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THE INFLUENCE OF A t-BUTYL GROUP ON THE CONFORMATIONAL EQUILIBRIUM AND THE HYDROGEN BROMIDE CATALYZED ISOMERIZATION OF 2-BROMOCYCLOHEXANONES

G. BELLUCCI,* G. INGROSSO and E. MASTRORILLI
Istituto di Chimica Organica, Facoltà di Farmacia, Via Bonanno 6, 56100 Pisa, Italy

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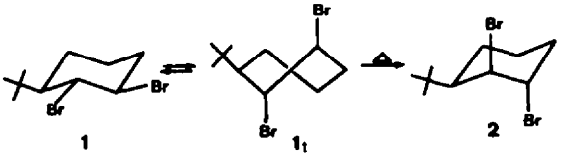
Abstract—The *trans* and *cis* diastereoisomers of 2-bromo-6-t-butylcyclohexanone (**7** and **8**) and of 2-bromo-3-t-butylcyclohexanone (**10** and **9**) have been prepared and subjected to hydrogen bromide catalyzed isomerization. Whereas bromoketones **7** and **8** underwent only epimerization, isomers **9** and **10** were completely converted into an equilibrium mixture of *cis*- and *trans*-2-bromo-5-t-butylcyclohexanone (**12** and **13**). The spectral parameters (IR, UV, NMR), as well as the equilibrium distribution of the couple **7**–**8**, were consistent with chair conformations for compounds **7**, **8** and **9**, but indicated for isomer **10** a flexible form in which both the bromine-t-butyl steric interaction and the electrostatic repulsion between Br and CO group are relieved.

Previous work on thermal equilibration of substituted cyclohexane *trans*-1,2-dihalides and bromohydrins revealed the existence of a strong repulsive interaction between an equatorial halogen atom and a vicinal t-Bu substituent.[1-3] This interaction, in conjunction with the additional steric and dipole-dipole repulsion between two equatorial Br atoms, caused an easy and complete isomerization of dibromide **1** to diastereoisomer **2** and an appreciable participation of non chair conformers of type 1_t to the conformational equilibrium of **1**.[4] Furthermore, a twist conformation, in which the t-butyl-bromine distance was higher than in the chair form and the Br-C-C-Br torsion angle was 152°, was found by X-ray diffraction of *cis*-2,*trans*-3-dibromo-*cis*-4-t-butylcyclohexyl *p*-nitrobenzoate.[5]

Since steric and dipolar effects similar to those operating in compounds of type **1** and **2** could be anticipated for *cis*- and *trans*-2-bromo-3-t-butylcyclohexanones (**9** and **10**), in which a C=O dipole replaces a C–Br one, an investigation of the HBr catalyzed isomerization of the latter bromoketones was expected to provide further information about the importance of gauche bromine-t-butyl interactions. Besides, in order to evaluate the effect of a t-Bu-CO eclipsing interaction, the HBr promoted isomerization of *trans*- and *cis*-2-bromo-6-t-butylcyclohexanones (**7** and **8**) was also examined.



1 1_t 2

RESULTS

Spectral data of bromoketones **7**–**10**, prepared by oxidation under non equilibrating conditions of the corresponding *trans* bromohydrins **3**–**6** of known structures and relative configurations,[6] are reported in Table 1.

All spectral parameters of the two epimeric 2-bromo-6-t-butyl derivatives **7** and **8** were consistent with the relative configurations anticipated from those of the parent bromohydrins **3** and **4**. Thus, taking 2-t-butylcyclohexanone as the reference, the $\nu_{C=O}$ of compound **8** was increased by 20 cm^{-1}, in agreement with the presence of an equatorial bromine α to CO,[7] whereas the $n \rightarrow \pi^*$ band in the UV spectrum was shifted to longer wavelength by 22 nm, with enhanced molar absorptivity, in epimer **7**, as expected for an axial α-bromo derivative.[7] Moreover, the narrow multiplet and the doublet of doublets present in the medium field part of the NMR spectra of **7** and **8** clearly confirmed the presence of an

