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THE TERTIARY AMINO EFFECT IN HETEROCYCLIC SYNTHESIS : MECHANISTIC AND COMPUTATIONAL STUDY OF THE FORMATION OF SIX-MEMBERED RINGS

L.C. GROENEN,[a] W. VERBOOM,[a] W.H.N. NIJHUIS,[a] D.N. REINHOUDT,*[a]
G.J. VAN HUMMEL[b] and D. FEIL*[b]

Laboratories of [a]Organic Chemistry and [b]Chemical Physics, University of Twente,
P.O. Box 217, 7500 AE Enschede, The Netherlands

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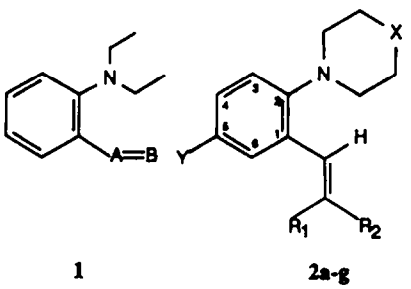
Abstract The mechanism of the ring closure of [2-(1-pyrrolidinyl)phenylmethylene]-propanedinitrile (**2a**) to 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (**3a**) has been studied by kinetic measurements using ^{1}H-NMR spectroscopy. It could be shown that the rate-determining step consists of an intramolecular 1,5 hydrogen transfer, which is accompanied by charge separation within the molecule. The calculated (AM1) and experimental (X-ray) molecular structure of **2a** are in fairly good agreement. In the ground state geometry a 1,5 hydrogen transfer will most likely take place suprafacially. Subsequent rotation of the former vinyl group and C-C-bond formation, leading to a six-membered ring, also take place in a stereochemically defined way.

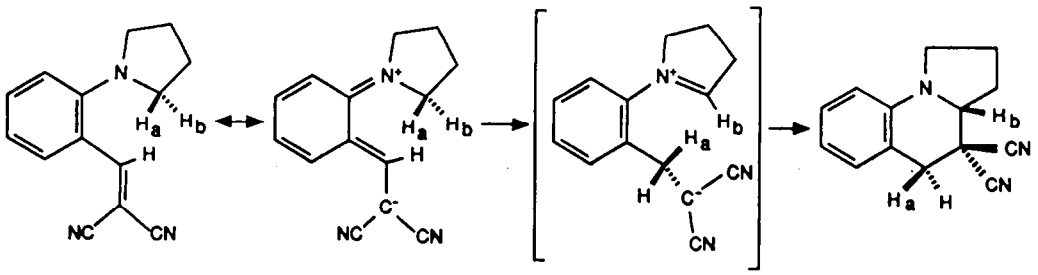
Tertiary anilines that bear an ortho substituent containing a π-bond can be used to synthesize nitrogen containing heterocycles. The reactions of these tertiary anilines have been generalized under the name "*tert*-amino effect" and have been reviewed a number of years ago by Meth-Cohn and Suschitzky.[1] In this review reactions of compounds **1** are described in which A=B contains at least one heteroatom. In our laboratories we have extended these reactions to compounds **1** in which A=B constitutes a vinyl group. The type of reaction that occurs upon heating depends on the substituents of the vinyl group.[2,3] It was shown that when the β-carbon atom of the vinyl moiety bears two electron-withdrawing groups, e.g. CN or COOR (**2**), ring closure to a six-membered ring occurs and compounds **3** are formed.[2] In a previous paper[4] we have described the self-reproduction of chirality that was observed when compound **2a**, in which the vinylic hydrogen atom is replaced by a methyl group and the amino group is the (*S*)-(-)-2-(methoxymethyl)pyrrolidinyl moiety, is cyclized. These results could be explained by assuming the following mechanism for this reaction (Scheme I): in the conformation in which the vinyl moiety points away from the amino group a sigmatropic [1,5]-H shift takes place. The migrating hydrogen atom H_a remains at the same face of the molecule and a dipolar intermediate (**4**) is formed. Subsequently, the former vinyl group rotates around its bond to the phenyl moiety, thus enabling bond formation between the two



1 **2a-g** **3a-g***

	R_1	R_2	X	Y
a	CN	CN	-	H
b	CN	CN	CH_2	H
c	CN	CN	O	H
d	CN	CN	-	NO_2
e	CN	CN	-	Br
f	CN	COOEt	-	H
g	COOMe	COOMe	-	H

* Compound **3** is numbered for the case that X = -



2a 4 3a

Scheme I

oppositely charged carbon atoms to take place, resulting in the formation of the six-membered ring.

In this paper we present the results of a detailed kinetic study of the cyclization of compounds **2**. Besides having determined the kinetic parameters of the ring closure reaction of **2a**, we have investigated the influence on the reaction rate of different electron-withdrawing groups in the vinyl moiety, of different amino groups, of substituents at the 7-position of the aromatic ring, and also of the solvent used. In an attempt to acquire information on the starting conformation and the pathway of the hydrogen transfer, we have performed semi-empirical quantum chemical calculations on the parent molecule **2a**.

