Tetrahedron. Vol. 32, pp. 975 to 978. Pergamon Press 1976 Printed in Great Britain

THE STEREOCHEMISTRY OF DICHLOROKETENE AND CHLOROSULFONYL ISOCYANATE CYCLO-ADDITION TO 4-t-BUTYLMETHYLENECYCLOHEXANE

E. DUNKELBLUM*
Department of Organic Chemistry, Hebrew University, Jerusalem, Israel

(*Received in UK* 20 *October* 1975; *Accepted for publication* 1 *November* 1975)

Abstract—The stereochemistry of the cycloaddition of dichloroketene (1) and chlorosulfonyl isocyanate (2) to 4-t-butylmethylenecyclohexane (4) has been investigated as a model for the $2\pi_s+2\pi_a$ cycloaddition to the methylenecyclohexane system. The reactions are kinetically controlled and proceed mainly by axial attack to yield the thermodynamically less stable isomers 7 and 10, as major products, respectively.

INTRODUCTION

The stereochemistry of nucleophilic and electrophilic additions to cyclohexanones[1-3] and methylenecyclohexanes[4,5] has been of much interest during the last 20 years. Several models have been proposed to explain the factors which control the axial and equatorial attack of different reagents to numerous cyclohexane compounds [2,3] and the problem is still open. On the other hand, the stereochemistry of cycloadditions to methylenecyclohexane has been neglected.† We would like to present our results on the cycloaddition of dichloroketene (1) and chlorosulfonyl isocyanate-CSI (2) to 4-t-butylmethylenecyclohexane (4) as a model for a $2\pi_s+2\pi_a$ reaction in this system.

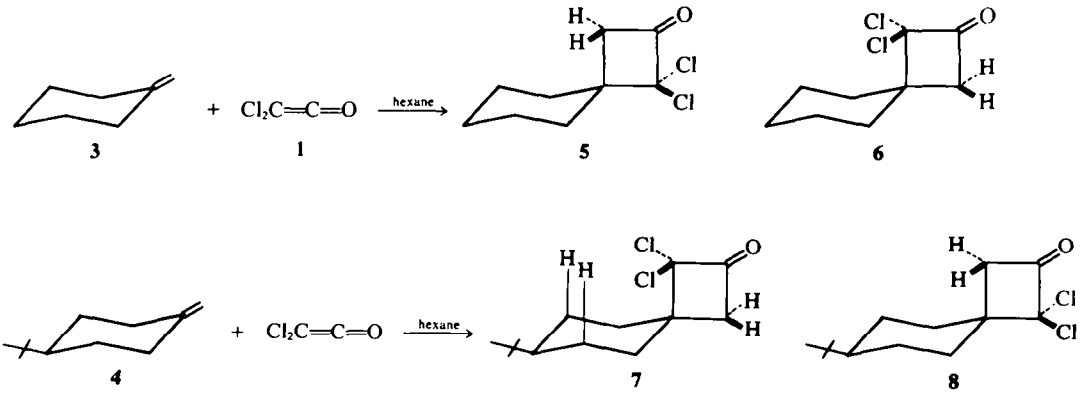
RESULTS AND DISCUSSION

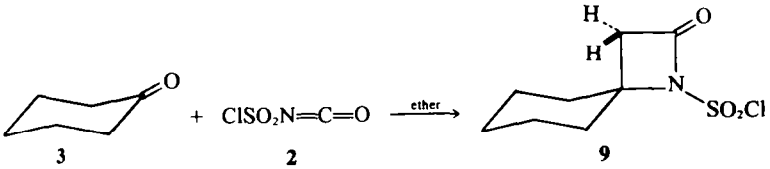
Our investigation consisted of the reaction of 1 and 2 with methylenecyclohexane (3) and 4-t-butylmethylenecyclohexane (4). Attempts to use the sterically hindered 3,5,5-trimethylmethylenecyclohexane failed because low yields and large amounts of unidentified products were obtained. Dichloroketene (1) was chosen because of its convenient, *in situ*, preparation[6,7] and relative high reactivity.[6] Chlorosulfonyl isocyonate CSI; (2) was added to the project due to its polar character and very high reactivity in 2+2 reactions.[8] Cycloaddition of 1 to 3 gave spiroketone 5 in 55% yield (ball oven). The structure was established by IR, NMR and mass spectra.

