

## Stereospecific Elimination Reactions with Cyclic Ketone Cyanohydrins

TORKIL HOLM

*Department of Organic Chemistry, The Technical University, Copenhagen, Denmark*

The cyanohydrins of 2-methylcyclopentanone and of the *cis* and *trans* isomers of 2-methylcyclohexanone were dehydrated, and the corresponding 2 pairs of isomeric unsaturated nitriles were characterized. A clear-cut *trans* mechanism was demonstrated for the dehydration with phosphorus oxychloride in pyridine, whereas *cis* elimination occurred by the pyrolysis of the acetates. Preferential formation of the Saytzeff product with maximum hyperconjugation was observed by both methods. Hydrolysis of the four nitriles led to the corresponding acids.

The steric course of the dehydration of the cyanohydrins of 2-methylcyclopentanone and 2-methylcyclohexanone has not previously been clarified.<sup>2-4</sup> The results of King and Robinson<sup>4</sup> seem surprising since these authors obtained an almost quantitative yield of a single product, although currently accepted theory would predict more or less equal probability for the formation of two products of different structure. In the work presented here this result was revised, and the detailed steric course of the dehydration as effected by two different methods was ascertained.

By elimination of water from the *cis/trans* isomeric 2-methylcyclohexanone cyanohydrins, which result from the addition of hydrogen cyanide to 2-methylcyclohexanone, the sole product isolated was 6-methyl-1-cyclohexene-1-carboxynitrile<sup>2,3</sup> (III). In the present investigation the elimination of water from the isolated *cis* and *trans* isomers was performed by pyrolysis of the acetates as well as by reaction with phosphorus oxychloride in pyridine solution. The results illustrate the *cis*-mechanism for the pyrolysis reaction and a clear-cut *trans*-mechanism for the POCl<sub>3</sub>-pyridine reaction. The latter reaction yielded one single product, namely the unsaturated nitrile III. This result is consistent with the fact, that a *trans* proton is available only in the 2-position as shown in Fig. 1.

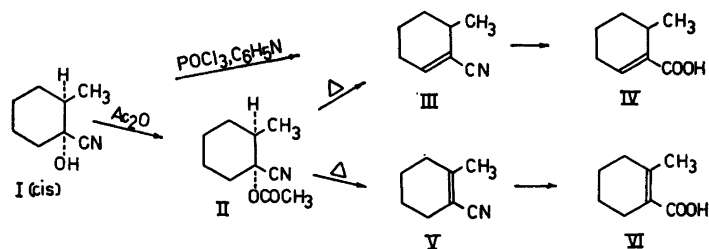


Fig. 1.

By the pyrolysis of the *cis* acetate II two products would be predicted, since *cis* protons are present in the 6 and the 2 positions. Actually both products III and V were obtained in a ratio of 2:3 as determined by gas chromatography. The reaction is thus shown to some extent to follow the Saytzeff rule.

The *trans* 2-methylcyclohexanone cyanohydrin was dehydrated by pyrolysis of the acetate yielding the anticipated product III. A small impurity of V in the product may well originate from a contamination of the starting material with some *cis* cyanohydrin. Dehydration of the *trans* cyanohydrin by means of  $\text{POCl}_3$ -pyridine led to a 7:3 mixture of V and III which clearly shows the preferential formation of the Saytzeff-product in this reaction.

Dehydration by means of  $\text{POCl}_3$ -pyridine of the mixture of the *cis* and *trans* cyanohydrin (Fig. 2), obtained from 2-methylcyclopentanone, yielded two products (VII) and (VIII), as demonstrated by gas chromatography. Samples of the pure products were prepared by fractional distillation and the following structures were assigned to the isomers on the basis of the NMR spectra. The spectra of III and VIII both showed a group of peaks between 6.45 and 6.65 ppm (using tetramethylsilane as an internal zero of reference), which is attributable to the vinylic proton. The signal was totally absent in the spectra of V and VII.

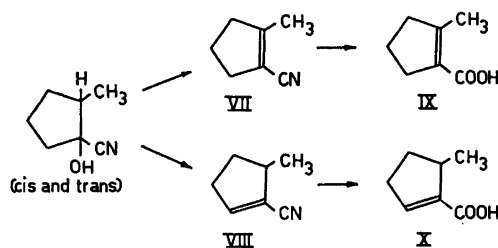


Fig. 2.

By hydrolysis of VII and VIII the acids IX and X were obtained, respectively. King and Robinson<sup>4</sup> from the same course of reactions reported the formation of VII and IX in a very high yield and did not mention VIII and X. In contrast, the present investigation showed by gas chromatography a 3:2 ratio of the nitriles VIII and VII in the crude elimination product.

