121. Stereoselective Syntheses of Benz[f]isoindoline-Derivatives by Intramolecular Cycloadditions of Styrenes to Olefins

by **Wolfgang Oppolzer**[1]**, Roland Achini, Emil Pfenninger** and **Hans Peter Weber**

Sandoz Ltd., Pharmaceutical Division, Chemical Research, CH-4002 Basel

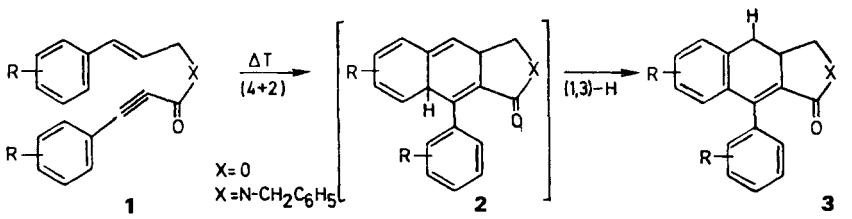
Dedicated to Professor *V. Prelog* on his 70th anniversary

(23. III. 76)

Summary. The N-allyl-N-cinnamyl amide **10** undergoes thermal cyclization to a 2:1-mixture of the *trans*- and *cis*-benz(*f*)isoindolines **11a** and **12a**. By comparison, the thermolysis of the corresponding bis-cinnamylamide **14** proceeds in a highly stereoselective manner to give the *cis*-fused[4+2]-adduct **16a**. Similarly, the *trans*-fused stereoisomeric adducts **30a** and **31a** were obtained with high stereochemical control on heating the N-allyl-N-diphenylallyl amide **28**. The thermal transformations **4** → **5**+**6a** and **17** → **18a**+**20a** show the competitive formation of [2+2]-adducts. An alternative approach to (substituted) benz[*f*]isoindolines **16** *via* the all-*cis*-isomer **24a** has been developed. The described structures have been assigned on the basis of spectral evidence, chemical correlations and by X-ray-diffraction study of the isomer **16b**. These results illustrate the utility of substituent interactions in order to direct intramolecular cycloadditions at will towards either *endo*- or *exo*-products.

The simple preparation of *Podophyllum lignans* (**3**, X=O) by thermolysis of the acetylenes **1** (X=O) [1] (*Scheme 1*) constitutes one of the first applications of intramolecular *Diels-Alder* reactions in the synthesis of natural products[2]).

Scheme 1



Apparently this transformation involves a thermal [4 + 2]-addition, in which the styrene reacts as the diene and the acetylene as the dienophile to give a non-aromatic intermediate **2**, which becomes aromatized to **3** by a subsequent [1,3]-H-shift. Whereas acetylenes readily undergo this reaction to give tricyclic lactones (**3**, X=O), or tricyclic lactams (**3**, X=NCH_2Ph [3]), olefinic double bonds were found to add only with difficulty to styrenes in an intramolecular fashion. For example, it has been reported [3] that both, the cinnamyl cinnamide **4** and the corresponding

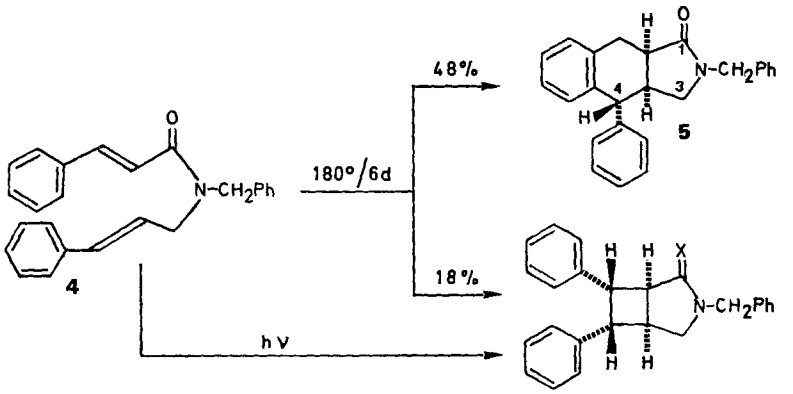
[1]) Present address: Département de Chimie Organique, Université de Genève, CH-1211 Genève 4.

[2]) For reviews on intramolecular *Diels-Alder* reactions see [2].

cinnamyl ester did not cyclize in boiling acetic anhydride (138°). However, in connection with recent studies on thermal intramolecular [4 + 2]- [4] and [2 + 2]-additions [5] of olefins to styrenes we have found that the diene **4** cyclizes using more stringent conditions (refluxing *o*-dichlorobenzene 180°).

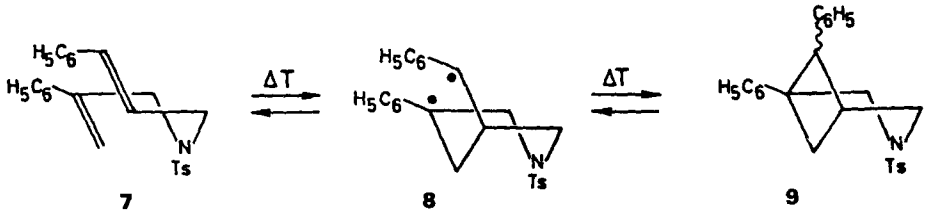
1. Thermolysis of the Cinnamyl Cinnamide 4. – After heating the diene **4** in boiling *o*-dichlorobenzene for 6 days the [2 + 2]-adduct **6a** was isolated in 18% yield together with the expected [4 + 2]-adduct **5** (48% yield).

Scheme 2



The *cis-anti-cis*-3-aza-bicyclo[3.2.0]heptane structure **6** was elucidated by reduction (AlH_3) of the lactam **6a** to the symmetric amine **6b**, followed by a comparison of its ^{1}H-NMR. spectrum with that of the analogous amide **20c**. In agreement with the proposed structure the [2 + 2]-adduct **6a** was also obtained (50% yield) on irradiation of the diene **4**. The thermal [2 + 2]-addition **4** → **6a** most probably involves a diradical intermediate in analogy to the related reaction: **7** ⇄ **8** ⇄ **9** (*Scheme 3*) (see also [5]).

Scheme 3

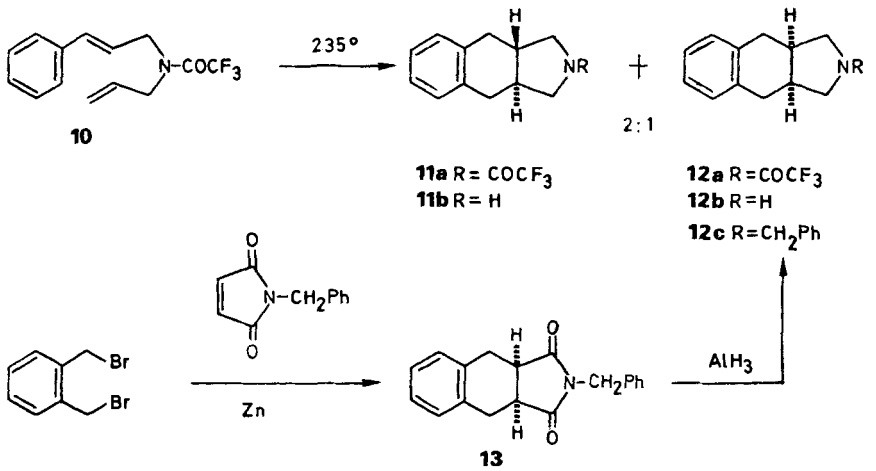


The carbon skeleton of **5**, and also its relative configuration, were assigned on the basis of ^{1}H-NMR.evidence (using the arguments described in section 6), and by conversion to the amine **16b**, whose structure is firmly established (X-ray). The

unexpected 1-position of the amide carbonyl group in **5** was unambiguously derived using a shift-reagent ($Eu(fod)_3$)) and double resonance techniques. Thus, the H–C(4) appearing as a doublet, is vicinal to a proton, which shows a multiplet with 4 vicinal couplings. Furthermore, the proton, whose signal is shifted most strongly by the shift reagent (assigned to the proton next to C=O) reveals no vicinal relationship to H–C(4). Because no other positional or stereoisomer of **5** was found in the reaction mixture it follows that, on thermolysis of **4** the carbonyl-conjugated styrene unit preferably reacts as the diene and the non-conjugated styrene unit as the dienophile[3]).

2. Thermolysis of the N-Allyl-N-cinnamyl Amide 10. – At higher temperatures even non-conjugated olefins seem to add effectively to an internal styrene unit. Thus, the allyl amide **10** on heating at 235° in toluene for 20 h furnished a nonseparable 2:1-mixture of the *trans*- and *cis*-[4 + 2]-adducts **11a** and **12a** in 61% yield (*Scheme 4*).

Scheme 4



After alkaline hydrolysis of the thermolysis mixture the resulting amines **11b** and **12b** were readily separated by chromatography. The *trans*-configuration of **11b** was assigned to the more polar amine on the basis of ^{1}H-NMR. evidence: The signals of the axial angular protons appear at $\delta = 1.6$–2.1 ppm, whereas those of the angular protons of the less polar *cis*-amine **12b** are at lower field: $\delta > 2.3$ ppm. (see section 6). Further evidence for this assignment was provided by an independent synthesis of the less polar *cis*-amine **12b** *via* the imide **13**[4]).

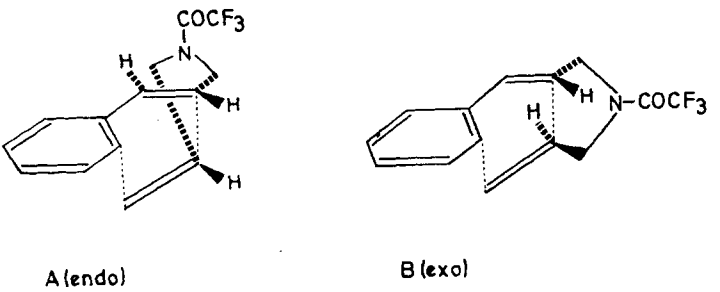
The lack of profound stereochemical control during the reaction **10** → **11a** + **12a** may be understood from examination of the two possible transition states (*Scheme 5*).

