JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

(Registered in U. S. Patent Office) (Copyright, 1953, by the American Chemical Society)

VOLUME 75 JULY 23, 1953 NUMBER 14

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Stereochemistry of α-Haloketones. II.[1] The Three α-Dibrominated Cyclohexanones

BY ELIAS J. COREY

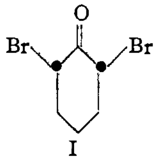
RECEIVED MARCH 21, 1953

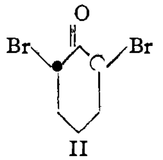
The synthesis and identification of *cis*-2,6-dibromocyclohexanone, *trans*-2,6-dibromocyclohexanone and 2,2-dibromocyclohexanone are presented.

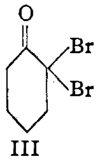
The reaction of cyclohexanone with two molecular equivalents of bromine affords a mixture of dibrominated products from which a crystalline dibromocyclohexanone, $C_6H_8OBr_2$, m.p. 110°,[2] can be isolated in 15–20% yield. The greater part of the reaction mixture, however, is a non-crystallizable oil which because of its instability is not amenable to fractionation by distillation or chromatography. The structure of the dibromide, m.p. 110°, has not been determined, even though the compound has been known for over twenty-five years and has been investigated in detail by Wallach.[2] Furthermore, no report has ever been made of the isolation of any of the remaining dibromocyclohexanones, either from the bromination of cyclohexanone or from other reactions.

In connection with the problem of determining the magnitude of steric and electrical repulsions between substituent groups in cyclic systems[1,3] we have investigated the stereochemistry and relative stabilities of certain members of the dihalocyclohexanone series and have determined the structure of the Wallach dibromide, m.p. 110°. In the present paper we report on the structure of the Wallach dibromide and also on the synthesis and stereochemistry of the two remaining α-dibrominated cyclohexanones.

The Wallach Dibromide, M.p. 110°.—None of the three possible structures (I–III) for the Wallach dibromide are in any way excluded by the known chemical reactions of this substance.[4] For example, reaction of the dibromide with aqueous hydroxide ion in the cold yields 1,2-cyclohexanedione, which could have been formed from either I, II or III.

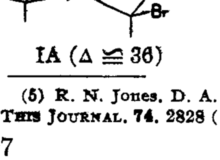

I

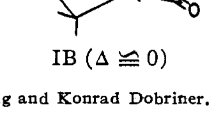

II


III

In the present work we have found by means of infrared absorption that the Wallach dibromide is *cis*-2,6-dibromocyclohexanone (I). This assignment of structure is possible because of the known occurrence of an upward shift in frequency of carbonyl absorption (Δ) of *ca.* 18 cm.$^{-1}$ for each α-carbon–bromine bond which is codirectional-coplanar with carbon-oxygen bond of an α-bromocyclohexanone and the absence of a shift when the carbon–bromine, and carbon–oxygen bonds are in quite different planes.[1,5]

cis-2,6-Dibromocyclohexanone (I) may be represented as one of two chair-formed cyclic rotational isomers IA and IB while the *trans*-2,6-dibromide II and the *geminal*-2,2-dibromide III may each be represented by one of two *energetically equivalent* chair formed structures. These are indicated below together with the predicted Δ value for each structure.


IA (Δ ≌ 36)


IB (Δ ≌ 0)

---

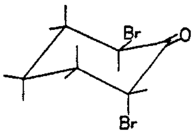
[1] Part I, THIS JOURNAL, 75, 2301 (1953).

[2] O. Wallach, *Ann.*, 414, 310 (1917); 437, 173 (1924). The melting point observed in the present work (110°) is somewhat higher than that previously reported (107°).

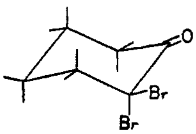
[3] E. J. Corey, THIS JOURNAL, in press.

[4] *Cf.* ref. 2; F. Galinovsky, *Ber.*, 76B, 230 (1943).

[5] R. N. Jones, D. A. Ramsay, F. Herling and Konrad Dobriner, THIS JOURNAL, 74, 2828 (1952).



II (Δ ≌ 18)



III (Δ ≌ 18)

Since the frequency increment, Δ, for cyclohexanone and the Wallach dibromide is 38 cm.$^{-1}$ (Table I), both carbon–bromine bonds in the dibromide must be codirectional–coplanar with the carbon–oxygen bond and the substance must be assigned structure IA in which the bromine atoms are *cis*.

