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Favorsky Rearrangements

IV. The Preparation of Some *cis*-α,β-Unsaturated Acids

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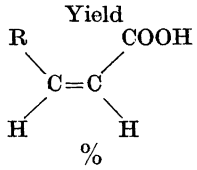
Ten *cis*-α,β-unsaturated acids have been prepared in good yields from the rearrangement of 1,3-dibromo-2-ones. The method seems to have general applicability.

The *cis*-isomers of α,β-unsaturated acids are in general more difficult to prepare than the *trans*-isomers. Often the *cis*-acid is prepared together with the thermodynamically more stable *trans*-isomer, and the separation of the two isomers is laborious; the boiling points are very close. One way of synthesizing only the *cis*-isomer is by hydrogenation of the corresponding acetylenic acid using special catalysts,[1,2] but this is laborious too, especially for the preparation of acetylenic acids. Because of this lack of good synthetic methods, only a limited number of *cis*-α,β-unsaturated acids are described in the literature.

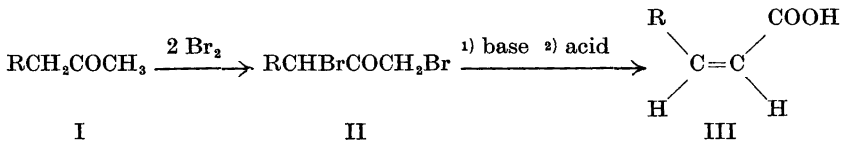
The Favorsky rearrangement of α,α'-dibromo ketones is known to give α,β-unsaturated acids.[3] In one example, the rearrangement of 1,3-dibromo-3-methylpentanone-2, Wagner and Moore found about the same quantities of both geometric isomers.[4] From this single experiment the Favorsky rearrangement was presumed to have no geometric specificity,[3] although Demarçay had already shown geometric specificity in 1880 for the rearrangement of 4,4-dibromo-2-methylacetoacetic acid.[5,6] Another geometrically specific Favorsky rearrangement was reported by Wallach for the preparation of 6-methyl-*cis*-2-heptenoic acid, but this experiment seems to have been neglected too.[7] Recently, however, one of us found that the rearrangement of 1,3-dibromobutanone-2 gave only one isomer, *cis*-crotonic acid.[8] The yield of this acid was as high as 77 %. Preliminary results showed that the method could have general applicability for preparing *cis*-α,β-unsaturated acids. These experiments were repeated under different conditions and in all cases the yields were good and the reaction showed geometric specificity throughout the series. Ten bromoketones were rearranged and the acids obtained were examined by means of NMR. In all cases the chemical shifts and the coupling constants (12 cycles/sec) showed that the products were pure *cis*-acids; see Table 1.

Table 1. Preparation and rearrangement of 1,3-dibromo-2-ones.

R	Yield $RCHBrCOCH_2Br$ %	Base	Yield  %	Time h	J_{HH} c/s
CH_3	58	$KHCO_3$	77	2½	12
C_2H_5	57	»	68	3	»
C_3H_7	51	»	61	24	»
iso-C_3H_7	58	»	85	24	»
C_4H_9	65	»	64	20	»
tert-C_4H_9	49	»	75	48	14
C_5H_{11}	40	»	50	48	12
$(CH_3)_2CH(CH_2)_2$	35	»	58	48	»
C_6H_{13}	41	»	28	96	»
$HOOCCH_2$	60	»	27	19	»

Another synthesis with geometrical specificity was reported by Kennedy *et al.* who obtained pure *cis*-α,β-unsaturated esters in high yields from the rearrangement of 1,1-dibromo-2-ones using sodium methoxide or methanolic triethylamine as a base.[9]

Among the ten acids, two were prepared for the first time. The method seems to have general applicability, so that *cis*-2-enoic acids (III) can be prepared from a methyl ketone (I) having the same number of carbon atoms in a two step synthesis according to the following scheme:



