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α,α′-Dibromocycloalkanones. Preparation and Conformation

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The stereoisomeric α,α′-dibromocycloalkanones from cyclohexanone to cyclododecanone have been prepared as far as this has been possible. Where known (n = 6, 10, 11, 12, 13) the cis (meso) isomers have higher melting points and higher ir carbonyl stretch frequencies and are more polar as well as less soluble than the trans (*dl*) analogs which are considered to be conformationally more mobile. Since the meso:*dl* ratio of the C_{11} and especially C_{12} dibromocycloalkanone at equilibrium approaches that of the most simple acyclic analog, *viz.*, 2,4-dibromo-3-pentanone, open-chain behavior and relatively free rotation in the larger rings are suggested.

As a class of compounds α,α′-dibromocycloalkanones have been investigated by a wide range of physical[1] and theoretical techniques[1a] and have also served as intermediates in synthesis.[2] A new synthetic application which has considerable potential for growth is their use as precursors of metal oxyallyl, especially zinc oxyallyl species as described in another paper.[3] From the very beginning of our work it seemed desirable to gain conformational insight into these compounds which would help us to understand differences in reactivity as well as steric and mechanistic features of the zinc-induced dehalogenation. Accordingly, we have prepared and isolated, as far as this has been possible, all stereoisomeric α,α′-dibromocycloalkanones from C_6 to C_{12} and have investigated their physical and spectroscopic properties.

Discussion

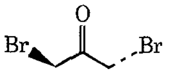
The compounds, together with their melting points and epimeric ratios at equilibrium are listed in Table I, which also indicates the earlier contributions of other workers, notably Corey,[4] Borsdorf, *et al.*,[5] and Garbisch.[2b]

One can see immediately that the diastereoisomeric ratio for the C_{11} and especially the C_{12} isomers approaches that of the most simple acyclic disecondary dibromo ketone, *viz.*, 2,4-dibromo-3-pentanone. It has been shown quite independently that these compounds resemble each other in forming a W cation on dehalogenation.[3] Apparently, in choosing their optimum conformation the C_{11} and C_{12} stereoisomers are relatively free to rotate and, in fact, approach the behavior of the acyclic model. For this reason we prefer the terms meso and *dl* to cis and trans when dealing with the C_{11}, C_{12}, and also C_{13} dibromocycloalkanones.[6]

The changeover from large to medium ring behavior occurs in the 10-membered system where the trans epimer is now somewhat more stable than the cis analog. Of the six possible C_7–C_9 dibromocycloalkanones only the trans isomers have so far been isolated, also after attempted epimerization.[16] Clearly, in this case the cis epimers must be markedly less stable (>2 kcal/mol), a fact to be discussed below.

Melting Points. The melting of solids may be treated thermodynamically, $\Delta G = \Delta H - T\Delta S$. At equilibrium, $\Delta G = 0$ and $T_m = \Delta H_m/\Delta S_m$. If the heat of fusion ΔH_m does not change much, as is often the case for related compounds, a high entropy of fusion ΔS_m entails a low melting point *vice versa*. Now ΔS_m is largely determined by the gain of conformational mobility in the liquid state, the conformation in the crystal lattice being unique.[7] On this model it is understandable that *cis*-2,6-dibromocyclohexanone melts higher than the trans form, because in the former isomer, population of the a,a conformer in the liquid state is not very favorable, while the latter may undergo degenerate interconversion (a,e $\rightleftharpoons$ e,a) and hence gain conformational mobility on melting (see Figure 1). For the same reason the *dl* isomers of C_{11} and C_{12} (which melt below the corresponding meso isomers) are considered to be conformationally more mobile and to have less well-defined energy wells than the meso analogs. Again, this conclusion accords with other evidence, such as the reduced polarity and broader ir carbonyl peaks (CCl_4 solvent, Table II) of the *dl* isomers. Of all the α,α′-dibromocycloalkanones which we have investigated, *trans*-2,10-dibromocyclodecanone is perhaps most interesting, because it is the only compound (n = 6–13), which is not a solid at room temperature. In fact, even on further cooling we never succeeded to crystallize the compound which remained a yellow liquid after redistillation at reduced pressure. On these grounds and also on the basis of chemical evidence[3] *trans*-2,10-dibromocyclodecanone appears to be conformationally less rigid, in contrast to cyclodecanone itself and its simpler derivatives, which have been shown to have a relatively well-defined, diamandoid conformation, similar to cyclohexane and adamantane.[8] Assuming that the trigonal carbon appears as a type III atom so as to remove intraannular repulsion,[8] one can see that the bromine atoms of the trans isomer are forced to adopt rather unfavorable positions, reminiscent of a syn-diaxial relationship in cyclohexanone (Figure 2); the resulting repulsion of unshared electron pairs on bromine might also account for the yellow color of the compound. Whatever further conformational details may come to light we believe that the structure of *trans*-2,10-dibromocyclodecanone is not a good model for that of the parent ring ketone.