RESULTS AND DISCUSSION

Synthesis of the starting materials and of their cyclization products

Compounds **2a-c** and **2g** were synthesized via a Knoevenagel condensation of the appropriate 2-(*N,N*-dialkylamino)benzaldehyde with malononitrile and dimethyl malonate, respectively, following the procedure described earlier.[2] Compounds **2d** and **2f** were synthesized in an analogous way, using 5-nitro-2-(1-pyrrolidinyl)benzaldehyde[5] and malononitrile, or 2-(1-pyrrolidinyl)benzaldehyde and ethyl cyanoacetate as the starting materials, respectively. In the case of **2f** exclusively the *E*-isomer is formed, as can be judged from the chemical shift of the vinylic proton at $\delta = 8.55$ in the ^{1}H-NMR spectrum. This is in full agreement with earlier published results of investigations on the stereochemistry of the Knoevenagel condensation.[6] Compound **2e** was prepared directly from **2a** in quantitative yield by bromination with NBS in DMF at room temperature.[7]

Upon heating in refluxing 1-butanol all compounds **2** afforded the ring closed products **3**. In the case of **2f** ring closure could in principle give two diastereomeric compounds, due to the introduction of an extra asymmetric center upon cyclization. The cyano group can either be on the same or on the opposite face of the molecule relative to the bridge-head hydrogen atom. ^{1}H-NMR and ^{13}C-NMR spectroscopy reveal that only one diastereomer is formed. It is, however, not possible to judge which of the two diastereomers is formed. Therefore

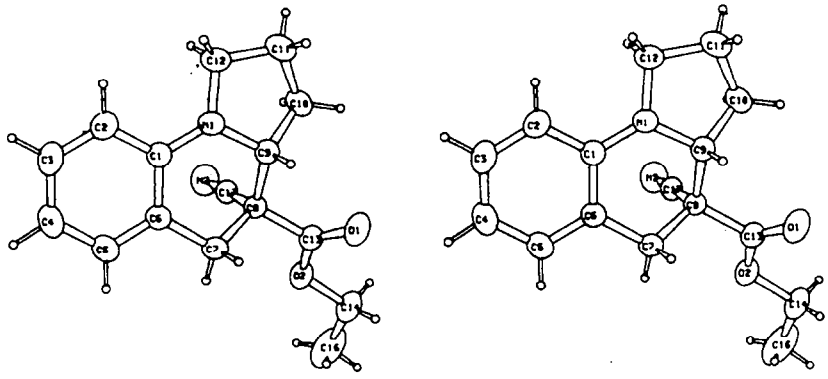


Figure 1. Stereoscopic view of the crystal structure of **3f**

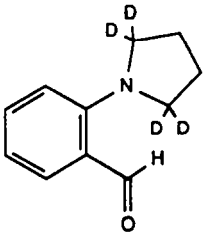
we resolved the crystal structure of the ring closed product **3f** using X-ray spectroscopy. Figure 1 shows clearly that the cyano group is on the opposite face relative to the bridge-head hydrogen atom. This implies that in the time between hydrogen migration and C-C-bond formation the β-carbon atom bearing the cyano and the ester group does not rotate around its bond to the α-carbon atom.

Kinetic Experiments

The reactions were monitored using ^{1}H-NMR spectroscopy. All reactions were carried out in DMSO-d_6. Measurement of the rate of reaction of **2a** at seven different temperatures in the range of 66.1 to 92.8 °C gave the following activation parameters of the reaction (at 90.0 °C) : $\Delta H^{\#} = 22.2 \pm 0.4$ kcal mol^{-1}, $\Delta S^{\#} = -12.0 \pm 1.1$ cal mol^{-1} K^{-1} and $\Delta G^{\#} = 26.6 \pm 0.8$ kcal mol^{-1}. The value of $\Delta H^{\#}$ is very low in comparison with activation enthalpies for other sigmatropic [1,5]-H shifts,[8] especially when we consider that in the transition state of this hydrogen shift the conjugation in the benzene ring must be at least partially destroyed. Indeed, Wehrli et al.[9] have found that the *E/Z*-isomerization of 2-(1-propenyl)toluenes, which could take place via two consecutive [1,5]-H shifts as in the case of the 2-(1-propenyl)anilines and -phenols, has such a high activation enthalpy ($\Delta H^{\#}$ = 49.2 kcal mol^{-1} in decane at 368 °C), that a biradical mechanism might be operative instead. It seems therefore unlikely that in our case the rate-determining step consists of a sigmatropic [1,5]-H shift. This conclusion was strengthened by the observation that the non-aromatic compound **8** reacts much slower than **2a**.[10] This clearly indicates that the aromatic part of the molecule is kept intact during the reaction and that another mechanism must be operative.

To ascertain if a hydrogen atom migrates at all in the rate-determining step, we determined the deuterium kinetic isotope effect of the reaction. For this purpose we synthesized the tetradeuterated compound **6**, starting from 2-fluorobenzaldehyde via a nucleophilic substitution[12] with pyrrolidine-2,2,5,5-d_4[13] to give **5**, followed by a Knoevenagel condensation with malononitrile, analogous to the synthesis of **2a**.[2] We measured a kinetic isotope effect of 3.0 ± 0.3 at 91.2 °C in DMSO-d_6. Although this kinetic isotope effect is the sum of a primary and a secondary kinetic isotope effect, its magnitude is a strong indication that in the rate-determining step of the reaction migration of a hydrogen atom does take place.

From the ^{1}H-NMR and mass spectra of the ring closed compound **7** it is clear that during the cyclization of **6** no deuterium is lost from the substrate. This definitely proofs that the hydrogen (deuterium) migration is an *intra*molecular process.