Prolonged heating of the nitriles with pyridine hydrochloride in pyridine solution failed to effect any rearrangement, and the stability of the compounds was further proved by the fact that no change in product was observed when the hydrolysis of the nitriles was performed with 85 % phosphoric acid at 140° for 3 h instead of the standard treatment with alcoholic base.

### EXPERIMENTAL

The *cis* and *trans* 2-methylcyclohexanone cyanohydrins were prepared according to Nazarov *et al.*<sup>1</sup> From 60 g of crude product 40 g of *cis* compound was crystallized from petroleum ether, and 18 g of crude *trans* compound obtained as an oil from the mother liquor. The mixture of isomeric 2-methylcyclopentanone cyanohydrins was prepared according to King and Robinson.<sup>4</sup>

The *cis*-2-methylcyclohexanone cyanohydrin acetate was prepared by mixing 40 g of the cyanohydrin with 12 ml of acetic anhydride and adding at 20° 1 drop of conc. sulphuric acid. The temperature rose to 60° and was maintained there for 3–4 min. The mixture was poured onto ice and the crystals were filtered. After recrystallization from petroleum ether the yield was 43 g, m.p. 62°–63°. (Found: C 66.25; H 8.23; N 7.64. Calc. for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>: C 66.26; H 8.33; N 7.73). The *trans*-2-methylcyclohexanone cyanohydrin acetate was prepared by applying the same procedure to the crude *trans* cyanohydrin. The product was extracted with petroleum ether. The extract was washed with water and with a solution of sodium hydrogen carbonate. The oil obtained by evaporation of the solvent *in vacuo* was used without further purification.

Pyrolysis was performed at 500° as described by Burns *et al.*<sup>6</sup> The yield of isomer mixture from 43 g of *cis*-2-methylcyclohexanone cyanohydrin acetate was 26.5 g. From 18 g of the crude *trans* acetate 10 g of the unsaturated nitriles was obtained. Gas-chromatographic analysis of the pyrolysis products showed a III/V ratio of 40:60 for the *cis* acetate and 95:5 for the crude *trans* acetate.

Dehydration of the cyanohydrins by the phosphorus oxychloride method was performed by mixing 20 g of cyanohydrin with 20 g of pyridine and adding this mixture at 0° to a cooled mixture of 30 g of phosphorus oxychloride and 50 g of pyridine. The mixture was maintained at 10° for 30 min, at 30° for 30 min, and finally at 95° for 1 h. After cooling, the mixture was poured on ice, the oil extracted with ether, the extract washed with dilute hydrochloric acid and with water. After drying over magnesium sulphate the product was distilled *in vacuo*. By the use of a 45 cm column,<sup>7</sup> the separation of 20 g of a mixture of the isomeric methylcyclopentenitriles VII and VIII yielded 3.2 g of pure VII, b.p. 92°/40 mm,  $n_D^{25} = 1.4793$ , and 1 g of pure VIII, b.p. 85°/40 mm,  $n_D^{25} = 1.4627$ .

The mixture of isomeric methylcyclohexenenitriles obtained by pyrolysis of the *cis* acetate was dissolved in 2 volumes of petroleum ether and cooled to –70°. The crystals obtained were filtered and washed with cold petroleum ether. After recrystallization from the same solvent the product was gas-chromatographically pure. From 25 g of isomer mixture was obtained 8 g of pure V, m.p. –9° to –8°, b.p. 84°/10 mm,  $n_D^{25} = 1.4842$ . Pure IV was obtained by POCl<sub>3</sub>-pyridine dehydration of I, b.p. 81°/10 mm,  $n_D^{25} = 1.4767$ .

Hydrolysis of the nitriles III, IV, VII, and VIII was performed by heating 0.5 g of the nitrile in a sealed ampoule with a mixture of 2 g of potassium hydroxyde, 2 g of water, and 10 ml of ethanol for 4 days at 120°. The alcohol was evaporated from the reaction mixture and 3 ml of conc. hydrochloric acid were added. The liberated acid was extracted with ether and the solvent evaporated. The crystalline acids were recrystallized from petroleum ether and the following melting points were obtained: IV, m.p. 103°–04°, reported<sup>3</sup> 105°; VI, m.p. 85°–87°, reported<sup>8</sup> 87°; IX, m.p. 129°–31°, reported<sup>4</sup> 125°. Compound X was obtained and is reported<sup>5</sup> as an oil. It was characterized as its S-benzylisothiuronium salt, m.p. 165°–66°. (Found: C 61.65; H 7.09; N 9.68. Calc. for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S: C 61.60; H 6.91; N 9.58).

Microanalyses were performed by Mr. Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen. The author wishes to thank Dr. J. Rastrup-Andersen, Department of Chemical Physics, The University of Copenhagen, for the interpretation of the NMR spectra.

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Received June 3, 1964.