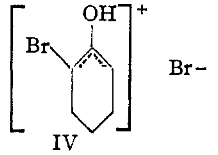
Thus, it is clear that the stable molecular configuration of I is IA rather than IB. The occurrence of only very slight absorption at 1712 cm.$^{-1}$ ($\Delta = 0$) in the spectrum of I indicates that at most 1 or 2% of form IB is present in solution at room temperature. Consequently, the energy due to electrostatic and steric repulsions between two polar bromine atoms in the 2- and 6-positions must be considerably greater than the energy due to dipole–dipole repulsions involving the carbonyl group and two codirectional–coplanar carbon–bromine dipoles.

***trans*-2,6-Dibromocyclohexanone.**—The fact that form IA of *cis*-2,6-dibromocyclohexanone is much more stable than form IB together with the previous finding that the stable form of α-bromocyclohexanone is that chair form in which the bromine atom occupies a polar position[1] suggests that *trans*-2,6-dibromocyclohexanone (II) should be more stable than the *cis* isomer (I) and, hence, derivable from it by isomerization. In accord with this idea we have found that a new isomer, m.p. 36°, is produced from the Wallach dibromide under the influence of acidic catalysts.

When the isomerization is conducted with hydrogen bromide in glacial acetic acid, a mixture results which at equilibrium consists of *ca.* 85% of the new dibromide, m.p. 36°, and *ca.* 15% of the *cis*-2,6-dibromide. A mixture of essentially the same composition is obtained at equilibrium using dry hydrogen chloride in ether.

The frequency of carbonyl absorption of the dibromide, m.p. 36°, (Table I, $\Delta = 20$) agrees with that predicted for either *trans*-2,6-dibromocyclohexanone (II) or the less likely 2,2-dibromocyclohexanone (III) and consequently a decision cannot be made between these two on this basis. The latter substance might be formed by the ionization of the Wallach dibromide to IV and subsequent reaction of IV with bromide ion.[6]

That the dibromide, m.p. 36°, is *trans*-2,6-dibromocyclohexanone (II) has been shown by the fact that it differs from authentic 2,2-dibromocyclohexanone (III) which has been prepared by an unambiguous synthesis (*vide infra*). However, attempts to secure a direct proof of a *trans* arrangement of the bromine atoms in the isomer, m.p. 36°, by preferential dehydrobromination of one optical antipode with brucine[7] were not successful.



IV

2,2-Dibromocyclohexanone.—An unequivocal synthesis of this compound starting with 2-carbethoxycyclohexanone was devised. Hydrolysis of the β-ketoester with dilute base proceeded rapidly at room temperature and afforded the corresponding β-ketoacid which upon treatment with two molecular equivalents of bromine in dilute aqueous sodium acetate underwent successive bromination, decarboxylation and bromination to produce the desired dibromoketone III (m.p. 49°) in over 70% yield. As expected absorption of the first molecular equivalent of bromine by the highly enolic β-ketoacid occurred very rapidly. Under the same conditions cyclohexanone is not brominated at all and, hence, it is necessary to consider the primary product of bromination as being 1-bromocyclohexan-2-one-1-carboxylic acid and not the 3-bromo acid. Upon warming the solution of the bromo acid (in equilibrium with its conjugate base) to 50° rapid decarboxylation took place with simultaneous absorption of bromine. Since decarboxylation of the bromo acid results in generation of the Δ^2-enolate ion and/or the Δ^2-enol[8] of 2-bromocyclohexanone, the reaction product in the presence of bromine must be III. It is unlikely that appreciable amounts of 2,6-dibromocyclohexanone or 2,2,6-tribromocyclohexanone could have been formed since as was mentioned previously cyclohexanone itself is unaffected under the conditions of the reaction.

The carbonyl absorption of 2,2-dibromocyclohexanone (Table I, $\Delta = 15$) is in complete agreement with that predicted for structure III.

TABLE I

Compound	Position of C═O absorption (cm.$^{-1}$)[a]	Shift (cm.$^{-1}$)[b]
Cyclohexanone	1712	. .
cis-2,6-Dibromocyclohexanone (m.p. 110°)	1750	38
trans-2,6-Dibromocyclohexanone (m.p. 36°)	1732	20
2,2-Dibromocyclohexanone (m.p. 49°)	1727	15

[a] Determined in carbon tetrachloride solution. [b] These values are ± a maximum of 2 cm.$^{-1}$.