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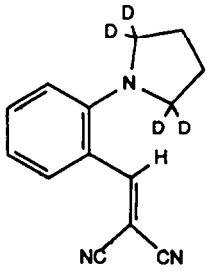

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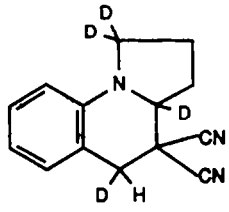
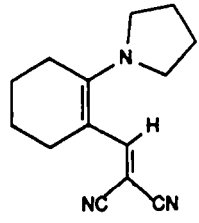


7



8

When the polar solvent DMSO-d_6 is replaced by the apolar toluene-d_8, the reaction rate decreases by a factor of about 150. This rather drastic solvent effect strongly indicates that the transition state of the rate-determining step is highly polar in comparison with the ground state of **2a**. In the apolar toluene-d_8 a polar molecule will be less solvated and stabilized than in DMSO-d_6. Assuming that the mechanism of the reaction is the same in both solvents, the slower reaction in the apolar toluene-d_8 must be due to a less favourable solvation of the transition state relative to the ground state than in the polar solvent DMSO-d_6. This indicates that charge separation takes place in the rate-determining step.

The effects of variations in the structure of **2** on the reaction rate in DMSO-d_6 are summarized in Table 1. Replacement of one or both of the cyano groups by the less electron-withdrawing ester groups (**2f** and **2g**) decreases the reaction rate by factors of 14 and 94, respectively. This can be explained in terms of less delocalization and stabilization of a partial negative charge on the β-carbon atom of the vinyl group in the transition state.

Table 1. Rate constants of the ring closure reactions of compounds 2a-g and 6

compound	solvent	temperature (°C)	rate constant (10^{-4} sec^{-1})
2a	toluene-d_8	93	0.067 ± 0.005
2a	DMSO-d_6	90.4	8.5 ± 0.3
2b	DMSO-d_6	90.3	4.9 ± 0.5
2c	DMSO-d_6	92	0.19 ± 0.05
2d	DMSO-d_6	90.9	0.29 ± 0.03
2e	DMSO-d_6	90.9	8.1 ± 0.7
2f	DMSO-d_6	90.7	0.60 ± 0.02
2g	DMSO-d_6	89	0.078 ± 0.010
6	DMSO-d_6	91.2	2.9 ± 0.2

In the same way introduction of the strongly electron-withdrawing nitro group (2d) decreases the reaction rate by a factor of 30, due to destabilization of the positive charge on the nitrogen atom of the amino substituent in the transition state. The effect of a bromo substituent (2e) is marginal, as it is both an (inductive) electron-withdrawing group and a (mesomeric) electron-donating group.

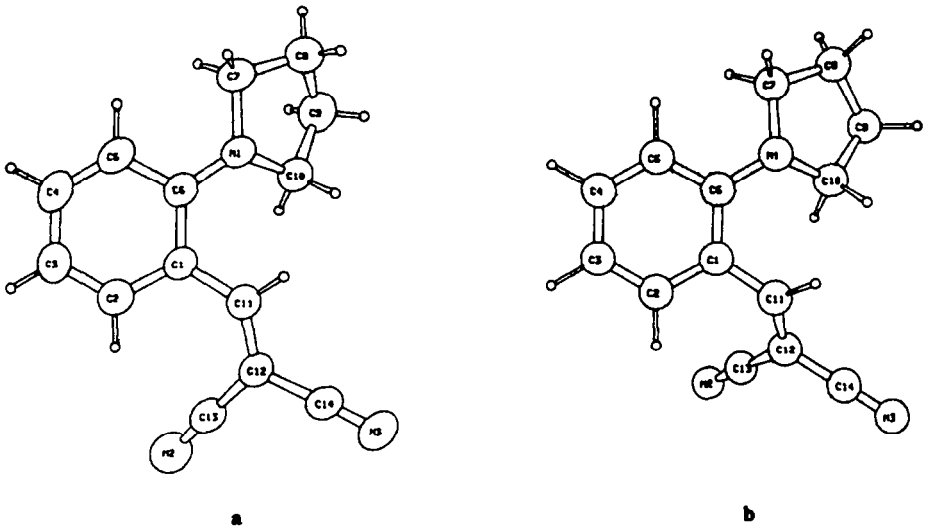
Changing the amino group from pyrrolidinyl to piperidinyl or morpholinyl (2a, 2b, and 2c) decreases the reaction rate by factors of 1.7 and 50, respectively. This can be explained in terms of decreased overlap of the lone pair of nitrogen with the benzene ring,[14] which renders delocalization of the positive charge on the nitrogen atom in the transition state less effective. In the case of morpholine, the transition state is even more destabilized by the presence of an electron-withdrawing oxygen atom in the ring.

Semi-empirical quantum chemical calculations

In order to gain more insight in the stereochemical course of the reaction, we performed some semi-empirical quantum chemical calculations on the ground state of molecule 2a and on a probable reaction path. The calculations were carried out with the AMPAC-programme.[15] The AM1-Hamiltonian was chosen for all calculations, as it seemed superior to both the MINDO/3- and the MNDO-Hamiltonian.[16]

The structure of the ground state of compound 2a was optimized and compared with the structure found by X-ray analysis (Figure 2 and Table 2). Pronounced differences between the calculated and experimental structure are found in the puckering of the benzene ring and the pyrrolidinyl ring, and in the dihedral angle between the benzene ring and the vinyl moiety. Both rings are calculated too flat in comparison with the observed structure. Calculated bond lengths and bond angles are in reasonable agreement with the experimental values. Bonds to hydrogen atoms are invariably calculated 0.10-0.15 Å longer than those found in the X-ray structure, reflecting partly the known fact that hydrogen bond lengths obtained by X-ray spectroscopy are on an average 0.09 Å too short. In the pyrrolidinyl ring the C-C-bond lengths are calculated to be longer and the C-C-C-angles to be larger than in the experimental structure. It seems that the calculated steric interactions in the five-membered ring are relaxed by expanding, instead of bending or puckering the ring. This calculation of a wrong geometry might well be caused by the neglect of the three- and four-center two-electron integrals in the evaluation of the electronic energy of the molecule, which are especially important in small rings. The fact that the vinyl moiety is rotated further away from coplanarity with the benzene ring in the calculated structure than in the X-ray structure, might partly be explained by crystal packing factors, in addition to the obvious errors due to simplifications in the calculations.