The postulated greater conformational mobility of the trans (*dl*) isomers (n = 6, 10–12) is also manifest in physical properties other than melting points. Thus, they showed a generally reduced polarity and tended to be more soluble, not only in the mother liquors during preparation but also in benzene and less polar hydrocarbons. Furthermore, the cis (meso) C_{10}, C_{11}, and C_{12} dibromocycloalkanones could be grown without effort to long, colorless needles, whereas the *dl* C_{11} and C_{12} forms tended to form microcrystals. Note also that the trans isomers have the lower ir carbonyl stretch frequency (Table II). Presumably, on a time-averaged basis they have C_2 symmetry **1**, while the cis isomers have C_s symmetry. As a consequence, dipole–dipole repulsion of the electronegative oxygen with the flanking bromines in the cis isomers **2** and partial cancelation of the C–Br dipoles in the trans isomers **1** conspire to increase the polarity of the *cis*-dihalo ketones. It should be mentioned that from a synthetic viewpoint the conformationally more mobile trans isomers—at least in the case of


1 (C_2)

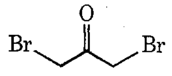
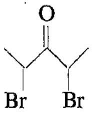

2 (C_s)

Table I
α,α'-Dibromocycloalkanones from Cyclohexanone to Cyclododecanone

No. of carbons	Diastereo-isomer	Mp, °C	Lit. mp, °C	Cis:trans ratio at equil	Lit. ref or elemental anal. (%)	Registry no.
6[a]	Cis	112	112	0.18	4	16080-75-4
6	Trans	35	36		4	16080-74-3
7	Trans	70	70	0	5	18315-97-4
8	Trans	82	82	0	5	16110-80-8
9[b]	Trans	51		0	Calcd for $C_9H_{14}OBr_2$: C, 36.27; H, 4.73. Found: C, 36.22; H, 4.74	52928-61-7
10	Cis	55		~0.5	Calcd for $C_{10}H_{16}OBr_2$: C, 38.48; H, 5.17. Found: C, 38.39; H, 5.02	52906-73-7
10	Trans	Bp 60–64° (0.001 mm)			Calcd for $C_{10}H_{16}OBr_2$: 38.48; H, 5.17. Found: C, 38.28; H, 5.11	52949-45-8
11	Meso	80	80	1.6	2b	19914-86-4
11	*dl*	54	56		2b	19914-87-5
12	Meso	126	126	3.8	2b	19914-84-2
12	*dl*	48	48		2b	19914-85-3
13	Meso	110				52906-74-8
	Meso *dl*			~5.0[c]		51513-32-7 51513-33-8

[a] 2,5-Dibromocyclopentanone, mp 67°, has also been obtained; see Experimental Section. [b] 2,2-Dibromocyclononanone, mp 69°, is formed as a major by-product. [c] Determined by $NaBH_4$ reduction into the diastereoisomeric dibromohydrins according to ref 2b.

