

Halogenation of Ketones

X.* The Halogenation of 2,3-Pentadione and 3-Methyl-1,2-cyclopentadione. Halogen Migration and Long Range Coupling in Cyclic Chloro and Bromo α -Diketones

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The halogenation of 2,3-pentadione and 3-methyl-1,2-cyclopentadione (I) was studied. In halogenation of 2,3-pentadione, the substitution of the methylene group is favoured over the methyl group more than in the halogenation of 2-butanone. The structures of the mono- and dihaloderivatives of I were determined by NMR. Some of the previously assigned structures required correction. The chloro (and bromo) ketone VIII was found to spontaneously rearrange to the enol IV. A novel type of long range coupling involving five single bonds was observed in the NMR-spectrum of I and IV.

In connection with studies on the acid-catalyzed halogenation and deuteration of ketones and haloketones,¹⁻⁴ it was of interest to study the corresponding substitution of some α -diketones and to compare this with that of the corresponding monoketones. In the present paper we have studied 2,3-pentadione and 3-methyl-1,2-cyclopentadione.

The acid catalyzed halogenation of ketones is supposed to pass *via* the enol. Cardwell and Kilner suggested that for unsymmetric ketones the orientation of enolization followed the Saytzeff rule.⁵ This investigation has been considered as a classic investigation of the orientation of enolization as well as of hyperconjugation.⁶⁻⁸ Very recently Rappe and Sachs studied the orientation of enolization by means of deuteration experiments, which are more exact than the method used by Cardwell and Kilner. Rappe and Sachs found that additional factors (as steric) seem to influence the orientation of the enolization and they considered that no general rules could be given.⁴

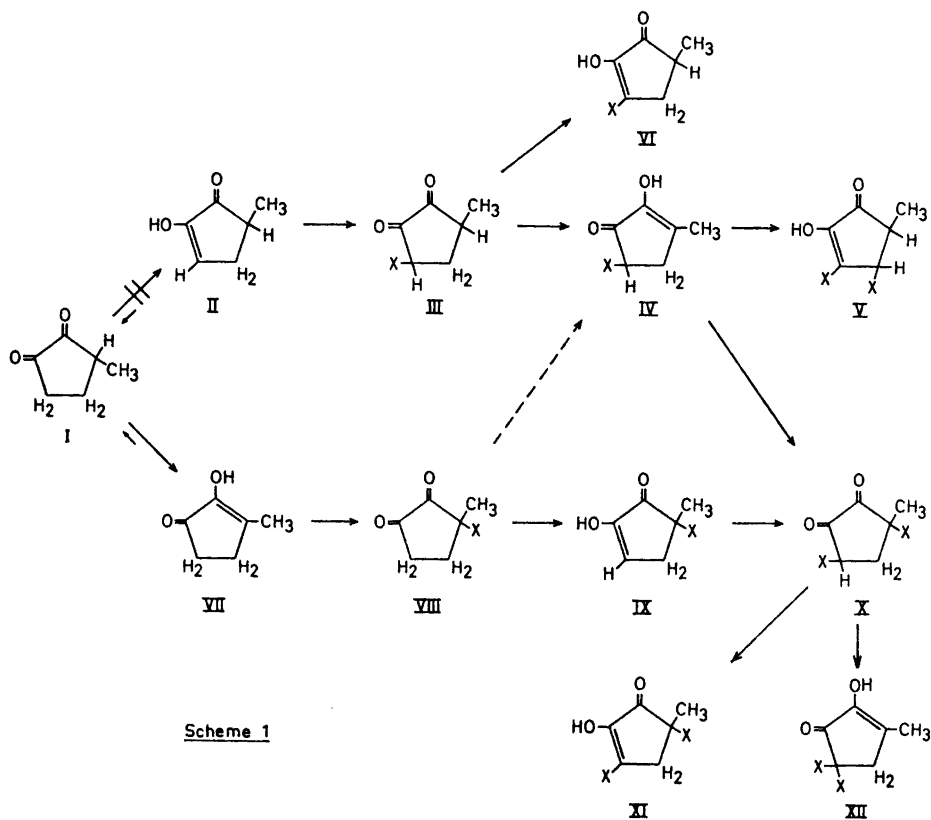
Of the two α -diketones studied in the present investigation 2,3-pentadione represents an α -diketone which exists almost exclusively in the keto form, whereas 3-methyl-1,2-cyclopentadione (I) is almost quantitatively enolized.⁹