We also tried to locate a transition state for the migration of a hydrogen atom from C_{10} to C_{11} (atom numbering according to Figure 2). On pulling a hydrogen atom from C_{10} to C_{11} we noted that in the molecule charge separation takes place, thus lending support to the interpretation of the results of the kinetic measurements. We could, however, not locate a transition state on this reaction path. We are well aware of the



a b

Figure 2. ORTEP[23] drawings of the crystal structure (a) and the calculated structure (b) of **2a**

Table 2. Selected geometry parameters of the observed and of the calculated molecular structure of **2a**

bond lengths (Å)			bond angles (°)			dihedral angles (°)		
	X-ray	AM1		X-ray	AM1		X-ray	AM1
$C_1\,C_2$	1.408	1.405	$C_1\,C_2\,C_3$	122.5	121.6	$C_1\,C_2\,C_3\,C_4$	-1.1	-0.6
$C_2\,C_3$	1.364	1.386	$C_2\,C_3\,C_4$	118.7	119.1	$C_2\,C_3\,C_4\,C_5$	3.9	1.7
$C_3\,C_4$	1.388	1.396	$C_3\,C_4\,C_5$	121.3	120.7	$C_3\,C_4\,C_5\,C_6$	0.1	0.0
$C_4\,C_5$	1.361	1.386	$C_4\,C_5\,C_6$	121.4	121.5	$C_1\,C_6\,C_5\,C_4$	-6.8	-2.8
$C_5\,C_6$	1.419	1.423	$C_1\,C_6\,C_5$	117.2	117.3	$C_2\,C_1\,C_6\,C_5$	9.2	3.9
$C_1\,C_6$	1.428	1.426	$C_2\,C_1\,C_6$	118.3	119.8	$C_3\,C_2\,C_1\,C_6$	-5.5	-2.3
$N_1\,C_6$	1.358	1.400	$N_1\,C_6\,C_1$	123.2	122.6	$N_1\,C_6\,C_1\,C_2$	-171.2	-180.0
$N_1\,C_7$	1.475	1.463	$C_6\,N_1\,C_7$	120.2	118.5	$C_7\,N_1\,C_6\,C_1$	-178.5	168.7
$C_7\,C_8$	1.502	1.536	$N_1\,C_7\,C_8$	103.9	108.3	$C_6\,N_1\,C_7\,C_8$	-171.4	-153.7
$C_8\,C_9$	1.502	1.522	$C_7\,C_8\,C_9$	103.1	105.8	$N_1\,C_7\,C_8\,C_9$	33.0	14.1
$C_9\,C_{10}$	1.511	1.538	$C_8\,C_9\,C_{10}$	103.4	105.9	$C_7\,C_8\,C_9\,C_{10}$	-40.1	-12.4
$N_1\,C_{10}$	1.468	1.460	$N_1\,C_{10}\,C_9$	103.8	108.8	$N_1\,C_{10}C_9\,C_8$	31.4	6.6
			$C_7\,N_1\,C_{10}$	110.1	109.3	$C_6\,N_1\,C_{10}C_9$	145.3	144.8
			$C_6\,N_1\,C_{10}$	125.4	120.6	$C_{10}N_1\,C_6\,C_1$	27.4	29.5
$C_1\,C_{11}$	1.436	1.451	$C_6\,C_1\,C_{11}$	120.6	122.3	$N_1\,C_6\,C_1\,C_{11}$	18.1	4.8
$C_{11}C_{12}$	1.357	1.355	$C_1\,C_{11}C_{12}$	130.1	125.9	$C_6\,C_1\,C_{11}C_{12}$	-167.6	-137.5
$C_{12}C_{13}$	1.427	1.423	$C_{11}C_{12}C_{13}$	125.3	124.0	$C_1\,C_{11}C_{12}C_{13}$	6.5	4.6
$C_{12}C_{14}$	1.435	1.425	$C_{11}C_{12}C_{14}$	121.0	120.6	$C_1\,C_{11}C_{12}C_{14}$	-172.5	-176.4
$N_2\,C_{13}$	1.145	1.163	$N_2\,C_{13}C_{12}$	177.4	179.1	$C_{13}C_{12}C_{11}H_{11}$	-178.5	-178.7
$N_3\,C_{14}$	1.140	1.163	$N_3\,C_{14}C_{12}$	178.6	180.0	$C_{14}C_{12}C_{11}H_{11}$	2.5	0.4
$C_{11}H_{11}$	0.96	1.108	$C_1\,C_{11}H_{11}$	115.2	115.4	$C_6\,C_1\,C_{11}H_{11}$	17.4	45.7

fact that the described procedure (see also Experimental) is not a guaranteed way for finding a transition state. A more thorough search of the AM1 potential surface, however, seemed not appropriate, the more so as the important stabilization of the developing dipole by solvation is not accounted for in the calculations. It is therefore also not at all certain that a transition state does exist on the AM1 potential surface of **2a**.

