196 (1.1), 179 (1.1), 178 (8.4), 168 (2.1); IR (oil mull) 3287 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 93.2, 74.1, 57.1, 43.o, 42.5, 33.1, 33.0, 30.9, 30.4, 30.2, 21.3, 18.6. Anal. (C, H, N) Calcd for $C_{12}H_{20}O_2$: C, 73,54; H, 10.29. Calibrated GC–MS analysis showed the crystals to contain 7 mol % *n*-hexane, which corresponds to the following: C, 73.73; H, 10.45. Found: C, 73.80; H, 10.61.

11-Oxotricyclo[4.4.2.0^{1,5}]dodec-5-yl Benzoate (12). Freshly distilled benzoyl chloride (2.5 mL, 21 mmol) was added to a stirring solution of 500 mg of **2d** (2.58 mmol) in 7.5 mL of pyridine. After 24 h at 115 °C the dark brown reaction mixture was cooled to 25 °C. Excess benzoyl chloride and pyridine were removed by vacuum transfer, and the remaining residue was dissolved in 75 mL of ether. This solution was extracted successively with 25 mL of water, 15% aqueous hydrogen chloride, and brine. The ether solution was dried with Na_2SO_4, and the solvent was removed. The remaining oil was dissolved in 3 mL of ethyl acetate and purified by column chromatography (3.5 × 12 cm flash silica, eluant 5% ethyl acetate/hexane). The product (530 mg, 69% yield) was obtained as a clear oil: ^{13}C NMR ($CDCl_3$) δ 210.9, 164.9, 133.5, 133.3, 130.2, 129.0, 98.8, 68.4, 44.7, 42.6, 39.9, 34.2, 31.8, 29.5, 28.3, 22.0, 20.4; HRMS calcd for $^{12}C_{19}{}^{1}H_{22}{}^{16}O_3$ 298.1569, found 298.1571, calcd for $^{12}C_{12}{}^{1}H_{16}{}^{16}O_1$ 176.1201, found 176.1195.

Crystal Structure Determination of 2. Long hexagonal columnar crystals of **2** were obtained by slow crystallization from petroleum ether. Fragments cleaved from some of these crystals were mounted on glass fibers by using poly(cyanoacrylate) cement. Precession photographs indicated rhombohedral Laue symmetry, but no conventional cell was found. The data collection was done in a Enraf-Nonius CAD-4 diffractometer. Automatic peak search and indexing procedures yielded a triclinic cell. Attempts to locate a rhombohedral cell were unsuccessful. Data were collected for the triclinic cell, $+h, \pm k, \pm l$, for 2θ from 3–45°. Only after solution and partial refinement of the structure the trigonal cell was found and transferred to the correct space group, *R*3.

The 4899 raw intensity data were converted to structure factor amplitudes and their esds by correction for scan speed, background, and Lorentz and polarization effects. Inspection of the intensity standards showed a decrease of 2.7% of the original intensity. The data were corrected for this decay. Inspection of the azimuthal scan data showed a variation of ±1% for the average curve.

The structure was solved with MULTAN 11/82 in space group *P*1, looking for three independent molecules in the unit cell. Refinement proceeded via standard least-squares and Fourier techniques. Clear patterns in the reflections with large ΔF led finally to the discovery of the rhombohedral cell, followed by averaging of data to yield 1635 unique reflections ($R(I)$ = 2.5% for all, 1.9% for "observed"). All further refinement was done in space group *R*3. Hydrogens were included in the structure factor calculations in their expected positions based on idealized bonding geometry but were not refined in least squares. All hydrogens were assigned isotropic thermal parameters 1–2 $Å^2$ larger than the equivalent Biso of the atom to which they were bonded. The hydroxyl hydrogens were located on difference Fourier from which all low-angle data [$(\sin\theta)/\lambda < 0.16$] had been removed. They were included in their discovered positions.

