Pergamon

Tetrahedron 55 (1999) 7893–7906

TETRAHEDRON

Intramolecular Transfer of Axial to Central Chirality in the Strecker Reaction. Synthesis and Stereochemistry of 5,7-Dicyano-6,7-dihydro-5*H*-dibenz[*c,e*]azepines

Miloš Tichý[a], Miloš Buděšínský[a], Jana Günterová[a], Jiří Závada[a]*, Jaroslav Podlaha[b] and Ivana Císařová[b]

[a]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague, Czech Republic*

[b]*Department of Inorganic Chemistry, Charles University, 128 40 Prague, Czech Republic*

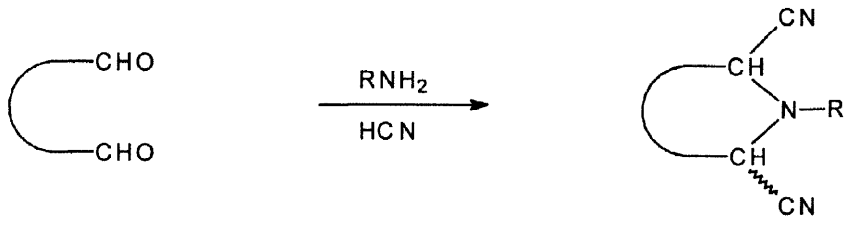
Received 15 February 1999; revised 13 April 1999; accepted 29 April 1999

Abstract: The reaction of unsubstituted as well as 6,6'-disubstituted biphenyl-2,2'-dicarboxaldehydes with HCN and ammonia or methylamine has been investigated. It has been found that the final reaction step, the addition of HCN to the intermediary cyclic imino nitriles, is a strictly diastereoselective process, yielding always only one of the two diastereoisomers of the title products, the stereoselection being controlled by the chiral twist of the biaryl axis. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: NMR, X-ray crystal structures, asymmetric induction, biaryls

Introduction

The Strecker reaction represents one of the most widely explored methods for preparing α-aminonitriles.[1] With dialdehydes, the reaction can lead to cyclic amino dinitriles (Scheme 1). Somewhat surprisingly, very little attention has been paid in the literature to this reaction. In particular, the stereochemistry of the cyclic dinitriles was examined only in a few instances.[2]



Scheme 1

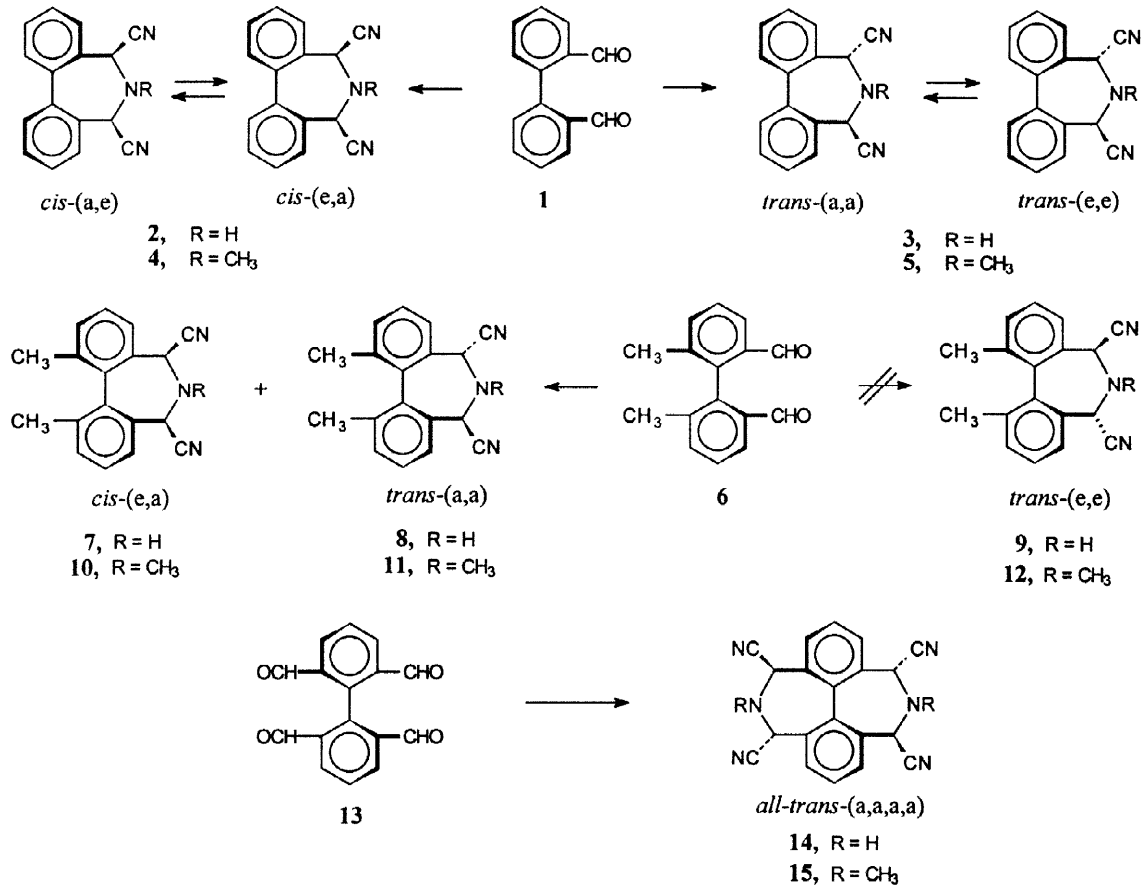
As part of our interest in axially chiral amino acids[3] we have investigated the Strecker reaction with biphenyl di- and tetraaldehydes. In this communication we report results of this investigation which displays some unique stereochemical aspects of the reaction.

PII: S0040-4020(99)00399-3

Results and discussion

Synthesis

The unsubstituted and 6,6'-dimethyl-substituted biphenyl-2,2'-dicarboxaldehydes **1** and **6**, differing in conformational mobility, and the corresponding tetraaldehyde **13** have been subjected to the Strecker reaction (Scheme 2).



Scheme 2. (Only one series of enantiomers shown).