The calculated and experimental structures of the ground state of **2a**, in which the vinyl moiety is more or less rotated away from coplanarity with the benzene ring, do give some clues for the stereochemical course of the reaction under investigation. When we look at Figure 2 (a or b) we see that in case of a hydrogen transfer from C_{10} to C_{11}, the hydrogen atom below the plane of the molecule will be favoured over the other hydrogen atom bonded to C_{10}. The migration of the first mentioned hydrogen atom will in this case most likely take place suprafacially, although it is not a sigmatropic [1,5]-H shift (*vide supra*). As the vinyl moiety is already partly rotated around C_1-C_{11} when this hydrogen atom is migrating, is seems likely that further rotation of the vinyl moiety to enable bond formation between C_{10} and C_{12}, will proceed in the same direction. As C_{10} and C_{12} are oppositely charged this rotation will be very quick, leaving no time for C_{12} to rotate around its bond to C_{11} (*vide supra*). In this way one enantiomer is formed with the hydrogen atom at C_{10} pointing upwards. In exactly the same way the other enantiomer can be formed, starting from the mirror image of the ground state, in which C_{13}-N_2 is pointing upwards instead of downwards.

CONCLUSION

The results of this kinetic study indicate that the first step in the reaction mechanism of the ring closure of [2-(1-pyrrolidinyl)phenylmethylene]propanedinitrile (**2a**) is an intramolecular 1,5 hydrogen transfer, although not a sigmatropic one. It seems likely, in view of the charge separation that takes place, that the migrating hydrogen atom bears a partially negative charge. When we consider the geometry of the ground state of **2a**, it seems probable that the hydrogen migration will occur suprafacially. Subsequent rotation of the former vinyl group will probably continue in the same direction as this group is already turned when the hydrogen migration takes place. The complete reaction is thus stereochemically well defined. This means that the results described earlier[4] can be satisfactorily explained by this revised mechanism.

EXPERIMENTAL

M.ps were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker WP-80 spectrometer and ^{13}C-NMR spectra were recorded with a Nicolet MT 200 spectrometer, using $CDCl_3$ as a solvent with Me_4Si as an internal standard. Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by A.M. Christenhusz of the Laboratory of Chemical Analysis of the University of Twente.

Compounds **2a-c,g** and **3a-c,g** were prepared as described earlier.[2]

2-Fluorobenzaldehyde was purchased from Janssen Chimica.

2-(1-Pyrrolidinyl-*2,2,5,5-d*$_4$)benzaldehyde (5). To a soln of 2-fluorobenzaldehyde (2.48 g, 0.020 mol) and K_2CO_3 (2.78 g, 0.020 mol) in DMF (10 ml) was added pyrrolidine-*2,2,5,5-d*$_4$[13] (1.50 g, 0.020 mol). The reaction mixture was refluxed for 5 hr under N_2. After cooling the mixture was poored in EtOAc/water (1:1, 20 ml). The water layer was extracted with EtOAc (3 x 20 ml). The combined extracts were washed with sat NH_4Cl aq (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Distillation afforded the pure **7** (17%), b.p. 122°/0.03 mm. ^{1}H-NMR δ: 10.08 (s, 1H, CHO), 7.9-7.6 (m, 1H, H-6), 7.5-7.2 (m, 1H, H-4), 6.9-6.6 (m, 2H, H-3 and H-5), 1.94 (s, 4H, CH_2).

General procedure[2] for the preparation of 2d and 6. To a soln of 5-nitro-2-(1-pyrrolidinyl)-benzaldehyde[5] or **5** (10 mmol) in toluene (15 ml) malononitrile (0.66 g, 10 mmol) was added. In the case of **2d** a few drops of piperidine were added as base. After stirring for 1 hr at room temp the solvent was removed under reduced pressure. The residue was recrystallized from methanol to give the pure compound.

[5-Nitro-2-(1-pyrrolidinyl)phenylmethylene]propanedinitrile (2d). Yield 97%, orange-brown needles, m.p. 165-168°. ^{1}H-NMR δ: 8.53 (d, 1H, J = 2.7 Hz, H-6), 8.18 (dd, 1H, J = 9.5 and 2.7 Hz, H-4), 8.03 (s, 1H, =CH), 6.85 (d, 1H, J = 9.5 Hz, H-3), 3.6-3.3 (m, 4H, NCH_2), 2.3-1.9 (m, 4H, CH_2). ^{13}C-NMR δ: 158.9 (d, =CH), 152.8 (s, C-2), 137.8 (s, C-5), 128.5 and 127.6 (d, C-4 and C-6), 127.8 (s, C-1), 115.4 and 113.6 (s, CN), 114.5 (d, C-3), 82.0 [s, $=C(CN)_2$], 53.0 (t, NCH_2), 26.0 (t, CH_2). IR (KBr) cm^{-1}: 2232 (C≡N), 1606 (C=C). MS: *m/e* 268.096 (M^+, calc.: 268.096). (Found: C, 62.56; H, 4.53; N, 20.90. Calc. for $C_{14}H_{12}N_4O_2$ (M_r 268.277): C, 62.68; H, 4.51; N, 20.88%.)

[2-(1-Pyrrolidinyl-*2,2,5,5-d*$_4$)phenylmethylene]propanedinitrile (6). Yield quant., red crystals, m.p. 92.5-94.5°. ^{1}H-NMR δ: 7.99 (s, 1H, =CH), 7.9-7.7 (m, 1H, H-6), 7.5-7.2 (m, 1H, H-4), 7.0-6.7 (m, 2H, H-3 and H-5), 1.99 (s, 4H, CH_2). ^{13}C-NMR δ: 159.6 (d, =CH), 151.6 (s, C-2), 134.6 (d, C-4), 129.9 (d, C-6), 119.0 (s, C-1), 118.5 and 115.5 (d, C-3 and C-5), 114.9 and 113.2 (s, CN), 77.1 [s, $=C(CN)_2$], 52.5 (quintet, NCD_2), 25.6 (t, CH_2). IR (KBr) cm^{-1}: 2218 and 2209 (C≡N), 1606 (C=C). MS: *m/e* 227.135 (M^+, calc.: 227.136). (Found: C, 73.86; H+D, 5.86; N, 18.59. Calc. for $C_{14}H_9D_4N_3$ (M, 227.304): C, 73.98; H+D, 5.76; N, 18.49%.)

