate reaction the product ratio Id:IId:IIId was 1.0:3.3:0, from the carbonate solution 1.0:7.0:0.4.

Rearrangement of 1,1,3,3-tetrabromo-2-butanone. This reaction has previously been studied by the present authors, who reported a 51 % yield of 3,3-dibromo-2-methacrylic acid (Ie) in rearrangements with sodium carbonate, while the yield was 52 % in experiments with sodium bicarbonate.[3] NMR

and TLC showed that this acid was the single acidic component formed in more than traces.

Rearrangement of 1,1-dichloro-3,3-dibromo-2-butanone. This rearrangement has been studied by Rappe, who isolated 64 % of 3,3-dichloro-2-methacrylic acid (Id).[4] In the acidic ethereal residue 2-hydroxy-3,3-dichloroisobutyric acid (IId) could be identified by NMR, mass spectrometry, and TLC. NMR gave the molar ratio Id:IId as about 10:1.

Preparation of 2-hydroxy-3-halosubstituted acids. In connection with the present investigation it was of interest to prepare authentic samples of some 2-hydroxy-3-halosubstituted acids. These acids are in general prepared in bad yields by hydrolysis of the corresponding cyanohydrin, which in turn is prepared from the halo ketone and hydrogen cyanide.

Ferris and Marks found that chloroacetone cyanohydrin was prepared more convenient if chloroacetone was first treated with sodium bisulfite and thereafter treatment with sodium cyanide without isolation of the addition compound.[17] Using this method followed by hydrolysis of the cyanohydrin we prepared five 2-hydroxy-3-halosubstituted acids, the results are collected in Table 1. In most cases the cyanohydrin was not isolated prior to the hydrolysis.

DISCUSSION

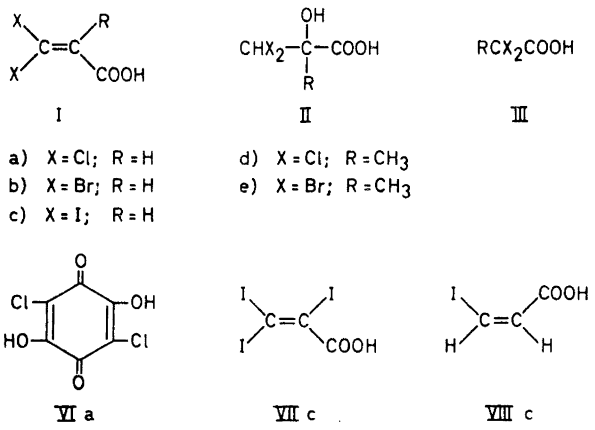
The variety of acids identified in the acidic ethereal extracts from the reaction of tetrahalo derivatives of acetone and 2-butanone are given in Scheme 1. One important question is to differentiate between products formed in com-

Table 1. 2-Hydroxy-3-halosubstituted acids prepared by analogy with the method of Ferris and Marks.[17]

$R-\underset{\displaystyle R'}{\overset{\displaystyle OH}{\overset{\vert}{\underset{\vert}{C}}}}-CO_2H$	$R-CO-R'$ [Ref. No.]	Overall yield %	m.p. °C corr.	lit. m.p. °C	Ref. No.
$R=H$ $R'=CHCl_2$	commercial	39	76–77	76.5–77	16
$R=H$ $R'=CHBr_2$	[18]	19	partly not crystalline		21
$R=CH_3$ $R'=CHCl_2$	[19]	68	87.5–88.5	82–83	22, 23
$R=CH_2Cl$ $R'=CH_2Cl$	commercial	48	91–92	93–94	24
$R=CH_2Br$ $R'=CH_2Br$	[20]	22	73–75	new compound	

petitive reactions and those formed in consecutive reactions. Another question is the mechanisms for the formation of these products.

The acids Ia and IIa could be recovered completely unchanged when treated under the conditions used in the rearrangement; thus these acids and chloranilic acid (which is only slightly soluble in aqueous basic solutions)



Scheme 1.

are formed in competitive reactions. As mentioned above, during the rearrangement of 1,1,3,3-tetraiodoacetone it has been shown that iodopropiolic acid was formed from 3,3-diiodoacrylic acid under the conditions used. Therefore the tri- and monoiodo acids VIIc and VIIIc are formed in competitive reactions, probably a type of disproportionation, which apparently takes place before the formation of 3,3-diiodoacrylic acid, *e.g.* disproportionation of starting tetraiodoketone or of the intermediate triiodocyclopropanone. Iodoketones are known to be highly unstable under various conditions and free iodine was observed during the work-up of the synthesis. 1,1,3-Triiodoacetone and 2,3-diiodocyclopropanone could be expected to give *cis*-3-iodoacrylic acid in analogy with the chloro and bromo isomers.[7,8] 2,3,3-Triiodoacrylic acid might also be formed by addition of iodine to iodopropiolic acid.

