The filtrate was concentrated and subjected to column chromatography on silica gel with ether/hexane (1:1) as eluent. The first yellow band (**11**) was isolated: yield, 20 mg (8%); yellow crystals (hexane, -20 °C), mp 86-87 °C; mass spectrum, *m/e* 243.101 (M^+, calcd 243.101).

Anal. Calcd for $C_{13}H_{13}N_3O_2$ (M_r 243.26): C, 64.18; H, 5.39. Found: C, 64.34; H, 5.40.

Reaction of 6d with 2a. To a solution of 155 mg (1 mmol) of **6d**[19] in 3 mL of dichloromethane was added 200 mg (1.8 mmol) of **2a** in 2 mL of dichloromethane. After being stirred for 2 h, the solution was concentrated. The residue was dissolved in 3 mL of ether, and 50 mL of hexane was added. The white precipitate (**10b**) was filtered and washed with hexane: yield, 100 mg (38%); white crystals (toluene/hexane), mp 119-120 °C; ^1H NMR δ 8.60 (s, 1 H), 8.42 (s, 1 H), 3.90 (s, 3 H, OCH_3), 3.5-3.0 (m, 4 H, NEt_2), 1.82 (s, 3 H, CH_3), 1.15-0.9 (m, 6 H, NEt_2); ^{13}C NMR δ 162.8 (C4, pyrimidine), 158.8 (J = 207 Hz, C2 pyrimidine), 152.5 (J = 181 Hz, C6 pyrimidine), 143.9 (C=NO).

Anal. Calcd for $C_{12}H_{18}N_4O_3$ (M_r 266.30): C, 54.12; H, 6.81. Found: C, 54.40; H, 6.66.

(19) Biffin, M. E. C.; Brown, D. J.; Lee, T. C. *Aust. J. Chem.* **1967**, *20*, 1041.

The filtrate was concentrated and subjected to column chromatography on silica gel with hexane/dichloromethane (4:1) as eluent. The yellow band (**8a**) was isolated: yield, 50 mg (21%).

Reaction of 6h with 2a. To a solution of 139 mg (1 mmol) of **6h** in 10 mL of dichloromethane was added 250 mg (2.3 mmol) of **2a**. After being stirrred for 0.5 h, the solution was concentrated. Column chromatography on alumina (act IV) with ether gave 27 mg (13%) of **8b** and 5.4 mg (2.4%) of **8c**. **8b**: yellow solid; mp 45-47 °C; mass spectrum, *m/e* 209.116 (M^+ calcd for $C_{10}H_{15}N_3O_2$ 209.116). **8c**: yellow oil; mass spectrum, *m/e* 223.132 (M^+, calcd for $C_{11}H_{17}N_3O_2$ 223.132).

Further elution of the column with ethyl acetate gave **7e**. This compound was not very stable and could not be isolated in a pure state: ^1H NMR δ 7.86 (d, J = 2.3 Hz, 1 H, H4), 4.42 (d, J = 2.3 Hz, 1 H, H2a); ^{13}C NMR δ 168.4 (C=O), 159.9 (C6), 159.2 (J = 194 Hz, C4), 149.5 (C8a), 132.6 (C7), 125.8 (C8), 86.1 (C2), 58.9 (J = 151 Hz, C2a).

Acknowledgment. We are indebted to Dr. C. A. Landheer and C. J. Teunis for the mass spectroscopic measurements, to H. Jongejan for performing the microanalyses, and to Dr. H. A. J. Holterman and A. van Veldhuizen for the ^{13}C NMR measurements.

A Mechanistic Study on the Degenerate Ring Transformation of 5-Nitropyrimidine into 2-Substituted 5-Nitropyrimidines with Nitrogen-15-Labeled Amidines

