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

The Stereochemistry of α-Brominated α-Methyl-, α-Dimethyl- and α-Dibenzylcyclohexanones[1]

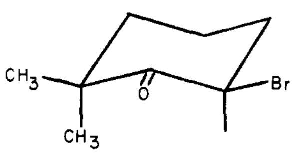
BY E. J. COREY, T. H. TOPIE AND W. A. WOZNIAK[2]

RECEIVED MAY 21, 1955

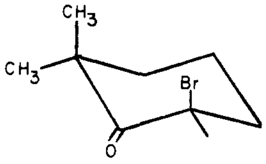
Data are reported on the equilibria between stereo- and rotational isomers of a number of mono-, di- and tribrominated α-substituted cyclohexanones which confirm and extend previous studies. The dibromination of 2,6-dimethylcyclohexanone and 2,6-dibenzylcyclohexanone has been found to be stereospecific and to produce what seems to be the *cis*-2,6-dibromide as the sole product in each case. The equilibrium between *cis*- and *trans*-2,6-dibenzylcyclohexanones, in which an unusually large amount of the *trans* form is present, has been studied at 25° ($K_{cis/trans} = 5.45$) and is discussed.

In the first two papers of this series[3] it was shown that the stable form of a monocyclic α-brominated cyclohexanone is determined by the combination of two opposing effects. The first of these is the electrical repulsion between the electronegative α-bromine and carbonyl oxygen atoms, which tends to cause the axial orientation of bromine to be the more stable. The second is the destabilizing steric repulsion between *cis*-axial groups, which favors the equatorial orientation of bromine. The relative importance of these two effects has been evaluated for a number of α-bromoketones by determination of molecular configuration using infrared analysis and this information has been used very successfully to predict the stable orientation of bromine in more complex structures, *e.g.*, bromoketosteroids. The present paper presents the results of a continuation of the study of brominated monocyclic cyclohexanone systems.

The α-monobromo derivative of 2,2-dimethylcyclohexanone, prepared by direct bromination, was found to exist in solution (CCl_4) as a *mixture* of the two possible chair forms, I (equatorial bromine) and II (axial bromine), in the ratio of 2.6 to 1, respectively (Table I). This ratio corresponds exactly to that observed previously for 7-bromospiro[4.5]decane-6-one, which allows the interesting conclusion to be drawn that an axial α-methyl group exerts the same steric effect as an axial α-methylene group in these systems.[4]

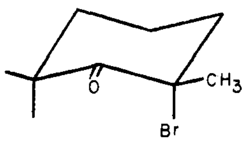


I

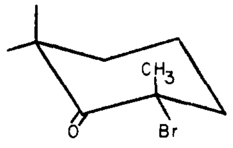


II

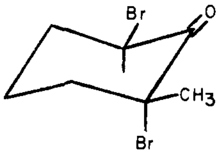
The direct bromination of 2-methylcyclohexanone produces 2-bromo-2-methylcyclohexanone[5] the stable form of which is that with methyl equatorial and bromine axial (III) rather than that with bromine equatorial and methyl axial (IV). In this case steric interactions are about the same for the two forms and the electrical effect, which is the only one of consequence, determines the molecular configuration. The dibromination of 2-methylcyclohexanone under equilibrating conditions (presence of hydrogen bromide) produces, as expected, the *trans*-2,6-dibromide of molecular configuration V. The location of the bromine atoms at C_2 and C_6 in this dibromide was proved by its non-identity with authentic 2-methyl-6,6-dibromocyclohexanone which was synthesized by the technique of decarboxylative bromination used previously.[3]



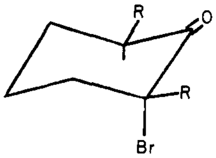
III



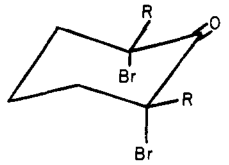
IV



V



VI



VII

R = CH_3, $CH_2C_6H_5$

The monobromination of 2,6-dimethyl- and 2,6-dibenzylcyclohexanones under equilibrating conditions yields bromoketones of structure VI, in harmony with the results described above for 2-bromo-2-methylcyclohexanone. Interesting results also were obtained by the dibromination of these ketones which appears to be stereospecific and to afford in each case a high yield of a single dibromide with both bromines axially oriented (Table I). These products are most likely the *cis*-dibromides of structure VII.[6] Infrared analysis of the crude

---

[1] Stereochemistry of α-Haloketones, part VI; part V, THIS JOURNAL, **76**, 175 (1954).

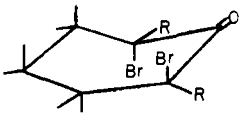
[2] Taken from the B.S. theses of T. H. Topie and W. A. Wozniak.