The same reaction with 4 was relative slow and gave variable yeilds (10–40%) of isomeric spiroketones 7 and 8 in a constant ratio of 4:1 (average of 6 experiments). This ratio was determined by NMR (integration of the CH_2 group α to carbonyl) and by GLC. Separation (GLC) with subsequent crystallization gave pure 7 and 8. The addition of 1 to 3 and 4 is regiospecific.[6,7]

The determination of the stereochemistry of 7 and 8 is based on a number of complimentary facts. The inspection of a Dreiding model of the cycloadduct from 3 shows clearly that the preferred conformation of this compound is 5 in which the dichloromethylene group is equatorial (and not 6). A rough molecular-mechanics calculation (by a combination of a ketone[9] and halide[10] force field) for the system 5⇄6 in the gas phase gives $\Delta E \approx 0{\cdot}7$ kcal/mole. The calculated dipole of the more stable conformer (5) is 4·1 D higher than that of 6 (3·5 D)—therefore ΔE in solution (e.g. CCl_4 or $CHCl_3$) is expected to be much greater.[11] These calculations confirm the strong preference for 5 over 6. The stereochemistry of 8 is the same as that of 5 and their NMR spectra are very similar; all the cyclohexane protons appear as a broad multiplet. On the other hand the NMR spectrum of 7 is different; the cyclohexane protons are divided into two groups, a low field multiplet of two protons at δ 2·50–2·24 and the other protons at δ 1·90–1·30. The low field multiplet is attributed to the two axial protons in proximity to the Cl atoms. A similar deshielding effect has been observed in decalin derivatives.[12] The measurements of wh/2 of the CH_2 singlets in 7 and 8 confirms the proposed assignments. The axial CH_2 in 8 has a wh/2 of 1·4 Hz and the equatorial CH_2 in 7 has a wh/2 of 0·9 Hz—in accordance with the established phenomenon that axial Me or methylene groups in rigid cyclohexanes

†*Note added in proof.* Recently a study on the stereochemistry of dihalo-carbenes addition to 4-t-butylmethylenecyclohexane has been published: E. V. Couch, J. A. Landgrebe and E. T. Castaned, *J. Org. Chem.* **40**, 1529 (1975).





3 2 9

have larger wh/2 than the equatorial ones.[13,14] The chemical shift of the axial CH_2 group in **8** is δ 2·92 whereas that of the equatorial CH_2 group in **7** is δ 2·88 There are many examples in which the axial CH_2 or Me group absorbs at lower field than the corresponding equatorial one;[15] however the differences in the chemical shifts are small[16] and there are a number of reverse cases[13,16] (compounds **10** and **11**).

The reaction of **3** and **4** with **2** in ether at 0° is fast and practically quantitative. Methylenecyclohexane (**3**) gave spirolactam **9** as reported in the literature.[17]

The conformation of this adduct is assumed to be **9** (Dreiding model) with the large $-N-SO_2Cl$ group being equatorial. The NMR spectrum of **9** is similar to that of the corresponding spiroketone **5**. The same reaction with **4** gave, over 90%, pure spirolactam **10** accompanied by small amounts of other products, which may contain **11**.

