70. A Stereoselective Approach to *cis*- and *trans*-1,2,3,4,4a,5,6,8a-Octahydroquinolines by Intramolecular *Diels-Alder* Reactions

Preliminary Communication

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(24. I. 75)

Zusammenfassung. N-Acyl-N-(4-penten-1-yl)-1-amino-1,3-butadiene (**1**) isomerisieren sich bei 190–215° über eine intramolekulare *Diels-Alder*-Reaktion stereoselektiv zu *cis*- verknüpften Octahydro-chinolinen **2**. Unter den gleichen Bedingungen erhält man aus dem N(Pent-4-enoyl)-N-propyl-1-amino-1,3-butadien (**4**) überwiegend das *trans*-verknüpfte Octahydrochinolin-2-on **5** neben dem *cis*-Isomeren **6**. Diese Selektivität wird auf eine bevorzugte koplanare Anordnung von Amid- und Dien-System im Übergangszustand zurückgeführt.

We have recently shown that the steric course of an intramolecular cycloaddition involving the quinodimethane grouping can be directed away from the *endo* adduct to the *exo* adduct by the judicious insertion of an amide group into the bridge connecting the quinodimethane and the dienophile [1]. Our interest [2] in the synthesis of decahydroquinolines[1]) led us to examine the possibility of realizing a similar steric control over intramolecular cycloadditions of the readily available N-acyl-N-alkyl-1-amino-1,3-butadienes [3].

On heating a 5% solution of the dienamide **1** ($R^1 = OCH_3$, $R^2 = H$) [3] in toluene, in a sealed ampoule for 24 h to 190° the oily *cis*-octahydroquinoline **2** ($R^1 = OCH_3$, $R^2 = H$) (dist. 90° (bath)/0.2 Torr; ^{1}H-NMR.: $J_{AB} \leqslant 9$ Hz; IR. (film): 1705 s, 775 m cm^{-1}) was obtained in 84% yield as the sole product[2]).

The *cis*-configuration of the product **2** ($R^1 = OCH_3$, $R^2 = H$) was confirmed by its conversion[3]) to the *cis*-decahydroquinoline **9** (R = H) (**9** · HCl, m.p. 224–226°) and by comparison with a sample of **9** (R = H) obtained (together with the *trans*-isomer **8** (R = H)) by catalytic hydrogenation of quinoline [4].

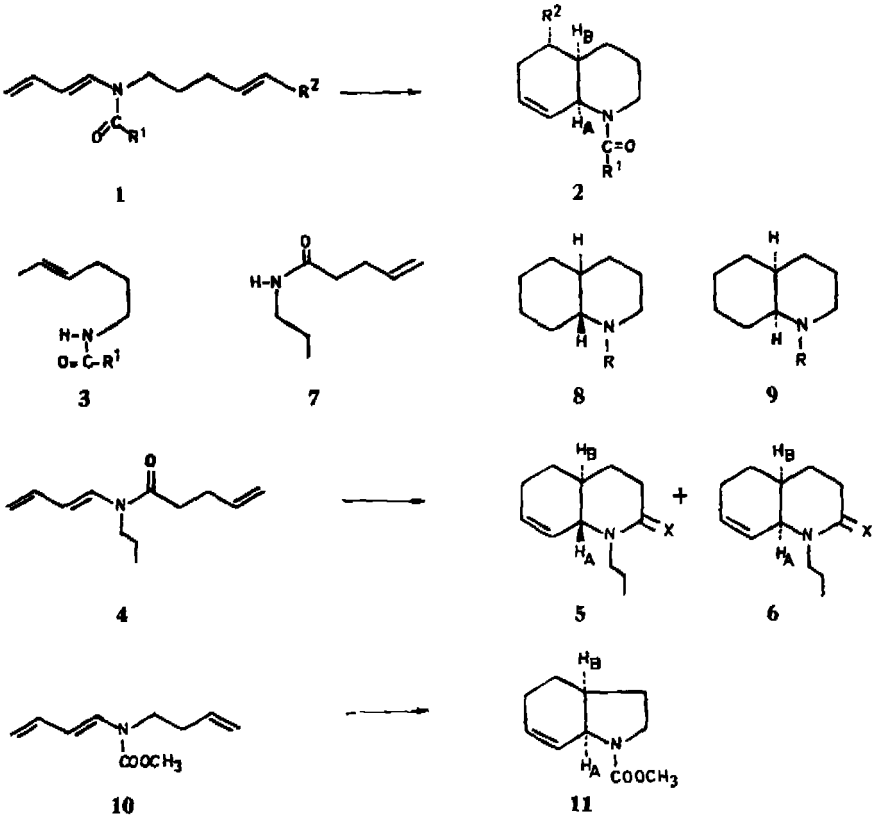
In a similar fashion the acetamide **1** ($R^1 = CH_3$, $R^2 = H$) [3] at 190° in 16 h rearranged to the oily *cis*-amide **2** ($R^1 = CH_3$, $R^2 = H$)[2]), dist. 140° (bath)/0.1 Torr, 59% yield, ^{1}H-NMR. (*d*-DMSO, 110°): $J_{AB} \leqslant 10$ Hz), IR. (film): 1639 cm^{-1}. The corresponding transformation of the triene **1** ($R^1 = OCH_3$, $R^2 = CH_3$) to the quinoline **2** ($R^1 = OCH_3$, $R^2 = CH_3$) (^{1}H-NMR.: $J_{AB} \leqslant 9$ Hz, 36% yield) required 205°/22 h and was accompagnied by formation of the urethane **3** ($R^1 = OCH_3$)[2]) (dist. 110°/0.4 Torr, 47% yield, MS.: *m/e* 157 (M^+)). Apparently, desactivation of the dienophile by the methyl substituent slows down the cycloaddition process to such an extent that elimination [3] to **3** ($R^1 = OCH_3$) becomes competitive. In spite of this side