Table 1. Spectral data of bromoketones **7** – **10**

Compound	IR [a]	UV [b]		NMR [c]			
	$\nu_{C=O}$ (cm^{-1})	λ_{max} (nm)	ε	δ >CHBr	$J_{AX} + J_{BX}$ or $W_{\frac{1}{2}}$ (Hz)		$-C(CH_3)_3$ δ
2-t-Butylcyclohexanone	1719	294	21				
7	1724	316	142	4.25 (m)		6.5	1.00
8	1739	286	24	4.60 (d of d)	17		1.01
3-t-Butylcyclohexanone	1719	278	34				
9	1726	306	113	4.34 (m) [d]		4	1.06
10	1724	310	142	4.30 (m) [d,e]		4	0.95

[a] Solvent CCl_4. [b] Solvent EtOH. [c] Solvent CCl_4. [d] The unresolved shape of this signal, which should be expected as a doublet, is probably due to the presence of small long range couplings. [e] Solvent $CDCl_3$.

equatorial and an axial hydrogen α to a Br atom, respectively.[8]

In contrast, a distinction between the two epimeric 2-bromo-3-t-butylcyclohexanones **9** and **10** on the basis of the spectral data of Table 1 was impossible, since all parameters were very similar for both compounds and consistent with an axial bromine. The axial orientation of bromine in **9** was however unambiguously confirmed by the NMR spectrum of its $NaBH_4$ reduction product **11** (Experimental), and this proved a *trans* relationship between Br and t-Bu in epimer **10**.[9]

The two bromoketones **7** and **8** were cleanly equilibrated when treated with HBr in CCl_4 or $CHCl_3$ solution. The epimerization, followed both through the signals of the protons α to bromine in the NMR spectra and by GLC, was carried out starting from both pure diastereoisomers. The equilibrium ratios of **7** to **8** are reported in Table 2.

On the other hand, bromoketone **9** completely disappeared after prolonged exposure to HBr in $CHCl_3$, while an equilibrium mixture of the two isomeric 2-bromo-5-t-butylcyclohexanones **12** and **13** was formed. The more abundant epimer **12** was identified, after chromatographic separation, by $NaBH_4$ reduction to the known bromohydrin **14**.[10] Furthermore, the $NaBH_4$ treatment of the crude isomerization product yielded, besides **14**, the diastereoisomeric bromohydrins **15** and **16**, arising from the reduction of the equatorial bromoketone **13**.[10] From the ratios between **14**, **15** and **16**, determined by GLC, the equilibrium ratio of **12** and **13** in the original mixture was inferred (Table 2). The same equilibrium mixture was obtained by similar HBr treatment of the epimeric bromoketone **10**.

DISCUSSION

The acid catalyzed equilibration of biased 2-bromocyclohexanones has been extensively investigated by Allinger[11,12] and more recently by Moreau and Casadevall.[10,13] The epimerization equilibrium of these compounds, as well as the conformational equilibrium of 2-bromocyclohexanone, is determined by a balance of steric and polar effects, and in non polar solvents the less polar axial bromoketone is favoured.[7] The differences in the equilibrium ratios in $CHCl_3$ and CCl_4 shown in Table 2 are consistent with the higher polarity of the first solvent.

On the basis of estimates of nonbonded interactions between t-butyl and carbonyl group, Allinger suggested[14] that 2-t-butylcyclohexanone should exhibit an appreciable population of boat forms. However, Stolow later set an upper limit of 10% upon the nonchair population of *cis*- and *trans*-2-t-butyl-4-hydroxycyclohexanone, and suggested extension of this conclusion to 2-t-butylcyclohexanone itself.[15] As underlined above, the spectral data of 2-bromo-6-t-butylcyclohexanones **7** and **8** are in agreement with chair conformations bearing respectively axial and equatorial Br α to CO group. Moreover, also the similarity of the equilibrium ratios of bromoketones **7–8** with those of isomers **12–13** (Table 2), in which the t-Bu is far away from the CO group, indicates that the t-Bu-CO eclipsing interaction present in the 2-t-butylcyclohexanone derivatives should not cause severe distortions in the cyclohexanone ring geometry.