[5-Bromo-2-(1-pyrrolidinyl)phenylmethylene]propanedinitrile (2e). To a soln of **3a** (1.12 g, 5 mmol) in DMF (5 ml) was added a soln of NBS (0.89 g, 5 mmol) in DMF (15 ml).[6] After stirring for 24 hr at room temp sat NH_4Cl aq (20 ml) was added to the soln and the mixture was extracted with EtOAc (3 x 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized

from methanol to afford pure **2e** (quant.) as orange needles, m.p. 139-141°. ^{1}H-NMR δ: 7.82 (s, 1H, =CH), 7.76 (d, 1H, J = 2.2 Hz, H-6), 7.36 (dd, 1H, J = 9.0 and 2.2 Hz, H-4), 6.71 (d, 1H, J = 9.0 Hz, H-3), 3.4-3.1 (m, 4H, NCH_2), 2.2-1.8 (m, 4H, CH_2). ^{13}C-NMR δ: 158.1 (d, =CH), 150.1 (s, C-2), 136.8 (d, C-4), 131.7 (d, C-6), 120.0 (s, C-1), 117.2 (d, C-3), 114.3 and 112.4 (s, CN), 110.1 (s, C-5), 79.2 [s, $=C(CN)_2$], 53.2 (t, NCH_2), 25.8 (t, CH_2). IR (KBr) cm^{-1}: 2260 (C≡N), 1597 (C=C). MS: *m/e* 301.017 (M^+, calc.: 301.021). (Found: C, 55.33; H, 4.02; N, 13.77. Calc. for $C_{14}H_{12}BrN_3$: C, 55.65; H, 4.00; N, 13.91%.)

Ethyl (*E*)-cyano[2-(1-pyrrolidinyl)phenyl]methylene]acetate (2f). A soln of 2-(1-pyrrolidinyl)-benzaldehyde (1.75 g, 10 mmol), ethyl cyanoacetate (1.13 g, 10 mmol) and 3 drops of pyrrolidine in toluene (15 ml) was stirred for 8 hr at room temp. After evaporation of the solvent the residue was purified by column chromatography (silica gel, $CHCl_3$/EtOAc 90:10) to afford the product as a yellow oil, which could not be crystallized (97%). ^{1}H-NMR δ: 8.55 (s, 1H, =CH), 8.0-7.8 (m, 1H, H-6), 7.5-7.2 (m, 1H, H-4), 7.0-6.7 (m, 2H, H-3 and H-5), 4.36 (q, 2H, J = 7.2 Hz, OCH_2), 3.5-3.1 (m, 4H, NCH_2), 2.1-1.7 (m, 4H, CH_2), 1.39 (t, 3H, J = 7.2 Hz, CH_3). ^{13}C-NMR δ: 163.4 (s, COOEt), 155.6 (d, =CH), 151.6 (s, C-2), 133.3 and 130.1 (d, C-4 and C-6), 119.7 (s, C-1), 118.3 and 115.0 (d, C-3 and C-5), 115.9 (s, CN), 99.0 [s, $=C$(CN)(COOEt)], 62.2 (t, OCH_2), 53.0 (t, NCH_2), 25.8 (t, CH_2), 14.2 (q, CH_3). IR (KBr) cm^{-1}: 2220 (C≡N), 1720 (C=O), 1599 (C=C). MS: *m/e* 270.134 (M^+, calc. for $C_{16}H_{18}N_2O_2$: 270.137).

General procedure[3] for the ring closure of 2d-f and 6. Preparation of 3d-f and 7. A soln of **2d-f** or **6** (0.5 g) in 1-butanol (10 ml) was refluxed for 20, 4, 6, and 4 hr, respectively. On cooling a precipitate was formed, which was filtered off and recrystallized from methanol to afford the pure product.

1,2,3,3a,4,5-Hexahydro-7-nitropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (3d). Yield 57%, yellow needles, m.p. 234-239°. ^{1}H-NMR δ: 8.2-7.9 (m, 2H, H-6 and H-8), 6.58 (d, 1H, J = 8.8 Hz, H-9), 3.94 (dd, 1H, J = 5.8 and 3.2 Hz, NCH), 3.8-3.3 (m, 4H, NCH_2 and $ArCH_2$), 2.8-1.9 (m, 4H, CH_2). ^{13}C-NMR δ: 146.7 (s, C-9a), 138.3 (s, C-7), 126.1 and 125.5 (d, C-6 and C-8), 113.9 and 113.2 (s, CN), 112.0 (s, C-5a), 111.1 (d, C-9), 63.0 (d, NCH), 48.4 (t, NCH_2), 37.8 (t, $ArCH_2$), 33.4 [s, $C(CN)_2$], 29.9 and 22.8 (t, CH_2). IR (KBr) cm^{-1}: 2259 (C≡N). MS: *m/e* 268.097 (M^+, calc.: 268.096). (Found: C, 62.00; H, 4.48; N, 20.55. Calc. for $C_{14}H_{12}N_4O_2$ (M_r 268.277): C, 62.68; H, 4.51; N, 20.88%.)

