2.5–2.0 (m, 4 H, CH_2), 2.31 (s, 3 H, CH_3); ^{13}C NMR δ 141.8 (s, C-9a), 139.0 and 133.4 (s, Ar C), 130.3, 129.5, and 129.0 (d, Ar C), 119.3 (s, C-5a), 117.7 (d, Ar C), 114.3 and 112.5 (s, CN), 112.0 (d, Ar C), 72.1 (t, CH_2OCH_3), 64.0 [d, NCH (bridgehead)], 59.1 (q, OCH_3), 57.1 and 53.2 [d, $NCH(CH_2OCH_3)$ and $ArCH(C_6H_4CH_3)$], 44.6 [s, $C(CN)_2$], 28.0 and 26.9 (t, CH_2), 21.2 (q, CH_3); IR (KBr) 2260 (CN) cm^{-1}; mass spectrum, *m/e* 357.189 (M^+, calcd 357.184). Anal. Calcd for $C_{23}H_{23}N_3O$ (M_r 357.456): C, 77.28; H, 6.49; N, 11.75. Found: C, 76.91; H, 6.58; N, 11.71.

X-ray Structure Determination of 6n. The crystal structure of **6n** was determined by X-ray diffraction. Crystal data $C_{18}H_{21}N_3O$: triclinic, space group $P\bar{1}$; a = 15.031 (1) Å, b = 8.190 (2) Å, c = 6.938 (1) Å, α = 79.86 (1)°, β = 78.55 (1)°, γ = 94.82 (1)°; V = 817.7 (3) Å^3; Z = 2, d_{calcd} = 1.20 g cm^{-3}; μ = 0.7 cm^{-1}. Reflections were measured in the $\omega/2\theta$ scan mode, using graphite monochromated Mo Kα radiation [scan width (ω) 1.40 + 0.6 tan θ]. The structure was solved by direct methods and refined with full-matrix least-squares methods. A total of 1583 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. The number of parameters refined was 284 [scale factor, extinction parameter, positional parameters of all atoms, and thermal parameters (isotropic for H atoms, anisotropic for others)]. The final R factors were R = 3.6%, R_w = 4.6%. All calculations were done with SDP.[24]

Acknowledgment. This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

(24) Structure Determination Package; Frenz, B. A. and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, 1983.

Registry No. **1a**, 446-52-6; **1b**, 445-27-2; **1c**, 68295-43-2; **2a**, 123-75-1; **2b**, 765-38-8; **2c**, 76946-27-5; **2d**, 110-89-4; **2e**, 109-05-7; **2f**, 1484-80-6; **2g**, 117607-54-2; **3a**, 58028-74-3; **3b**, 117677-92-6; **3c**, 117677-93-7; **3d**, 34595-26-1; **3e**, 117607-55-3; **3f**, 117607-56-4; **3g**, 117607-57-5; **3h**, 70243-84-4; **3i**, 117677-94-8; **3j**, 117677-95-9; **3k**, 39911-06-3; **3l**, 117607-58-6; **3m**, 117607-59-7; **3n**, 117607-60-0; **3o**, 117607-61-1; **3p**, 117607-62-2; **3q**, 117607-63-3; **4a**, 87698-95-1; **4b**, 107743-55-5; **4c**, 107743-57-7; **4d**, 87698-96-2; **4e**, 117607-64-4; **4f**, 117607-65-5; **4g**, 117607-66-6; **4h**, 117607-67-7; **4i**, 117607-68-8; **4j**, 107797-45-5; **4k**, 117607-69-9; **4l**, 117607-70-2; **4m**, 117607-71-3; **4n**, 117607-72-4; **5a**, 117607-73-5; **5b**, 107743-56-6; **5c**, 107743-58-8; **5d**, 117607-74-6; **5e**, 117607-75-7; **5f**, 117607-76-8; **5g**, 117607-77-9; **5h**, 117607-78-0; **5i**, 117677-96-0; **5j**, 107797-46-6; **5k**, 117607-79-1; **5l**, 117607-80-4; **5m**, 117607-81-5; **5n**, 117607-82-6; **5o**, 117607-83-7; **5p**, 117607-84-8; **5q**, 117607-85-9; **6c**, 107743-59-9; **6g**, 117607-86-0; **6j**, 107797-47-7; **6n**, 117607-87-1; **6p**, 117607-88-2; **6q**, 117607-89-3; **7c**, 107743-64-6; **7g**, 117607-90-6; **7j**, 107797-48-8; **7n**, 117677-97-1; **7p**, 117677-98-2; **7q**, 117677-99-3; **8o**, 117607-91-7; **8p**, 117607-92-8; **8q**, 117607-93-9; **9q**, 117678-00-9; **10q**, 117678-01-0; 2,4′-$H_3CC_6H_4CH(OH)C_6H_4F$, 117607-94-0; (4-methylphenyl)magnesium bromide, 4294-57-9; malononitrile, 109-77-3.

Supplementary Material Available: Tables of positional and thermal parameters, bond distances and bond angles for **6n** (6 pages). Ordering information is given on any current masthead page.

Stereochemical Aspects of the "*tert*-Amino Effect". 2. Enantio- and Diastereoselectivity in the Synthesis of Quinolines, Pyrrolo[1,2-*a*]quinolines, and [1,4]Oxazino[4,3-*a*]quinolines

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Thermal isomerization of the optically pure 2-vinyl-*N,N*-dialkylanilines, with a methyl or an ethyl substituent (R^2) at the α-position of the *N,N*-dialkyl moiety, **4a** (R^1 = H), **4b** (R^1 = CH_3), **5a** (R^1 = H), and **6a** (R^1 = H), affords *enantioselectively* the optically pure pyrrolo[1,2-*a*]quinolines **7a** and **7b** and the [1,4]oxazino[4,3-*a*]quinoline **11**, with the methyl or ethyl substituent (R^2) at the bridgehead carbon atom, and the quinoline **13**, respectively. The optical purity of these quinoline derivatives was determined by ^1H NMR spectroscopy in the presence of chiral shift reagents. Heating of the optically pure analogues in which R^2 is a methoxymethyl group (**4c** and **4d**) in refluxing 1-butanol yields, besides the compounds **7c,d** with the methoxymethyl group at the bridgehead carbon atom, also the regioisomers **8c,d** and **9c,d** that are enantiomerically pure. Mixtures of the diastereomers **12a,b** and **14a,b** were obtained by cyclization of compound **5b**, with a 3-ethylmorpholinyl group, and of the acyclic amine **6b**, respectively, in refluxing 1-butanol. The compounds **12a** and **14a,b** were proven enantiomerically pure. The configuration of the compounds **8**, **9**, **12**, and **14** was determined by X-ray analysis [(±)-**12a**] and ^1H NMR and ^1H NOE difference spectroscopy. These results provide conclusive evidence for the mechanism of these cyclization reactions, which are further examples of the "*tert*-amino effect". The effect of substituents on the enantio- and diastereoselectivity of the cyclization is discussed.

Introduction

In a previous paper on the C–C bond formation via the "*tert*-amino effect", we have described the influence of steric and electronic effects of substituents on the regioselectivity of the cyclization of 2-vinyl-*N,N*-dialkylanilines, yielding pyrrolo[1,2-*a*]quinolines and benzo[*c*]quinolizines.[1]

As a further extension we have investigated the possible synthesis of optically pure quinoline derivatives by thermal conversion of optically pure 2-vinyl-*N,N*-dialkylanilines. Moreover, cyclization of chiral 2-vinyl-*N,N*-dialkylanilines could provide conclusive evidence for the proposed

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(1) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.*, preceding paper in this issue.

0022-3263/89/1954-0209$01.50/0 © 1989 American Chemical Society

mechanism of these reactions.

In the literature, methods have been described for efficient asymmetric α-alkylation, e.g. of secondary amines,[2] of γ-oxo esters,[3] and of carboxylic acids.[4] The general feature in these syntheses is that they all require a chiral auxiliary, base or catalyst.

Recently, Seebach et al.[5] have described a novel method for the synthesis of chiral α-heterosubstituted carboxylic acids via α-alkylation at the chiral center. During this so-called "self-reproduction of chirality", the chirality at the reacting sp^3 C atom is temporary lost. However, the chirality of this center is memorized by a novel chiral center, and conformational effects direct the alkylation of the intermediate. At the original chiral center a highly stereospecific reaction takes place.

In this paper we describe *the self-reproduction of chirality, without the use of auxiliary reagents*, in the thermal isomerization of optically pure 2-vinyl-*N*,*N*-dialkylanilines to quinoline derivatives.

During this conversion, which takes place via a 1,5-hydrogen shift and subsequent cyclization, the center of chirality in the starting material is lost in the corresponding dipolar intermediate but reproduced with retention of configuration upon cyclization. In addition, the 1,5-hydrogen shift offers the possibility to introduce a second novel chiral center with >98% enantioselectivity.