The synthetic procedure employed was similar in all experiments. The di- or tetraaldehyde was treated with an excess of sodium cyanide and ammonium chloride or methylamine hydrochloride in aqueous methanol and the mixture, which in most cases gradually deposited a solid, was stirred for several days at ambient temperature. The *cis*- and *trans*-isomers resulting from the reaction of the dialdehydes **1** and **6** were separated by crystallization and/or column chromatography on silica gel in chloroform – ether mixtures. The only exception was the pair **4** and **5** where the silica gel column proved to be inefficient on the preparative scale. In this particular case, chromatography on a preparative triacetylcellulose column was successful (separating the diastereoisomers but not the antipodes). Prevalence of *trans*- over *cis*-isomers was found in all instances (**3**:**2**=2:1; **5**:**4**=2:1; **8**:**7**=2:1; **11**:**10**=3:2). In the reaction of the tetraaldehyde **13**, the *all-trans* isomer **15** was

obtained as the sole product, without any indication of other isomers. Attempted synthesis of the lower (non-methylated) homologue **14** failed.

Product structure in solution: NMR spectroscopic studies

Structural assignment of proton and carbon-13 NMR spectra (Tables I and II) has been achieved by combining characteristic chemical shift and coupling constant values, selective homonuclear decoupling experiments, difference 1D-NOE and 2D-HMQC spectra.

TABLE I Proton NMR data of compounds **2-5, 7, 8, 10, 11, 15-17** in $CDCl_3$ (for numbering of protons see Table II)

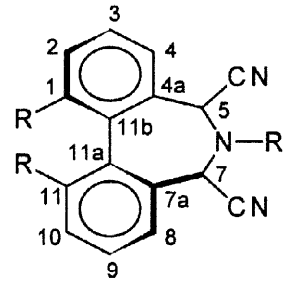
Compound	Config. CN	Aromatic H 1 / 11	2 / 10	3 / 9	4 / 8	>CH-N (J(CH,NH))	NH (N-Me)	Ar-Me
2 [a]	*cis*-(a,e)	7.61 7.61	7.65 7.65	7.70 7.53	7.91 7.39	H(a): 4.72 (7.8) H(e): 5.07 (4.1)	3.15	--
3 [a]	*trans*-(a,a)	7.68	7.71	7.56	7.45	H(e): 5.12 (4.6)	3.28	--
3 [a]	*trans*-(e,e)	7.55	7.64	7.60	7.85	H(a): 4.60 (9.0)	3.10	--
4 [a]	*cis*-(a,e)	7.65 7.62	7.67 7.64	7.71 7.54	7.91 7.38	H(a): 4.35 H(e): 4.78	2.76	--
5 [a]	*trans*-(a,a)	7.69	7.72	7.52	7.44	H(e): 4.77	2.80	--
5 [a]	*trans*-(e,e)	7.58	7.65	7.60	7.84	H(a): 4.28	2.72	--
7	*cis*-(e,a)	-- --	7.48 7.44	7.51 7.38	7.68 7.14	H(a): 4.46 (7.6) H(e): 4.92 (4.0)	3.15	2.21 2.24
8	*trans*-(a,a)	--	7.48	7.42	7.19	H(e): 4.93 (3.9)	2.91	2.26
10	*cis*-(e,a)	-- --	7.48 7.45	7.50 7.38	7.66 7.12	H(a): 4.12 H(e): 4.63	2.58	2.26 2.22
11	*trans*-(a,a)	--	7.49	7.42	7.17	H(e): 4.58	2.91	2.27
15	*trans*-(a,a,a,a)	--	7.70	7.62	7.70	H(e): 4.82	2.83	--
16	(e)	-- --	7.29 7.43	7.38 7.44	7.74 7.34	H(a): 4.77 [b] -CH=N: 8.37 [b]	--	2.10 2.30
17	(a)	-- --	~7.30 ~7.47	~7.30 ~7.47	~7.24 ~7.40	H(e): 5.81 -CH=N: 8.49	--	2.32 2.16

[a] Measured at –40 °C, other compounds at 20 °C; [b] J(CH-N=CH) = 1.5 Hz.

Proton NMR spectra of *unsubstituted* dinitriles **2-5** taken at room temperature (20 °C) showed typical features of time-averaged spectra under medium rate of conformational exchange (equilibrium). The alicyclic

CH-CN protons gave one very broad signal and the signals of aromatic protons also showed larger or smaller line broadening effects (see spectra of compounds **2** and **3** in Fig. 1). Severe line broadening effects, even obscuring the detection of some carbon atoms, were observed in the ^{13}C NMR spectra. To obtain more information about structure and dynamics we measured NMR spectra in the temperature range –40 to +50 °C.

TABLE II Carbon-13 NMR data of compounds **2-5, 7, 8, 10, 11, 15-17** in $CDCl_3$



Compound	Config. CN	Aromatic –CH= 1 / 11	2 / 10	3 / 9	4 / 8	Aromatic >C= 4a/7a	11b/11a	1/11	>CH-N 5 / 7	-CN 5 / 7	N-Me	Ar-Me 1 / 11
2 [a]	*cis*-(a,e)	129.34	130.88	129.31	126.82	138.50	129.47	--	47.98	117.21	--	--
		129.38	130.88	129.31	128.90	138.63	129.76	--	49.72	118.11		
3 [a]	*trans*-(a,a)	130.45	131.25	129.60	128.66	139.06	128.90	--	49.33	118.56	--	--
3 [a]	*trans*-(e,e)	129.41	129.88	129.60	126.70	137.99	128.66	--	48.46	117.04	--	--
4 [a]	*cis*-(a,e)	130.00	130.97	129.06	127.82	138.44	127.70	--	55.24	115.79	40.09	--
		129.46	130.97	129.18	128.77	138.72	128.09	--	57.50	116.82		
5 [a]	*trans*-(a,a)	129.91	131.31	129.30	128.38	138.74	128.65	--	56.89	116.22	41.97	--
5 [a]	*trans*-(e,e)	129.19	130.46	128.55	127.70	138.02	127.10	--	55.95	116.70	37.75	--
7	*cis*-(e,a)	--	132.30	129.62	123.62	138.25	130.22	135.64	48.15	117.39	--	19.61
		--	132.21	129.14	126.21	137.70	130.70	136.26	49.67	117.44		19.42
8	*trans*-(a,a)	--	132.40	129.41	126.39	138.77	131.03	136.65	49.17	117.86	--	19.38
10	*cis*-(e,a)	--	132.47	129.13	124.69	138.25	128.51	135.88	55.18	114.98	39.48	19.68
		--	132.29	128.66	126.87	137.63	128.91	136.06	57.56	117.03		19.49
11	*trans*-(a,a)	--	132.53	129.13	126.95	138.77	129.69	136.38	56.88	115.50	41.62	19.42
15	*trans*-(a,a,a,a)	--	132.11	131.74	132.11	135.80	130.21	135.80	56.69	114.72	42.18	--
16	(e)	--	132.04	128.05	125.12	138.12	132.93	137.66	55.42	118.90	--	20.02
		--	131.11	127.62	122.01	137.33	132.67	138.04	162.85			19.97
17	(a)	--	132.56	127.99	125.1	138.57	133.85	138.21	53.25	115.66	--	19.97
		--	131.43	127.94	124.88	137.40	133.20	138.18	165.57			19.84

[a] Measured at –40°C, other compounds at 20 °C.