I II III

This synthetic route for preparing *cis*-2-enoic acids seems to be more advantageous than that proposed by Kennedy *et al.*[9]

Several methyl ketones (I) are commercial, others can be prepared by an acetoacetic ester synthesis followed by a ketonic hydrolysis. The 1,3-dibromo-2-ones (II) used as starting material in the rearrangement are prepared by the acid catalyzed bromination of ketones according to a method given by Rappe.[10] The yields of the dibromination are given in Table 1. Some of the dibromo ketones are new compounds. Their structures were proved by NMR-analysis. A mono- and a dibromo compound of 6-methylheptanone-2 were prepared by Wallach and given the structures 1-bromo- and 1,1-dibromo-6-methylheptanone-2.[7] However, NMR-spectra showed that the structures should be 3-bromo- and 1,3-dibromo-6-methylheptanone-2, respectively. In all cases the two bromine atoms were substituted symmetrically.

In Table 1 the optimal yields of the rearrangement are also collected. In all cases the best yields were obtained when potassium bicarbonate was used as base. The reactions were followed by sampling at various time intervals and titrating with acid. The reactions were interrupted when constant titration values were obtained (see Table 1). When the syntheses were interrupted about 2 equivalents of base were consumed.

In this connection it is interesting to point out that three isomers of dihalobutanone-2 have been treated under Favorsky conditions. Both 1,3- and 1,1-dibromobutanone-2 gave isocrotonic acid,[8,9] while 3,3-dichlorobutanone-2 gave 2-methylacrylic acid.[11] The theoretical aspects of this and further aspects of the mechanism of the reaction will be published at later date together with aspects of the mechanism for the rearrangement of other dibromo and tribromo ketones.[12] Under the same experimental conditions the rearrangement of several tribromo methylketones also showed geometric specificity.[13-15]

Preparation of *cis*-2-enoic acids

Isocrotonic acid. The preparation of this acid is described in Ref. 8.

cis-*2-Pentenoic acid* was prepared by Bourguel [1] and by Schjånberg [2] from the hydrogenation of 2-pentynoic acid using a platinum or palladium catalyst. Schjånberg assigned this acid a *cis*-structure by analogy with the preparation of isocrotonic acid on the same manner.[2]

The rearrangement of 1,3-dibromopentanone-2 gave *cis*-2-pentenoic acid. The synthesis of isocrotonic acid showed great variation in the yields when different bases were used, weaker bases gave better yields than stronger bases; see Ref. 8, Table 1. The rearrangement of 1,3-dibromopentanone was also studied with different carbonates and bicarbonates as bases. The results of these experiments are collected in Table 2. Although the differences between the bases were not so pronounced as in the preparation of isocrotonic acid, it was found that potassium bicarbonate gave the best yield.

In small quantities (20 g) *cis*-2-pentenoic acids could be distilled without isomerisation using an oil pump. When distilled the acid could be stored in a refrigerator for six months without any detectible isomerisation. The acid crystallized at −60°C and had m.p. −43°C.

cis-*2-Hexenoic acid.* Two 2-hexenoic acids have been described, one crystalline (m.p. 36−37°C) and one liquid. The crystalline form has been assigned a *trans*-structure.[16] The *cis*-2-hexenoic acid was prepared by Bourguel by hydrogenation in the same way as the lower homologue.[1]

Crude products of good geometrical purity (*cis*) were obtained from the rearrangements of 1,3-dibromo-hexanone-2. Sodium and potassium bicarbonate were both used as bases, the sodium salt gave a 53 % yield, the potassium salt 61 %. It was possible to distill the acid without isomerization, and the distilled acid had m. p. 0−1°C.

4-Methyl-cis-*2-pentenoic acid.* One acid of this composition (2-isohexenoic acid) was prepared by Goldberg and Linstead according to a Doebner reaction of isobutyraldehyde.[17] Due to its low melting point (−22°C) and slow solidification, Linstead suggested that the acid was not geometrically pure.[18] Later

Table 2. Preparation of *cis*-2-pentenoic acid.