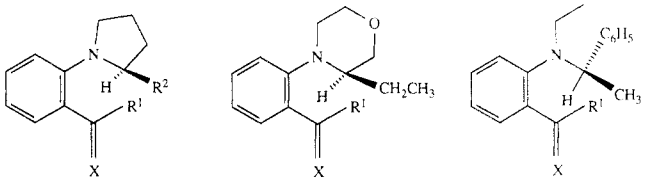
The enantioselectivity of the cyclization of *optically pure* 2-vinyl-*N*,*N*-dialkylanilines with a (*R*)-2-methyl- or (*S*)-2-(methoxymethyl)pyrrolidine (**4**), a (*R*)-3-ethylmorpholine (**5**), or a (*R*)-*N*-ethyl-*N*-(1-phenylethyl)amino group (**6**) as *N*,*N*-dialkylamino moiety was studied. Successively, we will describe the enantioselectivity of the cyclization of the optically pure pyrrolidinyl compounds **4a–d** to the pyrrolo[1,2-*a*]quinolines **7–9**, of the optically pure morpholinyl compounds **5a,b** to the [1,4]oxazino-[4,3-*a*]quinolines **11** and **12**, and of the optically pure acyclic *N*,*N*-dialkylaniline derivatives **6a,b** to the quinoline derivatives **13** and **14**, respectively.

Results[6]

Synthesis of the Optically Pure 2-Vinyl-*N*,*N*-dialkylanilines 4–6. The optically pure secondary amines were prepared according to the literature,[7-9] except (*R*)-2-methylpyrrolidine.[10]

For the synthesis of (*R*)-2-methylpyrrolidine we first reacted L-prolinol in chloroform with thionyl chloride to give the HCl salt of (*S*)-2-(chloromethyl)pyrrolidine (72%) [$[\alpha]^{25}_D$ + 11.9° (*c* 1.8, CH_2Cl_2)]. This compound was converted to (*S*)-2-(chloromethyl)-1-pyrrolidinecarboxylic acid phenylmethyl ester (76%) [$[\alpha]^{25}_D$ −43.5° (*c* 2.05, $CHCl_3$)] by treatment with benzyloxycarbonyl chloride in dichloromethane in the presence of triethylamine. Subsequently, the 2-chloromethyl moiety was reduced to the 2-methyl group via a radical reaction with tri-*n*-butyltin hydride and AIBN in refluxing benzene (87%).[11] The prepared (*R*)-2-methyl-1-pyrrolidinecarboxylic acid phenylmethyl ester [$[\alpha]^{25}_D$ −24.9° (*c* 2.02, $CHCl_3$)] was subsequently treated with 35% HBr in acetic acid to yield (*R*)-2-methylpyrrolidine hydrobromide quantitatively.

Chart I



1,4 2,5 3,6

X = O:

1a R^1 = H; R^2 = CH_3 **2a** R^1 = H **3a** R^1 = H

1b R^1 = R^2 = CH_3 **2b** R^1 = CH_3 **3b** R^1 = CH_3

1c R^1 = H; R^2 = CH_2OCH_3

1d R^1 = CH_3; R^2 = CH_2OCH_3

X = $C(CN)_2$:

4a R^1 = H; R^2 = CH_3 **5a** R^1 = H **6a** R^1 = H

4b R^1 = R^2 = CH_3 **5b** R^1 = CH_3 **6b** R^1 = CH_3

4c R^1 = H; R^2 = CH_2OCH_3

4d R^1 = CH_3; R^2 = CH_2OCH_3

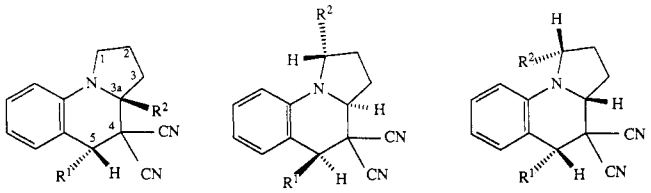
The optically pure[12] benzaldehyde (**1a**, **1c**, **2a**, and **3a**) and acetophenone derivatives (**1b**, **1d**, **2b**, and **3b**) were prepared from the appropriate optically pure secondary amines and 2-fluorobenzaldehyde or 2-fluoroacetophenone, respectively, via a nucleophilic substitution of the fluorine atom.[1,13,14] Subsequently, the compounds **1** and **2** were reacted in a Knoevenagel condensation reaction with malononitrile at room temperature in toluene to yield the starting compounds for cyclization (**4** and **5**) in good yields (Chart I).[1,14]

In the case of (*R*)-2-(2-methyl-1-pyrrolidinyl)benzaldehyde (**1a**) and the acetophenone derivative **1b** the malononitrile adduct could not be obtained pure. After several hours of reaction, mixtures of the condensation products (**4a** and **4b**, respectively) and the cyclized compounds (**7a** and **7b**, respectively) were isolated. No attempts were made to isolate compounds **4a** and **4b**. The condensation of the optically pure acyclic *N*,*N*-dialkylanilines **3a** and **3b** took place under these conditions at such a low rate that cyclization accompanied the condensation reaction. By elevating the reaction temperature, ring closure proceeds faster than condensation, and hardly any condensation product was present in the reaction mixture. Also in these cases, no attempts were made to isolate the condensation products **6a** and **6b**.

Thermal Isomerization of the Optically Pure 2-Vinyl-*N*,*N*-dialkylanilines. I: Cyclization of the Optically Pure Pyrrolidinyl Compounds 4a–d. Thermal isomerization of (*R*)-[[2-(2-methyl-1-pyrrolidinyl)phenyl]methylene]propanedinitrile (**4a**), generated in situ from **1a** and malononitrile, in refluxing 1-butanol gave *selectively* one enantiomer of the 3a-methylpyrroloquinoline **7a**.[1] Cyclization of the phenylethylidene derivative **4b**, a compound in which the α-carbon atom of the vinyl moiety is a prochiral center, generated in situ from **1b** and malononitrile, afforded *se-*

(2) Meyers, A. I.; Dickmann, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263. Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108.
(3) Agami, C.; Meynier, F.; Rizk, T. *Synth. Commun.* **1987**, *17*, 241.
(4) Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 656.
(5) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2074. Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144. Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243.
(6) Part of this work has been published as a preliminary communication: Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3136.
(7) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.
(8) van Elburg, P. A. Thesis, University of Twente, 1987.
(9) Bettoni, G.; Franchini, C.; Perrone, R.; Tortorella, V. *Tetrahedron* **1984**, *36*, 409.
(10) Prepared according to a procedure kindly provided by Prof. L. Ghosez (personal communication) with minor modifications (see the Experimental Section).
(11) Neumann, W. P. *Synthesis* **1987**, 665 and references cited therein.
(12) The optical purity of the compounds **1–5** was determined by ^1H NMR spectroscopy using chiral shift reagents [Eu(hfc)$_3$, Yb(hfc)$_3$, and AgFOD].
(13) Niewiadomski, K. B.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1679.
(14) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269.

Chart II



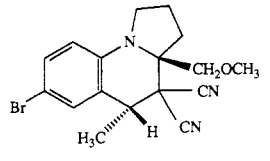
7 8 9

a $R^1 = H$; $R^2 = CH_3$

b $R^1 = R^2 = CH_3$

c $R^1 = H$; $R^2 = CH_2OCH_3$

d $R^1 = CH_3$; $R^2 = CH_2OCH_3$



10

lectively one enantiomer of the *trans*-3a,5-dimethylpyrroloquinoline **7b**, after reaction for 2 h in refluxing 1-butanol.

The observed regiospecificity in this reaction was lost in the ring closure of **4c** having a methoxymethyl substituent. Cyclization of **4c** gave a mixture of **7c** (46%) and two diastereomers, **8c** [1*S*-*cis*; 19%] and **9c** [1*S*-*trans*; 17%] (Chart II). The compounds **7d** (33%), **8d**, and **9d** (35% and 6%, respectively) were obtained upon cyclization of **4d**.

The enantiomeric purities (≥98%) of **7a–d**, **8c,d**, and **9c,d** were determined by ^1H NMR spectroscopy (200 and 500 MHz) with chiral shift reagents.[15,16] In order to determine the absolute configuration of **7d** by X-ray analysis, this compound was brominated with *N*-bromosuccinimide (NBS) in carbon tetrachloride at room temperature to give a compound brominated at C-7 [**10**: ^1H NMR δ 7.33 (s, 1 H, H-6), 7.27 and 6.52 (AB, 2 H, J = 9.5 Hz, H-8 and H-9)] in a yield of 78% (Chart II). Determination of the absolute configuration of **10** by X-ray analysis[6] showed that cyclization had taken place with retention of configuration at the chiral center, with the methoxymethyl group at the bridgehead carbon atom and the methyl group at the new chiral center in trans position. Hence, **7d** has the 3a*R*-trans configuration.