[3] E. J. Corey, THIS JOURNAL, **75**, 2301, 3297 (1953).

[4] For a comparison of the effect of an axial methyl at C_2 with one at C_4 in the cyclohexanone series see E. J. Corey and R. A. Sneen, *ibid.*, **77**, 2505 (1955).

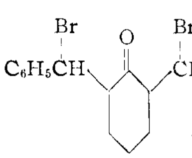
[5] See M. M. Godchot and P. Bedos, *Compt. rend.*, **181**, 919 (1925).

[6] The alternative boat structure which represents a *trans*-dibromide with two axial bromine substituents is also possible and in accord with the infrared data in Table I. Although on the basis of scale models it seems less likely to be the stable form of the *trans*-dibromide than the chair form, a clear decision cannot be made at present.



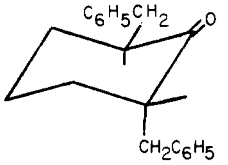
bromination mixtures provides a strong indication for the absence of other isomers, since the carbonyl absorption occurs as a single, sharp, shoulderless peak. It is possible that the observed stereospecificity is due to stereochemical equilibration of the product or to an inherent stereoselectivity during the introduction of the second bromine.

Weiss and Ebert[7] previously have reported the preparation of a 2,6-dibromo-2,6-dibenzylcyclohexanone by the addition of hydrogen bromide to 2,6-dibenzylidene cyclohexanone. Their dibromide (m.p. 139–141°) is different from that mentioned above (m.p. 113–114.5°) and shows carbonyl absorption at 1707 cm.$^{-1}$ indicating the lack of an equatorial α-bromine substituent. The Weiss–Ebert dibromide, therefore, is probably not a stereoisomer of the product of direct dibromination and, in our view, is best represented as 2,6-di-(α-bromobenzyl)-cyclohexanone (VIII).

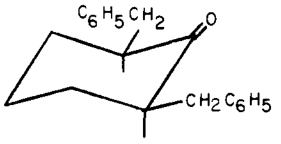


VIII

Incidental to the above work on the bromination of 2,6-dibenzylcyclohexanone we have investigated the equilibrium between the *cis* and *trans* forms of this substance, since it has been reported that considerable amounts (20–40%) of the *trans* isomer (IX) are present together with the *cis* isomer (X) at equilibrium.[8] This is a considerably larger fraction of molecules with axial alkyl group than has been observed previously for equilibria between various methyl- and dimethylcyclohexanes, *e.g.*, methylcyclohexane in which only *ca.* 5% of the molecules have the methyl group axially oriented.[9,10]

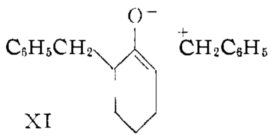


IX



X

Equilibration of pure *cis*-2,6-dibenzylcyclohexanone in chloroform containing 1% hydrogen chloride at 25° resulted in a mixture containing 84.5 ± 0.5% of the *cis* and 15.5 ± 0.5% of the *trans* isomer, corresponding to an equilibrium constant, $K_{cis/trans}$ of 5.45 and a ΔF of -0.6 kcal./mole.[11] This value of ΔF is considerably less than that (-1.8 kcal./mole) for the conversion of a methyl group from an axial to an equatorial orientation in the equilibration of *cis*- and *trans*-1,2-, 1,3- and 1,4-dimethylcyclohexanes.[10] Equilibration of *cis*- and *trans*-2,6-di-*p*-methoxybenzylcyclohexanones under the conditions described above gave a mixture containing exactly the same ratio of *cis* and *trans* isomers, *i.e.*, a value of $K_{cis/trans}$ of 5.45. This fact would seem to rule out the possibility that electrical effects such as described by the resonance form XI



XI

are important.[12] We are inclined, therefore, at present to ascribe the unusually large equilibrium concentration of species with an axial benzyl group to increased steric repulsion brought to bear on an equatorial benzyl substituent by the closely adjacent carbonyl oxygen, *i.e.*, to a purely steric effect peculiar to α-substituted cyclohexanones (and to substituted cyclohexanes possessing a similar trigonal center). The spreading of *cis*-axial substituents in the 2,6-positions of a cyclohexanone[4] also may be a factor in favor of the *trans* isomer, but in our opinion it is a less important one.

The infrared data on the carbonyl absorption of the bromoketones described above, along with several others, is given in Table I. It is noteworthy that in the case of *cis*- and *trans*-2,6-dibenzylcyclohexanones and their *p*-methoxy analogs the carbonyl absorption occurs three wave numbers higher for the *cis* than for the *trans* isomer. This may explain the fact that the carbonyl absorption band of 2,6-dimethylcyclohexanone is not sharp, but is somewhat flattened out at the maximum as if it were a combination of two bands. It may well be that ordinary 2,6-dimethylcyclohexanone, a liquid at room temperature, contains both *cis* and *trans* isomers in comparable amounts.