7-Bromo-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (3e). Yield 84%, colourless crystals, m.p. 172-173.5°. ^{1}H-NMR δ: 7.4-7.1 (m, 2H, H-6 and H-8), 6.44 (d, 1H, J = 8.5 Hz, H-9), 3.77 (dd, 1H, J = 7.7 and 5.8 Hz, NCH), 3.6-3.2 (m, 2H, NCH_2), 3.42 (s, 2H, $ArCH_2$), 2.7-1.9 (m, 4H, CH_2). ^{13}C-NMR δ: 141.0 (s, C-9a), 132.0 and 131.4 (d, C-6 and C-8), 115.5, 114.6 and 112.7 (s, C5-a and CN), 113.8 (d, C-9), 109.3 (s, C-7), 62.9 (d, NCH), 48.0 (t, NCH_2), 37.8 (t, $ArCH_2$), 33.7 [s, $C(CN)_2$], 29.9 and 22.8 (t, CH_2). IR (KBr) cm^{-1}: 2226 (C≡N). MS: *m/e* 301.020 (M^+, calc.: 301.021). (Found: C, 55.58; H, 4.04; N, 13.93. Calc. for $C_{14}H_{12}BrN_3$ (M_r 302.181): C, 55.65; H, 4.00; N, 13.91%.)

Ethyl (*cis*)-(±)-4-cyano-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-acetate (3f). Yield 69%, colourless crystals, m.p. 123-125°. ^{1}H-NMR δ: 7.2-7.0 (m, 2H, H-6 and H-8), 6.7-6.5 (m, 2H, H-7 and H-9), 4.30 and 4.27 (ABX_3, 2H, J_{AB} = -10.8, J_{AX} = 7.2, J_{BX} = 7.1 Hz, OCH_2), 3.73 (dd, 1H, J = 8.2 and 5.8 Hz, NCH), 3.6-3.2 (m, 4H, NCH_2 and $ArCH_2$), 2.3-1.9 (m, 4H, CH_2), 1.31 (dd, 3H, J = 7.1 and 7.2 Hz, CH_3). ^{13}C-NMR δ: 168.1 (s, C=O), 142.4 (s, C-9a), 129.0 and 128.4 (d, C-6 and C-8), 116.6 and 115.9 (s, C-5a and CN), 116.5 and 111.5 (d, C-7 and C-9), 63.1 (t, OCH_2), 62.0 (d, NCH), 47.3 (t, NCH_2), 45.2 [s, C(CN)(COOEt)], 37.1 (t, $ArCH_2$), 29.3 and 23.2 (t, CH_2), 14.1 (q, CH_3). IR (KBr) cm^{-1}: 2250 (C≡N), 1742 (C=O). MS: *m/e* 270.135 (M^+, calc.: 270.137). (Found: C, 70.97; H, 6.94; N, 10.27. Calc. for $C_{16}H_{18}N_2O_2$ (M_r 270.334): C, 71.09; H, 6.71; N, 10.36%.)

1,2,3,3a,4,5-Hexahydro-*1,3a,5-d*$_3$-pyrrolo[1,2-*a*]quinoline-*1-d*-4,4-dicarbonitrile (7). Yield 45%, colourless crystals, m.p. 132-142°. ^{1}H-NMR δ: 7.4-7.0 (m, 2H, H-6 and H-8), 6.9-6.5 (m, 2H, H-7 and H-9), 3.48 (d, 1H, J_{HD} = 1.5 Hz, ArCHD), 2.8-1.9 (m, 4H, CH_2). ^{13}C-NMR δ: 142.0 (s, C-9a), 129.2 and 129.0 (d, C-6 and C-8), 117.5 and 112.2 (d, C-7 and C-9), 115.0, 113.4 and 113.0 (s, C-5a and CN), 64.9 (t, NCD), 47.2 (quintet, (dt, ArCHD), 33.8 [s, $C(CN)_2$], 29.8 and 22.6 (t, CH_2). IR (KBr) cm^{-1}: 2250 (C≡N). MS: *m/e* 227.136 (M^+, calc.: 227.136). (Found: C, 73.23; H+D, 5.78; N, 18.31. Calc. for $C_{14}H_9D_4N_3$ (M_r 227.304): C, 73.98; H+D, 5.76; N, 18.49%.)

Kinetic experiments. The kinetic measurements were carried out using ^{1}H-NMR spectroscopy. As a probe for the progress of the reaction, the decreasing integral of the signal of the vinylic hydrogen atom was used. As internal reference signal the integral of the absorption peak of triptycene at δ = 5.60 (DMSO-d_6) was used. All reactions were carried out in DMSO-d_6 to assure that the signal of the vinylic hydrogen atom did not coincide with the aromatic hydrogen atom signals. All measurements were performed on a Bruker WP-80 spectrometer.

In a typical experiment the reacting compound (0.1 mmol) and triptycene (6.35 mg, 0.025 mmol) were dissolved in DMSO-d_6 (0.5 ml). The sealed NMR-tube was put in the thermostated probe and allowed to warm up to the desired temperature. At fixed intervals spectra were recorded and integrated. The temperature was measured once at the end of the reaction, using a thermocouple. The reaction rate constant k was calculated using a polynome fitting programme.

All reactions followed first order kinetics for at least two half lives. Compounds **2d** and **2f** were measured a little shorter in time, approximately 1½ half lives. The results are mentioned in the text and are summarized in Table 1.

Semi-empirical quantum chemical calculations. The calculations were carried out with the AMPAC programme[15] on a VAX 8650 computer. The ground state of **2a** was refined with respect to all 84 internal coordinates, using the AM1-Hamiltonian. The final gradient norm was 0.7.