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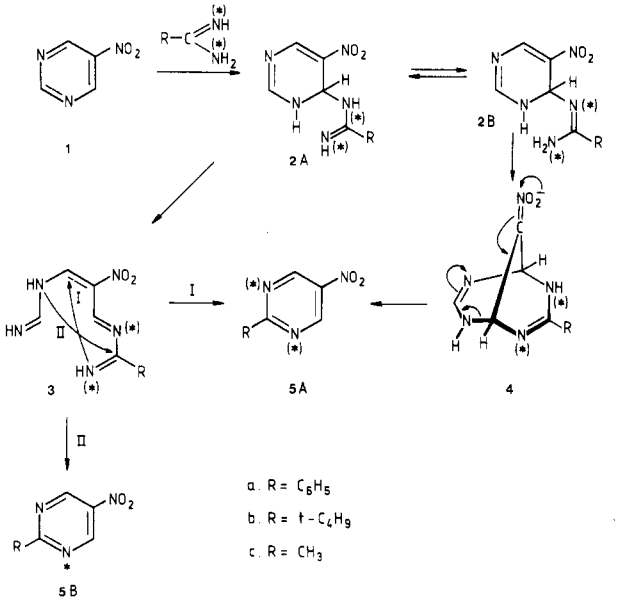
The conversion of 5-nitropyrimidine (**1**) with ^{15}N-labeled benzamidine, pivalamidine, and acetamidine into the corresponding 2-substituted 5-nitropyrimidines (**5**) has been investigated. It was found that three mechanisms are involved in this degenerate ring transformation: (a) an ANRORC mechanism leading to incorporation of the N-C-N fragment of the amidine into the pyrimidine ring of **5**; (b) an ANRORC mechanism which involves the incorporation of a C-N fragment of the amidine; (c) a regiospecific 1,4-cycloaddition reaction also leading to incorporation of a C-N fragment. The replacement of the N_1-C_2 fragment of the pyrimidine ring by the N-C moiety of the amidine dominates over the N-C-N incorporation.

The ability of pyrimidines and pyrimidinium salts to undergo ring transformations with ammonia, potassium amide, and hydrazine is very well documented.[1-3] Recently it has been reported that 5-nitropyrimidine (**1**) when treated with ambident nucleophiles such as benzamidine or pivalamidine gives 2-phenyl- and 2-*tert*-butyl-5-nitropyrimidine (**5a** and **5b**), respectively (Scheme I).[4] These so-called degenerate ring transformations were supposed to occur according to an ANRORC mechanism, involving the reactive Meisenheimer σ-adduct **2A** ⇄ **2B**, the open-chain product **3**, and/or the bicyclic adduct **4**. NMR evidence for the intermediacy of either **3** or **4** has not been obtained, and no ^{15}N-labeling experiments were carried out to substantiate the proposed mechanism.

Amidines, containing on the amidine carbon an alkyl group with active hydrogens, react with **1** in a completely different manner. When reacted with phenylacetamidine, **1** yields exclusively 2-amino-5-nitro-3-phenylpyridine (**10**) and not 2-benzyl-5-nitropyrimidine.[4] Reaction of **1** with acetamidine, in which the hydrogens of the methyl group

Scheme I



are less acidic than those in the methylene group of phenylacetamidine, gives a mixture of 2-methyl-5-nitro-

(1) Van der Plas, H. C. "Ring Transformations of Heterocycles"; Academic Press: New York, 1973; Vol. 1 and 2.
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(3) Van der Plas, H. C. *Heterocycles* **1978**, *9*, 33.
(4) Barczynski, P.; Van der Plas, H. C. *J. Org. Chem.* **1982**, *47*, 1077.

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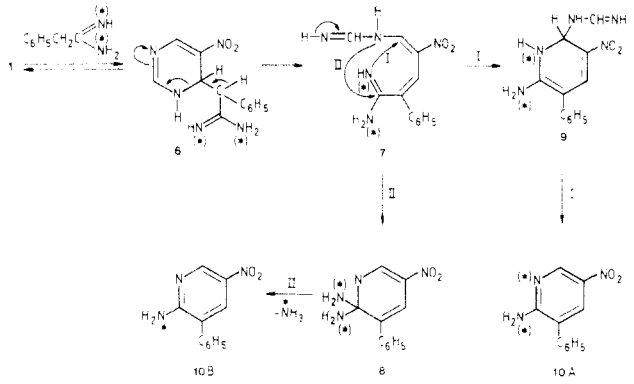
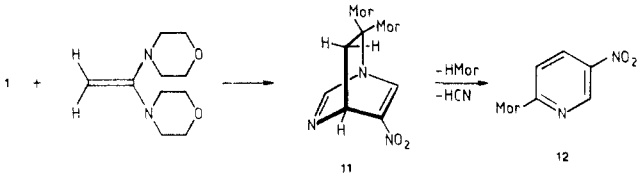
Scheme II



Scheme III



pyrimidine (**5c**) and 2-amino-5-nitropyridine. Experiments with ^{15}N-labeled phenylacetamidine show that only a part of the molecules of **10** are labeled with nitrogen-15 in the pyridine ring, suggesting that the ring transformation of **1** into **10** proceeds via different pathways, indicated in Scheme II by the routes I and II.[5]

Both pathways involve as common intermediate the open-chain compound **7**, formed by a facile ring opening of the Meisenheimer σ-adduct **6**. Pathway I describes a cyclization of **7** into **9** and subsequently into **10A**, pathway II yields the pyridine derivative **10B** via **8**.