Base	Reaction time (h)	Yield % [a]
Na_2CO_3	3	53
K_2CO_3	3	54
$NaHCO_3$	5	63
$KHCO_3$	3	68

[a] mean values of at least two determinations

David and Imer assigned it a *trans*-structure from consideration of the synthetic method.[19] Goldberg and Linstead's experiment was repeated by us and NMR-analysis showed that the acid was exclusively *trans* (coupling constant 18 cycles/sec). The melting point of this sample was −25°C. David and Imer also tried to prepare the *cis*-isomer from the hypohalite oxidation of *cis*-isobutylideneacetone, but they obtained the *trans*-isomer.[19]

From the rearrangement of 1,3-dibromo-4-methyl-pentanone-2 it was possible to synthesize pure *cis*-2-isohexenoic acid in 81 % yield when sodium bicarbonate was the base and in 85 % yield when potassium bicarbonate was used. On cooling (ice-salt) the distilled acid crystallized, m.p. 15.5—17.5°C.

The melting points are worth examining. Contrary to the accepted rule, the *cis*-acid had a higher melting point than the *trans*-isomer, the difference was as much as 40°C. Often the higher melting isomer has been assigned a *trans*-structure without any real structure determination.[20]

cis-*2-Heptenoic* acid was prepared by Silwa and Maitte by hydrogenation.[21] From the rearrangement of 1,3-dibromoheptanone-2 a *cis*-acid was prepared in a 64 % yield using potassium bicarbonate. The melting point of this acid was found to be −19°C. The refractive index ($n_D^{25} = 1.4515$), is in rather good accordance with that reported by Silwa and Maitte,[21] ($n_D^{22} = 1.449$) and NMR-analyses showed that our acid was geometrically pure. An acid, probably the *trans*-acid, has been prepared by Morton *et al.* and found to have m.p. −12 to −11°C.[22]

4,4-Dimethyl-cis-*2-pentenoic acid.* Foreman and Mc Elvain prepared 4,4-dimethyl-*trans*-2-pentenoic acid by aldehyde condensation with malonic ester.[23] The *trans*-acid had m.p. 62—63°C. The *cis*-acid, hitherto unreported, was prepared by us from the rearrangement of the corresponding dibromo ketone, 4,4-dimethylpentanone-2, in a 75 % yield, and a m.p. 11—12°C was found for the pure *cis*-acid.

cis-*2-Octenoic acid* was prepared by Bourguel[1] and by Knight and Diamond.[24] The refractive index of these two preparations were different, Bourguel reported $n_D^{15} = 1.456$ [1] and Knight *et al.* reported $n_D^{20} = 1.4441$. The refractive index of the pure *cis*-acid prepared in this work (yield 50 %), $n_D^{25} = 1.4530$, agrees more with that found by Bourguel. Contrary to Knight *et al.*, who reported a m.p. −6°C, our product would not crystallize, even at −78°C.

6-Methyl-cis-*2-heptenoic acid.* The *cis*-acid was prepared by Wallach by a Favorsky rearrangement of 1,3-dibromo-6-methylheptanone-2, erroneously

given the structure 1,1-dibromo-6-methylheptanone-2.[7] Wallach used potassium hydroxide as base but he gave no yield for the rearrangement. Repeating his experiment we obtained a yield of 22 %. A better yield was obtained using potassium bicarbonate (58 %). It was not possible to get the acid to crystallize even at −78°C. The *trans*-acid has been reported to have m.p. 3°C.[25]