In both other two isomers (**8d** and **9d**) formed by cyclization of **4d** the hydrogen atom at the bridgehead carbon atom (H-3a) is at the same face of the molecule as H-5 (determined by ^1H NOE difference spectroscopy). The crystal structure of **9d** was determined by X-ray analysis.[6] Due to the lack of anomalous scatterers, the absolute configuration could not be determined. Assuming that the original chiral center with the methoxymethyl group is retained the configuration is 1*S*-(1α,3aβ,5α). In this isomer

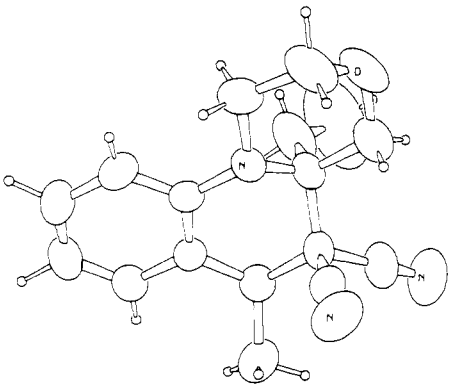
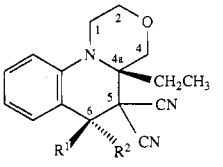


Figure 1. X-ray crystal structure of (±)-**12a**.

Chart III



11 $R^1 = R^2 = H$

12a $R^1 = H$; $R^2 = CH_3$

12b $R^1 = CH_3$; $R^2 = H$

(**9d**) all hydrogen atoms at the chiral centers are at the same face of the molecule.

The relative configuration of the products obtained by cyclization of **4a–c** were determined (^1H NMR and NOE difference spectroscopy), and from the results obtained by cyclization of **4d** we assigned the absolute configuration of **7a**, **7b**, **7c**, **8c**, and **9c** as depicted (Chart II).

On the basis of these results we conclude that there are two characteristic features in the formation of the pyrroloquinolines **7–9**. Firstly, in these product molecules the hydrogen that is transferred (H-5) and the bridgehead substituent (H or R^2) are at the same face of the molecule. Secondly, in the formation of **7a–d**, the cyclization takes place with retention of configuration of the original chiral center.

II: Cyclization of the Optically Pure Morpholinyl Compounds 5a and 5b. Thermal isomerization of (*R*)-2-[[2-(3-ethyl-4-morpholinyl)phenyl]methylene]propanedinitrile (**5a**) gave selectively one enantiomer of **11** [^1H NMR δ 3.39 (br dd, 1 H, J = 11.8 and 3.7 Hz, H-1_{eq}), 3.23 (ddd, 1 H, J = 11.8, 11.7, and 4.4 Hz, H-1_{ax}), 2.03 and 1.72 (ABX_3, 2 H, J_{AB} = 14.8 Hz, J = 7.6 Hz, CH_2CH_3); ^{13}C NMR δ 57.5 [s, $NC(CH_2CH_3)$]] (Chart III) in a yield of 75% and with an optical purity of more than 98%.[17]

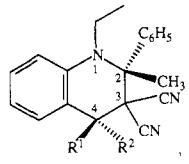
This stereoselectivity was lost in the reaction of the phenylethylidene derivative **5b**. Heating of **5b** in refluxing 1-butanol (30 h) gave a mixture of two diastereomers of **12**, which could not be separated by column chromatography. The ^1H NMR [C_6D_6; δ 1.39 and 1.37 [d, J = 6.7 Hz, $CH(CH_3)$], 0.85 and 0.72 (t, J = 7.6 Hz, CH_2CH_3)] and ^{13}C NMR [$CDCl_3$; δ 43.0 and 42.3 (t, NCH_2), 38.0 and 35.8 [d, $ArCH(CH_3)$]] spectra of the reaction mixture revealed

(15) The optical purities of **7a,b** and **7c–9c** were determined by using 1.0 equiv of Yb(hfc)$_3$ and 1.0 equiv of AgFOD. The spectra of the racemic **7a,b** and **7c–9c** showed a splitting of the methyl group at C-3a (**7a**) and at C-5 (**7b**) or a splitting of the methoxy singlet in the case of **7c–9c**.

(16) In ref 6 it was mentioned that the optical purity of **7d** was determined by ^1H NMR spectroscopy using Yb(tfc)$_3$. Recently, we have found that better results were obtained with Yb(hfc)$_3$ or a mixture of Yb(hfc)$_3$ and AgFOD. The 500-MHz spectra of the racemic **7d**, **8d**, and **9d** in the presence of 1.5 equiv of Yb(hfc)$_3$ or 0.75 equiv of Yb(hfc)$_3$ and 0.75 equiv of AgFOD showed two doublets whereas **7d**, **8d**, and **9d** obtained from the optically pure starting material showed one doublet of CH_3-5.

(17) The enantiomeric purities of **11** and **12a** were determined by using 0.3–0.4 equiv of Eu(hfc)$_3$. The racemic **11** and **12a** showed a splitting of CH_2CH_3 protons in the ^1H NMR spectrum when shift reagent was added. The triplet of CH_2CH_3 also showed some splitting, whereas the products obtained from the optically pure starting materials showed no splitting. The enantiomeric purities of the compounds **13** and **14a,b** were analogously determined with 1.0 equiv of Yb(hfc)$_3$ and 1.0 equiv of AgFOD [splitting of the singlet of $NC(CH_3)$ (**13** and **14a,b**), and of the doublet of CH_3-5 (**14a,b**)].

Chart IV



13 $R^1 = R^2 = H$

14a $R^1 = H$; $R^2 = CH_3$

14b $R^1 = CH_3$; $R^2 = H$

that two compounds were formed, *with the ethyl substituent at the bridgehead carbon atom* (C-4a) (90% yield, ratio 7:3). Unfortunately, we were not able to isolate one of the two isomers by fractional crystallization. The optical purity of **12a** (>95%), could be determined using the mixture of **12a,b** and chiral shift reagents,[17] while the optical purity of **12b** could not be determined in this way (coinciding peaks in the ^1H NMR spectrum). Upon fractional crystallization of the *racemic mixture* of **12a** and **12b**, obtained from racemic **5b**, we could obtain the major diastereomer pure [(±)-**12a**]. X-ray analysis revealed that in this compound the ethyl group at C-4a and the hydrogen atom at C-6 are at the same face of the molecule (Figure 1).

Obviously in the formation of the [1,4]oxazino[3,4-*b*]-quinolines **12** from **5b**, besides the compound in which the hydrogen that is transferred is at the same face of the molecule as the substituent at the bridgehead carbon atom (**12a**), also a minor isomer in which these substituents are related trans (**12b**) is formed.

III: Cyclization of the Optically Pure Acyclic Compounds 6a and 6b. The acyclic tertiary amine **6a**, prepared in situ from **3a** and malononitrile, resulted upon heating in refluxing 1-butanol in the *selective* ring closure at the benzylic carbon atom [^1H NMR δ 2.17 (s, 3 H, CH_3); ^{13}C NMR δ 65.2 [s, $NC(CH_3)$], 42.4 (t, NCH_2)], to give the quinoline derivative **13** in a yield of 73% (Chart IV) with an optical purity of ≥98%.[17]

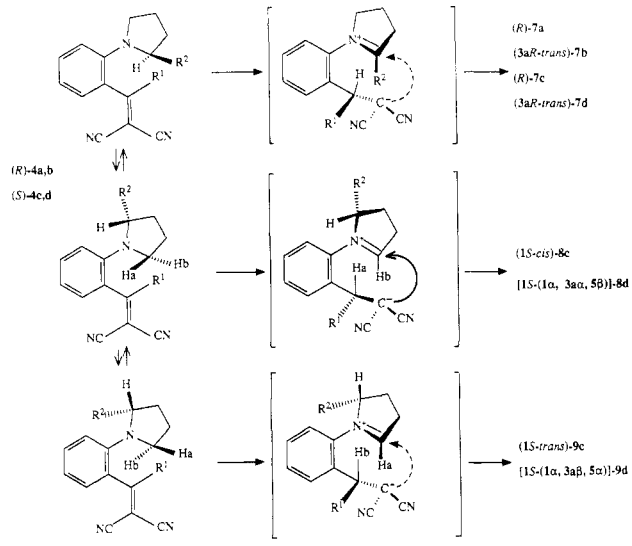
Heating of **6b** in refluxing 1-butanol also affords ring closure at the benzylic carbon atom. However, in this case two diastereomers were obtained (ratio of 3:1), which could not be separated [^1H NMR (major isomer) δ 2.29 [s, 3 H, $NC(CH_3)C_6H_5$], 1.63 [d, 3 H, J = 6.7 Hz, $ArCH(CH_3)$]; (minor isomer) δ 1.89 [s, 3 H, $NC(CH_3)C_6H_5$], 1.74 [d, 3 H, J = 6.7 Hz, $ArCH(CH_3)$]]. ^1H NOE difference spectroscopy revealed that in the major isomer both methyl groups at the chiral centers (C-2 and C-4) are at the same face of the molecule (**14b**) while in the minor isomer H-4 is at the same face of the molecule as the methyl group at C-2 (**14a**). The optical purity of both compounds was shown to be ≥98%.[17]

Discussion

In our studies on the mechanism of the thermal isomerization of the 2-vinyl-*N,N*-dialkylanilines to pyrrolo-[1,2-*a*]quinolines we have shown that the rate-determining step comprises an intramolecular 1,5-hydrogen transfer. In view of the charge separation that takes place, it seems likely that the migrating hydrogen atom is partially negatively charged.[18]

Cyclization of the pyrrolidinyl compound **4a**, the morpholinyl compound **5a**, and the acyclic amine **6a** with the *R* configuration afforded *selectively* the optically pure

Scheme I



pyrroloquinoline (*R*)-**7a**, the oxazinoquinoline (*S*)-**11**, and the quinoline (*R*)-**13**, respectively, with retention of configuration of the original chiral center. In the formation of these compounds, the chirality at the carbon atom with the methyl (**4a** and **6a**) or the ethyl substituent (**5a**) is lost after the intramolecular hydrogen transfer. However, in the cyclization step the original chiral center is formed enantioselectively because the chirality in the starting compound (e.g. (*R*)-**4a**) is memorized in the form of an unique chiral "anticlockwise" helical dipolar intermediate. Hence, in the case of formation of the compounds (*R*)-**7a**, (*S*)-**11**, and (*R*)-**13** the carbanion is forced to add to the iminium double bond from the side the hydrogen is transferred (Schemes I–III). In the same way optically pure (*R*)-**7c** is formed starting from (*S*)-**4c**.