It is clear, on steric grounds, that both the *endo* transition state **A**, which leads to the *cis*-adduct **12a** and the *exo*-state **B**, which yields the *trans*-adduct **11a** are

[3]) For 'inverse-type' intramolecular *Diels-Alder* additions of carbonyl-conjugated dienes to acetylenes and olefins see [3] and [6].

[4]) For the related cycloadditions of *o*-xylylene to maleic anhydride see [7].

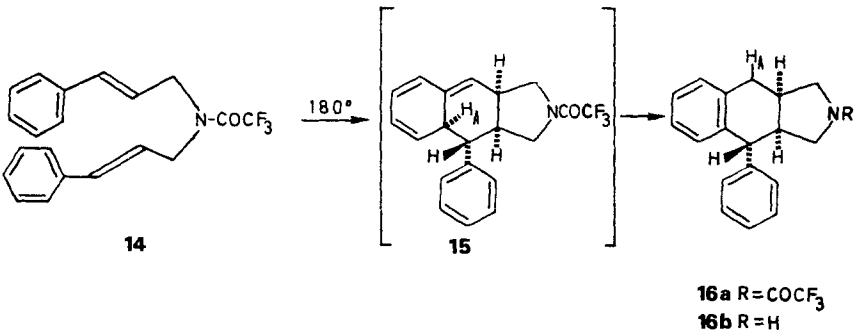
Scheme 5



energetically comparable; in agreement, the experimental evidence shows the formation of both isomers, there being a slight preference for the *exo*- as opposed to the *endo*-transition state. In order to direct the reaction towards either *cis*-fused or *trans*-fused tetrahydro-benz[*f*]isoindolines the influence of phenyl substituents on the stereochemical course of internal styrene-olefinadditions was investigated.

3. Thermolysis of the bis-Cinnamyl Amide 14. – On heating the symmetric bis-cinnamyl amide **14** in boiling *o*-dichlorobenzene for 20 h the *cis*-fused [4 + 2]-adduct **16a** was obtained in 78% yield. Gas chromatographic analysis of the reaction

Scheme 6

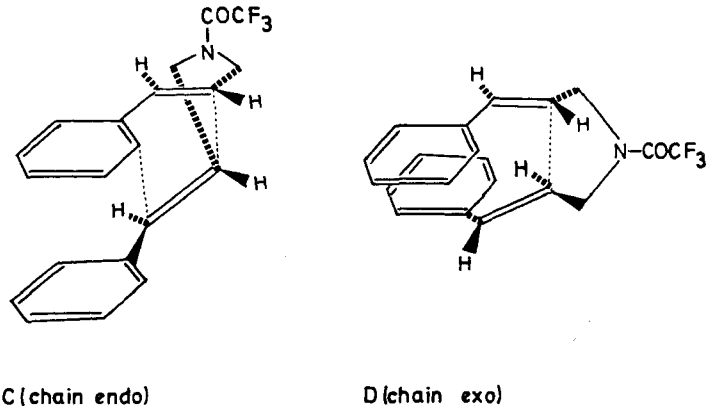


mixture revealed only a trace (0.6%) of the *trans*-fused stereoisomer **30a**. In comparison with the less selective internal addition of **10** (*cis*/*trans*-adduct = 1:2) the high degree of stereochemical control, observed on thermolysis of the diene **14** (*cis*/*trans*-adduct = 99:1) seems to be a result of the nonbonding interactions between the two phenyl rings which are present in the *exo*-transition state **D** and absent in the *endo*-transition state **C** (*Scheme 7*).

Therefore, the relative configuration of all three chiral centers is established in one step (**14** → **15**) *via* the strongly preferred transition state **C**. The structure of the adduct **16a** has been determined unambiguously both by ^{1}H-NMR. evidence and by an X-ray diffraction analysis (see sections 6 and 7). Similar results were obtained on thermolysis of several *meta*- and *para*-substituted bis-cinnamyl amides [4a].

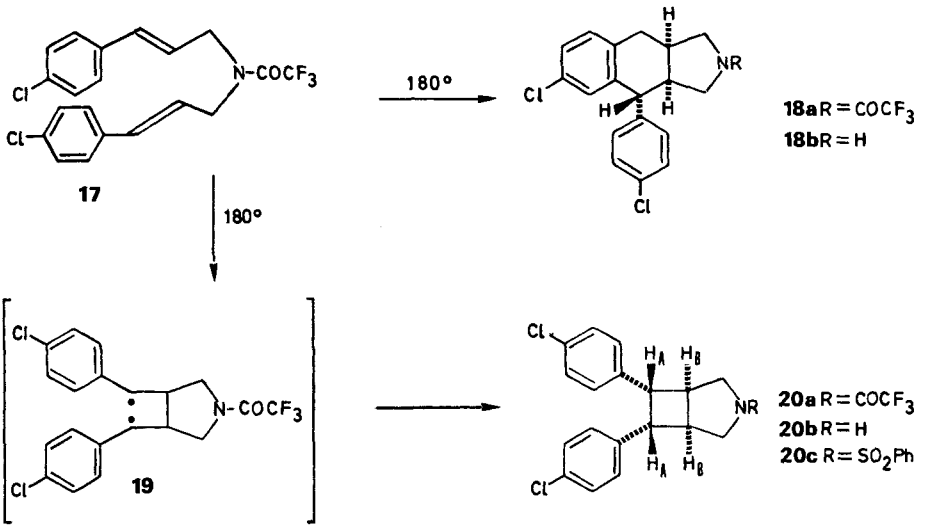
However, it was found that the bis-*p*-chlorocinnamyl amide **17**, on heating in boiling *o*-dichlorobenzene afforded, together with the [4 + 2]-adduct **18a**, the [2 + 2]-

Scheme 7



C (chain endo) D (chain exo)

Scheme 8



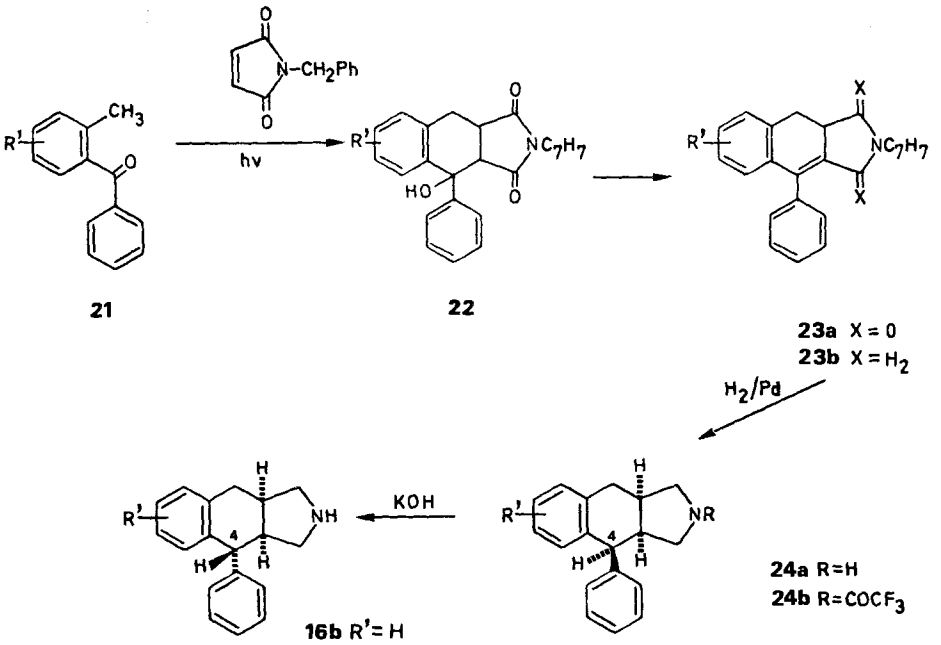
adduct **20a** in variable amounts. The structure of the [4 + 2]-adduct **18a**, isolated by crystallization of the reaction mixture, was established by conversion to the amine **16b**. The mother liquor, containing the [2 + 2]-adduct **20a** after saponification afforded the 3-azabicyclo[3.2.0]heptane **20b** isolated by crystallization of appropriate salts. The ^{1}H-NMR. spectrum of the corresponding benzenesulfonamide **20c** shows a vicinal coupling $J_{AB} = 4$ Hz, which indicates the depicted *cis-anti-cis*-configuration. This structural assignment was supported by shiftreagent and decoupling experiments. It is believed that the *p*-chloro substituents stabilize an intermediate diradical **19**[5]) to such an extent, that on thermolysis of the diene **17** [2 + 2]-

[5]) The intermediate **19** is proposed on the basis of stereochemical and kinetic evidence for the intermediacy of a diradical in the analogous reaction **7** ⇄ **8** ⇄ **9** (*Scheme 3*) [5].

addition becomes competitive with the [4 + 2]-addition. Therefore an alternative route to specifically substituted benz[*f*]indolines was developed.

4. Photochemical Approach to the Stereoisomeric Benz[*f*]isoindolines 24a and 16b. – This approach, which also provides access to the stereoisomeric all-*cis*-benz[*f*]isoindolines **24a** is based upon the smooth photoinduced addition of *o*-methylbenzophenones **21** to maleimides[6]) which affords the adducts **22** in yields ranging up to 95% (*Scheme 9*) [4].

Scheme 9



Subsequent dehydration to **23a**, followed by reduction and catalytic hydrogenation [9]led to the all-*cis*-benz[*f*]isoindolines **24a** (axial phenyl substituent) in good yields. Epimerization at C(4), using KOH in boiling butanol[7]) finally provided the more stable isomers **16b** (equatorial phenyl substituent).

