gemische wurden für Referenz und Probe einzeln hergestellt. Dabei wurden bei gleichen Konzentrationen jeweils dieselben Pipetten verwendet.

Als Test zur Reproduzierbarkeit wurden die gesamten Messreihen wiederholt durchgeführt unter Verwendung von Lösungen verschiedener Einwaagen (3 Einwaagen für II (Me), je 2 Einwaagen für II (*t*-Bu) und I(*t*-Bu). Das bei der Herstellung von Dimethyl-pentaacetylen erhaltene Eluat wurde als solches verwendet (s.o.). Eine Eichung der optischen Dichte von I(Me) erfolgte nach [10].

Frau Dr. *E. Schmidt* danken wir für wertvolle Ratschläge beim Durchführen der UV.-Messungen. Der Firma *Ciba-Geigy AG.* gebührt unser Dank für die finanzielle Unterstützung.

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LITERATURVERZEICHNIS

[1] *H. Christen & P. A. Straub,* Helv. *56,* 739 (1973).
[2] *F. Feichtmayr, E. Heilbronner, A. Nürrenbach, H. Pommer & J. Schlag,* Tetrahedron *25,* 5383 (1969).
[3] *H. Bock & H. Seidl,* J. chem. Soc. *1968,* 1158.
[4] *H. A. Stuart,* Die Struktur des freien Moleküls, Springer-Verlag, Berlin (1952).
[5] *J. Haink,* Lösungsmittelspektren im fernen UV., (unveröffentlicht).
[6] a) *J. B. Armitage, E. R. H. Jones & M. C. Whitting,* J. chem. Soc. *1952,* 2014.
b) *E. R. H. Jones,* Record Chem. Progr. *14,* 1 (1953).
[7] *F. Bohlmann, E. Inhoffen & P. Herbst,* Chem. Ber. *90,* 1661 (1957).
[8] *H. Schlubach & V. Franzen,* Liebigs Ann. Chem. *568,* 141 (1950) und *572,* 116 (1951).
[9] *J. B. Armitage, E. R. H. Jones & M. C. Whiting,* J. chem. Soc. *1952,* 1993.
[10] *F. Bohlmann,* Chem. Ber. *86,* 657 (1953).
[11] a) *E. R. H. Jones, M. C. Whiting, J. B. Armitage, C. L. Cook & E. Entwishle,* Nature *168,* 900 (1951).
b) *C. L. Cook, E. R. H. Jones & M. C. Whiting,* J. chem. Soc. *1952,* 2883, (vgl. auch [6] b).
[12] *E. Kloster-Jensen,* Angew. Chem. *84,* 483 (1972); Int. Ed. *11,* 438 (1972), und darin zitierte Referenzen.

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176. Intramolecular *Diels-Alder* reactions: construction of aza- and diaza-steroid type skeletons

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(24. IV. 73)

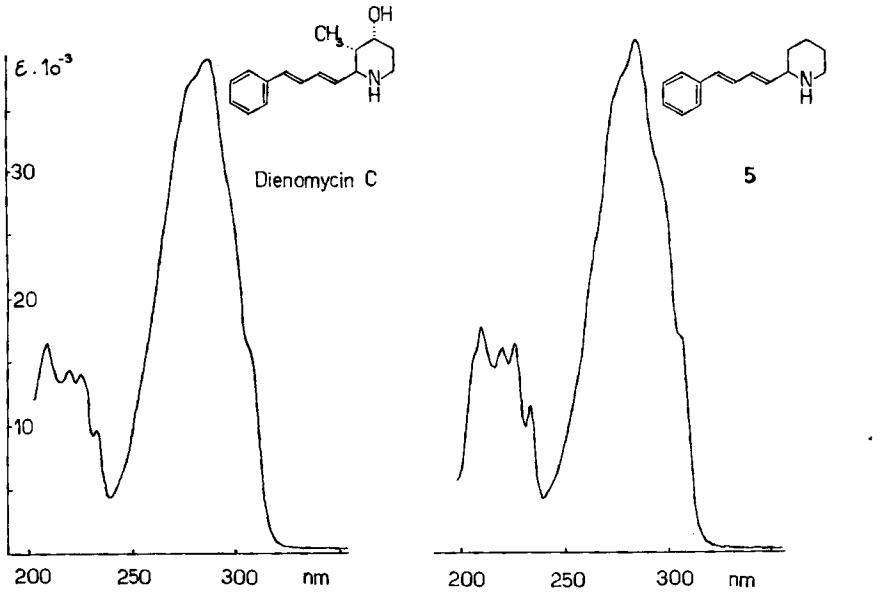
Summary. The preparation of 2-(4-phenyl)butadienyl-piperidine **5** is described. An intramolecular *Diels-Alder* reaction of the intermediately formed fumaramide thereof produces stereoselectively the tricyclic lactam **6**. Its structure, as well as the configurational relationship of its 5 asymmetric centers, is corroborated on the basis of the NMR.-data. Cycloacylation of the thermodynamically stable precursors **13** and **20** leads to pentacyclic aza- or diaza-steroid type skeletons. Their structures (**14**, **16** and **21**) and in particular their relative configurations are elaborated. A few qualitative kinetic aspects of this intramolecular (4 + 2)-cycloaddition are presented.

As we have reported earlier [1], the intramolecular *Diels-Alder* reaction of N-pentadienyl-acrylamides constitutes an extremely useful and facile way for the regiospecific and stereocontrolled construction of perhydroisoindolines. The present in-

vestigation provides a further example as to how such reactions can serve as a central key in the elaboration of more complex molecules, in particular of pentacyclic mono- or diazasteroid-like skeletons.