On the other hand, the results found for 2-bromo-3-t-butylcyclohexanones **9** and **10** stress the effect of a gauche Br-t-Bu interaction both on the conformational equilibrium and on the HBr promoted isomerization of these compounds. In fact, none of the spectral data reported in Table 1 for the *trans* epimer fit the chair conformation with equatorial Br and t-Bu shown in formula **10**. A doublet with high coupling constant due to the axial proton α to Br coupled with an axial proton α to t-Bu, an increased $\nu_{C=O}$ and similar λ_{max} and ϵ with respect to 3-t-butylcyclohexanone should be expected for such a conformation.

If one excludes the unlikely alternative chair conformation with axial Br and t-Bu, the above spectral data point to a high preference of *trans*-2-bromo-3-t-butylcyclohexanone for a flexible form, which in the light of the results obtained in the conformational analysis of dibromoderivative **1** and related compounds[4,5] was not unexpected. In fact, the enthalpy difference between chair and twist conformations in cyclohexanone is much lower than in cyclohexane, and several cyclohexanone derivatives with a destabilizing interaction between a t-Bu group and a *trans* vicinal substituent have been reported to exist with appreciable proportions of flexible forms.[16] In the case of **10**, a conformation like **10$_t$**, with a *ca.* 90° diedral angle between the C–H bonds α to Br and t-Bu, as suggested by the very low value of their coupling constant, and a large Br–C–C=O torsion angle, as suggested by the $\nu_{C=O}$ value, has the double advantage of easing both the steric Br-t-Bu interaction and the electrostatic repulsion between Br and CO group present in the chair form.

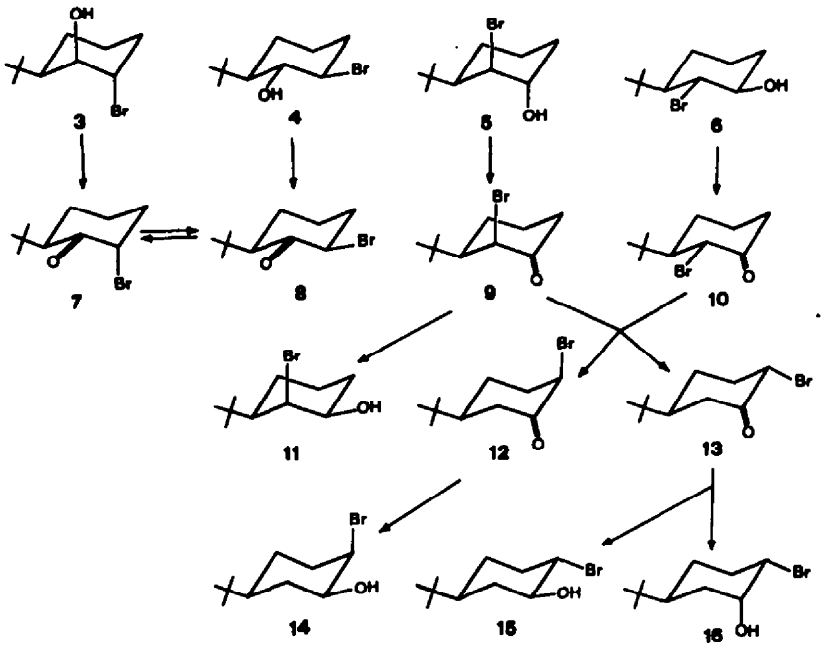
Migration of Br from the α to the α' position to a CO group in the presence of HBr has been frequently observed[17] and several different mechanisms have been

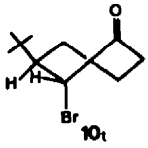
Table 2. HBr-Catalyzed equilibration of t-butyl substituted 2-bromocyclohexanones[a]

Starting compound	Solvent	Equilibrium composition (%)			
		7	8	12	13
7 or 8	CCl_4	80	20		
7 or 8	$CHCl_3$	57	43		
9 or 10	$CHCl_3$			61	39
12 or 13[b]	CCl_4			72	28

[a] The concentrations of bromoketones in the equilibration experiments were < 0.1M in order to avoid intermolecular associations [J. Petrissans, R. Ravelojaona and J. Deschamps, Bull. Soc. Chim., 1249 (1967)].