TABLE I

INFRARED ABSORPTION DATA

Cyclohexanone	ν_{max} C=O, cm.$^{-1}$	Shift due to α-Br, Δ, cm.$^{-1}$	Orientation of α-Br, atoms[a]
2-Methyl	1715	...	...
2-Bromo-2-methyl	1722	7	1a
2,6-Dibromo-2-methyl	1738	23	1a, 1e
6,6-Dibromo-2-methyl	1735	20	1a, 1e
2,6,6-Tribromo-2-methyl	1737	22	2a, 1e
2,2-Dimethyl	1702	...	...
6-Bromo-2,2-dimethyl	1700	−2	a
	1723	21	e
2,6-Dimethyl	1714	...	...
2-Bromo-2,6-dimethyl	1715	1	1a
2,6-Dibromo-2,6-dimethyl	1722	8	2a
cis-2,6-Dibenzyl	1716 (±0.5)	...	...
trans-2,6-Dibenzyl	1713 (±0.5)	...	...
2-Bromo-2,6-dibenzyl	1715	−1	1a
2,6-Dibromo-2,6-dibenzyl	1719	3	2a
cis-2,6-Di-*p*-methoxybenzyl	1715 (±0.5)	...	...
trans-2,6-Di-*p*-methoxybenzyl	1712 (±0.5)	...	...

[a] a = axial, e = equatorial.

---

(7) R. Weiss and J. Ebert, *Monatsh.*, **65**, 403 (1935).

(8) R. Cornubert, M. Andre, M. Demo, R. Joly and A. Strebel, *Bull. soc. chim.*, [5] **6**, 103 (1939).

(9) C. W. Beckett, K. S. Pitzer and R. Spitzer, This Journal, **69**, 2488 (1947).

(10) A. K. Roebuck and B. L. Evering, *ibid.*, **75**, 1631 (1953).

(11) Calculated from the expression $\Delta F = RT \ln K cis/trans + RT \ln 2$ to allow for optical isomerism of the *trans* isomer.

(12) The form XI would be expected to contribute most heavily when the benzyl group depicted as a cation possesses the axial orientation [see E. J. Corey, This Journal, **76**, 175 (1954)] and hence stabilize the *trans* isomer.

Experimental[13]

α-Bromo Derivatives of 2-Methylcyclohexanone.—**2-Bromo-2-methylcyclohexanone** was prepared by direct bromination,[14] b.p. 52° (2.0 mm.), $n^{20}\text{D}$ 1.5020.

2,6-Dibromo-2-methylcyclohexanone[15] was prepared from 2-methylcyclohexanone and two equivalents of bromine in acetic acid, m.p. 43–45°

2,6,6-Tribromo-2-methylcyclohexanone was prepared from 2-methylcyclohexanone and three equivalents of bromine in acetic acid, m.p. 82–83°.

Anal. Calcd. for $C_7H_9OBr_3$: C, 24.06; H, 2.60; Br, 68.58. Found: C, 24.46; H, 2.74; Br, 68.96.

6,6-Dibromo-2-methylcyclohexanone was prepared from 2-carboxy-6-methylcyclohexanone which was made from 2-carbethoxy-6-methylcyclohexanone[16] by hydrolysis with dilute base at room temperature followed by acidification and extraction, m.p. 90–91° dec. To the acid dissolved in water was added one equivalent of bromine (rapid absorption to an end point) followed by excess sodium acetate and a second equivalent of bromine. Gentle warming caused smooth decarboxylation and simultaneous absorption of bromine. The 2,2-dibromide was isolated by extraction and distillation, b.p. 80° (0.6 mm.), $n^{20}\text{D}$ 1.5390.

Anal. Calcd. for $C_7H_{10}OBr_2$: C, 31.14; H, 3.73; Br, 59.20. Found: C, 31.14; H, 3.81; Br, 59.60.

Mono- and Dibromination of 2,2-Dimethylcyclohexanone.—Monobromination of 2,2-dimethylcyclohexanone in methylene chloride and recrystallization from pentane afforded the monobromoketone[17] m.p. 56.9–58°.

Dibromination under the same conditions furnished the dibromide, m.p. 42–43°.

Anal. Calcd. for $C_8H_{12}OBr_2$: C, 33.83; H, 4.26; Br, 56.28. Found: C, 34.36; H, 4.40; Br, 56.22.

Mono- and Dibromination of 2,6-Dimethylcyclohexanone.—The monobromination was carried out in chloroform at 0° and the monobromide product was purified by crystallization from methanol at −70° and by sublimation at 40° (0.1 mm.), m.p. 42°.