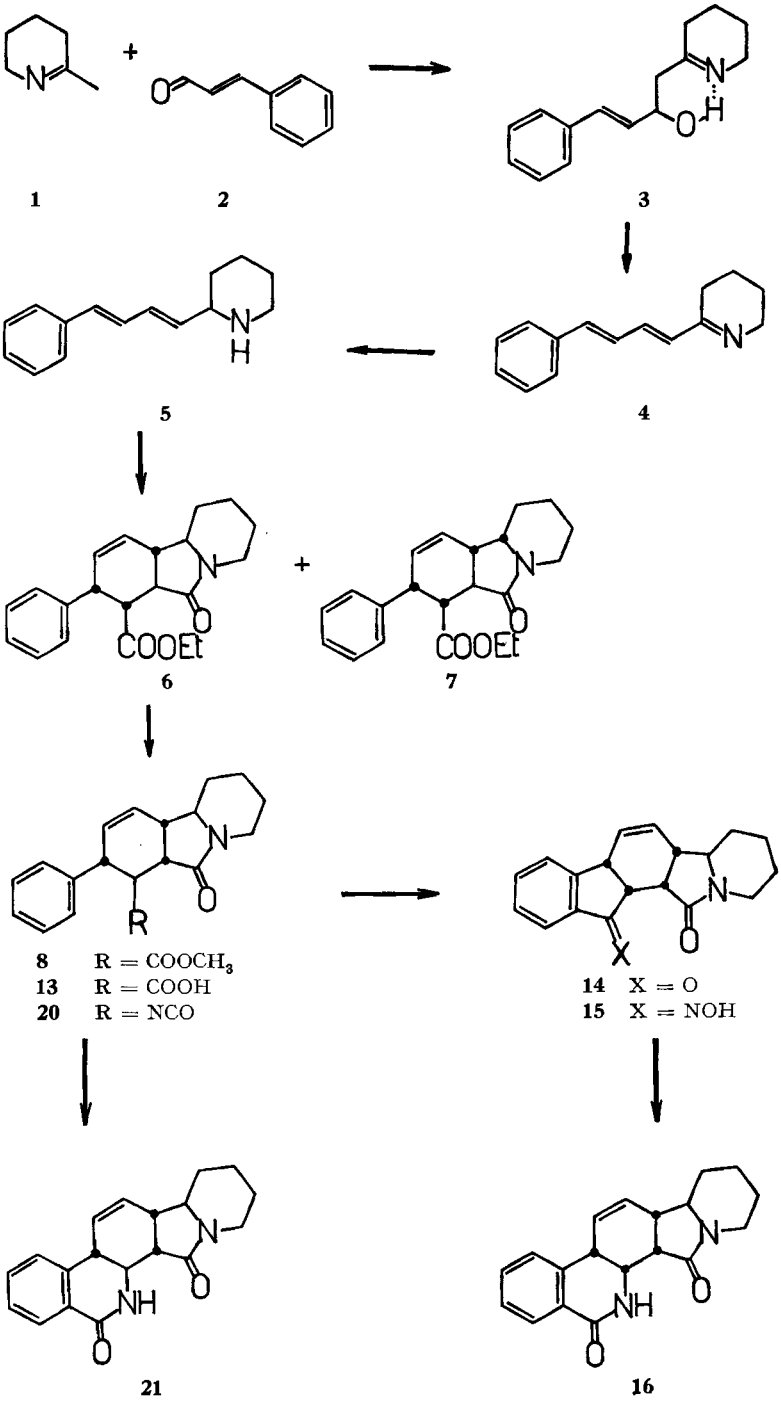
At the outset we chose 2-(4-phenyl)butadienyl-piperidine **5** with one center of asymmetry as the diene component for the intramolecular cycloaddition reaction. Its preparation from readily available starting materials was carried out in analogy to the reported synthesis of *Nigrifactin* [2] (scheme 1). A low temperature 1,2-addition of the lithiated 2-methyl-Δ^1-tetrahydropyridine **1** [3] to cinnamaldehyde **2** produced the relatively unstable β-imino alcohol **3** in essentially quantitative yield. Its NMR.-spectrum reveals, *inter alia*, the characteristic absorptions of the allylic H at $\delta = 4.7$ ppm with equal coupling constants of 6 Hz to both CH_2- and vinyl-protons, the adjacent vinylic hydrogen at $\delta = 6.21$ ppm with coupling constants of 16 Hz (*trans*) and 6 Hz (to allylic H) and the exocyclic α-imino methylene protons as a multiplet at $\delta = 3.55$ ppm. Dehydration in degassed 2N sulfuric acid at 110° led to the unsaturated imine **4**, which was isolated in 74% yield (based on **1**) as its hydrochloride salt. An undesired side reaction, observed during the acid catalyzed dehydration as well as by storing **3** at room temperature, was the readily occurring retro-aldol condensation. One of the more obvious features of the unsaturated imine **4** is its UV.-spectrum with a strong absorption at 310 nm ($\varepsilon = 25.200$) and the significant bathochromic shift to 354 nm ($\varepsilon = 27.000$) observed upon acidification of the solution. Bathochromic shifts of up to 50 nm of protonated *versus* nonprotonated unsaturated imines are most characteristic for this type of chromophore and are well documented [2] [4] [5].

Selective reduction of the (C=N)-bond was readily achieved using $NaCNBH_3$ [6] at pH 3–5 or, more economically and equally well, by reacting a solution of the



UV.-Spectrum in CH_3OH of Dienomycin-C-hydrochloride [7] *and* **5***-hydrochloride*

Scheme 1



hydrochloride salt of **4** in ethanol with an excess of $NaBH_4$. The reaction could very conveniently be monitored by observing the disappearance of the 354 nm absorption in the UV.-spectrum. The crystalline amine **5** was isolated in over 80% yield and again revealed a highly characteristic UV.-spectrum (fig.) which is virtually superimposable with the UV.-spectrum reported for *Dienomycin* [7] [8], a natural antibiotic isolated from the culture filtrate of strain *MC 67-ct.* Since the amine **5** essentially represents the basic skeleton of *Dienomycin*, lacking only the CH_3- and acyloxy-substituents in the 3 and 4 positions of the piperidine ring, this synthetic route seems to delineate one feasible approach towards an elaboration of the natural product itself.

The intramolecular *Diels-Alder* reaction of the amide derived from the amine **5** and the acid chloride of monoethyl fumarate proceeded very rapidly and under exceedingly mild conditions. Upon addition of the acid chloride to an ice cold mixture of **5** and a tertiary amine as HCl-scavenger, the intermediate substrate could not even be isolated. After work-up of the reaction mixture, the major crystalline product **6** of this two step sequence was isolated in better than 70% yield. The structure of **6** is secured on the basis of the analytical and spectral data. The IR.-spectrum shows the absorptions of the ester carbonyl at 1715 and of the lactam at 1690 cm^{-1}. The assignment of the configurational relationship of the four newly introduced asymmetric centers is primarily based on the assumption of an *endo* addition, *i.e.*, a maximal π-electron overlap in the transition state leading to the cycloaddition [9]. Stability considerations of transition state and product with the help of *Dreiding* models hardly permit a prediction or an actual assignment of the configurational relationship between the original asymmetric carbon atom and the newly created chiral centers. The actual stereochemical assignment as shown in **6**, in particular the *trans* diaxial relationship of protons H-5 and H-4, is based on the NMR.-spectrum and the analysis of double resonance experiments. Proton H-5 appears at 3.15 ppm (see Table) as a doublet of doublets with two large *trans* diaxial couplings ($J_{4,5} \sim 11$ Hz, $J_{5,\text{axial}} \sim 11$ Hz and $J_{5,\text{equatorial}} = 4$ Hz). Two additional and quite evident features in the NMR.-spectrum of **6** are: The equatorial H-8, strongly deshielded by the coplanar lactam carbonyl and the relatively high field signals of the ethyl ester protons at $\delta = 3.66$ and 0.84 ppm, shielded by the π-electrons of the co-equatorial phenyl ring. Furthermore, the CH_2-part of the ester protons appears as an ABX_3-system suggesting hindered rotation of the carboethoxy group.

Careful chromatography of the motherliquors of **6** gave access to small amounts (1–3% yield based on **5**) of the epimeric ester **7**, whose NMR.-spectrum differs from the one of **6** only in the region of the piperidine ring protons. Most significantly, H-5 appears at somewhat lower field (3.5 ppm) than in **6**, and the broadness of the signal reflects the two smaller couplings with H-4 and the adjacent axial proton in the piperidine ring.

Hydrogenation of **6** produced the lower melting dihydroderivative **9** (Scheme 2) in which the deshielded equatorial H-8 still appears as a broad doublet at $\delta = 4.07$ ppm ($J = 11$ Hz) unobstructed by H-1 which, as a simple benzylic proton, now absorbs at higher field.