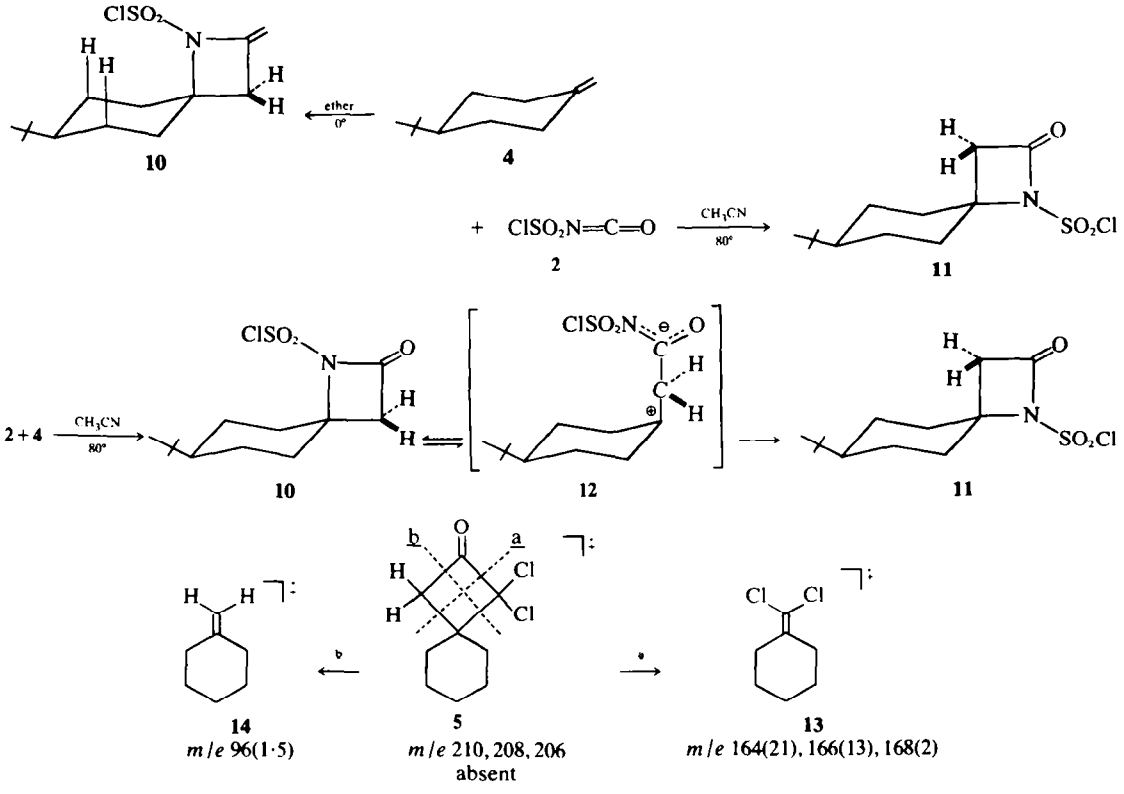
Attempts to isolate some **11** from this reaction mixture failed. A small amount of pure **11** could be obtained by conducting the cycloaddition in boiling acetonitrile. The yield was 5–10% and the purification was difficult; the rest was a thick oil which does not contain the β-lactam function (absence of the strong 1810 cm^{-1} band in IR). The formation of **11** at these conditions may be explained by primary formation of **10** and subsequent fast isomerization, through a dipolar intermediate (**12**),[18–20] to **11** which is the more stable isomer.

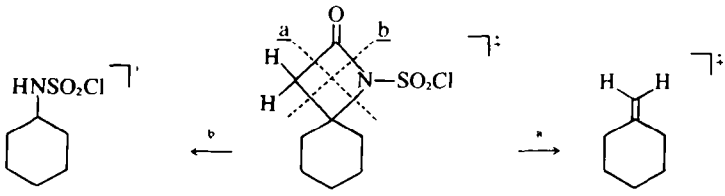
It is also possible that the reaction proceeds directly via **12** to yield **11**.[20b] The reaction of **3** and **4** with CSI is regiospecific as expected.[17–20] The stereochemistry of **10** and **11** was assigned in a similar manner as that of **7** and **8**. The NMR spectrum of **11** is similar to that of **9** (and of **5** and **8**). On the other hand, the NMR spectrum of **10** is different; the cyclohexane ring protons are divided into groups, a low field multiplet of two protons at δ 2·60–2·30 attributed to the axial protons close to the $-NSO_2Cl$ group and the rest at δ 2·00–1·50. The wh/2 of the axial CH_2 group α to CO in **11** is 1·9 Hz and that of the equatorial CH_2 in **10** is smaller—1 Hz as expected.[13,14] The chemical shift of these groups is practically identical—the equatorial one absorbing at δ 3·00 and the axial one at δ 2·99.

The fragmentation, in the mass spectrometer, of both the spiroketones (**5**, **6** and **8**) and the spirolactams (**9**, **10** and **11**) is basically similar. The first reaction, in both systems, which occurs, is cleavage of the 4-membered ring with formation of a methylene- or heteromethylenecyclohexane. This is a reverse $2\pi_a + 2\pi_s$ reaction which was already observed in the fragmentation of cyclobutanones.[21]

In the case of **5** the main cleavage is the loss of ketene (patch *a*) with formation of **13**. The second possible fragmentation (path *b*) occurs to a very small degree. The molecular ion (M^+) is absent in **5**, **7** and **8**.