5. Thermolysis of the N-Allyl-N-diphenylallyl Amide 28. – After the successful completion of different routes to the *cis*-fused 4-phenyl-benz[*f*]isoindolines **16** and **24** the selective preparation of the *trans*-fused stereoisomers **30** and **31** was envisaged. Accordingly, the diphenylallyl amide **28** was synthesized by N-alkylation of the amide **27b**, which is itself accessible *via* the sequence of reactions: **25** → **26** → **27** (*Scheme 10*).

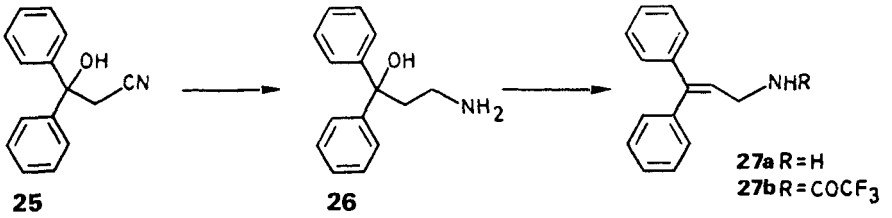
In order to effect internal addition of the terminal double bond to the 1-phenylstyrene unit, the amide **28** was heated for 6 days in boiling *o*-dichlorobenzene to give

6) For the analogous photoreaction of *o*-methylbenzophenone to maleic anhydride see [8].

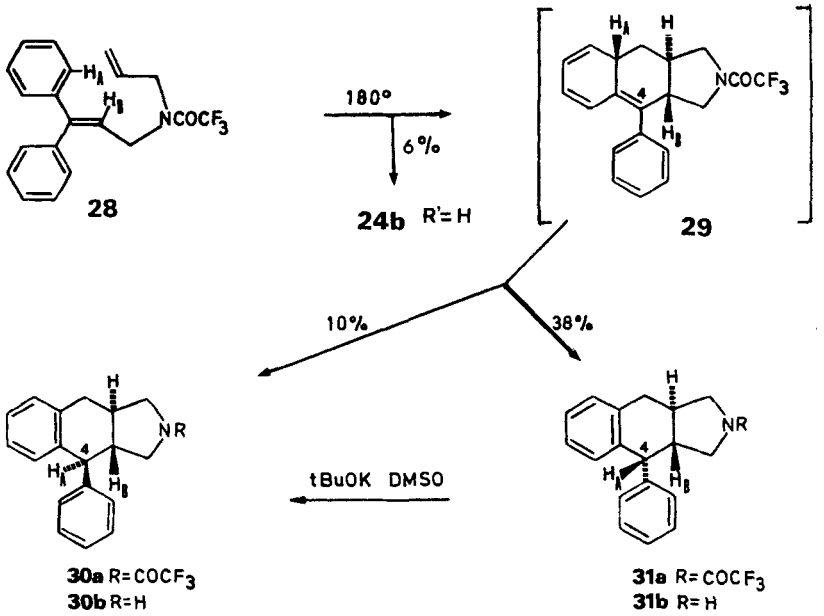
7) Analogous epimerisations had been carried out on 9-phenyl-hexahydro-indeno[2,1-*c*]pyridines [10].

a 1:4-mixture of the *trans*-fused adducts **30a** and **31a** in 65% yield, together with a small amount of the *cis*-fused isomer **24b** (R'=H) (6%)[8] (*Scheme 11*).

Scheme 10



Scheme 11



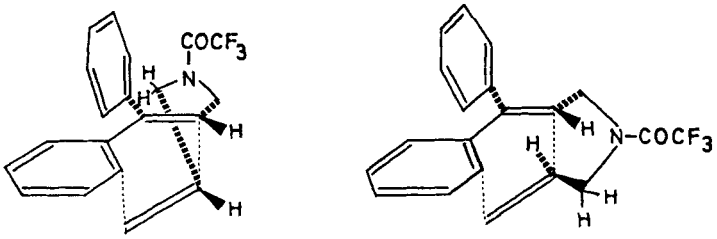
Fractional crystallization of the reaction mixture afforded the pure adducts **30a** and **31a** in isolated yields of 10% and 38%, respectively. The clear predominance of *trans*-fused products (*cis*/*trans* = 1:8), observed on the thermolysis of the diene **28**, may be attributed to unfavorable steric interactions of the allylic CH_2-group with the phenyl substituent in the *endo*-transition state **E** (*Scheme 12*).

Consequently, the preferred non-strained *exo*-transition state **F** leads to the *trans*-fused intermediate **29**, with the protons H_A and H_B *cis* to each other. This *cis*-relationship of H_A and H_B in the intermediate **29** indicates that a subsequent 1,3-shift of H_A occurs predominantly in a formally suprafacial fashion[9]) to give as

[8]) The amine **24a** was isolated from the saponified mother liquor as its hydrochloride.

[9]) The inter- *versus* intra-molecular nature of the proposed 1,3-H-shift was not examined.

Scheme 12



E (endo) F (exo)

the major product the thermodynamically less stable isomer **31a** (axial phenyl substituent); a formally antarafacial shift of H_A[9]) leads from **29** to the thermodynamically more stable minor product **30a** (equatorial 4-phenyl substituent). The free amine **31b**, obtained on hydrolysis of the major product **31a** was epimerized completely with potassium *t*-butoxide in dimethylsulfoxide to the more stable amine **30b**, which allows a highly selective synthesis of this stereoisomer from the amide **28**. In conclusion, all the four possible diastereoisomeric tetrahydro-4-phenylbenz[*f*]isoindolines may be separately prepared each in a stereocontrolled manner.

6. Configurational Assignment of the Stereoisomeric Tetrahydro-4-phenylbenz[*f*]isoindolines 16b, 24a, 30b and 31. – As indicated in Table 1 the *trans*-fused

Scheme 13

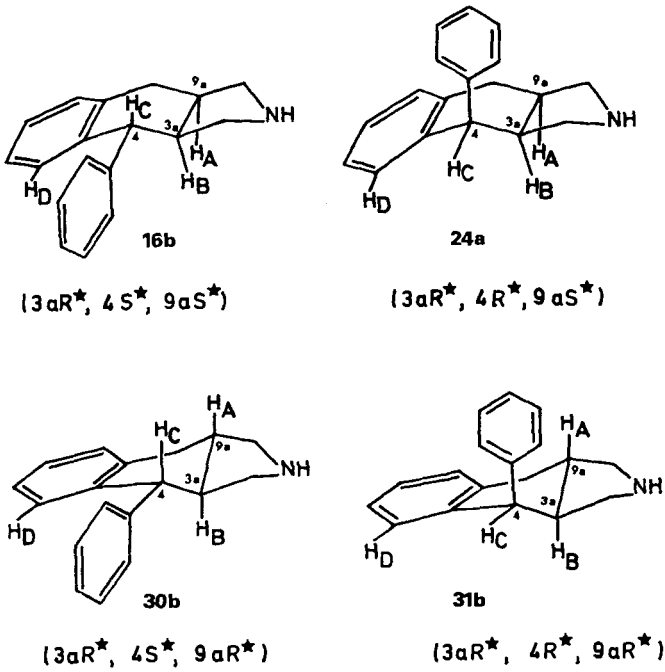


Table 1. *^{1}H-NMR. Data of the stereoisomeric tetrahydro-4-phenylbenz*[f]*isoindolines* **16b**, **24a**, **30b** *and* **31b** (Chemical shifts in $CDCl_3$ (ppm))

Stereoisomer	δ_{H_A, H_B}	δ_{H_C}	δ_{H_D}	$J_{B,C}$
16b (3a*R**, 4*S**, 9a*S**)	> 2.3	3.70	6.65	8 Hz
24a (3a*R**, 4*R**, 9a*S**)	> 2.3	4.15	> 6.8	2 Hz
30b (3a*R**, 4*S**, 9a*R**)	1.8–2.3	3.80	6.72	10 Hz
31b (3a*R**, 4*R**, 9a*R**)	1.8–2.4	4.42	> 6.8	3 Hz

isomers **30b** and **31b** (as well as **11b**) show at high field (δ = 1.8 to 2.4 ppm) the characteristic signals of the axial angular protons H_A and H_B. Because the *cis*-fused isomers **16b** and **24a** (as well as **12b**) exhibit no signals above δ = 2.3 ppm, the configuration of the ring fusion is readily assigned. The relative configuration at C(3a) and C(4) follows from the coupling constant J_{BC} (easily observed due to the clearly visible doublet of H_C); the larger coupling J_{BC} = 8 to 10 Hz indicates the *trans*- and the smaller coupling J_{BC} = 2 to 3 Hz the *cis*-relationship of H_B and H_C. Furthermore an axial H_C appears at higher field (δ = 4.15 to 4.4 ppm) than an equatorial H_C (δ = 3.70 to 3.80 ppm). Consequently, these data show for the isomers **16b** and **30b** an equatorial position of the C(4)-phenyl substituent, giving rise to a shielding of H_D, which appears at δ = 6.65 to 6.72 ppm, whereas the isomers **24a** and **31b** with an axial substituent exhibit no aromatic signals above δ = 6.8 ppm. These assignments could be confirmed by an X-ray analysis of the isomer **16b**, as described below.

7. The Crystal Structure Analysis of the 4-Phenyl-tetrahydro-benz[*f*]isoindoline 16b. – 7.1. *Crystallographic data.* Colourless, prismatic platelets of (3a*R**, 4*S**, 9a*S**)-3a,4,9,9a-tetrahydro-4-phenyl-benz[*f*]-isoindoline, $C_{18}H_{19}N$, Mol.-Wt. = 249.4, crystallised from ether, are monoclinic, a = 20.84(3), b = 5.86(1), c = 22.04(3) Å, β = 91.2(1)°, V = 2629 Å^3, space group C2/c, Z = 8, D_x = 1.26 g cm^{-3}. Intensity data were collected on a Linear Diffractometer with Mo$K\alpha$ radiation (graphite monochromator). 2108 reflexions within $\sin\theta/\lambda < 0.58$ Å^{-1} were measured, of which 1523 had a significant intensity, $I > 2.5\sigma(I)$, $\sigma(I) = \sqrt{P+B}+0.02\,(P-B)$ (P = peak counts, B = background counts). Reduction of the data to absolute values [11] yielded the following statistics: $\overline{B}$ = 3.68 Å^2, $<[E]>$ = 0.739, $<[E^2-1]>$ = 1.075, $<[E^2]>$ = 0.986. No absorption correction was applied.