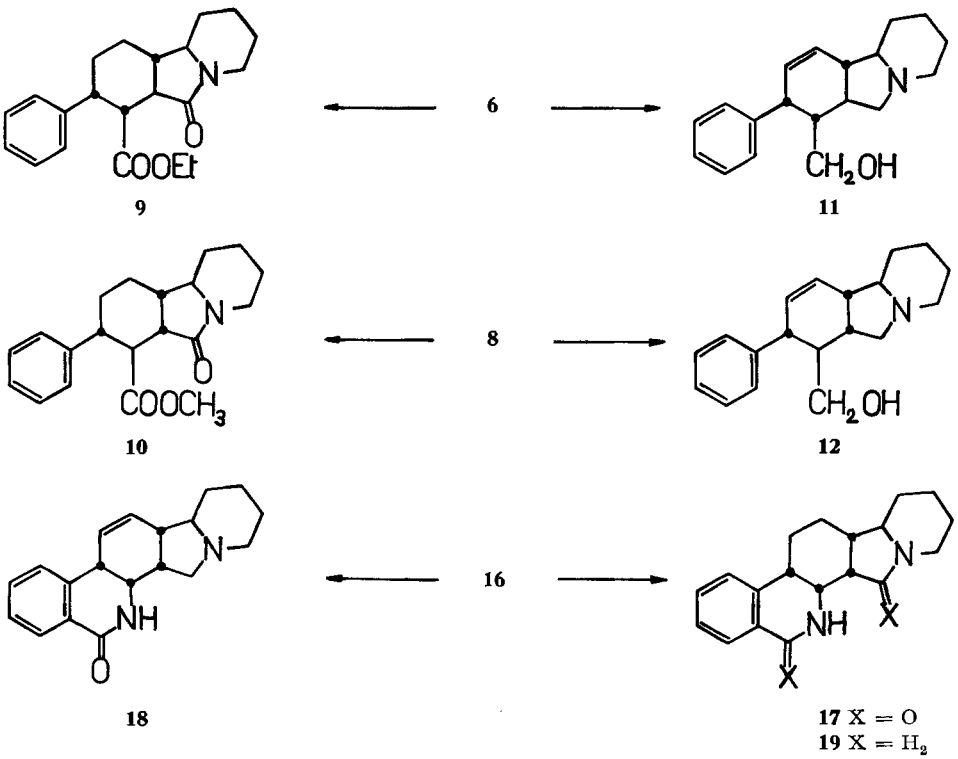
Reduction of **6** with $LiAlH_4$ in ether gave a high yield of the crystalline amino-alcohol **11**, exhibiting no internal hydrogen bonding and thus further confirming the

trans-fusion between cyclohexene and adjacent five membered ring. With the lactam carbonyl reduced, the NMR.-signal of H-8 is no longer deshielded.

Base catalyzed equilibration of **6** in anhydrous methanol gave access to the thermodynamically more stable ester **8** (90% conversion), in which both epimerizable centers had been inverted and the ester exchanged. The hexahydroisoindolone system is now *cis*-fused and the phenyl- and carbomethoxy substituents are in a *trans* diequatorial relationship. The ester carbonyl, no longer disturbed by the influence of the phenyl ring (as in **6**), appears at a normal frequency of 1731 cm^{-1}. One of the more evident features in the NMR.-spectrum of **8** (*cf.* Table) is the identity of the chemical shifts of the two vinyl protons, appearing as a virtual singlet at $\delta = 5.9$ ppm. The dideuterio derivative D_2-**8** was most conveniently prepared by subjecting **6** to the same equilibrating conditions in CH_3OD. According to its mass spectrum D_2–**8** contains less than 5% D_1 and less than 1% D_0. Its NMR.-spectrum in combination with those of **6**, **7** and **8** (Table) serves to firmly establish the trans diaxial relationship of H-7 to both H-1 and H-6. Whereas H-1 appeared as a doublet in **8** with a coupling constant of $J = 10$ Hz, it has now collapsed to a singlet in D_2-**8**.

Catalytic hydrogenation of **8** produced the dihydro derivative **10**, and reduction with $LiAlH_4$ produced the crystalline aminoalcohol **12**. The latter displays no intramolecular hydrogen bonding which would sterically only be possible with the methanol substituent in an axial position.

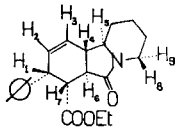
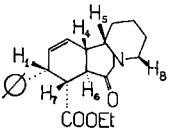
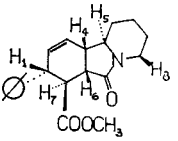
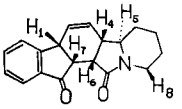
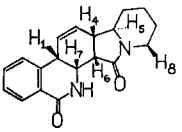
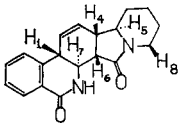
Scheme 2



Hydrolysis of the ester **8** gave access to the acid **13**, persistently cocrystallizing with methylenechloride. Reesterification with diazomethane reproduced the starting material **8**, thus excluding any additional epimerizations.

The acid **13** lent itself as an attractive precursor for pentacyclic structures. Cyclodehydration with polyphosphoric acid (ppa) proved to be the method of choice, since the formation of the acid chloride was rather difficult and could only be achieved in modest yields *via* the sodium salt/oxalyl chloride method [10]. The pentacyclic ketone **14** was isolated in 72% yield. Its UV.-spectrum with a λ_{max} at 242 nm (ε = 11800) and the IR.-absorptions at 1718 and 1688 cm^{-1} are in agreement with the newly formed indanone structure. Spin-spin decoupling experiments again not only permitted the assignment of protons H-1 – H-9 in the NMR.-spectrum of the ketone **14** (Table), but also provided enough information for the determination of the stereochemical relationships between these protons. Of particular interest was the question about the relative orientations of H-6 and H-7, protons at centers which seemed to

Table. *Chemical shifts δ of protons* in ppm

	Compound N°	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
	**6**	3.93	6.11	5.7	2.19	3.15	2.59	3.15	4.05	2.59
	**7**	4.0	6.1	5.7	2.72	3.5	2.72	3.13	4.0	2.72
	**8**	3.56	5.9	5.9	2.59	3.12	2.42	3.01	4.07	2.6
	$\mathbf{8}_{D_6D_7}$	3.56	5.9	5.9	2.59	3.12	–	–	4.07	2.6
	**14**	4.01	5.72	5.65	2.5	2.8	2.94	3.4	4.2	2.75
	**16**	3.56	5.4	5.82	2.62	3.3	2.88	4.42	4.22	2.88
	**21**	2.9–3.7	6.4	5.95	2.4–2.8	2.9–3.7	2.4–2.8	2.9–3.7	4.1	2.4–2.8

have a potential for inversion during the ppa-cyclization. According to the coupling constants of 7.5 Hz for both H-6 and H-7 the *trans* diaxial arrangement originally present in **8** and **13** no longer seems to exist. It is thus assumed that under the acidic cyclization conditions the intermediately formed *trans*-fused indanone is equilibrated to the thermodynamically more stable *cis*-fused product **14**, in which protons H-1, H-4, H-6 and H-7 are all positioned on the same side of the fused cyclohexene ring. Such an all-*cis* arrangement of the cyclohexene substituents moves the axial proton H-5 into the shielding area of the indanone carbonyl or phenyl π-electrons. It appears at $\delta = 2.8$ ppm, thus 0.35 ppm higher than in compounds **6** or **8**. This phenomenon adds additional evidence to the suggested *trans* diaxial arrangement of H-4 and H-5 in compounds **6**, **8** and **14**, as opposed to the *cis* relationship in **7**.