The spirolactam **9** undergoes cleavage in both ways, however with strong preference for path *a* namely the loss of CSI (**2**) to produce **14**. The cleavage of ketene (path *b*) is accompanied by a hydrogen transfer with formation of **15** (the mechanism of this transformation has not been





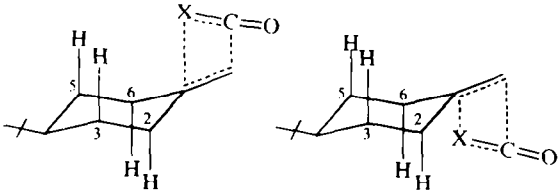
15
m/e 196(15), 198(5)

9
m/e 237(4), 239(1)

14
m/e 96(100)

investigated). The molecular ion M^+ is present in **9**, **10** and **11** although small in all three compounds. This fragmentation pattern confirms the gross structure of **5**, **7**, **8**, **9**, **10** and **11** and the regiospecifity of the dichloroketene (**1**) and CSI (**2**) cycloadditions to the methylenecyclohexane system.

We assume that both the addition of **1** and **2** are concerted reactions which proceed by the allowed $2\pi_s + 2\pi_a$ process.[22] The approach of **1** and **2**, which are the antara components, is orthogonal to the double bond.[6,23] These reactions are completely regiospecific due to the polar character of the transition state.[6,8,23] The cycloaddition of both **1** and **2** to **4** are stereoselective leading mainly to the thermodynamically less stable isomers **7** and **10**. These observations prove that the reactions are kinetically controlled and the stereochemistry of **7** and **10** is determined by the direction of the attack of **1** or **2** on the double bond in **4**. There are two possible transition states for these reactions namely **16a** or **16b** and



16a: X = CCl_2 **17a**: X = CCl_2
16b: X = NSO_2Cl **17b**: X = NSO_2Cl

17a or **17b**. The experimental results show clearly that the axial attack (giving **16a**, **16b**) is the main path for these cycloadditions. The very fast CSI reaction is practically stereospecific. The hindrance for equatorial attack of **1** and **2** on **4** may be explained by the repulsion of the orthogonally approaching **1** or **2** by the axial hydrogens at positions 2 and 6. On the other hand, the axial hydrogens at positions 3 and 5 are far away from **1** or **2** attacking from above.[2] (This explanation is confirmed by Dreiding models). Another reason for the preferred axial attack of **1** and **2** on the methylenecyclohexane system may be of electronic character as proposed recently for the stereochemistry of attack on trigonal atoms in cyclohexanes.[3]

EXPERIMENTAL

Microanalysis were performed by Mrs. M. Goldstein of the micro-analytical laboratory of the Hebrew University. B.ps and m.ps (Büchi Schmelzpunktbestimmungsapparat nach Dr. Tottoli) are uncorrected. NMR spectra were recorded on a Varian HA-100 spectrometer with TMS as internal standard. They are reported in δ units, ppm multiplicity (number of hydrogens). IR spectra were measured on a Perkin Elmer Infracord 337 machine. Mass spectra were recorded on a Varian Mat 311 spectrometer. GLC was performed on a Hewlett-Packard 7620 Apparatus with a stabilized DEGS 20% column, 1·5 m long × 1/4 inch.

Starting materials. All the methylenecyclohexanes were prepared by the Wittig reaction[24] from the corresponding cyclohexanones and purified on a silica column if necessary to remove unreacted ketone. Dichloroacetyl chloride and CSI (**2**) were commercial products (Fluka) and were distilled before use.