[b] Taken from ref. 10.





proposed.[18] Moreau and Casadevall reported[13b] the absence of 2-bromo-3-t-butylcyclohexanones (9 and 10) in the equilibrium mixtures obtained by HBr catalyzed epimerization of the 2-bromo-5-t-butyl isomers 12 and 13 as an evidence against the possibility of halogen migration during the epimerization and therefore against epimerization mechanisms involving the breaking of the C–Br bond. The present results show that, inversely, a rearrangement involving C–Br bond breaking does occur in compounds 9 and 10, which are completely transformed into an equilibrium mixture of 12 and 13. The driving force for this rearrangement, taking place under conditions in which optically active *trans*- and *cis*-2-bromo-4-t-butylcyclohexanones undergo only epimerization without migration or exchange of halogen,[13b] must be provided by the relief of steric repulsion between t-butyl and axial 2-bromine in 9 and by the change from a flexible to a more stable chair form in the case of 10_t.

In conclusion, the behaviour of the diastereoisomeric 2-bromo-3-t-butylcyclohexanones provides a further demonstration of the importance of strong gauche steric interactions in determining both the conformation[4,5] and the reactivity[1,3] of cyclohexane derivatives.

EXPERIMENTAL

M.ps. were determined on a Kofler block and are uncorrected. The NMR spectra were registered with a Jeol C-60 HL and a Jeol PS-100 instrument, using TMS as internal standard. The C=O stretching frequencies were measured with a Perkin-Elmer 238 spectrophotometer. The UV spectra were taken with a Zeiss PMQ II instrument. GLC analyses of the mixtures of bromoketones 7 and 8 were performed on a Perkin-Elmer F 11 gas chromatograph fitted with a 1 m glass column, 2.5 mm i.d. packed with 10% ethylene glycol succinate on silanized Chromosorb W 80–100 mesh [low isotherm 100° (8 min), high isotherm 140°, temperature increment 6°/min, N_2 flow 40 ml/min; relative retention times: 7, 1; 8, 2.2]. The mixtures of 14, 15 and 16 were analyzed with a C. Erba Fractovap GV instrument, equipped with a 1.5 m glass column, 2.5 mm i.d., packed with 10% ethylene glycol succinate on silanized Chromosorb 80–100 mesh (column 115°, evaporator and detector 200°, N_2 flow 40 ml/min; relative retention times: 16, 1; 15, 1.29; 14, 1.53). $MgSO_4$ was always used as the drying agent. Evaporations were made *in vacuo* (rotary evaporator). Petroleum ether refers to the fraction of boiling range 30–50°. CCl_4 and $CHCl_3$ used as the solvents for the isomerizations of bromoketones were refluxed and rectified over P_2O_5 and stored over molecular sieves.

Bromohydrins 3–6. The starting products 3, 4 and 5 have been prepared as described elsewhere.[6] Isomer 6 was more conveniently obtained by reduction of its acetate[6] with the stoichiometric amount of LAH in ethyl ether at room temp. for 20 min and purified by chromatography on a silica gel (grade III) column.

Bromoketones 7–10. Products 7–10 have been obtained by oxidation of bromohydrins 3–6 with Jones reagent in the usual way.[19] Isomers 7, 9 and 10 were liquids; they were freed from solvent *in vacuo*, but distillation was not attempted on account of possible decomposition and epimerization. Isomer 8 had m.p. 76–77° from petroleum ether. (Found: C, 51.41; H, 7.39; Br, 34.30. Calc. for $C_{10}H_{17}BrO$: C, 51.52; H, 7.35; Br, 34.27%).