In pathway I the amidine provides the C–C–N fragment of the pyridine ring, while in pathway II the amidine only donates two carbon atoms to the pyridine ring.

Very recently evidence has been presented that **1** is able to undergo a cycloaddition across N_1 and C_4 with electron-rich enediamines: reaction of **1** with 1,1-dimorpholinoethene gives 2-morpholino-5-nitropyridine (**12**); the 1,4-cycloadduct **11** is suggested as intermediate[6] (Scheme III).

These results stimulated us to reconsider the amidine induced mechanism of the reaction of **1** into **5a–c**, since it is possible that also in this degenerate ring transformation a cycloadduct would be involved, formed by addition of the C=N bond of the amidine, acting as a dienophile. Release of ammonia and hydrogen cyanide would then give **5** (Scheme IV).

In order to explore in more detail the mechanistic pathways involved in these reactions we investigated the reaction of **1** with labeled amidines. When **1** was reacted with the mono-nitrogen-15-labeled benzamidine (C_6H_5-C(=NH)NH_2, nitrogen-15 is equally scrambled over both nitrogen atoms) and we determined the excess of nitrogen-15 in 2-phenyl-5-nitropyrimidine (**5a**), we observed that the excess of nitrogen-15 (= 6.4%) is considerably lower than in the starting material (= 8.9%) (see Table I). This result justified the conclusion that benzamidine reacts as N–C–N donor as well as C–N donor. From the discussions given above it is evident that the incorporation of the C–N moiety can either involve the cycloadduct **13a**

Scheme IV

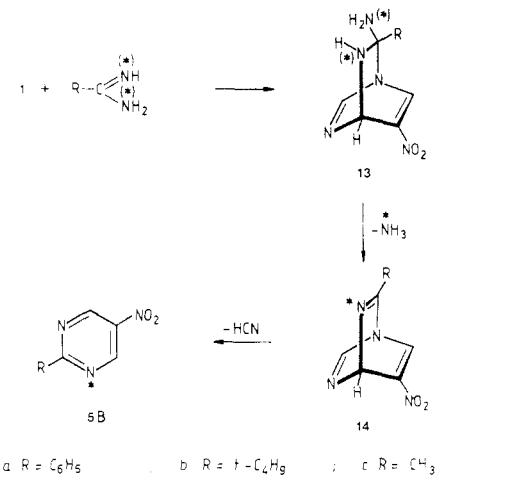


Table I. ^{15}N Excess in Amidines and in Products Obtained in the Reaction of 5-Nitropyrimidine (1) with Amidines

RC(=NH)NH_2		product		N–C–N	C–N
R	% ^{15}N		% ^{15}N	*donor, %*	*donor, %*
C_6H_5	8.9	**5a**	6.4	44	56
t-C_4H_9	8.3	**5b**	5.0	20	80
CH_3	8.7	**5c**	5.5	26	74

and/or the open-chain intermediate **3** (R = C_6H_5), which undergoes a ring closure according to route II in Scheme I.

When the reaction was studied with the mono-nitrogen-15-labeled pivalamidine and acetamidine and we measured the nitrogen-15 excess in **5b** and **5c**, we observed that the contribution of both amidines to act as C–N donor is considerably increased, when compared with benzamidine (see Table I). These results are certainly not in agreement with the C–N donation mechanism II (Scheme I) involving ring closure of the open-chain intermediate **3**, since it can be expected that the electron-donating character of the methyl and *tert*-butyl group should *disfavor* the nucleophilic attack of nitrogen to the carbon atom, attached to substituent R instead of promoting the ring closure, as experimentally observed. From these results we concluded prudently that the ring transformation reaction of **1** with amidines leading to C–N incorporation into **5a–c** certainly occurs according to a mechanism in which not only an open-chain compound but also a 1,4-cycloadduct is involved.

In order to test this hypothesis further we investigated the reaction of **1** with ^{15}N-labeled benzamidine hydrochloride; thus no triethylamine was added to liberate the benzamidine from the hydrochloride salt. In the amidinium salt the C–N bond lengths are about equal (1.314 Å)[7] and the C–N bonds have a small double bond character, suggesting that the cycloaddition reaction will certainly be disfavored; the only available routes for conversion of **1** into **5a** would be route I and/or II in Scheme I.