---

[6] Analogous $\alpha \rightarrow \alpha'$ isomerizations have been observed previously with the bromo derivatives of 1,3-diketones and B-ketoesters [C. Duisberg, *Ann.*, **213**, 137 (1882); F. Krohnke and H. Timmler, *Ber.*, **69**, 614 (1936)] and with α-bromoketosteroids [H. H. Inhoffen, *ibid.*, **70**, 1695 (1937); H. H. Inhoffen and G. Zuhlsdorf, *ibid.*, **76**, 233 (1943); I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 801 (1937); ref. 3]. The fact that the conversion of I to the isomer, m.p. 36°, occurs in ethereal hydrogen chloride does not definitely rule out the possibility of $\alpha \rightarrow \alpha'$ rearrangement since such rearrangement might take place internally without involving external halide ion. However, the finding of A. Hantzsch [*Ber.*, **27**, 255, 3168 (1894)] that hydrogen chloride does not catalyze bromine migration in β-ketoesters makes structure III seem unlikely for the isomer m.p. 36°.

[7] H. J. Lucas and C. W. Gould, THIS JOURNAL, **64**, 601 (1942); S. J. Cristol, *ibid.*, **71**, 1894 (1949).

[8] The presence of sodium acetate strongly accelerates the decarboxylation of 1-bromocyclohexan-2-one-1-carboxylic acid and, hence, it is probable that most of the decarboxylation of this substance is anionic. If the enolate ion so formed is brominated, III is produced directly. If the enolate ion is protonated the Δ^2-enol of 2-bromocyclohexanone, which is extremely susceptible to bromination, should result (*cf.* the protonation of ethyl acetoacetate enolate ion which occurs much faster on oxygen then on carbon [L. Knorr, O. Rothe and H. Auerbach, *Ber.*, **44**, 1138 (1911)].

Experimental[9]

Wallach Dibromide, *cis*-2,6-Dibromocyclohexanone.—We have found the following procedure to be most satisfactory for the preparation of this dibromide. To a solution of 37.0 g. (0.385 mole) of cyclohexanone in 200 ml. of glacial acetic acid containing 2 ml. of 7% hydrogen bromide in acetic acid 123.5 g. (0.772 mole) of bromine was added with rapid stirring at 15°. The reaction mixture was poured into ice-water and extracted with ether. The ethereal solution was separated, washed with water, cold dilute potassium carbonate and finally with water, dried and evaporated under reduced pressure. The residual oil was taken up in a little ether, a small amount of petroleum ether was added and the solution was allowed to stand at 0° for 2 hours. The crystalline dibromide, 10.2 g., m.p. 108.5–109.5°, was separated by filtration. A second crop was obtained from the filtrate on long standing in the presence of hydrogen bromide, weight, 9.4 g.; m.p. 105–106°; total yield 20%. One recrystallization of the first crop or two recrystallizations of the second crop from ether–ligroin furnished pure material, m.p. 109.5–110.5°, not increased by further recrystallization (lit.[2,4] m.p. 107°).

The **hydrate** of I was prepared by treatment of a solution of 2.00 g. of I in 15 ml. of glacial acetic acid with 1 ml. of concentrated sulfuric acid at room temperature for 5 minutes. The acetic acid solution was worked up as described above and gave 1.05 g. of starting material, m.p. 107–108°, and 0.297 g. of the hydrate, m.p. 80–92°,[10] resolidifies 104°[10] and melts at 109–110°. Further recrystallization from ether–pentane (long, colorless needles) did not affect the m.p.

Anal. Calcd. for $C_6H_{10}O_2Br$: C, 26.30; H, 3.68; Br, 58.34. Found: C, 26.51; H, 3.83; Br, 58.50.

The hydrate showed strong hydroxyl absorption in the infrared at 3463 cm.$^{-1}$ and no carbonyl absorption. Upon long standing in contact with solvents or upon heating at 105° under reduced pressure the hydrate was transformed into *cis*-2,6-dibromocyclohexanone, m.p. 109–110°, alone or admixed with an authentic sample.