Reduction of 9 *and* 10. A soln of $NaBH_4$ (0.25 g) in EtOH–water (10 ml) was added dropwise to a stirred soln of 9 (0.28 g) in ether (15 ml). After stirring for 4 h at room temp., dilution with water, extraction with ether, evaporation of the dried extract and crystallization form petroleum ether at −15° gave pure (GLC) 11, m.p. 68–70°; NMR ($CDCl_3$): δ 1.0 [9H, s, $-C(CH_3)_3$], 2.32 (1H, s, –OH), 3.37 (1H, m, $W_{\frac{1}{2}} = 18$ Hz, $\rangle$CH–OH), 4.76 (1H, m, $W_{\frac{1}{2}} = 6$ Hz, $\rangle$CHBr). (Found: C, 51.10; H, 8.57; Br, 33.72. Calc. for $C_{10}H_{19}BrO$: C, 51.07; H, 8.14; Br, 33.98%).

The reduction of 10 under identical conditions gave mainly *cis*-3-t-butylcyclohexanol, identified by IR and GLC.

Epimerization of 7 *and* 8. Samples of 7 or 8 (0.15 g) were dissolved in a *ca.* 0.25 M soln of dry HBr in $CHCl_3$ or CCl_4 (8 ml) and left at room temp. At intervals the solns were washed with water and satd $NaHCO_3$aq, dried, evaporated and subjected to NMR and GLC analysis. The mixtures were considered at equilibrium when three consecutive determinations gave the same

product composition. In each case the NMR analysis, based on the signals of the protons α to bromine of **7** and **8**, and the GLC analysis gave results agreeing with each other within ±1%. The equilibrium compositions, identical starting both from **7** and from **8**, are reported in Table 2.

Isomerization of **9** *and* **10**. Bromoketone **9** (1.2 g) was dissolved in a *ca* 0.3 M soln of HBr in $CHCl_3$ (120 ml) and left at room temp. Samples were withdrawn at intervals, worked-up as described above and subjected to NMR analysis, which showed a progressive decrease of the δ 1.06 and 4.34 signals of **9** and the appearance of signals at δ 0.94, 4.24 and 4.55 due to the isomeric bromoketones **12** and **13**.[10] After 9 days a 60:40 equilibrium ratio of **12** to **13**, based on the NMR signals at δ 4.24 and 4.55, was found.

An identical equilibrium mixture of **12** and **13** was obtained by similar HBr treatment of bromoketone **10**.

Chromatography of 1.0 g of this mixture on a 40 × 1.5 cm column of silica gel using petroleum ether as the eluant yielded pure **12** (0.25 g) as a liquid;[10] NMR (CCl_4): δ 0.94 [9H, s, $-C(CH_3)_3$], 4.24 (1H, m, $W_{\frac{1}{2}} = 7.5$ Hz, $\rangle CHBr$). Further elution with 98:2 petroleum ether-ethyl ether gave mixtures of **12** and **13** (0.65 g).

Reduction of **12**. Treatment of **12** (0.20 g) with $NaBH_4$ (0.20 g) as reported[10] gave bromohydrin **14** (0.18 g), m.p. 97.5–98.5° (from petroleum ether; lit.[10] m.p. 96°).

Reduction of the equilibrium mixture of **12** *and* **13**. The similar $NaBH_4$ reduction of the equilibrium mixtures of **12** and **13**, obtained by HBr catalyzed isomerization both of **9** and of **10**, followed by chromatography on a silica gel (grade III) column using 98:2 petroleum ether-ethyl ether as the eluant, yielded: pure (GLC) **15**, m.p. 54–55° (from petroleum ether; lit.[10] m.p. 74–75°), NMR ($CDCl_3$): δ 0.86 [9H, s, $-C(CH_3)_3$], 2.70 (1H, s, –OH), 3.48–3.96 (2H, XY part of an ABXYCD system,[20] $\rangle CH-OH$ and $\rangle CHBr$);[21] pure (GLC) **16**, m.p. 53° (from petroleum ether; lit.[10] m.p. 55–56°); pure (GLC) **14**, m.p. 97.5–98.5° (from petroleum ether; lit.[10] m.p. 96°).