After refinement of the molecule, many low-angle reflections had very large residuals, but no large peaks were observed on the difference Fourier map. Instead a large region of density 1.1 $e^-/Å^3$ was observed, centered around the 3-fold inversion at 1/2, 1/2, 1/2 and extending most of the way along the [1.1.1] direction. This was first modeled by placing partial occupancy oxygen atoms in the region and allowing them to refine, while limiting the sum of their occupancies to be the equivalent of one molecule of hexane disordered around 1/2, 1/2, 1/2. Continued adjustment finally resulted in a relatively flat difference map throughout the region, with density 0.25 ± 0.1 $e^-/Å^3$. The residuals for this model were R = 7.4%, wR = 10.3%, GOF = 3.51, Np = 153, No = 828. The seven occupancy parameters for the oxygen atoms were then allowed to refine, in an attempt to determine how much electron density was in the region. The final residuals for 160 variables refined against the 828 data for which $F^2 > 3\sigma(F^2)$ were R = 5.84% and GOF = 2.57. The R value for all 1635 data was 10.9%. The sum of the occupancies for the oxygen atoms is 1.9, corresponding to 91.2 electrons in the region around the three-bar symmetry axis.

The quantity minimized by the least-square program was $\sum w(|F_o| - |F_c|)^2$, where w is the weight of a given observation. The p factor, used to reduce the weight of intense reflections, was set to 0.04 for the last cycles of refinement. The analytical forms of the scattering factor tables for the neutral atoms were used[16] and all non-hydrogen scattering factors were corrected for both the real and imaginary components of anomalous dispersion.[17]

Inspection of the residuals ordered in ranges of $(\sin\theta)/\lambda$, $|F_o|$, and parity and value of the individual indexes showed no prominent features or trends. There was no evidence of secondary extinction in the low-angle, high-intensity data. The largest peak in the final difference Fourier map had an electron density of 0.24 $e^-/Å^3$, and was located near o1. The residual electron density in the region of disorder was ±0.1 $e^-/Å^3$.

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Supplementary Material Available: Table of positional parameters and view of one unit cell of diol **11d** (2 pages). Ordering information is given on any current masthead page.

(16) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch: Birmingham, 1974; Vol. IV, Table 2.2B.
(17) Cromer, D. T., in ref 16, Table 2.3.1.

A Mechanistic Study on the Amination of 2-Chloro-3,5-dinitropyridine with Liquid Ammonia

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Nucleophilic substitution in heteroaromatics is a subject of ongoing interest in our laboratory and especially the behavior of halogenoazines toward potassium amide/liquid ammonia has attracted our special attention.[1-3] From our studies and those of others it has become evident that many different mechanisms can be involved in these substitutions. They are known as $S_N(AE)^{ipso}$, $S_N(AE)^{cine}$, $S_N(AE)^{tele}$, $S_N(EA)^{ipso}$, $S_N(EA)^{cine}$, $S_N(EA)^{tele}$, $S_N(ANRORC)^{ipso}$, $S_N(ANRORC)^{tele}$, $S_{RN_1}{}^{ipso}$. In many nucleophilic substitutions more than one mechanism is often involved.

Very recently we reported that 2-chloro-5-nitropyridine, when subjected to treatment with potassium amide/liquid ammonia, is converted into the corresponding 2-amino compound via a mechanism involving a ring-opening reaction [$S_N(ANRORC)$].[4] The same mechanism has also been encountered in the hydroxy-dechlorination of 2-chloro-3- and -5-nitropyridine by sodium hydroxide.[5]

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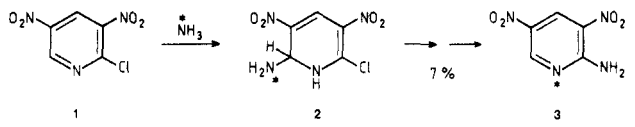
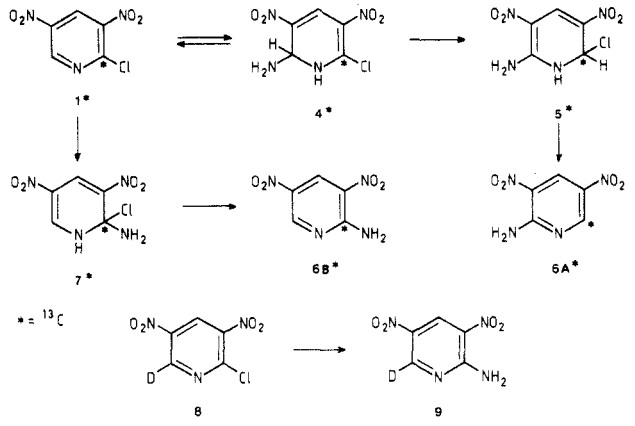
Scheme I