***trans*-2,6-Dibromocyclohexanone.**—*cis*-2,6-Dibromocyclohexane (5.00 g.) was dissolved in 35 ml. of glacial acetic acid with warming and the resulting solution was cooled to 40° and treated with 2.5 ml. of 0.1 *N* hydrogen bromide in acetic acid. After storage at room temperature for one hour the solution was diluted with 150 ml. of ether, washed successively with water (two portions of 25 ml.), cold potassium carbonate solution (100 ml., 3%) and water (50 ml.) dried over calcium chloride and concentrated under reduced pressure to 3 ml. The ethereal concentrate was diluted with 12 ml. of pentane and seeded with *cis*-2,6-dibromocyclohexanone. The mixture was kept overnight at 0° and separated by filtration. The recovered *cis*-2,6-dibromide so obtained, m.p. 106–107°, amounted to 1.037 g. (20.7%). The filtrate was concentrated to an oil which was taken up in 3 ml. of ether and caused to crystallize by slow chilling in an acetone bath cooled by addition of solid carbon dioxide. The cooled mixture was diluted dropwise with 7 ml. of pentane and the supernatant liquid removed by decantation. Recrystallization of the solid (with filtration to remove insoluble impurities) three times from ether–pentene (−70°) and three times from pentane (−70°) afforded 1.08 g. of pure *trans*-dibromide (II), m.p. 35–36°. A further quantity of less-pure material (1.9 g.), m.p. 29–33°, was obtained from the mother liquors by recrystallization.

Anal. Calcd. for $C_6H_8OBr_2$: C, 28.15; H, 3.15; Br, 62.45. Found: C, 28.42; H, 3.14; Br, 62.08.

Treatment of *trans*-2,6-dibromocyclohexanone with two equivalents of brucine in chloroform or in dioxane at room temperature for 2 hours followed by separation of the brucine salt did not lead to the appearance of optical activity in the brucine-free fraction.

Equilibration of *cis*- and *trans*-2,6-Dibromocyclohexanone.—Treatment of 2-g. samples of *cis*-2,6-dibromocyclohexanone with hydrogen bromide in acetic acid at room temperature (*ca.* 26°) using the same concentrations employed above for 0.5, 2.0, 3.25, 5, 7, 10 and 20 hours resulted in recovery of 46, 19, 17.7, 15, 15, 15 and 14% of *cis*-dibromide. Thus there is present at equilibrium under these conditions *ca.* 85% of the *trans*-isomer and *ca.* 15% of the *cis*-isomer. Treatment of the pure *trans*-isomer with hydrogen bromide in acetic acid for 6 hours likewise resulted in the formation of a mixture containing *ca.* 15% of the *cis*-isomer. The mixture obtained by equilibration of the *cis*- and *trans*-dibromides in 0.16 *N* hydrogen chloride in dry ether was also found to consist of *ca.* 85% of the *trans*-isomer and 15% of the *cis*-isomer.

2,2-Dibromocyclohexanone from 2-Carbethoxycyclohexanone.—2-Carbethoxycyclohexanone was hydrolyzed to the corresponding acid by treatment with four equivalents of sodium hydroxide in 5% methanol–95% water at room temperature for 4 hours (with stirring). The basic solution was extracted with four portions of ether, cooled to 0° and acidified with cold 6 *N* hydrochloric acid. The ethereal extract of the acid solution was diluted with petroleum ether, dried over calcium chloride and evaporated under reduced pressure until the solvent had been completely removed. The solid residue upon recrystallization from dry ether (−40°) afforded essentially pure acid as colorless needles, m.p. 80° (dec.).

To a solution at 15° of 1.0 g. (0.00705 mole) of the acid in 30 ml. of water containing 1.74 g. (0.0212 mole) of sodium acetate, 2.25 g. (0.0141 mole) of bromine was added dropwise over a few minutes. The first equivalent of bromine was taken up rapidly and the remaining only slowly. The mixture was heated to 50° on a steam-bath to complete the decarboxylation–bromination and then cooled and extracted with two 25-ml. portions of ether. The ethereal extract after washing with water, drying and evaporation (reduced pressure) yielded 1.52 g. of faintly colored solid. Recrystallization of the solid from pentane (acetone–solid carbon dioxide bath) afforded 1.30 g. (72.5%) of small, colorless prisms, m.p. 47.5–49°. A sample which was prepared for analysis by two recrystallizations from pentane had m.p. 48–49°. A mixture of this product and *trans*-2,6-dibromocyclohexanone, m.p. 35–36°, prepared as described above, melted below 20°.

Anal. Calcd. for $C_6H_8OBr_2$: C, 28.15; H, 3.15; Br, 62.45. Found: C, 28.25; H, 3.19; Br, 62.31.

URBANA, ILLINOIS

---

(9) We are indebted to Mr. Joseph Nemeth, Mrs. Katherine Pih and Mrs. Esther Fett for the microanalyses and to Miss Helen Miklas for the infrared determinations.

(10) These temperatures vary with the rate of heating.