cis-*2-Nonenoic acid* was prepared by Delaby *et al.*,[26] Bourguel[1] and by Silwa and Maitte.[21] Bourguel reported a refractive index of $n_D^{15} = 1.458$, Silwa and Maitte $n_D^{21} = 1.445$. The refractive index of the *cis*-acid prepared using the Favorsky rearrangement $n_D^{25} = 1.4549$, yield 28 %, agrees more with that reported by, Bourguel. Although Delaby *et al.* report no crystallization at −15°C, we were able to get the acid to crystallize, m.p. 2—3°C. It is noteworthy that the m.p. of the *trans*-acid prepared according to a Doebner synthesis is given as 1—2°C.[27]

cis-*Glutaconic acid* can be prepared from the *trans*-acid by treating with acetic anhydride and hydrolyzing the resultant *cis*-glutaconic anhydride with water for 2 h at 10—12°C.[28] The yield of crude product is reported to be 37 %. *trans*-Glutaconic acid can be prepared from propiolic acid by treating it with sodium hydroxide.

A more convenient method for the preparation of *cis*-glutaconic acid seems to be the Favorsky rearrangement of 3,5-dibromolaevulic acid, although the yield of the rearrangement was not more than 27 %. The dibromo ketone can be prepared in a 60 % yield.

EXPERIMENTAL

The micro analyses were carried out by the Analytical Laboratory at the Chemical Institute, University of Uppsala. The NMR-spectra were recorded on a Varian model A—60 spectrometer.

Preparation of α,α'-dibromo ketones. General procedure

The ketone was mixed with 48 % hydrobromic acid (100 ml/mole ketone) and chilled to 0°C with ice-water. Bromine was added dropwise (2 mole/mole ketone). After addition of water (200 ml/mole bromine) the heavier organic layer separated and it was immediately fractionated under reduced pressure. The yields of the bromo ketones are given in Table 1.

1,3-Dibromopentanone-2 was prepared according to Ref.[10], yield 57 %, b.p. 91—94°C/13 mm, $n_D^{25} = 1.5176$.

1,3-Dibromohexanone-2. 200 g (2.0 moles) of hexanone-2 gave 265 g of dibromoketone (51 %), b.p. 96—98°C/10 mm, $n_D^{25} = 1.5080$. (Found: C 28.02; H 3.92; Br 61.94; Calc. for $C_6H_{10}Br_2O$: C 27.93; H 3.91; Br 61.96).

1,3-Dibromo-4-methylpentanone-2. 200 g (2.0 moles) of 4-methylpentanone-2 gave 300 g of dibromoketone (58 %), b.p. 95—97°C/10 mm, $n_D^{25} = 1.5099$. (Found: C 27.79; H 3.90; Br 62.12; Calc. for $C_6H_{10}Br_2O$: C 27.93; H 3.91; Br 61.96).

1,3-Dibromoheptanone-2. 228 g (2.0 moles) of heptanone-2 gave 352 g of dibromoketone (65 %), b.p. 111—114°C/9 mm, $n_D^{25} = 1.5043$. (Found: C 30.86; H 4.44; Br 58.95; Calc. for $C_7H_{12}Br_2O$: C 30.91; H 4.45; Br 58.76).

1,3-Dibromo-4,4-dimethylpentanone-2. 68 g (0.6 moles) of 4,4-dimethylpentanone-2 gave 80 g of dibromoketone (49 %), b.p. 100—102°C/10 mm, $n_D^{25} = 1.5071$. (Found: C 31.00; H 4.44; Br 58.86; Calc. for $C_7H_{12}Br_2O$: C 30.91; H 4.45; Br 58.76).

1,3-Dibromooctanone-2. 256 g (2.0 moles) of octanone-2 gave 227 g of dibromoketone (40 %) b.p. 129—131°C/10 mm, $n_D^{25} = 1.5001$. (Found: C 33.58; H 4.91; Br 56.03; Calc. for $C_8H_{14}Br_2O$: C 33.59; H 4.93; Br 55.88).