From the above-mentioned experiments with optically pure **4a**, **4c**, **5a**, and **6a** we conclude that firstly, in the dipolar intermediate, the carbanion adds to the iminium double bond *exclusively from one side*, viz. from the side the migrating hydrogen is transferred. Secondly, there is *no equilibration* of the helical dipolar intermediate.

Besides **7c** also two regioisomers, **8c** and **9c**, were formed by cyclization of **4c**, since the 1,5-hydrogen shift will not take place exclusively from the carbon atom adjacent to nitrogen bearing the methoxymethyl substituent, because of the sterically more hindering and the inductive electron-withdrawing effect of the methoxymethyl substituent.[1]

In the products obtained by cyclization of **4b** and **4d**, compounds in which the α-carbon atom of the vinyl moiety is a prochiral center, the hydrogen atom that underwent a 1,5-hydrogen shift is at *the same face* of the molecule as the substituent at the bridgehead carbon atom, as was proven by ^1H NOE difference spectroscopy. Moreover, cyclization of **4d** to **7d** takes place with *retention of configuration* at the chiral center, with the methoxymethyl group at the bridgehead carbon atom and the hydrogen atom that underwent a 1,5-hydrogen shift at the same face of the molecule, and *exclusively* (3a*R-trans*)-**7d** is formed, as was concluded from X-ray analysis of the brominated derivative **10**.[6]

Determination of the absolute configuration of **9d** by X-ray analysis[6] confirmed that the hydrogen atoms at the bridgehead carbon atom (H-3a) and at the benzylic position (H-5) are cis.

The position of the vinyl moiety in compounds **4–6** determines the stereochemistry of **7–9** and **11–14**.[1] X-ray

(18) Groenen, L. C.; Verboom, W.; Nijhuis, W. H. N.; Reinhoudt, D. N.; van Hummel, G. J.; Feil, D. *Tetrahedron* **1988**, *44*, 4637.

Scheme II

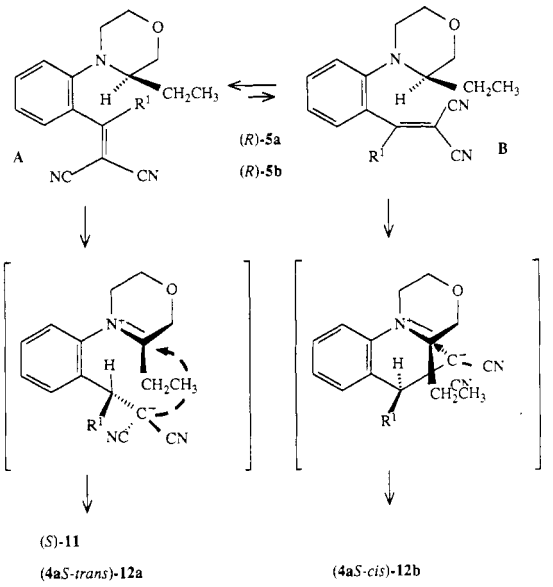
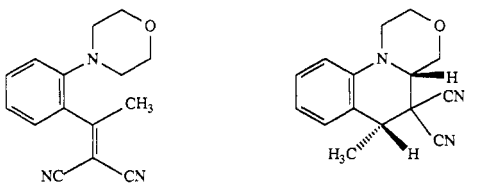


Chart V



analysis of **4** ($R^1 = R^2 = H$) showed that the vinyl moiety points away from the amino group (Scheme I).[18]

From these experiments we conclude that, besides the exclusive addition of the carbanion to the iminium double bond from the side the hydrogen was transferred and the nonequilibration of the helical dipolar intermediate, the 1,5-hydrogen shift proceeds *enantioselectively* in a *suprafacial manner* (Schemes I–III).

The diastereoselectivity of the reaction was lost in the cyclization of **5b** to yield a mixture of (4a*S-trans*)-**12a** and (4a*S-cis*)-**12b**. Whereas in the synthesis of the pyrroloquinoline derivatives (**7a–d**), with the substituent R^2 at the bridgehead, the hydrogen shift only takes place in one conformation (Scheme I), in the case of formation of **12a** and **12b** the hydrogen shift must take place in two different conformations (Scheme II).

We can explain this result by assuming that there is an interchange of the position of the vinyl group (A ⇔ B; Scheme II), because of steric hindrance caused by the substituent R^1 at the ethyl group. The hydrogen migration then takes place from a conformation (B) in which the substituent R^1 points away from the amino group. In the dipolar intermediates generated from A and B (Scheme II), leading to the diastereomers **12a** and **12b**, respectively, the newly created chiral center has the opposite geometry.

In order to determine the role of the ethyl substituent, the *unsubstituted* morpholinyl compound **15** was cyclized to **16** in refluxing 1-butanol (yield 83%) (Chart V). X-ray analysis of **16** (Figure 2) revealed that the hydrogen atom that underwent a 1,5-hydrogen shift is at the same face of the molecule as the hydrogen atom at the bridgehead carbon atom. No trace of a product in which these hydrogen atoms are trans was noticed. This means that, in this case, the hydrogen shift takes place in only one conformation.

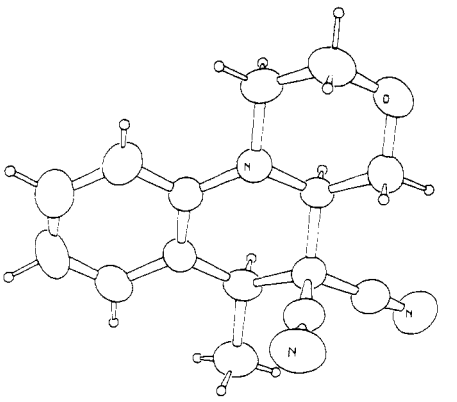
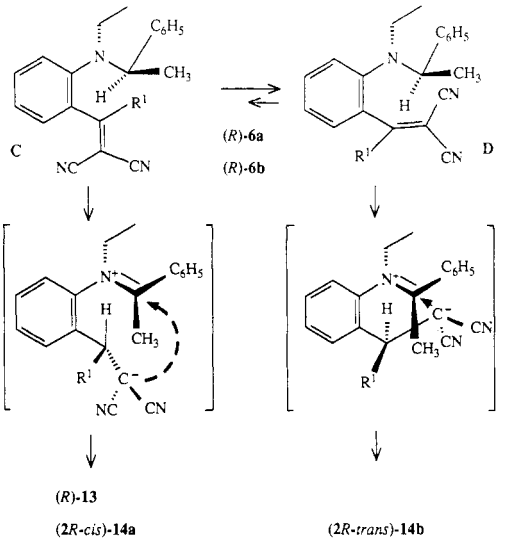


Figure 2. X-ray crystal structure of **16**.

Scheme III



In the chiral dipolar intermediates generated from **5b**, the carbanion is forced to add to the iminium double bond from the side the hydrogen is transferred because the upper side is shielded by the ethyl group.

The ring closure of the acyclic tertiary amines **6a** and **6b** takes place *exclusively* at the benzylic carbon atom because of the better stabilization of the iminium double bond in the dipolar intermediate when the benzylic hydrogen migrates compared to a migration of one of the methylene hydrogen atoms of the ethyl group.

Cyclization of **6a** gives selectively one enantiomer of **13**, while **6b** yields a diastereomeric mixture of **14a** and **14b**. In view of the results of the thermal conversion of **4a–d** and **5a,b**, we assume that the cyclization of **6a** and **6b** proceeds in the same way as that of **5a** and **5b**. The hydrogen shift also can take place in two conformations (C and D, Scheme III) and the addition of the carbanion to the iminium double bond is stereospecific due to shielding of that side of the dipolar intermediate from which the hydrogen was transferred. Hence, (*R*)-**13** is formed enantioselectively, and (2*R-cis*)-**14a** and (2*R-trans*)-**14b** are formed optically pure.