7.2. *Structure analysis and refinement.* The structure was solved by an automated symbolic addition procedure [12]. The atomic parameters (positional and vibrational), a scale factor and an isotropic extinction coefficient were refined by least squares. Hydrogen positions were obtained from a difference map and included into the refinement with individual, isotropic temperature factors. The weighting function used was $\omega = 1/\sigma(F)$, where $\sigma(F) = [\sigma(I)/2I] \cdot F$ for significant reflexions, ω = 0 for insignificant reflexions. Convergence of a total of 249 parameters was reached with R = 0.081 for 1523 (significant) reflections. A complete computer output of the structure factor calculation including parameter data may be obtained from the authors (*HPW*).

7.3. *Results and discussion.* Positional coordinates of the atoms are given in Table 2 (standard numeration) with the LS-computed e.s.d. On average the mean error of an atomic position is 0.005 Å (C,N-atoms). Assuming that the twelve aromatic bonds in the two phenyl rings should be equal, an e.s.d. of 0.008 Å for an individual bond is obtained, which would indicate that the LS-e.s.d.'s are fairly realistic.

Fig. 1 gives a stereoscopic view of the molecule from which the principal features of the molecular conformation may be recognized.

The middle ring of the tricyclic framework has a boat conformation, the *cis*-fused pyrrolidine ring has an envelope shape with the nitrogen atom as flap. The whole

tricyclic fragment has an approximate mirror plane passing through N(2), intersecting perpendicularly the bonds C(3a)–C(9a), C(4a)–C(8a) and C(6)–C(7). Viewed perpendicular to this plane, the three rings show a *zig-zag*-like profile with dihedral angles at C(4) . . . C(9) of about 133°, at C(3a)–C(9a) of about 123°, and at C(1) . . . C(3) of about 167°.

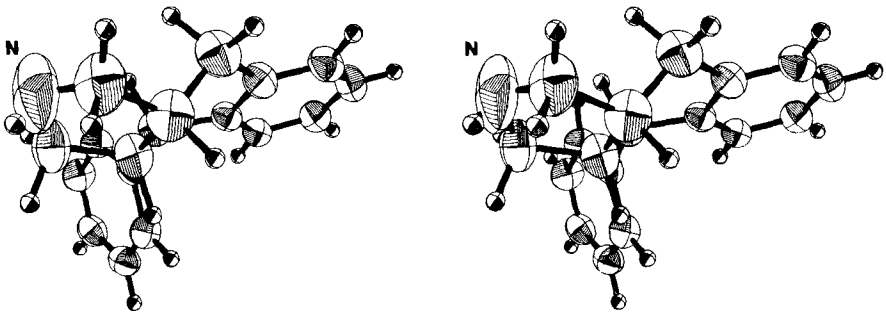


Fig. 1. *Stereoscopic view of* **16b** *with the 50% probability ellipsoids of the atomic vibrations for C and N atoms* (Hydrogen atoms are drawn as spheres corresponding to an isotropic B = 1 Å²)

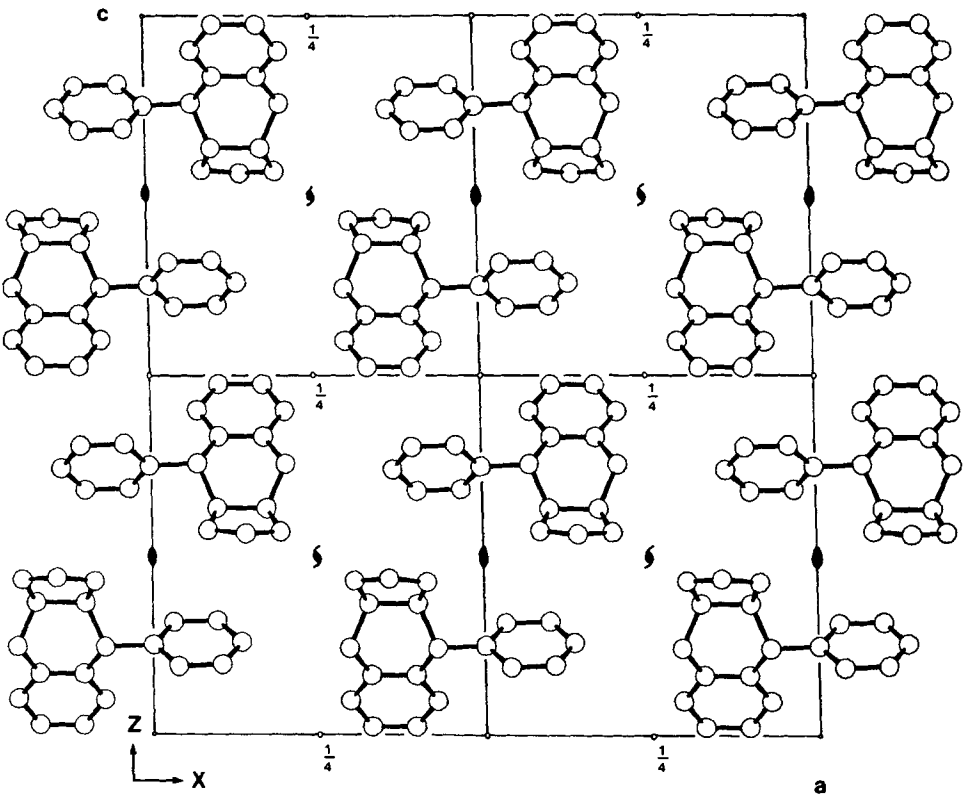


Fig. 2. *Packing diagram shown in projection parallel to* b.

The phenyl ring substituted on C(4) (atom numbers 10 to 15) is in equatorial position. The orientation of the ring is approximately parallel to the C(4)-H bond, a partial conformation also observed in other molecules with a phenyl ring on a tertiary carbon atom[10]).

As can be seen from Fig. 1, the nitrogen atom vibrates more anisotropically than the rest of the atoms. With due caution as to the physical significance of vibrational parameters obtained by an X-ray analysis, the size and orientation of this vibrational ellipsoid suggests that the nitrogen atom, as the flap of the envelope shaped pyrro-

Table 2. *Atomic coordinates with LS-computed e.s.d.'s.* (Values for C and N atoms are multiplied by 10^4, those for H atoms by 10^3)

	X	Y	Z
C(1)	3048(2)	−1633(9)	2158(2)
N(2)	3573(2)	−3077(9)	2187(2)
C(3)	4144(2)	−1884(8)	2141(2)
C(3a)	3999(1)	449(7)	1836(1)
C(4)	4290(1)	666(6)	1214(1)
C(4a)	3961(1)	2542(6)	841(1)
C(5)	4282(1)	4077(6)	483(1)
C(6)	3949(1)	5610(7)	120(1)
C(7)	3288(1)	5656(7)	120(1)
C(8)	2962(1)	4162(7)	487(1)
C(8a)	3289(1)	2592(6)	842(1)
C(9)	2960(1)	776(8)	1216(2)
C(9a)	3254(2)	567(8)	1837(2)
C(10)	5016(1)	869(6)	1250(1)
C(11)	5320(1)	2638(6)	1568(1)
C(12)	5984(1)	2794(7)	1593(1)
C(13)	6345(1)	1188(7)	1293(1)
C(14)	6050(1)	− 554(7)	980(1)
C(15)	5392(1)	− 698(7)	954(1)
H1(1)	268(2)	− 233(7)	199(2)
H2(1)	290(2)	− 116(10)	262(2)
H(2)	356(2)	− 296(11)	254(3)
H1(3)	447(2)	− 272(8)	195(2)
H2(3)	432(2)	− 143(9)	260(2)
H(3a)	425(2)	205(8)	206(1)
H(4)	412(1)	− 105(6)	106(1)
H(5)	475(1)	415(5)	49(1)
H(6)	419(1)	678(6)	− 11(1)
H(7)	304(1)	675(6)	− 13(1)
H(8)	247(1)	410(6)	49(1)
H1(9)	246(1)	112(7)	121(1)
H2(9)	305(2)	− 107(8)	107(2)
H(9a)	310(2)	227(7)	206(2)
H(11)	508(1)	382(6)	180(1)
H(12)	619(1)	405(6)	182(1)
H(13)	681(1)	124(6)	130(1)
H(14)	629(1)	− 164(8)	77(1)
H(15)	514(1)	− 177(7)	69(1)

[10]) *H. P. Weber*, Unpublished Results.

lidine ring, is swinging around an axis C(1) ... C(3) from an in-plane to an out-of-plane position.

The packing of the molecules in the crystal cell is shown in Fig. 2. There are no unusually short intermolecular distances present in the structure.

We thank Mrs. *K. Keller* for preliminary experiments.