1,3-Dibromo-6-methylheptanone-2. 11.4 g (0.09 moles) of 6-methylheptanone-2 gave 9.0 g of dibromoketone (35 %) b.p. 117–120°C/10 mm, $n_D^{25} = 1.4997$. Wallach gave b.p. 130–132°C/12 mm.[7]

1,3-Dibromononanone-2. 100 g (0.7 moles) of nonanone-2 gave 85 g of dibromoketone (41 %) b.p. 146–148°C/11 mm, $n_D^{25} = 1.4983$. (Found: C 36.10; H 5.42; Br 53.53; Calc. for $C_9H_{16}Br_2O$: C 36.03; H 5.37; Br 53.27).

3,5-Dibromolaevulic acid. 116 g (1.0 mole) of laevulic acid gave 163 g of 3,5-dibromolaevulic acid, (60 %) m.p. 111–113°C.[29]

Preparation of *cis*-2-enoic acids. General procedure

To 0.1 mole of dibromoketone was added a solution of 0.4 mole of the required carbonate in 1000 ml of water or 0.8 mole of the bicarbonate in 1000 ml of water. The mixture was thoroughly stirred and when constant titration-values against methylorange were obtained, the solution was extracted with ether (5 × 100 ml), acidified with hydrochloric acid and again extracted with ether (10 × 100 ml). After drying, the ether phase was evaporated *in vacuo* (water pump) to prevent superheating and isomerization. When the pressure had fallen to 10 mm, the last traces of ether were removed with an oil pump (0.4 mm) during 30 min. The yields of the crude products are given in Table 1. NMR-analyses showed the crude products to be pure. Before elementary analyses the products were distilled once. The loss during the distillations were minimal.

cis-*2-Pentenoic acid*, b.p. 39–41°C/0.4 mm, $n_D^{25} = 1.4473$, m.p. −43°C. (Found: C 59.58; H 7.99; Calc. for $C_5H_8O_2$: C 59.98; H 8.05).

cis-*2-Hexenoic acid*, b.p. 71–73°C/0.2 mm, $n_D^{25} = 1.4495$, m. p. 0–1°C. (Found: C 63.17; H 8.81; Calc. for $C_6H_{10}O_2$: C 63.13; H 8.83).

4-Methyl-cis-*2-pentenoic acid*, b.p. 59.5 −60°C/0.2 mm, m. p. 15.5–17.5°C, $n_D^{25} = 1.4420$. (Found: C 62.75; H 8.87; Calc. for $C_6H_{10}O_2$: C 63.13; H 8.83).

cis-*2-Heptenoic acid*, b.p. 69–70°C/0.4 mm, m.p. −19°C, $n_D^{25} = 1.4515$. (Found: C 65.11; H 9.41; Calc. for $C_7H_{12}O_2$: C 65.60; H 9.44).

4,4-Dimethyl-cis-*2-pentenoic acid*, b.p. 60–61°C/0.8 mm, m.p. 11–12°C, $n_D^{25} = 1.4432$. (Found: C 65.31; H 9.42; Calc. for $C_7H_{12}O_2$: C 65.60; H 9.44).

cis-*2-Octenoic acid*, b.p. 75–76°C/0.3 mm, $n_D^{25} = 1.4530$. (Found: C 67.11; H 9.87; Calc. for $C_8H_{14}O_2$: C 67.57; H 9.92).

6-Methyl-cis-*2-heptenoic acid*, b.p. 93–94°C/0.2 mm, $n_D^{25} = 1.4518$.

cis-*2-Nonenoic acid*, b.p. 91–92°C/0.8 mm, m.p. 2–3°C, $n_D^{25} = 1.4549$. (Found: C 68.51; H 10.25; Calc. for $C_9H_{16}O_2$: C 69.19; H 10.32).

cis-*Glutaconic acid*, m.p. 115°C (crude product), 133.5–134.5°C (recrystallized acid). Malachowski [28] gave m.p. 136–136.5°C (pure acid), (117–124°C, crude product).

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