Scheme II



However, it was found[4] that in the conversion of 2-chloro-3,5-dinitropyridine (1) into 2-amino-3,5-dinitropyridine (6) by treatment with liquid ammonia (not containing potassium amide) for only a very small part (7%)[6] the S_N(ANRORC) mechanism is involved, although ^1H NMR spectroscopy provided unequivocal evidence that the first step in the ANRORC mechanism, i.e., formation of the 6-amino-1,6-dihydropyridine derivative 2, actually takes place. The small degree of involvement of the S_N(ANRORC) mechanism was established by mass spectroscopic determinations of the excess of ^{15}N in 2-amino-3,5-dinitropyridine (8.2%) obtained in the reaction of 1 with ^{15}N-labeled ammonia and in 2-fluoro-3,5-dinitropyridine (0.6%), which was prepared from the obtained ^{15}N-labeled amino compound (percent S_N(ANRORC) = 0.6/8.2 × 100 = 7%).

Taking into account that only 7% of the amination of 1 proceeds via an S_N(ANRORC) mechanism, we wonder which mechanism occurs in the remaining 93%. Although it is tempting to assume that the amino-dechlorination takes place according to the classical $S_N(AE)^{ipso}$ mechanism, the well-established intermediacy of 2 at least suggests the possibility of an $S_N(AE)^{tele}$ reaction, in which a 1,5-sigmatropic suprafacial thermally allowed hydrogen shift in the 1,6-dihydro adduct gives the isomeric 1,2-dihydropyridine 5, and a subsequent base-induced elimination of hydrogen chloride yields the 2-amino compound **6A**.

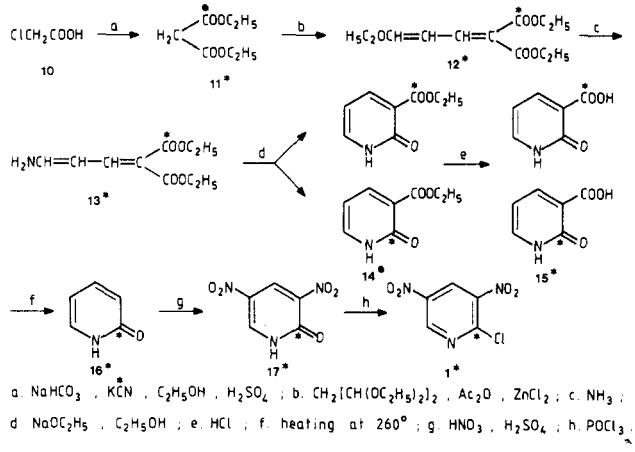
In order to find out whether this $S_N(AE)^{tele}$ mechanism is operative we prepared [2-^{13}C]-2-chloro-3,5-dinitropyridine (1*) and studied the ^{13}C-distribution in the amino product 6* by ^{13}C NMR spectroscopy (Scheme II). It is evident that if the reaction proceeds exclusively according to the $S_N(AE)^{tele}$ process, ^{13}C would exclusively be present at C-2, [2-^{13}C]-6-amino-3,5-dinitropyridine (**6A***) being formed.

Table I. ^{13}C Chemical Shifts (ppm), Coupling Constants (Hertz), and Relative Intensities of 1, 1*, 6, and 6* Obtained in the Reaction of 1* with Liquid Ammonia

	δ		relative intensities			
	1,1*[a]	6,6*[b]	1	1*	6	6*
C-2	148.8	155.7	6.3	30.5	2.0	11.3
C-3	144.0	125.3	1.0	1.0	1.0	1.0
C-4	129.4	131.3	21.5	23.8	3.4	3.5
	$^1J_{C_4H}$ = 178	$^1J_{C_4H}$ = 172				
C-5	142.8	133.7	1.6	1.5	1.1	1.0
C-6	147.0	151.4	16.3	17.2	2.6	2.9
	$^1J_{C_6H}$ = 204	$^1J_{C_6H}$ = 190				

[a] In $CDCl_3$. [b] In Me_2SO-d_6.