Table II
Carbonyl Stretch Frequencies (cm^{-1}) of α,α'-Dibromocycloalkanones[a]

No. of carbons	Parent cycloalkanone	*cis*-Dibromocycloalkanone		*trans*-Dibromocycloalkanone	
	Mull or smear	Mull or smear	CCl_4	Mull or smear	CCl_4
6	1715	1745	1755 v (1713)	1739 v	1739 v
7	1704	1721	1731 v		
8	1702 b22	1718	1727 v		
9	1702	1721	1719 b10		
10	1705	1721 b16	1731 v	1704 v	1708
11	1707	1730	1727 v	1712	1710 b8
12	1712	1727	1728 v	1713 v	1709 b8
13	1713		1716 v		

[a] The spectra were recorded on a Perkin-Elmer grating spectrometer, Model 257. The carbonyl regions were expanded so that 1 cm corresponded to 20 cm^{-1}. Abbreviations: v, sharp; b22, broad, approximate spread in cm^{-1}.

trans-2,10-dibromocyclodecanone[3]—seem to be more suitable for generating zinc oxyallyl, the formation of which is considered to require quasiaxial departure of bromine to optimize orbital overlap.

Why are the cis isomers (n = 7–9) as yet inaccessible by epimerization? Cycloheptane[9] and presumably cycloheptanone as well prefer the C_2 conformation (Figure 3) allowing the bromines of the observed trans isomer to occupy quasiequatorial positions at the periphery.[10] Similarly, the tendency to maintain time-averaged C_2 symmetry such that conformational imperfections may travel easily around the ring[7c] could account for our failure to obtain *cis*-2,8-dibromocyclooctanone and the cis C_9 derivative. Significantly, where cis and trans isomers do exist (n = 6, 10–12) the difference in melting points is apparently smaller in the odd-membered (n = 11) ring (Figure 1).

Attempts to analyze the pmr spectra of the C_7–C_{12} dibromocycloalkanones were not very successful, even after decoupling experiments, simulation of spectra by computer, and cooling of the solution down to the lowest possible temperatures (*ca.* −110°).[11] However, it is worthy of mention that the meso isomers of those α,α'-dibromocycloalkanones which displayed open-chain behavior (C_{11}, C_{12}, and also C_{13}) showed the CHBr quartet at lower field than the corresponding *dl* analogs (Table III). Consistently, *meso*-2,4-dibromo-3-pentanone had its methine quartet centered on δ(TMS, CCl_4) 7.01 ppm, while the quartet of the *dl* diastereoisomer appeared at higher field (δ 6.48). This finding is in accord with averaged C_s symmetry **2** for the more polar meso isomer and might serve as a criterion for the distinction of *dl* and meso diastereoisomers of comparable mobile systems.

Table III
Pmr Data for α,α'-Dibromocycloalkanones[a]

Compd	Chem shift of CHBr proton, δ (TMS, $CDCl_3$), ppm	Obsd sepn of of signals, Hz
C_7 trans	4.72	4.9, 5.3, 4.9
C_8 trans	4.68	5.9, 1.6, 1.6, 1.5, 6.0
C_9 trans	4.60	7.45, 7.5
C_{10} cis	4.90	4.75, 0.7, 4.25, 5.0
C_{10} trans	4.95	6.5, 6.4
C_{11} meso	4.81	3.75, 6.0, 3.75
C_{11} *dl*	4.70	4.8, 4.4, 4.8
C_{12} meso	5.02	3.75, 5.0, 3.75
C_{12} *dl*	4.62	4.6, 6.0, 4.6

[a] Spectra were recorded on a Varian HA 100 nmr spectrometer using 0.1 *M* $CDCl_3$ solutions containing 5% TMS as internal standard.