High temperature spectra in general showed sharpening of the signals on the way to fast exchange-rate limit. Much more information could be derived from low temperature spectra under slow exchange conditions. Due to the different symmetry of compounds with *cis*- and *trans*-relation of the nitrile groups the low temperature spectra of the *cis*-derivatives **2** and **4** correspond to an equilibrium between two symmetrically

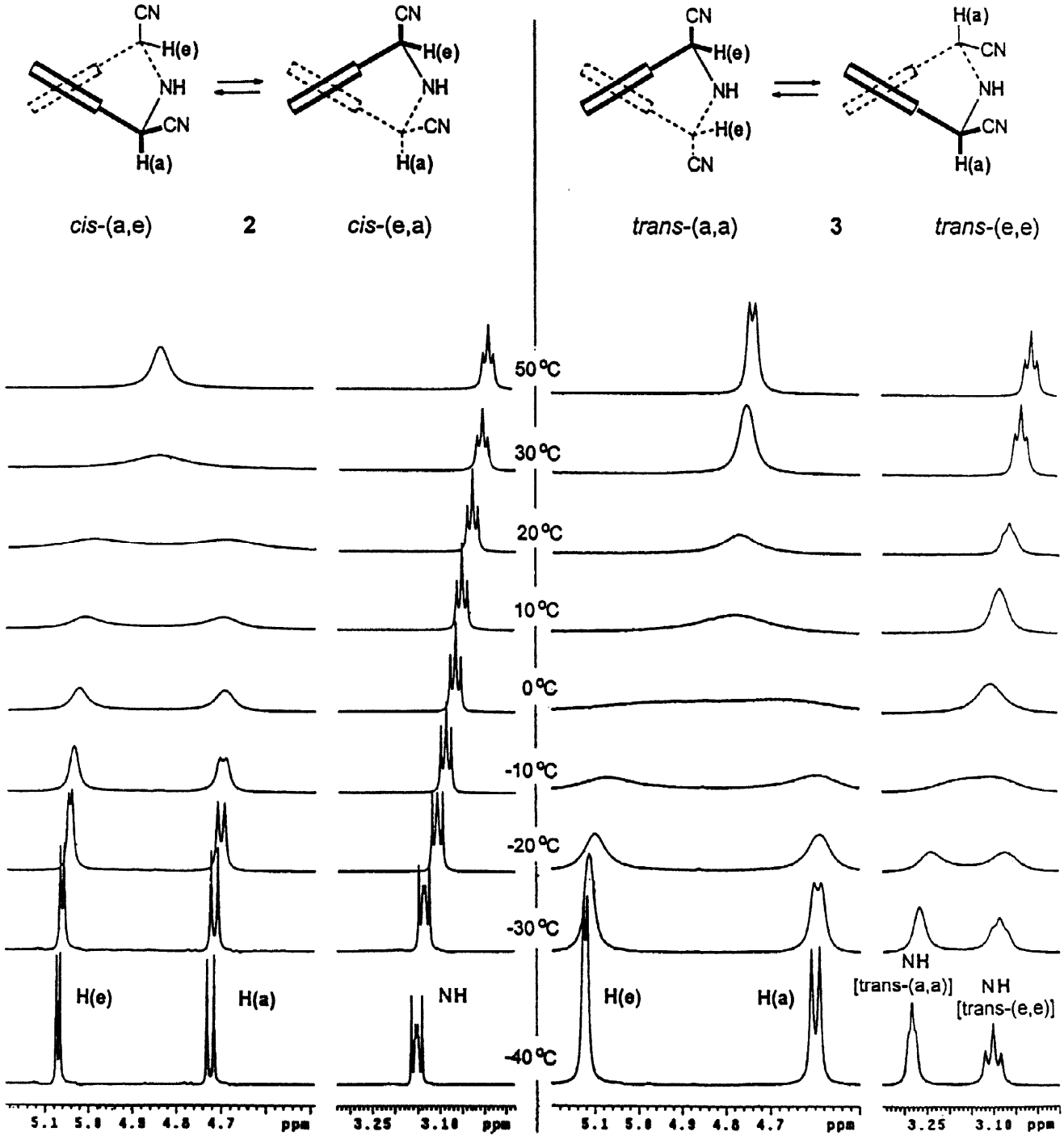


Fig. 1 Temperature dependence of ^{1}H NMR spectra of compounds **2** and **3** in $CDCl_3$ (only >CH-CN and NH protons are shown).

equivalent forms both with one axial- and one equatorial nitrile group. As a result, two different CH-CN signals but only one NH or N-CH_3 is observed in **2** (see Fig.1) or **4**. On the other hand, low temperature spectra of the *trans*-isomers **3** and **5** manifest the presence of two conformers, one with two axial and another with two equatorial nitrile groups, in a ratio close to 1:1 (*trans*-(a,a): *trans*-(e,e) = 53:47 in **3** and 45:55 in **5** at –40 °C). The signals due to the diaxial and diequatorial conformers can be assigned on the basis of J(CH,NH) (4.7 and 9.0 Hz, respectively, in **3**) and different chemical shifts of the CH-CN protons (5.12 and 4.60 ppm in **3** and 4.77 and 4.28 ppm in **5**).

In contrast, all the *6,6'-disubstituted* dinitriles **7, 8, 10** and **11** (as well as the other 6,6'-disubstituted derivatives **15-17**) provided "normal" NMR spectra with sharp lines indicating the presence of a single conformer in solution. The characteristic difference between the *cis*-isomers **7, 10** and *trans*-isomers **8, 11**, resulting from the different symmetry of the molecule, was easily recognized. The absence of any two-fold symmetry axis in the *cis*-derivatives **7, 10** leads to the observation of a single signal for each proton and carbon atom in the molecule. On the other hand, the presence of a two-fold axis passing through the amino nitrogen atom and the center of the phenyl-phenyl bond reduces the number of signals in the *trans*-derivatives **8, 11** to a half.

