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STERIC CONTROL OF INTRAMOLECULAR ORTHO-QUINODIMETHANE-CYCLOADDITIONS

Wolfgang Oppolzer*
Sandoz Ltd, Pharmaceutical Division, Chemical Research, Basle, Switzerland

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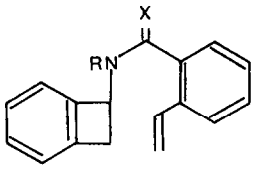
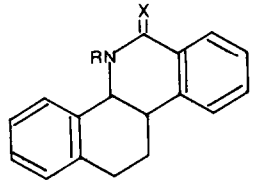
Endo-adducts normally predominate in the cycloaddition of non-conjugated dienophiles (1) although nonbonding interactions of substituents may force the reaction towards exo-adducts (2). A simple and effective control of the endo-exo-ratio has been exemplified recently by the intramolecular cycloadditions **1** ⟶ **2** and **3** ⟶ **4** (3).

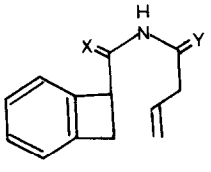


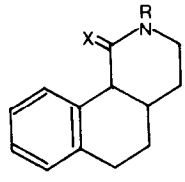


1: X=H_2, R=$COOCH_3$ —155°→ **2**: cis, X=H_2, R=$COOCH_3$

3: X=O , R=H —155°→ **4**: trans, X=O , R=H

Similar syntheses of either cis- or trans-fused ring systems from non-conjugated dienophiles were examined as follows.





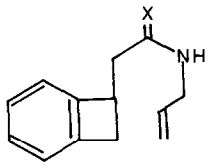
5: X=O , Y=H_2 —155 - 180°, 78 %→ **6a**: cis, X=C , R=H

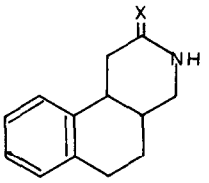
7: X=H_2, Y=O **6b**: cis, X=H_2, R=H

6c: cis, X=H_2, R=CH_3

8: X=H_2, Y=H_2 —180°, 62 %→ **9a**: trans, X=H_2, R=H

9b: trans, X=H_2, R=CH_3





10: X=O —180° / 66 %→ **11a**: cis, X=O; **11b**: cis, X=H_2

12: X=H_2 —180° / 78 %→ **13**: trans, X=H_2

Thermolysis of the butenylamide **5** in refluxing dichlorobenzene gave in 78 % yield the cis-fused lactam **6a** (4), which was reduced with aluminium hydride to the amine **6b** (5) (hydrogen maleinate, m.p. 182 - 183° C). However, after the butenylamine **8** (5) was refluxed in dichlorobenzene for 16 h, the trans-fused benz(h)isoquinoline **9a** (5) (hydrogen maleinate, m.p. 183 - 184° C) was isolated in 62 % yield. Under identical conditions the allylamide **10** (5, 6) afforded the cis-fused benz(f)isoquinoline **11a** (5, 8, 9), (m.p. 189 - 191° C, 66 % yield), whereas the amine **12** (5) gave the trans-product **13** (5) (m.p. 79 - 80° C, 78 % yield). A g.l.c. analysis of the crude pyrolysates (10) is outlined in Table 1.

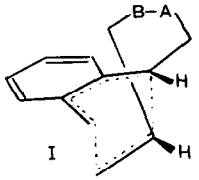
Table 1. G.l.c. analysis of stereoisomeric octahydrobenz-isoquinolines from 1-substituted benzocyclobutanes

starting material	reaction conditions	products cis	products trans
5	a,b	83 % **6b**	16 % **9a**
7	a,b	64 % **6b**	31 % **9a**
8	a	27 % **6b**	72 % **9a**
10	a,b	79 % **11b**	20 % **13**
12	a	12 % **11b**	87 % **13**

a) 16 h/180° C; b) AlH_3/THF

According to g.l.c. analysis (10), the isolated products **6b**, **9a**, **11a**, **11b** and **13** remained unchanged when refluxed in dichlorobenzene for 16 h, whereas equilibration of the isomeric methylamines **6c** (5) and **9b** (5) with 5 equiv. of potassium tert-butylate in dimethylsulfoxide at 60° C for 16 h led to a 2:3-mixture of cis-/trans-isomers. Hence it appears, that the stereochemistry of the reactions of the benzocyclobutenes **8**, **10** and **12** is controlled kinetically. Also the thermolysis of the amide **7** most probably is subject to kinetic control (11). Taking into account the intermediacy of trans-quinodimethanes (12) it follows that the

thermal reorganization of the amides **7** and **10** passes predominantly through the endo-transition state I, whereas the exo orientation II is favoured on cyclization of the amines **8** and **12** .



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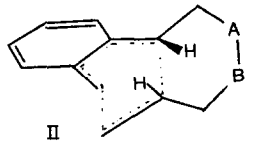

II

These results therefore illustrate the general possibility to direct the steric course of intramolecular cycloadditions by conformational variations of the bridge between the dipole and the dipolarophile.

[*] Present address: Département de Chimie Organique, Université de Genève, 1211 Genève 4.

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[5] Elemental analytical data, ir- and pmr-spectra in agreement with the assigned structures were obtained for all new compounds.

[6] The amide **10**, m.p. 44 - 46° C, was prepared in 81 % yield by reaction of benzocyclobutene--1-acetyl chloride, c.f. Ref. [7], with an excess of allylamine in dichloromethane.

[7] C.D. Gutsche, G.L. Bachmann and R.S. Coffey, Tetrahedron 18, 617 (1962)

[8] The structure of **11a** was deduced from pmr-decoupling experiments ($CDCl_3$ + 0.5 equiv. $Eu(DPM)_3$) kindly carried out by H.R. Loosli, Sandoz Ltd.

[9] For a previous approach to 1,2,3,4,4a,5,6,10b-octahydrobenz(f)isoquinolines see: R.J.P. Barende, W.N. Speckamp and H.O. Huisman, Tetrahedron Letters 1970, 5301.

[10] For g.l.c.-analysis (capillary column OV 225/185°) the amines were acylated with trifluoroacetic acid anhydride/pyridine in dichloromethane.

[11] Heating the amide **7** in boiling o-dichlorobenzene for 0.5 h, followed by reduction with AlH_3, gave the stereo-isomers **6b** and **9a** in yields of 0.84 % and 0.53 %, respectively (according to g.l.c. analysis). However, thermolysis of the amide **5** in refluxing bromobenzene for 5 h and subsequent reduction led to the epimers **6b** and **9a** in yields of 9 % and 11 % respectively, which indicates that the stereo-selective formation of the lactam **6a** in refluxing o-dichlorobenzene is at least partly the result of thermodynamic control.

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