Expansion of ring B to a δ-lactam, thus producing an 8,16-diazasteroid type skeleton, was feasible either *via* a *Beckmann* rearrangement of the corresponding oxime or a *Schmidt* reaction directly on the ketone **14**. Oximation of **14** predominantly produced the *syn*-isomer **15** (*syn* OH/phenyl). Upon rearrangement with thionyl chloride in methylene chloride, the pentacyclic dilactam **16** was obtained in 64% yield. The question as to which of the two possible isomeric lactams was actually formed was easily answered on the basis of the presence of an isoquinolone chromophore in the UV.-spectrum [232 nm ($\varepsilon = 9400$)], which disappeared upon reduction of both lactam groups with diborane, such as in **19** (Scheme 2). Furthermore a deshielded aromatic proton with an *ortho*- and *meta*-coupling (7 and 2 Hz respectively) is observed at $\delta = 8.06$ ppm. Spin-spin decoupling experiments permitted the assignment of protons 1–9 (Table). The proposed *cis*-fusion of rings B/C is based on the following observation: There is a definite absence of the large axial/axial couplings one would expect, and actually did observe in **8**, for H-1 and H-6 if H-7 assumed an axial position. The well defined doublet of doublets signal for H-7 with $J_{1,7} = J_{6,7} = 4$ Hz results from two equal axial-equatorial couplings. Furthermore, H-7 experiences as strong deshielding effect from the carbonyl of the γ-lactam. Thus, during the *Beckmann* rearrangement (as well as the *Schmidt* reaction, see below) the stereochemistry at the migrating carbon atom is retained. A *Schmidt* reaction on the ketone **14** produced the same dilactam **16** in 46% yield. Surprisingly, recrystallization of crude **16** from ethanol or ethyl acetate led to two isomorphic crystalline forms differing markedly in the IR.-spectrum recorded in nujol. While the crystals obtained from the more polar and protic solvent (ethanol) exhibit a sharp absorption band for a free, nonbonded N–H at 3390 cm^{-1} and a carbonyl frequency at 1670 cm^{-1} with a shoulder at 1680 cm^{-1}, the crystals grown in the nonprotic ethyl acetate, favoring internal hydrogen bonding, show a broad NH-absorption at 3250 cm^{-1} and two clearly separate carbonyl bands at 1655 and 1675 cm^{-1}. The solution spectra (in CH_2Cl_2 or $CHCl_3$) as well as the NMR.-spectra of both isomorphic forms, however, proved to be identical.

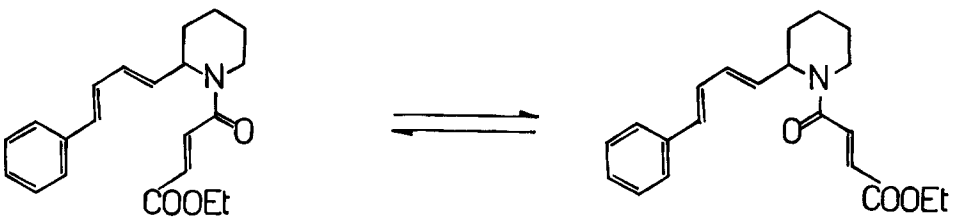
Unambiguous evidence for the *cis*-fusion of rings B/C/D in **16** was sought by synthesizing the epimer **21** (Scheme 1), in which the stereochemistry at C(7) would be inverted. The same acid **13**, which served as a precursor for the pentacyclic ketone **14**, was subjected to a *Curtius* degradation leading to the crystalline isocyanate **20** in virtually quantitative yield. Since this process is known to proceed under retention of configuration [11], the *trans* diaxial relationship of H-1 — H-7 — H-6 must be re-

tained in **20**. A cycloacylation of **20** under *Lewis* acid catalysis produced the new, epimeric pentacyclic lactam **21**. Besides a somewhat lower frequency of the NH-absorption in the IR.-spectrum of **21** (3355 cm^{-1} as against 3390 cm^{-1} in **16**), indicating intramolecular hydrogen bonding, it is the comparison of its NMR.- spectrum with the one of its epimer **16** which confirms the earlier configurational assignments. The following marked differences clearly and unambiguously support the stereochemistry as indicated (Scheme 1, Table): In **16** the vinyl proton H-2 appears at rather high field (5.4 ppm) due to the shielding exerted by the π-electrons of the aromatic ring[1]). In the epimer **21**, however, H-2 is coplanar with the phenyl ring and is hence deshielded, appearing 100 Hz lower at $\delta = 6.4$ ppm. In **16** H-7 (at $\delta = 4.4$ ppm) experiences a deshielding effect exerted by the γ-lactam carbonyl similar to the one of H-8. In **21** on the other hand, with H-7 in a *trans* diaxal position to both H-1 and H-6, this is no longer the case, and H-7 absorbs in the normal area of *ca.* 3 ppm.

Discussion. – While intramolecular cycloadditions have not received much attention in the past, this type of reaction most certainly has to be recognized as a powerful tool in the synthesis of complex organic molecules. This has been demonstrated very recently in the synthesis of various natural products [12–14].

The present study points to three aspects, all related to the intramolecularity of the *Diels-Alder* reaction. *First*, the exceedingly mild conditions that lead to the cycloaddition. As has been indicated [15] and actually demonstrated [1] before, this is mainly a consequence of the much more favorable entropy term as compared to the bimolecular (4 + 2)-cycloaddition. With $\Delta S^{\neq}$ below –20 e.u. the free energies of activation ($\Delta G^{\neq}$) are generally about 5–7 kcal/mol lower than in the bimolecular reactions. Another factor which seems to have a considerable effect on the rates of such intramolecular cycloadditions is the conformational equilibrium of the substrate.

Scheme 3



A **B**

Because of the rigidity added through the presence of the piperidine ring, conformers **A** and **B** (Scheme 3) are the most important ones to be considered for the intramolecular cycloaddition[2]). While it is difficult to assess the conformational equilibrium of a non isolable substrate, it suffices to state that the populations of conformers **A** and **B**, arising from a rotation around the (C–N)-amide bond, are pro-

[1]) H-2 lies beneath the plane of the phenyl ring as evinced by molecular models.

[2]) Clearly the *transoid* diene-conformers are quite important too, particularly in view of their large population. Because of their (and the chair/boat conformers of the piperidine ring) irrelevance to the point of interest, they are deliberately neglected.

bably within the same order of magnitude. With the conformer **A** thus expected to have a respectable population, the energy needed to bring the molecule into a conformation resembling the transition state (*i.e.* conformer **A**!) is minimal. As we have demonstrated in a similar case [16] the consequence of this phenomenon is most likely to be a yet lower enthalpy of activation. *Secondly*, the steric control during the cycloaddition with its rather high degree of stereoselectivity. From a qualitative kinetic aspect it should be noted that the seemingly minimal difference in the activation energies for either **6** or **7**[3]) is translated into a high degree of stereoselectivity. We ascribe this to the fact that due to the 'intramolecularity' of the reaction and consequently due to the low activation energy (low temperature), the cycloaddition is allowed to proceed under 'minimal conditions' with a maximal spread of the respective $\Delta G^{\neq}$'s. One might anticipate that at higher temperatures $\Delta\Delta G^{\neq}$ would become smaller and hence the stereoselectivity less pronounced. *Thirdly* and finally: Starting with a relatively simple and quite easily accessible starting material (*i.e.* **5**) with only one center of asymmetry, a complex pentacyclic molecule (*i.e.* **14**, **16** or **21**) with five asymmetric centers becomes accessible in just a few steps and in a stereocontrolled way. The terminology 'diazasteroid type skeletons' certainly points to the possibility that the carbocyclic skeletons of the well known parent compounds may well be accessible in a likewise synthetic sequence.