The reaction path was simulated by pulling one of the hydrogen atoms at C_{10} to C_{11}. At each step on the reaction path the distance between C_{11} and the migrating hydrogen atom was held constant. Only part of the rest of the molecule was optimized at each step, the internal coordinates of the benzene ring with hydrogen atoms and of the hydrogen atoms of the pyrrolidinyl ring were also held constant to reduce computation time.

X-ray structure of [2-(1-pyrrolidinyl)phenylmethylene]propanedinitrile (2a). $C_{14}H_{13}N_3$, triclinic, space group P$\bar{1}$. Cell constants: a = 7.955, b = 9.041, c = 9.103 Å, α = 99.21, β = 109.32 and γ = 99.71° (V = 592.3 Å^3). Z = 2, ρ_c = 1.252 g cm^{-3}.

X-ray diffraction data were collected at 293 K on an Enraf-Nonius CAD4 single crystal diffractometer, using Mo K_α radiation monochromated by a graphite crystal (λ = 0.71069 Å). The lattice parameters were determined by refinement of 25 reflections with the least-squares method. In total, 2093 unique reflections were measured ($-10 \le h \le 10$, $-12 \le k \le 12$, $0 \le l \le 12$) with the $\omega/2\theta$ scanning mode (maximum scan-speed 0.09° sec^{-1}, scan-width 1.0° + 0.34 tg θ). The maximum variation in three standard reflections was 0.3%.

The structure was solved by direct methods[24] and was refined using the full-matrix least-squares procedure,[25] using 1453 reflections with $I > 2\sigma(I)$. All hydrogen atoms were located by difference Fourier maps. The number of parameters refined was 207, including the scaling factor, isotropic extinction factor (final value 3.4×10^{-6}), positional parameters, anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. The weight of each reflection was taken to be $w = 1/\sigma^2(F)$, with $\sigma^2(F) = \sigma^2(I) + (p.F^2)^2$, $p = 0.02$. Scattering factors for non-hydrogen atoms were taken from "International Tables for X-ray Crystallography",[26] for hydrogen atoms the scattering factors of Stewart et al. were used.[27] The refinement converged to a final R-value of 0.035 ($R_w = 0.043$), $(\Delta/\sigma)_{max} = 0.03$.

X-ray structure of ethyl (*cis*)-(±)-4-cyano-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-acetate (3f). $C_{16}H_{18}N_2O_2$, triclinic, space group $P\bar{1}$. Cell constants: $a = 10.150$, $b = 8.988$, $c = 8.357$ Å, $\alpha = 84.84$, $\beta = 72.67$, $\gamma = 74.03°$ ($V = 699.4$ Å^3). $Z = 2$, $\rho_c = 1.284$ g cm^{-3}.

X-ray diffraction data were collected at 293 K on a Philips PW1100 single crystal diffractometer. The total number of unique reflections was 4080 ($-13 \le h \le 14$, $-12 \le k \le 12$, $0 \le l \le 11$), measured with the $\omega/2\theta$ scanning mode (maximum scan-speed 0.1° sec^{-1}, scan width 1.3° +0.7 tg θ). The maximum variation in three standard reflections was 2.3%.

All methods were identical to those reported above for **2a**, using $p = 0.04$ in the weighing-scheme. In the refinement of the 254 parameters 2833 reflections were used with $I > 3\sigma(I)$. The final extinction coefficient was 1.0×10^{-6}. The refinement converged to a R-value of 0.044 ($R_w = 0.059$). The three hydrogen atoms of the methyl group were badly characterized, probably due to thermal motion.

Atomic coordinates and bond lengths for both structures have been deposited with the Cambridge Crystallographic Data Centre. These can be obtained on request from The Director, Cambridge Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K..

Complete lists of positional parameters for all atoms, anisotropic thermal parameters for heavy atoms and isotropic thermal parameters for hydrogen atoms, and lists of bond lengths and bond angles have been deposited as Supplementary Material with the Britisch Library Lending Division, Boston Spa, Wetherby, West Yorks LS23 7BQ, U.K..

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10. Cyclization of compound **8**[11] in refluxing 1-butanol took approximately 2 days, instead of the 2 hours needed for compound **2a** under the same conditions[2] (unpublished results).
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16. AM1 has been introduced[17] as an improved version of MNDO,[18] which was in turn a successor of MINDO/3.[19] We checked the performance of AM1 against those of MNDO and MINDO/3 on two selected problems. Optimization of the sterically crowded cisoid conformation of (*Z*)-1,3-pentadiene revealed that only AM1 gave reasonable results. Both MINDO/3 and MNDO predicted a conformation in which the two double bonds are nearly perpendicular, whereas AM1 arrived at a dihedral angle of 38° between the two double bonds. This geometry is in reasonable agreement with published gas phase structures of some sterically crowded conjugated dienes and trienes.[20] Secondly, we calculated the activation energy for the sigmatropic [1,5]-H shift in (*Z*)-1,3-pentadiene. With AM1, MNDO and MINDO/3 we found a transition state with C_{2v}-symmetry. The calculated activation energies were 39.5, 57.0 and 45.4 kcal mol^{-1}, respectively. The experimental value is 35.4 kcal mol^{-1}.[21] The MINDO/3-value is nearly the same as the value (45.2 kcal mol^{-1}) published earlier by Dewar et al.[22] From these results we can conclude that AM1 seems best suited for calculations on sterically crowded conjugated molecules and on sigmatropic hydrogen shifts.
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