Experimental Section

Preparation of α,α'-Dibromocycloalkanones. The preparation and properties of some α,α'-dibromocycloalkanones have already been reported (see Table I). A general procedure is as follows. Cycloalkanone (1 mol) was stirred rapidly in anhydrous ether (300 ml) at 0–5°, 1 drop of bromine being introduced. Only after

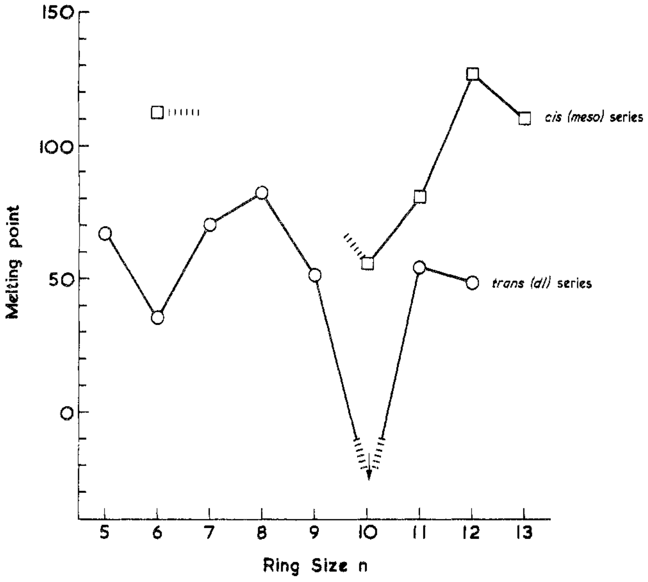


Figure 1. Melting points of stereoisomeric α,α′-dibromocycloalkanones as a function of ring size.

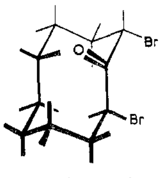


Figure 2. Dunitz conformation of *trans*-2,10-dibromocyclodecanone.

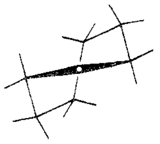


Figure 3. C_2 conformation of cycloheptanone.

the color of bromine had disappeared was the bulk of the bromine (1 mol) added so that the temperature did not exceed 10°. The reaction solution was allowed to warm to 25–30° and more bromine (1 mol) was added slowly. After being stirred for 1 hr further, the mixture was washed with 2% aqueous $Na_2S_2O_3$, 10% Na_2CO_3, and finally water. The solution was dried and the solvent was removed until crystallization occurred.

Special Procedures. 2,5-Dibromocyclopentanone (N. H. Burt). The bromination was carried out at 3° in glacial acetic acid, the HBr formed being blown out by a stream of nitrogen. The mixture was poured onto ice, neutralized with $NaHCO_3$ to pH 5, and extracted with CCl_4. The organic layer was washed with dilute $NaHCO_3$, dried ($MgSO_4$), filtered, and cooled for several hours to *ca.* −25°, giving a pale yellow oil which on fractional crystallization from *n*-pentane–CCl_4 (50:50 v/v) followed by repeated recrystallization from pentane yielded **2,5-dibromocyclopentanone:** white needles stable in air; mp 67°; ir (CCl_4, cm^{-1}) 1767 v; pmr δ (TMS, CCl_4) 2.5 (m, 4 H), 4.27 ppm (complex m, 2 H). Computer simulation of the spectrum, which, however, cannot stand on its own as a piece of evidence, suggests that the compound is the trans isomer.[12]

cis- **and** *trans*-**2,6-Dibromocyclohexanone.**[4] The reaction mixture was kept as dilute as possible to minimize formation of a wine red solution. After cooling to −78° the cis isomer was filtered off and recrystallized several times from a mixture of ligroin–diethyl ether: mp 112° (30%). The mother liquors were pooled, concentrated to *ca.* 50 ml, and stored at 0° over several days to yield another batch of product. Continued treatment in this way gave *cis*-2,6-dibromocyclohexanone in *ca.* 45% total yield. The equilibration of the cis and trans isomer was conveniently carried out at 25° for 4–6 hr using solvent ether saturated with anhydrous HBr and also anhydrous HCl.[13]

trans-**2,7-Dibromocycloheptanone.**[5] Recrystallization from petroleum ether (bp 80–120°) followed by treatment with activated charcoal in ether gave *trans*-2,7-dibromocycloheptanone: mp 70°; colorless solid (48% after purification).