The author would like to thank Dr. *N. Finch* for his encouragement and support of this work and Mr. *L. Dorfman* and his staff for the analytical data. It is a particular privilege to acknowledge the outstanding work of Mr. *Robert M. Grulich* in recording and interpreting the 100 MHz NMR.-spectra.

Experimental Part

The physical data were obtained as follows: M.p. (not corrected) in a *Thomas-Hoover* melting point apparatus; IR., *Perkin-Elmer* 521; *UV.*, *Cary* 14; Mass spectra *AEI* MS 902 by direct insertion; NMR., *Varian* A-60 or XL-100 or HR-220, using tetramethylsilane as internal standard. Abbreviations: (b) broad, (w) weak, (sh) shoulder, (ex) exchangeable with D_2O, (*s*) singlet, (*d*) doublet, (*t*) triplet, (*q*) quartet, (*m*) multiplet. The coupling constants are given in Herz (Hz).

Alcohol **3**. A solution of 1.6 M *n*-BuLi (31 ml, 50 mmol) in hexane was added dropwise to a cooled (0°) solution of 7.05 ml diisopropylamine (50 mmol) in 50 ml dry ether under an atmosphere of nitrogen. After the addition was complete, the temperature was lowered to $-30°$ whereupon a solution of 4.85 g 2-methyl-Δ^1-piperideine (**1**) (50 mmol) in 50 ml dry ether was added. After the addition stirring was continued for $^1/_2$ h and then the temperature was lowered to $-70°$. Then a solution of 6.6 g *trans*-cinnamaldehyde in 50 ml ether was slowly added and thereafter the temperature was allowed to reach 0°. The reaction mixture was then quenched with ice/water, the ethereal layer separated and dried over Na_2SO_4. After removal of the ether on the rotary evaporator, a solid residue (11.1 g) of the moderately stable alcohol **3** was obtained. NMR. ($CDCl_3$) on crude material: δ 1.3–2.5 (*m*, 8H), 3.55 (*m*, 2H); 4.7 ($J_{am} = J_{an} = J_{ax} = 6$, 1H); 6.1 (bs, *ex*, 1H); 6.21 ($J_{ab} = 16$, $J_{ax} = 5.5$, 1H); 6.7 ($J_{ab} = 16$, 1H); 7.1–7.6 (*m*, 5H).

4 g of the above crude product were dissolved in 30 ml acetone and neutralized with ethereal HCl to produce 4.2 g crystalline hydrochloride salt, m.p. 135–137°. – IR. (Nujol) 3200, 1690 (w) cm^{-1}. – UV. (CH_3OH): 253 nm/17500, 282 nm/3300, 291 nm/2600.

$C_{15}H_{19}NO \cdot HCl$ (275.76) Calc. C 67.80 H 7.59 N 5.27% Found C 67.57 H 7.59 N 5.56%

Dehydration of **3** *to* **4**. Crude solid imine alcohol **3**, from a 100 mmol experiment, was stirred for 45 min in 280 ml degassed 2N H_2SO_4 in an oil bath (110°) under an atmosphere of nitrogen. After

[3]) Stability considerations of the transition states leading to **6** or **7** with the help of *Dreiding* models do not permit an unambiguous prediction of the major kinetic product.

cooling the mixture in an ice bath, the acidic-aqueous phase was washed with ether, separated, then made basic with 30% NaOH solution and the product extracted into CH_2Cl_2. After drying over Na_2SO_4 and removal of the solvent on the rotary evaporator a solid residue of 18.7 g was obtained. The residue was dissolved in acetone and neutralized with ethereal HCl to give 18.3 g (74% overall) analytically pure salt: m.p. 178–180°. IR. (Nujol): 1650, 1620 cm^{-1}. – UV. (CH_3OH): acidic 247 nm/8200, 354 nm/27000, basic 226 nm/11300, 232 nm/11200, 302 (sh) nm/24900, 310 nm/25200.

$C_{15}H_{17}N \cdot HCl$ (247.7) Calc. C 72.73 H 7.33 N 5.65% Found C 72.41 H 7.31 N 5.71%

Reduction of **4** *to* **5**. A solution of 24.8 g imine hydrochloride (100 mmol) in 500 ml ethanol was stirred at room temperature and 4.0 g $NaBH_4$ was added in portions. After 1 h the ethanol was removed *in vacuo*, excess hydride destroyed with dilute NaOH and the product extracted into CH_2Cl_2. After drying the organic layer over Na_2SO_4 and removal of the solvent *in vacuo* a solid residue of 21.5 g was obtained. Recrystallization from *n*-hexane gave 17.2 g (81%) **5**, m.p. 94–96° and a second crop of 1.0 g (m.p. 91–94°). – IR. (CH_2Cl_2): 3330, 1595, 990 cm^{-1}. – UV. (CH_3OH): 209 nm/15800, 220 nm/13300, 226 nm/13400, 276 (sh) nm/33900, 286 nm/37400, 296 nm/27800, 307 (sh) nm/15100. NMR. ($CDCl_3$): δ 1.0–3.4 (*m*, 11H ex+9H); 5.6–6.9 (*m*, 3H); 7.1–7.5 (*m*, 6H).

$C_{15}H_{19}N$ (213.31) Calc. C 84.45 H 8.98 N 6.57 Found C 84.68 H 8.81 N 6.57%

Cycloaddition of **5** *with the acid chloride of monoethyl fumarate to* **6**+**7**. To an ice cooled solution of 32 g (0.15 mol) amine **5** and 13.8 ml pyridine in 1 l CH_2Cl_2 was dropwise added a solution of 27 g fumaric acid chloride monoethylester (0.166 mol) in 250 ml of CH_2Cl_2. After the addition was complete, the dark reaction mixture was stirred for an additional 2 h. at 0°. The CH_2Cl_2 was then removed on the rotary evaporator, the residue taken up in ethyl acetate/ether and washed with cold, dilute HCl, then in the following sequence with cold water, with dilute Na_2CO_3 and finally with saturated NaCl-solution. All aqueous layers were extracted again with ether. The combined organic layers were dried over Na_2SO_4 and simultaneously treated with charcoal. After filtration through celite and removal of the solvent, the solid residue was recrystallized from hot ethyl acetate/hexane to give a first crop of 33.2 g **6** (m.p. 129–131°) (65%) and a second crop of 7.2 g of less pure **6** (m.p. 115–120°). An analytical sample of **6**, m.p. 129–131°, showed the following characteristics: IR. (Nujol) 1715, 1690 cm^{-1}. – NMR. ($CDCl_3$, 220 MHz): δ 0.86 (*t*, J = 7, 3H); 1.0–1.55 (*m*, 3H); 1.7 (*m*, 1H); 1.93 (*m*, 1H); 2.19 (*m*, 2H); 2.59 (*t*, J = 12.5, 2H); 3.11 (*m*, 2H); 3.66 (*ABX*$_3$, J = 7 and 3.2, 2H); 3.93 (*m*, 1H); 4.05 (*d*(b), J = 12, 1H); 5.7 (6 lines, J = 10 and 3, 1H); 6.11 (6 lines, J = 10 and 2, 1H); 7.05–7.3 (*m*, 5H).