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2,3-Pentadione. No halogenation reaction of this compound seems to have been previously reported. For 2-butanone, the corresponding monoketone, both halogenation and deuteration experiments show that the substitution of the methylene group is favoured over the substitution of the methyl group by a factor of 2.5—2.7.^{4,5,10}

In the acid-catalyzed halogenation of 2,3-pentadione we have used bromine, chlorine, and sulfuryl chloride. NMR-analyses of the crude products showed that in all cases the substitution of the methylene group is favoured by a factor of 5—6 which is higher than in the case of 2-butanone. 4-Bromo- and 4-chloro-2,3-pentadione can be isolated from the reaction. Both compounds seem to have never been described before.

The best method to synthesize 4-bromo-2,3-pentadione was by means of a free-radical reaction using *N*-bromosuccinimide, yield 57%. In this reaction the substitution was found to be exclusively in the methylene group. For comparison it can be noted here that Rappe and Kumar found that the reaction of 2-butanone with NSB yielded the 3-bromo derivative in high purity.¹¹



Scheme 1

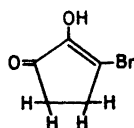
3-Methyl-1,2-cyclopentadione (I). The halogenation of 3-methyl-1,2-cyclopentadione (I) has been studied by Hesse and Breig.¹² Chlorine and bromine were used, and for each halogen the authors could isolate two different mono-halo isomers and one dihalo compound. The authors also found that the primary, lower melting isomer spontaneously rearranged to the secondary, higher melting product within a few days. By analysis of the degradation products Hesse and Breig assigned the products structures III, IV, and V, Scheme 1.¹² In the monohalogenation, 5-halo-3-methyl-1,2-cyclopentadione was formed, and the lower melting compound is the keto form (III), while the higher melting isomer is the enol form (IV). It was known that 3-methyl-1,2-cyclopentadione is completely enolized.⁹ From the structure of the halogenation products, Hesse and Breig concluded that the diketone is in the enol form II.¹²

However, later Bredenberg studied the α -diketone I by NMR-spectroscopy and found that the ketone was completely in the enol form VII.¹³ Other questions which can be raised in connection with the results reported by Hesse and Breig are concerning the enolization of III. This ketone can give two enols, IV and VI. Hesse and Breig propose the enol in which the methyl-bearing α -carbon forms part of the double bond.¹² However, it is known that 3-bromo-1,2-cyclopentadione (XIII) enolizes so that the halogen-bearing α -carbon forms part of the double bond, in the present case enol VI,³ cf. also Ref. 2.

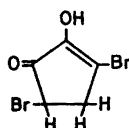
Concerning the dihalo derivatives, the second halogen atom has been reported to enter in the position β to the carbonyl group, structure V.¹² One of us has previously shown that a number of polyhalo ketones, which previously were ascribed structures with one or more halogens in position β or γ to the keto group, in fact were all α -haloketones.¹

In this situation we found it necessary to reinvestigate the structures of the halo compounds III, IV, and V using the more safe NMR-technique.

All of the six chloro- and bromoderivatives described by Hesse and Breig were synthesized.¹² In spite of repeated experiments we only obtained the higher melting, secondary product when the halogenations were performed according to Hesse and Breig. However, if we used *N*-bromosuccinimide as halogenating agent, we obtained a product with the same m.p. as that reported by Hesse and Breig for the lower melting bromo isomer. With this method the yield was increased from 32 %¹² to 56 %. If the chlorination (using free chlorine) was performed in dry carbon tetrachloride instead of water as in Ref. 12, the lower melting chloro isomer was obtained. According to this method the yield was 72 % (Hesse and Breig reported up to 60 %). *N*-Chlorosuccinimide gave the higher melting isomer. After standing at room tempera-



XIII



XIV

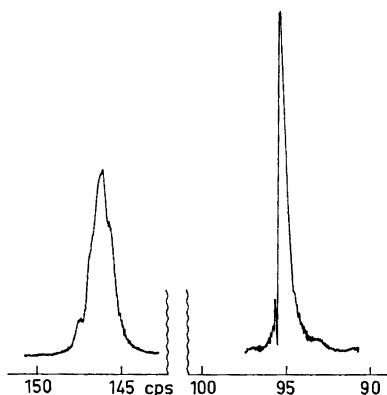


Fig. 1. NMR-spectrum of 3-chloro-3-methyl-1,2-cyclopentadione (VIII) in acetone- d_6 .