NMR spectra of the single isolated tetranitrile **15** showed still higher symmetry. The additional two-fold axis coincident with the phenyl-phenyl bond further reduces the number of signals (one signal is observed for all four alicyclic CH protons and carbons, aromatic protons in *meta*-positions as well as for four nitrile carbons, and aromatic carbons in *ortho*- and *meta*-positions). From the two possible structures fitting the above symmetry criteria (all-*trans*-(e,e,e,e) and all-*trans*-(a,a,a,a)), the latter was assigned to tetranitrile **15** by comparison of chemical shift of the CH-CN proton (δ 4.82 in **15**) with that of the corresponding conformer of dinitrile **5** (δ 4.77 in *trans*-(a,a) and 4.28 in *trans*-(e,e)).

Distinguishing between isomeric imines **16, 17** was achieved from difference proton 1D-NOE spectra. In accord with the interproton distances derived from analysis of molecular models, the structure **16** (equatorial nitrile group) was assigned to the isomer where olefinic N=CH proton showed NOE with both the nearest aromatic proton and alicyclic CH-CN proton, while the structure **17** (with an axial nitrile group) was assigned to the isomer where NOE between olefinic N=CH and CH-CN proton is absent and they both show NOE contacts to their nearest aromatic proton only. The assignment is supported by the allylic coupling J(HC=N-CH(CN)) which in **16** (axial >CH-CN proton) is 1.5 Hz and in **17** (equatorial >CH-CN proton) is ~0 Hz.

Barriers to rotation

The observation of separate signals of the individual conformers in low temperature ^{1}H NMR spectra and estimation of coalescence temperature allowed us to calculate free energy of activation $\Delta G^{\#}$ for compounds **2 – 5** using the equation $\Delta G^{\#} = R.T_c\,[22.96 + \ln (T_c / \delta\nu)]$, where R is the universal gas constant, T_c is the coalescence temperature and $\delta\nu$ is the frequency difference between the signals (the most separated signals of the CH-CN

protons were used for the calculation). The *cis*-derivatives **2** and **4** showed slightly higher T_c (25 and 20 °C), and consequently $\Delta G^{\#}$ values (13.9 and 13.6 kcal/mol), in comparison with the *trans*-derivatives **3** and **5** (T_c = 10 and 5 °C; $\Delta G^{\#}$ = 12.9 and 12.8 kcal/mol). Only slightly lower value of $\Delta G^{\#}$ (12.3 kcal/mol) was found for the structurally similar dibenzo[*a,c*]cycloheptadiene.[7]

Another dynamic process occurring in compounds **2-5, 7, 8, 10-12** and **15** in solution is the inversion at the nitrogen atom. Single pyramidal configuration was found by X-ray analysis in compounds **3, 5** and **8** in crystal (*vide infra*). The NMR spectra show only one NH and/or N-CH_3 signal for each conformer indicating that the inversion at the nitrogen atom is fast on the NMR time scale even at low temperature (-40 °C).

Product structure in solid phase: single crystal X-ray diffraction

Whereas the dimethyl derivative **8** crystallizes as a racemate in the centrosymmetric space group $P\bar{1}$, crystals of the non-methylated compound **3** in the chiral space group $P2_1$ are composed of one enantiomer. Figures 2 and 3 show the perspective view of the molecular structures with atom labelling, the *S*-enantiomer being arbitrarily chosen in both cases. The two symmetry-independent molecules in the unit cell of **3** are almost identical in their geometry (within two estimated standard deviations of the distances and angles) and therefore only one of them is depicted and discussed. All distances and angles are unexceptional and deserve no comment.

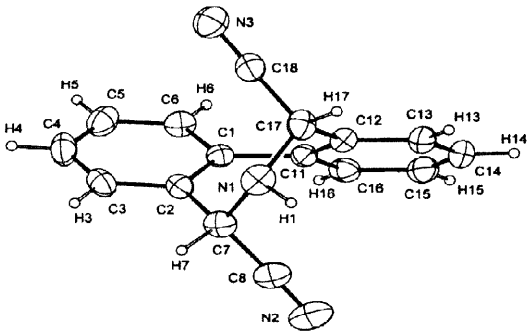


Fig. 2. Perspective view of one of the two crystallographically independent molecules of compound **3** with atom labelling (ORTEP, 30% probability ellipsoids)

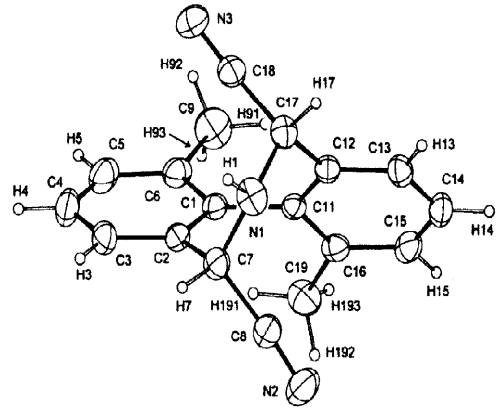


Fig. 3. Perspective view of the molecule of **8** with atom labelling (ORTEP, 30% probability ellipsoids)

Comparison of the structures of **3** and **8** revealed that the presence of the methyl groups attached to the aromatic nuclei in **8** has no significant influence on the overall conformation as shown in Fig. 4 where the two molecules are superimposed using one of the phenyl rings as reference. As expected, the most prominent difference is in the dihedral angle of the mean aromatic planes amounting to 57.26(6)° for the sterically more crowded dimethyl derivative **8** and 46.33(9)° for the non-methylated analogue **3**. The conformation of the

seven-membered heterocyclic ring, bearing mutually *trans*-disposed, slightly bent nitrile groups, is also very similar in both compounds. The ring atoms of each phenyl group are coplanar within better than 0.021 Å but there are remarkable differences in the displacement of the pivot carbon atoms of the substituents from these planes. For the non-methylated derivative **3** the pivot atoms of the seven-membered ring lie almost within the parent phenyl plane (distance from the plane: 0.042; 0.024 Å). In contrast, the corresponding distances in the dimethyl analogue **8** are 0.129; 0.155 Å and, moreover, 0.161; 0.180 Å for the appropriate methyl carbon atoms. The pivot atom of the seven-membered ring and the methyl carbon atom are always located on the same side of the phenyl plane. In both crystals, no intermolecular contacts shorter than those at the usual van der Waals level were observed.