1,1-*Dichloro-spiro*[3,5]-2-*nonanone* (**5**). To a stirred refluxing soln of **3** (0·96 g, 10 mmol) and triethylamine (1·5 g, 15 mmol) in 10 ml hexane dichloroacetyl chloride (1·5 g, 10 mmol) in 10 ml hexane was added dropwise. The mixture was refluxed for 1 hr and then cooled, poured into water, the organic phase was separated and the aqueous phase was extracted with more hexane. The combined extracts were washed with $NaHCO_3$ aq, dil HCl, water and dried. Removal of the solvent and ball oven distilation at 75–80° (0·2 mmHg) gave 1·1 g (55%) of **5**, pure by NMR δ (CCl_4): 3·00 (2H, s) 2·00–1·00 (10, bm); ν_{max} (neat): 1815 s cm^{-1}; *m/e* 168 (2) 166 (13) 164 (21) ($M^+ - 42$), base peak 68 (100). An analytical sample was obtained by GLC at 150°. (Found: C, 53·0; H, 5·8. Calc. for $C_9H_{12}Cl_2O$: C, 52·4; H, 5·9%).

cis- *and* trans-1,1-*Dichloro-7-t-butylspiro*[3,5]-2-*nonanone* (**7** + **8**). Compound **4** (0·76 g, 5 mmol) was reacted with dichloroacetyl chloride as described for **5**. The crude product from one run was recycled a second time under the same conditions. The yield after the first run was 10–20% (NMR, relative to starting material) and after the second run, yeilds of 50% were obtained. Ball oven distillation at 100–105° (0·2 mm Hg) gave samples (sometimes solidified) which contained mainly **7** and **8** in a 4:1 ratio (GLC at 170°) accompanied by small amounts of other compounds which were not isolated. Separation by GLC at 170° and subsequent crystallization from MeOH + water gave: the *cis* isomer (**7**) m.p. 64–65°; δ (CCl_4): 2·88 (2H, s), 2·50–2·24 (2H, m), 1·90–1·30 (7H, bm), 0·88 (9H, s); ν_{max} (CCl_4): 1815 s cm^{-1}; *m/e* 224 (1, 5) 222 (8) 220 (15) ($M^+ - 42$) base peak 57 (100); the *trans* isomer (**8**) m.p. 110–112°; δ (CCl_4): 2·92 (2H, s), 2·00–1·00 (9H, bm), 0·86 (9H, s); ν_{max} (CCl_4): 1815 cm $^{-1}$; *m/e* 224 (1) 222 (7) 220 (12) ($M^+ - 42$), base peak 57 (100); (Found: C, 59·9; H, 7·5. Calc. for $C_{13}H_{20}Cl_2O$ (**7** + **8**): C, 59·5; H, 7·5%).

N-*Chlorosulfonyl*-1-*azaspiro*[3,5]-2-*nonanone* (**9**). To **3** (0·96 g, 10 mmol) in 10 ml ether, at 0°, **2** (1·48, 10·5 mmol) in 15 ml ether was added dropwise. The product precipitated gradually. After 15 min at 0° the ice bath was removed and the mixture stirred for 1 hr, cooled again and filtered to yield 2·2 g (92%) of **9**. Crystalization from ether gave a pure sample, m.p. 88–90° (lit[14] m.p. 88–90°); δ ($CDCl_3$): 3·01 (2H, s), 2·40–1·00 (10H, bm); ν_{max} ($CHCl_3$): 1815 s, cm^{-1}; *m/e* 239 (1) 237 (4) (M^r, base peak 96 (100).

cis-N-*Chlorosulfonyl*-1-*aza*-7-*t*-*butylspiro*[3,5]-2-*nonanone* (**10**). The reaction of **4** (0·76 g, 5 mmol) with **2** (0·77 g, 5·5 mmol) as described gave after crystalization from ether 1·20 g (82%) of **10** m.p. 112–113°; δ ($CDCl_3$): 3·00 (2H, s), 2·60–2·30 (2H, m), 2·00–1·60 (6H, m), 1·25–1·00 (1H, m), 0·88 (9H, s); ν_{max} ($CHCl_3$): 1820 s cm^{-1}; *m/e* 295 (0·22) 293 (0·64) (M^+), base peak 57 (100). (Found: C, 48·8; H, 6·5. Calc. for $C_{12}H_{20}ClNO_3S$: C, 49·1; H, 6·8%).