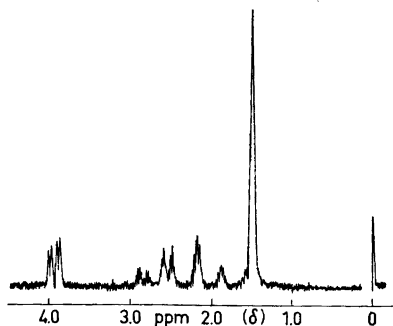


Fig. 2. NMR-spectrum of 5-chloro-3-methyl-1,2-cyclopentadione (IV) in acetone- d_6 .

ture for a few days, crystals of the lower melting compounds were isomerized to the higher melting isomers in good yields.

The two lower melting isomers were analyzed by infrared and by NMR-spectroscopy. Very similar results were obtained for the chloro and bromo compounds. The IR-spectra contained a strong carbonyl band, but no bands for carbon—carbon double bonds or for hydroxyl groups. Thus the structure is either III or VIII. The NMR-spectra contained one sharp singlet at $\delta=1.5-1.6$ and a broader band at $\delta=2.3-2.4$ with the signal ratio 3:4, see Fig. 1. This is in disagreement with structure III, which was proposed by Hesse and Breig¹² because this compound would give vicinal coupling in the methyl peak, but it is in harmony with structure VIII. This product, which is the keto form of 3-halo-3-methyl-1,2-cyclopentadione, is the expected from the halogenation of the enol VII, the four protons in the vicinal CH_2 -groups being slightly different.

By IR it could be established for the two higher melting compounds that they are both enols. In addition to the carbonyl band, the spectra contained a strong hydroxyl band and a strong band for carbon—carbon double bonds.

In order to differentiate between the three enols IV, VI, and IX, the NMR-spectra were recorded. The bromo and chloro compound gave nearly identical spectra (Fig. 2). From the absence of the vicinal coupling in the methyl peak, it could be concluded that the structure was either IV or IX.

The three remaining protons gave an AMX-spectrum (Fig. 2) very similar to that previously described for 3,5-dibromo-1,2-cyclopentadione (XIV).³ This is only in accordance with structure IV; the structure proposed by Hesse and Breig.¹² From the expanded spectrum (Fig. 3) the coupling constants could be determined, and these were also very close to those previously given for XIV (Table 1). A careful study of Fig. 3 revealed long range coupling between the methyl group and the hydrogens at 4-C and 5-C, and these coupling constants are also given in Table 1.

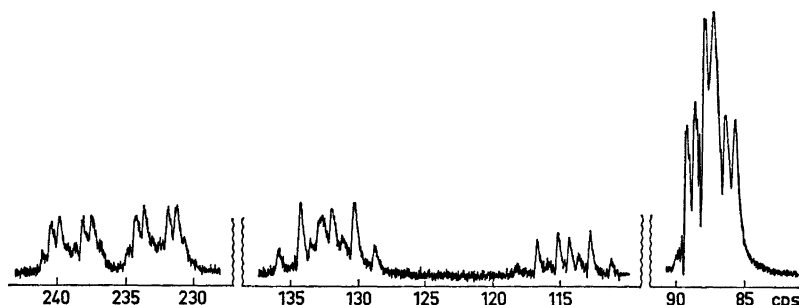


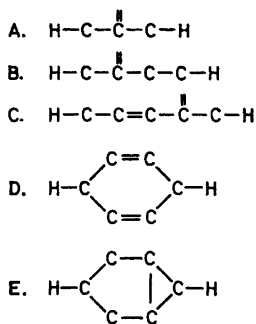
Fig. 3. Expanded NMR-spectrum of 5-chloro-3-methyl-1,2-cyclopentadione (IV) in acetone- d_6 .

Table 1. Coupling constants (in Hz) for 1,2-cyclopentadiones.

Compound	J_{gem}	J_{cis}	J_{trans}	J_{CH_3-4-H}	J_{CH_3-5-H}
XIV	18.7	6.5	2.2	—	—
IV	17.5	6.4	2.3	1.6	0.6
VII		not determined		0.6	0.1 (?)