$C_{21}H_{25}NO_3$ (339.42) Calc. C 74.31 H 7.42 N 4.13% Found C 74.08 H 7.38 N 4.33%

Chromatography of a part of the mother liquor of **6** on silica gel (benzene with increasing portions of ether) gave access to small amounts (450 mg) of the epimeric ester **7**, pure by TLC. Recrystallization from ethyl acetate/hexane produced an analytical sample, m.p. 146–148°. – IR. (Nujol): 1724, 1681 cm^{-1}. – NMR. ($CDCl_3$): δ 0.89 (*t*, J = 7, 3H); 1.2–2.2 (*m*, 7H); 2.4–4.1 (*m*, 7H); 4.22 (*m*, 1H); 5.75 (6 lines, J = 10 and 2.5, 1H); 6.17 (6 lines, J = 10 and 2, 1H); 7.0–7.5 (*m*, 5H).

$C_{21}H_{25}NO_3$ (339.42) Calc. C 74.31 H 7.42 N 4.13% Found C 74.36 H 7.80 N 4.18%

Equilibration of **6** *to* **8**. A solution of 32.5 g (95.8 mmol) ester (**6**) in 500 ml methanol and 235 ml of a freshly prepared 0.92M solution of $NaOCH_3$ (217 mmol) in methanol was refluxed under an atmosphere of nitrogen for 19 h. After cooling, the methanol was removed on the rotary evaporator and the residue taken up in 1 l of ether and 110 ml ice cold 2N H_2SO_4 and 20 ml of a saturated NaH_2PO_4 solution. The layers were separated, the organic phase washed successively with dilute ice cold NaOH, water, NaH_2PO_4 solution and finally with a saturated NaCl solution. The solvent was then evaporated and the solid residue recrystallized from CH_2Cl_2/hexane to give 25.05 g (81%) of **8** (m.p. 132.5–134°) and a second crop of 2.25 g (m.p. 128–130°). – IR. (Nujol): 1731, 1677 cm^{-1}. – NMR. ($CDCl_3$): δ 1.0–3.3 (*m*, 9H); 3.49 (*s*, 3H); 3.59 (*d*(b), $J \simeq 10$, 1H); 4.07 (*d*(b), J = 13, 1H); 5.9 (*s*, 2H); 7.0–7.4 (5H).

$C_{20}H_{23}NO_3$ (325.39) Calc. C 73.82 H 7.12 N 4.30% Found C 73.99 H 7.35 N 4.51%

Equilibration of **6** *to* D_2-**8**. A solution of 500 mg ester **6** in 10 ml CH_3OD containing 100 mg Na was refluxed under an atmosphere of nitrogen for 19 h. After cooling the solution, the methanol was removed *in vacuo* and the residue taken up in ice cold D_2O/ether. The ether was subsequently

washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated. The residue was crystallized from ether/hexane to give 280 mg D_2-**8**, m.p. 133°. – Ms.: 327 (100) 326 (8.7) 325 (0.5) ∴ less than 5% D_1-material. – NMR. ($CDCl_3$, 220 MHz): δ 1.13–1.45 (*m*, 3H); 1.73 (*m*, 1H); 1.91 (*m*, 1H); 2.15 (*d*, J = 12, 1H); 2.59 (*m*, 2H); 3.14 (*t* (b), J = 10, 1H); 3.49 (*s*, 3H); 3.59 (*s*, 1H); 4.07 (*d*, J = 12, 1H); 5.9 (*s*, 1H); 7.13 (*d*, $J \cong 5$, 2H); 7.28 (*m*, 3H).

Hydrolysis of **8** *to* **13**. A solution of 14 g **8** (43 mmol) in 180 ml ethanol and 180 ml 0.5N aqueous NaOH was refluxed for $4^1/_2$ h. The ethanol was then removed on the rotary evaporator, the aqueous phase washed with ether and then acidified with HCl. The acid was extracted into CH_2Cl_2, the solvent partially removed after drying over Na_2SO_4 and the product crystallized from CH_2Cl_2/ether to give 15.95 g acid **13**, m.p. 185–187°. (The acid co-crystallizes with $\sim {}^1/_2$ CH_2Cl_2).– IR. (Nujol): 1735, 1665 cm^{-1}.

$C_{19}H_{21}NO_3 + 0.55\ CH_2Cl_2$	Calc.	C 65.58	H 6.07	Cl 10.89%	N 3.91
(358)	Found	,, 65.22	,, 6.37	,, 10.79%	,, 4.01

Reduction of **6** *to* **9**. A solution of 6.0 g (17.7 mmol) of **6** in 150 ml of ethanol was hydrogenated over 500 mg 10% Pd/C at 3.4 atm. hydrogen pressure for $1^1/_2$ h. After filtration from the catalyst and removal of the ethanol *in vacuo*, the residue was crystallized from ether/hexane to give 4.5 g (75%) crystalline dihydroester **9**, m.p. 90–91°. – IR. (Nujol): 1720, 1691 cm^{-1}. – NMR. ($CDCl_3$): δ 0.83 (*t*, J = 7, 3H); 1.0–3.5 (16H); 3.75 (*q*, J = 7, 2H); 4.07 (*d* (b), J = 11, 1H); 7.23 (*s*, 5H).

$C_{20}H_{25}NO_3$ (341.43) Calc. C 73.87 H 7.97 N 4.10% Found C 74.05 H 8.16 N 4.22%

Reduction of **8** *to* **10**. A solution of 3.5 g ester **8** (10.8 mmol) in 100 ml of ethanol was hydrogenated over 300 mg 10% Pd/C at 3.4 atm. hydrogen pressure for $1^1/_2$ h. After filtration from the catalyst and removal of the solvent *in vacuo*, the residue was crystallized from ether to give 3.0 g (86%) crystalline dihydroester **10**, m.p. 130–132°. – IR. (Nujol): 1731, 1680 cm^{-1}. – NMR. ($CDCl_3$): δ 0.9–3.3 (16H); 3.36 (*s*, 3H); 4.13 (*d*(b), J = 13, 1H); 7.23 (*m*, 5H).

$C_{20}H_{25}NO_3$ (327.41) Calc. C 73.36 H 7.70 N 4.28% Found C 73.53 H 7.74 N 4.30%

Reduction of **6** *to the amino alcohol* **11**. 7.7 g (22.7 mmol) of the ester **6** were dissolved in 570 ml dry ether and refluxed for 4 h. with 4.5 g (120 mmol) $LiAlH_4$. Excess hydride was then destroyed by careful addition of 4.5 ml H_2O, 4.5 ml 15% NaOH and 13.5 ml water. The granular inorganic precipitate was filtered and the volume of the clear filtrate reduced to 100 ml. The product (**11**) thus crystallized to give 4.46 g (m.p. 151–152°) and 1.32 g (m.p. 147–148°) (total 90%). – IR. (CH_2Cl_2): 3610, 3100–3400 (broad), 1595 (w), 1490 cm^{-1}. – NMR. ($CDCl_3$): δ 1.0–3.4 (17H incl. 1 ex); 3.8 (broad, 1H); 5.63 (*m*, J = 10 and 3 and 1, 1H); 6.1 (*d*×*d*, J = 10 and 1, 1H); 7.28 (*s*, 5H).