trans-N-*Chlorosulfonyl*-1-*aza*-7-*t*-*butylspiro* [3,5] -2-*nonanone* (**11**). To **4** (0·38 g, 2·5 mmol) in 5 ml acetonitrile at reflux **2** (0·38 g, 2·7 mmol) in 10 ml acetonitrile was added dropwise over 5 min. After a further 3–5 min the mixture was cooled and concentrated to dryness *in vacuo*. The oily residue was dissolved in part in hot ether and the soln was filtered and concentrated to a small volume of *ca.* 5 ml and cooled overnight in a deep freezer. The product precipitated slowly in fine needles. The yield was 50 mg in two crops m.p. 144–146° with gas evolution. This sample was pure by NMR δ ($CDCl_3$): 2·99 (2H, s), 2·45–1·00 (9H, bm), 0·88 (9H, s); ν_{max} ($CHCl_3$): 1815 s cm^{-1}, *m/e* 295 (0·25) 293 (0·75) (M^-), base peak 57 (100). An analytical sample was obtained by a second

crystalization from ether, m.p. 151–152° with gas evolution. (Found: C, 48·9; H, 6·7. Calc. for $C_{12}H_{20}ClNO_3S$: C, 49·1; H, 6·8%).

Acknowledgements—The author wishes to thank Prof. J. Klein for helpful discussion and Dr. A. Meyer for the molecular calculations. The Central Research Fund of the Hebrew University is acknowledged for financial support.

REFERENCES

[1]A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron* **18**, 705 (1962).
[2]J. D. Morrison and H. S. Mosher, *Asymetric Organic Synthesis*. Prentice Hall, 121 (1071).
[3a]J. Klein, *Tetrahedron Letters* 4307 (1973); [b]J. Klein, *Tetrahedron* **30**, 3349 (1974).
[4]J. Klein and D. Lichtenberg, *J. Org. Chem.* **35**, 2654 (1970).
[5]G. Berti, *Topics in Stereochemistry*, Vol. 7, p. 93. Wiley Interscience, New York (1973).
[6]L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde and P. Mollet, *Tetrahedron* **27**, 615 (1971).
[7]W. T. Brady and A. Patel, *J. Org. Chem.* **38**, 4106 (1973).
[8a]R. Graf, *Angew. Chem.* Intern. Ed. **7**, 172 (1968); [b]E. J. Moriconi, *Mechanism of Reactions of Sulfur Compounds* **3**, 131 (1968).
[9]N. L. Allinger, M. T. Tribble and M. A. Miller, *Tetrahedron* **28**, 1173 (1972).
[10]A. Y. Meyer and N. L. Allinger, *Ibid.* **31**, 1971 (1975).
[11]S. Mizushima, *Structure of Molecules and Internal Rotation*, p. 38. Academic Press, New York (1954).
[12]M. Lasperas, A. Casadeval and F. Casadeval, *Bull. Soc. Chim. Fr.* 3209 (1971).
[13]R. G. Carlson and N. S. Behn, *J. Org. Chem.* **32**, 1363 (1967).
[14]We would like to thank Prof. S. Sternhell for discussing with us some of this unpublished results concerning this phenomenon.
[15a]F. Johnson, N. A. Starkovsky and W. D. Gurowitz, *J. Am. Chem. Soc.* **87**, 3492 (1965); [b]H. O. House and Th. M. Bare, *J. Org. Chem.* **33**, 943 (1968).
[16]P. J. Beeby and S. Sternhell, *Aust. J. Chem.* **23**, 1005 (1970).
[17]T. Durst and M. J. O'Sullivan, *J. Org. Chem.* **35**, 2043 (1970).
[18]T. J. Barton and R. J. Rigido, *Tetrahedron Letters* 3901 (1972).
[19]J. R. Malpass and N. J. Tweddle, *Chem. Comm.* 1244 (1972).
[20a]T. W. Doyle and T. T. Conway, *Tetrahedron Letters* 1889 (1969); [b]E. Dunkelblum, *Ibid.* 1551 (1972).
[21a]H. J. Hoffman, *Ibid.* 2329 (1964); [b]H. Audier, J. M. Conia, M. Fetizon and J. Gore, *Bull. Soc. Chim. Fr.* 787 (1967).
[22]R. B. Woodward and R. Hoffman, *The Conservation of Orbital Symmetry* p. 163. Verlag Chemie (1970).
[23]M. Rey, S. Roberts, A. Diffenbacher and A. S. Dreiding, *Helv. Chim. Acta* **53**, 417 (1970).
[24]G. Wittig and U. Schoelkopf, *Organic Synthesis Coll.* Vol. V, 751 (1973).