The coupling between the methyl group and 4-H is a long range coupling over four single bonds, including two sp^3 - and one sp^2 -hybridized carbons, see route A, Scheme 2. This type of long range coupling has been studied previously, but only in cases where the double bond is in a carbonyl function.^{14,15} The magnitude of the coupling constant (1.6 Hz) is within the limits previously reported.

The coupling between the methyl group and 5-H (coupling constant 0.6 Hz) seems to represent a novel type of long range spin-spin coupling in cyclic systems. Here the transmission is across five single bonds including three sp^3 - and one sp^2 -hybridized carbons, route B, Scheme 2. It is possible the transmission is increased by transmission along the alternate pathway



Scheme 2

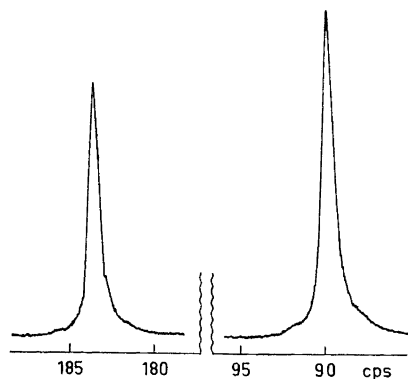


Fig. 4. NMR-spectrum of 3,5-dichloro-3-methyl-1,2-cyclopentadione (XI) in acetone- d_6 .

in the ring, C, which includes five single bonds and one double bond or two sp^3 - and three sp^2 -hybridized carbons.

Long range spin-spin coupling across five bonds has been reported previously, but in these examples either one or more double bonds are involved as in *cis*- and *trans*-1,4-dihydrobenzenes,¹⁶ D, Scheme 2, or a cyclopropane ring as in *endo*-tricyclo-[3,2,1,0^{2,4}]-oct-6-ene, pathway E.¹⁷

The dihalo derivatives of I were prepared according to Ref. 12. The IR-spectra contained bands for hydroxyl groups, carbonyl groups and carbon-carbon double bonds for both compounds. Thus the compounds are enols; V, XI, or XII.

The NMR-spectra contained two singlets ($\delta=1.4-1.5$, $\delta=2.9-3.1$) with a signal ratio 3:2. This excludes compound V, the structure proposed by Hesse and Breig.¹² However, it is more difficult to differentiate between XI and XII. Since the four methylene protons in VIII were found to be nearly identical (Fig. 1), it was not possible to separate between XI and XII from the formal equivalence and non-equivalence of the methylene protons in XI and XII. However, it was found that the long range coupling was missing in the expanded NMR-spectra of the dihalo derivatives, Fig. 4. Since coupling between the methyl group and 4-H could be expected in XII as in IV, this is an indication that structure XI is the correct structure.

This indication is strengthened by the observation of long range coupling in the non-halogenated enol VII, Fig. 5. Here the coupling constants are smaller than for IV as given in Table 1. It can be noticed here that the rings in VII and IV (as in XII) are planar.

The reaction when the higher melting isomer IV is formed spontaneously from VIII includes an enolization and a halogen migration. Halogen migrations are well established for bromo ketones,^{18,19} but rare for chloro ketones.²⁰ In fact, only few examples have been reported for halogen migration in chloro ketones, and in these cases vigorous conditions are used.²¹⁻²³ Blaise found that heating 1,1-dichloro-2-butanone in acetic acid and hydrogen chloride at 100°C for several hours resulted in rearrangement to the 1,3-dichloro isomer. In fact, we could establish by NMR that about 20 % of the 1,1-dichloro ketone was rearranged to the 1,3-isomer under the conditions given

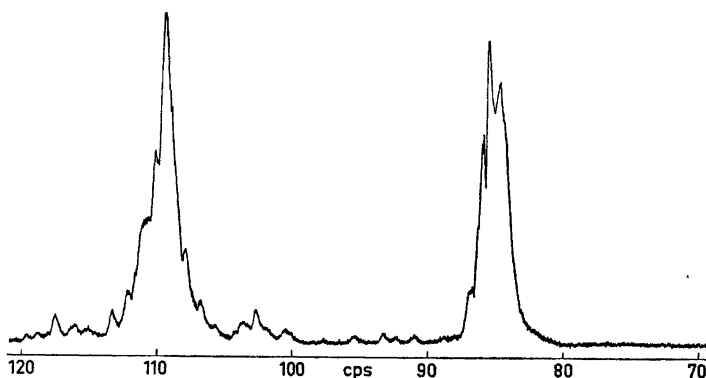


Fig. 5. NMR-spectrum of 3-methyl-1,2-cyclopentadione (VII) in acetone- d_6 .