The formation of **12** and **14** also takes place with conservation of chiral information in the dipolar intermediate, like in the formation of **7–9**, although the hydrogen transfer occurs in two different conformations and consequently is not stereospecific. As a consequence, compounds **12** and **14** are not formed *diastereoselectively*. However, the original chiral center is reproduced on cyclization to give **12a,b** and **14a,b**.

Table I. Optical Rotations of the Compounds 1a–d, 4c,d, 7a–d, 8c,d, and 9c,d

compd	$[\alpha]^{25}_D$, deg (c, $CHCl_3$)	compd	$[\alpha]^{25}_D$, deg (c, $CHCl_3$)	compd	$[\alpha]^{25}_D$, deg (c, $CHCl_3$)
1a	−513 (0.19)	**4d**	+397 (3.5)	**8c**	−193 (1.2)
1b	−482 (0.7)	**7a**	+323 (0.31)	**8d**	−158 (0.2)
1c	−542 (4.4)	**7b**	+33 (0.8)	**9c**	+17 (0.4)
1d	−499 (1.22)	**7c**	+77.5 (2.0)	**9d**	−29.5 (0.17)
4c	+599 (1.75)	**7d**	+42.5 (0.4)		

In conclusion, convincing evidence is provided for the mechanism of these reactions and we have shown that by proper choice of the chiral *N,N*-dialkylamino group and of the substituents R^1 and R^2 we can form pyrrolo[1,2-*a*]quinolines, [1,4]oxazino[3,4-*a*]quinolines, and quinoline derivatives *enantiomerically pure with self-reproduction of chirality, without the need of any auxiliary reagent*, and with the creation of an additional chiral center.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer, unless stated otherwise, and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Nicolet NT 200-WB spectrometer (Me_4Si as an internal standard). Mass spectra were recorded with a Varian Mat 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter.

Elemental analyses were carried out by A. Christenhusz of the Laboratory of Chemical Analysis of the University of Twente.

2-Fluorobenzaldehyde and 2-fluoroacetophenone are commercially available (Janssen). (*S*)-2-(Methoxymethyl)pyrrolidine is commercially available (Merck) or was synthesized, just as (*S*)-2-(hydroxymethyl)pyrrolidine, according to the literature.[7] (*R*)-*N*-Ethyl-α-methylbenzenemethanamine was synthesized from (*R*)-α-methylbenzenemethanamine (Janssen).[8] (*R*)-3-Ethylmorpholine was prepared according to the literature.[9] The chiral shift reagents used were purchased from Aldrich and from Janssen.

The experimental and spectral data of the optically pure compounds **1a–d**, **4a–d**, **7a–d**, **8c,d**, and **9c,d** are as given for the corresponding racemic compounds.[1] The optical rotations of these compounds, except for **4a** and **4b**, are summarized in Table I. In the case of reaction of (*R*)-2-methylpyrrolidine hydrobromide with 2-fluorobenzaldehyde or 2-fluoroacetophenone one extra equivalent of potassium carbonate was added.

(*S*)-2-(Chloromethyl)pyrrolidine Hydrochloride. A solution of (*S*)-(+)-2-(hydroxymethyl)pyrrolidine (40 g; 0.4 mol) in chloroform (120 mL), at −4 °C, was saturated with HCl, dried by bubbling through a H_2SO_4 trap. Then thionyl chloride (58 mL, 0.8 mol) was added dropwise at −4 °C. The temperature was slowly raised to 20 °C, and the reaction mixture was refluxed for 2 h. The chloroform and excess of thionyl chloride were removed under reduced pressure, and methanol (300 mL) and a small quantity of active charcoal were added to the residue. The mixture was refluxed for 1 h and filtered through Celite; this operation was repeated three times. After removal of the methanol, the orange oil was crystallized by addition of some ethanol, yield 72%; mp 137–138 °C; $[\alpha]^{25}_D$ +11.9° (*c* 1.8, CH_2Cl_2).

(*S*)-2-(Chloromethyl)-1-pyrrolidinecarboxylic Acid Phenylmethyl Ester. A solution of (*S*)-2-(chloromethyl)pyrrolidine hydrochloride (10 g; 65 mmol) in dichloromethane (100 mL) was cooled to 0 °C. Triethylamine (12.8 g; 125 mmol) was added, and subsequently a solution of benzyloxycarbonyl chloride (16.5 g; 65 mmol) in dichloromethane (20 mL) was added dropwise over a period of 4–5 h. The mixture was stirred for 15 h at room temperature. Subsequently, the solvent was removed under reduced pressure, and the residue was taken up in diethyl ether (200 mL) and washed with 2 N HCl (3 × 100 mL). The organic layer was filtered through Celite and concentrated. The residue was taken up in dichloromethane (50 mL) and dried ($MgSO_4$). The solvent was removed to give an oil, which was purified by column chromatography (SiO_2, CH_2Cl_2): yield 76%; $[\alpha]^{25}_D$ −43.5° (*c* 2.05, $CHCl_3$); ^1H NMR δ 7.34 (s, 5 H, Ar H), 5.14 (s, 2 H, $ArCH_2$), 4.25–3.95 (m, 1 H, NCH), 3.8–3.4 (m, 4 H, CH_2Cl and NCH_2), 2.2–1.7 (m, 4 H, CH_2); ^{13}C NMR δ 154.8 (s, C=O), 136.7 (s, Ar C), 128.5, 127.9, and 127.8 (d, Ar C), 66.9 (t, $ArCH_2$), 58.4 (d, NCH), 47.2 and 45.3 (t, NCH_2 and CH_2Cl), 28.5 and 23.7 (t, CH_2); mass spectrum, *m/e* 253.086 (M^+, calcd for $C_{13}H_{16}ClNO_2$ 253.087); IR (KBr) 1702 (C=O) cm^{-1}.

(*R*)-2-Methyl-1-pyrrolidinecarboxylic Acid Phenylmethyl Ester. A solution of (*S*)-2-(chloromethyl)-1-pyrrolidinecarboxylic acid phenylmethyl ester (7.6 g; 30 mmol) and a small quantity of AIBN in benzene (75 mL) was added dropwise to a refluxing solution of tri-*n*-butyltin hydride (16 g; 53.5 mmol) in benzene (75 mL). The reaction mixture was refluxed over a period of 3 days. After removal of the solvent, the residue was purified by column chromatography (SiO_2, CH_2Cl_2): yield 87%; $[\alpha]^{25}_D$ −24.9° (*c* 2.02, $CHCl_3$); ^1H NMR δ 7.34 (s, 5 H, Ar H), 5.13 (s, 2 H, $ArCH_2$), 4.3–3.8 (m, 1 H, NCH), 3.7–3.3 (m, 2 H, NCH_2), 2.2–1.5 (m, 4 H, CH_2), 1.18 (d, 3 H, *J* = 6.3 Hz, CH_3); ^{13}C NMR δ 154.8 (s, C=O), 137.3 (s, Ar C), 128.4 and 127.7 (d, Ar C), 66.5 (t, $ArCH_2$), 53.2 (d, NCH), 46.5 (t, NCH_2), 33.0 and 23.5 (t, CH_2), 20.9 (q, CH_3); mass spectrum, *m/e* 219.125 (M^+, calcd for $C_{13}H_{17}NO_2$ 219.126); IR (KBr) 1698 (C=O) cm^{-1}.

(*R*)-2-Methylpyrrolidine Hydrobromide. To (*R*)-2-methyl-1-pyrrolidinecarboxylic acid phenylmethyl ester (2.19 g; 10 mmol) was added a solution of HBr in glacial acetic acid (35%) (10 mL). The solution was stirred until no more gas deceases (≈15 min). Subsequently, diethyl ether (50 mL) was added, and the salt was decanted. This was repeated thrice, to afford (*R*)-2-methylpyrrolidine hydrobromide quantitatively, which was used without further purification.

General Procedure for the Synthesis of the Morpholinyl Compounds 2a,b and the Acyclic Amines 3a,b. To a solution of 2-fluorobenzaldehyde or 2-fluoroacetophenone (1 equiv) and (*R*)-3-ethylmorpholine or (*R*)-*N*-ethyl-α-methylbenzenemethanamine (1.15 equiv) in DMF (1 mL per millimole fluoro compound) was added potassium carbonate (1.15 equiv), and the mixture was heated for several hours at 152 °C. When the reaction was complete, as followed from TLC, the reaction mixture was allowed to cool. The crude reaction mixture was taken up in water and extracted with ethyl acetate. The combined organic layers were washed with a saturated aqueous solution of ammonium chloride and subsequently dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, CH_2Cl_2).