GLC analysis of the crude mixtures of bromohydrins arising from the reduction of the crude isomerization products both from **9** and from **10** gave the following product composition: **14**, 61%; **15**, 27%; **16**, 12%.

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REFERENCES

[1]P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili and I. Morelli, *J. Chem. Soc.* Perkin II, 58 (1972).
[2]G. Bellucci, G. Ingrosso, F. Marioni, E. Mastrorilli and I. Morelli, *J. Org. Chem.* **39**, 2562 (1974).
[3]G. Bellucci, M. Ferretti, G. Ingrosso, F. Marioni, A. Marsili and I. Morelli, *Tetrahedron Letters*, 3527 (1972).
[4]P. L. Barili, G. Bellucci, G. Ingrosso, F. Marioni and I. Morelli, *Tetrahedron* **28**, 4583 (1972).
[5]G. Bellucci, G. Berti, M. Colapietro, R. Spagna and L. Zambonelli, *J. Chem. Soc.* Perkin II, 1214 (1976).
[6]G. Bellucci, G. Berti, M. Ferretti, G. Ingrosso and E. Mastrorilli, *J. Org. Chem.* in press.
[7]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, pp. 460–469. Interscience, New York (1966).
[8]R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963); K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.* **83**, 4623 (1961); N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field*, Chap. 6. Holden-Day, San Francisco (1966).
[9]Surprisingly, the $NaBH_4$ reduction of **10** was accompanied by extensive debromination to *cis*-3-t-butylcyclohexanol.
[10]P. Moreau, A. Casadevall and E. Casadevall, *Bull. Soc. Chim.* 2021 (1969).
[11]N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.* **80**, 5476 (1958).
[12]N. L. Allinger, J. Allinger, L. E. Geller and C. Djerassi, *J. Org. Chem.* **25**, 6 (1960).
[13a]P. Moreau, A. Casadevall and E. Casadevall, *Bull. Soc. Chim.* 2013 (1969); [b]*Ibid.* 3973 (1971); [c]*Ibid.* 649 (1972); [d]*Ibid.* 1014 (1973).
[14]N. L. Allinger, H. M. Blatter, L. A. Freiberg and F. M. Karkowski, *J. Am. Chem. Soc.* **88**, 2999 (1966).
[15]R. D. Stolow, T. Groom and M. Gerace, *Ibid.* **90**, 3290 (1968).
[16]G. M. Kellie and F. G. Riddel, *Top. Stereochem.* **8**, 225 (1974).
[17]I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.* 801 (1937); C. W. P. Crowne, R. M. Evans, G. F. H. Green and A. G. Long, *Ibid.* 4351 (1956); E. R. H. Jones and D. J. Wluka, *Ibid.* 907, 911 (1959); H. E. Zimmerman and A. Mais, *J. Am. Chem. Soc.* **81**, 3644 (1959); J. Fishman, *J. Org. Chem.* **27**, 1745 (1962); M. D. Mehta, D. Miller and D. J. D. Tidy, *J. Chem. Soc.* 4614 (1963); M. Gaudry and A. Marquet, *Bull. Soc. Chim.* 1849 (1967).
[18]For a survey of these mechanisms see Ref. 13*b*.
[19]G. Bellucci and G. Berti, *J. Org. Chem.* **32**, 268 (1967).
[20]H. R. Buys, H. J. A. De Vries, H. J. Hageman and C. Altona, *Rec. Trav. Chim.* **89**, 245 (1970).
[21]Although the m.p. was different from the reported one, the 100 MHz NMR spectrum of this compound was fully consistent with structure and relative configuration **15**.