by Blaise.²¹ By way of contrast, one drop of hydrobromic acid caused a complete rearrangement of 1,1-dibromo-2-butanone in a variety of products within a few minutes at 30°C.¹⁹ Voitila found that 4,4-dichlorodimedone in an acetic acid solution of hydrogen chloride after five weeks was rearranged to the 2,4-dichloro isomer.²² Caujolle and Dang Quoc Quan have recently reported chlorine migration in 2,2-dichlorocyclohexanone after treatment with a mixture of acetic acid and hydrochloric acid at 90°C for 3 h.²³

Thus the spontaneous rearrangement of the chloro ketone VIII to IV is remarkable. At the present state it is not certain if III is an intermediate in this migration or not. If this is the case, the enolization of III seems to take place in an unexpected direction. As mentioned above, it has been found that monohalo ketones enolize so that the halogen-bearing α -carbon forms part of the double bond.^{2,3} Examination of the crude reaction mixture from the halogenation of IV by NMR, indicated the existence of an intermediate, probably X.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian A-60 spectrometer. The δ -scale was calibrated against a solution of benzene and tetramethylsilane in carbon tetrachloride. The substances were examined as about 10 % solutions in acetone- d_6 at ca. 40°C.

4-Bromo-2,3-pentadione. Method A: using free bromine. This experiment was performed according to the general procedure outlined in Ref. 1. The crude product was analyzed by NMR prior to distillation. 4-Bromo-2,3-pentadione distilled at 60–62°C/20 mm, $n_D^{24,5} = 1.4629$.

Method B: Using *N*-bromosuccinimide. This experiment was performed according to Ref. 11. Yield 57 % of distilled product.

1,4-Dibromo-2,3-pentadione. This compound could be isolated after repeated distillations from experiments using two equivalents of bromine.¹ 1,4-Dibromo-2,3-pentadione distilled at 134–136°C/40 mm.

4-Chloro-2,3-pentadione. The parent ketone was treated with one equivalent of sulfuryl chloride in boiling carbon tetrachloride for 6.5 h. The solvents were evaporated and the residue analyzed by NMR prior to distillation. 4-Chloro-2,3-pentadione could be isolated after repeated distillations, b.p. 64–66°C/50 mm, $n_D^{24,5} = 1.4269$.

3-Bromo-3-methyl-1,2-cyclopentadione (VIII). N-Bromosuccinimide (7.9 g) was added to a solution of 3-methyl-1,2-cyclopentadione (5.0 g) in dry carbon tetrachloride (300 ml). The mixture was kept at 50°C for 10 min. After cooling the succinimide was filtered off, the solvent evaporated and the residue recrystallized from light petrol. Yield 4.8 g (56 %), m.p. 76–77°C.

5-Bromo-3-methyl-1,2-cyclopentadione (IV). When kept a few days at room temperature in the air, the diketo compound VIII had rearranged to the enol IV. After recrystallizing from cyclohexane the yield was 3.7 g (43 % counted on I), m.p. 117–118°C.

3-Chloro-3-methyl-1,2-cyclopentadione (VIII). Chlorine was bubbled through a solution of 5.0 g of 3-methyl-1,2-cyclopentadione in 300 ml of carbon tetrachloride until the gain in weight was 3.2 g. The solvent was evaporated *in vacuo*, the residue recrystallized from light petrol, 4.7 g of yellow crystals, 72 %, m.p. 50–51°C.

5-Chloro-3-methyl-1,2-cyclopentadione (IV). After a few days in the air the enol IV could be obtained and recrystallized from cyclohexane, 4.4 g (67 % counted on I), m.p. 98–99°C.

3,5-Dichloro- and 3,5-dibromo-3-methyl-1,2-cyclopentadione (XI). These compounds were prepared according to Ref. 12.

1,1-Dichloro-2-butanone. This ketone was prepared from the diazoketone and chlorine according to the method previously described by Rappe and Albrecht.²⁴ The distilled crude product contained some of the 1,3-dichloro isomer, but it was used without further purification.

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