Now the question arises how all these products are formed. The formation of the Favorsky products Ia—e has been discussed previously,[3,4,25] the halogenated acids IIIa and IIId are formed in a haloform fission of the tetrahalo ketones. Mono- and dihalogenated propionic acids are identified among the products from the weak base-catalyzed halogenation of 2-butanone.[26–28]

More experimental work is needed to clarify the mechanisms for the dimerization to chloranilic acid, VIa, and for the formation of the hydroxyhalo acids IIa, IIb and IId. For the formation of the latter compounds a substitution of the 2,3,3-trihalo derivatives of propionic acid and isobutyric acid seems to be excluded by the observation that elimination is the ordinary reaction reported under these alkaline conditions.[29,30] 2-Hydroxycarboxylic acids are known to be formed in an internal Cannizzaro reaction from α-ketoaldehydes and 1,1-dihalo-2-ones.[31]

From the discussion of the identified products above, it is evident that the alkaline treatment of tetrachloro ketones yielded a larger number of compounds than the alkaline treatment of the tetrabromo and tetraiodo ketones. This is interesting and is opposite to the behavior of the halocyclohexyl ketones studied by Loftfield and Schaad [6] and different from the behavior reported by Olsen *et al.*[9] for halo steroids.

It was also observed that the amounts of the acids IIa, IIe, IIIa, and IIIe increased when a stronger base was used for the reaction. Another result of the use of a stronger base was stronger colour on the alkaline reaction mixture (black-violet), which markedly faded on acidification of the reaction solution.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian model A-60 spectrometer and the mass spectra on an LKB 9000. The mass spectra were taken on pure samples or on samples directly from the TLC-plate using the direct inlet.

1,1,3,3-Tetrachloroacetone. A commercial sample (Aldrich) was purified by distillation on a Büchi spinning-band column. The fraction 78.5—79.5°C/19 mm was collected, $n_D^{20}=1.4949$. NMR-spectrum gave only one singlet.

1,1,3,3-Tetrabromoacetone. This compound was prepared according to Ref. 32, b.p. 129—130°C/7 mm, m.p. 37—38°C.

1,1,3,3-Tetraiodoacetone. This compound was prepared according to Gupta *et al.*[12] with the modification that iodine and potassium iodide was added prior to the addition of potassium permanganate. Recrystallization from acetic acid yielded pure crystals, m.p. 143—144°C. Yield 10 %. NMR-spectrum on a DMSO-solution contained one singlet at $\delta=6.06$ ppm; the mass spectrum had the molecular peak at 562. The preparation of polyiodoacetones will be discussed elsewhere.

1,1,3,3-Tetrachloro-2-butanone. A gentle stream of chlorine was let into a mixture of 2.0 moles of 2-butanone in 200 ml of aqueous hydrochloric acid (1:1) at room temperature. The temperature of the exothermic reaction was gradually raised to 80°C in the first two hours and maintained there for 12 h. The chlorination was continued at 115°C for additional 24 h by heating. The heavy oil was separated from the hydrochloric acid and in case of a black tarry oil it was distilled, the fraction of 60°C/25 mm being collected.

The heavy oil was placed in a washing flask arranged for efficient gas inlet, the flask surrounded with a shield with the inside covered with aluminia sheet to give efficient reflection. The chlorination was continued with a photo-sun lamp (1000 W) at a close distance (about 20 cm) on the front of the reflex shield to give vigorous reflux. After 24 h the yellow oil was distilled and a fraction b.p. <85°C/10 mm was collected (178 g).

The crude fraction was redistilled and fractionated on a Büchi spinning-band column. From 40 ml crude distillate 20 ml pure 1,1,3,3-tetrachloro-2-butanone was collected. b.p. 76.0—76.5°C/19 mm, $n_D^{20}=1.4795$, m.p. 8.5°C.

1,1,3,3-Tetrabromo-2-butanone was prepared according to Ref. 32, m.p. 52.5—53.5°C.