Experimental Part

General remarks. – Elemental analytic data (C, H, N) in excellent accord with theory were obtained for all crystalline compounds reported herein. *Melting points* (m.p.) are not corrected, IR. spectra: *Perkin-Elmer* 21, max in cm^{-1}. ^1H-NMR spectra: *Varian* A60, *Varian* HA-100 and *Bruker* HX 90E in $CDCl_3$ (internal standard: tetramethylsilane, $\delta = 0$ ppm). Abbreviations: *s* = singulet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, br. = broad, *J* = spin-spin coupling constant (Hz). GC.: *Varian Aerograph* 1520, glass column = 3 m/2 mm, 3% OV225 on Chromosorb W-HP, 230°, 30 ml N_2/min.

trans-*N-Benzylcinnamylamine-hydrochloride.* A solution of *trans*-cinnamylamine (56.6 g) and benzaldehyde (26 ml) in benzene (750 ml) was heated under reflux for 15 h in a flask equipped with a *Dean-Stark* water separator. After evaporation of the solvent the crude imine was reduced with an excess of $NaBH_4$ in methanol. The *trans*-N-benzylcinnamylamine was isolated in 92% overall yield (based on *trans*-cinnamylamine) as its hydrochloride, m.p. 213–215° (MeOH/ether). – ^1H-NMR. (60 MHz, d-DMSO): 3.75 (*d*, *J* = 6, 2H); 4.15 (*s*, 2H); 6.45 (*d* × *t*, *J* = 6 and 15.5, 1H); 6.8 (*d*, *J* = 15.5, 1H); 7.2–7.8 (10H); 9.8 (br., 2H, NH_2^+).

trans-*N-Benzyl-N-*(trans-*cinnamyl*)*cinnamide* (**4**). To a solution of *trans*-N-benzylcinnamylamine (38.0 g, free base) and pyridine (24 ml) in CH_2Cl_2 (500 ml) was added a solution of *trans*-cinnamoyl chloride (30 g) in CH_2Cl_2 (250 ml) at –40° during 30 min. The mixture was warmed to room temp. and washed with aqu. 2N HCl, 2N NaOH and water. The crude, almost pure product was filtered through silica gel (1 kg) (petroleum ether/ethyl acetate 6:4), giving 40.0 g of the title compound as an oil. – IR. (film): 1640, 970 cm^{-1}. – ^1H-NMR. (100 MHz, d-DMSO, + 120°): 4.25 (*d*, *J* = 5, 2H); 4.75 (*s*, 2H); 6.2 (*d* × *t*, *J* = 5 and 15.5, 1H); 6.5 (*d*, *J* = 15.5, 1H); 7.1 (*d*, *J* = 15.5, 1H); 7.0–7.7 (15H); 7.6 (*d*, *J* = 15.5, 1H).

Thermal cyclization of trans-*N-Benzyl-N-*(trans-*cinnamyl*) *cinnamide* (**4**). A solution of **4** (18.0 g) in *o*-dichlorobenzene (600 ml) was heated under reflux for 135 h under argon. After evaporation of the solvent at 0.01 Torr, chromatography of the crude product on 1.3 kg silica gel (petroleum ether/ethyl acetate 1:1) gave 3.3 g (18%) of *cis-anti-cis*-3-benzyl-6,7-diphenyl-3-azabicyclo[3.2.0]heptan-1-one (**6a**) [m.p. 112–114°, (CH_2Cl_2/ether), IR. (CH_2Cl_2): 1675, ^1H-NMR. (100 MHz): 3.0–4.2 (6H); 4.55 (*AB*-system: J_{gem} = 15, 2H); 6.6–7.5 (15H)] and 8.7 g (48%) of (3a*R**, 4*S**, 9a*S**)-2-benzyl-3a,4,9,9a-tetrahydro-4-phenyl-benz[*f*]isoindolin-1-one (**5**) [m.p. 135–137° (CH_2Cl_2/ether), IR. (film): 1680, ^1H-NMR. (100 MHz): 2.7–3.5 (6H); 3.7 (*d*, *J* = 6, 1H, H–C(4)); 4.4 (*AB*-system, J_{gem} = 15, 2H); 6.7 (*d*, *J* = 7, 1H); 6.8–7.5 (13H)].

Photochemical cyclization of trans-*N-benzyl-N-*(trans-*cinnamyl*) *cinnamide* (**4**). A solution of **4** (5.0 g) in CH_2Cl_2 (450 ml) was irradiated for 20 h (mercury 150W-high pressure lamp, pyrex filter), then filtered and evaporated. The residue was chromatographed (silica gel, petroleum ether/ethyl acetate 1:1) to give 2.5 g (50%) of the cycloaddition product **6a**, m.p. 110–112° (ethyl acetate/petroleum ether), identical with the [2+2]-cycloaddition product from the thermal cyclization of **4** according to TLC., mixed m.p., IR.- and ^1H-NMR. spectra.

Conversion of the lactam **5** *to* [*3aR**, *4S**, *9aS**]-*3a,4,9,9a-tetrahydro-4-phenyl-benz*[f]-*isoindoline* (**16b**). 0.37 ml of 100% H_2SO_4 were added dropwise to a stirred solution of $LiAlH_4$ (0.8 g) in THF (50 ml) at –5° under N_2. After 30 min a solution of **5** (2.0 g) in THF (20 ml) was added dropwise at –5°, the mixture stirred for 2 h and then a saturated aqu. solution of Na_2SO_4 added dropwise until a granular precipitate was formed. Filtration, evaporation of the filtrate and extraction of the residue with CH_2Cl_2 gave, after evaporation and crystallization from ether/petroleum ether, 1.77 g (92%) of [3a*R**, 4*S**, 9a*S**]-2-benzyl-3a,4,9,9a-tetrahydro-4-phenyl-benz[*f*]isoindoline, m.p. 94–96°, IR. (CH_2Cl_2) no C=O. – ^1H-NMR. (100 MHz): 2.0–3.2 (8H); 3.55 (*s*, 2H); 3.75 (*d*, *J* = 8, 1H, H–C(4)); 6.6 (*d*, *J* = 6, 1H); 6.8–7.6 (13H), which was hydrogenated at room temp./1 atm. with 10% Pd/C catalyst in methanol to [3a*R**, 4*S**, 9a*S**]-

3a,4,9,9a-tetrahydro-4-phenyl-benz[*f*]isoindoline (**16b**), m.p. 135–138° (ether), identical with authentic **16b** according to TLC., mixed m.p., IR.- and ^{1}H-NMR. spectra.

cis-anti-cis-*3-Benzyl-6,7-diphenyl-3-aza-bicyclo[3.2.0]heptane* (**6b**). Analogous reduction of the lactam **6a** (1.0 g) using $LiAlH_4$ (0.4 g) and 100% H_2SO_4 (0.185 ml) gave 0.96 g (100%) of 3-benzyl-6,7-diphenyl-3-azabicyclo[3.2.0]hetane (**6b**), oil, ^{1}H-NMR. (100 MHz): 2.3 (2H); 2.9–3.2 (4H); 3.75 (*s*, 2H); 3.9 (*d*, *J* = 3.5, 2H, H–C(6) and H–C(7)); 6.7–7.5 (15H); hydrogen oxalate salt: m.p. 188–189° (methanol/ether).

*N-Allyl-N-*trans*-cinnamyl-trifluoracetamide* (**10**). A solution of N-cinnamyl-trifluoracetamide [5] (343 g) in hexamethylphosphoramide (600 ml) was added dropwise to a stirred and cooled suspension of 80% sodium hydride (45 g) in hexamethylphosphoramide (200 ml) under N_2. When the gas evolution had ceased a solution of allylbromide (199 g) was slowly added to the stirred solution. The mixture was allowed to stand at room temp. for 16 h, diluted with water and extracted with ether. Evaporation of the washed (water) and dried (Na_2SO_4) extracts, followed by chromatography of the oily residue on 2.4 kg of silica gel (toluene/petroleum ether 3:1) gave pure N-allyl-N-*trans*-cinnamyl-trifluoracetamide (347 g, 86%) as a colourless oil. – IR. (film): 1690, 976. – ^{1}H-NMR. (60 MHz): 3.7–4.2 (4H); 4.8–6.2 (4H); 6.4 (*d*, *J* = 15.5, 1H); 7.07 (*s*, 5H). – MS.: 269 (M^+).

*Thermolysis of N-allyl-N-*trans*-cinnamyl-trifluoroacetamide* (**10**) *and hydrolysis of the product mixture.* A solution of **10** (11 g) in toluene (110 ml) was heated under N_2 in a stainless steel autoclave at 235° during 20 h. Chromatography of the evaporated mixture (110 g of silica gel/1.1 l toluene/petroleum ether 4:1, followed by 1.1 l toluene) furnished a nonseparable mixture of *cis*- and *trans*-3a,4,9,9a-tetrahydrobenz[*f*]isoindoline-2-trifluoracetamides (6.7 g, 61%) **12a** and **11a**. 164 g of this mixture was stirred with a solution of KOH (168 g) in methanol (1.5 l) at room temp. for 1 h under N_2. Evaporation of the mixture, shaking the residue with water/ether, followed by evaporation of the dried ($MgSO_4$) ether extracts yielded an oily residue, which was chromatographed on silica gel, (1.25 kg, eluent: CH_2Cl_2/MeOH/25% aqu. NH3 40:10:1) collecting fractions of 1.25 l. The fractions 4–5, were combined, evaporated and the residue taken up in an excess of methanolic HCl-solution. Evaporation of the solution and crystallization of the residue (methanol/ether) yielded 31 g (24%) of the *cis*-3a,4,9,9a-tetrahydrobenz[*f*]isoindoline (**12b**)-hydrochloride: m.p. 166–167°. – ^{1}H-NMR. (100 MHz): 2.4–3.1 (8H); 3.3–3.7 (2H); 7.0–7.3 (4H); 8.2–9.3 (2H, NH_2^+).

The **12b**-hydrochloride on shaking with 2N NaOH/CH_2Cl_2 was converted to the free *cis*-3a,4,9,9a-tetrahydrobenz[*f*]isoindoline (**12b**): m.p. 104–105° (after crystallisation from ether/pentane). – IR. (Nujol): 3300, no C=O. – ^{1}H-NMR. (100 MHz): 1.60 (*s*, 1H, NH); 2.3–2.95 (8H); 2.95–3.4 (2H); 7.1 (*s*, 4H). The fractions 6–15 were combined, evaporated and the residue taken up in methanolic hydrochloric acid. Evaporation of the solution and crystallization of the residue (methanol/ether) yielded 55 g (43%) of *trans*-3a,4,9,9a-tetrahydrobenz[*f*]isoindoline (**11b**)-hydrochloride: m.p. 259–266°. – ^{1}H-NMR. (100 MHz): 1.9–2.3 (2H, H–C(3a) and H–C(9a)); 2.3–3.3 (6H); 3.6–3.9 (2H); 7.1 (*s*, 4H); 9.8 (br., 2H, NH_2^+).