Scheme III



a. $NaHCO_3$, KCN, C_2H_5OH, H_2SO_4; b. $CH_2[CH(OC_2H_5)_2]_2$, Ac_2O, $ZnCl_2$; c. NH_3; d. $NaOC_2H_5$, C_2H_5OH; e. HCl; f. heating at 260°; g. HNO_3, H_2SO_4; h. $POCl_3$.

After reacting 1* in the usual way (see Experimental Section) and comparing the ^{13}C NMR spectrum of the amino product 6* with that of the unlabeled compound 6, measured under *identical* NMR conditions, it was found that the relative intensity of the signal of C-2 (to which the amino group is attached) in 6* is about 6 times larger than that of C-2 in unlabeled 6 (see Table I). Moreover, the relative intensities of the signals of C-6 in 6* and in 6 are about the same. Also the ratio of the relative intensities of C-4 and C-5 in 6* and 6 is nearly one. From these observations we have to conclude that the amination of 1* with liquid ammonia leads exclusively to the formation of [2-^{13}C]-2-amino-3,5-dinitropyridine (**6B***). Thus it is obvious that a 1,5-sigmatropic shift in 4* leading to 5* and subsequently to **6A*** does not play a role in the amination. Thus, the results are in agreement with the occurrence of an $S_N(AE)^{ipso}$ process involving the intermediacy of 7*.

Additional support for the $S_N(AE)^{ipso}$ mechanism comes from the reaction of 6-deuterio-2-chloro-3,5-dinitropyridine (8, 70% D) which gave after reaction with liquid ammonia 6-deuterio-2-amino-3,5-dinitropyridine (9), containing the same percentage of deuterium as present in the starting material.

In conclusion, it can be stated that the ^{15}N-labeling study points out that the S_N(ANRORC) mechanism is involved for 7% in the amination of 1 and that the ^{13}C-labeling study shows that the $S_N(AE)$ mechanism is operating for 93%.

Synthesis of [2-^{13}C]-2-Chloro-3,5-dinitropyridine (1*). The synthesis of 1* was performed via the route presented in Scheme III. ^{13}C-Labeled diethyl malonate (11*) was obtained from chloroacetic acid (10) by a reaction with ^{13}C-labeled potassium cyanide, followed by hydrolysis and esterification. Treatment of 11* with 1,1,3,3-tetraethoxypropane affords the allylidene malonate 12*, which could be converted by ammonia into the corresponding

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(6) In the original paper it was mentioned that in this amino-dechlorination reaction the S_N(ANRORC) mechanism was not involved.[4] However, a recently developed method to obtain more accurate mass spectrometric data, which consisted of conversion of the ^{15}N-labeled amino product into the 2-fluoro-3,5-dinitropyridine, instead of into 3,5-dinitropyridin-2(1*H*)-one as published, showed that a small part (7%) of 1 reacts according to the S_N(ANRORC) mechanism.

amino compound 13*. Cyclisation of 13* yields 3-(ethoxycarbonyl)pyridin-2(1*H*)-one (14*), which after hydrolysis gives the acid 15*, and subsequent decarboxylation yields pyridin-2(1*H*)-one (16*). Nitration of 16* to give 17* followed by treatment with phosphorus oxychloride yields 1*.

Experimental Section

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R24B spectrometer and a Varian EM 390 spectrometer equipped with a Varian EM 3940 variable-temperature controller. Me_4Si was used as internal standard (δ = 0 ppm). The ^{13}C NMR spectra were recorded at 75.460 MHz on a Bruker CXP-300 spectrometer. Spectral parameters: spectral width 15000 Hz, pulse width 7 μs (30°), pulse delay 2 s.

Mass spectra were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was carried out over Merck silica gel 60 (70–230-mesh ASTM).

Preparation of Starting Materials and Reference Compounds. A. 2-Chloro-3,5-dinitropyridine (1),[7] 2-amino-3,5-dinitropyridine (6),[8] and 6-deuterio-2-chloro-3,5-dinitropyridine (8)[4] were all prepared according to known synthetic procedures.