1,1-Dichloro-3,3-dibromo-2-butanone was prepared according to Ref. 33, m.p. 51—51.5°C.

Table 2. Authentic samples for identification purpose.

Acid	Ref. No.	Recrystallized from	m.p. °C	b.p./mm	NMR-spectrum δ (ppm)	solvent
Ia	36	Hexane	77	—	6.38	$CHCl_3$
Ib	3	Light petrol	86.5—87	—	7.20	CCl_4
Id	4	—»—	63—64.5	—	2.12	$CHCl_3$
Ie	3	H_2O	98.5—99	—	2.24	CCl_4
IIIa	[a]	—	—	—	6.03	$CHCl_3$
IIIb	37	—	—	122—127/10		
IIIc	38	Water	110	—		
IIId	[a]	—	—	—	2.32	$CHCl_3$
VI	11	—	—	—	—	—
VIIIc	14	Hexane	64—65	—	6.98, 7.69	$CHCl_3$

[a] Determined on crude product.

Table 3. NMR-data on the crude products from the rearrangements.

1,1,3,3-Tetrachloro-acetone			1,1,3,3-Tetrabromo-acetone			1,1,3,3-Tetraiodo-acetone			1,1,3,3-Tetrachloro-2-butanone			1,1-Dichloro-3,3-dibromo-2-butanone		
Acid	δ (ppm)	ratio	Acid	δ (ppm)	ratio	Acid	δ (ppm)	ratio	Acid	δ (ppm)	ratio	Acid	δ (ppm)	ratio
Ia	6.38	1.0	Ib	7.04	24	Ic	7.75	—	Id	2.05	1.0	Id	2.05	10
IIa	4.51, 6.13	6.9	IIb	4.64, 6.12	4	VIIc	6.98	—	IId	1.55, 5.97	7.0	IId	1.55, 5.97	1
IIIa	6.10	2.1	IIIb	5.98	1	VIIIc	7.69	—	IIId	2.20	0.4	—	—	—
IV	4.05	2.5	—	—	—	—	—	—	—	—	—	—	—	—
V	8.03	1.4	—	—	—	—	—	—	—	—	—	—	—	—

Thin layer chromatography (TLC). We used plates with 0.25 mm Kieselgel G, as eluting solvent a water containing mixture of acetic acid, hexane, and benzene (1:3:6 by volume). A similar eluting solvent has previously been used by Rappe and Hellström.[34] After 40 min the front had moved 16 cm. The chromatograms were developed either using bromocresol green after drying at 100°C for 1 h or according to Pásková *et al.*[35] after drying at room temperature.

Favorsky rearrangement. General procedure. The halo ketones were treated with 1.0 M solutions of sodium carbonate or sodium bicarbonate (10 ml/mmole ketone) at 22°C under efficient stirring. Aliquots were withdrawn until constant value when titrated with hydrochloric acid (0.1 M). The mixture was extracted twice with ether (30 ml/100 ml solution) thereafter acidified and reextracted four times with ether (30 ml/100 ml solution). The ether phase was washed with water, dried ($MgSO_4$) and the ether evaporated. The residue was analyzed by NMR and TLC and compared with authentic samples, see Tables 1, 2, and 3.

Rearrangement of 1,1,3,3-tetrachloroacetone. 100 mmoles (19.6 g) of the haloketone was used, the reaction mixture became immediately strongly coloured in black-violet. The reaction was run for 1.25 h, and the yield was 1.4 g of a semisolid residue.

Rearrangement of 1,1,3,3-tetrabromoacetone. In this rearrangement 20 mmoles (7.5 g) of the halo ketone was used. The reaction mixture became dark-coloured pretty soon. The reaction was interrupted after 1 h and yielded 1.7 g of a brown crystalline crop.

Rearrangement of 1,1,3,3-tetraiodoacetone. 20 mmoles (11.2 g) of the halo ketone yielded 2.6 g of a black-brown crystalline mass. When treated with boiling water the ethereal residue yielded 0.9 g of light-brown needles, m.p. 131—132.5°C. Homolka and Stolz [13] gave the m.p. 133°C for 3,3-diiodoacrylic acid after recrystallization from water. The oily residue was extracted with boiling carbon tetrachloride. Upon cooling, crystals could be isolated, m.p. 205—207°C. The m.p. of 2,3,3-triiodoacrylic acid is given as 207°C.[16]

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