$C_{19}H_{25}NO$ (283.4) Calc. C 80.52 H 8.89 N 4.94% Found C 80.40 H 8.83 N 4.93%

Reduction of **8** *to amino alcohol* **12**. 8.1 g (25 mmol) of the ester **8** were dissolved in 600 ml dry ether and refluxed for 4 h. with 4.9 g $LiAlH_4$ (0.13 mol). The excess hydride was then destroyed by carefully adding 4.9 ml water, 4.9 ml 15% NaOH and 14.7 ml water. After stirring for 1 h. at room temperature, the granular precipitate was filtered off and the volume of the filtrate reduced to about 100 ml. The amino alcohol **12** crystallized out to give 4.0 g, m.p. 113–114° (an additional 3.15 g were isolated from the mother liquor as the HCl salt, m.p. 305–307°; total yield: 94%). – IR. (CH_2Cl_2): 3625, 3100–3500 (broad), 1600 (w), 1493 cm^{-1}. – NMR. ($CDCl_3$): δ 1.0–3.6 (18H incl. 1 ex); 5.78 (*s*, 2H); 7.0–7.5 (*m*, 5H).

$C_{19}H_{25}NO$ (283.4) Calc. C 80.52 H 8.89 N 4.94% Found C 80.36 H 8.56 N 4.97%

Cyclization of **13** *to pentacyclic ketone* **14**. 6.0 g (17.2 mmol) of the acid were stirred for 1 h in 180 g polyphosphoric acid in an oil bath of 140°. The hot dark red mixture was then poured on crushed ice and the product extracted into CH_2Cl_2. The organic layer was subsequently washed with dilute NaOH and dried over Na_2SO_4. After removal of the solvent 4.09 g neutral material was obtained. The ketone **14** was crystallized from ethyl acetate to give a first crop of 2.63 g (m.p. 196–198°) and a second crop of 1.0 g (m.p. 194–196°) (total 72%). – IR. (CH_2Cl_2): 1718, 1688 cm^{-1}. – UV. (CH_3OH): 242 nm/11800, 288 nm/2100. – NMR. ($CDCl_3$, 100 MHz): δ 1.0–1.5 (*m*, 3H); 1.5–2.1 (*m*, 3H); 2.5 (*m*, 1H); 2.6–3.0 (*m*, 2H); 2.94 (*t*, J = 8, 1H); 3.4 (*t*, J = 7.5, 1H); 4.01 (*m*, J = 6 and 2, 1H); 4.2 (*d*×*d* (b), J = 13 and ~ 3, 1H); 5.65 (8 lines, J = 10.5 and 2, 1H); 5.82 (*d*(b), J = 10.5, 1H); 7.25–7.75 (*m*, 4H).

$C_{19}H_{19}NO_2$ (293.35) Calc. C 77.79 H 6.53 N 4.77% Found C 78.13 H 6.59 N 4.79%

Oxime **15**. A solution of 1.465 g ketone **14** (5 mmol) and 420 mg hydroxylamine hydrochloride (6 mmol) in 6.5 ml ethanol and 1.25 ml pyridine was refluxed for $2^1/_2$ h. The mixture was cooled, diluted with CH_2Cl_2 and washed with dilute Na_2CO_3. After drying the organic layer over Na_2SO_4 and evaporating, the solid residue was recrystallized from ethanol to give 1.1 g of the pentacyclic oxime **15**, dec. p. 255°. – IR. (Nujol): 3170, 3060, 1670 cm^{-1}. – UV. (CH_3OH): 247 nm/9000, 284 nm/3200.

$C_{19}H_{20}N_2O_2$ (308.37) Calc. C 74.00 H 6.54 N 9.09% Found C 74.16 H 6.48 N 8.83%

Rearrangement to pentacyclic dilactam **16**.–a) *From oxime* **15**. A suspension of 500 mg of the oxime **15** in 40 ml CH_2Cl_2 was refluxed under an atmosphere of nitrogen with 0.6 ml $SOCl_2$. The homogenous solution was then stirred with some water for 10 min., transferred to a separatory funnel and the organic layer was dried over Na_2SO_4. After removal of the solvent, the residue of 500 mg was recrystallized from ethyl acetate to give 320 mg crystalline product (**16**), m.p. 245–248° (64%). – IR. (Nujol): 3250, 1675, 1655 cm^{-1}, in ($CHCl_3$): 3390, 1667 cm^{-1}. – UV. (CH_3OH): 232 nm/9400, 278 (s) nm/1000, 286 (s) nm/700. – NMR. ($CDCl_3$, 100 MHz): δ 0.95–1.6 (*m*, 3H); 1.6–2.1 (*m*, 2H); 2.16 (*d*, J = 12.5, 1H); 2.4–2.9 (*m*, 2H); 2.9 (*q*, J = 4, 1H); 3.3 (*m*, 1H); 3.56 (*s* (b), 1H); 4.22 (*d* (b), J = 12.5, 1H); 4.42 (*t*, J = 4, 1H); 5.4 (*d* (b), J = 10, 2H incl. 1 ex); 5.82 (6 lines, J = 10 and 3, 1H); 7.2–7.6 (*m*, 3H); 8.06 (*d*×*d*, J = 7 and 2, 1H).

$C_{19}H_{20}N_2O_2$ (308.37) Calc. C 74.00 H 6.54 N 9.09% Found C 74.38 H 6.55 N 9.00%

b) *From ketone* **14**. To a cold solution of 2.93 g (10 mmol) ketone in 60 ml benzene and 7.5 ml conc. sulfuric acid are added, dropwise with stirring, 10 ml of a 1.55 M HN_3 solution in benzene. After the addition the mixture is stirred for another $3^1/_2$ h. The mixture is then carefully neutralized with conc. Na_2CO_3 and the product extracted into chloroform. After drying over Na_2SO_4 and removal of the solvent the residue is crystallized from CH_2Cl_2/ether to give 1.67 g, m.p. 240–250°. Recrystallization from ethanol gave 1.35 g, m.p. 249–251° (46%). – IR. (Nujol): 3390, 1680 (s), 1670 cm^{-1}. – IR. (CH_2Cl_2), UV. (CH_3OH) and NMR. ($CDCl_3$) identical to **16** obtained *via Beckmann* rearrangement.

$C_{19}H_{20}N_2O_2$ (308.37) Calc. C 74.00 H 6.54 N 9.09% Found C 74.36 H 6.46 N 9.07%

Reduction of **16** *to* **17**. A solution of 1.5 g dilactam **16** in 100 ml ethanol was hydrogenated over 200 mg 10% Pd/C at 3.4 atm. hydrogen pressure for $1^1/_2$ h. Filtration of the catalyst and removal of the solvent *in vacuo* gave 1.5 g of a residue which was crystallized from CH_2Cl_2/ether to give 1.4 g, m.p. 192–205°. Recrystallization from ethyl acetate/ethanol gave 950 mg, m.p. 202–205°. – IR. (Nujol): 3270, 1670 (s) cm^{-1}. – UV. (CH_3OH): 233 nm/9800, 272–280 nm/940, 288 (sh) nm/710.