B. [2-^{13}C]-2-Chloro-3,5-dinitropyridine (1*). This compound was synthesized following the route given in Scheme III. The ^{13}C-labeled compounds 11*–15* were all prepared according to the procedures described for the unlabeled compounds 11[9] and 12-15.[10] In the synthesis of ^{13}C-labeled diethyl malonate (11*), potassium cyanide enriched with about 10% ^{13}C was used. In our hands the best result in the synthesis of 3-ethoxyallylidene malonate (12*) was obtained after a reaction time of 72 h instead of the 1 h reaction time mentioned in the literature.[10]

The decarboxylation of [2-^{13}C]-3(1-^{13}C)-carboxypyridin-2-(1*H*)-one (15*) into [2-^{13}C]pyridin-2(1*H*)-one (16*) was achieved by heating 1 g of 15* to a temperature just above its melting point (about 260 °C) in an open Carius tube. After the evolution of carbon dioxide had ceased, the residue was extracted with dichloromethane. After filtration of the solution and evaporation of the solvent in vacuo, 16* was obtained in quantitative yield, mp 105–106 °C (lit.[11] mp 106–107 °C). The conversion of 16* into 1* via 17* was performed according to the procedures described for the unlabeled compound 16.[7] ^{13}C NMR data are given in Table I.

Amination of 1* in Liquid Ammonia. This reaction was carried out as described for unlabeled 1, to yield [2-^{13}C]-2-amino-3,5-dinitropyridine (6B*).[4]

Amination of 6-Deuterio-2-chloro-3,5-dinitropyridine (8). This reaction was carried out as described for 1 and gave 6-deuterio-2-amino-3,5-dinitropyridine.[4]

Amination of 1 in ^{15}N-Labeled Liquid Ammonia. This reaction was carried out as described before to yield ^{15}N-labeled 2-amino-3,5-dinitropyridine.[4] The conversion of the ^{15}N-labeled 2-amino-3,5-dinitropyridine thus obtained into 2-fluoro-3,5-dinitropyridine was performed by the procedure described for unlabeled 6.[12]

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An Improved Synthesis of 2′-Deoxy-5-azacytidine by Condensation of a 9-Fluorenylmethoxycarbonyl-Protected Sugar onto the Silylated Base

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Recent reports describing the role of 2′-deoxy-5-azacytidine (6β) in the regulation of gene expression through the inhibition of DNA methylation[1,2] have generated renewed interest in this nucleoside. 2′-Deoxy-5-azacytidine was first synthesized in 1964 by a multistep procedure described by Pliml and Sorm.[3] More recently, improved yields were obtained by a direct glycosylation procedure of silylated 5-azacytosine[4-6] or via a total synthesis using glycosyl isocyanates as intermediates.[7]

During the synthesis of deoxynucleosides by the glycosylation procedure, the sugar protecting groups play an important role in the regulation of the relative amounts of the two anomeric forms, α and β, in the final product mixture. The contributing factors in this regulation seem to be the steric and the electronic effects exerted by these groups on the C-1 position of the sugar ring.[8] Aroyl groups such as benzoyl,[9] nitrobenzoyl, chlorobenzoyl, and especially toluoyl[10] have been sucessfully used to date. The latter was found to be the protecting group of choice in the synthesis of 2′-deoxy-5-azacytidine,[6] although the strongly basic conditions (sodium methoxide in methanol) necessary for deprotection led to a significant hydrolysis of the product.[11,12] The difficulties associated with the removal of the sugar protecting groups are not confined to 2′-deoxy-5-azacytidine; the synthesis of any base-labile nucleoside analogue would meet with the same problems.

The benzyl group, removable under the neutral conditions of hydrogenolysis, was also employed in nucleoside synthesis,[9] although the 3,5-di-*O*-benzyl-2-deoxypentofuranosyl chloride is not a suitable intermediate for this purpose.[8,9] Moreover, some reduction of the aromatic ring of the nucleoside during the hydrogenolytic removal of this protecting group has been observed.[13]

Our attempts at the synthesis of 2′-deoxy-5-azacytidine via the glycosylation procedure described by Piskala,[5] using the toluoyl group for protection of the sugar moiety, were largely unsuccessful, due to the hydrolysis of the product during the final deprotection procedure. We therefore decided to investigate other protecting groups that would eliminate this problem.

In choosing a sugar protecting group suitable for the synthesis of labile nucleosides by the glycosylation pro-

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