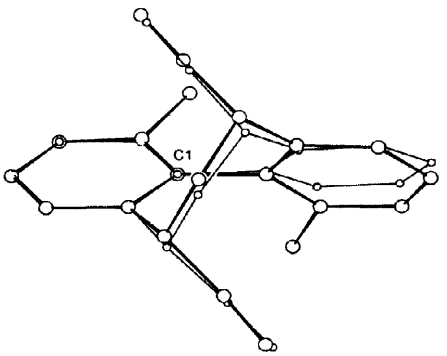


Fig 4. Superposition of the molecules of **3** and **8** with one phenyl ring as the reference

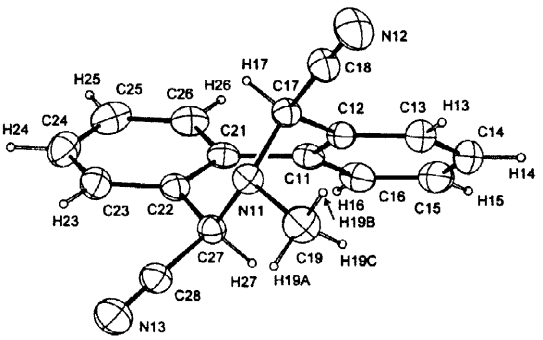


Fig. 5. Perspective view of one of the independent molecules of **5** with atom labelling (ORTEP, 30% probability ellipsoids)

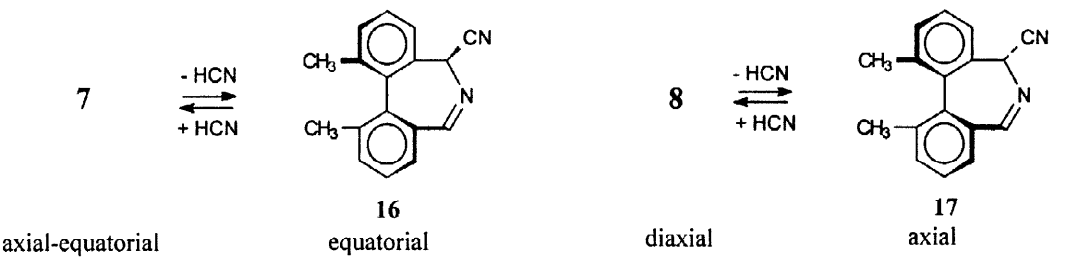
The N-methyl derivative **5** is racemic and crystallizes in the centrosymmetric space group $P2_1/c$ with two crystallographically distinct independent molecules which differ only marginally in their overall geometry. In Fig. 5 the perspective view of one of them is depicted with atom labelling. The average molecular parameters closely resemble those of the NH-derivative **3** (the crystals of which in space group $P2_1$ are, however, composed of a single enantiomer). Thus, for example, the dihedral angle of the mean phenyl planes is 46.15(7)°, compared to 46.33(9)° in **3**. The major, and principal, difference between the two structures is in the arrangement of the almost linear (within 1.5°) nitrile substituents which are *trans-axial* in **3** but *trans-equatorial* in **5**. One of the reasons may be the crystal packing which for the two compounds is entirely different.

Acidobasic transformations

Attempts to isomerize the prepared dinitriles thermally or with bases were unsuccessful. Heating in toluene (80 °C, without or with triethylamine) or mesitylene (150 °C) gave no isomerization whereas treatment with 0.5M NaOMe/MeOH at r.t. or with 0.2 M KOH/EtOH under reflux resulted in extensive decomposition

that hindered the HPLC measurements. In contrast, replacement of bases with a Lewis acid provided clear-cut, though not easily predictable results.

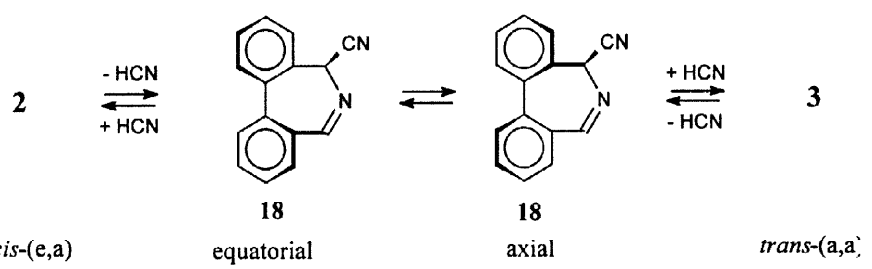
It has been found that treatment of the conformationally rigid compounds **7** and **8** with $ZnBr_2$ in dichloromethane brought about no isomerization but evidently led to a rapid equilibrium between the individual dinitrile and the corresponding imino compound arising by loss of hydrogen cyanide (Scheme 3).



Scheme 3 (Only one enantiomer shown)

The axial-equatorial dinitrile **7** and its diaxial isomer **8** gave distinctly different imines (**16** and **17**, respectively), but no isomerization of **7** to **8** (and *vice versa*) has been observed. It indicates that *the elimination of HCN is stereoselective and proceeds exclusively in the* anti-*fashion so that only the axial CN group can be involved.* Moreover, and much more interestingly, this observation demonstrates that the reverse reaction, *the* anti-*addition of HCN proceeds exclusively from one side of the C=N bond* and represents thus *a diastereoselective process.*

At apparent, but not real, discord with this situation is the behaviour of the non-methylated, conformationally mobile, isomers **2** and **3**. Each of the two isomers upon the same treatment gave the same equilibrium mixture of the imine **18** and of *both* diastereoisomers **2** and **3**. Assumedly, in this particular case, a rapid conformational equilibrium takes place between the equatorial and the axial conformer of the imine **18** which on diastereoselective addition of HCN gives rise to the respective isomers **2** and **3** (Scheme 4).

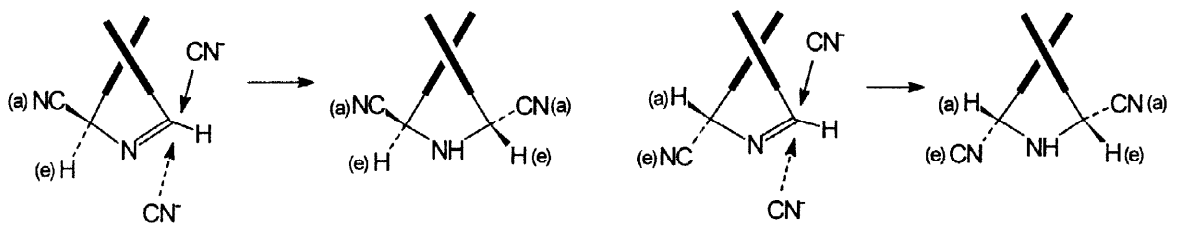


Scheme 4 (Only one series of enantiomers shown)

In this way, the easy interconversion between the two alternative conformers of the imine **18** occurring by low-energy torsion around the biphenyl axis, rather than non-selectivity of the elimination-addition reaction, is responsible for the observed isomerization of the conformationally mobile amino nitriles **2** and **3.**

On the origin of the diastereoselectivity of the HCN addition

The observation that the *anti*-addition of HCN to the imino nitriles **16** and **17** proceeds practically exclusively from one side of the C=N bond raises an immediate question concerning the origin of this diastereoselectivity. It is seen that in both isomeric imines **16** and **17** the addition takes place from the same direction, irrespective of the orientation (axial or equatorial) of the neighbouring cyano group (Scheme 5).