The **11b**-hydrochloride on shaking with 2N NaOH/CH_2Cl_2 was converted to the free *trans*-3a,4,9,9a-tetrahydrobenz[*f*]isoindoline (**11b**): m.p. 75–78°. – IR. (Nujol): 3250, no C=O. – ^{1}H-NMR. (100 MHz): 1.6–2.1 (2H, H–C(3a) and H–C(9a)); 2.17 (*s*, 1H, NH); 2.4–2.9 (4H); 3.1 (*d*×*d*, *J* = 16 and 4, 2H); 3.33 (*d*×*d*, *J* = 10 and 6.5, 2H); 7.12 (*s*, 4H).

cis-*N-Benzyl-1,2,3,4-tetrahydro-2,3-naphthalenedicarboximide* (**13**). To a vigorously stirred mixture of N-benzylmaleimide (10 g) and zinc dust (2 g) in dimethylformamide (250 ml) was added over a period of 6 h a mixture of *o*-xylylene dibromide (23 g) and N-benzylmaleimide (5 g) in dimethylformamide (50 ml), as well as six portions of zinc dust (1 g each). The filtered solution, after addition of water (1 l) and of conc. HCl-solution (10 ml) was extracted with ether. The washed (aqu. $NaHCO_3$) and dried (Na_2SO_4) ether solution on evaporation and crystallization of the residue (CH_2Cl_2/ether) gave 5.4 g (22%) of the imide **13**: m.p. 157–159°. – IR. (CH_2Cl_2): 1780*w*, 1709*s*. – ^{1}H-NMR. (100 MHz): 2.7–3.4 (6H); 4.45 (*s*, 2H); 6.55 (*m*, 2H); 6.9–7.3 (7H).

cis-*N-Benzyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**12c**) *and its hydrogenolysis to* cis-*3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**12b**). A solution of $AlCl_3$ (0.55 g) in ether (4 ml) was added dropwise to a stirred solution of $LiAlH_4$ (0.38 g) in ether (10 ml) under N_2 at +5°. After addition of *cis*-N-benzyl-1,2,3,4-tetrahydro-2,3-naphthalenedicarboximide (**13**) (0.58 g) the mixture was stirred at room temp. for 30 min, refluxed for another 90 min and finally decomposed

with saturated aqu. Na_2SO_4-solution. The filtered solution was evaporated and the residue taken up in methanolic HCl-solution. Evaporation and crystallization (methanol/ether) furnished 0.35 g (67%) of the *cis*-benzyl-3a,4,9,9a-tetrahydro-benz[*f*]isoindoline (**12c**)-hydrochloride m.p. 192–195°. – IR. (CH_2Cl_2): no C=O. – ^{1}H-NMR. (90 MHz): 1.9–3.8 (10H); 3.95 (*s*, 2H); 6.9–7.8 (9H). The free *cis*-2-benzyl-3a,4,9,9a-tetrahydro-benz[*f*]isoindoline (**12c**) (0.25 g) (prepared from the hydrochloride by shaking with aqu. NaOH/ether) was hydrogenated in 50 ml of methanol at 5 atm. H_2/50° with Pd/C (10%, 0.25 g). The filtered mixture on evaporation, followed by crystallization of the residue (ether/pentane) furnished 0.06 g (24%) of crystals: m.p. 100–103°; mixed m.p. and ^{1}H-NMR. (100 MHz) confirm identity with authentic **12b**.

N,N-Bis-(trans-*cinnamyl*)-*trifluoroacetamide* (**14**). A solution of N-(*trans*-1-phenyl-2-propenyl)-trifluoroacetamide [5] (22.9 g) in hexamethylphosphoramide (50 ml) was added to a stirred and cooled (ice/methanol) slurry of sodium hydride (2.52 g washed with pentane) in hexamethylphosphoramide (45 ml) under N_2. When the gas evolution had ceased a solution of cinnamylbromide (20.7 g) in hexamethylphosphoramide (45 ml) was slowly added to the stirred solution. This mixture was allowed to stand at room temp. for 16 h, then diluted with water and extracted with ether. Evaporation of the dried (Na_2SO_4) extracts followed by chromatography of the oily residue on 600 g of silica gel (toluene) gave 29.4 g (85%) of N,N-bis-(*trans*-cinnamyl)-trifluoroacetamide (**14**) as a viscous oil. – IR. (CH_2Cl_2): no NH, 1690, 969. – ^{1}H-NMR. (60 MHz): 4.25 (*d*, J = 6.0, 4H); 6.15 (*d*×*t*, J = 15.5 and 5.5, 2H); 6.6 (*d*, J = 15.5, 2H); 7.2–7.5 (10H).

(*3aR*, 4S*, 9aS**)-*2-Trifluoroacetyl-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**16a**). A solution of **14** (29.0 g) in *o*-dichlorobenzene (580 ml, purified by distillation over K_2CO_3) was refluxed under N_2 for 16 h. Crystallization of the evaporated reaction mixture (CH_2Cl_2/pentane) afforded 22.6 g (78%) of the benz[*f*]isoindoline **16a**: m.p. 150–153°. – IR. (CH_2Cl_2): 1690, no band at 670. – ^{1}H-NMR. (60 MHz): 2.3–4.2 (9H); 6.8 (*m*, 1H); 6.9–7.5 (8H).

(*3aR*, 4S*, 9aS**)-*4-Phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**16b**). A solution of **16a** (65.0 g) in 3N methanolic KOH (330 ml) was stirred for 30 min at room temp. Evaporation of the mixture, shaking the residue with water/CH_2Cl_2, and evaporation of the dried CH_2Cl_2 extracts gave an oily residue, which on crystallization (ether/pentane) yielded 45.1 g (96%) of **16b**: m.p. 144–145°. – IR. (CH_2Cl_2): 3300 br., no C=O. – ^{1}H-NMR. (100 MHz): 2.25 (*s*, 1H, NH); 2.3–3.5 (8H); 3.7 (*d*, J = 8, 1H, H–C(4)); 6.65 (*d*, J = 6, 1H); 6.9–7.5 (8H).

N-[trans-*1-(4-Chlorophenyl)-2-propenyl*]-*trifluoroacetamide*. Following the procedure, described for the preparation of N-*trans*-1-phenyl-2-propenyl)trifluoroacetamide [5] *trans-p*-chlorocinnamylamine tartrate [13] (350 g) was converted to the corresponding trifluoroacetamide (157 g): m.p. 102–103°. – ^{1}H-NMR. (60 MHz): 4.1 (*t*, J = 6, 2H); 6.15 (*d*×*t*, J = 16 and 6, 1H); 6.2–6.8 (1H, NH); 6.57 (*d*, J = 16, 1H); 7.27 (*s*, 4H).

N,N-Bis(trans-p-*chlorocinnamyl*)-*trifluoroacetamide* (**17**). N-alkylation of N-(*trans*-1-(4-chlorophenyl)-2-propenyl)-trifluoroacetamide (7 g) with *trans*-1-(4-chlorophenyl)-2-propenyl bromide [14] (7.4 g) in analogy to the preparation of **14** furnished 9.4 g (85%) of **17** as a viscous oil (after chromatography on 100 g silica gel, benzene). – IR. (film): no NH, 1690, 970. – ^{1}H-NMR. (60 MHz): 4.25 (*d*, J = 5.5, 4H); 6.1 (*d*×*t*, J = 15.5 and 5.5, 2H); 6.55 (*d*, J = 15.5, 2H); 7.35 (*m*, 8H).

(*3aR*, 4S*, 9aS**)-*6-Chloro-4-*(p-*chlorophenyl*)-*2-trifluoroacetyl-3a,4,9,9a-tetrahydro-benz*[f]-*isoindoline* (**18a**). A solution of **17** (30 g) in *o*-dichlorobenzene (600 ml, purified by distillation over K_2CO_3) was heated under reflux for 16 h under N_2. The evaporated mixture was chromatographed (250 g silica gel, benzene) to give a viscous oil (18,0 g) which from ether/pentane furnished 5.5 g (18%) of crystals: m.p. 115–118°. – ^{1}H-NMR. (60 MHz): 2.4–3.1 (4H); 3.2–4.2 (5H); 6.74 (*s*, 1H); 6.9–7.5 (6H).

(*3aR*, 4S*, 9aS**)-*6-Chloro-4-*(p-*chlorophenyl*)-*3a,4,9,9a-tetrahydrobenz*[f]*isoindoline* (**18b**) *and its reduction to* **16b**. A solution of **18a** (14.0 g) in 3N methanolic KOH (140 ml) was heated under reflux for 45 min, then concentrated and diluted with water. Extraction with CH_2Cl_2 and crystallization from ether afforded 7.8 g (73%) of the amine **18b**: m.p. 133–135°. – ^{1}H-NMR. (60 MHz): 1.8–3.5 (9H); 3.6 (*d*, J = 8, 1H); 6.59 (*s*, 1H); 6.9–7.5 (6H). A solution of **18b** (0.106 g) and of NaOH (0.035 g) in ethanol (5 ml) was stirred with Pd/C (10%, 0.03 g) under 1 atm of hydrogen for 16 h. The filtered and evaporated solution was shaken with ether/2N NaOH. Evaporation of the dried ($NaSO_4$) ether extracts and crystallization (ether/pentane) afforded 0.02 g of **16b**: m.p. 136–138°. – ^{1}H-NMR. (100 MHz): identical with the spectrum of authentic **16b**.