trans-**2,8-Dibromocyclooctanone.**[5] The compound was obtained as described for the lower homolog and had mp 82° after recrystallization.

trans-**2,9-Dibromocyclononanone and 2,2-Dibromocyclononanone.** Careful bromination at 0° gave two hand-separable crystalline forms from *n*-pentane in about 40% yield after purification: *trans*-2,9-dibromocyclononanone, rhomboids, mp 51°, and needles of a second isomer which on the basis of its pmr and mass spectra was 2,2-dibromocyclononanone,[14] mp 69°. *Anal.* Calcd for $C_9H_{14}OBr_2$: C, 36.27; H, 4.73. Found: C, 35.75; H, 4.60.

cis- **and** *trans*-**2,10-Dibromocyclodecanone.** Fractional crystallization from *n*-pentane yielded solid *cis*-**2,10-dibromocyclodecanone,** mp 55°. The filtrate was cooled to −78° for several hours to yield an oil, which was distilled and gave *trans*-**2,10-dibromocyclodecanone** as a stable yellow oil, bp 60–64° (0.001 mm). On cooling to −78° the oil set to a solid glass. The combined yield of the two stereoisomers, which were isolated in a ratio of 35:65, amounted to *ca.* 65%.

meso- **and** *dl*-**2,11-Dibromocycloundecanone.**[2b] The bromination yielded two forms which were easily separated by fractional crystallization from ether–*n*-pentane to give *meso*-2,11-dibromocycloundecanone, mp 80°, and *dl*-2,11-dibromocycloundecanone, mp 54°, in 85% overall yield.

meso-**2,12-Dibromocyclododecanone.**[2b] During bromination it was often found that the predominant meso isomer, mp 126°, separated as a solid. If so, it was filtered off before bromination was resumed. The *dl* isomer was obtained by epimerization with anhydrous acid.

Preparation of Parent Cycloalkanones. Cyclononanone, cyclodecanone, and cycloundecanone were synthesized in a number of ways,[15] the sequence of Garbisch[2b] being found to be most satisfactory.

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Registry No.—Dibromocyclopentanone, 53778-21-5; 2,2-dibromocyclononanone, 52951-33-4.

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(16) **Note Added in Proof.** The preparation of both *cis*-2,5-dibromocyclopentanone and *cis*-2,7-dibromocycloheptanone has recently been implied, although no experimental details have been given; see R. H. Prager and J. M. Tippett, *Tetrahedron Lett.*, 5199 (1973). We believe that the assignment of at least the seven-membered derivative must be reversed.