(*R*)-2-(3-Ethyl-4-morpholinyl)benzaldehyde (2a): reaction time 48 h; oil; yield 25%; $[\alpha]^{25}_D$ −295° (*c* 3.0, $CHCl_3$); ^1H NMR δ 10.49 (s, 1 H, CHO), 7.95–7.05 (m, 4 H, Ar H), 4.1–3.5 and 3.3–2.8 (m, 7 H, NCH_2, CH_2O, NCH), 1.6–1.2 (m, 2 H, CH_2CH_3), 0.74 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR δ 191.6 (s, CHO), 154.5 (s, Ar C-2), 134.7, 129.1, 123.8, and 122.0 (d, Ar C), 130.8 (s, Ar C-1), 69.8 and 67.1 (t, CH_2O), 61.6 (d, NCH), 52.1 (t, NCH_2), 20.4 (t, CH_2CH_3), 10.3 (q, CH_2CH_3); IR (KBr) 1688 (C=O) cm^{-1}; mass spectrum, *m/e* 219.126 (M^+, calcd for $C_{13}H_{17}NO_2$ 219.126).

(*R*)-1-[2-(3-Ethyl-4-morpholinyl)phenyl]ethanone (2b): reaction time 72 h; oil; yield 23%; $[\alpha]^{25}_D$ −62° (*c* 0.32, $CHCl_3$); ^1H NMR δ 7.6–7.0 (m, 4 H, Ar H), 4.05–3.45 and 3.3–2.8 (m, 7 H, NCH_2, NCH, CH_2O), 2.66 (s, 3 H, CH_3), 1.6–1.3 (m, 2 H, CH_2CH_3), 0.74 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR δ 196.8 (s, C=O), 149.5 (s, Ar C-2), 137.9 (s, Ar C-1), 131.5, 128.7, 123.9, and 121.7 (d, Ar C), 70.0 and 67.2 (t, CH_2O), 61.2 (d, NCH), 51.9 (t, NCH_2), 30.3 (q, CH_3), 20.4 (t, CH_2CH_3), 10.5 (q, CH_2CH_3); IR (KBr) 1681 (C=O) cm^{-1}; mass spectrum, *m/e* 233.142 (M^+, calcd for $C_{14}H_{19}NO_2$ 233.142).

(*R*)-2-[Ethyl(1-phenylethyl)amino]benzaldehyde (3a): reaction time 48 h; oil; yield 15%; $[\alpha]^{25}_D$ +231° (*c* 1.2, $CHCl_3$); ^1H NMR δ 10.72 (s, 1 H, CHO), 7.95–7.0 (m, 9 H, Ar H), 4.32 [q, 1 H, *J* = 6.6 Hz, $NCH(CH_3)$], 3.25–2.7 (m, 2 H, CH_2CH_3), 1.29 [d, 3 H, *J* = 6.6 Hz, $NCH(CH_3)$], 0.87 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR δ 192.3 (d, CHO), 153.5, 143.2, and 133.8 (s, Ar C), 134.3, 128.5, 128.4, 128.0, 127.1, 124.7, 124.2, and 121.2 (d, Ar C), 64.3 (d, NCH), 45.2 (t, NCH_2), 20.5 [q, $NCH(CH_3)$], 12.6 (q, CH_2CH_3); IR (KBr) 1688 (C=O) cm^{-1}; mass spectrum, *m/e* 253.148 (M^+, calcd for $C_{17}H_{19}NO$ 253.147).

(*R*)-1-[2-[Ethyl(1-phenylethyl)amino]phenyl]ethanone (3b): reaction time 72 h; oil; yield 13%; $[\alpha]^{25}_D$ +73° (*c* 0.4, $CHCl_3$); ^1H NMR δ 7.5–7.0 (m, 9 H, Ar H), 4.32 [q, 1 H, *J* = 6.85 Hz, NC*H*(CH_3)], 3.3–2.75 (m, 2 H, CH_2CH_3), 2.74 (s, 3 H, CH_3), 1.33 [d, 3 H, *J* = 6.8 Hz, NCH(CH_3)], 0.89 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR δ 205.3 (s, C=O), 142.6, 140.1, and 129.5 (s, Ar C), 130.5, 128.3, 128.2, 127.5, 127.0, 124.1, and 123.7 (d, Ar C), 63.3 [d, NCH(CH_3)], 43.9 (t, CH_2CH_3), 30.9 [q, O=C(CH_3)], 19.7 [q, NCH(CH_3)], 11.9 (q, CH_2CH_3); IR (KBr) 1684 (C=O) cm^{-1}; mass spectrum, *m/e* 267.161 (M^+, calcd for $C_{18}H_{21}NO_2$ 267.162).

General Procedure for the Preparation of the Morpholinyl Compounds 5a and 5b. To a solution of the benzaldehyde **2a** (2.19 g, 10 mmol) or the acetophenone **2b** (2.33 g, 10 mmol) in toluene (10 mL) was added malononitrile (0.67 g, 10 mmol) in one portion. After the mixture was stirred for several hours at room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2; CH_2Cl_2).

(*R*)-2-[[2-(3-Ethyl-4-morpholinyl)phenyl]methylene]propanedinitrile (5a): reaction time 12 h; oil; yield 91%; $[\alpha]^{25}_D$ +235° (*c* 3.0, $CHCl_3$); ^1H NMR δ 8.36 (s, 1 H, =CH), 8.25–8.1 and 7.65–7.5 (m, 2 H, Ar H), 7.4–7.15 (m, 2 H, Ar H), 4.1–3.5 and 3.05–2.8 (m, 7 H, NCH, NCH_2, CH_2O), 1.6–1.15 (m, 2 H, CH_2CH_3), 0.74 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR δ 157.1 (d, =CH), 153.0 (s, Ar C-2), 134.9 and 129.1 (d, Ar C), 127.0 (s, Ar C-1), 124.5 and 122.7 (d, Ar C), 114.2 and 112.7 (s, CN), 82.0 [s, =*C*($CN)_2$], 69.8 and 67.0 (t, CH_2O), 61.2 (d, NCH), 52.2 (t, NCH_2), 20.5 (t, CH_2CH_3), 10.2 (q, CH_3); IR (KBr) 2228 (CN) cm^{-1}; mass spectrum, *m/e* 267.134 (M^+, calcd for $C_{16}H_{17}N_3O$ 267.137).

(*R*)-2-[1-[2-(3-Ethyl-4-morpholinyl)phenyl]ethylidene]propanedinitrile (5b): reaction time 20 h; yield 81%; mp 149–150 °C (ethanol); $[\alpha]^{25}_D$ +266° (*c* 0.4, $CHCl_3$); ^1H NMR δ 7.55–7.1 (m, 4 H, Ar H), 4.05–3.45 and 3.3–2.7 (m, 7 H, CH_2O, NCH, NCH_2), 2.67 [s, 3 H, =C(CH_3)], 1.6–1.15 (m, 2 H, CH_2CH_3), 0.77 (t, 3 H, *J* = 6.8 Hz, CH_2CH_3); ^{13}C NMR δ 179.2 [s, =*C*(CH_3)], 148.9 (s, Ar C-2), 133.2 (s, Ar C-1), 132.0, 128.7, 124.4, and 122.7 (d, Ar C), 112.3 (s, CN), 86.8 [s, =*C*($CN)_2$], 69.8 and 67.2 (t, CH_2O), 61.3 (d, NCH), 51.1 (t, NCH_2), 24.0 [q, =C(CH_3)], 20.0 (t, CH_2CH_3), 11.0 (q, CH_2CH_3); IR (KBr) 2240 (CN) cm^{-1}; mass spectrum, *m/e* 281.150 (M^+, calcd 281.153). Anal. Calcd for $C_{17}H_{19}N_3O$ (M_r 281.358): C, 72.57; H, 6.81; N, 14.93. Found: C, 72.23; H, 6.90; N, 14.81.

(3a*R*-*trans*)-7-Bromo-1,2,3,3a-tetrahydro-3a-(methoxymethyl)-5-methylpyrrolo[1,2-*a*]quinoline-4,4(5*H*)-dicarbonitrile (10). To a stirred solution of **7d** (150 mg, 0.53 mmol) in carbon tetrachloride (5 mL) was added *N*-bromosuccinimide (95 mg, 0.53 mmol) at room temperature. A catalytic amount of dibenzoylperoxide was added to the slurry. Subsequently, the mixture was refluxed for 1.5 h. The mixture was allowed to cool, the solid substance was filtered off, and the filtrate was washed with water (3 × 5 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2; CH_2Cl_2) to give **10** as a solid in a yield of 78%: mp 128–130 °C (MeOH); $[\alpha]^{25}_D$ 71.3° (*c* 0.59, $CHCl_3$); ^1H NMR δ 7.33 (s, 1 H, H-6), 7.27 and 6.52 (AB, 2 H, *J* = 9.5 Hz, H-8 and H-9), 3.85–3.2 [m, 3 H, NCH_2, ArC*H*(CH_3)], 3.40 (s, 2 H, CH_2OCH_3), 3.28 (s, 3 H, OCH_3), 2.65–2.0 (m, 4 H, CH_2), 1.74 (d, 3 H, *J* = 6.8 Hz, CH_3); ^{13}C NMR δ 140.5 (s, C-10a), 131.6 and 129.9 (d, Ar C), 121.3 (s, C-6a), 115.1 (d, Ar C), 114.6 and 113.0 (s, CN), 109.8 (s, C-7), 73.8 (t, CH_2OCH_3), 66.3 [s, N*C*(CH_2OCH_3)], 59.6 (q, OCH_3), 49.2 (t, NCH_2), 45.3 [s, *C*($CN)_2$], 36.3 [d, *C*H(CH_3)], 34.1 and 22.0 (t, CH_2), 16.7 [q, CH(*C*H_3)]; IR (KBr) 2245 (CN) cm^{-1}; mass spectrum, *m/e* 359.059 (M^+, calcd 359.063). Anal. Calcd for $C_{17}H_{18}BrN_3O$ (M_r 359.148): C, 56.85; H, 5.05; N, 11.70. Found: C, 56.96; H, 5.03; N, 11.79.