6,7-Bis-(4-chlorophenyl)-5-aza-bicyclo[3.2.0]heptane (**20b**). The mixture, obtained on thermolysis of N,N-bis-(*trans-p*-chlorocinnamyl)-trifluoroacetamide (30 g) gave after crystallisation of the benz[*f*]isoindoline **18a** a mother liquor (11.5 g) which in 3N methanolic KOH (120 ml) was heated under reflux for 30 min, then evaporated, diluted with water and extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave an oil (8.0 g) which with 3.9 g of naphthalene-1,5-disulfonic acid afforded a crystalline salt (methanol/ether): m.p. 277–279° (9.0 g). The latter was converted (*via* the free base) to the corresponding hydrogen maleinate: m.p. 160–165° (ethanol/ether, 5.3 g, 17%) which on shaking with sat. Na_2CO_3/ether furnished pure 6,7-bis-(4-chlorophenyl)-5-aza-bicyclo[3.2.0]heptane (**20b**): m.p. 100–102° (ether/pentane). – IR. (CH_2Cl_2): 1490, 1090, 1010. – ^{1}H-NMR. (100 MHz): 2.8–3.3 (7H); 3.6 (*d*, J = 3.5, 2H, H–C(6) and H–C(7)); 6.85 (*d*, J = 8.0, 4H, aromatic, *m*-Cl); 7.05 (*d*, J = 8.0, 4H, aromatic, *o*-Cl).

$C_{18}H_{17}Cl_2N$ Mol-Wt. Calc. 318.2 Found 336 (vapor pressure osmometry).

3-Benzenesulfonyl-6,7-bis-(4-chlorophenyl)-3-azabicyclo[3.2.0]heptane (**20c**). To a stirred mixture of **20b** (0.25 g) pyridine (0.12 g) and CH_2Cl_2 (2 ml) was added at 0° a solution of benzenesulfonyl chloride (0.17 g) in CH_2Cl_2 (1 ml). The reaction mixture was allowed to stand at room temp. for 2 h to give after usual work-up, chromatography (silica gel, benzene) and crystallization (ether/pentane) 0.093 g of crystals: m.p. 130–133°. – ^{1}H-NMR. (100 MHz): 2.9 (*m*, 2H, *exo*–H–C(2) and *exo*–H–C(4)); 3.15 (*m*, 2H, H–C(1) and H–C(5)); 3.75 (*d*, J = 10, 2H, *endo*–H–C(2) and *endo*–H–C(4)); 3.9 (*d*, J = 4, 2H, H–C(6) and H–C(7); 6.8 (*d*, J = 8.0, 4H); 7.1 (*d*, J = 8, 4H); 7.5–7.75 (3H); 7.9 (*m*, 2H).

2-Benzyl-4-hydroxy-4-phenyl-3a,4,9,9a-tetrahydro-benz[f]*isoindolin-1,3-dione* (**22**, R′ = H). A solution of *o*-methylbenzophenone [15] (3.9 g) and N-benzylmaleimide (3.74 g) in acetone (160 ml) was irradiated at 25° with a high pressure mercury lamp (150 W, pyrexfilter) for 4 h. The filtered solution after evaporation and crystallization (methanol) gave 3.4 g (45%) of the adduct **22** (R′ = H): m.p. 147–149°. – IR. (CH_2Cl_2): 3450, 1770, 1690. – ^{1}H-NMR. (60 MHz): 2.55 (*d*×*d*, J = 15 and 8, 1H); 2.95 (*d*×*d*, J = 15 and 2, 1H); 3.25 (*d*×*t*, J = 9, 8 and 2, 1H); 4.0 (*d*, J = 9, 1H); 4.5 (*s*, 2H); 5.45 (br., 1H, OH); 6.5–8.0 (14H).

2-Benzyl-4-phenyl-9,9a-dihydro-benz[f]*isoindolin-1,3-dione* (**23a**; R′ = H). A solution of **22** (R′ = H) (21.7 g) in trifluoroacetic acid (150 ml) was allowed to stand at room temp. for 1 h and evaporated. Crystallization of the residue (CH_2Cl_2/ether) afforded 19.0 g (92%) of **23a** (R′ = H): m.p. 177–180°. – IR. (CH_2Cl_2): no OH, 1762, 1703. – ^{1}H-NMR. (60 MHz): 2.8–3.9 (*m*, 3H); 4.7 (*s*, 2H); 7.0–7.6 (14H).

2-Benzyl-4-phenyl-9,9a-dihydro-benz[f]*isoindoline* (**23b**, R′ = H). 100% sulfuric acid (7.6 ml) was added dropwise to a stirred solution of $LiAlH_4$ (5.9 g) in tetrahydrofuran (130 ml) under N_2 at –10°. After stirring the mixture for 45 min, at +10°, a solution of the imide **23a** (R′ = H) (19.0 g) in tetrahydrofuran (170 ml) was added dropwise at –5°. The mixture was allowed to stand at room temp. for 16 h and worked-up at 0° by slow addition of an excess of 1N aqu. NaOH. Filtration and evaporation of the filtrate gave a residue, which was taken up in CH_2Cl_2. Further filtration and evaporation, followed by crystallization (ether/pentane) afforded 15.5 g (90%) of the benzylamine **23b** (R′ = H): m.p. 113–115°. – IR. (CH_2Cl_2): no C=O. – ^{1}H-NMR. (100 MHz): 2.25 (*t*, J = 7, 1H); 2.5–3.5 (4H); 3.0 (*d*, J = 15, 1H); 3.7 (*s*, 2H); 3.85 (*d*, J = 15, 1H); 6.7–7.6 (14H).

(*3a*R*, *4*R*, *9a*S*)-*4-Phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**24a**, R′ = H) (all-*cis*) Palladium(II) chloride (4.2 g) and a solution of NaCl (3.1 g) in water (25 ml) was added to a solution of **23b** (R′ = H) (15.5 g) in ethanol (1 l). This solution was added dropwise to $NaBH_4$ (4.2 g) in water (25 ml) at 0°. The mixture was adjusted to pH = 2 with conc. aqu. HCl-solution and then hydrogenated at 4 atm H_2/60° for 14 h. Filtration, evaporation and crystallization of the residue (methanol/ether) furnished 12.4 g of **24a** (R′ = H). HCl: m.p. 256–258°. The foregoing hydrochloride of **24a** (R′ = H) (1.4 g) was shaken with 2N aqu. NaOH/CH_2Cl_2. Evaporation of the dried CH_2Cl_2 solution and crystallization (methanol/pentane) of the residue gave 1.0 g of the free amine **24a** (R′ = H): m.p. 102–104°. – ^{1}H-NMR. (100 MHz): 1.5 (*s*, 1H, NH); 2.2–3.3 (8H); 4.15 (*d*, J = 2, 1H); 6.8–7.6 (9H).

(*3a*R*, *4*R*, *9a*S*)-*2-Trifluoroacetyl-3a,4,9,9a-tetrahydro-4-phenyl-benz*[f]*isoindoline* (**24b**, R′ = H). The amine **24a** (R′ = H) (0.125 g) was acylated with trifluoroacetic anhydride (as described for the preparation of **27b**) to give 0.110 g of crystalline (ether/pentane) **24b** (R′ = H):

m.p. 132–134°. – IR. (CH_2Cl_2: 1690. – ^{1}H-NMR. (60 MHz): 2.4–4.0 (8H); 4.29 (*d*, J = 3, 1H); 6.8–7.5 (9H).

Epimerisation of (3aR, 4R*, 9aS*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**24a**, R′ = H) *to (3aR*, 4S*, 9aS*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**16b**). A solution of the all-*cis*-amine **24a** (R′ = H) (0.2 g) in a saturated solution of powdered KOH in *n*-butanol (5 ml) was heated under reflux for 17 h under N_2. After evaporation of this reaction mixture the residue was shaken with water/ether. The dried ether extracts on evaporation and crystallization (ether/pentane) gave 0.11 g of the C(4)-epimer (**16b**): m.p. 136–138°; ^{1}H-NMR. (100 MHz): identical with the spectrum of authentic **16b**.

3-Hydroxy-3,3-diphenyl-propylamine (**26**). 100% sulfuric acid (19.2 g) was added dropwise to a stirred solution of $LiAlH_4$ (14.8 g) in tetrahydrofuran (390 ml) under N_2 at –10°. After stirring the mixture for 1 h at +10°, a solution of 3-hydroxy-3,3-diphenyl-propionitrile [16] (58 g) in tetrahydrofuran (520 ml) was added dropwise. The mixture was heated under reflux for 1 h and finally decomposed at 0° by slow addition of a slight excess of aqu. 2N NaOH. The filtered and evaporated mixture was dissolved in 10% aqu. citric acid solution, washed with ether, basified with NaOH and extracted with CH_2Cl_2. The dried (Na_2SO_4) and concentrated CH_2Cl_2 solution on addition of petroleum ether yielded 30 g (51%) of crystals: m.p. 140–143°. – IR. (CH_2Cl_2): 3390, 3200 broad. – ^{1}H-NMR. (60 MHz): 2.1–2.3 (2H); 2.3–3.05 (2H); 3.14 (*s*, br., 3H, —NH_2, —OH); 7.0–7.3 (10H).

3,3-Diphenyl-prop-2-en-1-ylamine (**27a**)*-hydrochloride.* A solution of **26** (32 g) in 5N aqu. HCl (1 l) was heated for 90 min under reflux, cooled to 20° and filtered. The separated crystals were washed with ether and dried i.V. to give 30 g (87%) of the amine **27a**-hydrochloride: m.p. 213°.

The hydrochloride was converted to the free amine (**27a**): dist. (bath) 150°/0.1 Torr. – IR. (film): 3460, 3270 broad. – ^{1}H-NMR. (60 MHz): 1.07 (*s*, 2H, —NH_2); 3.14 (*d*, J = 7, 2H); 6.02 (*t*, J = 7, 1H); 6.9–7.2 (10H). – MS.: 209 (M^+).