Synthesis of Phthalimidines from Aromatic Dicarbonyl Compounds

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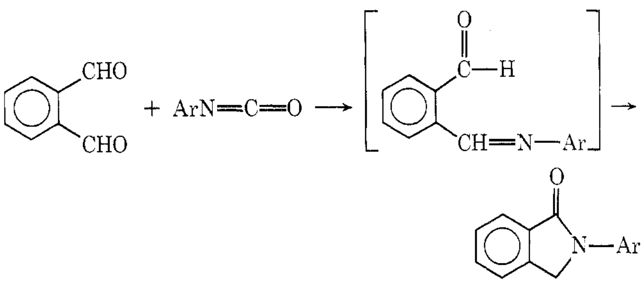
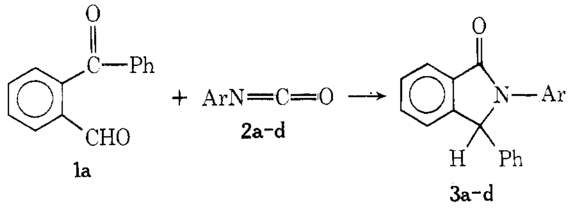
The reaction between *o*-benzoylbenzaldehyde (**1a**) and aromatic isocyanates (**2a–d**) afforded 2,3-disubstituted phthalimidines **3a–d** in good yield, which would be formed *via* *o*-benzoylbenzylideneaniline intermediate followed by migration of phenyl group. The same product **3a** was obtained by the reaction using **1a** and aniline. On the other hand, no reaction was observed between *o*-carbetoxybenzaldehyde (**23**) and **2a**, but the reaction of **23** with aniline gave *o*-carbetoxybenzylideneaniline (**24**) and 3-anilino-2-phenylphthalimidine (**21a**), in 83 and 7% yield, respectively.

Previously we reported a synthetic method for *N*-arylphthalimidines by the reaction of an aromatic isocyanate and phthalaldehyde.[1] In the present paper, we report the reactions of isocyanates with aromatic dicarbonyl compounds and a new synthetic method for 2,3-disubstituted phthalimidines.

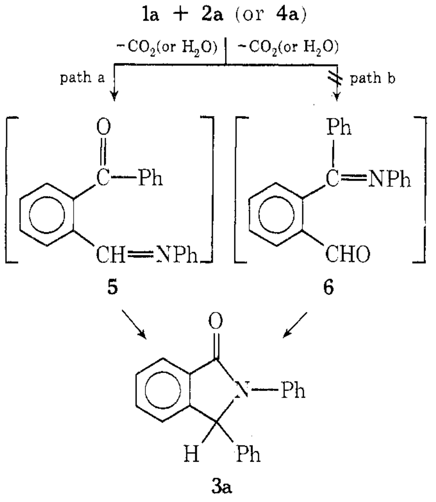


o-Benzoylbenzaldehyde. Treatment of *o*-benzoylbenzaldehyde (**1a**) with an equimolar amount of phenylisocyanate (**2a**) at 200° for 15 hr afforded 2,3-diphenylphthalimidine (**3a**) in 67% yield. The reaction of **1a** with other isocyanates gave phthalimidines **3b–d.** Both the ir (C=O at 1680 cm^{-1}) and nmr (singlet for CH at δ 6.05) spectra of **3a** are fully consistent with the structure; **3b–d** also showed nmr singlets at δ 5.98–6.02. The mass spectrum of **3a** exhibited a molecular ion peak at *m/e* 285, in accordance with a general formula $C_{20}H_{15}ON$, and the fragmentation pattern was in agreement with phthalimidine structure.



2a and 3a, Ar = C_6H_5
2b and 3b, Ar = m-$CH_3C_6H_4$
2c and 3c, Ar = α-naphthyl
2d and 3d, Ar = β-naphthyl

Chart I



As expected, treatment of **1a** with aniline (**4a**) gave **3a** in 65% yield. These observations suggest that the reaction be-

Table I
The Reaction of Aromatic Isocyanate with *o*-Benzoylbenzaldehyde[a]

Products	Reaction time, hr[b]	Yield, %[c]	Mp, °C	Ir(C=O),[d] cm^{-1}	λ_{max}, nm	Nmr, δ CH	Nmr, δ CH_3	Nmr, δ Aromatic
3a	15	67	192–194	1680	275	6.05		7.0–8.1
3b	16	54	175–176	1680	275	6.02	2.25	6.7–8.0
3c	19	84	190–191	1705	275, 283, 293	5.98		6.8–8.2
3d	19	81	200–201	1680	260, 268, 283, 300	5.99		6.7–8.2
3e	9	52	190–190.5	1680		6.03	2.24	7.0–8.1

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds. [b] The reaction was monitored by ir. [c] Based on isocyanate. [d] Nujol mull.