Scheme 5

The configuration at the CN-bearing carbon atom is thus apparently unimportant and the chiral biaryl axis must be the responsible factor controlling the diastereoselectivity of the addition. It is thus justifiable to conclude that *the addition of HCN proceeds with an intramolecular transfer of axial into central chirality.*[5]

Two complementary experiments have been performed, demonstrating a broader significance of this conclusion. In the first experiment, stability of the individual isomeric amino nitriles **7** and **8** has been examined specifically under conditions of the Strecker reaction. It has been found that both nitriles remained entirely unchanged even after 15 days of standing at room temperature. In the other experiment, the individual imines **16** and **17** have been subjected to the specific conditions of the Strecker reaction. Upon treatment with ammonium chloride and sodium cyanide in aqueous methanol at room temperature, the imine **16** yielded exclusively the dinitrile **7** whereas imine **17** gave solely the dinitrile **8**. In both cases, the reaction was clean and rapid, the axial imine **17** reacting about 7 times faster than the equatorial isomer **16**.

The results of the two experiments thus demonstrate that the above conclusions concerning the intramolecular transfer of axial to central chirality are also valid for the Strecker reaction.

Experimental

Proton and carbon-13 NMR spectra were measured on a Varian UNITY-500 instrument (^{1}H at 500 MHz; ^{13}C at 125.7 MHz frequency) at room temperature (~20°C) in $CDCl_3$ solution and referenced to internal tetramethylsilane (^{1}H) or solvent signal (^{13}C; δ ($CDCl_3$) = 77.0 ppm). Temperature dependence of NMR spectra of conformationally flexible compounds **2** – **5** was studied in the range –40°C to +50°C. Selective homonuclear decoupling, 2D-COSY spectra and difference 1D-NOE spectra have been used for structural assignment of proton signals. Carbon-13 signals were assigned using chemical shifts, signal multiplicities (distinguishing between methine and quaternary aromatic carbons were obtained from "attached proton test" and partially relaxed spectra) and/or 2D-HMQC experiments. FT-IR spectra were taken on a Bruker IFS-88 spectrometer by the KBr technique and mass spectra were obtained with a ZAB-SEQ instrument.HPLC analyses were carried out

on a 250 x 4.5 mm Partisil 10 column (gradient 20% EtOAc in light petroleum // 1%EtOAc/min // 100% EtOAc; flow rate 1 ml / min, detection at 270 nm). Analytical samples were processed as follows: the sample of the reaction mixture was partitioned between water and dichloromethane, washed with water and dried. After evaporation, the residue was dissolved in ethyl acetate and injected into the chromatograph.

cis- *and* trans-*5,7-Dicyano-6,7-dihydro-5*H-*dibenz[*c,e*]azepine* ***2 and 3***

To a stirred solution of ammonium chloride (1.6 g, 30.2 mmol), sodium cyanide (1.50 g, 30.6 mmol) in water (10 ml) was added at r.t. dialdehyde **1** (1.83 g, 8.7 mmol) in methanol (20 ml). After 1 h the originally clear solution began to deposit a solid. The mixture was stirred at r.t. for 3 days and then diluted with water and extracted several times with chloroform. The combined organic extracts were washed with water and dried. Evaporation of the solvent gave 1.66 g (78%) of a 1:4 mixture of *cis*- and *trans*-diastereoisomers **2** and **3** (HPLC). Two crystallizations from ethanol afforded 734 mg (34%) of the pure *trans*-isomer **3** as colourless needles m.p. 203-205 °C (decomp.). IR 3309 (NH), 2233, 2224 (CN), 1604, 1570, 1485 cm^{-1} (arom.). For ^{1}H and ^{13}C NMR data see Tables I and II. MS (FAB): 246 (M + 1), 219 (M - CN, base peak). Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.16; H, 4.62; N, 16.93. Mother liquors from the crystallization were subjected to chromatography on silica gel in chloroform-ether (4:1), the *cis*-isomer being eluted first (in contrast to the HPLC, *vide supra*). The separation was not very good and only a small amount (55 mg; 2.6%) of the pure *cis*-isomer as white crystals, m.p. 216-218 °C (ethyl acetate) was obtained. Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.24; H, 4.54; N, 17.13. For ^{1}H and ^{13}C NMR data see Tables I and II.

cis- *and* trans-*5,7-Dicyano-6-methyl-6,7-dihydro-5*H-*dibenz[*c,e*]azepine* ***4 and 5***

A solution of dialdehyde **1** (420 mg, 2 mmol) in methanol (10 ml) was added to a solution of methylamine hydrochloride (670 mg, 10 mmol) and sodium cyanide (500 mg, 10 mmol) in water (2 ml). After stirring at r.t. for 2 days, the mixture was partitioned between water and chloroform, the organic layer was washed with water, dried and the solvent evaporated. The obtained crude mixture (508 mg; 98%) of **4** and **5** (1:3) was purified by chromatography on silica gel. Several crystallizations from ethanol afforded 255 mg (49%) of **5**, as colourless needles, mp. 162-164°C. IR 2249 (CN), 1603, 1567, 1479 cm^{-1} (arom.). Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 79.08; H, 5.18; N, 16.14. For the NMR data see Tables I and II. Combined mother liquors were taken down and part of the residue (320 mg) was chromatographed on triacetylcellulose in ethanol (column length 50 cm, diameter 3 cm; injections: 100 mg and 220 mg dissolved in 5 ml of warm ethanol, flow rate 3 ml/min). Evaporation of the first fraction and crystallization from ethanol gave 28.4 mg of cis-isomer **4** as white crystals, mp. 141-143 °C. IR 2250, 2240 (CN), 1600, 1568, 1482 cm^{-1} (arom.). Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.64; H, 5.03; N, 15.96. For the NMR data see Tables I and II.

cis- *and* trans-*5,7-Dicyano-1,11-dimethyl-6,7-dihydro-5*H-*dibenz[*c,e*]azepine* ***7 and 8***

A solution of dialdehyde **6** (1.41 g, 5.9 mmol) in methanol (35 ml) was added to a solution of ammonium chloride (1.5 g, 28.3 mmol) and sodium cyanide (1.44 g, 29.4 mmol) in water (7 ml). After stirring at r.t. for 5 days, the mixture was partitioned between water and chloroform and the organic layer was washed with water, dried and the solvent evaporated. The residue, consisting of a 1 : 2 mixture of *cis*- and *trans*-isomers, was chromatographed on silica gel (200 g) in chloroform-ether (1:1), affording 457 mg (28%) of the *cis*-isomer **7** and 766 mg (48%) of the *trans*-isomer **8**. Total yield 76%.