N-(3,3-Diphenyl-prop-2-en-1-yl-trifluoracetamide (**27b**). To a stirred mixture of **27a** (24.5 g), pyridine (23.7 g) and CH_2Cl_2 (200 ml) trifluoroacetic anhydride (2.0 g) was added dropwise at 0°. After 0.5 h at room temp. the mixture was shaken 3 times with 10% aqu. citric acid, once with sat. aqu. $NaHCO_3$-sol., dried and evaporated. The residue on crystallization (ether/petroleum ether) furnished 25 g. (66%) of **27b**: m.p. 117–118°. – IR. (CH_2Cl_2): 3420, 1720. – ^{1}H-NMR. (60 MHz): 4.05 (*t*, J = 7, 2H); 6.1 (*t*, J = 7, 1H); 6.5 (br., 1H, NH); 7.1–7.6 (10H).

N-Allyl-N-(3,3-diphenyl-prop-2-en-1-yl)-trifluoracetamide (**28**). A solution of **27b** (22.3 g) in hexamethylphosphoramide (240 ml) was added to a stirred and cooled slurry of 80% sodium hydride (2.25 g) in hexamethylphosphoramide (120 ml) under N_2. When the gas evolution had ceased, allyl bromide (12.0 g) was added to the mixture, which was allowed to stand at room temp. for 16 h, then was diluted with water and extracted with ether. Chromatography of the evaporated ether extracts (250 g silica gel, toluene) yielded 21.5 g (85%) of **28** as a colourless oil. – IR. (CH_2Cl_2): 1690. – ^{1}H-NMR. (60 MHz): 3.7–4.3 (4H); 4.9–6.5 (4H); 7.1–7.6 (10H).

Thermolysis of N-Allyl-N-(3,3-diphenyl-prop-2-en-1-yl)-trifluoroacetamide (**28**). A solution of **28** (21 g) in *o*-dichlorobenzene (distilled over K_2CO_3) (1 l) was heated under reflux for 3 to 5 days under N_2. The mixture was stirred with 40 g of silica gel, filtered and evaporated. Fractional crystallization of the residue (CH_2Cl_2/ether) furnished 2.2 g (10%) of (3a*R**, 4*S**, 9a*R**)-2-trifluoroacetyl-4-phenyl-3a,4,9,9a-tetrahydro-benz[*f*]isoindoline (**30a**) [m.p. 202–204°. – IR. (CH_2Cl_2): 1690. – ^{1}H-NMR. (100 MHz): 1.9–2.6 (2H, H—C(3a) and H—C(9a)); 2.6–3.5 (4H); 3.65 (*d*×*d*, J = 6 and 12, 1H); 3.9 (*d*, J = 10, 1H, H—C(4)); 4.1 (*d*×*d*, J = 7 and 12, 1H); 6.75 (*m*, 1H); 6.9–7.4 (8H). Irradiated at 2.4: 3.9 (*s*)], as well as 7.0 g of (3a*R**, 4*R**, 9a*R**)-2-trifluoroacetyl-4-phenyl-3a,4,9,9a-tetrahydro-benz[*f*]isoindoline (**31a**) [m.p. 159°.] – IR. (CH_2Cl_2): 1690. – ^{1}H-NMR. (60 MHz): 2.0–3.6 (6H); 3.7–4.2 (2H); 4.5 (*d*, J = 3, 1H, H—C(4); 6.8–7.5 (9H)]. The combined mother liquors were chromatographed (130 g of silica gel, toluene) to give a viscous oil (4.5 g) which on crystallization (CH_2Cl_2/ether) afforded another crop (1 g, total isolated yield: 38%) of pure (3a*R**, 4*R**, 9a*R**)-2-trifluoroacetyl-4-phenyl-3a,4,9,9a-tetrahydro-benz[*f*]isoindoline (**31a**): m.p. 159°. The remaining mother liquor (3.4 g) on alkaline hydrolysis gave the all-*cis*-amine **24a** (R′ = H) as described below.

(3aR, 4R*, 9aR*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**31b**). A solution of **31a** (m.p. 159°, 5.0 g) in 1 N ethanolic KOH was heated under reflux for 1 h under N_2, then concentrated and diluted with water. Extraction with CH_2Cl_2 and evaporation of the extracts furnished an oil which was taken up in methanolic HCl-Solution. Evaporation of the solution, followed by crystallization of the residue (methanol/ether) yielded 2.5 g (61%) of **31b**-hydrochloride: m.p. 212–217° (dec.). – ^{1}H-NMR. (100 MHz) DMSO-d_6): 1.9–3.6 (8H); 4.53 (*d*, *J* = 5, 1H, H–C(4)); 6.8–7.4 (9H); 7.7 (br., 2H, NH_2^+).

The foregoing **31b**-hydrochloride (1.0 g) was converted to the free amine **31b** (0.82 g). – ^{1}H-NMR. (100 MHz): 1.8–2.3 (3H); 2.4–3.3 (6H); 4.42 (*d*, *J* = 3, 1H, H–C(4)); 6.7–7.3 (9H).

(3aR, 4S*, 9aR*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**30b**). A solution of **30a** (m.p. 202–204°, 130 g) in 2 N methanolic KOH (800 ml) was heated under reflux for 30 min under N_2, then concentrated and diluted with water. Extraction with CH_2Cl_2, evaporation of the extracts and crystallization of the residue afforded 68.1 g (76%) of **30b**: m.p. 128–130°. – IR. (CH_2Cl_2): 3380*w*, no C=O. – ^{1}H-NMR. (100 MHz): 1.8–2.3 (2H, H–C(3a) and H–C(9a)); 2.45 (*s*, 1H, NH); 2.5–3.5 (6H); 3.8 (*d*, *J* = 10, 1H, H–C(4)); 6.7 (*d*, *J* = 6, 1H); 6.8–7.5 (8H).

Epimerization of (3aR, 4R*, 9aR*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**31b**) *to (3aR*, 4S*, 9aR*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**30b**). A solution of KOBu^t (0.25 g) in DMSO (3 ml) was added to a solution of **31b** (0.82 g) in DMSO (8 ml). The mixture was stirred at room temp. for 70 h, then diluted with water. The precipitate was separated by filtration, washed with water and dissolved in CH_2Cl_2. Evaporation of the dried (Na_2SO_4) organic phase gave a residue (0.78 g) which was taken up in methanolic HCl-solution. Evaporation of the solution and crystallization of the residue (methanol/ether) furnished the hydrochloride of **30b** (0.66 g, 70%), which was converted to the free amine **30b** (0.45 g, after crystallization from ether): m.p. 128–130°. – IR.- and ^{1}H-NMR.-spectra identical with the spectra of authentic **30b**.

Isolation of (3aR, 4R*, 9aS*)-4-phenyl-3a,4,9,9a-tetrahydro-benz*[f]*isoindoline* (**24a**, R′ = H) *from the hydrolysed mixture obtained on thermolysis of N-allyl-N-(3,3-diphenyl-prop-2-en-1-yl-trifluoroacetamide* (**28**). The combined and evaporated mother liquors (3.4 g) obtained on thermolysis of **28** (21 g) followed by crystallization of **30a** and **31a** was heated under reflux in 1 N ethanolic KOH (70 ml) for 1 h. The evaporated mixture was diluted with water and extracted with CH_2Cl_2. The combined and evaporated extracts were taken up in methanolic HCl-solution.

Evaporation of the solution, followed by crystallization of the residue (methanol/ether) furnished 1.27 g (6%) of the all-*cis*-amine (**24a**, R′ = H)-hydrochloride: m.p. 230° which was converted to the free amine (**24a**, R′ = H) (0.91 g): m.p. 104–105°; mixed m.p. IR.- and ^{1}H-NMR. spectral comparison confirmed its identity with authentic **24a** (R′ = H).

REFERENCES

[1] *L. H. Klemm & K. W. Gopinath*, Tetrahedron Letters, *1963*, 1243.
[2] *R. C. Carlson*, Ann. Rep. Med. Chem., *9*, 270 (1974); *W. Oppolzer*, Angew. Chem. (in preparation).
[3] *L. H. Klemm & T. M. McGuire*, J. Heterocyclic Chem., *9*, 1215 (1972).
[4] a) *Sandoz Ltd.* (*W. Oppolzer, R. Achini & E. Pfenninger*), Belg. patent 805504 (1974), DOS 2348593 (1974), Belg. patent 827087 (1975), DOS 2511621 (1975). b) *M. T. Cox*, J. C. S. Chem. Comm., *1975*, 903.
[5] *W. Oppolzer & H.-R. Loosli*, Helv. *57*, 2605 (1974); *W. Oppolzer*, Helv. *57*, 2610 (1974).
[6] *G. Frater*, Helv. *57*, 172 (1974).
[7] *K. Alder & M. Fremery*, Tetrahedron, *14*, 190 (1961).
[8] *F. Nerdel & W. Brodowski*, Chem. Ber., *101*, 1398 (1968).
[9] *A. Canas-Rodriguez*, J. C. S. Perkin I, *1972*, 554.
[10] *A. L. Ham & P. R. Leeming*, J. chem. Soc. (C), *1969*, 523.
[11] *A. J. C. Wilson*, Nature *150*, 151 (1942).
[12] *J. Karle & I. L. Karle*, Acta Cryst. *21*, 849 (1966).
[13] *W. N. White & W. K. Fife*, J. Amer. chem. Soc., *83*, 3846 (1961).
[14] *J. L. Brewbaker & H. Hart*, J. Amer. chem. Soc., *91*, 711 (1969).
[15] *D. J. Reiding & W. Th. Nauta*, Rec., *80*, 399 (1961).
[16] *H. Lettré & K. Wick*, Liebigs Ann. Chem. *603*, 189 (1957).