$C_{19}H_{22}N_2O_2$ (310.38) Calc. C 73.52 H 7.14 N 9.03% Found C 73.71 H 7.11 N 9.09%

Reduction of **16** *to monolactam* **18**. 300 mg (~1 mmol) dilactam was stirred in 20 ml tetrahydrofuran with 200 mg $LiAlH_4$ at 25° for 3 h. Excess hydride was destroyed with 0.2 ml water, 0.2 ml 15% NaOH and 0.6 ml water. The mixture was diluted with ether, filtered and all solvent evaporated. The residue of 300 mg was crystallized from ether to produce 80 mg **18**, m.p. 188–191°. – IR. (Nujol): 3260, 1647, 1590, 1570 cm^{-1}. – UV. (CH_3OH): 230 nm/8400, 280 (sh) nm/900. – NMR. ($CDCl_3$): δ 0.9–3.7 (14H); 4.0 (*t*, J = 4, 1H); 5.47 (*d* (b), J = 10, 1H); 5.9 (6 lines, J = 10 and ~3, 1H); 6.95 (*s*, 1H ex.); 7.2–7.6 (*m*, 3H); 8.1 (*d*×*d*, J = 7 and 2, 1H).

$C_{19}H_{22}N_2O$ (294.4) Calc. C 77.52 H 7.53 N 9.52% Found C 77.12 H 7.38 N 9.41%

Reduction of **17** *to* **19**. A solution of 740 mg of dilactam **17** in 45 ml dry tetrahydrofuran was refluxed for $2^1/_2$ h. with 12 mmol diborane. Then the mixture was cooled in an ice bath and 18 ml 5N HCl were carefully added. Subsequently the tetrahydrofuran was evaporated at atmospheric pressure, the acidic residue made basic with saturated Na_2CO_3-solution and the product extracted into CH_2Cl_2. After drying and evaporating the solvent, the residue of 720 mg was dissolved in ethanol and neutralized with ethereal hydrochloric acid. Thus 720 mg of crystalline dihydrochloride of **19** were obtained, dec. p. > 260° (88%). – IR. (Nujol): 3300–3600 (b), 1570, 1490 cm^{-1}. – UV. (CH_3OH): benzene absorption.

$C_{19}H_{26}N_2 \cdot 2\,HCl$ (353.3) Calc. C 64.58 H 7.99 N 7.93% Found C 64.20 H 8.17 N 7.92%

Isocyanate **20** from **13**. To a solution of 1.4 g (4 mmol) acid **13** in 8 ml of acetone, 0.8 ml of water and 0.61 ml of triethylamine was added at 0° 0.44 ml ethyl chloroformate. The mixture was stirred at 0° for $^1/_2$ h and then a conc. aqueous solution of NaN_3 (5.5 mmol) was added. After stirring

for 1 h at 0°, the acetone was removed *in vacuo* without external heating, the residue taken up in CH_2Cl_2 and washed with ice cold water. After drying the organic layer over Na_2SO_4, the solution (*ca.* 150 ml) was refluxed for $3^1/_4$ h. The solvent was removed to give a crystalline, colorless residue (1.32 g) of isocyanate **20**, which was used in the next step without purification. – IR. (CH_2Cl_2): 2270, 1683 cm^{-1}.

Cyclization of **20** to **21**. A solution of 920 mg of **20** (3 mmol) in 60 ml of CH_2Cl_2 was refluxed with 850 mg $AlCl_3$ (6.4 mmol) for 5 h. The reaction mixture was poured on ice/dilute HCl, the organic layer dried over Na_2SO_4 and the solvent removed. The solid residue (920 mg) was recrystallized from hot ethanol to give 440 mg of pure **21**, m.p. 248–249°. – IR. (CH_2Cl_2): 3355, 1665–1675 (broad) cm^{-1}. – UV. (CH_3OH): 231 nm/9700, 276 nm/980. – NMR. ($CDCl_3$, 100 MHz): δ 1.0–2.3 (*m*, 6H); 2.4–2.82 (*m*, 3H); 2.9–3.7 (*m*, 3H); 4.1 (*d* × *d*, J = 12 and 4, 1H); 5.95 (6 lines, J = 10 and 3, 1H); 6.4 (*d*, J = 10, 1H); 7.18 (*s*, exch., 1H); 7.25–7.62 (*m*, 3H); 8.12 (*d* × *d*, J = 7 and 1.5, 1H).

$C_{19}H_{20}N_2O_2$ (308.37) Calc. C 74.00 H 6.54 N 9.09% Found C 74.13 H 6.69 N 9.11%

REFERENCES

[1] *H. W. Gschwend & H. P. Meier*, Angew. Chem. *84*, 291 (1972).
[2] *H. W. Gschwend*, Tetrahedron Letters *1970*, 2711.
[3] *M. F. Grundon & B. E. Reynolds*, J. chem. Soc. *1964*, 2445.
[4] *T. Terashima, Y. Kuroda & Y. Kanako*, Tetrahedron Letters, 2535 (1969).
[5] *E. M. Kosower & T. S. Sorensen*, J. org. Chemistry *28*, 692 (1963).
[6] *R. F. Borch, M. D. Bernstein & H. D. Durst*, J. Amer. chem. Soc. *93*, 2897 (1971).
[7] *S. Umezawa, T. Tsuchiya, K. Tatsuta, Y. Horiuchi, T. Usui, H. Umezawa, M. Hamada & A. Yagi*, J. Antibiot. (Tokyo) *23*, 20 (1970).
[8] *S. Umezawa, K. Tatsuta, Y. Horiuchi, T. Tsuchiya & H. Umezawa*, J. Antibiot. (Tokyo) *23*, 28 (1970).
[9] *S. Seltzer* in 'Advances in Alicyclic Chemistry': The mechanism of the *Diels-Alder* reaction. *H. Hart & G. J. Karabatsos* ed., vol. *2.*, p. 1, Academic press, New York and London (1968).
[10] *A. L. Wilds & C. H. Shunk*, J. Amer. chem. Soc. *70*, 2427 (1948).
[11] *A. Hofmann, H. Ott, R. Griot, P. A. Stadler & A. J. Frey*, Helv. *46*, 2306 (1963).
[12] *W. Oppolzer & K. Keller*, J. Amer. chem. Soc. *93*, 3836 (1971).
[13] *O. L. Chapman, M. R. Engel, J. P. Springer & J. C. Clardy*, J. Amer. chem. Soc. *93*, 6696 (1971).
[14] *D. J. Bichan & P. Yates*, J. Amer. chem. Soc. *94*, 4773 (1972).
[15] *H. O. House & T. H. Cronin*, J. org. Chemistry *30*, 1061 (1965).
[16] *H. W. Gschwend, A. O. Lee & H. P. Meier*, J. org. Chemistry *38*, 2169 (1973).

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177. Über die Cyclialkylierung von Dimethylarylhexanolen [1])

Vorläufige Mitteilung [2])

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(19. VI. 73)

Einleitung. – In unsere Untersuchungen über die Cyclialkylierung der Dimethylarylpentanole **1** und **2** in Schwefelsäure, über welche wir demnächst in dieser Zeitschrift berichten werden, haben wir auch – in einem weiteren Schritt – die

[1]) Teil der geplanten Dissertation von *K. Brandenberger*, Universität Freiburg.
[2]) Ein ausführlicher Bericht erfolgt demnächst in dieser Zeitschrift.