General Procedure for the Thermal Conversion of the Condensation Products 5a and 5b. Synthesis of 11 and 12. A solution of the condensation product **5a** (1.34 g, 5 mmol) or **5b** (1.41 g, 5 mmol) in 1-butanol (5 mL) was heated (118 °C) for several hours until all the starting material had disappeared according to TLC. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2).

(*S*)-4a-Ethyl-1,2,4,4a-tetrahydro[1,4]oxazino[4,3-*a*]quinoline-5,5(6*H*)-dicarbonitrile (11): reaction time 20 h; yield 75%; mp 124–125 °C (EtOH); $[\alpha]^{25}_D$ +1.3° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz) δ 7.3–7.15 and 7.1–7.0 (m, 2 H, Ar H), 6.9–6.7 (m, 2 H, Ar H), 4.36 and 3.91 (AB, 2 H, *J* = 11.7 Hz, H-4), 4.15 (br dd, 1 H, *J* = 11.6 and 4.4 Hz, H-2_{eq}), 3.80 (ddd, 1 H, *J* = 11.6, 11.7, and 3.7 Hz, H-2_{ax}), 3.51 (s, 2 H, $ArCH_2$), 3.39 (br dd, 1 H, *J* = 11.8 and 3.7 Hz, H-1_{eq}), 3.23 (ddd, 1 H, *J* = 11.8, 11.7, and 4.4 Hz, H-1_{ax}), 2.03 and 1.72 (ABX_3, 2 H, J_{AB} = 14.8 Hz, *J* = 7.6 Hz, CH_2CH_3), 1.08 (t, 3 H, *J* = 7.6 Hz, CH_3); ^{13}C NMR δ 142.7 (s, C-10a), 129.2, 129.0, 119.5, and 112.6 (d, Ar C), 115.1 (s, C-6a), 114.8 and 114.1 (s, CN), 70.6 and 66.5 (t, CH_2O), 57.5 [s, N*C*(CH_2CH_3)], 42.3 (t, NCH_2), 38.2 [s, *C*($CN)_2$], 34.0 (t, Ar CH_2), 23.1 (t, CH_2CH_3), 9.6 (q, CH_3); IR (KBr) 2260 (CN) cm^{-1}; mass spectrum, *m/e* 267.136 (M^+, calcd 267.137). Anal. Calcd for $C_{16}H_{17}N_3O$ (M_r 267.331): C, 71.89; H, 6.41; N, 15.72. Found: C, 71.61; H, 6.56; N, 15.75.

(4a*S*-*trans*)- and (4a*S*-*cis*)-4a-ethyl-1,2,4,4a-tetrahydro-6-methyl[1,4]oxazino[4,3-*a*]quinoline-5,5(6*H*)-dicarbonitrile (12a and 12b): reaction time 30 h; yield 90%; ratio 7:3. Major isomer (**12a**): ^1H NMR (200 MHz, C_6D_6) δ 7.1–6.95 (m, 1 H, Ar H), 6.85–6.6 (m, 2 H, Ar H), 6.4–6.3 (m, 1 H, Ar H), 4.16 and 3.78 (AB, 2 H, *J* = 11.7 Hz, CH_2O), 3.49 (ddd, 1 H, *J* = 11.9, 5.0, and 1.2 Hz, H-2_{eq}), 3.29 (ddd, 1 H, *J* = 11.9, 11.7, and 6.7 Hz, H-2_{ax}), 2.84 [q, 1 H, *J* = 6.7 Hz, ArC*H*(CH_3)], 2.49 (m, 2 H, H-1_{eq} and H-1_{ax}), 1.58 and 1.23 (ABX_3, 2 H, J_{AB} = 14.6 Hz, *J* = 7.6 Hz, CH_2CH_3), 1.39 [d, 3 H, *J* = 6.7 Hz, ArCH(*C*H_3)], 0.72 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3); ^{13}C NMR δ 142.5 (s, C-10a), 128.9 and 127.3 (d, Ar C), 120.7 (s, C-6a), 119.6 (d, Ar C), 114.2 and 112.3 (s, CN), 112.4 (d, Ar C), 70.8 and 66.5 (t, CH_2O), 58.0 [s, N*C*(CH_2CH_3)], 42.4 [s, *C*($CN)_2$], 42.3 (t, NCH_2), 35.8 [d, ArCH(CH_3)], 23.4 (t, CH_2CH_3), 16.9 [q, ArCH(*C*H_3)], 9.6 [q, CH_2CH_3]; IR (KBr) 2260 (CN) cm^{-1}; mass spectrum, *m/e* 281.153 (M^+, calcd 281.153). **(±)-12a**: crystallized from the mixture of (±)-**12a** and (±)-**12b**; mp 119–120 °C (EtOH). Anal. Calcd for $C_{17}H_{19}N_3O$ (M_r 281.358): C, 72.57; H, 6.81; N, 14.93. Found: C, 72.23; H, 6.50; N, 15.26.

General Procedure for the Conversion of 3a and 3b with Malononitrile. Synthesis of 13 and 14. A solution of the benzaldehyde **3a** (1.26 g, 5 mmol) or the acetophenone **3b** (1.34 g, 5 mmol) and malononitrile (0.33 g, 5 mmol) in 1-butanol (5 mL) was heated (118 °C) for several hours until all the starting material had disappeared according to TLC. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2).

(*R*)-1-Ethyl-1,2-dihydro-2-methyl-2-phenylquinoline-3,3-(4*H*)-dicarbonitrile (13): reaction time 48 h; yield 73%; mp 172–173 °C (EtOH); $[\alpha]^{25}_D$ +231° (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.6–6.7 (m, 9 H, Ar H), 3.38 and 3.27 (ABX_3, 2 H, J_{AB} = 15.8 Hz, *J* = 7.0 Hz, CH_2CH_3), 3.23 and 3.01 (AB, 2 H, *J* = 15.9 Hz, $ArCH_2$), 2.17 (s, 3 H, CH_3), 1.28 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR δ 144.1 (s, C-10a), 136.4 (s, C-6a), 129.4, 129.0, 128.7, 127.6, 117.6, and 111.8 (d, Ar C), 115.2, 114.6, and 114.0 (s, Ar C, CN), 65.2 [s, N*C*(CH_3)], 42.8 [s, *C*($CN)_2$], 42.4 (t, NCH_2), 34.8 (t, $ArCH_2$), 25.1 [q, NC(*C*H_3)], 14.9 (q, CH_2CH_3); IR (KBr) 2225 (CN) cm^{-1}; mass spectrum, *m/e* 301.155 (M^+, calcd 301.158). Anal. Calcd for $C_{20}H_{19}N_3$ (M_r 301.392): C, 79.70; H, 6.35; N, 13.94. Found: C, 79.45; H, 6.45; N, 13.75.

(2*R*-*cis*)- and (2*R*-*trans*)-1-ethyl-1,2-dihydro-2,4-dimethyl-2-phenyl-3,3(4*H*)-quinolinedicarbonitrile (14a and 14b): reaction time 72 h; oil; yield 75%; ratio 1:3. Minor isomer (**14a**): ^1H NMR (200 MHz, $CDCl_3$) δ 7.75–6.7 (m, 9 H, Ar H), 3.56 [q, 1 H, *J* = 6.7 Hz, ArC*H*(CH_3)], 3.26 and 3.11 (ABX_3, 2 H, J_{AB} = 15.4 Hz, *J* = 6.9 Hz, CH_2CH_3), 1.89 [s, 3 H, NC(*C*H_3)C_6H_5], 1.74 [d, 3 H, *J* = 6.7 Hz, ArCH(*C*H_3)], 1.19 (t, 3 H, *J* = 6.9 Hz, CH_2CH_3). Major isomer (**14b**): ^1H NMR (200 MHz, $CDCl_3$) δ 7.75–6.7 (m, 9 H, Ar H), 3.55 and 3.41 (ABX_3, 2 H, J_{AB} = 15.8 Hz, *J* = 7.1 Hz, CH_2CH_3), 3.05 [q, 1 H, *J* = 6.7 Hz, ArC*H*(CH_3)], 2.29 [s, 3 H, NC(*C*H_3)C_6H_5], 1.63 [d, 3 H, *J* = 6.7 Hz, ArCH(*C*H_3)], 1.33 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3).