Anal. Calcd. for $C_8H_{13}OBr$: C, 46.84; H, 6.39; Br, 38.97. Found: C, 46.53; H, 5.98; Br, 38.95.

The dibromide was prepared in a similar way with two equivalents of bromine in chloroform at 10° for 30 minutes and was purified by evaporative distillation. The yield of pure material, m.p. 27–28°, amounted to 88%.

Anal. Calcd. for $C_8H_{12}OBr_2$: C, 33.83; H, 4.26; Br, 56.28. Found: C, 33.62; H, 4.09; Br, 56.72.

Mono- and Dibromination of 2,6-Dibenzylcyclohexanone.—The monobromination was conducted in chloroform at 0° starting with pure *cis*-2,6-dibenzylcyclohexanone[8] and yielded 91% of pure monobromide, m.p. 107–108°, after three recrystallizations from *n*-hexane.

Anal. Calcd. for $C_{20}H_{21}OBr$: C, 67.23; H, 5.92; Br, 22.37. Found: C, 67.30; H, 5.99; Br, 22.09.

The pure dibromide, m.p. 113–114.5°, was prepared in the same way with two equivalents of bromine in 93% yield.

Anal. Calcd. for $C_{20}H_{20}OBr_2$: C, 55.07; H, 4.62; Br, 36.64. Found: C, 55.34; H, 4.80; Br, 36.47.

Equilibration of *cis*- and *trans*-2,6-Disubstituted Cyclohexanones.—The same procedure was used for the equilibration of *cis*- and *trans*-2,6-dibenzylcyclohexanone and their bis-*p*-methoxy analogs. For analysis advantage was taken of the great difference in solubility of the *cis* and *trans* isomers. Two grams of the *cis*-ketone dissolved in 20 ml. of 1% hydrogen chloride in chloroform was maintained at 25° for 65, 120 and 200 hours in three separate runs. The chloroform was evaporated under reduced pressure, a small amount of ethereal diazomethane was added (to destroy remaining traces of hydrogen chloride) and the solution again evaporated to dryness. Methylene chloride (25 ml.) and methanol (70 ml.) were added, the solution was concentrated *in vacuo* to 25 ml. and the resulting mixture was filtered while still cold. The resulting solid, *cis*-ketone was washed with four 2-ml. portions of cold methanol and dried. Rapid vacuum concentration of the mother liquor and washings to 5 ml. yielded a further quantity of the *cis* isomer. Dilution of the mother liquor with water afforded the *trans* isomer in nearly pure condition.

With 2,6-dibenzylcyclohexanone the first two crops from methanol amounted to 1.69 g. and consisted of pure *cis* isomer,[8] m.p. 124–125°, unchanged by further recrystallization. The material recovered from the mother liquor (0.29 g.) had m.p. 49–51° indicating that it was substantially pure *trans* isomer.[8]

cis-2,6-Di-*p*-methoxybenzylcyclohexanone was prepared by catalytic reduction of 2,6-di-*p*-methoxybenzylidenecyclohexanone[18] using palladium-on-charcoal catalyst and acetic acid or dioxane as solvent. The *cis*-ketone, m.p. 159–160°, was isolated readily by crystallization from methanol. Further quantities were obtained by treating the filtrate, rich in the much more soluble *trans* isomer, with a few drops of concentrated hydrochloric acid which caused the formation and gradual precipitation of the less soluble *cis* isomer. The analytical sample of *cis*-2,6-di-*p*-methoxybenzylcyclohexanone had m.p. 159.5–160°.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 78.07; H, 7.75. Found: C, 77.95; H, 7.70.

The equilibration experiment described above starting with 2.00 g. of *cis*-2,6-di-*p*-methoxybenzylcyclohexanone yielded 1.69 g. of the pure *cis* isomer, m.p. 159–160°, and 0.29 g. of the *trans* isomer, m.p. 47.5–48°. For analysis the *trans* isomer was recrystallized from methanol–water.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 78.07; H, 7.75. Found: C, 78.25; H, 7.85.

The infrared spectra of the *cis* and *trans* isomers described above were so nearly identical as to preclude use of infrared for the quantitative analysis of mixtures of these isomers.

Urbana, Illinois

---

[13] We are indebted to Mr. Joseph Nemeth and associates for the microanalyses.

[14] A. Kotz and H. Stenhorst, *Ann.*, **379**, 15 (1911).

[15] O. Wallach, *ibid.*, **414**, 314 (1918).

[16] N. N. Chatterjee and A. Bose, *J. Indian Chem. Soc.*, **18**, 196 (1941).

[17] F. Ramirez and A. F. Kirby, This Journal, **74**, 4331 (1952).

[18] O. Wallach, *K. Ges. Wiss. Gottingen*, 399 (1907); *Chem. Zentr.*, **79**, **I**, 639 (1908).