[1]) For previous approaches to decahydroquinolines see [4] [5]; for configurational assignment see [6].

[2]) The IR.- and ^{1}H-NMR. ($CDCl_3$)-spectra are in agreement with the assigned structure.

[3]) The urethane **2** ($R^1 = OCH_3$, $R^2 = H$) was saponified with 5N KOH in methanol/water 4:1, 200°/20 h; Hydrogenation of the resulting crude amine with Pd/C in ethanol gave **9** (R = H).

Scheme 1



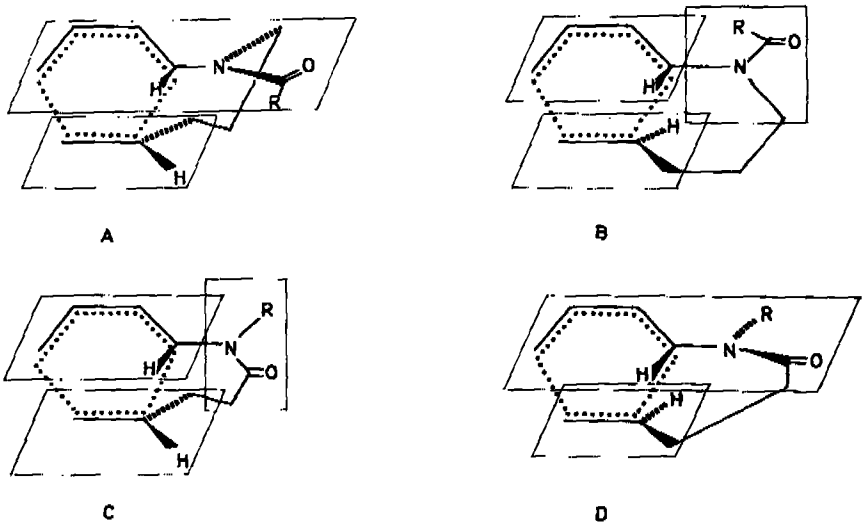
reaction, the cycloaddition is highly stereoselective affording the *cis*-fused isomer **2**[4] ($R^1 = OCH_3$, $R^2 = CH_3$).

In contrast, thermolysis of the N-(4-pentenoyl)-N-(*n*-propyl)-1-amino-1,3-butadiene (**4**) [3] furnished the *trans*-lactam **5** (X = O)[2] (dist. 95° (bath)/0.2 Torr, MS.: *m/e* 193 (M^+), IR. (film): 1645 cm^{-1}, 37% yield, together with the *cis*-lactam **6** (X = O)[2] (dist. 95° (bath)/0.2 Torr, MS.: *m/e* 193 (M^+), IR. (film): 1645 cm^{-1}, 25% yield) and the sec. amide **7**[2] (IR. (CH_2Cl_2): 3450, 1673 cm^{-1}, 15% yield). The product mixture was separated by chromatography on silica gel (C_6H_6/EtOAc 9:1). In order to assign their configuration the isolated lactams **5** (X = O) and **6** (X = O) were reduced with $LiAlH_4$ in refluxing ether to the unsaturated amines **5** ($X = H_2$)[2] (dist. 70° (bath)/0.1 Torr, ^{1}H-NMR.: J_{AB} = 12.2 Hz) and **6** ($X = H_2$)[2] (dist. 70° (bath)/0.1 Torr, ^{1}H-NMR.: J_{AB} = 3.5 Hz). Clearly, the larger ^{1}H-NMR.-coupling of H_A with H_B in the amine **5** ($X = H_2$) indicates the *trans*-configuration for the less polar main product **5** (X = O). This assignment was confirmed by catalytic hydrogenation of the amine **5** ($X = H_2$) to the amine **8** ($R = n\text{-}C_3H_7$)[2] (**8** · HCl: m.p. 177–179°), iden-