When ^{15}N-labeled benzamidine hydrochloride (8.9% of ^{15}N excess) is reacted with **1** in dimethyl sulfoxide, **5a** is obtained with an excess of 8.4% of ^{15}N. This almost complete incorporation of nitrogen-15 in **5a** shows that the degenerate ring transformation of **1** into **5a** for more than 90% occurs according to route I in Scheme I. This result is in accordance with our expectation and supports our view that with the *free* amidines the conversion of **1** into

(5) Charushin, V. N.; Van der Plas, H. C. *J. Org. Chem.* **1983**, *48*, 2667.
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5 can certainly proceed according to a mechanism involving the regiospecific 1,4-cycloaddition.

Experimental Section

Melting points are uncorrected. The ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 B spectrometer and a Varian EM 390 spectrometer. Me_4Si was used as internal standard (δ 0). IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer.

Mass spectra were determined on a AEI MS 902 mass spectrometer equipped with VG ZAB console and GC-MS analysis was performed on a VG micromass 7070F apparatus.

Preparation of Starting Materials. 5-Nitropyrimidine (1) was prepared by the method described in the literature.[8] Amidines were prepared according to known synthetic procedures.[9,10] The amidines were isolated and used as hydrochlorides. ^{15}N-labeled amidines were prepared according to the method described for the preparation of ^{15}N-labeled benzamidine.[11]

Reactions of 5-Nitropyrimidine (1) with Amidines. The reactions of 1 with benzamidine, pivalamidine, and acetamidine were carried out according to known procedures.[4] The reactions of 1 with ^{15}N-labeled amidines were carried out in the same manner to yield **5a***-**5c***.

Reaction of 1 with Benzamidine Hydrochloride in the Absence of Triethylamine. 1 (125 mg, 1 mmol) and 1 mmol of benzamidine hydrochloride were dissolved in 2 mL of Me_2SO. The mixture was heated at 100 °C for 12 h. After cooling, the precipitate was collected, washed with water and ethanol, and recrystallized from ethanol. Yield of **5a** was 46 mg (23%). The same procedure was used for the reaction of 1 with ^{15}N-labeled benzamidine hydrochloride.

Acknowledgment. We are indebted to Dr. M. A. Posthumus, Dr. C. A. Landheer, and C. J. Teunis for mass spectrometric data.

Registry No. 1, 14080-32-1; **5a**, 68906-00-3; benzamidine, 618-39-3; pivalamidine, 59950-56-0; acetamidine, 143-37-3; benzamidine hydrochloride, 1670-14-0.

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Chiral 3-Substituted Aldehydes: Determination of Absolute Configurations and Enantiomeric Excesses by NMR Analysis of Derived Oxazolidines

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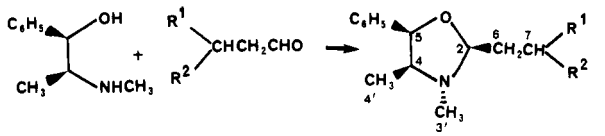
The absolute configurations and the enantiomeric excesses of chiral 3-alkyl- and 3-aryl-substituted aldehydes are determined by ^{13}C NMR and ^1H NMR analysis of the corresponding oxazolidines derived from (-)-ephedrine.

NMR spectroscopy is a well-documented method of determining optical purities and absolute configurations of partially resolved enantiomers;[1] chiral shift reagents, chiral solvating agents, and diastereomeric derivatives have been the subject of countless articles.

In this paper, we will report the use of oxazolidines derived from the condensation of (-)-ephedrine with chiral 3-substituted aldehydes providing both a measure of the enantiomeric ratios of the aldehydes and the assignments of their absolute configurations. Related determinations of the enantiomeric excesses of 2-substituted (and a few 3-substituted) aldehydes and ketones via their diastereomeric imines or acetals have already been reported.[2]

This method makes use of the stereoselective condensation of naturally occuring (1*R*,2*S*)-(-)-ephedrine with aldehydes (eq 1), leading to oxazolidines which exhibit the



2*S* configuration (2*S*/2*R* ~ 93/7) when the reaction is performed under the usual conditions, i.e., under thermodynamic control.[3]

Very mild conditions (methylene chloride solution, molecular sieves, room temperature) are required for reaction 1 to proceed quantitatively; therefore, ephedrine is perfectly suited as a chiral derivatizing agent for aldehydes. As the main ^1H NMR and ^{13}C NMR features of oxazolidines are well established,[4,5] analysis of the diastereomeric

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