2-[1-[2-(4-Morpholinyl)phenyl]ethylidene]propanedinitrile (15) was prepared by reaction of 1-[2-(4-morpholinyl)-phenyl]ethanone[19] (1.03 g, 5 mmol) and malononitrile (0.34 g, 5 mmol) in toluene (5 mL) in a similar way as described for **5**. Reaction time 8 h; yield 86%; mp 131–132 °C (EtOH); ^1H NMR δ 7.6–7.1 (m, 4 H, Ar H), 3.9–3.7 (m, 4 H, CH_2O), 3.1–2.8 (m, 4

(19) 1-[2-(4-Morpholinyl)phenyl]ethanone was prepared from 1-(2-fluorophenyl)ethanone and morpholine via a nucleophilic substitution (78%).[13,14]

H, NCH_2), 2.68 (s, 3 H, CH_3); ^{13}C NMR δ 177.7 [s, $=C(CH_3)$], 150.2 (s, C-2), 132.3 (d, Ar C), 131.4 (s, C-1), 128.7, 123.8, and 120.2 (d, Ar C), 112.5 and 112.4 (s, CN), 87.0 [s, $=C(CN)_2$], 66.9 (t, CH_2O), 52.6 (t, NCH_2), 23.7 (q, CH_3); IR (KBr) 2240 (CN) cm^{-1}; mass spectrum, m/e 253.119 (M^+, calcd 253.121). Anal. Calcd for $C_{15}H_{15}N_3O$ (M_r 253.304): C, 71.12; H, 5.97; N, 16.59. Found: C, 71.39; H, 5.93; N, 16.48.

***(trans)*-(±)-1,2,4,4a-Tetrahydro-6-methyl[1,4]oxazino-[4,3-*a*]quinoline-5,5(6*H*)-dicarbonitrile (16)** was prepared by reaction of **15** (0.51 g, 2 mmol) in 1-butanol (2 mL) in a similar way as described for **11** and **12**. Reaction time 8 h; yield 83%; mp 172–173 °C (EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.4–7.3 and 7.1–6.95 (m, 4 H, Ar H), 4.50 (dd, 1 H, J = 11.1 and 3.6 Hz, H-4_{eq}), 4.21 (ddd, 1 H, J = 11.7, 4.0, and 1.2 Hz, H-2_{eq}), 3.90 (ddd, 1 H, J = 11.7, 11.7, and 3.1 Hz, H-2_{ax}), 3.86 (dd, 1 H, J = 10.6 and 11.1 Hz, H-4_{ax}), 3.79 (br d, 1 H, J = 11.9, 3.1, and 1.2 Hz, H-1_{eq}), 3.67 [q, 1 H, J = 6.8 Hz, ArC*H*(CH_3)], 3.62 (dd, 1 H, J = 10.6 and 3.6 Hz, H-4a), 3.04 (ddd, 1 H, J = 11.9, 11.7, and 4.0 Hz, H-1_{ax}), 1.86 [d, 3 H, J = 6.8 Hz, ArCH(CH_3)]; ^{13}C NMR δ 143.7 (s, C-10a), 129.0, 127.3, 120.5, and 113.1 (d, Ar C), 121.3 (s, C-6a), 113.8 and 111.6 (s, CN), 68.2 and 66.6 (t, CH_2O), 57.2 (d, NCH), 45.8 (t, NCH_2), 41.4 [s, $C(CN)_2$], 40.1 [d, ArCH(CH_3)], 16.5 (q, CH_3); IR (KBr) 2260 (CN) cm^{-1}; mass spectrum, m/e 253.117 (M^+, calcd 253.121). Anal. Calcd for $C_{15}H_{15}N_3O$ (M_r 253.304): C, 71.12; H, 5.97; N, 16.59. Found: C, 71.34; H, 5.95; N, 16.53.

X-ray Crystal Structure Determination. The crystal data of compounds **9d** and **10** have been reported.[6]

Crystals of (±)-**12a** are monoclinic; space group $P2_1/n$; a = 8.000 (3) Å, b = 22.181 (6) Å, c = 9.338 (4) Å, β = 114.51 (3)°, Z = 4, d_c = 1.24 g cm^{-3}. Reflections measured with an Enraf-Nonius CAD4 diffractometer (MoKα radiation, graphite monochromator, $\omega - 2\theta$ scans, $3 < \theta < 25°$, scan width (ω) (1.0 + 0.34 tg θ)°. The structure was determined and refined by using 1195 reflections with $F_o > 3\sigma(F_o)$. The number of parameters refined was 247 [scale factor, extinction factor, positional and thermal (isotropic for H-atoms, anisotropic for others) parameters of all atoms]. The final R factor was 6.3%. As evident from Figure 1 the C atoms of the ethyl group show large thermal vibrations. Therefore H atoms could not be located for these atoms. Consequently the H atoms for these atoms have been treated as riding atoms.

Crystals of **16** belong to the triclinic space group $P\bar{1}$ with a = 8.683 (4) Å, b = 9.878 (4) Å, c = 10.070 (5) Å, α = 61.76 (3)°, β = 68.53 (3)°, γ = 61.16 (4)°, Z = 2, d_c = 1.23 g cm^{-3}. The experimental conditions were the same as for (±)-**12a**, except for the scan angle (ω), which was taken as (1.5 + 0.34 tg θ)°. The number of reflections used was 1684. The number of parameters refined was 233, and the R factor was 5.3%.

All calculations have been done with SDP.[20]

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Registry No. **1a**, 117607-29-1; **1b**, 117607-30-4; **1c**, 117607-31-5; **1d**, 117607-32-6; **2a**, 117607-14-4; **2b**, 117607-16-6; **3a**, 117607-15-5; **3b**, 117607-17-7; **4c**, 117677-84-6; **4d**, 107743-60-2; **5a**, 117607-18-8; **5b**, 117607-19-9; **7a**, 117677-85-7; **7b**, 117607-33-7; **7c**, 117677-86-8; **7d**, 107743-61-3; **8c**, 117677-87-9; **8d**, 107743-62-4; **9c**, 117677-88-0; **9d**, 107797-44-4; **10**, 107743-63-5; **11**, 117607-20-2; (±)-**12a**, 117607-21-3; (±)-**12b**, 117607-22-4; **12a**, 117677-89-1; **12b**, 117677-90-4; **13**, 117607-23-5; **14a**, 117607-24-6; **14b**, 117607-25-7; **15**, 117607-27-9; **16**, 117607-28-0; (*S*)-(+)-2-(hydroxymethyl)-pyrrolidine, 23356-96-9; (*S*)-2-(chloromethyl)pyrrolidine hydrochloride, 35120-33-3; (*S*)-2-(chloromethyl)-1-pyrrolidinecarboxylic acid phenylmethyl ester, 61350-66-1; (*R*)-2-(chloromethyl)-1-pyrrolidinecarboxylic acid phenylmethyl ester, 117607-12-2; (*R*)-2-methylpyrrolidine hydrobromide, 117607-13-3; 2-fluorobenzaldehyde, 446-52-6; 2-fluoroacetophenone, 450-95-3; (*R*)-3-ethylmorpholine, 74572-05-7; (*R*)-*N*-ethyl-α-methylbenzenemethanamine, 70811-66-4; 1-[2-(4-morpholinyl)phenyl]ethanone, 117607-26-8.

Supplementary Material Available: Lists of atomic positions, bond distances, and bond angles for compounds (±)-**12a** and **16** (8 pages). Ordering information is given on any current masthead page.

(20) Structure Determination Package; Frenz B. A. and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, 1983.

Synthesis of 1,2-Dihydro-1-oxo-3*H*-3-benzazepine and 3-Acyl Derivatives

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Facile preparation of 1-oxo-1,2-dihydro-3*H*-3-benzazepine, **1**, is afforded by an unusual base-induced oxidative elimination of 1-oxo-3-sulfonyl-1,2,4,5-tetrahydro-3*H*-3-benzazepines **6**. This unstable eneamino–ketone can be isolated and characterized as an oil or derivatized after in situ generation. A series of 3-acyl derivatives of **1** were prepared. The chemistry of these derivatives and the mechanism of reaction for their formation is discussed. Molecular mechanics calculations of **1** and related tautomers were neither consistent with the favored tautomer observed experimentally nor predictive of a mechanistic pathway for its formation.

We report the first isolation and derivatization of the unstable parent 1,2-dihydro-1-oxo-3*H*-3-benzazepine, **1**.[1] Its formation occurs via the facile oxidative elimination of sulfinate from sulfonamide with subsequent hydrogen rearrangement and results in introduction of functionality into the unactivated carbons of a tetrahydroazepine ring. This remote functionalization provides access to unique preparative opportunities for a number of biologically important natural or unnatural products containing the benzazepine ring system, e.g. antitumor alkaloids of the cephalotaxine class.[2]

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