cis-*Isomer 7*: colourless crystals, m.p. 224-227 °C (decomp.). IR 3302 (NH), 2236, 2249 (CN), 1596, 1470 cm^{-1} (arom.). ^{1}H and ^{13}C NMR data see Tables I and II. MS(FAB)-HR: 274.1269, for $C_{18}H_{16}N_3$ (M + 1) calculated: 274.1344. Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.37. Found: C, 79.41; H 5.49; N, 15.53.

trans-*Isomer 8*: yellowish crystals, m.p. 216-222 °C (methanol). IR 3347 (NH), 2221, 2231 (CN), 1571, 1598 cm^{-1} (arom.). For ^{1}H and ^{13}C NMR data see Tables I and II. MS(FAB)-HR: 274.1217, for $C_{18}H_{16}N_3$ (M + 1) calcd: 274.1344. Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N 15.37. Found: C, 79.01; H 5.57; N, 15.34.

cis- *and* trans-*5,7-Dicyano-1,6,11-trimethyl-6,7-dihydro-5*H-*dibenz[*c,e*]azepine* ***10 and 11***

A solution of dialdehyde **6** (546 mg, 2 mmol) in methanol (10 ml) was added to a stirred solution of methylamine hydrochloride (670 mg, 10 mmol) and sodium cyanide (500 mg, 10.2 mmol) in water (2 ml). After

stirring for 2 days, the mixture was partitioned between water and chloroform, the organic layer was washed with water and dried. Evaporation of solvent gave a crude product (**10** : **11** = 2:3) which was chromatographed on silica gel (100 g) in chloroform-ether (5:1). The separated stereoisomers were then obtained pure on crystallization from ethanol.

cis-*Isomer* ***10***: colourless needles, m.p. 212-213 °C, yield 121 mg (21%). IR 2232, 2247 (CN), 1594, 1469 cm^{-1} (arom.). For NMR data see Tables I and II. MS-FAB: 288 (M + 1). Anal. Calcd. for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.14; H, 6.04; N, 14.60.

trans-*Isomer* ***11***: yellowish crystals, m.p. 233-237 °C, yield 227 mg (39.5 %). IR 2229, 2238 (CN), 1583, 1596 cm^{-1}. For NMR data see Tables I and II. MS-FAB: 288 (M + 1). Anal. Calcd. for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.32; H, 6.04; N, 14.45.

Intermediate fractions, together with mother liquors, gave on evaporation further 134 mg of a mixture of the two isomers, the overall yield thus being 84 %.

all-trans-*5,11-Dimethyl-4,6,10,12-tetracyano-5,6,11,12-tetrahydro-4*H,*10*H-*5,11-diazadibenzo[*ef,kl*]heptalene* ***15***

A solution of tetraaldehyde **13** (532 mg, 2 mmol) in warm methanol (25 m) was added to a stirred solution of sodium cyanide (750 mg, 15.3 mmol) and methylamine hydrochloride (1000 mg, 15 mmol) in water (3 ml) and the mixture was stirred 5 days. The reaction mixture was diluted with water and the precipitated product was collected and washed thoroughly with water. The crude product was boiled briefly with ethanol (5 ml) and after cooling collected on filter. Yield 507 mg (70 %) of white microcrystalline product which according to NMR spectrum was pure and melted at 276-280 °C with decomposition. No other isomers were isolated. IR 2227, 2237 (CN), 1570, 1597 cm^{-1}. For the NMR data see Tables I and II. MS-EI, m/z (rel.%): 364 (100), 338 (65), 310 (45), 306 (68), 296 (37), 281 (86), 270 (80), 252 (31). MS-HR: For $C_{22}H_{16}N_6$ calculated m/z 364.14364; found: 364.14300. Elemental analyses gave consistently erroneous (and differing) results due to non-combustible residue.

*(5*RS*)-5-Cyano-1,11-dimethyl-(*SR*)-5*H*-dibenz[*c,e*]azepine* ***16***

A mixture of dinitrile 7 (200 mg), $ZnBr_2$ (40 mg) and dichloromethane (10 ml) was slowly distilled for about 2 h. The residue was partitioned between dichloromethane and water, the organic phase dried and the solvent evaporated. Chromatography on silica gel in chloroform-ether (1:1) and crystallization from methanol afforded 117 mg (65%) of **16** as white crystals, m.p. 176-177 °C. IR 2252 (CN), 1581 (arom.), 1615 cm^{-1} (C=N). For NMR data see Tables I and II. HPLC (*vide supra*): ret. time 9.5 min. Anal. Calcd. For $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.82; H, 5.93; N, 11.29.

*(5*SR*)-5-Cyano-1,11-dimethyl-(*SR*)-5*H*-dibenz[*c,e*]azepine* ***17***

Dinitrile **8** (200 mg) was treated in the same manner as described above for the isomer **7**; analogous isolation afforded the product **17** (88 mg, 49 %) as white crystals,, m.p. 179-181 °C (methanol-ether). IR 2225 (CN), 1563, 1584, 1596 (arom.), 1626 cm^{-1} (C=N). For NMR data see Tables I and II. MS-HR(FAB): Calcd for $C_{17}H_{15}N_2$ (M+1): 247.1235. Found: 247.1237. HPLC (*vide supra*): ret. time 16 min.

Treatment of dinitrile 2 and 3 with $ZnBr_2$

In a closed vial with septum, dinitrile **2** or **3** (20 mg) was dissolved in dichloromethane (1 ml) and $ZnBr_2$ (10 mg) was added. The mixture was stirred at room temperature and aliquots were taken by means of syringe at hour's intervals and analyzed by HPLC (*vide supra*). After 5 h, no further change in the composition was observed. The reaction mixtures from both the isomers were practically the same and contained about 85% of a new compound of lower retention time (imine **18**), the rest being **2** and **3** in the ratio 48: 52.

Treatment of dinitrile 7 and 8 with $ZnBr_2$

The experiments and analyses were carried out exactly as described for **2** and **3**. After 2 h, no further change in the composition was observed and the reaction mixtures from both isomers **7** and **8** contained, in addition to about 60 % of the corresponding imine (**16** and **17**, respectively), about 40 % of the starting isomer **7** or **8**. On stirring the reaction mixtures at r.t. for several days, the second isomer gradually appeared: after 5 days, the

reaction mixture from **8** contained about 6 % of **7** and the mixture from **7** contained about 10 % of **8** (both percentages were referenced to the actual total content of **7** and **8**).