[4] In the product **2** ($R^1 = OCH_3$, $R^2 = CH_3$) the *cis*-relation of the protons H_A and H_B was derived from their ^{1}H-NMR.-coupling constant, whereas the relative position of the methyl substituent was correlated with the *trans*-configuration of the dienophile in **1** ($R^1 = OCH_3$, $R^2 = CH_3$) considering the supra-supra-facial character [7] of the *Diels-Alder* Reaction.

tical (m.p., mixed m.p.) with a sample prepared from the known [4] [6] *trans*-decahydroquinoline **8** (R = H)[5]. The isomeric lactams **5** (X = O) and **6** (X = O) were not interconverted on heating in toluene for 20 h at 210°. Consequently the stereochemistry of the reaction **4** → **5** (X = O) + **6** (X = O) is controlled kinetically. On the assumption that also the thermolyses of the dienamides **2** are controlled kinetically the observed stereoselectivity can be understood by inspection of appropriate models (*Scheme 2*).

Scheme 2



Thus, for the intramolecular cycloadditions of the amides **2** the *endo* transition state **A** seems to be favored due to satisfactory overlap of the amide π-orbitals with the diene π-system, which is not the case in the *exo* orientation **B**. This factor may be reinforced by the usual *endo*-preference of the *Diels-Alder*-reaction, thus assuring exclusive formation of *cis*-fused ring systems[6]. On the other hand, comparison of the *endo*- and *exo*-transition states **C** and **D** for the cyclisation of the dienamide **4** (where the whole amide bond is incorporated into the bridge connecting diene and dienophile) shows only the *exo*- state **D** to be stabilised by amide conjugation. However, in this case the expected selectivity for *trans*-product-formation may be reduced by the general tendency of the *Diels-Alder* reaction to prefer the *endo* orientation.

An analogous approach to the synthesis of hexahydroindoles is illustrated by the thermal (160°/16 h) transformation **10** [3] → **11**[2]) (dist. 90° (bath)/0.2 Torr, ^{1}H-NMR.: $J_{AB} \leqslant 9$ Hz, 38% yield).

The method described here may prove to be of value in the synthesis of natural products, as exemplified by the following communication [2]. Further modifications, using other substituted dienamides are studied.

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[5]) The amine **8** (R = *n*-C_3H_7) was obtained by acylation of *trans*-decahydroquinoline [4] with propionylchloride/NEt_3, followed by reduction of the resulting amide with $LiAlH_4$ in refluxing ether.

[6]) Consequently, cyclisation of the amide **1** (R^1 = OCH_3, R^2 = CH_3) also prefers a coplanar transition state of the type **A** with the C-methyl group in *exo*-position.

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71. The Total Synthesis of (±)-Pumiliotoxin-C[1])

Preliminary Communication

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Zusammenfassung. Die erste Totalsynthese des racemischen Alkaloids Pumiliotoxin-C (**9**) ausgehend von *trans*-1-Brom-3-penten (**1**) wird beschrieben. Die Schlüsselstufe **6** → **7** verläuft über eine intramolekulare *Diels-Alder*-Reaktion unter weitgehender sterischer Kontrolle von vier Chiralitätszentren. Die Struktur des synthetischen Produkte **9** wurde durch eine Röntgenstrukturanalyse des kristallinen Hydrogenmalcinates bestätigt.

Pumiliotoxin-C, isolated from the skin of *Dendrobates pumilio* [1] and of *Dendrobates auratus*[2]) has been shown by X-ray analysis of its hydrochloride to have structure **9** [1][3]).

We wish to report the first total synthesis of racemic pumiliotoxin-C (*Scheme 1*), which exploits a stereoselective approach to *cis*- fused octahydroquinolines, described in the preceding communication [2].

The *Grignard* reagent, prepared from *trans*-1-bromo-3-pentene (**1**) [3] was reacted with 1.1 mol of butyronitrile in refluxing ether [4] to give after acidic aqueous work up

[1]) Presented in a lecture, given at the University of Giessen, December 5, 1974.
[2]) *W. Kissing*, TH Darmstadt, private communication.
[3]) The absolute configuration of pumiliotoxin-C, as depicted in formula **9**, has been established by X-ray analysis: *I. L. Karle*, private communication.