Attempted equilibration of 7 and 8 under Strecker conditions

A solution of compound **7** or **8** (10 mg) in methanol (5 ml) was added to a solution of sodium cyanide (30 mg) and ammonium chloride (30 mg) in water (0.4 ml). After standing for 15 days, the clear solution contained solely the starting dinitrile without any trace of the other isomer (HPLC).

Reaction of imines 16 and 17 under Strecker conditions

A solution of imine **16** (ret. time 9.5 min; 5 mg) in methanol (0.5 ml) was added to a solution of sodium cyanide (20 mg) and ammonium chloride (20 mg) in water. After stirring at r.t. for 4 h, the mixture contained exclusively the *cis*-dinitrile **7** (HPLC analysis (*vide supra*): ret. time 19 min). Under the same conditions, reaction of imine **17** gave solely the *trans*-dinitrile **8** (ret. time 26 min).

In a comparative experiment, a solution of **16** (2.5 mg) and **17** (2.5 mg) in methanol (1.5 ml) was mixed with a solution of sodium cyanide (10 mg) and ammonium chloride (10 mg) in water (0.5 ml). After 2 min, about 70 % of **17** reacted whereas only 10 % of **16** was consumed (HPLC, *vide supra*).

Single crystal X-ray diffraction analysis

Dinitrile 3: $C_{16}H_{11}N_3$, M = 245.28, monoclinic, space group $P2_1$ (No. 4), a = 7.4872(4), b = 9.9397(9), c = 18.227(1) Å, β = 114.260(5)°, V = 1236.7(2) Å^3, F(000) = 512, D_c = 1.317 g/cm^3 for Z = 4. A colourless parallelepiped of the dimensions 0.40 x 0.26 x 0.22 mm (grown by vapour diffusion of hexane into acetone solution) was measured on a CAD4 diffractometer at 293(2) K (MoK_α radiation, λ = 0.71073 Å). From a total of 1887 reflections measured in the range h = -8 to 7, k = 0 to 10, l = 0 to 19, 1831 were independent (R_{int} = 0.012) and 1483 were regarded as observed according to the $I > 2\sigma(I)$ criterion. Three standard reflections monitored every 1 h showed 3% total decay. Absorption was neglected (μ = 0.081 mm^{-1}). The structure was solved by direct methods (SHELXS86, ref.[8]) and refined by full-matrix least squares based on F^2 (SHELXL93, ref.[9]). The aromatic hydrogens were fixed in calculated positions and assigned the temperature parameters 1.2 of those of their bonding partners; the remaining hydrogens were refined isotropically. The refinement converged to R = 0.0306, wR = 0.0743, GOF = 1.183 for 367 parameters. The final difference map displayed no peaks of chemical significance. The atomic coordinates, bond lengths and angles were deposited by CSD and can be also obtained in the form of standard CIF files as produced by SHELX from the author (J.P.) by e-mail.

Dinitrile 5: $C_{17}H_{13}N_3$, M = 259.31, monoclinic, space group $P2_1/c$ (No. 14), a = 9.374(5), b = 22.020(5), c = 13.183(5) Å, β = 93.740(5)°, V = 2715.4(2) Å^3, F(000) = 1088, D_c = 1.269 g/cm^3 for Z = 8, colourless plate, 0.5 x 0.4 x 0.2 mm, selected from the preparative batch. From a total of 4521 reflections measured in the range h = 0 to 9, k = 0 to 25, l = -15 to 15, 4243 were independent (R_{int} = 0.007) and 3256 were regarded as observed. Three standard reflections monitored every 1 h showed 5 % total decay. Absorption was neglected (μ = 0.077 mm^{-1}), R = 0.0367, wR = 0.0881, GOF = 1.036 for 378 parameters. Other details as for **3**.

Dinitrile 8: $C_{18}H_{15}N_3$, M = 273.33, triclinic, space group $P\bar{1}$ (No. 2), a = 7.5939(5), b = 8.8092(5), c = 11.8737(6) Å, α = 72.236(4)°, β = 87.228(5)°, γ = 72.048(7)°, V = 718.69(7) Å^3, F(000) = 288, D_c = 1.263 g/cm^3 for Z = 2, colourless plate, 0.52 x 0.40 x 0.16 mm, 2520 independent reflections measured in the range h = -8 to 9, k = -9 to 10, l = 0 to 14 (total decay 4%), 1965 of them observed, μ = 0.077 mm^{-1}, R = 0.0366, wR = 0.0963, GOF = 1.051 for 226 parameters. Other details as for **3**.

Acknowledgement

This work was supported by the Grant Agency of the Czech Republic (Grants No. 203/96/0288 and 203/96/0111).

References

1. March J.: "*Advanced Organic Chemistry. Reactions, Mechanisms and Structure*", 4th Ed., p. 965, Wiley 1992, and references cited therein.
2. (a) Takahashi K., Mikajiri T., Kurita H., Ogura K., Iida H.: *J. Org. Chem.* **1985**, *50*, 4372-4375; (b) Bonin M., Chiaroni A., Riche C., Beloeul J.-C., Grierson D.S., Husson H.-P.: *J. Org .Chem.* **1987**, *52*, 382-385; (c) Takahashi K., Saitoh H., Ogura K., Iida H.: *Heterocycles* **1986**, *24*, 2905-2910.
3. This is the tenth of the series of papers dealing with axially chiral biaryl amino acids, their derivatives and analogues; for previous papers see ref. 4.
4. (a) Tichý M., Holanová J., Závada J.: *Tetrahedron:Asymmetry* **1998**, *9*, 3497-3504; (b) Ridvan L., Buděšínský M., Tichý M., Závada J.: *Tetrahedron*, submitted.
5. Only a few examples of an intramolecular transfer of axial into central chirality have been so far recorded in the literature, our pertinent observation concerning the Stevens rearrangement of the axially twisted dihydroazepinium and dihydrothiepinium salts being probably the most recent example (see reference 6).
6. Stará I.G., Starý I., Tichý M., Závada J., Hanuš V.: *J. Amer. Chem. Soc.* **1994**, *116*, 5084-5088.
7. Müllen K., Heinz W., Klärner F.-G., Roth W.R., Kindermann I., Adamczak O., Wette M., Lex J.: *Chem. Ber.* **1990**, *123*, 2349-2371.
8. Sheldrick, G.M. SHELXL-93. Program for Crystal Structure Refinement from Diffraction Data, University of Göttingen, 1993.
9. Sheldrick, G.M. *Acta Crystallogr.* **1990**, *A46*, 467-473.